Single Technology Appraisal

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission summary** from Johnson & Johnson Innovative Medicine
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2. **Company summary of information for patients (SIP) from Johnson & Johnson Innovative Medicine**

3. **Clarification responses**
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4. **Patient group, professional group and NHS organisation submissions from:**
   a. EGFR Positive UK
   b. Roy Castle Lung Cancer Foundation
   c. Association of Respiratory Nurse Specialists
   d. British Thoracic Oncology Group

5. **Expert personal perspectives** from:
   a. Dr Adam P Januszewski, Consultant Medical Oncologist – clinical expert, nominated by British Thoracic Oncology Group
   b. Professor Gini Harrison – Patient Expert nominated by EGFR Positive UK

6. **External Assessment Report prepared by ScHARR**
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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.

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Single technology appraisal

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

Document B

Company evidence submission

January 2025

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List of Abbreviations

Abbreviation	Definition
1L	First-Line
2L	Second-Line
3L+	Third-Line or Later
AE	Adverse Event
AESI	Adverse Events Of Special Interest
AIC	Akaike Information Criterion
AUC	Area Under The Curve
BIC	Bayesian Information Criterion
BICR	Blinded Independent Central Review
BIM	B-cell Chronic Lymphocytic Leukaemia-Lymphoma Like 11
BNF	British National Formulary
BOR	Best Overall Response
BSA	Body Surface Area
BSC	Best Supportive Care
cEGFR	Common Epidermal Growth Factor Receptor
cEGFRm	Common Epidermal Growth Factor Receptor-Mutated
CEM	Cost Effectiveness Model
CI	Confidence Interval
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Response
CRD	Centre for Reviews and Dissemination
CRU	Cost And Resource Use
CSR	Clinical Study Report
DCO	Data Cut-Off
DoR	Duration Of Response
DSU	Decision Support Unit
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic Acid
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC	European Organisation For Research And Treatment Of Cancer
ESME	Epidemiological Strategy And Medical Economics
ESMO	European Society For Medical Oncology
EQ-5D-5L	EuroQoL-Five Dimension-Five Levels
Exon19del	Exon 19 Deletions
FAS	Full Analysis Set

FDA	Food and Drug Administration
GLHs	Genomic Laboratory Hubs
HR	Hazard Ratio
HRU	Healthcare Resource Utilisation
HSUV	Health State Utility Value
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ILD	Interstitial Lung Disease
INV	Investigator
IO	Immuno-oncology
IPD	Individual Patient Data
IQR	Interquartile Range
IRR	Infusion Related Reactions
ISPOR	International Society For Pharmacoeconomics And Outcomes Research
ITT	Intention To Treat
IV	Intravenous
KM	Kaplan-Meier
MET	Mesenchymal-Epithelial Transition Factor
MHRA	Medicines And Healthcare Products Regulatory Agency
MMRM	Mixed-Effects Model For Repeated Measures
mOS	Median Overall Survival
mPFS	Median Progression Free Survival
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration And Analysis Service
NE	Not Estimable
NGS	Next-Generation Sequencing
NHS	National Health Service
NICE	National Institute Of Health And Care Excellence
NR	Not Reported
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PBC	Platinum-Based Chemotherapy
PCR	Polymerase Chain Reaction
PDC	Platinum-Doublet Chemotherapy
PFS	Progression-Free Survival
PFS2	Progression-Free Survival After First Subsequent Therapy
PR	Partial Response
PRO	Patient-Reported Outcomes
PS	Propensity Score
PSM	Partitioned Survival Model

PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QA	Quality Assessment
QALE	Quality-Adjusted Life Expectancy
QALY	Quality-Adjusted Life Year
QD	Once Daily
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RWD	Real-World Data
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SC	Subcutaneous
SCLC	Small Cell Lung Cancer
SLR	Systematic Literature Review
SoC	Standard of Care
TA	Technology Appraisal
TEAE	Treatment-Emergent Adverse Events
TKI	Tyrosine Kinase Inhibitor
TSD	Technical Support Document
TTD	Time To Treatment Discontinuation
TTNT	Time To Next Therapy
TTSP	Time To Symptomatic Progression
TTST	Time To Subsequent Therapy
UK	United Kingdom
UKLCC	United Kingdom Lung Cancer Coalition
US	United States
VAS	Visual Analogue Scale
VAT	Value Added Tax
VEGFI	Vascular Endothelial Growth Factor inhibitors
VTE	Venous Thromboembolism
WCLC	World Conference on Lung Cancer

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

Submission Summary

- This submission considers amivantamab in combination with lazertinib, hereafter referred to as amivantamab-lazertinib, in line with its anticipated marketing authorisation: [redacted].[1]
- EGFR Exon19del and L858R substitution mutations are the most common EGFR mutation subtypes, accounting for 85–90% of EGFR mutations in NSCLC; these are collectively referred to as common EGFR (cEGFR) mutations throughout this submission.[2, 3]
- NSCLC is most often diagnosed at an advanced stage (66% in 2022 in England), where patient outcomes (survival) are poor.[4]

Patients with cEGFR mutation-positive (cEGFRm) NSCLC suffer a substantial disease burden, largely due to the poor prognosis and development of resistance mechanisms associated with current standard of care (SoC). Despite the availability of osimertinib as SoC for patients with cEGFRm NSCLC in the United Kingdon (UK), this population remains in need of access to 1L treatment options that can provide a sustained benefit and reduce the risk of treatment resistance, thereby delaying cancer relapse or progression to second-line (2L) treatment, improving survival outcomes and maintaining overall quality of life (QoL).

- The long-term prognosis for patients with cEGFRm NSCLC is poor; only 24% of patients diagnosed at the average age of 64 years survive longer than five years.[5]
    - The poor prognosis of these patients is more striking given they represent a generally younger population (mean: 63.1 years; interquartile range [IQR]: 54.6–72.8) compared with patients with other types of lung cancer, who are on average 70 years or older.[6]
- Current treatment guidelines recommend the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib as SoC for patients with untreated advanced cEGFRm NSCLC (recommended for use in this population in 2020, NICE TA654).[7, 8] Although osimertinib provides a clinical benefit compared with first and second generation EGFR TKIs, patients inevitably develop resistance mutations, leading to disease progression and fewer second- and later-line treatment options.[9]
    - UK real-world evidence (RWE) is available from a descriptive standing cohort study among patients diagnosed with advanced NSCLC between 2016–2024, collected from the National Cancer Registration and Analysis Service (NCRAS) dataset.[10] This population is referred to as the 'MARIPOSA-expanded' cohort throughout this submission (N=1,469).[10] Data from this cohort show that patients with cEGFRm advanced NSCLC who are treated with 1L osimertinib monotherapy (n=278) have a low median overall survival (OS) of 26.2 months (95% confidence interval [CI]: 22.0, 30.0).[10]
    - This was supported by a 2024 retrospective analysis of French and Danish patient databases, which highlighted that patients with cEGFRm NSCLC receiving 1L osimertinib (n=319) had a median OS (mOS) and PFS of 26.2 and 11.9 months, respectively. Furthermore, at least 26.7% of patients died before receiving 2L treatment due to clinical deterioration.[11]
    - After progression on 1L treatment, 2L options are limited and currently consist of non-targeted, non-specific treatments that result in poor prognosis for patients at 2L.[7, 12-15] Given the high number of patients dying before reaching 2L treatment, and the poor

options available at 2L, patients with cEGFRm NSCLC need effective therapeutic options that can avoid treatment resistance and provide better disease control, leading to more sustained responses upfront, in the 1L setting.
    - Notably, the most common mechanisms of resistance to osimertinib are due to alterations in the EGFR and mesenchymal epithelial transition (MET) pathways; a targeted therapy with activity against both EGFR and MET would therefore be particularly beneficial in this setting, to negate a key mechanism of resistance.[16]
- Patients with cEGFRm NSCLC experience worse health-related quality of life (HRQoL) compared with the general population, particularly in late-stage or progressive disease.
    - UK market research conducted by Johnson & Johnson in 2024 demonstrated that NSCLC and/or its treatment negatively impacted the daily activities and emotional functioning of patients with cEGFRm NSCLC and their caregivers, and therefore negatively impacted overall QoL.[17] Compared to similar patients with no disease progression, patients with progressive cEGFRm NSCLC experience greater physical and mental wellbeing impairments, further highlighting the notable humanistic burden associated with the disease and its progression.[18]

Amivantamab-lazertinib is anticipated to address the unmet need for a more efficacious, targeted and chemotherapy-free combination therapy that uses a dual mode of action to target multiple resistance pathways, which ultimately extends PFS and OS for patients with untreated cEGFRm NSCLC, thereby maximising long-term effectiveness and maintaining HRQoL.

- Amivantamab-lazertinib proactively addresses downstream resistance mechanisms and improves clinical outcomes.[19]
    - The synergy of the distinct mechanisms of action of amivantamab (EGFR-MET bispecific antibody) and lazertinib (highly selective, central nervous system [CNS]-penetrant, third-generation EGFR TKI), which target the extracellular ligand domain and the intracellular active site of EGFR, respectively, has the potential to inhibit the EGFR pathway more potently than either agent alone. Simultaneous inhibition of both EGFR and MET by amivantamab in combination with lazertinib is anticipated to improve overall treatment efficacy and has proven to limit the compensatory pathway activation and target the two major mechanisms of resistance to TKIs.[20, 21]
- Addressing treatment resistance and delaying progression in patients with cEGFRm NSCLC is crucial; results from the registrational Phase 3 MARIPOSA randomised controlled trial (RCT) demonstrate that amivantamab-lazertinib is a highly efficacious treatment regimen, leading to improved survival outcomes and response rates, and a more durable response compared with osimertinib.
- The MARIPOSA trial met its primary endpoint and provided a head-to-head comparison of osimertinib versus amivantamab-lazertinib, demonstrating that patients treated with amivantamab-lazertinib achieved a statistically significant improvement in median PFS (mPFS) assessed by blinded independent central review (BICR); after a median follow-up of 22.0 months (11th August 2023 data cut-off [DCO]), a statistically significant ($p<0.001$) and clinically meaningful improvement in PFS was observed, translating to a 30% reduction in the risk of disease progression or death in patients receiving amivantamab-lazertinib compared with those receiving osimertinib (HR [hazard ratio]: 0.70; 95% CI: 0.58, 0.85, $p<0.001$).[21]
- At the 13th May 2024 DCO, with a longer-term median follow-up of 31.1 months, mOS was not reached in the amivantamab-lazertinib arm, compared with 37.3 months in the osimertinib arm, but there was a strong trend towards improvement in OS in the amivantamab-lazertinib arm compared with the osimertinib arm (HR: 0.77; 95% CI: 0.61, 0.96; $p=0.019$).[19]
- A press release shared by Johnson & Johnson earlier this month communicated that with a longer duration of follow-up ([redacted]), amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in OS compared to osimertinib in the phase 3

MARIPOSA trial ([redacted]). This means that the combination of amivantamab-lazertinib [redacted] in the intention-to-treat (ITT) population.[22, 23]

- The mOS was not estimable ([redacted]) in the amivantamab-lazertinib arm, while the mOS for osimertinib was reached at [redacted] months ([redacted]).[22, 23] These significantly improved OS results reinforce the importance of amivantamab-lazertinib and its potential to significantly improve patient prognosis. It is noteworthy that amivantamab-lazertinib is the only chemotherapy-free treatment to demonstrate a significant survival benefit versus osimertinib in the first-line treatment of patients with EGFR-mutated lung cancer.
- In addition to increasing time to disease progression or death, receiving amivantamab-lazertinib at 1L confers a benefit in prolonging the time until patients receive currently limited
- 2L treatment options, as well as maintaining treatment benefit after the first subsequent therapy. At the 13th May 2024 DCO, fewer patients in the amivantamab-lazertinib arm (34.7%) progressed after first subsequent therapy compared with patients in the osimertinib arm (43.8%).[24]
- Safety data from the MARIPOSA trial and other ongoing trials (Section B.2.11) demonstrate that adverse events (AEs) reported in the amivantamab-lazertinib arm are manageable.[21, 25-28]
- In the economic analysis of amivantamab-lazertinib versus osimertinib, amivantamab-lazertinib was found to be a cost-effective use of National Health Service (NHS) resources at amivantamab and lazertinib patient access scheme (PAS) prices when compared to osimertinib at its list price, dominating osimertinib in the probabilistic and deterministic analyses.
- Furthermore, all scenario analyses (probabilistic and deterministic), which explored key modelling assumptions and approaches, resulted in amivantamab-lazertinib (PAS price) remaining cost-effective compared to osimertinib, demonstrating robustness of the economic model results.
- It is therefore expected that the reimbursement of amivantamab-lazertinib will address the significant unmet need for a more efficacious, targeted and chemotherapy-free 1L treatment option for patients with cEGFRm advanced NSCLC, that proactively addresses downstream resistance mechanisms, and delays disease progression, upon which there are limited 2L treatment options.

B.1.1 Decision problem

The aim of this submission is to determine the clinical and cost-effectiveness of amivantamab-lazertinib, in line with its anticipated marketing authorisation: [redacted].[1]

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	People with untreated advanced NSCLC which has an EGFR exon19del or exon 21 (L858R) substitution mutation	[redacted]	This population is in alignment with the anticipated licensed indication and with the population included within the pivotal MARIPOSA trial (NCT04487080)
Intervention	Amivantamab with lazertinib	Amivantamab-lazertinib	As per NICE scope
Comparator(s)	• Osimertinib monotherapy • Dacomitinib • Afatinib • Erlotinib • Gefitinib • Osimertinib with chemotherapy (subject to NICE appraisal)	Osimertinib monotherapy	Osimertinib monotherapy was identified to be the only relevant comparator in the ongoing appraisal of osimertinib with platinum-doublet chemotherapy (PDC) for untreated cEGFRm advanced NSCLC (NICE ID6328), given that 86% of patients with EGFRm NSCLC in the UK currently receive it.[29] Advisory boards with UK oncologists (held in January 2023, June 2023 and October 2024) and UK RWE (collected from the NCRAS dataset) further support that osimertinib, a third generation TKI, represents the current SoC in the UK for patients in the population considered in this appraisal.[10, 30-32] **First- and second-generation TKIs** First- (erlotinib and gefitinib) and second- (dacomitinib and afatinib) generation TKIs are recommended by NICE for use in the population of interest to this appraisal. However, clinical expert opinion, gathered from advisory boards held in January 2023, June 2023, and October 2024, informed Johnson & Johnson that these treatments have very limited use in patients with untreated advanced NSCLC who have EGFR exon19del or exon 21 (L858R) substitution mutations, following the reimbursement of osimertinib monotherapy in 2020 (TA654).[33] This is supported by evidence from the NCRAS dataset, which provides data for patients in the UK with cEGFRm NSCLC who had similar baseline characteristics to patients in the MARIPOSA trial (the 'MARIPOSA-like' cohort, N=617). From 2021 (following the introduction of osimertinib to UK clinical practice in 2020[33]) to 2023, 95 patients in the 'MARIPOSA-like' cohort received 1L treatment, of whom 90.5% (86/95) were treated with

			osimertinib, demonstrating the preferential use of osimertinib as a third-generation TKI as compared with earlier-generation TKIs.[10] This is further supported by the results of the FLAURA trial, which found patients treated with osimertinib to have statistically significantly longer OS than patients treated with gefitinib or erlotinib (mOS: 38.6 months versus 31.8 months, respectively).[34] Clinical experts also support that osimertinib is a beneficial treatment option compared with first- and second-generation TKIs, as it is better tolerated with fewer side effects.[29] In this appraisal, erlotinib, gefitinib, dacomitinib, and afatinib are therefore not regarded as relevant comparators, as they do not align with the current SoC in the UK. Therefore, osimertinib monotherapy is considered the only relevant comparator for this appraisal. **Osimertinib with chemotherapy** Given that at the time of submission, this proposed indication is currently undergoing NICE appraisal and is not an established treatment option in clinical practice, osimertinib with chemotherapy does not represent current SoC. Furthermore, draft guidance issued in October 2024 does not recommend osimertinib with chemotherapy for this proposed indication (NICE ID6328).[29] As such, it does not represent a relevant comparator in this appraisal.
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rate • Time to treatment discontinuation (TTD)/time to subsequent therapy (TTST) • AEs • HRQoL	Outcomes addressed in the submission include: • PFS • OS • Objective response rate (ORR) • Duration of response (DoR) • TTD/time to symptomatic progression (TTSP) • AEs • HRQoL	As per NICE scope

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. • If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost comparison may be carried out. • Costs will be considered from a National Health Service (NHS) and	• 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 30-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	**EGFR testing costs:** • The introduction of amivantamab-lazertinib 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 mutations is included in the National Genomic Test Directory.[35] Therefore, EGFR 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 genomic laboratory hubs (GLHs) and different hospitals throughout the UK. Testing for EGFR 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-lazertinib 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.

	Personal Social Services (PSS) perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account.	within the base-case economic model.	
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: type of EGFR mutation, co-mutation (e.g. TP-53), disease stage, histology, treatments had at previous stages, and presence of CNS metastases.	Analyses are presented for PFS for the following subgroups: type of EGFR mutation, presence of CNS metastases, age, sex, race, weight, ECOG performance and history of smoking.	Subgroups based on disease stage, co-mutation (e.g. TP-53), histology (squamous or non-squamous), and treatments had at previous stages are not available and therefore could not be explored.
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-lazertinib is presented within its anticipated marketing authorisation for the treatment of [redacted]	The United Kingdom Lung Cancer Coalition (UKLCC) report on health inequalities in lung cancer highlights the crucial fact that lung cancer has the biggest deprivation gap compared to any other cancer in the UK.[36] Deaths associated with socio-economic variation are shown to be most commonly reported in lung cancer and as such, there is an ever growing need not only to acknowledge the health inequality associated with this disease, but also to identify drivers of health inequality in order to ensure all patients have equal access to life changing treatments. Health inequality associated with stigma is a major concern for lung cancer patients as it is largely driven by a perception that it is 'self-inflicted' due to the public recognising the link between lung cancer and smoking.[37] This is particularly damaging for patients with cEGFRm NSCLC as these

		[redacted] • 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.	mutations disproportionately affect never-smokers, women and people of Asian ethnicity.[36, 38, 39] Specifically in communities of Asian ethnicity, there is evidence that symptoms of lung cancer are stigmatised, which could reinforce treatment delaying behaviour.[40, 41] A recent study assessing differences in screening, diagnosis, and initial care between people with newly diagnosed lung cancer of Asian and White ethnicity reported that, compared with people of White ethnicity, people of Asian ethnicity were more likely to be diagnosed with later-stage lung cancer and had a longer median time to treatment initiation.[42] The impact of stigma on people living with lung cancer, including patients and caregivers has been well-reported. In one qualitative study, barriers to symptom reporting for people with lung cancer included blame, stigma and cultural influences.[40] Additionally, an observational, cross-sectional study has shown that some patients report feeling uncomfortable communicating their symptoms leading, to delay in presentation, diagnosis and treatment (or low uptake of treatment).[41] The effects of stigma associated with lung cancer should be included within the decision-making process and are not inherently captured within the cost per QALY framework. Stigma is included in the NICE social value judgements principles document and as such, should be considered when deciding whether amivantamab-lazertinib is cost-effective in this population.

Abbreviations: AE: Adverse Event; CNS: Central Nervous System; DoR: Duration of Response; EGFR: Epidermal Growth Factor Receptor; GLH: Genomic Laboratory Hub; HRQoL: Health-Related Quality of Life; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; NSCLC: Non-Small Cell Lung Cancer; ORR: Objective Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; 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 Subsequent Progression; TTST: Time to Subsequent Therapy.

B.1.2 Description of the technology being evaluated

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

Table 2: Technology being appraised

UK approved name and brand name	Amivantamab (Rybrevant®) in combination with lazertinib (Lazcluze®)
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 and MET receptors.[43] Amivantamab demonstrates activity against NSCLC tumours via three mechanisms of action, thereby inhibiting tumour growth and survival regulatory pathways:[43] • EGFR/MET receptor degradation • Inhibition of ligand binding • Immune cell-directing activity Further details on the mechanism of action of amivantamab in treating NSCLC with EGFR Exon19del or Exon 21 L858R mutations are provided in B.1.2.1. Lazertinib is third-generation EGFR TKI that selectively inhibits both cEGFR and the EGFR T790M mutation.[21, 44] The combination of amivantamab-lazertinib demonstrates activity through the following mechanisms:[21] • Synergistic inhibition of primary EGFR-activating mutations • Prevention of EGFR- or MET-based resistance mutation acquisition • Recruitment of Fc-bearing immune cells in the anti-tumour response via the Fc domain of amivantamab
Marketing authorisation/CE mark status	Amivantamab, in combination with lazertinib, is anticipated to receive marketing authorisation from the Medicines And Healthcare Products Regulatory Agency (MHRA) [redacted] in [redacted]. An application for the extension of the marketing authorisation for the use of subcutaneous (SC) amivantamab-lazertinib in this indication is expected [redacted]. Lazertinib, in combination with amivantamab, is anticipated to receive marketing authorisation from the MHRA [redacted] in [redacted].[44] An application for the extension of the marketing authorisation for the use of subcutaneous (SC) amivantamab in combination with lazertinib in this indication is expected [redacted]
Indications and any restriction(s) as described in the SmPC	Amivantamab is currently indicated:[43] • in combination with carboplatin and pemetrexed for the treatment of adult patients with advance NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior

	therapy including an EGFR TKI • In combination with carboplatin and pemetrexed for the 1L treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations • As monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon20 insertion mutations, after platinum-based chemotherapy (PBC) Contraindications for amivantamab include hypersensitivity to the active substance or to any of the excipients listed below:[43] • EDTA (ethylenediaminetetraacetic acid) disodium salt dihydrate • L-Histidine • L-Histidine hydrochloride monohydrate • L-Methionine • Polysorbate 80 • Sucrose • Water for injections Lazertinib does not currently hold a marketing authorisation in the UK. Anticipated contraindications for lazertinib include hypersensitivity to the active substance or to any of the excipients listed below:[44] • Silica, hydrophobic colloidal • Croscarmellose sodium • Cellulose, microcrystalline • Mannitol • Magnesium stearate • Macrogols • Polyvinyl alcohol • Glycerol monocaprylocaprate type I • Titanium dioxide • Talc • Yellow iron oxide

Method of administration and dosage	Amivantamab is administered via IV infusion, in combination with lazertinib oral tablets, at the following doses:
	Amivantamab
	• Body weight at baseline <80 kg:
	  ○ Weeks 1–4: 1,050 mg weekly (total of 4 doses)
	  ○ Week 1 – split infusion on Day 1 and 2
	  ○ Weeks 2 to 4 – infusion on Day 1
	  ○ Week 5 onwards: 1,050 mg every 2 weeks
	• Body weight at baseline ≥80 kg:
	  ○ Weeks 1–4: 1,400 mg weekly (total of 4 doses)
	  ○ Week 1 – split infusion on Day 1 and 2
	  ○ Weeks 2 to 4 – infusion on Day 1
	  ○ Week 5 onwards: 1,400 mg every 2 weeks
	Lazertinib
	• 240 mg once daily (QD)
	
	An SC formulation of amivantamab is being developed with an anticipated UK launch date [redacted].[25]

Additional tests or investigations	The presence of an EGFR Exon19del or Exon 21 L858R substitution mutation must be established prior to initiation of treatment with this combination. An accurate and validated assay for the presence of EGFR mutations, such as next-generation sequencing (NGS)- or polymerase chain reaction (PCR)-based method, is necessary for the selection of patients for treatment with amivantamab-lazertinib.[45] Testing for these patients is standard in clinical practice and covered under the National Genomic Test Directory.[46]
List price and average cost of a course of treatment	The list price for amivantamab is £[redacted] per 350 mg vial. The list price for lazertinib 80 mg (56 tablets) is £[redacted] per pack, and the list price for lazertinib 240 mg (28 tablets) is £[redacted] per pack. At list price, the total drug acquisition cost of treating patients with amivantamab-lazertinib is £[redacted] per week during the induction period, and £[redacted] per week during the maintenance period.
Patient access scheme (if applicable)	A confidential simple PAS discount of [redacted]% has been proposed for amivantamab. Therefore, the proposed with-PAS price for amivantamab is £[redacted] per 350 mg vial (excluding VAT). A confidential simple PAS discount of [redacted]% has been proposed for lazertinib. Therefore, the proposed with-PAS price for lazertinib 80 mg (56 tablets) is £[redacted] per pack, and the with-PAS price for lazertinib 240 mg (28 tablets) is £[redacted] per pack (excluding VAT). Using the PAS discounted prices, the total drug acquisition cost of treating patients with amivantamab-lazertinib is £[redacted] per week during the induction period, and £[redacted] per week during the maintenance period.

Abbreviations: AUC5: area under the concentration-time curve 5 mg/mL per minute; EDTA: ethylenediaminetetraacetic acid; 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 cancer; PAS: Patient Access Scheme; SmPC: summary of product characteristics. VAT: value added tax.
Source: Medicines and Healthcare Products Regulatory Agency. Amivantamab SmPC.[1] Lazertinib SmPC.[44]

B.1.2.1 Amivantamab and lazertinib

Amivantamab-lazertinib is anticipated to be licensed for the [redacted]. This section describes the mechanism of action of each treatment separately, and the synergy of the combination.

Amivantamab

Amivantamab (represented graphically in Figure 1) is a novel, fully human, bispecific antibody that simultaneously targets two proteins found on the surface of cancer cells: EGFR and MET.[43, 47] Specifically, one portion of the antigen-binding fragment of amivantamab recognises EGFR, whilst the other recognises the protooncogene MET.[47]

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.[48] 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.[49]

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

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 internalisation and lysosomal degradation.[47, 50] Trogocytosis also contributes to receptor degradation (see below).[50]

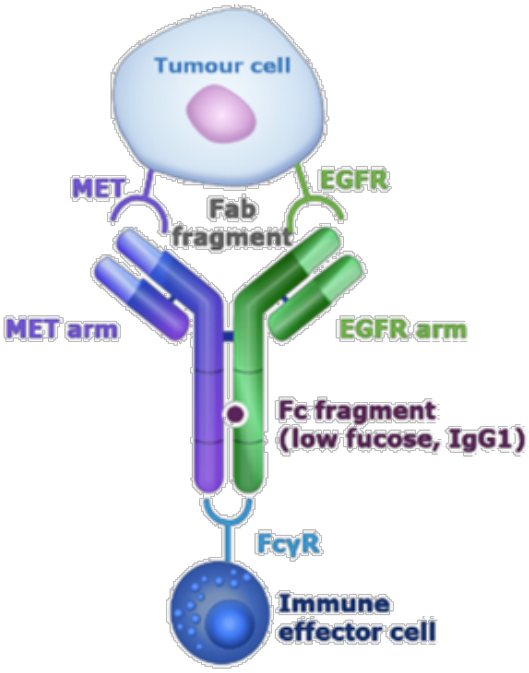
2. Inhibition of ligand binding

The binding of amivantamab to the extracellular domains of EGFR and MET further blocks ligand binding.[50] 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.[51]

3. Immune cell-directing activity

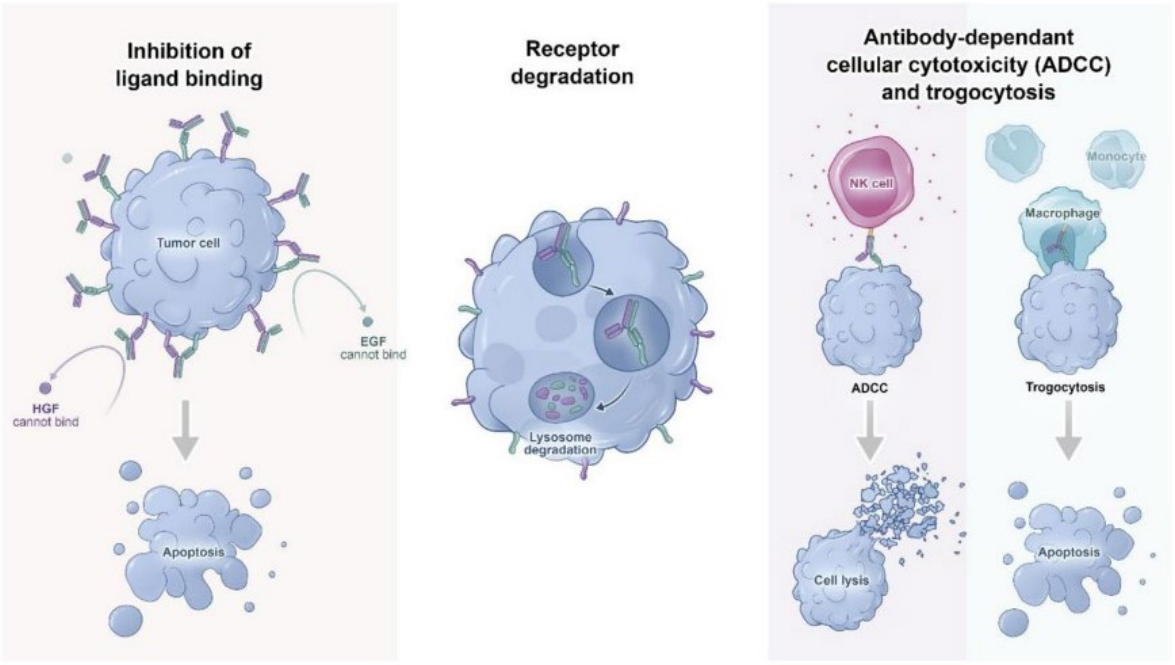
The resulting amivantamab-EGFR-MET complex on the tumour cell surface also allows for targeting of cancer cells for destruction by immune effector cells.[43, 50] For instance, the binding of amivantamab to EGFR and MET can induce tumour cell death through antibody-dependent cellular cytotoxicity, mediated by natural killer cells, as well as initiating trogocytosis (cell gnawing), where plasma membrane fragments are transferred from tumour cells to macrophages.[50] 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 the structure of amivantamab and its binding to EGFR and MET



Abbreviations: EGFR: epidermal growth factor receptor; Fab: antigen-binding fragment; FcγR: Fc gamma receptor; IgG1: immunoglobulin G1; MET: mesenchymal epithelial transition factor.
Source: Cho et al. 2022.[52]

Figure 2: Schematic of three MOAs of amivantamab – 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. 2022.[52]

Lazertinib

Lazertinib is a highly selective, CNS-penetrant, third-generation EGFR TKI that targets activating EGFR mutations and the T790M resistance mutation, a common resistance mechanism acquired during treatment with first- and second-generation TKIs.[53, 54] Lazertinib was first approved in the Republic of Korea for the treatment of previously treated patients with NSCLC and a EGFR T790M mutation.[55] Lazertinib is selective for mutated EGFR, with a safety profile suitable for use in combination therapy.[55-57] 1L treatment with lazertinib was shown to improve PFS compared with the first-generation TKI gefitinib in the phase 3 LASER301 trial (20.6 versus 9.7 months; $p<0.001$).[53]

Amivantamab in combination with lazertinib

Amivantamab in combination with lazertinib proactively addresses downstream resistance mechanisms, and improves clinical outcomes.[19] The distinct mechanisms of action of amivantamab and lazertinib, which target the extracellular ligand domain and the intracellular active site of EGFR, respectively, have the potential to inhibit the EGFR pathway more potently than either agent alone. Simultaneous inhibition of both EGFR and MET by amivantamab in combination with lazertinib is anticipated to improve overall treatment efficacy and has proven to limit the compensatory pathway activation by targeting the two major mechanisms of resistance to TKIs.[20, 21]

Patients with NSCLC treated with EGFR TKIs may acquire resistance through secondary mutations. EGFR T790M point mutation is the most common mechanism of developing resistance to EGFR TKIs (accounting for 40% to 60% of cases).[58] 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,[20] as stimulation of this pathway provides an alternative mechanism to bypass the TKI

block of EGFR and facilitate the survival of cancer cells.[20] Osimertinib, the current SoC for the 1L treatment of advanced cEGFRm NSCLC, provides activity against the EGFR T790M resistance mutation and may penetrate the blood-brain barrier better as compared with first- and second-generation TKIs, potentially delaying the incidence of brain metastases.[59] Nevertheless, almost all patients treated with 1L osimertinib will develop resistance to the treatment.[60]

The most common mechanisms of resistance to osimertinib are due to alterations in the EGFR and MET pathways.[16] It is thought that the EGFR and MET pathways compensate for each other in situations where one pathway is inhibited, leading to the so called 'kinase switch' drug resistance (seen with EGFR TKIs).[61] Amivantamab in combination with lazertinib is therefore anticipated to limit the compensatory pathway activation by simultaneously inhibiting EGFR and MET;[20, 21] this is supported by head-to-head data versus osimertinib from the MARIPOSA trial, in which amivantamab-lazertinib significantly reduced the incidence of MET amplifications and EGFR resistance alterations versus osimertinib (MET amplification: 4.4% vs 13.6% [p=0.017]; EGFR resistance mutation: 0.9% vs 7.9% [p=0.014]).[62]

The combination of amivantamab plus lazertinib provides a chemotherapy-free regimen for patients with advanced cEGFRm NSCLC, offering an innovative therapeutic option of two targeted treatments that deliver a statistically and clinically meaningful difference in efficacy. As described further in Section B.2.6, at the 11th August 2023 DCO of the MARIPOSA trial, patients treated with amivantamab-lazertinib achieved a statistically significant improvement in median PFS assessed by BICR. Patients receiving amivantamab-lazertinib reported a median PFS of 23.7 months (95% CI: 19.1, 27.7) compared to 16.6 months (95% CI: 14.8, 18.5) with osimertinib monotherapy (p<0.001). This represents a 30% reduction in the risk of disease progression or death compared with osimertinib treatment (p<0.001).[19] More recently, survival data shared by Johnson & Johnson earlier this month demonstrated that with a longer duration of follow-up ([redacted] months), amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in OS compared to osimertinib in the phase 3 MARIPOSA trial ([redacted]).[22, 23] A consistent benefit in PFS and OS was observed across all pre-specified and high-risk subgroups with amivantamab-lazertinib compared with osimertinib, including in patients with or without a history of brain metastases, and subgroups based on race and EGFR mutation type.[21, 63, 64] This regimen, combining a first-in-class therapy (amivantamab) and a third-generation TKI (lazertinib), has a manageable safety profile, consistent with each individual treatment component.[19]

Treatment with amivantamab-lazertinib has the additional benefit of preserving chemotherapy for use in later lines of therapy, meaning patients are provided with both an effective treatment regimen upfront, and increased options in later lines if needed, as further discussed in B.3.13.

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

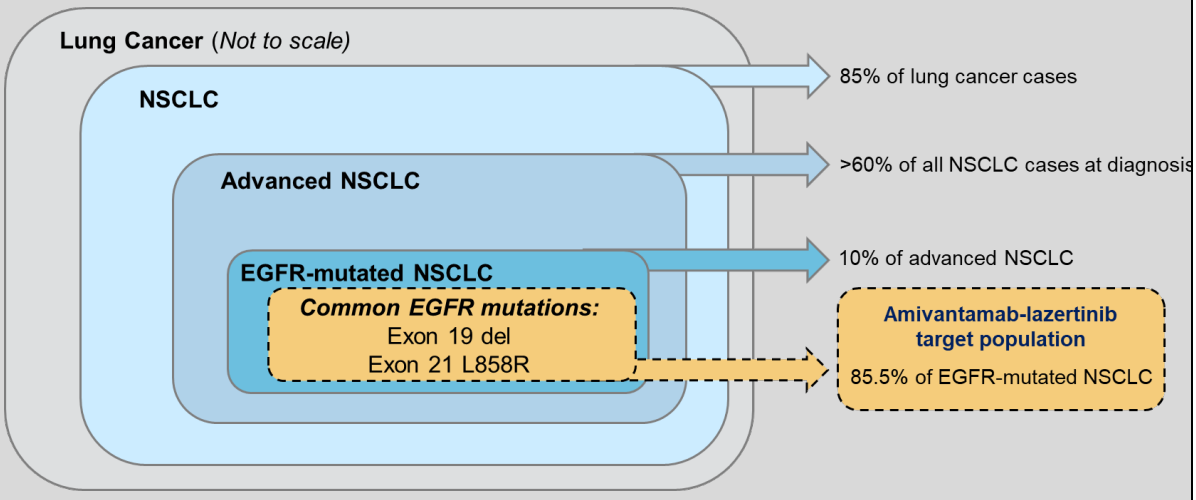
Disease overview summary

Disease classification, epidemiology and prognosis

- Lung cancer represents one of the five most common types of cancers in England, and 66% of newly diagnosed lung cancer cases in England in 2022 were at an advanced stage, where patient outcomes (survival) are poor.[29]

- NSCLC is one of two major subtypes of lung cancer and accounts for around 80–85% of all lung cancer cases.[65, 66]
- NSCLC is typically classified based on characteristic mutations present in tumours, with alterations in the EGFR gene among the most common. Exon19del and Exon 21 L858R mutations make up the majority of cases of NSCLC worldwide, with a frequency of 47% and 41% of EGFR mutations, respectively.[67] In the UK specifically, a large-scale UK study (n=18,920 patients with NSCLC) by Evans *et al.* (2019) found the frequency of cEGFRm NSCLC to be 85.5% among patients with EGFR-mutated NSCLC.[68] A recent retrospective study of patients with NSCLC in Ireland (N=2,052; June 2017–June 2022) identified similar results: 8.8% (n=181) of NSCLC tumours were identified to harbour mutations in EGFR, with 48.1% of these being Exon19del (n=87) and 24.9% being Exon 21 L858R (n=45).[69] A visual representation of the patient population intended to be treated with amivantamab-lazertinib is presented in Figure 3.

Figure 3: Overview of cEGFRm advanced NSCLC in the UK



Abbreviations: del: deletion; EGFR: epidermal growth factor receptor; L858R: leucine-to-arginine substitution at position 858; NSCLC: non-small cell lung cancer.
Sources: Evans *et al.* 2019.[68] Tweedie *et al.* 2019.[70]

Disease burden

- Despite the availability of osimertinib as SoC for patients with cEGFRm NSCLC in the UK (Section B.1.3.2), there remains a need to optimise patient outcomes by maximising the benefit of 1L treatment options whilst avoiding treatment resistance, thereby delaying cancer relapse or progression to 2L treatment, improving survival outcomes and maintaining overall QoL.
    - Patients with advanced cEGFRm NSCLC experience poor prognosis; the median age of diagnosis is 64 years, with a 5-year survival of 24%.[5, 71] These patients have an average life expectancy five years shorter than the general population.[5] The poor prognosis of these patients is more striking given they represent a generally younger population (mean: 63.1 years; IQR: 54.6–72.8) compared with patients with other types of lung cancer, who are on average 70 years or older.[6]
    - This prognosis of patients with cEGFRm NSCLC is worse than for those with other driver alterations, such as anaplastic lymphoma kinase (ALK; mOS: 37 months) or c-ros oncogene 1 receptor tyrosine kinase (ROS; mOS: 47.8 months).[72-74]
    - UK RWE from the 'MARIPOSA-expanded' cohort of the NCRAS dataset (2016–2024) demonstrates that patients with untreated, advanced cEGFRm NSCLC who received osimertinib monotherapy (n=278) have a mOS of 26.2 months (95% CI: 22.0, 30.0).[10]
    - When considering a subset of patients from the 'MARIPOSA-expanded' cohort who had similar baseline characteristics to patients in the MARIPOSA trial (referred to as the

'MARIPOSA-like' cohort; n=617), mOS was 28.1 months (95% CI: 23.0, 35.7) in patients who received osimertinib monotherapy (n=126).[10] This is considerably shorter than the mOS reported in the osimertinib monotherapy arm of the FLAURA clinical trial (38.6 months).[34]
    - Furthermore, a 2024 retrospective study in France and Denmark found that at least 26.7% of patients with locally advanced or metastatic cEGFRm NSCLC (n=319; 73.6% female, 40.3% Eastern Cooperative Oncology Group [ECOG] Performance Status [PS] 0–1) receiving 1L osimertinib did not reach 2L treatment, due to clinical deterioration or death.[11]
    - Almost all patients treated with 1L osimertinib will develop resistance, most commonly due to alterations in the EGFR and MET pathways, which compensate for each other in situations where one pathway is inhibited, leading to 'kinase switch' drug resistance.[60]
    - As a result of the development of resistance mechanisms, patients treated with osimertinib inevitably experience disease progression, leading to worsening HRQoL and death before 2L therapy, with limited second- and later-line treatment options available.[9] There are no approved targeted therapies available for the treatment of these patients once resistance has developed, meaning there remains a need to improve 1L treatment, prior to the development of resistance.[9]

- The humanistic burden of NSCLC is substantial and well documented, with patients experiencing reduced HRQoL compared with the general population.[75]
    - Market research studies conducted by Johnson & Johnson in 2021 and 2024 show that patients experience high levels of stress and anxiety, reduced self-esteem and an overall negative impact on their mental health/emotional wellbeing.[17, 76] Additionally, these studies show that this patient population experience a significant symptom burden, including fatigue, cough and breathlessness, leading to a negative impact on patient HRQoL and a substantial emotional impact.[17, 76]
    - This is correlated with significant burden on caregivers, impacting their ability to work, and increasing their risk of anxiety or depression.[77]

Treatment pathway

- Treatment guidelines for the management of lung cancer in the UK are provided by the NICE lung cancer diagnosis and management guidelines (NG122), which recommend the use of EGFR TKIs and PDC for the 1L treatment of cEGFRm NSCLC.[78]
- However, UK clinicians noted that first- and second-generation TKIs are no longer routinely used in UK clinical practice due to the availability of osimertinib, with osimertinib representing the sole SoC for patients with cEGFRm NSCLC.[71]
    - This is supported by European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines, which recommend osimertinib as the preferred 1L treatment option for cEGFRm NSCLC.[7, 15]
    - Osimertinib monotherapy was also identified to be the only relevant comparator in the ongoing appraisal of osimertinib with PDC for untreated cEGFRm advanced NSCLC (NICE ID6328), given that 86% of patients with EGFRm NSCLC in the UK currently receive it.[29]
    - Furthermore, UK RWE from the 'MARIPOSA-like' cohort of the NCRAS dataset demonstrates that, of the patients with cEGFRm NSCLC receiving 1L treatment between 2021 and 2023, 90.5% (86/95) were treated with osimertinib.[10]
    - Advisory boards with UK oncologists (held in January 2023, June 2023 and October 2024) further support that osimertinib, a third generation TKI, represents the current SoC in the UK for the patient population considered in this appraisal.[30-32]
    - Johnson & Johnson are aware that osimertinib with chemotherapy is, at the time of this submission, undergoing NICE appraisal within this indication, h it is not an established treatment option in clinical practice and therefore does not represent current SoC. Additionally, draft guidance issued in October 2024 does not recommend osimertinib with chemotherapy for this proposed indication (NICE ID6328). Therefore, it does not represent a relevant comparator in this appraisal.

- As such, osimertinib represents the sole comparator for consideration in this submission, aligned with clinical guidelines, UK RWE, and feedback from UK clinical experts.

Unmet need

- While the treatment landscape for patients with untreated, advanced cEGFRm NSCLC in the UK has progressed in recent years with the introduction of third-generation TKI osimertinib as SoC, patients continue to experience low OS due to the development of resistance mechanisms. As such, there remains a clear need for a more efficacious, well-tolerated, chemotherapy-free and targeted combination therapy that extends PFS and OS and maintains QoL.
- The combination of amivantamab-lazertinib is anticipated to fulfil this unmet need, while also helping to avoid treatment resistance, thereby maximising long-term effectiveness and maintaining HRQoL for patients with advanced cEGFRm NSCLC.

B.1.3.1 Disease overview

Disease classification and prognosis

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.[65, 66] 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.[79]

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 66% of patients with lung cancer in England and Wales presenting with Stage III or IV disease at the time of diagnosis.[29] Advanced NSCLC refers to both inoperable (unresectable), locally advanced (Stage IIIb/IIIc) and metastatic (Stage IV) disease.[80] The five-year survival rate for patients with metastatic NSCLC is poor, estimated to be less than 5%.[81]

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.[82] 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.[39, 82] In NSCLC, mutations in the EGFR gene typically occur in Exons 18–21.[83] Approximately 85.5% of EGFR mutations comprise Exon 19 deletions and L858R substitutions in Exon 21.[68]

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.[84] Lung cancer accounts for 21% of all cancer deaths in the UK, with around 34,800 lung cancer deaths per year (2017–2019 data).[85] Lung cancer predominantly affects older individuals, with the most recent data from the National Lung Cancer Audit reporting an average age at the time of diagnosis of 74 years.[84]

In the UK, the prevalence of EGFR mutations in any NSCLC histology is estimated to range from 4 to 17%, with a RWE study from the National Lung Cancer Audit in collaboration with Public

Health England estimating the prevalence of EGFR mutations in advanced or metastatic NSCLC to be 10.1%.[70]

Exon19del and Exon 21 L858R mutations make up the majority of cases of NSCLC worldwide, with a frequency of 47% and 41% of EGFR mutations, respectively.[67] Considering the UK specifically, a large-scale UK study (n=18,920 patients with NSCLC) by Evans *et al.* (2019) found the frequency of cEGFRm NSCLC to be 85.5% among patients with EGFR-mutated NSCLC.[68] A recent retrospective study of patients with NSCLC in Ireland (N=2,052; June 2017–June 2022) identified similar results: 8.8% (n=181) of NSCLC tumours were identified to harbour mutations in EGFR, with 48.1% of these being Exon19del (n=87) and 24.9% being Exon 21 L858R (n=45).[69]

NSCLC with cEGFR mutations is more commonly seen in women (>70%), people of Asian ethnicity, never-smokers and in younger patients, with a median age at diagnosis of 64 years compared with patients with other types of lung cancer, who are on average 70 years or older.[6, 39, 71] Previous studies indicate that lung cancers in never-smokers account for 10–25% of all lung cancers in the overall lung cancer population.[86]

Burden on patients with cEGFRm NSCLC

Despite the availability of osimertinib as SoC for patients with cEGFRm NSCLC in the UK (Section B.1.3.2), there remains a need to optimise patient outcomes by maximising the benefit of 1L treatment options whilst avoiding treatment resistance, thereby delaying cancer relapse or progression to 2L treatment, improving survival outcomes and maintaining overall QoL.

Poor prognosis

Patients with advanced cEGFRm NSCLC experience poor prognosis; the median age of diagnosis is 64 years, with a 5-year survival of 24%.[5, 71] These patients have an average life expectancy five years shorter than the general population.[5] The poor prognosis of these patients is more striking given they represent a generally younger population (mean: 63.1 years; IQR: 54.6–72.8) compared with patients with other types of lung cancer, who are on average 70 years or older.[6] Furthermore, among patients with advanced NSCLC, including those with cEGFRm NSCLC, approximately 40% present with a history of CNS metastases at baseline,[19] and more than half of patients are estimated to have CNS metastases at five years.[87] Patients with CNS metastases experience worse clinical outcomes compared to those without CNS metastases when treated with EGFR TKIs;[88, 89] while the risk of CNS progression is lower with osimertinib compared to earlier generation EGFR TKIs, approximately 20% of patients treated with osimertinib will still experience CNS progression, typically due to the development of new lesions.[59] Patients with cEGFRm advanced NSCLC therefore require an effective 1L treatment that is efficacious regardless of CNS metastases.

Johnson & Johnson conducted an observational, UK population-based standing cohort study using data from the NCRAS database.[90] The study included patients with registered NSCLC diagnoses between 2016 and 2024 in England, of which 1,469 had cEGFRm NSCLC (the 'MARIPOSA-expanded' population).[10] Of these patients, 617 patients met the criteria for analysis as part of the 'MARIPOSA-like' cohort.[10] The 'MARIPOSA-like' cohort closely matched the inclusion criteria of the MARIPOSA trial, described in Section B.2.3.2 (adult patients with locally advanced or metastatic cEGFRm NSCLC, with an ECOG PS of 0 or 1, with no untreated CNS metastases), while patients in the wider 'MARIPOSA-expanded' cohort (N=1,469) were not restricted based on ECOG PS status or presence of CNS metastases, and therefore represent a

broader patient group than the MARIPOSA trial.[91] Within the 'MARIPOSA-expanded' and 'MARIPOSA-like' cohorts, 278 and 126 patients, respectively, were treated with 1L osimertinib monotherapy.

Both cohorts of osimertinib-treated patients predominantly included women ('MARIPOSA-like': 95/126, 75.4%; 'MARIPOSA-expanded': 196/278, 70.5%), people of white ethnicity ('MARIPOSA-like': 98/126, 77.8%; 'MARIPOSA-expanded': 219/278, 78.8%) with stage IV (including IVA/B) NSCLC at diagnosis ('MARIPOSA-like': 122/126, 96.8%; 'MARIPOSA-expanded': 266/278, 95.7%). Sixty-six (66/126, 52.4%) and 125 (125/278, 45.0%) patients were 65 or younger in the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts, respectively, and the majority harboured Exon19del mutations ('MARIPOSA-like': 120/126, 95.2%; 'MARIPOSA-expanded': 261/278, 93.9%). The key difference in patient characteristics between the two cohorts was that all patients in the 'MARIPOSA-like' cohort had an ECOG PS of 0 or 1 as per the MARIPOSA trial inclusion criteria, whereas 21.6% (60/278) the 'MARIPOSA-expanded' cohort included patients with an ECOG PS of 2, 3 or unknown.[10] The mOS was 28.1 months (95% CI: 23.0, 35.7) and 26.2 months (95% CI: 22.0, 30.0) in the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts, respectively.[10] Both of these are considerably lower than the mOS (38.6 months) reported in the osimertinib monotherapy arm of the FLAURA clinical trial, and also demonstrate a worse prognosis for patients with cEGFRm NSCLC than reported for those with other driver alterations, such as ALK (mOS: 37 months) or ROS (mOS: 47.8 months).[34, 72-74, 90]

Treatment resistance

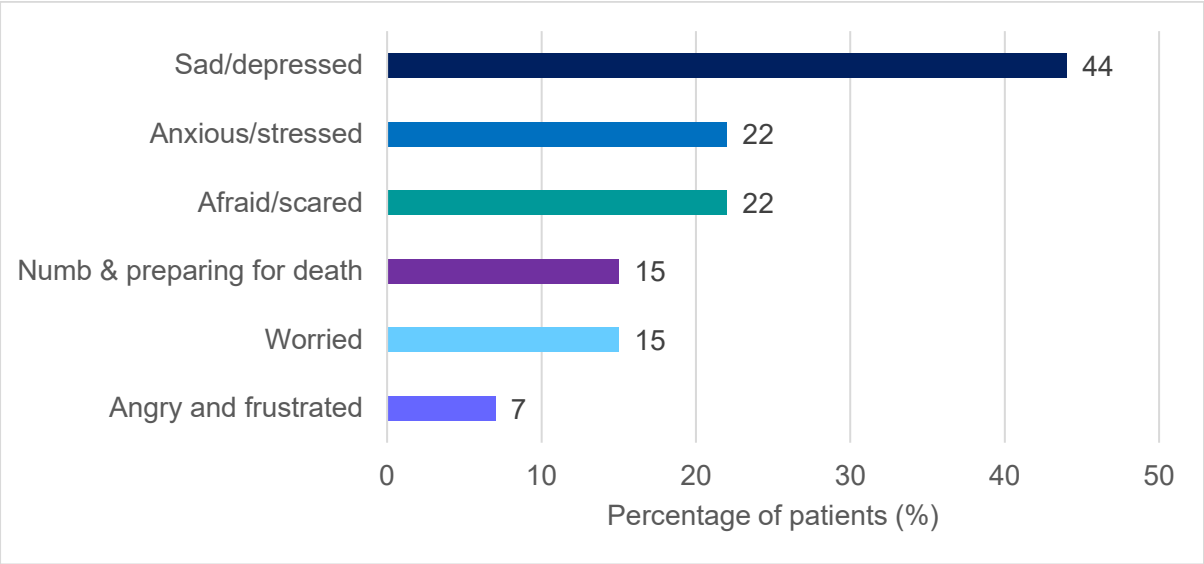
Almost all patients treated with 1L osimertinib will develop resistance, as described in Section B.1.2.1. Several resistance mechanisms have been described, including a phenotypic switch to SCLC, though the primary mechanism is due to alterations in the EGFR and MET pathways.[16, 92] Developing treatment resistance leads to disease progression and limited second- and later-line treatment options. There are no approved targeted therapies available for the treatment of these patients once resistance has developed, meaning there remains a need to improve 1L treatment, prior to the development of resistance.[9]

Impact on patients

The humanistic burden of NSCLC is substantial and well-documented, with patients experiencing reduced HRQoL compared with the general population and those with other advanced cancers.[77, 93]

In a qualitative patient-reported outcome (PRO) study of patients with cEGFRm NSCLC carried out by Johnson & Johnson, the most commonly reported symptoms among patients (ECOG PS 0–1, receiving 1L treatment and enrolled from USA, UK, Canada, Spain or India) were pain in areas other than the chest (17/23, 74%), cough (14/23, 61%) and fatigue (14/23, 61%).[94] A total of 77% of patients (receiving 1L or adjuvant treatment) reported an impact of their NSCLC on activities of daily living, while 82% of patients said their emotional functioning was negatively impacted (further broken down in Figure 4).[94]

Figure 4: Percentage of patients who reported negative impact of cEGFRm NSCLC on emotional functioning (n=36)[a]



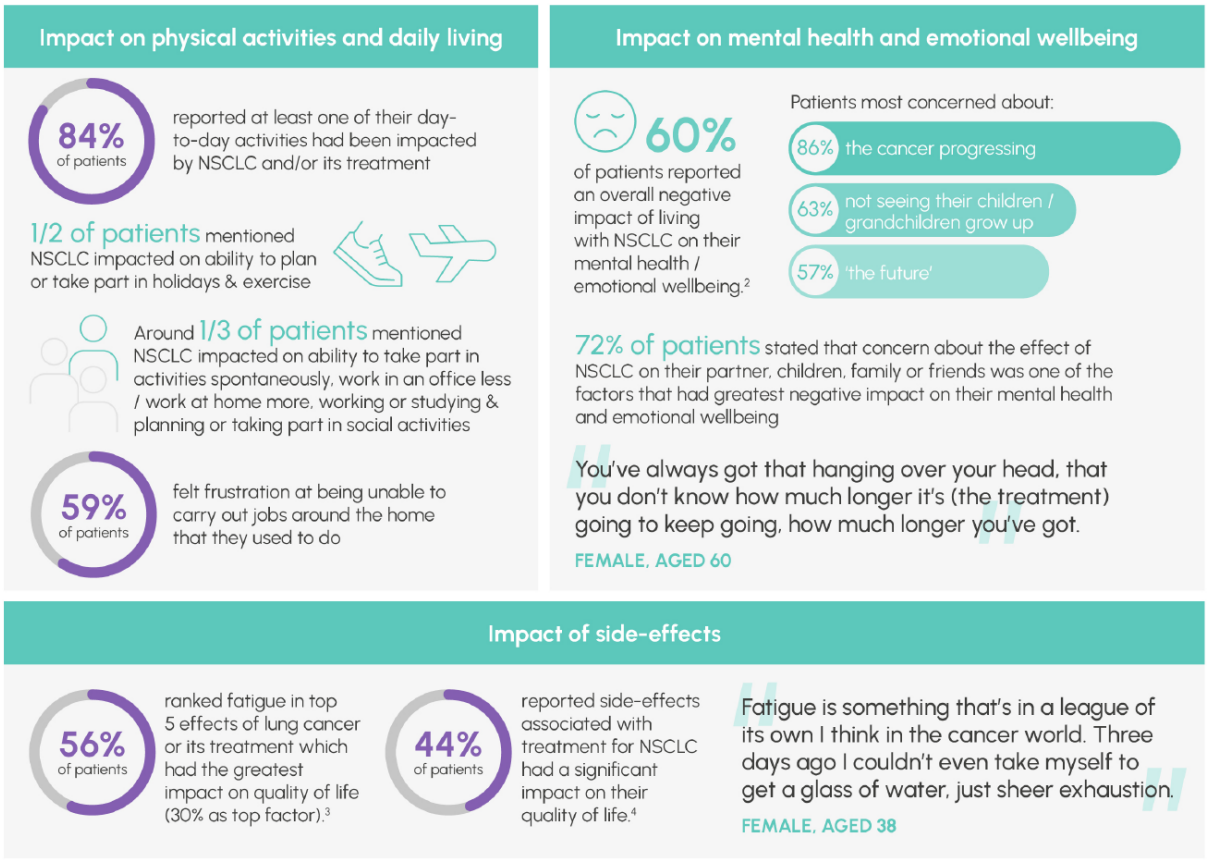
Footnotes: Percent values are based on the total number of patients who experienced emotional impacts (30/36).
[a] Not all questions were asked to all participants due to the interview duration. Specific concepts may be endorsed by fewer/more individuals that the general concept.
Abbreviations: cEGFRm: common epidermal growth factor receptor mutated; NSCLC: non-small cell lung cancer.
Source: Horn et al. 2023.[94]

Market research conducted by Johnson & Johnson aimed to understand the unmet needs and societal burdens faced by patients with cEGFRm NSCLC in the UK.[17] Twenty-six percent of patients experienced anxiety in this UK study (n/N=11/43), and the majority of patients reported an overall negative impact associated with living with NSCLC on their mental health/emotional wellbeing (26/43, 60%), further contributing to a reduction in QoL.[17] Within this context, there exists an unmet need for patients around the emotional support they receive at all stages of their care.

Overall, the UK market research study demonstrated that NSCLC and/or its treatment had varied physical and mental health effects on patients with cEGFRm NSCLC, in relation to impact on daily activities and emotional wellbeing, which negatively impacted QoL. Fatigue (24/43, 56%), diarrhoea (18/43, 42%), cracked or split nails (15/43, 35%), anxiety (11/43, 26%) and skeletal pain (11/43, 26%) were amongst the five most impactful effects of cEGFRm NSCLC or its treatment on patient QoL.[17] Patients were particularly worried about disease progression and their future; the factors considered most important for patients related to their treatment included delaying progression, maintaining stable disease, increasing length of life as well as enabling enjoyment of daily activities.[17] Key results of the 2024 market research study are summarised in Figure 5.

Patients with advanced NSCLC experience deterioration in their physical functioning, which negatively impacts their daily activities, work productivity and HRQoL.[77] Compared with similar patients with no disease progression, patients with progressive cEGFRm NSCLC experience a greater impairment in mobility, self-care, usual activities, anxiety and depression, as well as pain and discomfort.[18] Therefore, there is an unmet need to reduce the impact of symptoms whilst delaying clinical progression and improving overall mental health and emotional wellbeing in this patient population. By providing an effective 1L treatment option with a manageable safety profile for patients with advanced cEGFRm NSCLC, amivantamab-lazertinib can contribute towards reducing the impact of symptoms and maintaining overall HRQoL.[95]

Figure 5: Summary of the impact of advanced cEGFRm NSCLC on patients



Conclusions and quotes based on 20 interviews with 18 patients and two carers of patients with advanced cEGFRm NSCLC. Percentage data are based on online survey among 43 patients and six carers of patients with advanced cEGFRm NSCLC.
[2] Scoring 7 or more out of 10, where 0 is no negative impact and 10 is a significant negative impact. [3] Ranked up to 5 effects of lung cancer or its treatment that have had the most impact on quality of life where 1=had the most impact, 2=second most impact etc. [4] Scoring 7 or more out of 10, where 0 is no impact and 10 is a significant impact.
Abbreviations: cEGFRm: common epidermal growth factor receptor mutated; NSCLC: non-small cell lung cancer.
Source: Johnson & Johnson Data on File. Unmet needs in EGFR+ NSCLC Patients Market Research. (2023).[17]

Impact on caregivers/supporters

The poor HRQoL experienced by patients diagnosed with cEGFRm NSCLC is correlated with significant burden on caregivers, impacting their ability to work, and increasing their risk of anxiety or depression.[77] The 5th Lung Cancer Europe (LuCE) report, which surveyed 194 caregivers and 365 patients with NSCLC across Europe in 2020, reported that lung cancer negatively impacted independence, emotional wellbeing, family and future expectations; caregivers reported that lung cancer mostly impacted their emotional wellbeing.[96] Caregivers reported that the main emotional barriers were difficulties in managing emotions (41.5%), concerns about patient QoL (14.5%), feelings about the patient dying (13.8%) and worries associated with their caregiving (12.3%). Furthermore, while only 7.8% of caregivers had been diagnosed with depression, 20.3% thought they were depressed, demonstrating the substantial impact of caregiving for a patient with NSCLC on mental wellbeing.[96]

In a 2021 market research study conducted by Johnson & Johnson, 94% of caregivers reported that supporting someone with EGFR-mutated NSCLC had an impact on their QoL, having both an emotional impact and affecting their ability to participate in everyday life.[76] In particular, the majority of caregivers felt anxious and worried (12/13, 92%) as well as sad (9/13, 69%) and stressed (7/13, 54%) following news of their patient's diagnosis.[76] A real-world study on the

humanistic burden of advanced NSCLC on 427 informal caregivers in France, Germany and Italy found that the percentage of caregivers at risk of depression is higher compared with non-caregivers,[93] and increases with subsequent lines of therapy (1L: 65.4% versus second or later line: 76.7%; p=0.0221).[77] This is supported by the 2024 market research study interviewing caregivers of patients with cEGFRm NSCLC, which revealed that a particular area of emotional burden is the need to feel more supported upon patient disease progression, due to the uncertainty around available efficacious 2L treatments.[17]

The real-world European study also noted that 8.2% of caregivers (n/N=35/427) missed time from formal work; the average time spent providing care to patients was 29.5 hours per week, suggesting that caregiver performance at work may be impaired due to the additional hours spend providing care for the patient with advanced NSCLC.[77]

Caregivers of patients with NSCLC (and cEGFRm NSCLC, specifically) face an emotional and physical burden when providing care for patients with NSCLC, both of which negatively impact their QoL and are not adequately addressed by available treatment options. There is therefore an unmet for an effective 1L treatment which can reduce the day-to-day impact of cEGFRm NSCLC on patients and delay their disease progression, to not only improve outcomes for patients, but improve QoL for their caregivers as well.

Economic burden of disease

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 with any NSCLC mutation type reported costs of €15,787 (approximately £11,453) per patient within the first year of follow up in England, based on treatment costs (accounting for €8,593 [approximately £6,234] per patient) and resource use data (inpatient and outpatient costs).[97] Healthcare resource use (HRU) costs increase with each successive line of treatment: a United States (US) study on 409 patients with advanced EGFRm NSCLC reported that inpatient admissions increased from 27.9% in 1L to 33.5% in 2L.[98] Additionally, it is estimated that a quarter of patients who progress on 1L TKIs do not receive any subsequent treatment, resulting in more hospital visits which could increase strain on healthcare capacity compared with those who receive a 2L treatment.[99]

Beyond these healthcare system costs, advanced NSCLC is also associated with a substantial cost burden to patients themselves, as a result of work and work-related activity impairment. A real-world medical chart review and survey study of patients with Stage IIIB or IV NSCLC and a mean age of 64.5 years was conducted across France, Germany and Italy, with financial data collected from May 2015 to June 2016. Overall, more than half (53%) of the 1,030 patients included in the cross-sectional study experienced work-related activity impairment, and 37% experienced overall work impairment, based on the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire. As patients with cEGFRm NSCLC have a median age at diagnosis of 64 years, the loss in productivity could impact years these patients could be working.[71] Due to the reduction of worked hours, these patients incurred a mean annual wage loss of €2,077 (approximately £1,698) and productivity losses of €1,484 (approximately £1,213).[100] The financial burden experienced by caregivers was even greater, with estimated mean annual total direct and indirect out-of-pocket costs of €3,477 (approximately £2,842; n=194) compared with €2,644 (approximately £2,161) for patients (n=518).[100] Although productivity is not captured in QALYs, it is important to consider as an element of value with an impact on the overall health and wellbeing of patients, as well as a potential societal impact, as

noted in the Professional Society for Health Economics and Outcomes Research (ISPOR) value "flower", and represents an unmet need in the treatment of cEGFRm NSCLC.[101]

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 and caregivers also expected to experience out-of-pocket costs and productivity losses, which are additionally associated with negative societal impact and on patient QoL. These data suggest that through delaying disease progression at 1L, the associated economic burden on HRU may be reduced.

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.[37] This is particularly evident in the case of patients with cEGFRm NSCLC, as this mutation disproportionately affects never-smokers.[39] The 2020 LuCE report showed that 20% of 557 respondents felt guilty because of their lung cancer, likely linked to the stigma associated with smoking.[96] Furthermore, 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.[76]

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.[41]

B.1.3.2 Clinical pathway of care

Advanced NSCLC is a progressive, deadly disease. The goal of treatment in advanced NSCLC is not curative, rather the focus is on the need to delay disease progression, prolong survival, maintain QoL and alleviate symptoms. In seeking out therapies that meet these treatment goals, there is also a critical need to ensure patient safety is not compromised and, as such, risk of toxicities is considered. The choice of therapy depends largely on the presence or absence of driver mutations, and factors such as disease staging, volume, and histology.[78]

As described in Table 2, patients undergo genetic screening to identify the presence of driver mutations that are amenable to targeted therapy. EGFR mutations are included in the National Genomic Test Directory for cancer under the EGFR gene panel as part of clinical practice in the UK.[35] NGS is considered the most appropriate method of diagnostic testing for these patients.[102]

Treatment guidelines for the management of lung cancer in the UK are provided by the NICE lung cancer diagnosis and management guidelines (NG122).[78] There are a number of EGFR TKIs that are recommended by NICE (afatinib, dacomitinib, erlotinib, gefitinib and osimertinib) for the 1L treatment of EGFR-mutated NSCLC.[78] However, first- and second-generation TKIs (afatinib, dacomitinib, erlotinib, gefitinib) are associated with T790M resistance mutations which lead to an increased chance of disease progression.[12] For this reason, UK clinicians noted that first- and second-generation TKIs are no longer routinely used in UK clinical practice. Instead, the third-generation TKI osimertinib now represents SoC given that it specifically targets these T790M resistance mutations.[8, 71] NICE guidelines (NG122) further recommend PDC as an alternative treatment option to TKIs.[78] However, expert opinion provided by UK clinicians is that

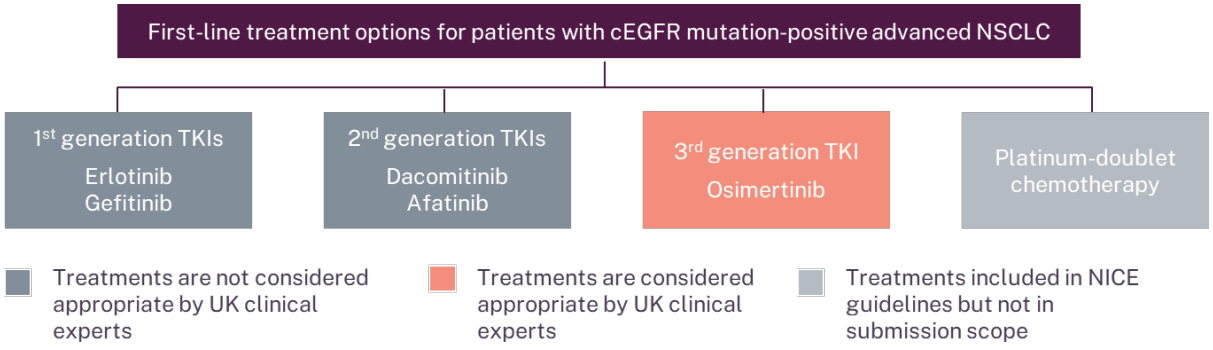
since testing is carried out routinely at diagnosis, the presence of a targetable mutation will guide clinicians to treat with TKIs over non-targeted, non-specific treatments such as PDC.[32]

In addition to those available from NICE (NG122), guidelines for the treatment of NSCLC are available from the ESMO and NCCN.[7, 15] In alignment with NICE NG122, the ESMO guidelines recommend that all patients with a sensitising EGFR mutation should receive a TKI in 1L, noting that osimertinib is the preferred 1L option for treating cEGFR mutations, and that erlotinib, gefitinib, afatinib and dacomitinib are considered alternative options.[7, 103] NCCN guidelines are in further alignment, recommending osimertinib as the preferred EGFR-TKI option for the 1L treatment of cEGFRm NSCLC and first- and second-generation TKIs considered to be alternative options.[15]

Treatment pathway

The current SoC for patients with cEGFRm NSCLC in UK clinical practice is osimertinib, a third-generation EGFR-targeted TKI (Table 1). As discussed above, NICE guidelines recommend a variety of TKIs for the 1L treatment of cEGFRm NSCLC; however, due to the superior efficacy of osimertinib over first and second generation TKIs and its oral administration, clinicians noted that this is the SoC in UK clinical practice.[8, 32, 78] This is supported by ESMO and NCCN guidelines which recommend osimertinib as the preferred 1L treatment for these patients,[7, 15, 103] and has been recently accepted as SoC by the NICE Committee in the ongoing appraisal of osimertinib with PDC for untreated cEGFRm advanced NSCLC [ID6328] in October 2024.[29] Furthermore, UK RWE from the NCRAS dataset demonstrates that 90.5% of patients with cEGFRm NSCLC in the 'MARIPOSA-like' cohort who received 1L treatment between 2021 and 2023 were treated with osimertinib (86/95).[10] PDC is recommended as an alternative option to TKIs but is not relevant to this appraisal given that UK clinicians have confirmed that PDC would not be prescribed to patients with targetable cEGFR mutations. As such, PDC is not considered as a relevant comparator in this submission.[32] The treatment landscape for patients with untreated cEGFRm advanced NSCLC in UK clinical practice, informed by NICE guidelines, UK clinical expert feedback, and UK RWE, is illustrated in Figure 6 below.

Figure 6: Current treatment options for patients with untreated cEGFRm advanced NSCLC in UK clinical practice



Abbreviations: EGFR: epidermal growth factor receptor; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; TKI: tyrosine kinase inhibitor.
Sources: NICE. Lung cancer: diagnosis and management: NICE guideline (NG122). 2019;[78] Johnson & Johnson Data on File. MARIPOSA Advisory Board (October 2024).[32]

Johnson & Johnson are aware that, at the time of submission, osimertinib with chemotherapy is undergoing NICE appraisal within this indication, hence it is not an established treatment option in clinical practice and therefore does not represent current SoC. Additionally, draft guidance issued in October 2024 does not recommend osimertinib with chemotherapy for this proposed

indication (NICE ID6328). Therefore, it does not represent a relevant comparator in this appraisal.

In summary, the only comparator considered relevant to this submission is osimertinib, in line with UK clinical expert feedback and the treatment landscape discussed and agreed during the ongoing NICE appraisal of osimertinib in combination with chemotherapy.[29, 32] As such, amivantamab-lazertinib is anticipated to displace osimertinib in the treatment pathway, if recommended for use in UK clinical practice.

Unmet need in patients with cEGFRm NSCLC

The majority of patients with NSCLC are diagnosed when the disease is already advanced, with around 66% of patients with lung cancer in England and Wales presenting with Stage III or IV disease at the time of diagnosis, which, regardless of mutation status, is associated with a poor prognosis.[29] As described in Section B.1.3.1, patients with cEGFRm advanced NSCLC have a poorer prognosis compared to patients with other driver mutations, such as ALK or ROS.[72-74]

Disease progression on osimertinib inevitably occurs as a result of primary and acquired resistance.[11, 104] Patients can exhibit primary resistance to osimertinib due to co-alterations, such as B-cell Lymphoma 2-like protein 11 (BIM) deletion polymorphism and EGFR exon 20 insertion mutations.[104, 105] Acquired resistance mechanisms comprise both EGFR-dependent (on-target) and EGFR-independent (off-target) mechanisms, such as C797S mutations and MET amplifications, respectively.[106, 107] As discussed in Section B.1.3.1, this resistance to osimertinib means that many patients either progress quickly onto 2L treatment, or die before being able to access 2L treatment.[11]

Results from the UK population-based cohort study conducted by Johnson & Johnson using data from the NCRAS database demonstrated that patients with cEGFRm NSCLC treated with osimertinib (n=278) have a mOS of 26.2 months (95% CI: 22.0, 30.0), or 28.1 months (95% CI: 23.0, 35.7) if narrowed down to a 'MARIPOSA-like' cohort (n=126).[10] Pérol *et al.* (2024) reported similar results in a retrospective study using secondary data from the Epidemiological Strategy and Medical Economics (ESME; France) and the Rigshospitalet (RH; Denmark) databases on 757 patients with locally advanced or metastatic cEGFRm NSCLC, treated with first- or 2L osimertinib.[11] Patients were predominantly female (73.6%) and never smokers (50.7%) with an ECOG PS of 0–1 (normal activity or some symptoms; 40.3%). Patients receiving 1L osimertinib (n=319) had a mOS and mPFS of 26.2 and 11.9 months, respectively. This was considerably lower than the mOS (38.6 months) and mPFS (18.9 months) reported from the osimertinib monotherapy FLAURA clinical trial.[34, 71, 104] The median TTD was 16.9 months, while time to next therapy (TTNT) was 11.5 months, suggesting patients may not receive 2L treatment immediately after discontinuation of osimertinib. Importantly, at least 26.7% of patients died before they reached a 2L treatment, due to clinical deterioration.[11]

An additional burden experienced by patients with cEGFRm NSCLC is the occurrence of brain metastases, with a prevalence at diagnosis of 40.6% reported at baseline in the MARIPOSA trial (Section B.2).[108] RWE has suggested that more than half of patients are estimated to have CNS metastases at five years, despite treatment with EGFR TKIs, which is associated with poor clinical outcomes.[87-89] While the risk of CNS progression is lower with osimertinib than earlier generation EGFR TKIs, approximately 20% of patients treated with 1L osimertinib will still experience CNS progression.[59] Furthermore, osimertinib is less effective in patients at high risk of disease progression, including those with TP53 co-mutations, brain or liver metastases, and patients with detectable circulating tumour deoxyribonucleic acid (ctDNA) at baseline or during

treatment.[11, 89, 109-111] Patients with cEGFRm advanced NSCLC require a 1L treatment that is efficacious regardless of CNS metastases, making therapies that offer improved CNS disease control an important clinical priority.[112]

Following disease progression due to primary or acquired resistance to osimertinib, 2L treatment options after progression on osimertinib are currently limited, consisting of non-targeted, non-specific treatments, resulting in poor prognosis for these patients at 2L, with some patients also not considered fit for systemic therapy.[7, 12-15, 32] The UK-based NCRAS database analysis conducted by Johnson & Johnson showed that of the 'MARIPOSA-expanded' cohort who received osimertinib monotherapy 1L, 61.2% (170/278) did not receive a subsequent line of therapy after progression. Of the 108 patients who did receive subsequent therapy, the median TTNT was 16.6 months (95% CI: 14.6, 21.1).[10, 11] The most common subsequent treatments in this cohort were platinum-based chemotherapy regimens (carboplatin or cisplatin combination therapy) (41/108; 38.0%) and osimertinib (37/108; 34.3%), highlighting the current lack of targeted treatment options following progression on 1L osimertinib.[10] A US real-world study (conducted between August 2015–July 2020) reported very poor outcomes for patients with cEGFRm NSCLC who receive PDC after progression on 1L osimertinib treatment (n=53), with a mPFS of 4.3 months and a mOS of 10.4 months.[113] These data suggest that, despite osimertinib being available 1L as SoC for patients with cEGFRm NSCLC in the UK, response with osimertinib is not sustained. As such, there remains a significant unmet need for more efficacious 1L treatment options for cEGFRm NSCLC, to delay treatment resistance and subsequent progression, and improve survival outcomes at 1L.

The humanistic burden of NSCLC is substantial and well-documented, with patients experiencing reduced HRQoL compared with the general population and those with other advanced cancers.[77, 93] UK market research conducted by Johnson & Johnson has demonstrated that NSCLC and/or its treatment had varied physical and/or mental health effects on patients with cEGFRm NSCLC, in relation to impact on daily activities and emotional wellbeing, which negatively impacted QoL.[17] Furthermore, compared to similar patients with no disease progression, patients with progressive cEGFRm NSCLC experience a greater impairment in mobility, self-care, usual activities, anxiety and depression, as well as pain and discomfort.[18] The poor HRQoL experienced by patients diagnosed with cEGFRm NSCLC is also correlated with significant burden on caregivers, impacting their ability to work, and increasing their risk of anxiety or depression.[77] Therefore, there is an unmet need to reduce the impact of symptoms whilst delaying clinical progression and improving overall mental health and emotional wellbeing in this patient and caregiver population.

Amivantamab-lazertinib

Amivantamab-lazertinib fulfils a significant unmet need for an alternative targeted 1L treatment option for patients with cEGFRm advanced NSCLC that proactively addresses downstream resistance mechanisms upfront, and delays disease progression, upon which there are limited 2L treatment options.[19, 62]

Simultaneous inhibition of both EGFR and MET by amivantamab in combination with lazertinib is anticipated to improve overall treatment efficacy, and has proved to limit the compensatory pathway activation and targeting the two major mechanisms of resistance to TKIs.[20, 21] Preliminary results on the mechanisms of acquired resistance for patients receiving amivantamab-lazertinib, compared with osimertinib, suggest that acquired MET amplifications were ~3-fold lower (4.4% versus 13.6%, respectively; p=0.017) and EGFR resistance mutations were ~8-fold lower (0.9% versus 7.9%, respectively; p=0.014).[62] By preventing the emergence of

acquired EGFR resistance mutations and MET amplifications that could drive disease progression, amivantamab in combination with lazertinib alters tumour biology, reducing the complexity of acquired resistance compared with osimertinib.[62] Results from the MARIPOSA trial demonstrate that amivantamab-lazertinib is accordingly associated with prolonged PFS (Section B.2.6.1) and time to subsequent progression (Section B.2.6.5), extended OS (Section B.2.6.2) and DoR (Section B.2.6.4), improved overall response rate (ORR) (Section B.2.6.3), and reduced treatment discontinuation overall, primarily driven by a reduction in progression (Section B.2.10.1) as compared with osimertinib. The positive impact of amivantamab-lazertinib on these key clinical outcomes is anticipated to contribute to maintained QoL for both patients and caregivers.

B.1.4 Equality considerations

There is an important equality consideration with respect to the stigma of lung cancer. The UKLCC report on health inequalities in lung cancer highlights the crucial fact that lung cancer has the biggest deprivation gap compared to any other cancer in the UK.[36] Deaths associated with socio-economic variation are shown to be most commonly reported in lung cancer and as such, there is an ever growing need to not only acknowledge the health inequality associated with this disease, but also identify drivers of health inequality in order to ensure all patients have equal access to life changing treatments.

Health inequality associated with stigma is a major concern for lung cancer patients, as it is largely driven by a perception that it is 'self-inflicted' due to the public recognising the link between lung cancer and smoking.[37] This is particularly damaging for patients with cEGFRm NSCLC as these mutations disproportionately affect never-smokers, women and patients of Asian ethnicity.[36, 38] Specifically in communities of Asian ethnicity, there is evidence that symptoms of lung cancer are stigmatised, which could reinforce treatment delaying behaviour.[40, 41] A recent study assessing differences in screening, diagnosis, and initial care between patients with newly diagnosed 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.[42]

The impact of stigma on people living with lung cancer, including patients and caregivers has been well-reported. In one qualitative study, barriers to symptom reporting for lung cancer patients included blame, stigma and cultural influences.[40] Additionally, an observational, cross-sectional study has shown that some patients report feeling uncomfortable communicating their symptoms leading to delay in presentation, diagnosis and treatment (or low uptake of treatment).[41]

The effects of stigma associated with lung cancer should be included within the decision-making process and are not inherently captured within the cost per QALY framework. Stigma is included in the NICE social value judgements principles document and as such, should be considered when deciding whether amivantamab-lazertinib is cost-effective in this population.

B.2 Clinical effectiveness

Clinical effectiveness summary

MARIPOSA is an RCT that forms the principal evidence base for amivantamab-lazertinib in untreated cEGFRm advanced NSCLC

- The MARIPOSA trial is a registrational Phase 3, randomised, multicentre clinical trial that provides the main clinical evidence base for amivantamab-lazertinib (hereafter referred to as 'amivantamab-lazertinib', N=429) compared with osimertinib monotherapy (osimertinib, N=429) and lazertinib monotherapy (lazertinib, N=216) in patients with untreated cEGFRm locally advanced or metastatic NSCLC.[19] Efficacy results are presented for amivantamab-lazertinib versus osimertinib (full analysis set [FAS]) only. The lazertinib monotherapy arm was only included to assess the contribution of each individual component.[19]

The primary endpoint of MARIPOSA was met, with amivantamab-lazertinib demonstrating a clinically meaningful and statistically significant improvement in progression-free survival (PFS) (assessed by BICR) compared to osimertinib. The efficacy of amivantamab-lazertinib in this population was supported by several key secondary endpoints and patient reported outcomes (PROs)

- The primary endpoint in the MARIPOSA trial was PFS assessed by BICR using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 guidelines, with secondary endpoints including OS, ORR, DOR, PFS after first subsequent therapy (PFS2) and TTSP. Key exploratory endpoints included TTD, TTST and EuroQoL-five dimension-five levels (EQ-5D-5L).[21, 95]
- A press release shared by Johnson & Johnson earlier this month communicated that with a longer duration of follow-up ([redacted]), amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in OS compared to osimertinib in the phase 3 MARIPOSA trial ([redacted]). This means that the combination of amivantamab-[redacted] in the ITT population.[22, 23]
- The mOS was not estimable ([redacted]) in the amivantamab-lazertinib arm, while the mOS for osimertinib was reached at [redacted] months ([redacted], [redacted] [redacted].[22, 23] These significantly improved OS results reinforce the importance of amivantamab-lazertinib and its potential to significantly improve patient prognosis. It is noteworthy that amivantamab-lazertinib is the only chemotherapy-free treatment to demonstrate a significant survival benefit versus osimertinib in the first-line treatment of patients with EGFR-mutated lung cancer.
- Due to the recency in the availability of the latest datacut, the efficacy data for this submission are informed by the FAS at the 11th August 2023 DCO for PFS and the 13th May 2024 DCO for all other efficacy outcomes. Results from the MARIPOSA trial demonstrate that amivantamab-lazertinib is a highly efficacious treatment regimen, leading to improved survival outcomes and response rates, and a more durable response compared with osimertinib:
    - The primary endpoint (PFS by BICR) was met; after a median follow-up of 22.0 months (11th August 2023 DCO), a statistically significant ($p<0.001$) and clinically meaningful improvement in PFS was observed, translating to a 30% reduction in the risk of disease progression or death in patients receiving amivantamab-lazertinib compared with those receiving osimertinib (HR: 0.70; 95% CI: 0.58, 0.85).[19]
    - At the 13th May 2024 DCO, with a longer-term median follow-up of 31.1 months, mOS was not reached in the amivantamab-lazertinib arm, compared with 37.3 months in the osimertinib arm, but there was already a strong trend towards improvement in OS

in the amivantamab-lazertinib arm (that is now confirmed with the latest final analysis results) compared with the osimertinib arm (HR: 0.77; 95% CI: 0.61, 0.96; p=0.019).[19]
    - The ORR was [redacted]% in the amivantamab-lazertinib arm and [redacted]% in the osimertinib arm, indicating that patients receiving amivantamab-lazertinib are [redacted]% more likely to achieve ORR compared with those receiving osimertinib (OR: [redacted]; 95% CI: [redacted]; [redacted]).[95]
    - The median DOR was prolonged in the amivantamab-lazertinib arm, reported as [redacted] months (95% CI: [redacted]), compared with [redacted] months (95% CI: [redacted]) in the osimertinib arm.[95]
    - In addition to increasing time to disease progression or death, receiving amivantamab-lazertinib at 1L confers a benefit in prolonging the time until patients receive currently-limited 2L treatment options (Section B.2.6.8), as well as maintaining treatment benefit after the first subsequent therapy (Section B.2.6.5). At 36 months, 57% of patients in the amivantamab-lazertinib arm remained progression-free after first subsequent therapy, whereas more than half of patients in the osimertinib arm (51%) experienced progression after first subsequent therapy.[24]
    - Median TTSP was not estimable in the amivantamab-lazertinib arm, compared with [redacted] months in the osimertinib arm, representing a statistically significant reduction in risk of symptomatic progression or death compared with participants in the osimertinib arm (HR: [redacted]; 95% CI: [redacted], nominal p=[redacted]).[95]
    - A broadly consistent benefit in PFS was observed across all pre-specified subgroups with amivantamab-lazertinib. In particular, the same statistically significant benefit of amivantamab-lazertinib versus osimertinib on PFS was seen across the subgroups for those with or without a history of brain metastases, with an observed HR of 0.69 in both patient cohorts. A treatment benefit, as indicated by HRs <1, was additionally observed for amivantamab-lazertinib in subgroups of race and EGFR mutation type.[19]
    - HRQoL as assessed by EQ-5D-5L was comparable between the amivantamab-lazertinib and osimertinib arms, indicating that amivantamab-lazertinib has a similar impact on the HRQoL of patients as osimertinib.[114]

Safety data from the MARIPOSA trial demonstrate that AEs reported in the amivantamab-lazertinib are manageable

- Safety data are reported for the safety population of the MARIPOSA trial (amivantamab-lazertinib: N=421; osimertinib: N=428) at the 11th August 2023 DCO.[19]
- Although more Grade 3 or higher treatment-emergent adverse events (TEAEs) were observed in the amivantamab-lazertinib arm (316/421, 75%) compared with the osimertinib arm (183/428, 43%), this was primarily driven by the incidence of Grade 3 TEAEs ([redacted]% and [redacted]%, respectively).[19, 21] In both arms, Grade 3 or higher TEAEs were mostly consistent with the on-target activity of amivantamab, lazertinib and osimertinib against the EGFR pathway (rash/dermatitis acneiform, stomatitis, and paronychia) and of amivantamab against the MET pathway (hypoalbuminemia and peripheral oedema).[21]
    - TEAEs were manageable in both treatment arms through treatment interruptions, dose reductions and best supportive care (BSC). At a median follow-up of 22.0 months, 49% of patients in the amivantamab-lazertinib arm had a dose interruption within the first four months of treatment.[115] The corresponding mPFS was 23.9 months, compared with 23.7 months for those who did not have a dose interruption, suggesting that early dose modifications do not adversely affect the efficacy of amivantamab-lazertinib.[115]
    - At the 11th August 2023 DCO, 230 patients (55%) and 213 patients (50%) remained on treatment in the amivantamab-lazertinib and osimertinib arms, respectively.[19]
- Adverse events of special interest (AESIs) in the amivantamab-lazertinib arm included infusion-related reactions (IRRs), rash, pneumonitis/interstitial lung disease and venous thromboembolism (VTE), which were mostly low grade and occurring early in the treatment regimen (Section B.2.10.2.5). These AESIs can be managed with prophylactic medicines and dermatological care (Section B.2.10.2).

The results from MARIPOSA illustrate that amivantamab-lazertinib fulfils an unmet need for an upfront highly efficacious and tolerable therapy for patients with locally advanced or metastatic cEGFRm NSCLC in UK clinical practice

- An unmet need exists for an alternative, more efficacious targeted treatment that can improve therapeutic value at 1L. By providing a novel dual mechanisms of action (MoA) that proactively addresses downstream acquired resistance mechanisms, such as MET alterations and EGFR resistance mutations (Section B.1.2), amivantamab-lazertinib combination therapy can delay progression and improve survival compared with the current SoC for patients with untreated, advanced cEGFRm NSCLC, osimertinib. As such, a recommendation for amivantamab-lazertinib is anticipated to fulfil this unmet need.

B.2.1 Identification and selection of relevant studies

A *de novo* clinical systematic literature review (SLR) was conducted in May 2020 to identify relevant evidence on clinical efficacy and safety outcomes in patients with cEGFRm advanced NSCLC. This SLR was subsequently updated in July 2022, September 2023, March 2024, June 2024 and October 2024 to ensure recently published relevant evidence has been identified.

The SLR was designed to collect data from RCTs, non-RCTs, and observational studies. It focused on relevant outcomes, including baseline characteristics of patients, the efficacy and safety of treatments, HRQoL, and PRO data.

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 1L setting for patients with cEGFR 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.[116]

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 306 publications reporting on 85 unique studies in the 1L setting for cEGFRm NSCLC identified in the SLR, the MARIPOSA trial was the only study identified reporting clinical evidence for amivantamab-lazertinib in the patient population of interest to this submission: adult patients with advanced NSCLC with activating cEGFR mutations.

As such, the MARIPOSA registrational trial represents the main body of evidence for amivantamab-lazertinib in the patient population specified in the decision problem of this submission. The MARIPOSA trial is a Phase 3, randomised study investigating the safety and efficacy of amivantamab-lazertinib as a treatment for patients with untreated, advanced NSCLC with cEGFR mutations as compared with the two control arms: osimertinib monotherapy, and lazertinib monotherapy. An overview of the key evidence provided by the MARIPOSA trial is presented in Table 1, with the methodology and results of the trial presented from Section B.2.3 onwards.

Published results from the MARIPOSA trial are available from the Cho *et al.* 2024 publication (11th August 2023 DCO)[19] and the Gadgeel *et al.* 2024 World Conference on Lung Cancer (WCLC) presentation (13th May 2024 DCO),[24] with the clinical study report (CSR; 11th August 2023 and 13th May 2024 DCOs) also used to populate this submission.[21, 95]

Table 3: Clinical effectiveness evidence

Study	MARIPOSA (NCT04487080)
Study design	Phase 3, randomised, multicentre study
Population	Adult patients (aged ≥18 years) with treatment-naïve locally advanced or metastatic NSCLC with cEGFR mutations
Intervention(s)	Amivantamab intravenous (IV) in combination with lazertinib (open-label; treatment blinding was not feasible in this trial, due to differences in administration, pre-medication requirements and safety profiles of the two regimens). **Amivantamab:** • Body weight at baseline <80 kg: ○ Weeks 1–4: 1,050 mg weekly (total of 4 doses) ▪ Week 1 – split infusion on Day 1 and 2 ▪ Weeks 2 to 4 – infusion on Day 1 ○ Week 5 onwards: 1,050 mg every 2 weeks • Body weight at baseline ≥80 kg: ○ Weeks 1–4: 1,400 mg weekly (total of 4 doses) ▪ Week 1 – split infusion on Day 1 and 2 ▪ Weeks 2 to 4 – infusion on Day 1 ○ Week 5 onwards: 1,400 mg every 2 weeks **Lazertinib:** • 240 mg QD (oral)
Comparator(s)	• Osimertinib 80 mg QD (oral) plus matching placebo for lazertinib QD (blinded) • Lazertinib 240 mg QD (oral) plus matching placebo for osimertinib QD (blinded)
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]	Primary outcome: • PFS by BICR Key secondary outcomes: • OS • ORR

Study	MARIPOSA (NCT04487080)
	• DoR • TTSP • Incidence and severity of AEs Exploratory outcomes: • TTD HRQoL outcomes: • EQ-5D-5L
All other reported outcomes	Secondary outcomes: • Complete response (CR), partial response (PR), stable disease (SD) and progressed disease (PD) • PFS2 • Intracranial PFS (see Appendix M.1.1) Exploratory outcomes: • TTST • Dose interruption • Intracranial ORR (see Appendix M.1.2) • Intracranial DoR (see Appendix M.1.3)

Abbreviations: AE: adverse event; AUC: area under the concentration-time curve; CR: complete response; DOR: duration of response; EGFR: epidermal growth factor receptor; EQ-5D-5L: EuroQoL five-dimensional descriptive system (five level version); HRQoL: health-related quality of life; N/A: not applicable; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PD: progressed disease; PR: partial response; PROMIS-PF: Patient-Reported Outcomes Measurement Information System – Physical Function; PFS: progression-free survival; PFS2: PFS after subsequent therapy; SD: stable disease; QD: once daily; TTSP: time to symptomatic progression; TTST: time to subsequent therapy.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023).[21] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024).[95] Cho *et al.* 2024.[19] Gadgeel *et al*. WCLC 2024.[24] Nguyen *et al.* WCLC 2024.[117]

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

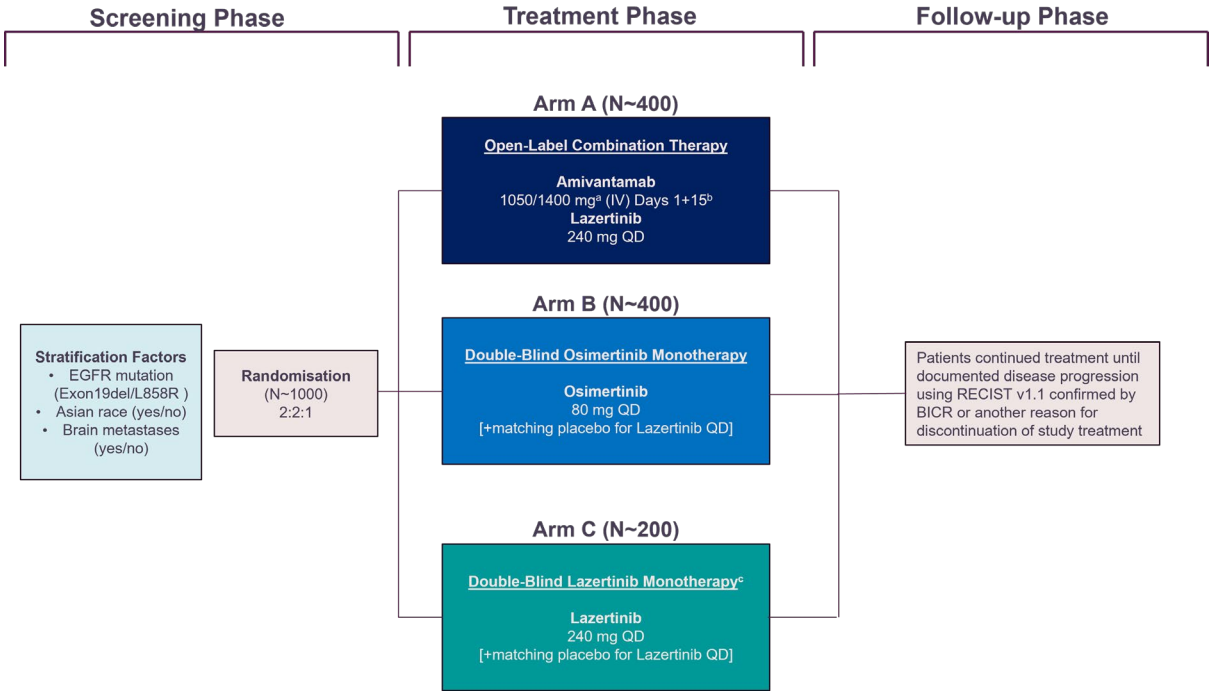
B.2.3.1 Trial design

The clinical evidence for amivantamab-lazertinib as a treatment for adult patients with untreated cEGFRm advanced NSCLC is from the registrational MARIPOSA trial. The MARIPOSA trial is an ongoing, randomised multicentre, Phase 3 trial which compares amivantamab-lazertinib to osimertinib in combination with placebo (the osimertinib arm) and lazertinib in combination with placebo (the lazertinib arm) for patients with treatment-naïve, locally advanced or metastatic cEGFRm NSCLC. The lazertinib monotherapy arm was only included to assess the contribution of each individual component.

In the MARIPOSA trial, patients were randomly assigned in a 2:2:1 ratio, based on a computer-generated randomisation schedule, to receive amivantamab-lazertinib, osimertinib or lazertinib in 28-day cycles. Randomisation was stratified according to mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no) and history of brain metastases (yes or no). Treatment blinding was not feasible for the amivantamab-lazertinib arm, due to differences in administration compared with the osimertinib and lazertinib arms.[19, 21]

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

Figure 7: Design of the registrational MARIPOSA trial (NCT04487080)



Abbreviations: EGFR: epidermal growth factor receptor; IV: intravenous; NSCLC: non-small cell lung cancer; PFS: progression free survival; QD: once daily.
Footnotes: Arm A: amivantamab-lazertinib arm; Arm B: osimertinib arm; Arm C: lazertinib arm. [a] Weight-based dosing: <80 kg/≥80 kg. [b] Cycle 1: Days 1/2 (split dose), 8, 15, 22; Cycles 2+: Days 1, 15. [c] The lazertinib monotherapy arm was only included to assess the contribution of each individual component.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023).[21]

The MARIPOSA trial is comprised of a screening phase, a treatment phase and a follow-up phase. The screening phase was performed 28 days before randomisation; after screening and enrolment, patients were stratified and randomly assigned to either the amivantamab-lazertinib arm, the osimertinib arm, or the lazertinib arm as described above.[21]

The treatment phase for each patient started at Cycle 1 Day 1 and continued in 28-day cycles until the 'end of treatment' visit (approximately 30 days after discontinuation of study treatment). The study protocol required all patients to undergo regular disease assessments to monitor their underlying disease, including imaging of the chest, abdomen, pelvis and any other disease locations. All patients were required to have a brain magnetic resonance imaging (MRI) at screening, followed by serial post-baseline brain MRIs, providing a robust evaluation of CNS outcomes for patients. Study treatment was continued until documented disease progression using RECIST v1.1 (confirmed by BICR) or another reason for discontinuation of study treatment. Continuation of study treatment after confirmed disease progression was allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believed the patient was deriving clinical benefit.[21]

Patients who discontinued their assigned study treatment for any reason were followed for survival and symptomatic progression in the follow-up phase. The follow-up phase started after the last dose of study treatment or disease progression (whichever occurred first), and survival, subsequent anticancer treatment, and disease status were assessed at least every 12 weeks (±14 days) until the end of study, death, loss to follow-up, or withdrawal of consent from participation by the patient, whichever came first.[21]

B.2.3.2 Trial methodology

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

Table 4: Summary of the MARIPOSA trial methodology

Trial name	MARIPOSA (NCT04487080)
Location	International: 267 sites across 28 countries, including 7 UK sites
Trial design	Phase 3, randomised multicentre study
Population	Adult patients (aged ≥18 years) with treatment-naïve locally advanced or metastatic NSCLC with cEGFR mutations
Eligibility criteria for patients	**Key inclusion criteria**: • Adult patients (≥18 years of age)[a] • Newly diagnosed, histologically- or cytologically-confirmed locally advanced or metastatic NSCLC that is treatment-naïve and not amenable to curative therapy, including surgical resection or chemoradiation • The tumour must have documented EGFR Exon19del or Exon 21 L858R substitution, as detected by a Food and Drug Administration (FDA)-approved or other validated test in an accredited local laboratory, in accordance with SoC. A copy of the test report (documenting the EGFR mutation) must be included in the participant records and must also be submitted to the sponsor • At least one measurable lesion, according to RECIST v1.1, that has not been previously irradiated • ECOG PS of 0 or 1 • Adequate organ and bone marrow function, without history of red blood cell transfusion, platelet transfusion, or granulocyte colony-stimulating factor within 7 days prior to the date of the test. **Key exclusion criteria**: • Have received any prior systemic treatment at any time for locally advanced or metastatic disease (adjuvant or neoadjuvant therapy for Stage I or II disease is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease). • Symptomatic brain metastases. A participant with asymptomatic or previously treated and stable brain metastases may participate in this study. Participants who have received definitive radiation or surgical treatment for symptomatic or unstable brain metastases and have been clinically stable and asymptomatic for at least 2 weeks before randomization are eligible, provided they have been either off corticosteroid treatment or are receiving low-dose corticosteroid treatment (≤10 mg/day prednisone or equivalent) for at least 2 weeks prior to randomization. • Have received prior EGFR TKI treatment • Active or past medical history of leptomeningeal disease • A history of spinal cord compression that has not been treated definitively with surgery or radiation • Uncontrolled tumour-related pain • Active or past medical history of interstitial lung disease (ILD)/pneumonitis, including drug-induced ILD, or radiation

	ILD/pneumonitis • Uncontrolled inter-current illness • Concurrent or prior malignancy other than the disease under study. • Have active cardiovascular disease • Positive hepatitis B, C, or other clinically active infectious liver disease at screening • Received an investigational drug within 12 months before randomisation or is currently enrolled in an investigational study The full list of inclusion and exclusion criteria are presented in the MARIPOSA protocol included in the reference pack.[118]

Study intervention and administration	Amivantamab is administered *via* IV infusion, in combination with lazertinib oral tablets, at the following doses:
	Amivantamab:
	• Body weight at baseline <80 kg:
	  ○ Weeks 1–4: 1,050 mg weekly (total of 4 doses)
	  ▪ Week 1 – split infusion on Day 1 and 2
	  ▪ Weeks 2 to 4 – infusion on Day 1
	  ○ Week 5 onwards: 1,050 mg every 2 weeks
	• Body weight at baseline ≥80 kg:
	  ○ Weeks 1–4: 1,400 mg weekly (total of 4 doses)
	  ▪ Week 1 – split infusion on Day 1 and 2
	  ▪ Weeks 2 to 4 – infusion on Day 1
	  ○ Week 5 onwards: 1,400 mg every 2 weeks
	Lazertinib:
	• 240 mg QD (three 80 mg tablets)

Comparator(s)	**Osimertinib arm:** one osimertinib 80 mg capsule QD plus three placebo tablets QD. Osimertinib was provided as 80 mg tablet (initial dose) and 40 mg tablet (as needed for dose reduction) and over-encapsulated to maintain blinding **Lazertinib arm:** three lazertinib 80 mg tablets QD plus one placebo capsule QD. Lazertinib was provided as 80 mg tablets (initial dose was 240 mg/3 tablets). The lazertinib monotherapy arm was only included to assess the contribution of each individual component; as such, results for this treatment arm are not presented throughout this submission but are available within the MARIPOSA CSR included in the reference pack.[21] All cycles are 28 days and each study visit must be scheduled based on date of Cycle 1 Day 1.
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. Medications allowed or disallowed before and during the study are described below: **Permitted:** • Supportive care, such as antibiotics, analgesics, transfusions, diet, osteoclast inhibitors • Localised, limited radiotherapy of short duration (e.g., 5 days), for palliative purposes, following consultation with the Medical

	Monitor. Radiotherapy should be scheduled for the week between scheduled biweekly doses of amivantamab. • Prophylactic medications[b] • Hormonal contraception throughout the study and through 6 months after the last dose of study treatment. **Disallowed:** • Any chemotherapy, systemic anticancer therapy, or experimental therapy (other than study treatments) • Radiotherapy to tumour lesions being assessed for tumour response prior to radiographic progression • Medications, herbal supplements and/or ingestions of foods with known potent (strong) inducer effects on CYP3A4/A5 activity For further detail on the permitted, prohibited, or restricted concomitant medication, refer to the MARIPOSA protocol.
Primary outcome	PFS assessed by BICR
Secondary and exploratory outcomes	Secondary outcomes assessed in the MARIPOSA trial were: • OS • ORR • DoR • TTSP • PFS2 • Intracranial PFS • PFS and OS versus lazertinib-placebo • Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) • European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) • Pharmacokinetic/Pharmacodynamic analyses**:** Serum amivantamab and plasma lazertinib concentrations, anti-amivantamab antibodies • Characterisation of tumour genetics • Characterisation of tumour protein markers (to explore mechanisms of response or resistance) • Immunogenicity analyses The following exploratory outcomes were also assessed: • TTD • DCR • TTST • Intracranial ORR, DoR and time to intracranial disease progression • EQ-5D-5L A broad range of safety outcomes were analysed including: • Overview of TEAEs • Common TEAEs by preferred term • Grade 3 or higher TEAEs • Serious adverse events (SAEs) • Deaths • AESIs (IRRs, VTE and rash)

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 • Baseline ECOG PS: 0 versus 1 • History of smoking: yes versus no • History of brain metastasis: yes versus no • EGFR mutation: Exon19del versus Exon 21 L858R substitution

Abbreviations: BICR: blinded independent central review; CYP: cytochrome P450; DCR: disease control rate; DoR: duration of response; ECOG: Eastern Cooperative Oncology Group; (c)EGFR: (common) epidermal growth factor receptor; EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: EuroQoL five-dimensional descriptive system (five level version); exon19del: exon 19 deletion; FDA: Food and Drug Administration; ILD: interstitial lung disease; IRR: infusion-related reactions; IV: intravenous; mg: milligram; NSCLC: non-small cell lung cancer; NSCLC-SAQ: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival after first subsequent therapy; QD: once daily; RECIST: Response Evaluation Criteria in Solid Tumours; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TKI: tyrosine kinase inhibitor; TTD: time to treatment discontinuation; TTSP: time to symptomatic progression; TTST: time to subsequent therapy; UK: United Kingdom; VTE: venous thromboembolism.
Footnotes: [a] Or the legal age of consent in the jurisdiction in which the study is taking place. [b] Due to the increased risk of VTE events for patients receiving treatment in the amivantamab-lazertinib arm during the first four months of combination treatment, an Urgent Safety Measure was implemented. The protocol was amended to recommend prophylactic-dose anticoagulation as per local guidelines for the first four months of therapy for all patients receiving treatment in the amivantamab-lazertinib arm.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023).[21] Johnson & Johnson Data on File. MARIPOSA Clinical Trial Protocol.[118] ct.gov. MARIPOSA.[119]

Analysis sets

In this submission, efficacy results presented in Section B.2.6 are presented for the FAS unless otherwise specified. The FAS was defined as all randomised patients, classified according to their assigned treatment arm regardless of the actual treatment received.

Safety results are reported for the safety analysis set (SAS) unless otherwise specified, with safety data summarised in Section B.2.10. The SAS included all randomised patients who received at least one dose of study treatment.

The number of patients included in these analysis sets is presented in Table 5.

Table 5: Number of patients in the FAS and SAS in the MARIPOSA trial

Analysis set	Amivantamab-lazertinib	Osimertinib	Lazertinib	Total
FAS, N	429	429	216	1,074
SAS, N (proportion of FAS, %)	421 (98.1%)	428 (99.8%)	213 (98.6%)	1,062 (98.9%)

Abbreviations: FAS: full analysis set; SAS: safety analysis set.
Source: Cho *et al.* 2024.[19]

Endpoint definitions

The definitions of the key primary, secondary and exploratory efficacy endpoints and the TEAE safety endpoint from the MARIPOSA trial presented in this submission are outlined in Table 6 below.

Table 6: Summary of endpoint definitions from the MARIPOSA trial

Endpoint	Definition
Primary endpoint	
PFS (assessed by BICR)	The time from randomisation until the date of objective disease progression (assessed by BICR) using RECIST v1.1 or death, whichever comes first
PFS (assessed by INV) (sensitivity analysis)	The time from randomisation until the date of objective disease progression (assessed by INV) using RECIST v1.1 or death, whichever comes first
Secondary endpoints	
OS	The time from the date of randomisation until the date of death due to any cause
ORR	The proportion of patients who achieve either a CR or PR as defined by BICR using RECIST v1.1
DOR	The time from the date of first documented response (CR or PR) until the date of documented progression or death, whichever comes first
PFS2	The time from randomisation to 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
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
Exploratory endpoints	
TTD	The time from randomisation to discontinuation of all study treatments for any reason
TTST	The time from randomisation to the start date of the subsequent anticancer therapy, following study treatment discontinuation or death, whichever comes first
EQ-5D-5L	Measurement of health state and health utility
Intracranial PFS	Time from randomisation until the date of objective intracranial disease progression or death, whichever comes first, based on BICR using RECIST v1.1 in participants who had a history of brain metastasis at screening in the FAS
Safety endpoints	
TEAE	Any adverse event occurring at or after the initial administration of study treatment through the day of last dose plus 30 days, or until the start of subsequent anticancer therapy (if earlier)

Abbreviations: BICR: blinded independent central review; CR: complete response; DOR: duration of response; eCRF: electronic case report form; EQ-5D-5L: EuroQoL five-dimensional descriptive system (five level version); FAS: full analysis set; ORR: objective response rate; OS: overall survival; 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 therapy.
Source: Johnson & Johnson Data on file. MARIPOSA Clinical Study Protocol 2023 (Page 92-94).[118] Johnson & Johnson Data on file. MARIPOSA Statistical Analysis Plan (SAP) 2021.[120]

B.2.3.3 Baseline characteristics

The baseline demographic characteristics for patients in the amivantamab-lazertinib arm, the osimertinib arm and the lazertinib arm are presented in Table 7. The lazertinib monotherapy arm was only included to assess the contribution of each individual component.

Overall, demographic and baseline characteristics were well-balanced between the three treatment arms. The median age of the amivantamab-lazertinib arm, the osimertinib arm and the lazertinib arm was 64 years (range: 25–88), 63 years (range: 28–88 years) and 63 years (range: 31–87 years), respectively.[19] There was a slightly higher proportion of female patients in the amivantamab-lazertinib arm (64%) and the lazertinib arm (63%) versus the osimertinib arm (59%). Race was broadly balanced between the treatment arms: the amivantamab-lazertinib arm was comprised of 58% of people of Asian ethnicity compared to 59% in the osimertinib arm and 59% in the lazertinib arm. Additionally, patients with a history of smoking were well-balanced across the three treatment arms with 30% of patients reporting a history of smoking in the amivantamab-lazertinib arm, 31% in the osimertinib arm and 34% in the lazertinib arm.[19, 95] Clinical validation obtained as part of the October 2024 advisory board confirmed that, overall, the baseline characteristics observed in the MARIPOSA trial are generalisable to the patient population in the UK and do not affect the impression of the trial outcomes.[32]

The baseline characteristics seen in the MARIPOSA 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 cEGFRm NSCLC (described in B.1.3.1). In this study, a cohort of patients similar to those recruited to the MARIPOSA trial was identified, using a selection of the eligibility criteria applied in the MARIPOSA trial (the 'MARIPOSA-like' cohort, n=617).[19, 91] Of these patients, 126 (20%) received 1L osimertinib monotherapy.[10] These 126 patients receiving osimertinib had a similar mean age (63.06 years) to patients across all three treatment arms in the MARIPOSA trial ([redacted] years).[10, 21]

There were a lower proportion of patients of Asian ethnicity in the 'MARIPOSA-like' cohort of the NCRAS database who received osimertinib monotherapy (9.5%) than in the three treatment arms in the MARIPOSA trial ([redacted]).[10] A subgroup analysis of PFS by Asian ethnicity in the MARIPOSA trial is presented in Section B.2.7. Feedback received from expert clinicians at the October 2024 advisory board was that the baseline characteristics observed in the MARIPOSA trial are generalisable to the patient population in the UK, and that the ethnicity data from the NCRAS database are aligned with the characteristics of patients seen in clinical practice.[32] The proportion of patients of Asian ethnicity is broadly in line with previous NICE appraisals in this patient population, the key clinical trials for which enrolled 62–64% of patients of Asian ethnicity.[8, 29] Of note, in the ongoing appraisal for osimertinib in combination with pemetrexed and PBC for untreated EGFR mutation-positive advanced NSCLC (ID6328), this proportion has not been raised as a key concern by the External Assessment Group (EAG) or NICE Committee.[29]

The baseline lung cancer characteristics were generally balanced between the treatment arms of the MARIPOSA trial, as presented in Table 8. The proportion of patients with Exon19del and Exon 21 L858R substitution mutations was well balanced between treatment arms: in both the amivantamab-lazertinib and osimertinib arms, 60% of patients had Exon19del and 40% had Exon 21 L858R substitutions, and the proportions were similar in the lazertinib arm, with 61% and 39% of patients with Exon19del and Exon 21 L858R substitutions, respectively.[19]

The majority of patients in the amivantamab-lazertinib arm, the osimertinib arm and the lazertinib arm were diagnosed with adenocarcinoma (97%, 97% and 98%, respectively) and had Stage IV

disease at initial diagnosis ([redacted]%, [redacted]% and [redacted]%, respectively), and the proportion of patients with brain metastases at screening was likewise similar across arms (41%, 40% and 40%, respectively).[19, 21] These disease characteristics are highly aligned with the overall EGFR mutation-positive NSCLC patient population identified in the cohort study conducted by Johnson & Johnson (N=[redacted]), in which [redacted]% of patients presented with Stage IV disease and [redacted]% presented with adenocarcinoma.[90]

Prior therapies received by patients in the MARIPOSA trial are presented in Table 9, with the proportions of prior treatments received, including systemic therapy, radiotherapy, and cancer-related surgery, generally balanced across the three treatment arms. Importantly, in the MARIPOSA trial, patients were required to have received no previous systemic treatment for locally advanced or metastatic cEGFRm NSCLC; however, adjuvant or neoadjuvant therapy for Stage I or II disease was allowed if administered more than 12 months prior to disease progression to locally advanced or metastatic disease. As such, all prior systemic therapies received by patients in any treatment arm (n=[redacted] [[redacted]%]) were received in an adjuvant/neoadjuvant setting.[21]

Table 7: Summary of patient demographics and baseline characteristics in the MARIPOSA trial (FAS; N=858)

Characteristic	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	64 (25, 88)	63 (28, 88)	63 (31, 87)
<65, n (%)	235 (55)	237 (55)	119 (55)
65 to <75, n (%)	143 (33)	139 (32)	79 (37)
≥75, n (%)	51 (12)	53 (12)	18 (8)
Sex, n (%)			
Female	275 (64)	251 (59)	136 (63)
Male	154 (36)	178 (41)	80 (37)
Race, n (%)[a]			
Asian	250 (58)	251 (59)	128 (59)
White	164 (38)	165 (38)	79 (37)
American Indian or Alaska Native	7 (2)	7 (2)	4 (2)
Black	4 (1)	3 (1)	4 (2)
Native Hawaiian or Pacific Islander	1 (<1)	1 (<1)	0
Multiple	1 (<1)	1 (<1)	0
Unknown	2 (<1)	1 (<1)	1 (<1)
Weight, kg			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	62.5 (32, 118)	62 (35, 109)	60.5 (41, 118)
<80, n (%)	376 (88)	368 (86)	197 (91)
≥80, n (%)	53 (12)	61 (14)	19 (9)
Body mass index, kg/m^2			

Characteristic	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
History of smoking, n (%)			
No	299 (70)	295 (69)	143 (66)
Yes	130 (30)	134 (31)	73 (34)

[a] Race or ethnic group was reported by the patients.
Abbreviations: FAS: full analysis set; SD: standard deviation.
Source: Cho *et al.* (2024) (Table 1, Page 10; Table S2, Page 32).[19] Johnson & Johnson MARIPOSA CSR 2023 (Table 8, Page 51).[21]

Table 8: Summary of baseline patient clinical disease characteristics in the MARIPOSA trial (FAS; N=858)

Characteristic	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
EGFR mutation, n (%)[a]			
Exon19del	258 (60)	257 (60)	131 (61)
Exon 21 L858R substitution	172 (40)	172 (40)	85 (39)
History of brain metastasis, n (%)			
Yes	178 (41)	172 (40)	86 (40)
ECOG PS, n (%)[b]			
0	141 (33)	149 (35)	76 (35)
1	288 (67)	280 (65)	140 (65)
Initial diagnosis NSCLC subtype, n (%)			
Adenocarcinoma	417 (97)	415 (97)	212 (98)
Large cell carcinoma	3 (1)	0	0
Squamous cell carcinoma	6 (1)	5 (1)	2 (1)
Other [c]	2 (<1)	9 (2)	2 (1)
Not reported	1 (<1)	0	0
Histology grade at initial diagnosis, n (%)			
Poorly differentiated	[redacted]	[redacted]	[redacted]
Moderately differentiated	[redacted]	[redacted]	[redacted]
Well differentiated	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis, n (%)			
IA	[redacted]	[redacted]	[redacted]
IB	[redacted]	[redacted]	[redacted]
IIA	[redacted]	[redacted]	[redacted]
IIB	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]

Characteristic	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
IVB	[redacted]	[redacted]	[redacted]
Cancer stage at screening, n (%)			
IIIA	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]
Location of metastasis at screening, n (%)[d]			
N	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Brain	[redacted]	[redacted]	[redacted]
Lymph Node	[redacted]	[redacted]	[redacted]
Adrenal Gland	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Time since initial lung cancer diagnosis, months[e]			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	1.5 (0.2, 207.9)	1.4 (0.3, 162.8)	1.3 (0.2, 197.3)
Time since metastatic disease diagnosis, months[e]			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	1.3 (0.2, 24.1)	1.2 (0.1, 11.7)	1.2 (0.2, 9.2)

[a] One patient in the amivantamab–lazertinib group had both *EGFR* mutation types.
[b] Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
[c] Other histologic types included adenocarcinoma and squamous-cell carcinoma, lepidic adenocarcinoma, non–small- cell carcinoma, pleomorphic carcinoma, and unknown.
[d] Patients can be counted in more than one category.
[e] Relative to the date of randomisation.
Abbreviations: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Exon19del: exon 19 deletions; FAS: full analysis set; NSCLC: non-small cell lung cancer; PS: performance status; SD: standard deviation.
Source: Cho *et al.* (2024), (Table 1, Page 10; Table S2, Page 32).[19] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). (Table 9, Page 53).[21]

Table 9: Prior therapies for lung cancer received by patients in the MARIPOSA trial (FAS; N=1,074)

Prior therapy, n (%)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Any prior therapy for lung cancer	[redacted]	[redacted]	[redacted]
Systemic therapy	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Cancer-related surgery	[redacted]	[redacted]	[redacted]

Abbreviations: FAS: full analysis set.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023) (Table 10, Page 55).[21]

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 MARIPOSA trial are summarised in Table 10. Full details are available in the statistical analysis plan (SAP) included in the reference pack.

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

Hypothesis objective	• **Primary hypothesis:** The combination of amivantamab and lazertinib would reduce the risk of disease progression or death compared with osimertinib, in patients with treatment naïve, cEGFRm, locally advanced or metastatic NSCLC. • **Secondary hypothesis:** The combination of amivantamab and lazertinib would prolong OS compared with osimertinib in the above population. • The lazertinib monotherapy arm was only included to assess the contribution of each individual component and, as such, is not relevant to the comparative effectiveness of amivantamab-lazertinib in this submission.
Statistical analysis	**Primary endpoint analysis: PFS assessed by BICR** • The primary hypothesis was tested at an overall 2-sided significance level of 0.05. • PFS was defined as the time from randomisation until the date of objective disease progression or death, whichever came first, based on BICR using RECIST v1.1. 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. • PFS was analysed using the FAS. The treatment effect of the amivantamab-lazertinib arm was compared with the osimertinib arm based on the log-rank test stratified by mutation type (Exon19del vs Exon 21 L858R substitution), race (Asian vs non-Asian) and history of brain metastases (present vs absent). • 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. • The comparison for amivantamab-lazertinib and the lazertinib arm was carried out using the same analysis model. • The mPFS 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.

Secondary endpoint analysis

OS

- OS was defined as the time from the date of randomisation until the date of death due to any cause. 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.
- To control the overall type I error rate for the hypotheses testing of the primary and the secondary endpoints strongly at 5%, a hierarchical testing strategy was used. As the key secondary endpoint, OS was only tested with a total 2-sided alpha of 0.05 if statistical significance for PFS was achieved.
- The comparison between the amivantamab-lazertinib and osimertinib arms, as well as between amivantamab-lazertinib and lazertinib in OS, were analysed using a similar methodology and model as for the primary analysis of PFS for the FAS.
- The analysis of OS was conducted at two timepoints, based on the group sequential design with the O'Brian Fleming alpha spending approach:
    - At the time of the final analysis of PFS, when approximately 340 deaths overall (all treatment arms combined) were anticipated. With approximately 270 deaths in the amivantamab-lazertinib and osimertinib arms combined, based on the O'Brian Fleming alpha spending approach, a 2-sided alpha of 0.0140 was allocated to the interim analysis.
    - Approximately 60 months after the first participant is enrolled, when 490 deaths overall (all treatment arms combined) were anticipated, with approximately 390 deaths from the amivantamab-lazertinib and osimertinib arms combined.

ORR

- ORR was analysed based on the FAS using a logistic regression model stratified by mutation type (Exon19del vs Exon 21 L858R substitution), race (Asian vs non-Asian) and history of brain metastases (present vs absent). The results of the analysis were presented in terms of an odds ratio together with its associated 95% CI and corresponding p-value. Treatment comparisons for amivantamab-lazertinib versus osimertinib, and amivantamab-lazertinib versus lazertinib, were made with the same model.
- The same analysis was carried out for ORR based on confirmed PR or CR from subsequent assessments; the confirmation of subsequent assessments were performed not less than four weeks after criteria for PR or CR were met.

DOR was assessed by producing a KM plot and median DOR with 95% CI calculated from the KM estimate for each treatment group.

PFS2 was analysed using the same methods as the primary analysis of PFS in the FAS.

TTSP was analysed using a similar method as the primary analysis of PFS in the FAS. Similar analyses were carried out for the following components of TTSP:

- The time from randomisation to documentation in the eCRF of any of the following (whichever came first): onset of new

	symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires a change in anticancer treatment. • The time from randomisation to documentation in the eCRF of any of the following (whichever came first): onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires clinical intervention to manage symptoms. TTD and TTST were analysed using a similar method as the primary analysis of PFS in the FAS. EQ-5D-5L • Compliance rates for completion of EQ-5D-5L at each time point were generated based on the actual number of assessments received over the number of expected. • Change from baseline: descriptive statistics were reported for the Visual Analogue Scale (VAS) and utility score at baseline, and at each visit for absolute value and for change from baseline. The change in the VAS and utility score from baseline over time were analysed using Mixed Models for Repeated Measures (MMRM). Randomised patients who received at least one dose of study treatment and have at least one evaluable post-baseline measurement were included in the analysis.
Sample size, power calculation	As per the statistical analysis plan (SAP) for the MARIPOSA trial, the sample size calculation was based on the assumption that amivantamab-lazertinib would result in a 27% reduction in the risk of either disease progression or death over osimertinib (an HR of 0.73, prolonging the mPFS from 19 months[71] to 26 months). A total of 450 PFS events across the amivantamab-lazertinib and osimertinib treatment arms provides approximately 90% power to detect a statistically significant difference between the two treatment arms with the stratified log-rank test (2-sided alpha = 0.05). Therefore, the total sample size needed for the study was approximately 1000 patients (randomised in a 2:2:1 ratio to the amivantamab-lazertinib, osimertinib, and lazertinib treatment arms, respectively). The sample size calculation took into consideration an annual dropout rate of 5%. Assuming a 25-month recruitment period, 560 PFS events (approximately 450 events in the amivantamab-lazertinib and osimertinib arms combined) were expected to occur approximately 42 months after the first patient was enrolled. When approximately 390 deaths (amivantamab-lazertinib and osimertinib arms combined) are observed from long-term survival follow-up, the final analysis of OS will occur, providing approximately 80% power to detect a 25% reduction in the risk of death (HR of 0.75, prolonging the mOS from 39 months[34] to 52 months) with a log-rank test at a 2-sided alpha of 0.05. This final data analysis is anticipated in [redacted].

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; FAS: full analysis set; HR: hazard ratio; icPFS: intracranial PFS; 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 Data on file. MARIPOSA Clinical Study Protocol 2023 (Page 92-94).[118] Johnson & Johnson Data on file. MARIPOSA Statistical Analysis Plan (SAP) 2021.[120]

B.2.4.2 Patient flow in the MARIPOSA trial

The Consolidated Standards of Reporting Trials (CONSORT) diagram for the MARIPOSA trial is presented in Appendix D.

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 MARIPOSA trial, according to the York CRD QA, is presented in Table 11. Overall, the quality assessment found the MARIPOSA trial to be robust and of high-quality with a minimal risk of bias.

Table 11: Quality assessment of the MARIPOSA trial (NCT04487080)

Source of bias	Risk of bias
Randomisation	Low
Allocation concealment	Low
Patient/care provider blinding	Medium
Outcome assessor blinding	Low
Balanced groups	Low
Unexpected imbalance in discontinuations	Low
More outcomes measured than reported	Low
ITT used appropriately	Low

Abbreviations: ITT: intention to treat.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024).[95] Johnson & Johnson Data on file. MARIPOSA Clinical Study Protocol 2023.[118]

B.2.6 Clinical effectiveness results of the relevant studies

Efficacy results are presented for amivantamab-lazertinib versus osimertinib (FAS). PFS data are presented for the interim DCO (11th August 2023), with a total median follow-up across both treatment arms of 22.0 months and median follow-up of [redacted] and [redacted] months in the amivantamab-lazertinib arm and osimertinib arm, respectively.[19, 21] For all other efficacy endpoints, data are presented for the DCO for the MARIPOSA trial (13th May 2024), with a total median duration of follow-up across both treatment arms of [redacted] months.[95] Intracranial endpoints of PFS, ORR and DoR are presented in Appendix M.1.

A press release shared by Johnson & Johnson earlier this month communicated that with a longer duration of follow-up ([redacted]), amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in OS compared to osimertinib in the phase 3 MARIPOSA trial ([redacted]). This means that the combination of amivantamab-lazertinib [redacted] in the ITT population.[22, 23] The mOS was not estimable ([redacted]) in the amivantamab-lazertinib arm, while the mOS for osimertinib was reached at [redacted] months ([redacted], [redacted].[22, 23] These significantly improved OS results reinforce the importance of amivantamab-lazertinib and its potential to significantly improve

patient prognosis. It is noteworthy that amivantamab-lazertinib is the only chemotherapy-free treatment to demonstrate a significant survival benefit versus osimertinib in the first-line treatment of patients with EGFR-mutated lung cancer. Johnson & Johnson would be pleased to provide further analyses using the updated data once full data are available.

A summary of key clinical results from the MARIPOSA trial at the 13th May 2024 DCO is presented in Table 12, with PFS results presented from the 11th August 2023 DCO. Overall, results from the MARIPOSA trial demonstrate that amivantamab-lazertinib is a more efficacious treatment for patients with cEGFRm advanced NSCLC when compared with osimertinib monotherapy.

These results evidence that amivantamab-lazertinib addresses the unmet need for a more efficacious, targeted therapy at 1L for patients with untreated cEGFRm NSCLC, by extending PFS and OS, thereby maximising long-term effectiveness and maintaining HRQoL.

Table 12: Summary of key clinical results from the MARIPOSA trial (13th May 2024 DCO; FAS)

Outcome	Amivantamab-lazertinib	Osimertinib	Treatment effect, HR (95% CI)
Median PFS (assessed by BICR), months (95% CI)[a]	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)	0.70 (0.58, 0.85)
Median PFS (assessed by INV), months (95% CI)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	NE (NE, NE)	37.3 (32.5, NE)	0.77 (0.61, 0.96)
ORR, % (95% CI)[b]	[redacted]	[redacted]	[redacted]
Median DOR months (95% CI)[d]	[redacted]	[redacted]	[redacted]
Median PFS2, months (95% CI)	NE (36.0, NE)	32.4 (29.3, NE)	0.73 (0.59, 0.91)
Median TTSP, months (95% CI)	[redacted]	[redacted]	[redacted]
Median TTD, months (95% CI)	26.3 (22.3, 30.4)	22.6 (20.3, 24.5)	0.80 (0.68, 0.96)
Median TTST, months (95% CI)	30.0 (26.3, 36.0)	24.0 (22.5, 26.2)	0.77 (0.65, 0.93)
Mean change from baseline in EQ-5D-5L utility score at end of treatment	[redacted]	[redacted]	NR

[a] PFS data are presented from the interim 11th August 2023 DCO.
[b] Defined as complete or partial response, assessed by BICR. The analysis included [redacted] patients in the amivantamab-lazertinib arm and [redacted] patients in the osimertinib arm who had measurable disease at baseline. The treatment effect is shown as an odds ratio, which was calculated from a logistic-regression model with stratification according to EGFR mutation type, Asian race, and history of brain metastasis. The widths of the 95% CIs have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.
[c] Treatment effect is presented as an odd ratio rather than a hazard ratio.
[d] Based on subjects with confirmed complete response or partial response by BICR.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; DOR: duration of response; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PFS2: progression-free survival after first subsequent therapy; TTD: time to treatment discontinuation; TTSP: time to symptomatic progression; TTST: time to subsequent therapy.

Source: Cho *et al*. 2024.[19] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023).[21] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024).[95] Johnson & Johnson Data on File. MARIPOSA HRQoL Data.[114] Gadgeel *et al*. WCLC 2024.[24]

B.2.6.1 Primary endpoint: Progression-free survival (assessed by BICR)

The primary endpoint of the MARIPOSA trial, PFS assessed by BICR, was met by amivantamab-lazertinib. Following a median follow-up of 22.0 months at the 11th August 2023 DCO, a statistically significant (p<0.001) and clinically meaningful treatment effect was observed for PFS, with a 30% reduction in the risk of disease progression or death in patients receiving amivantamab-lazertinib compared with patients receiving osimertinib (HR: 0.70; 95% CI: 0.58, 0.85, p-value <0.001) (Table 13).[19, 121]

The mPFS (BICR-assessed) was 23.7 months (95% CI: 19.1, 27.7) in the amivantamab-lazertinib arm and 16.6 months (95% CI: 14.8, 18.5) in the osimertinib arm, improving mPFS by 7.1 months. Notably, the PFS benefit associated with amivantamab-lazertinib as compared with osimertinib increased at later timepoints, from 8% at 12 months to 14% at 24 months, demonstrating that the benefit provided by amivantamab-lazertinib is durable over time.[19] This is supported by the numerically higher proportion of patients in the amivantamab-lazertinib arm than the osimertinib arm achieving a CR (see Section B.2.6.3) and the observed increased DoR to ≥36 months (see Section B.2.6.4).

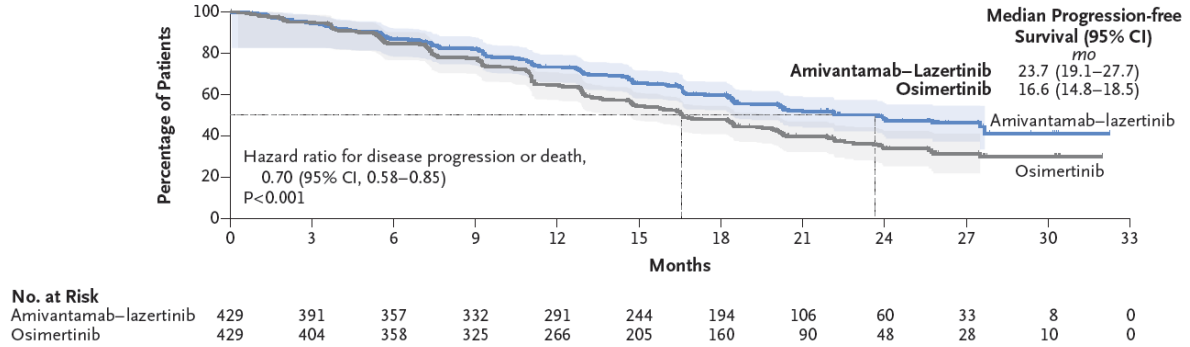
The KM and cumulative hazard plots for PFS in both treatment arms are presented in Figure 8 and Figure 9, respectively. The plots show a distinct, early, and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around six months after randomisation.

Table 13: Summary of PFS assessed by BICR (11th August 2023 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
12-month event-free rate, % (95% CI)	73 (69, 77)	65 (60, 69)
18-month event-free rate, % (95% CI)	60 (55, 64)	48 (43, 53)
24-month event-free rate, % (95% CI)	48 (42, 54)	34 (28, 39)
Treatment difference		
p-value[a]	<0.001	
HR (95% CI)[b]	0.70 (0.58, 0.85)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable.
Sources: Cho *et al.* 2024.[19] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 12, page 60.[21]

Figure 8: KM plot of PFS assessed by BICR (11th August 2023 DCO; FAS)



Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; mo: months; PFS: progression-free survival.
Source: Cho *et al.* 2024. Figure 1A.[19]

Figure 9: Cumulative hazard plot for PFS assessed by BICR (11th August 2023 DCO; FAS)

[redacted]

Abbreviations: A+L: amivantamab-lazertinib; BICR: blinded independent central review; DCO: data cut-off; FAS: full analysis set; OSI: osimertinib; PFS: progression-free survival.
Source: Johnson & Johnson Data on File. Cost effectiveness model (CEM) Technical Report. Figure 19, page 86.[122]

Progression-free survival (assessed by INV)

At the 11th August 2023 DCO, a clinically meaningful treatment effect was observed for PFS as assessed by INV, with a [redacted] reduction in the risk of disease progression or death in patients receiving amivantamab-lazertinib compared with patients receiving osimertinib ([redacted]) (Table 14).[21] In alignment with the results of the primary endpoint (PFS assessed by BICR), this represents a statistically significant reduction in risk ([redacted]).

The mPFS (INV-assessed) was [redacted] months ([redacted]) in the amivantamab-lazertinib arm and [redacted] months ([redacted]) in the osimertinib arm, improving mPFS

by [redacted] months. Additionally, 18- and 24-month event-free rates of [redacted]% and [redacted]% were observed for patients in the amivantamab-lazertinib treatment arm, with rates of [redacted]% and [redacted]% observed for patients in the osimertinib treatment arm. The KM and cumulative hazard plots for PFS in both treatment arms are presented in Figure 10 and Figure 11, respectively.

Table 14: Summary of PFS assessed by INV (11th August 2023 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
12-month event-free rate, % (95% CI)	[redacted]	[redacted]
18-month event-free rate, % (95% CI)	[redacted]	[redacted]
24-month event-free rate, % (95% CI)	[redacted]	[redacted]
30-month event-free rate, % (95% CI)	[redacted]	[redacted]
Treatment difference		
p-value[a]	[redacted]	
HR (95% CI)[b]	[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; INV: investigator; NE: not estimable.
Sources: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Page 281.[21]

Figure 10: KM plot of PFS assessed by INV (11th August 2023 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; INV: investigator; OSI: osimertinib; PFS: progression-free survival.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Page 205.[21]

Figure 11: Cumulative hazard plot for PFS assessed by INV (11th August 2023 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; INV: investigator; OSI: osimertinib; PFS: progression-free survival.
Source: Johnson & Johnson Data on File. CEM Technical Report. Figure 25, page 89.[122]

The primary endpoint of the MARIPOSA trial, PFS assessed by BICR, was met by amivantamab-lazertinib at a median follow-up of 22.0 months, with a [redacted] reduction in the risk of disease progression or death in patients receiving amivantamab-lazertinib compared with patients receiving osimertinib. Notably, the PFS benefit associated with amivantamab-lazertinib as compared with osimertinib increased at later timepoints, from [redacted] at 12 months to [redacted] at 24 months, demonstrating that the benefit provided by amivantamab-lazertinib is durable over time.[19]

These results demonstrate that combination therapy with amivantamab and lazertinib improves PFS outcomes and maximises long-term effectiveness of 1L therapy compared with osimertinib, due to the synergy of the distinct mechanisms of action of amivantamab and lazertinib, and addresses an unmet need to improve 1L treatment, prior to the development of resistance and availability of limited targeted treatment options.

B.2.6.2 Key secondary endpoint: Overall survival

On January 7th, Johnson & Johnson announced that amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in overall survival compared to osimertinib in the phase 3 MARIPOSA trial.[23] With the final analysis featuring a median follow-up of [redacted] months, the mOS improvement of this chemotherapy-free combination is anticipated to exceed one year compared to osimertinib.[22, 23] Johnson & Johnson are not yet able to include these data in the submission as currently only top line data are available ([redacted]).[22, 23] This means that the combination of amivantamab-lazertinib [redacted] in the ITT population.[22, 23] The mOS was not estimable ([redacted]) in the amivantamab-lazertinib arm, while the mOS for osimertinib was reached at [redacted] months ([redacted], [redacted][22, 23] Johnson & Johnson would be pleased to provide further analyses using the updated data once full data are available.

At the 13th May 2024 DCO, [redacted] patients in the amivantamab-lazertinib arm and [redacted] in the osimertinib arm had died, which represented a survival benefit of 23% for amivantamab-lazertinib (HR: 0.77; 95% CI: 0.61, 0.96; p=0.019) (Table 15).[24] At 30 months, [redacted]% of patients in the amivantamab-lazertinib arm versus [redacted]% of patients treated with osimertinib had died.[24, 95] This trend towards improved OS with amivantamab-lazertinib compared with osimertinib was maintained, with 61% versus 53% of patients alive at three years, respectively. The mOS for amivantamab-lazertinib remained not estimable, while it was 37.3 months in the osimertinib arm.[24]

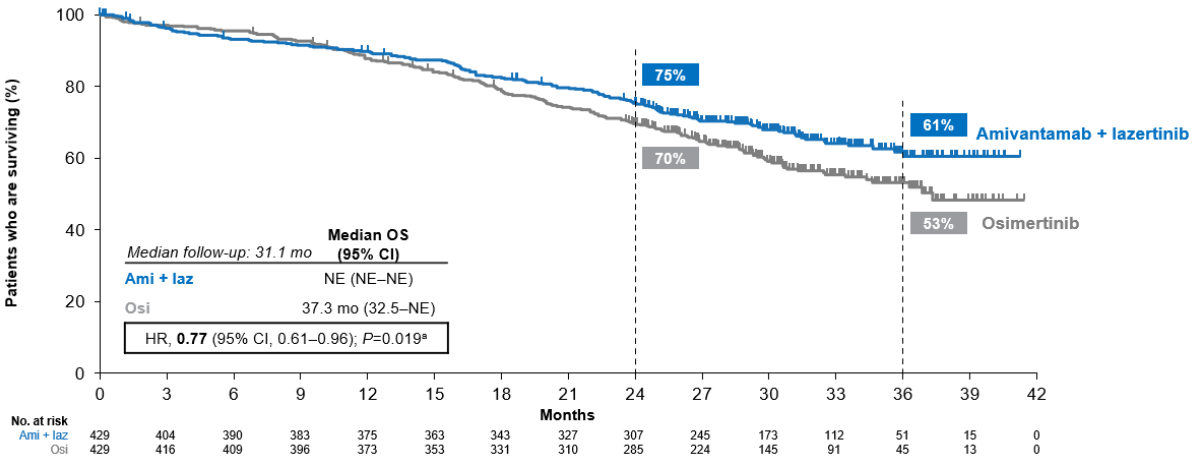
The KM and cumulative hazard plots for OS at the 13th May 2024 DCO are presented in Figure 12 and Figure 13, respectively. After a slight imbalance in deaths during the first year of the study, the plots demonstrate a strong trend towards improved survival in the amivantamab-lazertinib arm. Notably, the cumulative hazard curve for osimertinib is relatively steep in the later parts, indicating a higher risk of events which is increasing over time in comparison to amivantamab-lazertinib.

Table 15: Summary of OS (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	NE (NE, NE)	37.3 (32.5, NE)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.75 [redacted]	0.70 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.61 [redacted]	0.53 [redacted]
Treatment difference		
p-value[a]	0.019	
HR (95% CI)[b]	0.77 (0.61, 0.96)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; OS: overall survival.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024).[95] Gadgeel *et al.* WCLC 2024.[24]

Figure 12: KM plot of OS (13th May 2024 DCO; FAS)



Abbreviations: Ami + laz: amivantamab-lazertinib; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; NE: not estimable; No.: number; OS: overall survival; Osi: osimertinib.
Footnotes: [a]p-value was calculated from a log-rank test stratified by mutation type (Ex19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified proportional hazards model.
Source: Gadgeel *et al.* WCLC 2024.[24]

Figure 13: Cumulative hazard plot for OS (13th May 2024 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; OS: overall survival; OSI: osimertinib.
Source: Johnson & Johnson Data on File. CEM Technical Report. Figure 19, page 86.[122]

The updated OS analysis at the 13th May 2024 DCO was unplanned and performed in response to requests from health authorities. The lack of pre-planned statistical powering meant that a p-value of ≤0.00001 would have been required for statistical significance to be determined. While statistical significance was not reached, a strong trend towards improved OS with amivantamab-lazertinib compared with osimertinib was observed, with 61% versus 53% of patients alive at three years, respectively.[24]

These data demonstrate that amivantamab-lazertinib offers an innovative therapeutic option of two targeted treatments that deliver a clinically meaningful difference in efficacy compared with SoC. The MARIPOSA study is ongoing and a pre-specified final OS analysis with formal statistical testing is planned. In a press release shared by Johnson & Johnson earlier this month, amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in OS compared to osimertinib in the Phase 3 MARIPOSA trial.[23] With the final analysis featuring a median follow-up of [redacted] months, the mOS improvement of this chemotherapy-free combination is anticipated to exceed one year compared to osimertinib.[22, 23] The combination of amivantamab-lazertinib [redacted] in the ITT population ([redacted]).[22, 23] These significantly improved OS results reinforce the importance of amivantamab-lazertinib and its potential to significantly improve patient prognosis. It is noteworthy that amivantamab-lazertinib is the only chemotherapy-free treatment to demonstrate a significant survival benefit versus osimertinib in the first-line treatment of patients with EGFR-mutated lung cancer.

In addition to data from the MARIPOSA trial, real-world OS data from patients in UK clinical practice are available from an observational, UK population-based standing cohort study among patients diagnosed with advanced NSCLC between 2016–2024 conducted by Johnson & Johnson. This study uses data from the NCRAS database; the cohort is referred to as the 'MARIPOSA-like' cohort (N=617), which included patients who had cEGFRm NSCLC and similar baseline characteristics to patients in the MARIPOSA trial. Of these patients, 126 were treated with 1L osimertinib monotherapy and reported a mOS of 28.1 months (95% CI: 23.0, 35.7;

n=126).[10] Furthermore, in the 'MARIPOSA-expanded' cohort (N=1,469), which explored a broader patient population with high-risk features, 278 were treated with 1L osimertinib monotherapy and were demonstrated to have a mOS of 26.2 months (95% CI: 22.0, 30.0).[10] These data suggest that the real-world survival of patients receiving osimertinib may be even lower than that reported in the MARIPOSA trial (mOS: 37.3 months; 95% CI: 32.5, NE).[95]

B.2.6.3 Key secondary endpoint: Objective response rate

ORR was assessed in patients with measurable disease at baseline and responders were defined as patients achieving either CR or PR, as assessed by BICR assessment per RECIST v1.1 criteria. Based on BICR assessment, [redacted] of the 429 patients enrolled in the amivantamab-lazertinib arm and [redacted] of the 429 patients enrolled in the osimertinib arm had measurable disease at baseline and were included in the analysis of ORR (Table 16).

At the 13th May 2024 DCO, the ORR was [redacted]% in the amivantamab-lazertinib arm and [redacted]% in the osimertinib arm. This indicates that patients receiving amivantamab-lazertinib are [redacted]% more likely to achieve an ORR compared with patients receiving osimertinib (OR: [redacted]; 95% CI: [redacted]; [redacted]). Of note, a [redacted] proportion of patients in the amivantamab-lazertinib arm achieved a CR ([redacted]%) compared with the osimertinib arm ([redacted]%). Additionally, there were [redacted] patients in the amivantamab-lazertinib arm with PD compared with the osimertinib arm ([redacted]% and [redacted]%, respectively).

Through the simultaneous inhibition of both EGFR and MET, targeting the two major mechanisms of primary resistance to osimertinib, amivantamab-lazertinib offers a greater ORR compared with osimertinib, providing patients with a more efficacious treatment option at first line.

Table 16: Summary of ORR based on RECIST v1.1 criteria in patients with measurable disease at baseline by BICR (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Number of patients with measurable disease at baseline	[redacted]	[redacted]
ORR, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Treatment difference		
p-value[a]	[redacted]	
Odds ratio (95% CI)[b]	[redacted]	
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE	[redacted]	[redacted]

[a] p-value and odds ratio are from a logistic regression model stratified by mutation type (Exon 19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] Odds ratio >1 favours amivantamab-lazertinib 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; FAS: full analysis set; NE: not estimable; ORR: objective response rate; PD: progressive disease; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours; SD: stable disease.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 3, page 7.[95]

B.2.6.4 Key secondary endpoint: Duration of response

Among the confirmed responding patients at the 13th May 2024 DCO, [redacted]% of patients in the amivantamab-lazertinib arm had disease progression or died, compared with [redacted]% of patients in the osimertinib arm.[95] Correspondingly, median DOR was prolonged in the amivantamab-lazertinib arm: [redacted] months (95% CI: [redacted]), compared with [redacted] months (95% CI: [redacted]) in the osimertinib arm (Table 17). The percentage of patients remaining in confirmed response at 18- and 24-months was [redacted]% and [redacted]%, respectively, for patients receiving amivantamab-lazertinib, compared with [redacted]% and [redacted]%, respectively, for patients receiving osimertinib. These data indicate that amivantamab-lazertinib results in more durable responses in patients when compared with osimertinib, which may contribute to the observed delay in progression (see Section B.2.6.1) and the subsequently improved OS (see Section B.2.6.2).

A KM plot for DoR in both treatment arms is presented in Figure 14. The plot shows a distinct, early, and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning [redacted].

The combination of amivantamab-lazertinib fulfils the unmet need for a more efficacious therapy that extends PFS and OS compared with osimertinib, thereby maximising long-term effectiveness of 1L treatment for patients with advanced cEGFRm NSCLC.

Table 17: Summary of DoR in confirmed responders based on patients with measurable disease at baseline by BICR (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Patients with measurable disease at baseline, n	[redacted]	[redacted]
Confirmed responders (CR+PR), n	[redacted]	[redacted]
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)[a]		
Median (95% CI)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
DoR ≥6 months, n (%)	[redacted]	[redacted]
DoR ≥12 months, n (%)	[redacted]	[redacted]
DoR ≥18 months, n (%)	[redacted]	[redacted]
DoR ≥24 months, n (%)	[redacted]	[redacted]
DoR ≥30 months, n (%)	[redacted]	[redacted]
DoR ≥36 months, n (%)	[redacted]	[redacted]

[a] Quartiles and 95% CIs are estimated with Kaplan-Meier method.
+ censored observation

Note: Percentages are based on the number of subjects who achieved Confirmed CR or Confirmed PR.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; CR: complete response; DCO: data cut-off; DOR: duration of response; FAS: full analysis set; NE: not estimable; PR: partial response.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 4, page 8.[95]

Figure 14: KM plot of DoR in confirmed responders with measurable disease at baseline assessed by BICR (13th May 2024 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; DoR: duration of response; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Figure 2, page 9.[95]

B.2.6.5 Key secondary endpoint: Progression-free survival after first subsequent therapy

First subsequent systemic therapy

As of the 13th May 2024 DCO, the proportion of patients that went on to receive a subsequent anti-cancer therapy after treatment discontinuation due to disease progression was similar between the two treatment arms: 72% of patients in the amivantamab-lazertinib arm and 74% of patients in the osimertinib arm (Table 18).[24] In both the amivantamab-lazertinib arm and osimertinib arm, the most commonly received subsequent systemic therapy by patients that received a subsequent systemic therapy was doublet chemotherapy (41% and 45%, respectively).[24] Less commonly, patients received a third-generation TKI (27% and 16%, respectively) or chemotherapy plus IO/ Vascular Endothelial Growth Factor inhibitors (VEGFi) (12% and 20%, respectively).[24]

During clinical feedback from the October 2024 advisory board, all three UK clinicians confirmed that the treatment expected to be most commonly received by patients with advanced cEGFRm NSCLC in 2L, after prior osimertinib, would be PDC.[32] This is in line with NICE guidelines for the 2L treatment of advanced cEGFRm NSCLC, after failure of osimertinib, which recommend PBC,[78] and with the subsequent treatments used in the MARIPOSA trial, in which doublet chemotherapy represented the most common option for patients in both the amivantamab-lazertinib and osimertinib arms (Table 18).[24]

This is further supported by real-world data (RWD) from the NCRAS database.[10] These data show that, of patients in the 'MARIPOSA-like' cohort who received osimertinib 1L, 44% (56/126) received a subsequent treatment. Of these, 61% (34/56) received a platinum-based chemotherapy regimen (with or without IO), 32% (18/56) received a third generation TKI (osimertinib), and only 4% (2/56) received another TKI (non-third generation).[10] This aligns with NICE guidelines, in which platinum-based chemotherapy, with or without IO, is recommended following upfront osimertinib use.[78]

Table 18: Summary of 1L of subsequent systemic therapy received by patients who discontinued treatment due to disease progression (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=111)	Osimertinib (N=173)
Patients receiving one or more subsequent systemic therapies after treatment discontinuation due to disease progression, %	72	74
1L of subsequent systemic therapies, %		
Doublet chemotherapy	41	45
Chemotherapy plus VEGFi and IO	12	20
Third-generation TKI	27	16
Other TKIs (not including third-generation)	7	5
TKI-based combination regimen	8	7

Abbreviations: 1L: first-line; DCO: data cut-off; FAS: full analysis set; IO: immuno-oncology; TKI: tyrosine kinase inhibitor; VEGFi: Vascular Endothelial Growth Factor inhibitors.
Source: Gadgeel *et al.* WCLC 2024.[24] Cho *et al.* 2024.[19]

Key secondary endpoint: progression-free survival after first subsequent therapy

At the 13th May 2024 DCO, a higher proportion of patients had experienced progression after first subsequent therapy in the osimertinib arm ([redacted]%) compared with amivantamab-lazertinib arm ([redacted]%) (Table 19).[95] This represented a statistically significant reduction in the risk of second disease progression or death in the amivantamab-lazertinib arm compared with the osimertinib arm (HR: 0.73 [95% CI: 0.59, 0.91]; nominal p=0.004).[24] Therefore, these results suggest that, in addition to increasing time to disease progression or death (Section B.2.6.1), the durable response observed with amivantamab-lazertinib in 1L confers a benefit in delaying patients' subsequent progression on 2L treatment.

The median PFS2 was 32.4 months in the osimertinib arm and not estimable in the amivantamab-lazertinib arm.[24] At 36 months, the majority of patients in the amivantamab-lazertinib arm had not experienced progression after first subsequent therapy (event-free rate: 0.57) whereas more than half of patients in the osimertinib arm had experienced progression after first subsequent therapy (event-free rate: 0.49).[24] The associated KM plot for PFS2 is presented in Figure 15. The plot shows a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around twelve months after randomisation.

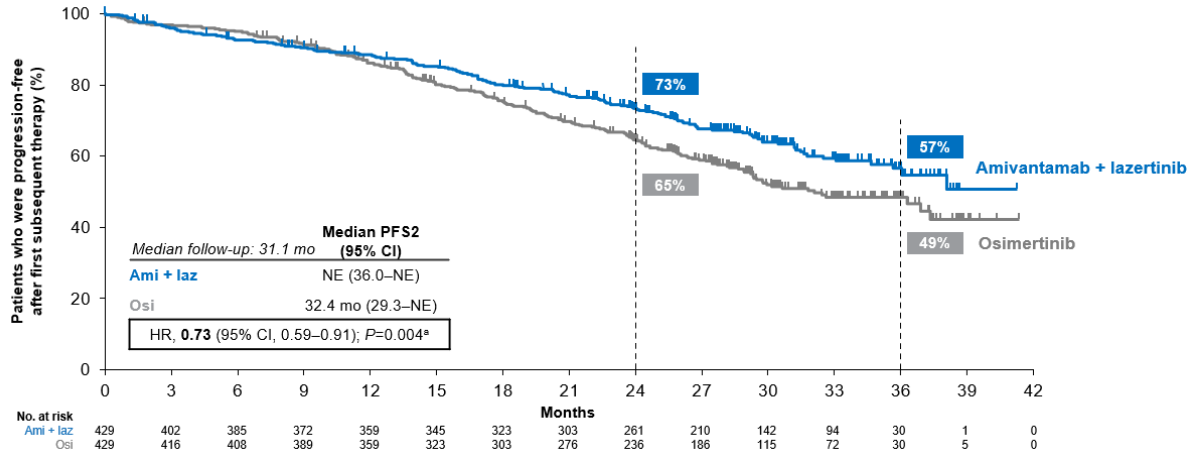
Importantly, treatment with amivantamab-lazertinib has the additional benefit of preserving chemotherapy for use in later lines of therapy, meaning patients have access to an effective treatment regimen upfront as well as increased options in later lines, if needed.

Table 19: Summary of PFS2 (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	NE (36.0, NE)	32.4 (29.3, NE)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.73[redacted]	0.65[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.57[redacted]	0.49[redacted]
Treatment difference		
Nominal p-value[a]	0.004	
HR (95% CI)[b]	0.73 (0.59, 0.91)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; PFS2: progression-free survival after first subsequent therapy.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 5, page 10.[95] Gadgeel *et al.* WCLC 2024.[24]

Figure 15: KM plot of PFS2 (13th May 2024 DCO; FAS)



Abbreviations: Ami + laz: amivantamab-lazertinib; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; mo: months; NE: not estimable; No.: number; Osi: osimertinib; PFS2: progression free survival after first subsequent therapy.
Footnotes: [a]p-value is calculated by log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified proportional hazards model.
Source: Gadgeel *et al.* WCLC 2024.[24]

B.2.6.6 Key secondary endpoint: Time to symptomatic progression

At the 13th May 2024 DCO, fewer patients had experienced symptomatic progression or death in the amivantamab-lazertinib arm compared with the osimertinib arm ([redacted]% versus [redacted]%). This represented a statistically significant reduction in risk of symptomatic progression or death compared with participants in the osimertinib arm (HR: [redacted]; 95% CI: [redacted], nominal p=[redacted]; Table 20). Median TTSP remained not estimable in the amivantamab-lazertinib arm, compared with [redacted] months in the osimertinib arm. At 24- and 36-months, [redacted] patients had experienced symptomatic progression in the amivantamab-lazertinib arm (event-free rates of [redacted] and [redacted], respectively) compared with patients in the osimertinib arm (event-free rates of [redacted] and [redacted], respectively).

The associated KM plot for TTSP is presented in Figure 16. The plot shows a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around 12 months after randomisation.

Table 20: Summary of TTSP (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Symptomatic PD, n (%)	[redacted]	[redacted]
Death without symptomatic PD, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	0.74 [redacted]	0.67 [redacted]
24-month event-free rate (95% CI)	0.67 [redacted]	0.59 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	[redacted]	[redacted]
Treatment difference		
p-value[a]	[redacted]	
HR (95% CI)[b]	[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; PD: progressive disease; TTSP: time to symptomatic progression.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 6, page 12.[95] Nguyen *et al.* WCLC 2024.[117]

Figure 16: KM plot of TTSP (13th May 2024 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; Osi: osimertinib; TTSP: time to symptomatic progression.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Figure 4, page 13.[95]

B.2.6.7 Exploratory endpoint: Time to treatment discontinuation

TTD was investigated as an exploratory endpoint in the MARIPOSA trial. At the 13th May 2024 DCO, a higher proportion of patients in the osimertinib arm had discontinued treatment or died compared with the amivantamab-lazertinib arm ([redacted] versus [redacted]), as presented in Table 21.[95] Additionally, a prolonged median TTD was observed in the amivantamab-lazertinib arm (26.3 months; 95% CI: 22.3, 30.4) as compared with the osimertinib arm (22.6 months; 95% CI: 20.3, 24.5) (HR: 0.80; 95% CI: 0.68, 0.96), which was statistically significant (p=0.014).[24]

At 18- and 24-months, [redacted]% and [redacted]% of patients were still on active treatment in the amivantamab-lazertinib arm, respectively, compared with [redacted]% and [redacted]% of patients in the osimertinib arm, respectively. At three years, more patients in the amivantamab-lazertinib arm remained on treatment compared with the osimertinib arm (40% versus 29%, respectively).[24]

The associated KM plot for TTD is presented in Figure 17. The plot shows a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around 22 months after randomisation.

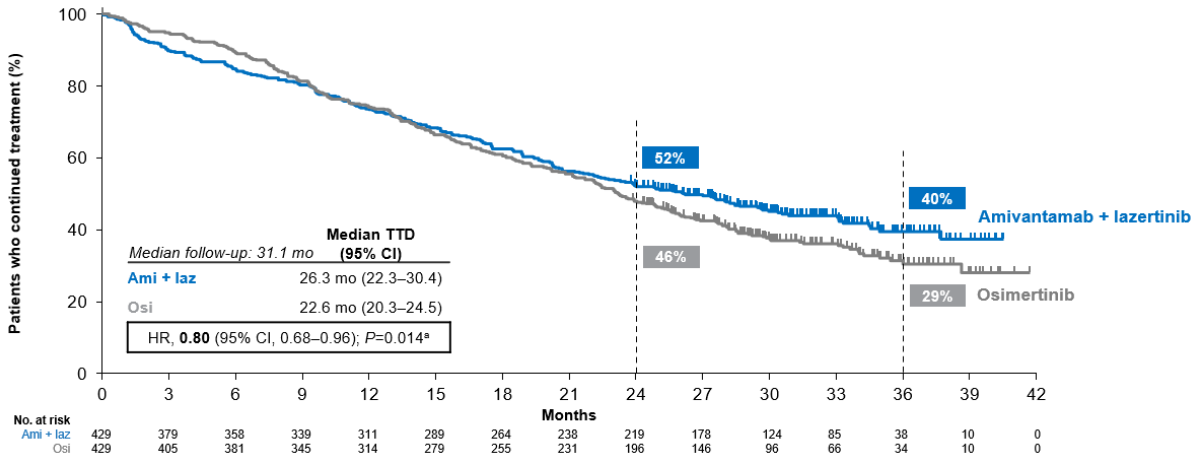
Through delaying treatment resistance and subsequent progression, amivantamab-lazertinib prolongs TTD and addresses the unmet need for a more efficacious 1L treatment option that maximises long-term effectiveness.

Table 21: Summary of TTD (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	26.3 (22.3, 30.4)	22.6 (20.3, 24.5)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.52 [redacted]	0.46 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.40 [redacted]	0.29 [redacted]
Treatment difference		
p-value[a]	0.014	
HR (95% CI)[b]	0.80 (0.68, 0.96)	

[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; TTD: time to treatment discontinuation.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 10, page 19.[95] Gadgeel *et al.* WCLC 2024.[24]

Figure 17: KM plot of TTD (13th May 2024 DCO; FAS)



Abbreviations: Ami + laz: amivantamab-lazertinib; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; Osi: osimertinib; TTD: time to treatment discontinuation.
Footnotes: [a]p-value is calculated by log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified proportional hazards model.
Source: Gadgeel *et al.* WCLC 2024.[24]

B.2.6.8 Exploratory endpoint: Time to subsequent therapy

At the 13th May 2024 DCO, fewer patients in the amivantamab-lazertinib arm had initiated subsequent systemic therapy compared with the osimertinib arm ([redacted]% versus [redacted]%, respectively) (Table 22).[95] Furthermore, the median time to initiation of any subsequent anti-cancer therapy was longer in the amivantamab-lazertinib arm (30.0 months; 95% CI: 26.3, 36.0) compared with the osimertinib arm (24.0 months; 95% CI: 22.5, 26.2).[24] This represents a [redacted]% reduction in risk for TTST in the amivantamab-lazertinib arm compared with the osimertinib arm, which was statistically significant (HR: 0.77; 95% CI: 0.65, 0.93; nominal p=0.005).[24, 95]

These results demonstrate the durability of clinical benefit offered by amivantamab-lazertinib, prolonging time until patients require a subsequent therapy versus osimertinib. This is also supported by the event-free rates observed for these patients; at 24 months, 50% of patients in the osimertinib arm had initiated subsequent therapy or died, compared with 43% in the amivantamab-lazertinib arm.[24]

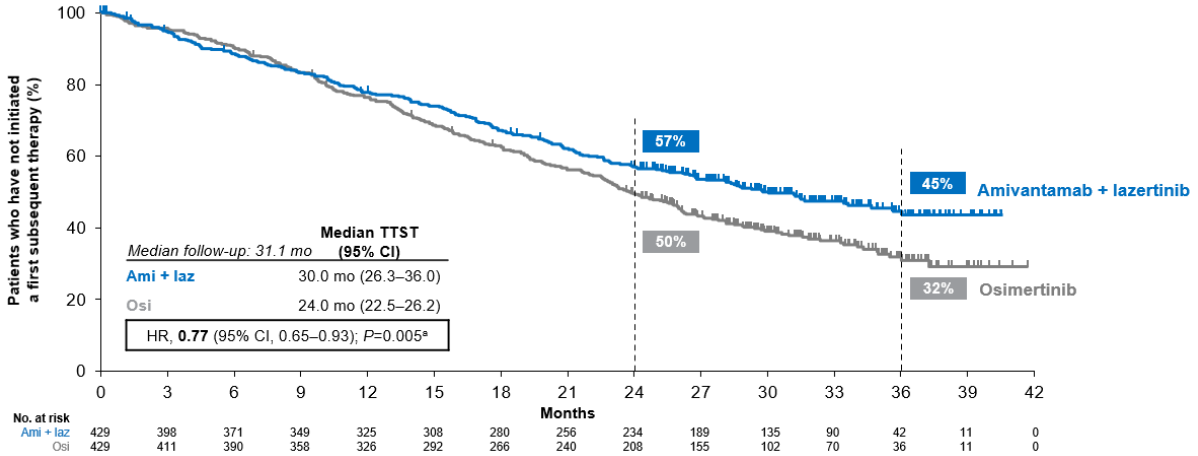
The KM curve for TTST is presented in Figure 18, showing a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around 12 months after randomisation.

Table 22: Summary of time to subsequent systemic anti-cancer therapy (13th May 2024 DCO; FAS)

	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	30.0 (26.3, 36.0)	24.0 (22.5, 26.2)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.57 [redacted]	0.50 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.45 [redacted]	0.32 [redacted]
Treatment difference		
p-value[a]	0.005	
HR (95% CI)[b]	0.77 (0.65, 0.93)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 11, page 21.[95] Gadgeel *et al*. WCLC 2024.[24]

Figure 18: KM plot of time to subsequent anti-cancer therapy (13th May 2024 DCO; FAS)



Abbreviations: Ami + laz: amivantamab-lazertinib; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; No.: number; Osi: osimertinib; TTST: time to subsequent therapy.
Footnotes: [a]p-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified proportional hazards model.
Source: Gadgeel *et al.* WCLC 2024.[24]

B.2.6.9 Exploratory endpoint: EQ-5D-5L

As outlined in Table 4 in Section B.2.3.2, three PRO measures were reported in the MARIPOSA trial: EORTC-QLQ-C30, NSCLC-SAQ, and EQ-5D-5L. For brevity, only EQ-5D-5L utility scores are presented in this submission, published from the FAS at the 13th May 2024 DCO.[95]

EQ-5D-5L was an exploratory endpoint in the MARIPOSA 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).[120] The change in utility score from baseline over time was analysed using MMRM.[120] 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.[120]

Changes in EQ-5D-5L utility scores from baseline across the two treatment arms are presented in Table 23 and Figure 19. Scores were broadly consistent between the two treatment arms at each key timepoint in the trial (baseline, start of Q2W dosing schedule and end of treatment), indicating that amivantamab-lazertinib has a similar impact on the HRQoL of patients as osimertinib, thereby providing a more efficacious treatment option that maintains HRQoL.

Table 23: Analysis of EQ-5D-5L utility scores (13th May 2024 DCO; FAS)

Utility score	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Baseline		
n	[redacted]	[redacted]
Mean (SD) utility	[redacted]	[redacted]
Initiation of Q2W dosing (Cycle 2 Day 1)		
n	[redacted]	[redacted]

Utility score	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Mean (SD) utility	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD) utility	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]

n for measured value is the number of patients with a non-missing value at the specified time point.
Abbreviations: DCO: data cut-off; FAS: full analysis set; SD: standard deviation; Q2W: once every two weeks.
Source: Johnson & Johnson Data on File. MARIPOSA HRQoL Data.[114]

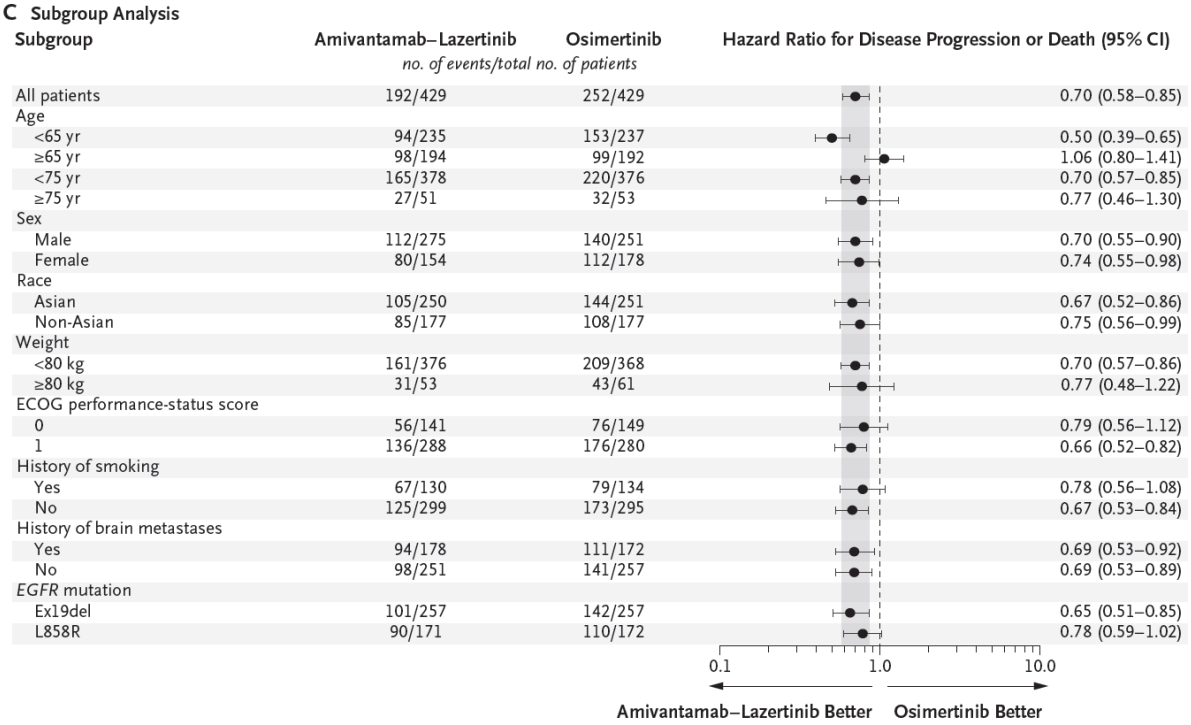
Figure 19: Change from baseline of EQ-5D-5L utility score over time (13th May 2024 DCO; FAS)

Note: N is the number of subjects with a non-missing change from baseline value for the specified patient reported outcome at the specified time point.
Abbreviations: A+L: amivantamab-lazertinib; C: cycle; DCO: data cut-off; D: day; FAS: full analysis set; Laz: lazertinib; Osi: osimertinib; SE: standard error.
Source: Johnson & Johnson Data on File. MARIPOSA HRQoL Data.[114]

B.2.7 Subgroup analysis

PFS assessed by BICR was analysed according to baseline disease characteristics, with the corresponding forest plot presented in Figure 20. A broadly consistent benefit with amivantamab-lazertinib was observed across all pre-specified subgroups, including those outlined by NICE in the draft scope, where available.[123] In particular, the same statistically significant benefit of amivantamab-lazertinib versus osimertinib was seen across the subgroups for those with or without a history of brain metastases, with an observed HR of 0.69 in both patient cohorts. A treatment benefit, as indicated by HRs <1, was additionally observed for amivantamab-lazertinib in subgroups of race and EGFR mutation type.[19]

Figure 20: Forest plot of PFS assessed by BICR for subgroups defined by baseline disease characteristics (11th August 2023 DCO; FAS)



Footnotes: The shaded area indicates the 95% confidence interval for the overall hazard ratio among all the patients (primary end point). Except for the primary end point, 95% confidence intervals in the subgroup analysis were not adjusted for multiplicity, with the hazard ratios for progression or death obtained from an unstratified proportional-hazards model, and should not be used to infer definitive treatment effects. Race was reported by the patient. ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Ex19del: exon 19 deletion; FAS: full analysis set; HR: hazard ratio; L858R: exon 21 L858R substitution mutations; PFS: progression-free survival; PS: performance status; yr: years.
Source: Cho *et al.* 2024 (Figure 1C).[19]

A secondary analysis of patients in the MARIPOSA trial with biomarkers of high-risk disease (n=636), including detectable ctDNA, TP53 co-mutations or metastases in the liver or brain, has shown that the PFS benefit observed with amivantamab-lazertinib compared with osimertinib is maintained for those with high-risk features (mPFS: 20.3 months versus 15.0 months, respectively; HR: 0.72; 95% CI: 0.58, 0.90; p=0.004), representing a promising new SoC for the 1L treatment of cEGFRm advanced NSCLC.[63, 64]

An analysis of OS by subgroup demonstrated a [redacted], as indicated by [redacted], across subgroups of history of brain metastases, EGFR mutation type and race (Figure 21).

Figure 21: Forest plot of OS for subgroups defined by baseline disease characteristics (13th May 2024 DCO; FAS)

Abbreviations: CI: confidence interval; DC: data cut; EGFR: epidermal growth factor receptor; Exon 19del: exon 19 deletion; FAS: full analysis set; HR: hazard ratio; Exon 21 L858R: exon 21 L858R substitution mutations; OS: overall survival; strat: stratification.
Source: Johnson & Johnson Data on File.

Similarly, the overall incidence of TEAEs was broadly consistent between subgroups. Full safety results for subgroups within the MARIPOSA trial are presented from the 11th August 2023 DCO in the CSR included in the reference pack, and full safety results for the SAS are presented in Section B.2.10.

B.2.8 Meta-analysis

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

B.2.9 Indirect and mixed treatment comparisons

The MARIPOSA trial provides a head-to-head comparison between amivantamab-lazertinib and the sole comparator considered appropriate for this submission, osimertinib monotherapy. Therefore, indirect treatment comparisons were not necessary to conduct, and this section is not applicable. For this reason, sections of the appendices document related to indirect comparison have been removed.

B.2.10 Adverse reactions

Safety results from the MARIPOSA trial are presented from the 11th August 2023 DCO. Results are presented from the SAS, defined as randomised patients who received at least one dose of study treatment, which included 421 patients in the amivantamab-lazertinib arm and 428 patients in the osimertinib arm.[19] As noted in Section B.2.6, results for the lazertinib arm are not relevant to the decision problem of this appraisal and are therefore not presented, but are available in the CSR included in the reference pack.[21]

B.2.10.1 Treatment disposition

At the 11th August 2023 DCO, 230 patients (55%) and 213 patients (50%) remained on treatment in the amivantamab-lazertinib and osimertinib arms, respectively (Table 24).[19] The most common reason for discontinuation of study treatment was disease progression, occurring in 86 (20%) and 154 (36%) patients in each treatment arm, respectively. Overall, more patients discontinued all study treatment due to an AE from the amivantamab-lazertinib arm (86/421, 20%) than the osimertinib arm (50/428, 12%).[19]

At a median follow-up of 22.0 months, 49% of patients in the amivantamab-lazertinib arm had a dose interruption within the first four months of treatment.[115] The corresponding mPFS for those who had an early dose interruption was [redacted], compared with [redacted] for those who did not, suggesting that early dose modifications do not adversely affect the efficacy of amivantamab-lazertinib.[115]

Table 24: Summary of treatment disposition (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Treatment disposition		
Patients ongoing	230 (55)	213 (50)
Discontinued all study treatment	191 (45)	215 (50)
Interruption of amivantamab[a]	206 (49)	N/A
Reason for discontinuation of all study treatment		
Progressive disease	86 (20)	154 (36)
AE	86 (20)	50 (12)
Withdrawal by patient	14 (3)	10 (2)
Physician decision	2 (0.5)	1 (0.2)
Non-compliance with study drug	1 (0.2)	0
Lost to follow-up	1 (0.2)	0
Other	1 (0.2)	0

[a] Within the first four months.
Abbreviations: AE: adverse event; DCO: data cut-off; IRR: infusion-related reaction; N/A: not applicable; SAS: safety analysis set.
Sources: Cho *et al.* 2024 (Figure S2).[19] Campelo *et al.* ELCC 2024.[115]

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 MARIPOSA trial at the 11th August 2023 DCO is presented in Table 25.[19, 21] In both treatment arms, almost all patients experienced at least one AE: 100% of patients in the amivantamab-lazertinib arm and 99% of patients in the osimertinib arm.[19, 21] Overall, the safety profile of amivantamab-lazertinib was consistent with the established safety profile of the individual components. VTE events were identified as a risk for the amivantamab-lazertinib arm and was added as an AESI during the study (see Section B.2.10.2.5). The MARIPOSA trial was not designed to mitigate AEs; however, ongoing studies are assessing the proactive management of AEs in patients receiving amivantamab and are discussed in detail in Section B.2.10.2.

Grade 3 or higher TEAEs were observed with a higher incidence in the amivantamab-lazertinib arm (316/421, 75%) compared with the osimertinib arm (183/428, 43%).[19] This difference is almost entirely driven by the incidence of Grade 3 TEAEs in the amivantamab-lazertinib and osimertinib arms ([redacted] and [redacted] respectively).[21] Rates of Grade 4 and 5 TEAEs were comparable between the treatment arms. In both arms, Grade 3 or higher TEAEs were mostly consistent with the on-target activity of amivantamab, lazertinib and osimertinib against the EGFR pathway (rash/dermatitis acneiform, stomatitis, and paronychia) and of amivantamab against the MET pathway (hypoalbuminemia and peripheral oedema).[21] Grade ≥3 TEAEs considered related to study treatment were reported in 252 patients (60%) in the amivantamab-

lazertinib arm and 59 patients (14%) in the osimertinib arm (Table 25).[19] Incidence of SAEs was comparable between the two treatment arms, experienced by 205 patients (49%) and 143 patients (33%) in the amivantamab-lazertinib and osimertinib arms, respectively.[19] Overall, TEAEs were manageable in both treatment arms with treatment interruptions, dose reductions and BSC.

Table 25: Overall summary of TEAEs (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with ≥1 AE	421 (100)	425 (99)
Related AEs[a]	414 (98)	378 (88)
AEs leading to death[b]	34 (8)	31 (7)
Serious AEs	205 (49)	143 (33)
Related serious AEs[a]	97 (23)	24 (6)
AEs leading to discontinuation of any study agent	147 (35)	58 (14)
AEs leading to discontinuation of amivantamab	145 (34)	N/A
Related AEs to amivantamab[a]	100 (24)	N/A
AEs leading to dose reduction of any study agent	249 (59)	23 (5)
AEs leading to dose reduction of amivantamab	193 (46)	N/A
Related AEs to amivantamab[a]	184 (44)	N/A
AEs leading to dose interruption of any study agent[c]	350 (83)	165 (39)
AEs leading to dose interruption of amivantamab	328 (78)	N/A
Related AEs to amivantamab[a,c]	282 (67)	N/A
Grade ≥3 AEs	316 (75)	183 (43)
Related grade ≥3 AEs[a]	252 (60)	59 (14)
Maximum toxicity grade		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]

[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.
[c] Excludes infusion related reactions.
Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set; TEAE: treatment-emergent adverse event.
Sources: Cho *et al.* 2024 (Table 3, S10, S11).[19] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 24, page 103.[21]

B.2.10.2.2 Common TEAEs by preferred term

TEAEs observed with a frequency of at least 15% in either treatment arm are presented in Table 26.[19] 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. EGFR-associated TEAEs were generally higher in the amivantamab-lazertinib arm compared with the osimertinib arm, and included rash (62% and 31%, respectively), dermatitis acneiform (29% and 13%, respectively), stomatitis (29% and 21%, respectively) and diarrhoea (29% and 44%, respectively).[19] Common TEAEs associated with MET inhibition activity of amivantamab included hypoalbuminemia (48%) and peripheral oedema (36%), which were observed more frequently in the amivantamab-lazertinib arm compared to the osimertinib arm; [redacted] and [redacted] respectively; however, these were generally Grade 1 or 2 and were not commonly serious.[19, 21]

Table 26: Number of patients with TEAEs with a frequency of at least 15% in any treatment group by system organ class and preferred term (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more AEs	421 (100)	425 (99)
Skin and subcutaneous tissue disorders		
Rash	260 (62)	131 (31)
Dermatitis acneiform	122 (29)	55 (13)
Dry skin	67 (16)	60 (14)
Pruritus	99 (24)	73 (17)
Peripheral oedema	150 (36)	24 (6)
Stomatitis	122 (29)	90 (21)
Gastrointestinal disorders		
Constipation	123 (29)	55 (13)
Nausea	90 (21)	58 (14)
Diarrhoea	123 (29)	190 (44)
Infections and infestations		
Paronychia	288 (68)	121 (28)
COVID-19	111 (26)	103 (24)
Metabolism and nutrition disorders		
Hypoalbuminaemia	204 (48)	26 (6)
Decreased appetite	103 (24)	76 (18)
Hypocalcaemia	88 (21)	35 (8)
Blood and lymphatic system disorders		
Anaemia	96 (23)	91 (21)
Leukopenia	26 (6)	66 (15)
Thrombocytopenia	66 (16)	84 (20)
General disorders and administration site conditions		
Asthenia	78 (19)	46 (11)
Fatigue	70 (17)	42 (10)
Muscle spasms	70 (17)	32 (7)
Pain in extremity	64 (15)	22 (5)
Investigations		
Alanine aminotransferase increased	152 (36)	57 (13)
Aspartate aminotransferase increased	121 (29)	58 (14)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Injury, poisoning and procedural complications		
Infusion related reaction	265 (63)	0
Respiratory, thoracic and mediastinal disorders		
Cough	65 (15)	88 (21)
Dyspnoea	51 (12)	68 (16)
Pulmonary embolism	73 (17)	20 (5)

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; SAS: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Cho *et al.* 2024.[19]

B.2.10.2.3 Grade 3 or higher TEAEs

Grade ≥3 TEAEs were reported in 316 patients (75%) in the amivantamab-lazertinib arm and 183 patients (43%) in the osimertinib arm at the 11th August 2023 DCO (Table 27).[19] Out of the patients who experienced a Grade ≥3 TEAE, [redacted]% in the amivantamab-lazertinib arm and [redacted]% in the osimertinib arm experienced a maximum severity grade of Grade 3 (Table 25).[21] A maximum severity of Grade 4 or 5 events was reported in [redacted]% and [redacted]% of patients in the amivantamab-lazertinib arm compared with [redacted]% and [redacted]% of patients in the osimertinib arm, respectively (Table 25).[21]

In both arms, Grade 3 or higher TEAEs were mostly consistent with the on-target activity of amivantamab, lazertinib and osimertinib against the EGFR pathway (rash/dermatitis acneiform, stomatitis, and paronychia) and of amivantamab against the MET pathway (hypoalbuminemia and peripheral oedema).[21] An incidence difference of ≥5% was observed for Grade ≥3 rash (15% versus 1%), paronychia (11% versus <1%), dermatitis acneiform (8% versus 0%), IRR (6% versus 0%), pulmonary embolism (8% versus 2%), and hypoalbuminemia (5% versus 0%) between the amivantamab-lazertinib and osimertinib treatment arms, respectively (Table 27).[19]

Table 27: Number of patients with Grade ≥3 TEAEs with frequency of at least 5% in either relevant treatment group by system organ class and preferred term (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more Grade ≥3 AEs	316 (75)	183 (43)
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	65 (15)	3 (1)
Dermatitis acneiform	35 (8)	0
Infections and infestations	[redacted]	[redacted]
Paronychia	46 (11)	2 (<1)
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pulmonary embolism	35 (8)	10 (2)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypoalbuminaemia	22 (5)	0
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	21 (5)	8 (2)
Injury, poisoning and procedural complications	[redacted]	[redacted]
IRR	27 (6)	0
Blood and lymphatic system disorders	[redacted]	[redacted]

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.
The event experienced by the patient with the worst toxicity is used.
Abbreviations: AE: adverse event; DCO: data cut-off; IRR: infusion-related reaction; SAS: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 26, page 111.[21] Cho *et al.* 2024.[19]

B.2.10.2.4 Serious adverse events

A summary of the SAEs reported in at least 2% of patients in the MARIPOSA trial is presented in Table 28. SAEs were defined in the MARIPOSA 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.[118] 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, and/or is medically important.

The overall incidence of SAEs was comparable between treatment arms, with SAEs reported in [redacted] patients ([redacted]%) in the amivantamab-lazertinib arm and [redacted] patients ([redacted]%) in the osimertinib arm.[21] The most frequently reported SAEs in the amivantamab-lazertinib or osimertinib arms were pulmonary embolism ([redacted]% versus [redacted]%, respectively), pneumonia ([redacted]% versus [redacted]%, respectively) and pleural effusion ([redacted]% versus [redacted]%, respectively).[21] No SAE preferred term had a ≥5% difference in incidence between the two arms. IRRs were reported in [redacted]% of patients in the amivantamab-lazertinib arm.[21]

Table 28: Number of patients with treatment-emergent SAEs with frequency of at least 2% in any treatment group by system organ class and preferred term (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more SAEs[a]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
COVID-19	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]

Footnotes: [a] Patients with 1 or more SAEs of any frequency. Patients were counted only once for any given event, regardless of the number of times they experienced the event. AEs were coded using MedDRA Version 25.0.
Abbreviations: DCO: data cut-off; SAE: serious adverse event; SAS: safety analysis set.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 29, page 120.[21]

B.2.10.2.5 AEs of special interest

AESIs were prospectively identified based upon the identified safety profile of amivantamab. Pre-defined AESIs per the protocol were IRRs, rash, and pneumonitis/interstitial lung disease.[118] VTE events were later identified as a risk for the amivantamab-lazertinib arm within the first four months of study treatment and were added as an AESI during the study. Ongoing studies to address these AESIs are discussed in Section B.2.10.2.

Overall, [redacted] patients ([redacted]%) in the amivantamab-lazertinib arm and [redacted] patients ([redacted]%) in the osimertinib arm had at least one AESI. As expected, all the prospectively identified AESIs, which are known to be associated with amivantamab, were reported at a higher frequency in the amivantamab-lazertinib arm than in the osimertinib arm, providing reason for the differences in incidence between treatment arms for TEAEs (specifically Grade ≥3 TEAEs) and dose modifications.[21]

Infusion-related reactions

In line with the well-established safety profile of amivantamab, IRRs were one of the most frequently occurring TEAEs in the amivantamab-lazertinib arm, reported in 265 patients (63%).[19] Most of the IRR events were Grade 1 or 2, with only 27 patients in the amivantamab-lazertinib arm (6%) experiencing Grade 3 IRR and [redacted] patients experiencing a Grade 4 IRR ([redacted]%).[19] No patients experienced a Grade 5 IRR.[21]

Of those who experienced IRRs ([redacted]; [redacted] they mostly occurred early in the treatment regimen, reported in [redacted]% of patients on Cycle 1 Day 1 ([redacted]), reducing to [redacted]% of patients in Cycle ≥2 ([redacted]).[21]

Rash

Due to the on-target activity of amivantamab, lazertinib and osimertinib against the EGFR pathway, rash was commonly observed in both the amivantamab-lazertinib ([redacted]%) and osimertinib ([redacted]%) treatment arms.[21] More patients in the amivantamab-lazertinib arm experienced a Grade 3 event: [redacted]%, compared with [redacted]% of participants in the osimertinib arm.[21] No patients in either treatment arm experienced a Grade 4 or 5 rash, and serious rash TEAEs were uncommon in both the amivantamab-lazertinib and osimertinib arms ([redacted]% versus [redacted]%, respectively).[21]

Rash events leading to discontinuation of any study treatment occurred in [redacted]% of participants in the amivantamab-lazertinib arm (amivantamab discontinuation: [redacted]% patients; lazertinib discontinuation: [redacted]% patients) compared with no patients in the osimertinib arm.[21]

Pneumonitis/Interstitial Lung Disease

The incidence of pneumonitis or interstitial lung disease was similar between treatment arms, reported in [redacted] patients in the amivantamab-lazertinib arm ([redacted]%) and [redacted] patients in the osimertinib arm ([redacted]%).[21]

Venous thromboembolism

During the study, VTEs were identified as a high-risk for patients in the amivantamab-lazertinib arm, largely occurring in the first four months of treatment.[21] As such, a protocol amendment was implemented, recommending that patients in the amivantamab-lazertinib arm receive prophylactic anticoagulation for the first four months of treatment.[21] An overall summary of the AESI VTE events is provided in Table 29.[21] A higher proportion of patients in the amivantamab-lazertinib arm experienced at least one VTE event as compared with osimertinib ([redacted] versus [redacted]), but the same proportion of patients in each of these arms experienced VTEs leading to death ([redacted]).[21] Additionally, the difference in risk between the amivantamab-lazertinib arm and the osimertinib arm for VTE event onset was greatest during the first 4 months of treatment, after which the risk discordance decreased.[21]

VTE events that were symptomatic or required hospitalisation are summarised in Table 30. Overall, [redacted] ([redacted]) patients in the amivantamab-lazertinib arm required hospitalisation or prolongation of hospitalisation due to a VTE, with the main reason for hospitalisation being the initiation of anti-coagulation treatment ([redacted]%).[21] In contrast, a higher proportion of patients in the osimertinib arm required hospitalisation or prolongation of hospitalisation due to a VTE ([redacted]%), with management of symptoms representing the most common reason for hospitalisation ([redacted]).[21]

Table 29: Overall summary of TEAE VTEs (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more VTEs	[redacted]	[redacted]
VTEs leading to death[a]	[redacted]	[redacted]
Serious VTEs	[redacted]	[redacted]
VTEs leading to discontinuation of any study agent	[redacted]	[redacted]
Maximum toxicity grade		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]

Footnotes: [a] VTEs leading to death are based on AE outcome of Fatal.
Abbreviations: DCO: data cut-off; SAS: safety analysis set; TEAE: treatment-emergent adverse event; VTE: venous thromboembolism.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 37, page 136.[21]

Table 30: Patients with TEAE VTEs that required hospitalisation, of those who experienced a VTE (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (n=157)	Osimertinib (n=39)
VTEs requiring hospitalisation or prolongation of hospitalisation	[redacted]	[redacted]
Reason for hospitalisation[a]		
Initiation of anti-coagulation treatment	[redacted]	[redacted]
Management of symptoms	[redacted]	[redacted]
Required by local standard of care	[redacted]	[redacted]
Other	[redacted]	[redacted]

Footnotes: [a] Patients can be counted in more than one category.
Abbreviations: DCO: data cut-off; SAS: safety analysis set; TEAE: treatment-emergent adverse event; VTE: venous thromboembolism.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 37, page 136.[21]

Deaths

A summary of deaths that occurred at any time during the MARIPOSA trial up until the 11th August 2023 DCO in the SAS is presented in Table 31. At the DCO, a smaller proportion of patients in the amivantamab-lazertinib arm had died during the study (n=[redacted], [redacted]%) as compared with the osimertinib arm (n=[redacted], [redacted]%).[21] Progressive disease was the most frequent cause of death in both treatment arms but was more common in the osimertinib arm: [redacted] ([redacted]%) and [redacted] ([redacted]%) patients in the amivantamab-lazertinib and osimertinib arms, respectively.[21]

TEAEs leading to death in the MARIPOSA trial are summarised in Table 32.[19, 21] An in-depth review of the TEAEs in the 34 patients (8%) in the amivantamab-lazertinib arm and the 31 patients (7%) in the osimertinib arm suggested no new safety signals.[19] Of the AESIs defined in Section B.2.10.2.5, [redacted]lead to death in the amivantamab-lazertinib arm ([redacted]).[19]

Table 31: Summary of death and cause of death (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Deaths during study	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
AE	[redacted]	[redacted]
Other	[redacted]	[redacted]
Deaths within 90 days of first dose	[redacted]	[redacted]
AE	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Deaths within 30 days of last dose	[redacted]	[redacted]
AE	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Other	[redacted]	[redacted]

Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 27, page 112.[21]

Table 32: Number of patients with TEAEs leading to death by system organ class and preferred term (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more AEs leading to death	34 [redacted]	31 [redacted]
Infections and infestations		
COVID-19	1 (<1)	3 (1)
COVID-19 pneumonia	1 (<1)	0
Pneumonia	5 (1)	4 (1)
Septic shock	2 (<1)	1 (<1)
Acinetobacter sepsis	1 (<1)	0
Urosepsis	1 (<1)	0
Lower respiratory tract infection	0	1 (<1)
Pneumonia aspiration	0	1 (<1)
Respiratory tract infection	0	1 (<1)
Sepsis	0	1 (<1)
Cardiac disorders		
Myocardial infarction	3 (1)[a]	0
Arteriosclerosis coronary artery	1 (<1)	0
Cardiopulmonary failure	1 (<1)	0
Coronary artery disease	1 (<1)[b]	0
Myocardial rupture	1 (<1)	0
Pericardial effusion	1 (<1)	1 (<1)
Cardiac failure	0	1 (<1)
General disorders and administration site conditions		
Sudden death	4 (1)[c]	1 (<1)
Death	3 (1)	2 (<1)
Nervous system disorders		
Cerebral infarction	1 (<1)	0
Ischaemic cerebral infarction	1 (<1)	0
Cerebral haemorrhage	0	1 (<1)
Cerebrovascular accident	0	1 (<1)
Respiratory, thoracic and mediastinal disorders		
Respiratory failure	4 (1)	2 (<1)
Pulmonary embolism	2 (<1)	2 (<1)
Acute respiratory distress syndrome	1 (<1)	0
Pneumonitis	1 (<1)[b]	0
Dyspnoea	0	3 (1)
Haemoptysis	0	1 (<1)
Interstitial lung disease	0	2 (<1)
Pleural effusion	0	1 (<1)
Vascular disorders		
Circulatory collapse	1 (<1)	0

Metabolism and nutrition disorders		
Ketoacidosis	0	1 (<1)
Metabolic acidosis	0	1 (<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.
[a] Two events were deemed related to any study treatment by the investigator. [b] Deemed as related to any study treatment by the investigator. [c] One event was deemed related to any study treatment by the investigator.
Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 28, page 113.[21] Cho *et al.* 2024. Table S12.[19]

B.2.11 Ongoing studies

The MARIPOSA trial is ongoing, and we anticipate that the data from the final analysis will be available in approximately [redacted]. On 7th January 2025, Johnson & Johnson announced via a press release that amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in OS compared to osimertinib in the Phase 3 MARIPOSA trial.[23] With the final analysis featuring a median follow-up of [redacted] months, the mOS improvement of this chemotherapy-free combination is anticipated to exceed one year compared to osimertinib.[22, 23] The combination of amivantamab-lazertinib [redacted] in the ITT population ([redacted]).[22, 23] Only top line data are currently available from this final analysis, but Johnson & Johnson would be pleased to provide further analyses using the updated data once full data are available.

Subcutaneous amivantamab

As discussed in Table 2 in Section B.1.2, the clinical trial programme PALOMA is assessing the safety and feasibility of a SC amivantamab formulation in advanced solid malignancies, including NSCLC, with the potential to reduce treatment administration durations and address AEs associated with IV delivery of amivantamab, such as IRRs and VTEs.[26, 124] The SC formulation of amivantamab is expected to receive marketing authorisation from the MHRA between [redacted]. The programme comprises three trials:

- The Phase 1b, PALOMA clinical trial, assessing SC amivantamab for the treatment of advanced solid malignancies following progression on current SoC.[124] Of the patients enrolled (N=83), 88% had NSCLC, of whom 43% had Exon19del and 18% had Exon 21 L858R substitution mutations.[125]
- The Phase 2, open-label PALOMA-2 trial, which has eight patient cohorts aligned with both current and future indications for amivantamab (including different SC dosing schedules). Cohorts 1 and 6 of the trial include patients with NSCLC with untreated cEGFR mutations ('MARIPOSA' population) receiving 1L SC amivantamab in combination with lazertinib.[27, 126]
- The ongoing Phase 3, open-label RCT PALOMA-3, a non-inferiority study assessing the non-inferiority of pharmacokinetics, efficacy and safety of SC amivantamab versus IV amivantamab, both in combination with oral lazertinib, in patients with cEGFRm NSCLC whose disease has progressed on or after osimertinib and PBC irrespective of order.[28]

The population investigated in the PALOMA-3 trial is different than the population being investigated in the MARIPOSA trial: PALOMA-3 included patients whose disease had progressed on or after osimertinib and PBC, irrespective of order, whereas MARIPOSA recruited patients in line with the indication of interest for this appraisal (patients with untreated EGFR mutation-positive advanced NSCLC).[28] However, PALOMA-3 is a non-inferiority pharmacokinetic

study and the pharmacokinetic results are not expected to be affected by line of therapy or combinations with agents that do not affect the pharmacokinetic profile of amivantamab. In addition, the ideal clinical setting in which to identify the impact of changing amivantamab from an IV administration to a SC route of administration is one in which amivantamab is anticipated to be the major contributor to the observed anti-tumour activity. Amongst patients who have already experienced disease progression on a third-generation EGFR TKI such as osimertinib, it is unlikely that the third-generation EGFR TKI lazertinib alone would have significant activity. Therefore, the ORR in the PALOMA-3 setting more closely reflects the clinical activity of amivantamab. For these reasons, PALOMA-3 is considered the most appropriate clinical setting to demonstrate the non-inferiority of amivantamab SC versus amivantamab IV combinations.

Overall, data from the PALOMA-3 trial show that SC amivantamab is associated with a reduced incidence of AEs compared with IV amivantamab, particularly those related to IV delivery, such as chills (6% versus 14%) nausea (3% versus 20%) and vomiting (2% versus 15%).[28] SC amivantamab was associated with a five-fold reduction in the incidence of IRRs compared with IV amivantamab (13% versus 66%, respectively) and these events were primarily mild in nature (0.5% versus 4%, respectively, were Grade ≥3).[28] Additionally, SC amivantamab was associated with a reduced incidence of VTEs compared with the IV formulation (9% versus 14%, respectively).[28]

The incidence of dose reductions, interruptions and discontinuations with SC amivantamab was generally consistent with the rates observed with IV amivantamab; however, notably no patients receiving SC amivantamab reported treatment discontinuation due to IRRs, whilst this was reported in 2% of patients in the IV treatment arm.[28] In addition to the differences in the incidence and severity of AEs, the SC formulation demonstrated non-inferior pharmacokinetics and ORR, led to numerically longer median DOR (11.2 months versus 8.3 months) and PFS (6.1 months versus 4.3 months), and displayed a significant improvement in OS (HR: 0.62; nominal p=0.02), compared with the IV formulation.[28] The generalisability of the PALOMA-3 data to the population of interest to this submission is supported by preliminary results from Cohorts 1 and 6 of PALOMA-2, which demonstrated that SC amivantamab in combination with lazertinib had a similar response rate to historic IV amivantamab in combination with lazertinib in 1L cEFGRm advanced NSCLC, with an improved safety profile.[27]

From an administrative perspective, the results of the PALOMA-3 trial indicate that the SC formulation reduced the administration time of amivantamab compared with IV, with median administration times of 4.8 minutes (range: 0, 18) versus 5.0 hours (range: 0.2, 9.9), respectively.[28] By cycle 3, patient satisfaction, measured through the Therapy Administration Satisfaction Questionnaire (TASQ), was higher with SC administration compared to IV for a range of domains including patient convenience, psychological impact, and overall treatment satisfaction. Furthermore, a significantly higher number of patients expressed satisfaction with SC administration, with 85% of patients preferring SC amivantamab compared to 35% with IV administration (reported at the end of treatment; p<0.001).[28]

Maintenance of adverse events

In addition to the PALOMA trial programme, the ongoing SKIPPirr and COCOON studies are proactively assessing the prophylactic management of AEs associated with IV amivantamab.[127] [128]

The SKIPPirr trial is a Phase 2, open label trial investigating the use of premedication to reduce IRRs associated with IV amivantamab.[127] The study enrolled patients with EGFR exon19 deletion

or L858R-mutated advanced or metastatic NSCLC whose disease progressed on prior osimertinib and PBC. Preliminary data suggests that prophylaxis with 8 mg oral dexamethasone results in a meaningful reduction in the incidence of IRRs and is an effective strategy to reduce IRRs.[129]

Enhanced dermatologic care to reduce rash and paronychia is being proactively evaluated in the ongoing phase II COCOON trial (NCT06120140). This trial aims to evaluate the impact of enhanced versus standard dermatologic management on the incidence of dermatological AEs among patients with cEGFRm advanced or metastatic NSCLC receiving first line IV amivantamab in combination with lazertinib (MARIPOSA population). The estimated primary study completion is in [redacted].[128]

Summary of ongoing studies

There is an ongoing effort to explore ways in which patient safety can be improved and effective management strategies implemented to ensure the best experience for patients during treatment with amivantamab-lazertinib. Based on these ongoing studies, it is anticipated that the majority of the tolerability concerns will be effectively mitigated.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal findings from the clinical evidence base

Patients with cEGFRm advanced NSCLC face an urgent unmet need for a more efficacious, targeted treatment that can improve the therapeutic value for patients at 1L, by delaying progression and improving survival, compared with osimertinib which is current SoC

In the management of advanced cEGFRm NSCLC, it is important for patients to receive the most effective treatment possible as their 1L therapy, due to their poor prognosis and limited 2L treatment options. Patients treated with 1L osimertinib typically progress in less than two years (approximately 17 to 19 months) based on RCT data;[21, 71] furthermore, at least a quarter of the patients receiving 1L osimertinib die before receiving 2L treatment in the real-world setting (further described in Section B.1.3.2).[11, 130] Importantly, although osimertinib provides initial disease control and is considered the SoC for patients with cEGFRm NSCLC in the UK, almost all patients treated with 1L osimertinib experience primary or secondary resistance, with the most common mechanisms of resistance to osimertinib related to alterations in the EGFR and MET pathways.[11, 104] Following disease progression due to primary or acquired resistance, 2L treatment options after progression on osimertinib are currently limited, consisting of non-targeted, non-specific treatments that result in poor prognosis for these patients at 2L, with some patients also not considered fit for systemic therapy.[7, 12-15, 32]

The UK-based NCRAS database analysis conducted by Johnson & Johnson showed that patients receiving osimertinib monotherapy have poor survival outcomes in both the 'MARIPOSA-like' (mOS: 28.1 months; 95% CI: 23.0, 35.7; n=126) and 'MARIPOSA-expanded' (mOS: 26.2 months; 95% CI: 22.0, 30.0; n=278) cohorts.[10] Of the 'MARIPOSA-expanded' cohort who received osimertinib monotherapy in 1L, 61.2% (170/278) did not receive a subsequent line of therapy after progression on 1L osimertinib.[10] Of those that did receive subsequent therapy, the median TTNT was 13.0 months (95% CI: 11.5, 14.5) , which is broadly comparable to the value reported in the European database study conducted by Pérol *et al.* (11.5 months).[10, 11] The most common subsequent treatment in this cohort were platinum-based chemotherapy regimens

(carboplatin or cisplatin combination therapy; 41/108; 38.0%) and osimertinib (37/108; 34.33%), highlighting the current lack of targeted treatment options following progression on 1L osimertinib. These data suggest that, despite osimertinib being available 1L as SoC for patients with cEGFRm NSCLC in the UK, response with osimertinib is not sustained. As the primary mechanism of osimertinib resistance is due to alterations in the EGFR and MET pathways, a targeted therapy with activity against both EGFR and MET would be particularly beneficial in this setting.[16]

UK market research conducted by Johnson & Johnson has also demonstrated that NSCLC and/or its treatment had varied physical and mental health effects on patients with cEGFRm NSCLC and their caregivers, negatively impacting QoL.[17] Compared with similar patients with no disease progression, patients with progressive cEGFRm NSCLC experience a greater impairment in mobility, self-care, usual activities, anxiety and depression, as well as pain and discomfort, highlighting the notable humanistic burden associated with the disease and its progression.[18]

There is, therefore, a clear unmet need for a more efficacious, chemotherapy-free and targeted combination therapy that improves PFS and OS and maintains QoL, while minimising the risk of treatment resistance for patients with cEGFRm NSCLC.

Amivantamab-lazertinib is a more efficacious treatment for these patients versus osimertinib, the current SoC in UK clinical practice

The MARIPOSA registrational trial represents the main body of evidence for amivantamab-lazertinib as a treatment for adult patients with untreated advanced cEGFRm NSCLC. In the Phase 3 MARIPOSA trial, patients were randomised 2:2:1 to receive amivantamab-lazertinib, osimertinib, or lazertinib, with efficacy and safety endpoints compared between the three treatment arms.

The MARIPOSA trial demonstrated the ability of amivantamab-lazertinib to improve survival outcomes for patients by meeting its primary endpoint: PFS by BICR. After a median follow-up of 22.0 months (11th August 2023 DCO), a statistically significant ($p<0.001$) and clinically meaningful improvement in PFS was observed, translating to a 30% reduction in the risk of disease progression or death in patients receiving amivantamab-lazertinib compared with those receiving osimertinib (HR: 0.70; 95% CI: 0.58, 0.85).[19, 21, 121]

The key secondary endpoints from the MARIPOSA trial provide strong supporting evidence of the superiority of amivantamab-lazertinib versus osimertinib:

- At the 13th May 2024 DCO, mOS was not reached in the amivantamab-lazertinib arm, but there was a strong trend towards improvement in OS in the amivantamab-lazertinib arm compared with the osimertinib arm (HR: 0.77; 95% CI: 0.61, 0.96; p=0.019), with 61% of patients alive at 3 years versus 53%.[24]
- At the 13th May 2024 DCO, the ORR was [redacted]% in the amivantamab-lazertinib arm and [redacted]% in the osimertinib arm, yielding an odds ratio of [redacted] (95% CI: [redacted]; [redacted]). Of note, a [redacted] proportion of patients in the amivantamab-lazertinib arm achieved a CR ([redacted]%) compared with the osimertinib arm ([redacted]%). Additionally, there were [redacted] patients in the amivantamab-lazertinib arm with PD compared with the osimertinib arm ([redacted]% and [redacted]%, respectively).[95]

- The median DOR was prolonged in the amivantamab-lazertinib arm; [redacted] months (95% CI: [redacted]), compared with [redacted] months (95% CI: [redacted]) in the osimertinib arm.[95]
- Median TTSP remained not estimable in the amivantamab-lazertinib arm, compared with [redacted] months in the osimertinib arm, representing a statistically significant reduction in risk of symptomatic progression or death compared with participants in the osimertinib arm (HR: [redacted]; 95% CI: [redacted], nominal p=[redacted]).[95]

In addition to increasing time to disease progression, subsequent progression, or death, receipt of amivantamab-lazertinib at first line additionally confers a benefit in extending patients' receipt of subsequent therapy and delaying subsequent progression. Median time to initiation of any subsequent anti-cancer therapy was 30.0 months in the amivantamab-lazertinib arm (95% CI: [redacted]) compared with 24.0 months in the osimertinib arm (95% CI: [redacted]).[24] In alignment with this, the majority of patients in the amivantamab-lazertinib arm had not experienced progression after first subsequent therapy at 36 months (event-free rate: 0.57) whereas more than half of patients in the osimertinib arm had experienced progression after first subsequent therapy by this timepoint (event-free rate: 0.49).[24]

Furthermore, a press release shared by Johnson & Johnson earlier this month communicated that with a longer duration of follow-up, amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in overall survival compared to osimertinib in the phase 3 MARIPOSA trial.[23]

Overall, amivantamab-lazertinib has been shown to significantly improve PFS and OS as well as achieve a more durable response compared with osimertinib. This enables patients to maintain their level of HRQoL for a longer period of time.

The key primary and secondary efficacy outcomes for the osimertinib monotherapy arm in MARIPOSA are in line with the data reported for the osimertinib monotherapy arms in the FLAURA trial.[34, 71] After a median follow-up of [redacted] months across both treatment arms, the mOS for patients receiving osimertinib monotherapy in the MARIPOSA trial was 37.3 months, compared to 38.6 months after a median follow-up of 35.8 months in the FLAURA trial.[24, 34, 95] Similarly, the osimertinib arm of the MARIPOSA trial and the osimertinib arm of the FLAURA trial showed similar mPFS (16.6 months vs 18.9 months, respectively), DOR ([redacted] months vs 17.2 months, respectively) and ORR ([redacted] vs 80%, respectively).[19, 71, 95]

A broadly consistent benefit in PFS was observed across all pre-specified subgroups with amivantamab-lazertinib. In particular, the same statistically significant benefit of amivantamab-lazertinib versus osimertinib (HR: 0.69) was seen in the subgroup of patients with a history of brain metastases (95% CI: 0.53–0.92) as those without (95% CI: 0.53–0.89). A survival benefit, as indicated by HRs <1, was additionally observed for amivantamab-lazertinib in subgroups of race and EGFR mutation type.[19]

Impacts on EQ-5D-5L utility scores at the start of Q2W dosing and end of treatment time points were comparable between the amivantamab-lazertinib and osimertinib arms, indicating that amivantamab-lazertinib has a similar impact on the HRQoL of patients as osimertinib.[114]

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

Overall, amivantamab-lazertinib was shown to be manageable, with the safety profiles consistent with each individual treatment component. Grade 3 or higher TEAEs were observed with a higher

incidence in the amivantamab-lazertinib arm (316/421, 75%) compared with the osimertinib arm (183/428, 43%), primarily driven by the incidence of Grade 3 TEAEs ([redacted]% and [redacted]%, respectively).[19, 21] In both arms, Grade 3 or higher TEAEs were mostly consistent with the on-target activity of amivantamab, lazertinib and osimertinib against the EGFR pathway (rash/dermatitis acneiform, stomatitis, and paronychia) and of amivantamab against the MET pathway (hypoalbuminemia and peripheral oedema).[21] Fewer patients discontinued all study treatment due to an AE in the amivantamab-lazertinib arm (86/421, 20%) than the osimertinib arm (50/428, 12%).[19] Overall, TEAEs were manageable in both treatment arms with treatment interruptions, dose reductions and BSC.

Additional ongoing studies are exploring the incidence and impact of AEs associated with IV amivantamab, evidencing that they can be managed through SC administration (PALOMA) and prophylactic medicine administration (SKIPPirr and COCOON) (see Section B.2.10.2).[25, 27, 28, 128, 129]

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, MARIPOSA, as the primary evidence source for amivantamab-lazertinib in the population of interest to this submission: first-line treatment of adult patients with advanced NSCLC with EGFR exon19del or exon 21 L858R substitution mutations. The results of the quality assessment of the MARIPOSA 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 MARIPOSA trial considered a wide range of endpoints (PFS, OS, ORR, DOR, TTST, PFS2, TTSP and TTD) that are clinically relevant to patients with untreated cEGFRm advanced NSCLC and reflect outcomes assessed in prior appraisals of therapies within both EGFR mutation-positive and wild-type advanced NSCLC.[131, 132]

Limitations

The baseline characteristics of patients in the MARIPOSA trial report that [redacted] of patients overall were of Asian ethnicity which is higher than the proportion amongst patients receiving osimertinib monotherapy in the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts of the NCRAS database (12/126 [9.5%] and 26/278 [9.4%], respectively).[10, 21] This suggests that the trial may overrepresent the proportion of patients of Asian ethnicity that would be observed in UK clinical practice.[90] This was validated by clinicians during the October 2024 advisory board, who noted that the ethnicity data from the NCRAS database is more aligned with the proportions seen in clinical practice.[32] However, the clinicians further confirmed that the baseline characteristics observed in the MARIPOSA trial are broadly generalisable to the patient population and that any differences in baseline characteristics are not expected to affect the impression of the trial outcomes. Additionally, this proportion is broadly in line with previous NICE appraisals in this patient population, the key clinical trials for which enrolled 62–64% of patients of Asian ethnicity.[8, 29] Of note, the proportion of patients of Asian ethnicity in the MARIPOSA trial is lower than the proportion enrolled in the key clinical trial of the ongoing appraisal for osimertinib in combination with pemetrexed and PBC for untreated EGFR mutation-positive advanced NSCLC (ID6328),

(n=355/557; 63.7%).[29] This proportion has not been raised as a key concern by the EAG or NICE Committee.[29]

In addition, mOS had been reached in the osimertinib treatment arm at the 13th May 2024 DCO, but had not been reached in the amivantamab-lazertinib arm. This is reflective of the greater proportion of patients remaining alive in the amivantamab-lazertinib arm during the trial period compared to the control arm, in which mOS has been reached, and thus underscores the superior efficacy of amivantamab-lazertinib as compared with osimertinib. After a slight imbalance in deaths during the first year of the study, the KM plot demonstrates a strong trend towards improved survival in the amivantamab-lazertinib arm (Figure 12). Surrogate efficacy endpoints, such as PFS (Section B.2.6.1) and PFS2 (Section B.2.6.5), support the survival benefit expected for patients receiving amivantamab-lazertinib versus osimertinib. Available OS data from the MARIPOSA trial are relatively mature at the latest data cut, but full final OS data from the MARIPOSA trial are expected in approximately [redacted]. As noted above, only top-line data are currently available from this final analysis, but the mOS improvement of this chemotherapy-free combination is anticipated to exceed one year compared to osimertinib,[23] and Johnson & Johnson would be pleased to provide further analyses using the updated data once full data are available.

Conclusions

The registrational Phase 3 MARIPOSA trial demonstrated that amivantamab-lazertinib improves survival, achieves higher, more durable response rates and prolongs the time until disease progression compared with osimertinib in adult patients with cEGFRm advanced NSCLC.

The MARIPOSA trial met its primary endpoint, given amivantamab-lazertinib demonstrated a statistically significant and clinically meaningful improvement in BICR-assessed mPFS over osimertinib (23.7 months versus 16.6 months, HR: 0.70; 95% CI: 0.58, 0.85, p<0.001).[19]

Furthermore, amivantamab-lazertinib has a tolerable and manageable safety profile, with the safety profiles consistent with the individual treatment components. Ongoing studies have shown that the incidence and impact of AEs associated with IV amivantamab can be reduced through SC administration (PALOMA trial programme) and prophylactic medicine administration (SKIPPirr and COCOON) (see Section B.2.10.2).[25, 27, 28, 128, 129]

The data available for amivantamab-lazertinib provide strong evidence supporting its efficacy in patients with cEGFRm advanced NSCLC, and ability to maintain patients' HRQoL for longer through prolonging PFS, TTSP and PFS2, compared with osimertinib.

In conclusion, amivantamab-lazertinib fulfils a substantial unmet need for an alternative, more efficacious targeted treatment that can improve therapeutic value at 1L, by providing a chemotherapy-free and targeted combination therapy that can delay subsequent progression and improve survival at 1L compared with the current SoC in patients with cEGFRm advanced NSCLC.

B.3 Cost effectiveness

A de novo economic model assessed the cost-effectiveness of amivantamab-lazertinib versus osimertinib monotherapy, the current SoC in UK clinical practice for untreated cEGFRm advanced NSCLC

- The model adopted a partitioned survival model (PSM) approach with three health states: progression-free, progressed disease, and death. The analysis was conducted from the perspective of the NHS and Personal Social Services Research Unit (PSSRU) over a 30-year lifetime horizon.
- Efficacy for amivantamab-lazertinib and osimertinib arms were informed by the Phase III MARIPOSA trial (Section B.2.6). Clinical efficacy parameters used in the model included PFS, OS and TTD.
- Health state utility values (HSUVs) for each health state were derived from EQ-5D-5L data from the MARIPOSA trial, converted to EQ-5D-3L using the method supported by Hernández Alava et al. (2020).[133]
- Costs included in the model included drug acquisition and administration costs, follow-up and monitoring costs, AE management costs, co-medication costs and end-of-life costs.

Model results indicate that amivantamab-lazertinib is a cost-effective treatment option versus osimertinib for treating patients with untreated cEGFRm advanced NSCLC

- With the confidential PAS discount of [redacted] for amivantamab and [redacted] for lazertinib, amivantamab-lazertinib dominated osimertinib at its list price in the probabilistic base case.
- All scenario analyses, which explored key modelling assumptions and approaches, resulted in amivantamab-lazertinib (PAS price) remaining a cost-effective use of NHS resources, demonstrating the robustness of the economic model results.
- Therefore, amivantamab-lazertinib represents a cost-effective treatment option versus osimertinib, offering value for money for the NHS.

Amivantamab-lazertinib represents a highly efficacious and cost-effective treatment for patients with untreated cEGFRm advanced NSCLC, which is anticipated to displace osimertinib and provide more second and later line treatment options by reducing treatment resistance

- Patients with cEGFRm NSCLC in the UK remain underserved and in need of access to more 1L treatment options that also provide more second and later line treatment options through reducing the risk of treatment resistance.
- An urgent unmet need exists for a more efficacious, targeted treatment that can improve therapeutic value upfront to delay progression and improve survival at 1L in patients with untreated, advanced cEGFRm NSCLC.
- The introduction of amivantamab-lazertinib into UK clinical practice is anticipated to fulfil this unmet need by reducing the risk of treatment resistance, thereby delaying progression to 2L treatment, improving survival outcomes and improving overall QoL.

B.3.1 Published cost-effectiveness studies

A *de novo* economic SLR was conducted in May 2020 and subsequently updated in July 2022, September 2023, March 2024, July 2024 and October 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 NSCLC with either cEGFR or EGFR Exon20 insertion mutations. The economic evaluation

stream of the economic SLR included all patients with EGFR mutations and was not limited to the cEGFRm NSCLC population, to ensure all potentially useful evidence was captured. 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.

In total, across the original and SLR updates, 57 economic evaluations, reporting on 53 unique studies, were included. Full details of the cost-effectiveness SLR methods and results, including search terms and eligibility criteria, can be found in Appendix G.

B.3.2 Economic analysis

None of the CEMs identified in the SLR were found to be relevant for investigating amivantamab-lazertinib for the 1L treatment of cEGFRm advanced NSCLC 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-lazertinib compared with relevant therapies used in the UK to treat adult patients with untreated advanced cEGFRm NSCLC. As noted in Section B.1.3.2, the current SoC for this population is osimertinib monotherapy and, as such, osimertinib monotherapy was modelled as the sole key comparator in this evaluation (see Section B.3.2.3).

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 MARIPOSA trial was 62.3 years at the initiation of treatment, and since this disease is generally associated with a poor prognosis.[21, 90] 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 the CEM was adult patients with advanced NSCLC with cEGFR mutations in the 1L setting. As outlined in the decision problem in Table 1, Section B.1.1, this population is in line with the anticipated marketing authorisation for amivantamab-lazertinib, and with the population within the MARIPOSA trial. The baseline characteristics of modelled patients are presented in Section B.3.3.1.

The patient population considered in the model was informed by the FAS of the MARIPOSA trial. As the trial met its primary endpoint of PFS by BICR and demonstrated broadly consistent benefit for amivantamab-lazertinib versus osimertinib monotherapy across all pre-specified subgroups (see Section B.2.7), no subgroup analyses were considered in the economic analysis.

B.3.2.2 Model structure

A *de novo* CEM was built in Microsoft Excel® to conduct a cost-utility analysis of amivantamab-lazertinib 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).[134]

Partitioned survival model

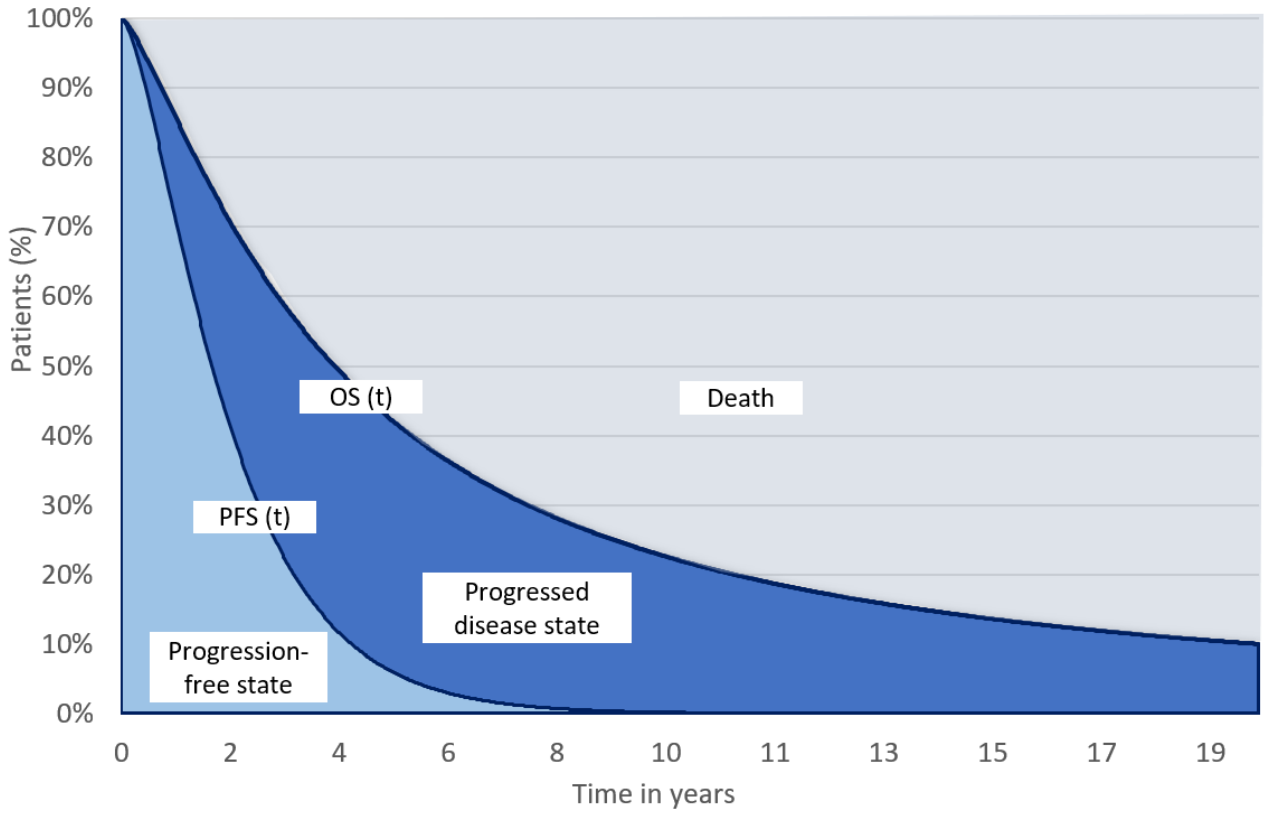
The CEM used a PSM approach to track the costs and health outcomes of the modelled cohort from initiation of 1L treatment until the end of the time horizon. This is in line with the approach taken in previous appraisals on TKIs for cEGFRm NSCLC, including the NICE appraisals of osimertinib monotherapy in untreated EGFR mutation-positive NSCLC (TA654) and of dacomitinib monotherapy for untreated EGFR mutation-positive NSCLC (TA595).[8, 135] This is further aligned with the Company-submitted model in the ongoing NICE appraisal of osimertinib with chemotherapy in untreated EGFR mutation-positive advanced NSCLC (ID6328), noted to be considered appropriate by the Committee in the published draft guidance.[29]

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.

The PSM directly utilised treatment specific projections for PFS and OS to allocate patients into their respective health states, as shown in Figure 22. PFS and OS were modelled independently and the percentage of patients in each health state at any given time was estimated using an area under the curve (AUC) approach. The proportion of patients in the progression-free state was estimated by the difference between zero (the x-axis) and the BICR-assessed PFS survival function. The proportion of patients in the post-progression state at any given timepoint was estimated by taking the difference between the OS and PFS survival functions at that timepoint. The proportion of patients who were dead in each model cycle was estimated by one minus estimated survival.

TTD data were used to accurately model the associated costs for amivantamab-lazertinib and osimertinib over the time horizon. TTD from the MARIPOSA trial was defined as the time from the date of randomisation to discontinuation of treatment for any reason, and thus may capture clinical benefit for participants who continued treatment beyond disease progression. TTD of individuals with ongoing treatment at the DCO were censored at the time of last treatment exposure.

Figure 22: Partitioned survival AUC approach



Abbreviations: AUC: area under the curve; OS: overall survival; PFS: progression-free survival.

Features of the *de novo* CEM

The analysis was conducted from the perspective of the NHS and PSS, with only direct costs and benefits considered. The time horizon for the base case was 30 years, which was considered sufficient to capture the lifetime of the targeted population, given the mean starting age of patients in the model (62.3 years, as per the population in the MARIPOSA trial) and their poor prognosis. However, a time horizon of 37.7 years, which results in a mean average age at the end of the time horizon of 100 years, was explored in a scenario analysis (see Section B.3.11.3).

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.[136] 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 33, as compared to the relevant previous NICE evaluation of osimertinib monotherapy for cEGFRm advanced NSCLC (TA654).[8]

Table 33: Features of the economic analysis

Factor	Previous evaluation	Current evaluation	
	TA654	Chosen values	Justification
Model structure	PSM	PSM	The model structure is in line with previous appraisals.
Time horizon	20 years	30 years	As per NICE guidelines, the model horizon should be sufficiently long to capture all important differences in costs or outcomes between the technologies being compared.[137] As the mean cohort starting age was 62.3 years in the model, 30 years was considered to be the maximum time required for a lifetime analysis, as the vast majority of modelled patients would die within this time frame.
Cycle length	30 days	1 week	A more granular cycle length allows the capture of varied dosing schedule of intervention arm cycles.
Discount	3.5%	3.5%	As per NICE reference case[137]
Health effects measure	QALYs	QALYs	As per NICE reference case[137]
Perspective	NHS/PSS	NHS/PSS	As per NICE reference case[137]
Source of health state utilities	FLAURA. EORTC QLQ-C30 outcomes were mapped to EQ-5D-3L values.	MARIPOSA	MARIPOSA is the relevant pivotal trial for amivantamab-lazertinib in this indication so represents the most recent source of utility data for in this indication. EQ-5D-5L data are available from the MARIPOSA trial and, as such, were used to inform the health state utility values considered within the model. EQ-5D-5L results were mapped to EQ-5D-3L using the method supported by Hernández Alava *et al.* (2020), in line with the NICE reference case.[133, 137] See Section B.3.4 for more information.
Source of costs	PSSRU, NHS reference costs, British National Formulary (BNF), electronic market information tool (eMIT).	PSSRU, NHS reference costs, BNF, and eMIT are used.	As per NICE reference case[137]

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.

B.3.2.3 Intervention technology and comparators

Intervention

The intervention considered in the CEM for this submission was amivantamab-lazertinib. The dosing for amivantamab included in the model was in line with the regimen included in the Phase 3 MARIPOSA trial and the SmPC for amivantamab; amivantamab (body weight at baseline <80 kg: 1,050 mg; body weight at baseline ≥80 kg: 1,400 mg) was administered via IV infusion once weekly for four weeks, then once every two weeks, in combination with lazertinib oral tablets (240 mg) QD.[1]

Comparator

The CEM compares amivantamab (IV) in combination with lazertinib with osimertinib monotherapy, as informed by the MARIPOSA trial.

The dosing regimen for osimertinib used to inform the model was osimertinib oral tablets (80 mg) QD, in line with the regimen included in the osimertinib SmPC and the Phase 3 MARIPOSA trial.[138]

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 FAS population of the MARIPOSA trial, as presented in Table 34.

Table 34: Baseline characteristics of modelled cohort

Characteristic	Base case value
Mean age, years (SD)	62.3[redacted]
Female, %	61.3
Mean weight, kg (SD)	[redacted]
Patients <80 kg, %	86.7

Abbreviations: BSA: body surface area; SD: standard deviation.
Source: Cho *et al.* (2024).[19] Johnson & Johnson MARIPOSA CSR 2023.[21]

B.3.3.2 Survival inputs and assumptions

The key efficacy inputs in the model were PFS, OS and TTD.

Efficacy data for amivantamab-lazertinib and osimertinib were informed by the Phase 3 MARIPOSA trial, using the most recent DCO available for each endpoint: PFS data for both treatment arms were informed by the 11th August 2023 DCO (median trial follow-up of 22 months across all three treatment arms of the MARIPOSA trial) and OS and TTD for both treatment arms were informed by the 13th May 2024 DCO (median trial follow-up of 31.1 months).

Approach to curve selection

Clinical outcomes for amivantamab-lazertinib and osimertinib were modelled using parametric survival analysis. Parametric survival analysis methods were explored for their ability to handle censored observations and accommodate the skewed distributions of time-to-event variables. A series of statistical distributions were fitted to the MARIPOSA PFS, OS, and TTD data. The

distributions that were considered in the fitting process included the exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma distributions.

The proportional hazard assumption was tested for all efficacy endpoints informing the model and were suggestive of non-proportional OS hazards, therefore parametric distributions were fitted separately to the amivantamab-lazertinib and osimertinib arms (the log-log plots for amivantamab-lazertinib and osimertinib PFS and OS are presented in Appendix N.1). The analytical process consisted of testing various potential statistical distributions and assessing fit over the observed data period and beyond to ensure reliable projection for PFS, OS, and TTD. The process of selecting a best fitting distribution was in line with NICE decision support unit (DSU) guidance on the analysis of survival outcomes for economic evaluations alongside clinical trials and involved both statistical and clinical considerations, as well as considerations based on the observed data in assessing goodness of fit and plausibility of results.[139, 140]

1. **Visual inspection**: For each endpoint, the visual fit of the parametric models considered (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalised gamma) to the KM curves, and the smoothed hazard plots, were evaluated.

2. **Statistical criteria**: The Akaike information criterion (AIC) and Bayesian information criterion (BIC) provide a measure of relative quality of a model for the data, with lower values indicating a better model. For each distribution, the AIC and BIC values were compared and used to help determine the best model for the observed data (note that these criteria only assess models over the observed trial period, and not the extrapolation period).

3. **Assessment of clinical plausibility and face validity**: Clinical judgment of the plausibility of extrapolations of the models beyond the observed period based on examination of the long-term predictions of the model (in terms of estimated median and mean), in addition to the smoothed hazard plots, were sought at an advisory board. Expert opinion of clinical plausibility was considered in the selection of an appropriate model.[32] In addition, the crossing of the PFS curve or the TTD curve with the OS curve was considered implausible, so avoidance of this represented an additional consideration in the selection of appropriate distributions. The PFS and TTD extrapolations were capped by OS to prevent crossing in at late time points, by which point all curves were at very low values. Additionally, to ensure plausible mortality rates were predicted at old age, PFS, OS, and TTD rates used in the model were bound by the age- and sex-specific mortality of the general population as a minimum (calculated using England and Wales life tables, 2020–2022).[141]

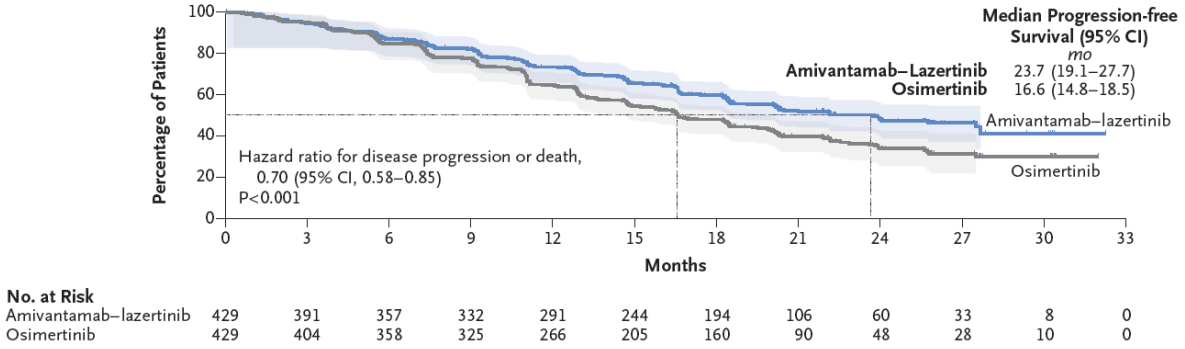
4. **Smoothed hazard plots:** Smoothed hazard plots served as a valuable diagnostic tool when selecting the appropriate parametric model for survival data used in the model. Smoothening of the hazard function allows for better visualisation of the hazard rate over time and enables a comparison of hazard functions across various parametric distributions. Furthermore, an important additional benefit of examining smoothed hazard plots is to compare hazard functions of each curve with clinical expectations for hazards over time.

B.3.3.2.1 PFS

Base case: PFS by BICR

PFS by BICR was the primary endpoint from the MARIPOSA trial. The KM curves for PFS by BICR in the amivantamab-lazertinib and osimertinib arms (11th August 2023 DCO, median FU of 22 months across all three treatment arms of the MARIPOSA trial) are shown in Figure 23. BICR and IRC (independent review committee) are used interchangeably and describe the same approach.

Figure 23: MARIPOSA PFS (BICR) KM curves for amivantamab-lazertinib and osimertinib (11th August 2023 DCO; FAS)



Abbreviations: A+L: amivantamab-lazertinib; BICR: blinded independent central review; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib; PFS: progression-free survival.
Source: Cho *et al.* 2024. Figure 1A.[19]

Amivantamab-lazertinib

The long-term PFS (BICR) extrapolations for amivantamab-lazertinib are presented in Figure 24, and the smoothed hazard plot is presented in Figure 25. Table 35 presents AIC, BIC, 5- and 10-year PFS, and mPFS outcomes for each distribution. Additionally, the mid-point of the estimates for PFS at 4, 6 and 8 years for amivantamab-lazertinib from clinicians consulted during the Johnson and Johnson-led advisory board in October 2024 are presented in Table 36.

Figure 24: Long-term PFS (BICR) projections of amivantamab-lazertinib

[redacted]

Abbreviations: BICR: blinded independent central review; IRC: independent review committee; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 25: Smoothed hazard plot with parametric extrapolations for amivantamab-lazertinib for PFS (BICR)

Abbreviations: BICR: blinded independent central review; IRC: independent review committee; PFS: progression-free survival.

Table 35: PFS (BICR) individual fits for amivantamab-lazertinib

Distribution	AIC	BIC	5-year PFS	10-year PFS	Median PFS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BICR: blinded independent central review; PFS: progression-free survival.

Table 36: Summary of clinician PFS estimates at 4, 6 and 8 years for amivantamab-lazertinib

Timepoint	Clinician estimate (mid-point), %
4 years	[redacted]
6 years	[redacted]
8 years	[redacted]

Footnote: The mid-point was defined as halfway between the upper and lower estimates provided by clinicians.
Abbreviations: PFS: progression-free survival.

In the MARIPOSA advisory board meeting (October 2024) the Gamma and Log-logistic curves were suggested as plausible by the health economists who attended. Both of the curves selected were less optimistic than the clinician estimates, and both curves had similar AIC and BIC scores. While the Log-logistic curve had a slightly higher AIC and BIC than the Gamma curve, the Log-logistic curve was selected for the base case long-term extrapolation of amivantamab PFS data on the basis that it more closely matched the clinical estimates, had a hazard function that closely resembled the observed smoothed hazard and had plausible long-term estimates.[32] The impact of using curves that resulted in lower (Gamma) and higher (Log-normal) long-term estimates of PFS was explored in scenario analyses (see Section B.3.11.3).

Osimertinib

The long-term PFS (BICR) extrapolations for osimertinib are presented in Figure 26. The smoothed hazard plot for the osimertinib arm from MARIPOSA versus the seven extrapolations explored is presented in Figure 27 below. Table 37 presents AIC, BIC, 5- and 10-year PFS, and mPFS outcomes for each distribution. Additionally, the mid-point of the estimates for PFS at 4, 6 and 8 years for osimertinib from clinicians at the advisory board are presented in Table 38.

Figure 26: Long-term PFS (BICR) projections for osimertinib

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

Figure 27: Smoothed hazard plot with parametric extrapolations for osimertinib PFS (BICR)

Abbreviations: BICR: blinded independent central review; IRC: independent review committee; PFS: progression-free survival.

Table 37: PFS (BICR) individual fits for osimertinib

Distribution	AIC	BIC	5-year PFS	10-year PFS	Median PFS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BICR: blinded independent central review; PFS: progression-free survival.

Table 38: Summary of clinician PFS estimates at 4, 6 and 8 years for osimertinib

Timepoint	Clinician estimate (mid-point), %
4 years	[redacted]
6 years	[redacted]
8 years	[redacted]

Footnote: The mid-point was defined as halfway between the upper and lower estimates provided by clinicians.
Abbreviations: PFS: progression-free survival.

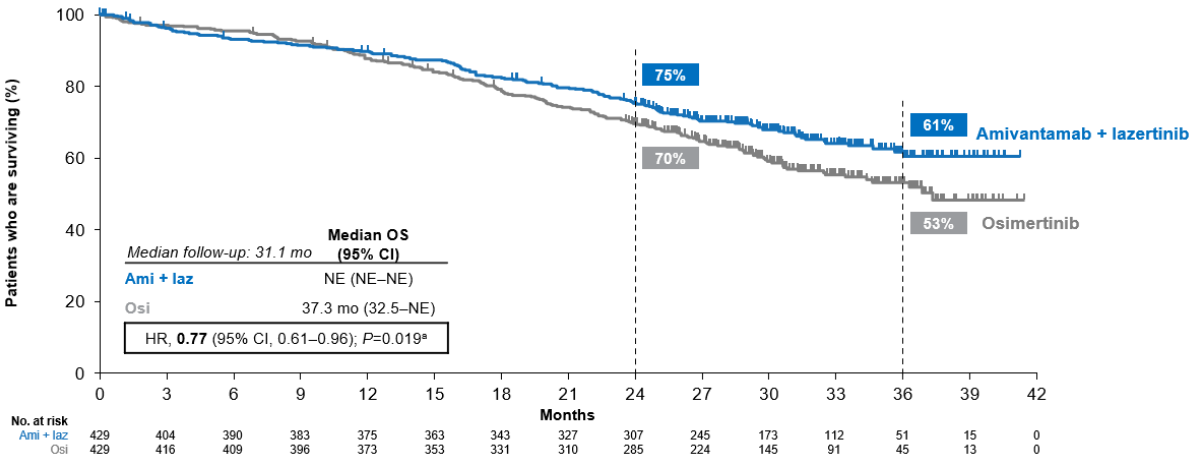
The PFS data in the model are relatively mature, given that mPFS had been reached in the MARIPOSA trial. During the MARIPOSA advisory board meeting (October 2024) a consensus was reached amongst health economists that Log-logistic was the most appropriate curve selection, given that it is most consistent with the 8 year estimates provided by the clinicians, matching hazard function and has strong biological plausibility.[32] Additionally, Log-logistic was ranked the highest in terms of statistical plausibility. Therefore, the Log-logistic curve was selected for the base case long-term extrapolation of osimertinib PFS. The impact of using curves that resulted in lower (Gamma) and higher (Log-normal) long-term estimates of PFS was explored in scenario analyses (see Section B.3.11.3).

An additional scenario analysis was performed in which PFS as assessed by INV was modelled (see Section B.3.11.3).

B.3.3.2.2 OS

In the base case, OS for amivantamab-lazertinib and for osimertinib were both modelled using data from the respective arms of the MARIPOSA trial, as presented in Section B.2.6.2. The OS KM curves for amivantamab-lazertinib and osimertinib based on the May 2024 DCO (median FU 31.1 months) are presented in Figure 28.

Figure 28: MARIPOSA OS KM curves for amivantamab-lazertinib and osimertinib (13th May 2024 DCO; FAS)



Abbreviations: A+L: amivantamab-lazertinib; FAS: full analysis set; KM: Kaplan-Meier; OS: overall survival; OSI: osimertinib.
Source: Adapted from Gadgeel *et al.* WCLC 2024.[24]

Amivantamab-lazertinib

The OS KM curve and independently fitted extrapolations for amivantamab-lazertinib are presented in Figure 29, and the smoothed hazard plots in Figure 30. Table 39 presents AIC, BIC, 5- and 10-year OS, and mOS outcomes for each distribution. Additionally, the mid-point OS estimates at 5-, 10- and 15-years for amivantamab-lazertinib from clinicians at the advisory board are presented in Table 40.

Figure 29: Long-term OS projections of amivantamab-lazertinib

Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival.

Figure 30: Smoothed hazard plot with parametric extrapolations for amivantamab-lazertinib for OS

Abbreviations: Ami: amivantamab; OS: overall survival.

Table 39: OS individual fits for amivantamab-lazertinib

Distribution	AIC	BIC	5-year OS	10-year OS	Median OS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Table 40: Summary of clinician estimates for OS at 5, 10 and 15 years for amivantamab-lazertinib

Timepoint	Clinician estimate (mid-point), %
5 years	[redacted]
10 years	[redacted]
15 years	[redacted]

Footnote: The mid-point was defined as halfway between the upper and lower estimates provided by clinicians.
Abbreviations: NR: not reported; OS: overall survival.

Long-term OS estimates provided by clinicians in the MARIPOSA advisory board (October 2024) were most closely aligned with the Weibull curve, which was also selected as the preferred curve by health economists who attended the meeting. As such, the Weibull curve was selected for the base case long-term extrapolation of amivantamab OS data.

The impact of using curves that resulted in lower (Gompertz) and higher (Gamma) long-term estimates of OS were explored in scenario analyses (see Section B.3.11.3). The Gompertz curve has been presented for completeness, but results in estimated five- and 10-year survival rates ([redacted]% and [redacted]%, respectively) which are considerably lower than the estimates provided by clinicians for these timepoints ([redacted]% and [redacted]%, respectively). As such, despite its presentation for completeness, the Gompertz curve is not considered to be an appropriate choice for the OS extrapolation of amivantamab-lazertinib as it does not represent typical outcomes in UK clinical practice.

Osimertinib

The long-term OS extrapolations for osimertinib are presented in Figure 31. The smoothed hazard plot for osimertinib OS data showing all explored parametric extrapolations is presented in Figure 32. Table 41 presents the AIC, BIC, 5- and 10-year OS, and mOS outcomes for each distribution. Additionally, the mid-point of the estimates for OS at 5-, 10- and 15-years for osimertinib from clinicians at the advisory board are presented in Table 42.

Figure 31: Long-term OS projections for osimertinib

[redacted]

Abbreviations: ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival.

Figure 32: Smoothed hazard plot with parametric extrapolations for osimertinib for OS

Abbreviations: Ami: amivantamab; OS: overall survival.

Table 41: OS individual fits for osimertinib

Distribution	AIC	BIC	5-year OS	10-year OS	Median OS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Table 42: Summary of clinician estimates for OS at 5, 10 and 15 years for osimertinib

Timepoint	Clinician estimate (mid-point), %
5 years	[redacted]
10 years	[redacted]
15 years	[redacted]

Footnote: The mid-point was defined as halfway between the upper and lower estimates provided by clinicians.
Abbreviations: NR: not reported; OS: overall survival.

The Weibull curve was selected for the base case long-term extrapolation of osimertinib OS data. This curve choice was selected as the most plausible curve in the previous NICE technology appraisal (TA654), and the use of this curve was discussed and validated by consensus amongst clinicians and health economists in the advisory board meeting.[8, 32]

The impact of using curves that resulted in lower (Gompertz) and higher (Gamma) long-term estimates of OS was explored in scenario analyses (see Section B.3.11.3). The Gompertz curve has been presented for completeness, but results in estimated five- and 10-year survival rates ([redacted]% and [redacted]%, respectively) which are considerably lower than the estimates provided by clinicians for these timepoints ([redacted]% and [redacted]%, respectively). As such, despite its presentation for completeness, the Gompertz curve is not considered to be an appropriate choice for the OS extrapolation of osimertinib as it does not represent plausible outcomes in UK clinical practice.

A separate scenario analysis was also explored in which OS data for osimertinib, available from the FLAURA trial, were used to augment the osimertinib OS data available from the MARIPOSA trial (see Section B.3.11.3).

B.3.3.2.3 TTD

In the economic model, TTD was defined as the time from the date of randomisation to discontinuation of treatment for any reason, including death. TTD models were fitted separately in the economic model for amivantamab and lazertinib in the amivantamab-lazertinib arm. This ensures that the efficiency gains and costs associated with each component of the combined therapy regimen is reflective of what is reported in the MARIPOSA trial and is representative of clinical practice. The decision to model the TTD separately was informed by clinical insights and data from the MARIPOSA CSR.[95] Figure 33 presents the TTD KM curves for amivantamab, lazertinib and osimertinib based on the May 2024 DCO.

Figure 33: MARIPOSA TTD KM curves for amivantamab-lazertinib and osimertinib (13th May 2024 DCO; FAS)

Abbreviations: AMI: amivantamab; FAS: full analysis set; KM: Kaplan-Meier; LAZ: lazertinib; OSI: osimertinib; TTD: time to treatment discontinuation or death.
Source: Adapted from Gadgeel *et al.* WCLC 2024.[24]

Figure 33 shows that the TTD associated with amivantamab is shorter on average than both lazertinib and osimertinib, despite amivantamab-lazertinib being associated with longer PFS (mPFS 23.7 months) than osimertinib (mPFS 16.6 months). This suggests more patients discontinue amivantamab for reasons other than disease progression, which can be explained by the increased toxicity of amivantamab compared with the other treatments.

Clinical insights from the advisory board meeting highlighted that the mode of action of osimertinib and lazertinib are similar, and as such, there is an expectation that patients would receive them for similar duration. However, the observed TTD is longer on average for lazertinib compared with osimertinib, which according to one of the clinicians who attended the advisory board could suggest greater efficacy given their clinical similarities.[32]

The TTD KM curve for amivantamab-lazertinib combined and osimertinib is presented in Figure 17 of Section B.2.6.7. While the combined TTD KM is not used in the economic model, these KM curves represent the key efficacy comparison in the MARIPOSA trial between the two treatment arms. This comparison demonstrates a longer median TTD for patients treated with amivantamab-lazertinib (26.3 months) than osimertinib (22.6 months) (HR: 0.80; 95% CI: 0.68, 0.96, p-value: 0.014).

Amivantamab

The long-term TTD extrapolations for amivantamab are presented in Figure 34, and the smoothed hazard plot can be found in Figure 35. Table 43 presents AIC, BIC, 5- and 10-year TTD, and median TTD outcomes for each distribution. Additionally, the mid-point of the estimates for TTD at 4, 6 and 8 years for amivantamab from clinicians at the advisory board are presented in Table 40.

Figure 34: Long-term TTD projections for amivantamab

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

Figure 35: Smoothed hazard plot with parametric extrapolations for amivantamab for TTD

Abbreviations: Ami: amivantamab; TTD: time to treatment discontinuation or death.

Table 43: TTD outcomes individual fits for amivantamab

Distribution	AIC	BIC	5-year TTD	10-year TTD	Median TTD (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Table 44: Summary of clinician estimates for TTD at 4, 6 and 8 years for amivantamab

Timepoint	Clinician estimate (mid-point), %
4 years	[redacted]
6 years	[redacted]
8 years	[redacted]

Footnote: The mid-point was defined as halfway between the upper and lower estimates provided by clinicians.
Abbreviations: NR: not reported; TTD: time to treatment discontinuation.

The exponential fit was selected for the base case long-term extrapolation of amivantamab TTD, on the basis that this curve had the lowest, and second lowest AIC and BIC values, respectively, while also being selected as the second-most preferred curve by clinicians in the MARIPOSA advisory board meeting (October 2024) and aligning closely with the clinical estimates for TTD.[32]

Using this base case curve selection, it was modelled that a proportion of patients on amivantamab discontinued treatment before experiencing disease progression. This conclusion is supported by the fact that the proportion of patients remaining on treatment with amivantamab was lower than the proportion of those who were progression-free on amivantamab-lazertinib treatment at the 5-year (9.7% versus 20.4%) and 10-year (0.9% versus 8.6%) time points.

The impact of using curves for amivantamab that resulted in lower (Generalised Gamma) and higher (Gamma) long-term estimates of TTD was explored in scenario analyses (see Section B.3.11.3).

Lazertinib

The long-term TTD extrapolations for amivantamab are presented in Figure 36, and the smoothed hazard plot can be found in Figure 37. Table 45 presents AIC, BIC, 5- and 10-year TTD, and median TTD outcomes for each distribution. Additionally, the mid-point of the estimates for TTD at 4, 6 and 8 years for lazertinib from clinicians at the advisory board are presented in Table 40.

Figure 36: Long-term TTD projections of lazertinib

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

Figure 37: Smoothed hazard plot with parametric extrapolations for lazertinib for TTD

Abbreviations: Ami: amivantamab; LAZ: lazertinib; TTD: time to treatment discontinuation or death.

Table 45: TTD outcomes individual fits for lazertinib

Distribution	AIC	BIC	5-year TTD	10-year TTD	Median TTD (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Table 46: Summary of clinician estimates for TTD at 4, 6 and 8 years for lazertinib

Timepoint	Clinician estimate (mid-point), %
4 years	[redacted]
6 years	[redacted]
8 years	[redacted]

Footnote: The mid-point was defined as halfway between the upper and lower estimates provided by clinicians.
Abbreviations: NR: not reported; TTD: time to treatment discontinuation.

The exponential fit was selected for the base case long-term extrapolation of lazertinib TTD, on the basis that this curve had the strongest statistical plausibility, while being selected as the second-most preferred curve by clinicians in the MARIPOSA advisory board meeting (October 2024) and aligning closely with the clinical estimates for TTD.[32]

With this base case curve selection, the proportion of patients receiving lazertinib who were modelled to be remaining on treatment was approximately equal to the proportion of patients receiving amivantamab-lazertinib who were progression-free at the 5-year (21.2% versus 20.4%) and lower than at the 10-year (4.5% versus 8.6%) time points.

The impact of using curves for lazertinib that resulted in lower (Weibull) and higher (Gamma) long-term estimates of TTD was explored in scenario analyses (see Section B.3.11.3).

Osimertinib

The long-term TTD extrapolations for osimertinib are presented in Figure 38, and the smoothed hazard plot can be found in Figure 39. Table 47 presents the goodness of fit, 5- and 10-year TTD, and median TTD outcomes for each distribution. Additionally, the mid-point of the estimates for TTD at 4, 6 and 8 years for osimertinib from clinicians at the advisory board are presented in Table 48.

Figure 38: Long-term TTD projections for osimertinib

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

Figure 39: Smoothed hazard plot with parametric extrapolations for osimertinib for TTD

Abbreviations: TTD: time to treatment discontinuation or death.

Table 47: TTD individual fits for osimertinib

Distribution	AIC	BIC	5-year TTD	10-year TTD	Median TTD (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Table 48: Summary of clinician estimates for TTD at 4, 6 and 8 years for osimertinib

Timepoint	Clinician estimate (mid-point), %
4 years	[redacted]
6 years	[redacted]
8 years	[redacted]

Footnotes: The mid-point was defined as halfway between the upper and lower estimates provided by clinicians.
Abbreviations: NR: not reported; TTD: time to treatment discontinuation.

The exponential fit was selected for the base case extrapolation of osimertinib TTD in the model. Given the use of osimertinib as the SoC in NHS clinical practice, the estimation of TTD for osimertinib was highlighted by clinicians in the MARIPOSA advisory board (October 2024) as being the most reliable out of the three TTD estimations. Further, two out of three of the clinicians who attended the meeting agreed that the estimates hold true to clinical practice. The

exponential curve aligned closest with the clinical estimates for patients remaining on treatment, leading to its selection as the base case. With this base case curve selection, the proportion of patients modelled to be remaining on treatment with osimertinib was slightly higher than the proportion modelled to be progression-free at 5 years ([redacted] versus [redacted], respectively) and slightly lower at 10 years ([redacted] versus [redacted], respectively). The impact of using curves for osimertinib that resulted in lower (Weibull) and higher (Gamma) long-term estimates of TTD was explored in scenario analyses (see Section B.3.11.3).

B.3.3.3 Adverse event incidence

Grade 3 or higher TEAEs were included if they occurred in ≥5% of patients in one of the modelled treatment arms, as informed by the MARIPOSA Phase 3 trial.[95] Adverse events for subsequent treatments were also considered using the same cut-off rule. Additionally, Grade ≤2 VTE was included given that this is a clinically relevant consideration for amivantamab treatment. Incidence rates and durations of AEs for 1L treatment were sourced from the MARIPOSA trial for amivantamab-lazertinib and osimertinib (Table 49).

Table 49: Incidence of AEs included in the CEM

Adverse Event	Amivantamab-lazertinib (%)	Osimertinib (%)
Dermatitis acneiform	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Hypalbuminaemia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]
Grade ≤2 VTE	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

[a] Incidence of Grade ≤2 VTE in MARIPOSA includes patients with maximum Grade 1 or 2 VTE events (i.e., patients who experienced both Grade ≤2 and Grade ≥3 VTE were not counted) to avoid double-counting.
Abbreviations: AE: adverse event; CEM: cost-effectiveness model; VTE: venous thromboembolism.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023)[21]

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. Patient utilities were calculated based on UK-specific tariffs.

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in Section B.2.3, in the MARIPOSA trial, patients completed PRO questionnaires related to their HRQoL. These included the EQ-5D-5L, EORTC QLQ-C30 and NSCLC-SAQ. For the cost-effectiveness analysis base case, utility values for the progression-free and PD health states were obtained from analysis of the MARIPOSA EQ-5D-5L data, in line with NICE's preferred measure of HRQoL.[136]

In MARIPOSA, EQ-5D-5L data were collected at C1D1, C2D1, on the first day of every other following cycle (Cycle 3, 5, 7, etc.) ±2 days, 30 days after last dose (±7 days) and every 12 weeks (±14 days) during study follow-up for 1 year (4 visits/calls).

B.3.4.2 Mapping

EQ-5D-5L utility scores were derived using UK-specific utility weights. In alignment with NICE guidelines,[136] 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 supported by Hernández Alava et al. (2020).[133]

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 cEGFRm NSCLC. The utilities stream of the economic SLR included all patients with NSCLC with any mutation status and was not limited to the cEGFRm NSCLC population, to ensure all potentially useful evidence was captured.

In the October 2024 economic SLR update, 63 articles reporting on 61 unique utility studies were identified for patients with advanced or metastatic NSCLC. Of these, ten reported utilities related to the treatment of patients with EGFRm NSCLC. Full details on the methods and results of this SLR are presented in Appendix H.

Given the MARIPOSA trial provides utility data from a patient group within the correct indication, directly comparing against osimertinib, and represents the same population that informs the efficacy data used in the model, the MARIPOSA trial represents the most relevant source of utility data.

B.3.4.4 Adverse events

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 the MARIPOSA trial, plus Grade ≤2 VTE events. The AE impact on HRQoL was considered for 1L treatment only.

A pooled AE disutility of [redacted] was derived from a repeated-measures linear mixed model from Grade 3 or higher AEs in progression-free MARIPOSA participants. In the base case, this pooled disutility was applied to each Grade 3 or higher AE. The mean cumulative AE durations in years for each event type was calculated from Grade 3 or higher TEAEs in MARIPOSA (pooled across both treatment arms), and the AE QALYs were calculated by multiplying the pooled disutility by their durations (in years) and the probability of experiencing each AE (Table 79). As Grade ≤2 VTE was also included in the model, the utility decrement was calculated separately for this AE based on the MARIPOSA trial, with the mean disutility estimate of [redacted].

Table 50: Durations and calculated QALYs for each AE

AE	Mean Cumulative Duration (Days)	AE QALYs
Dermatitis acneiform	[redacted]	[redacted]
Alanine aminotransferase increase	[redacted]	[redacted]
Hypalbuminaemia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
IRR	[redacted]	[redacted]
Rash	[redacted]	[redacted]

Pulmonary embolism	[redacted]	[redacted]
Grade ≤2 VTE	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Abbreviations: AE: adverse events; IRR: infusion-related reaction; QALY: quality-adjusted life year; VTE: venous thromboembolism.

A scenario analysis was performed in which disutilities derived from the literature were implemented (see Section B.3.11.3).

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The MARIPOSA trial represents the most appropriate source of health state utilities available, given that the utilities are obtained from the same source as the efficacy data. A mean utility per health state was calculated based on the total MARIPOSA population, combining both treatment arms. UK-specific tariffs were used to calculate health state utilities from HRQoL data collected in the MARIPOSA trial (see Section B.3.4.2). Progression-free and PD utilities were estimated separately using MMRMs, with only individuals with known progression status (i.e., not censored for PFS) included in the estimation of PD utility. Modelling utilities based on specific health states, rather than treatment specific utilities, enables the model to capture the variation in HRQoL over time to model the decline in patient HRQoL associated with increasing disease stages.

The health state utility values used in the model are presented in Table 51. The progression-free utility value implemented within the model is similar to the average age-matched general population utility of 0.822 at 64 years.[142]

Table 51: Health state utilities

Health State	Mean (SE) Utility Value
Progression-free	[redacted]
Progressed disease	[redacted]

Abbreviations: SE: standard error.

Age adjustment was applied to utilities within the model when calculating QALYs to account for the perceived loss of utility for patients as they age. The model uses using the HSE 2014 data set for age adjustment, as recommended by the NICE DSU.[142]

A scenario analysis was performed using progression-free and PD utility values informed by the EAG-preferred values in the recent NICE appraisal of osimertinib in combination with pemetrexed and PBC in the same population (see Section B.3.11.3).[29]

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 1L treatment of cEGFRm NSCLC that should be included in the model. The cost and HRU use stream of the economic SLR included all

patients with advanced NSCLC (with EGFR mutations or not otherwise stated), and was not limited to the cEGFRm NSCLC population, to ensure all potentially useful evidence was captured. Studies not reporting on populations with EGFRm were deprioritised for extraction. Full details of the SLR search strategy, study selection process, and results are presented in Appendix I.

In the October 2024 economic SLR updates, 172 articles reporting on 156 CRU studies were identified and included. A total of 76 articles reporting on 68 unique studies either exclusively focused on treatments indicated for patients with EGFR-mutated NSCLC or reported outcomes of interest separately for patients with EGFR mutations.

Costs incorporated into the cost-effectiveness analysis

The CEM was conducted from the perspective of the NHS, and therefore, only included costs which would be incurred directly by the healthcare system. Unit costs used in the model were extracted from a range of sources, including the PSSRU, NHS Reference Costs, and eMIT.

The following cost types were used in the model:

- Drug acquisition costs
- Drug administration costs
- Follow-up and monitoring costs
- Subsequent treatment costs
- AE management costs
- End-of-life costs

Indirect costs such as caregiver and sick leave were not included in the model, in alignment with the NICE reference case in the guide to the methods of Technology Appraisal.[133]

B.3.5.1 Intervention and comparators' costs and resource use

B.3.5.1.1 Drug acquisition costs

Due to the variation in dosing schedules, drug costs vary by treatment cycle and patient weight. Amivantamab-lazertinib and osimertinib are both treat to progression therapies, so the duration of therapy was based on TTD (see Section B.3.3.1).

The drug acquisition unit costs used in the model for amivantamab-lazertinib and for the comparator osimertinib are presented in Table 53. These costs were sourced from the BNF and eMIT.

The weekly drug acquisition costs for amivantamab-lazertinib and for osimertinib are presented in Table 53 and Table 52, respectively

Table 52: Drug acquisition unit costs

Treatment	Administration route	Dose (mg)	Units per pack	Price per pack (£)	Cost per unit (£)	Source

Amivantamab (list price)	IV	350	1	1,079.00	1,079.00	BNF, Rybrevant[143]
Amivantamab (PAS price)	IV	350	1	[redacted]	[redacted]	BNF, Rybrevant; [144] J&J Data on File
Lazertinib (list price)	Oral	240	28	[redacted]	[redacted]	J&J Data on File
Lazertinib (list price)	Oral	80	56	[redacted]	[redacted]	J&J Data on File
Lazertinib (PAS price)	Oral	240	28	[redacted]	[redacted]	J&J Data on File
Lazertinib (PAS price)	Oral	80	56	[redacted]	[redacted]	J&J Data on File
Osimertinib	Oral	80	30	5,770.00	192.33	BNF, Tagrisso[144]
Osimertinib	Oral	40	30	5,770.00	192.33	BNF, Tagrisso[144]

Abbreviations: BNF: British National Formulary; IV: Intravenous.

Table 53: Drug acquisition cost per dose for amivantamab-lazertinib

Component	Dose (mg)	Treatment duration	Units (vials/caps) per admin	Cost per average dose required (£)
Amivantamab (list price)	1,050	<80 kg patients: 4 weeks (up to C2D1)	3	[redacted]
Amivantamab (PAS price)	1,050	<80 kg patients: 4 weeks (up to C2D1)	3	[redacted]
Amivantamab (list price)	1,400	≥80 kg patients: 4 weeks (up to C2D1)	4	[redacted]
Amivantamab (PAS price)	1,400	≥80 kg patients: 4 weeks (up to C2D1)	4	[redacted]
Lazertinib (list price)	240	Taken once daily until progression	1	[redacted]
Lazertinib (PAS price)	240	Taken once daily until progression	1	[redacted]

Abbreviations: C2D1: Day 1 of cycle 2; kg: kilogram; mg: milligram; PAS: patient access scheme.

Table 54: Drug acquisition cost per dose for osimertinib

Component	Dose (mg)	Treatment duration	Units (vials/caps) per admin	Cost per average dose required (£)
Osimertinib	80	Taken once daily until progression	1	192.34

Abbreviations: mg: milligram.

Acquisition and administration costs of amivantamab, lazertinib and osimertinib were corrected for the proportion of missed doses estimated from MARIPOSA trial data. The correction was based on a ratio of administered doses to the expected number of doses for each patient based on their duration of treatment. An additional correction for dose reductions was also applied to

the amivantamab-lazertinib arm to account for the fact that the average dose per administration could be different from the initially scheduled dose. It is included in the CEM as a proportion of the planned dose received, based on MARIPOSA.

For amivantamab, missed doses and the proportion of planned doses were estimated separately for patients in different weight categories (<80 kg and ≥80 kg). Amivantamab dose changes in the trial corresponded to multiples of full vial contents (350 mg), which means that there was no drug wastage associated with dose modifications. The model assumed no vial sharing, and dose reductions only affected drug acquisition (not administration) costs.

The proportion of doses missed, and the proportion of planned dose received for all interventions, are presented in Table 55. The total weekly drug acquisition costs for amivantamab-lazertinib, including missed doses and dose reductions, and for osimertinib, including missed doses, are presented in Table 56 and Table 57, respectively.

Table 55: Drug dosing, including doses missed and proportion of planned doses received

Regimen	Component	Doses Missed	Planned dose received (full vials/tablets)	Source
Amivantamab-lazertinib	Amivantamab (patient weight <80 kg)	[redacted]	[redacted]	MARIPOSA trial
	Amivantamab (patient weight ≥80 kg)	[redacted]	[redacted]	
	Lazertinib[b]	[redacted]	[redacted]	
Osimertinib	Osimertinib	[redacted]	N/A[a]	MARIPOSA trial

[a] Flat pricing of osimertinib means that dose reductions (switching to 40 mg tablets) does not impact costs.
[b] For lazertinib and osimertinib there's a distribution of doses received in the trial, each with an associated cost (determined by the combination of tablet of different strengths required for that dose), and the final cost is calculated as a weighted average.
Abbreviations: kg: kilogram; N/A: not applicable.

Table 56: Total weekly drug acquisition cost for amivantamab-lazertinib including missed doses and dose reductions

Component	Treatment duration	Dosing frequency per week (induction)	Dosing frequency per week (maintenance)	Cost per week of induction (£)[a]	Cost per week of maintenance (£)[a]
Amivantamab (list price)	<80 kg patients: 4 weeks (up to C2D1)	1	0.5	[redacted]	[redacted]
Amivantamab (PAS price)	<80 kg patients: 4 weeks (up to C2D1)	1	0.5	[redacted]	[redacted]
Amivantamab (list price)	≥80 kg patients: 4 weeks (up to C2D1)	1	0.5	[redacted]	[redacted]
Amivantamab (PAS price)	≥80 kg patients: 4	1	0.5	[redacted]	[redacted]

	weeks (up to C2D1)				
Lazertinib (list price)	Taken once daily until progression	7	0.23	[redacted]	[redacted]
Lazertinib (PAS price)	Taken once daily until progression	7	0.23	[redacted]	[redacted]
Total amivantamab-lazertinib (list price)[b]				[redacted]	[redacted]
Total amivantamab-lazertinib (PAS price)[b]				[redacted]	[redacted]

[a] Calculated accounting for doses missed and proportion of planned doses received.
[b] Weighted based on the % of patients over and under 80 kg.
Abbreviations: C2D1: Day 1 of cycle 2; kg: kilogram; mg: milligram.

Table 57: Total weekly drug acquisition cost for osimertinib including missed doses

Component	Dosing frequency per week (induction)	Cost per week (£)
Osimertinib	7	[redacted]

B.3.5.1.2 Drug administration costs

The drug administration costs used in the model are presented in Table 58. The model includes administration costs for simple IV (SB12Z), complex IV (SB14Z), and a one-off oral therapy cost (SB11Z). IV and oral therapy costs are assumed to be outpatient costs based on NHS reference costs from 2022/23, as indicated by the codes above.[145]

Table 58: Drug administration unit costs

Mode of administration	Cost (£)	Source
Cost per IV administration, monotherapy	191.16	National Schedule of NHS Costs 2022/23, SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; Outpatient; Medical Oncology Service[145]
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[145]
Oral therapy one-off cost[b]	316.22	National Schedule of NHS Costs 2022/23, SB11Z - Deliver Exclusively Oral Chemotherapy; Medical Oncology Service[145]

Abbreviations: IV: Intravenous; NHS: National Health Service.

B.3.5.1.3 Concomitant medication

The cost of concomitant medications, defined as any drugs given in addition to the active treatment regimens, were incorporated into the model. Inputs were consistent with the MARIPOSA trial where co-medications were given alongside amivantamab.[118]

Table 59 lists the drug acquisition unit costs for the co-medications included in the CEM, and Table 60 presents the weekly co-medication costs for each intervention, accounting for the proportion of doses missed.

Table 59: Co-medication drug acquisition unit costs

Treatment	Units per pack	Unit strength (mg)	Price per pack (£)	Cost per unit (£)	Source
Dexamethasone	1	10	28.34	28.34	eMIT 2023;[146] 10 mg/5 ml oral solution sugar free 50 ml
Paracetamol	100	500	0.84	0.01	eMIT 2023[147]
Diphenhydramine	20	25	1.50	0.08	NHS dictionary of medicines and devices (dm+d) indicative price (generic from Flamingo Pharma)[148]
Rivaroxaban	100	10	180.00	1.80	BNF, Xarelto[144]

Abbreviations: eMIT: drugs and pharmaceutical electronic market information tool; mg: milligram.

Table 60: Weekly co-medication costs

Component	Co-medication	Duration of treatment	Dose (mg)	Dosing frequency	Units Per Admin	Cost Per Admin (£)	Cost Per Week of Induction (£)[a]	Cost Per Week of Maintenance (£)[a]
Amivantamab	Dexamethasone	2 cycles	10.0	C1D1, C1D2	1	28.34	11.56	-
	Paracetamol	Until progression	825.0	Once per admin	2	0.02	0.01	0.01
	Diphenhydramine	Until progression	37.5	Once per admin	2	0.15	0.12	0.06
	Rivaroxaban	12 weeks	10 mg	Once daily	1	1.80	5.40	-

[a] After correcting for doses missed
Abbreviations: C1D1: cycle 1, day 1; C1D2: cycle 1 day 2; mg: milligram.

B.3.5.1.4 Subsequent treatment costs

Subsequent treatments costs include the cost associated with drug acquisition, administration, comedication, monitoring and AE management. The cost of subsequent treatment was applied as a one-off cost upon 1L treatment discontinuation.

Subsequent treatment costs are split into 2L and third-line or later (3L+), and the proportion of patients receiving 2L or 3L+ therapy is first split by those receiving subsequent treatment or not. Those receiving subsequent treatment are then split based on a distribution of specific therapies. Patients who do not receive 2L or 3L+ therapy assumed to receive BSC, which is assumed to have no associated cost.

2L and 3L+ subsequent costs are applied as single aggregate costs at 1L treatment discontinuation. A one-off cost for subsequent treatment was considered appropriate given the relatively short-term duration of subsequent treatments that is expected in this indication, and since the same approach was taken in relevant NICE appraisals of osimertinib (TA654 and GID-TA11408).[8, 29]

The number of patients eligible for subsequent treatment was calculated based on number of people discontinuing 1L treatment in each cycle, subtracting discontinuations due to death. Deaths were considered to occur proportionally between patients on and off 1L treatment. In the case of amivantamab-lazertinib, the number of patients on 1L treatment was assumed to be equal to the number of patients on lazertinib, due to longer TTD of that treatment component.

The proportion of patients receiving 2L treatment was derived from analysis of MARIPOSA, while patients receiving 3L+ treatment was derived from MARIPOSA-2 data, and calculated by dividing the number of patients who received any subsequent systemic therapy by the number of patients who discontinued their 1L treatment for reasons other than death. The MARIPOSA-2 trial was used to inform patients on 3L+ treatment as it was a Phase III RCT that assessed the efficacy and safety of amivantamab-chemotherapy in patients with *EGFR*-mutated advanced NSCLC whose disease had progressed on or after osimertinib monotherapy. The proportion of patients receiving treatment within each line of therapy was calculated separately for the amivantamab-lazertinib and the osimertinib arms, as presented in Table 61.

Table 61: Proportion of patients receiving 2L and 3L+ treatments by 1L regimen

1L Regimen	% Receiving 2L Treatment[a]	% Receiving 3L+ Treatment[a]	Sources	
Amivantamab-lazertinib	[redacted]	[redacted]	2L: MARIPOSA	3L+: MARIPOSA-2
Osimertinib	[redacted]	[redacted]		

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

The distribution of 2L and 3L+ treatment options were derived from clinical estimates from the advisory board meeting held by Johnson and Johnson in October 2024, as this was considered to be the most relevant source for UK clinical practice.[32] The clinical estimates provided were applicable to both the amivantamab-lazertinib and the osimertinib arms. The duration of subsequent treatments was estimated based on published literature sources.

The distribution and duration of the subsequent treatments and the calculated total costs per week are presented in Table 62 and Table 63 for 2L and 3L+ respectively. A summary of the total subsequent treatment costs, including drug acquisition, administration, co-medication, monitoring and adverse events costs are presented in Table 64.

Table 62: Distribution and duration of 2L subsequent treatments including a summary of treatment costs

2L Regimen	Distribution of 2L treatments[a]	Mean duration on 2L treatment (weeks)	Source for duration of 2L treatment
Platinum-based chemotherapy	[redacted]	[redacted]	J&J data on file: MARIPOSA-2; CP PFS
EGFR MoA/ TKI or TKI-based regimen	[redacted]	43.9	AURA3; median PFS (osimertinib group)[149]
Non-platinum-based chemotherapy	[redacted]	[redacted]	Assumed same as platinum-based chemotherapy
IO ± chemotherapy ± VEGFi	[redacted]	36.1	IMPOWER 150; ABCP median PFS[150]

[a] Average based on the two out of three clinical representatives that responded to the pre-meeting survey question.
Abbreviations: 2L: second-line; ABCP: atezolizumab plus bevacizumab plus carboplatin plus paclitaxel; CP: carboplatin in combination with pemetrexed; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.
Source: Johnson & Johnson Data on File: Advisory Board Report for MARIPOSA (October 2024).[32]

Table 63: Distribution and duration of 3L+ subsequent treatments including a summary of treatment costs

3L Regimen	Distribution of 3L+ treatments[a]	Mean duration on 3L+ treatment (weeks)	Source for duration of 3L+ treatment
Platinum-based chemotherapy	[redacted]	11.3	Park 2019 (supplementary figure 2)[151]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	12.6	Park 2019 (supplementary figure 2)[151]
Non-platinum-based chemotherapy	[redacted]	10.9	Park 2019 (supplementary figure 2)[151]
IO ± chemotherapy ± VEGFi	[redacted]	18.3	Park 2019 (supplementary figure 2)[151]

[a] Average based on the two out of three clinical representatives that responded to the pre-meeting survey question.
Abbreviations: 3L+: third-line or later; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.
Source: Johnson & Johnson Data on File: Advisory Board Report for MARIPOSA (October 2024).[32]

Table 64: Summary of total one-off subsequent treatment costs

1L Regimen	2L Drug Costs (£)	3L+ Drug Costs (£)	Total Subsequent Treatment Costs (£)
Amivantamab-lazertinib	[redacted]	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]	[redacted]

Abbreviations: 1L: first-line therapy; 2L: second-line therapy; 3L+: third-line or later.

Scenarios were explored in which the subsequent treatment distributions were derived from data from the MARIPOSA trial and from UK RWE. These scenarios are described in more detail in Section B.3.11.3.

B.3.5.2 Health-state unit costs and resource use

Health state-specific routine monitoring and follow-up care costs for disease management are included in the model via a micro-costing approach. The costs, frequencies and types of medical resources used are presented in Table 65. The types and frequencies of resources were based on previous Health Technology Assessment (HTA) submissions, primarily TA531 and TA705,[152, 153] and unit costs were based on the 2022/23 National Schedule of NHS Costs[145] or the 2023 PSSRU report on unit costs of health care.[154]

Table 65: Resource use and costs for routine follow-up care by health state

Resource	Unit Cost (£)	Source	PF (number of visits)	PD (number of visits)	Source
Oncology outpatient visit	190.53	National Schedule of NHS Costs 202/23, WF01A. Consultant Led, Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology Service[145]	9.61	7.91	NICE TA531[152]
Clinical nurse specialist (hours)	88.00	PSSRU 2023, Cost per hour Band 8B nurse P.61 (as per TA705)[155]	12.00	12.00	NICE TA584[156]
GP surgery visit	49.00	PSSRU 2023, Unit costs for a GP Per surgery consultation lasting 10 minutes including direct care staff costs & qualifications p.64[155]	12.00	0.00	NICE TA584[156]
Therapist visit	52.00	PSSRU 2023, Cost per hour for a community occupational therapist (local authority), incl. qualification p.77 (as per TA705)[155]	0.00	26.09	NICE TA584[156]
GP home visit	49.00	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[155]	0.00	26.09	NICE TA584[156]
Community nurse home visit (20 minutes)	76.00	PSSRU 2023, Cost per hour Band 8A nurse P.61 (as per TA705)[155]	8.70	8.70	NICE TA584[156]
Chest radiography	73.79	National Schedule of NHS Costs 2022/23, IMAGCDC Plain Film (as per TA654)[145]	6.79	6.50	NICE TA531[152]
CT scan (chest)	154.13	National Schedule of NHS Costs 2022/23, RD24Z, IMAG Computerised Tomography Scan of Two Areas, with Contrast[145]	0.62	0.24	NICE TA531[152]

CT scan (other)	172.76	National Schedule of NHS Costs 2022/23, RD26Z, IMAG Computerised Tomography Scan of Three Areas, with Contrast[145]	0.36	0.42	NICE TA531[152]
ECG	177.96	National Schedule of NHS Costs 2022/23, EY51Z, Outpatient, Electrocardiogram Monitoring or Stress Testing (as per TA705)[145]	1.04	0.88	NICE TA531[152]
Average annual cost by health state (£)			4,980.06	6,605.17	Calculation
Average weekly cost by health state (£)			95.44	126.59	Calculation

Abbreviations: CG: clinical guideline; CT: computed tomography; ECG: electrocardiogram; 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; TA: technology appraisal.

B.3.5.3 Adverse event unit costs and resource use

Most AEs were costed by taking a weighted average of non-elective short stay admissions from the 2022/23 National Schedule of NHS Costs.[145] The AE unit costs included in the model are detailed in Table 66.

Table 66: Unit costs for adverse events

AE	Unit Cost (£)	Source
Dermatitis acneiform	483.99	Weighted average of National Schedule of NHS Costs 2022/23, JD07A–JD07K (non-elective short stay)[145]
Alanine aminotransferase increased	686.39	National Schedule of NHS Costs 2022/23, GC01F (non-elective short stay)[145]
Hypoalbuminaemia	686.39	Assumed same as ALT increase
Paronychia	483.99	Assuming same as rash: weighted average of National Schedule of NHS Costs 2023/23, JD07A–JD07K (non-elective short stay)[145]
Infusion related reaction	443.83	IRR costs included in TA651, inflated to 2021/2022 prices using the NHS Cost Inflation Index[145]
Rash	483.99	Weighted average of National Schedule of NHS Costs 2022/23, JD07A–JD07K (non-elective short stay)[145]
Pulmonary Embolism	625.13	Weighted average of National Schedule of NHS Costs 2022/23, DZ09J–DZ09Q (non-elective short stay)[145]
Grade ≤2 VTE	2.13	Price of 3 months 5 mg Wafarin per day (eMIT price 22/23 Warfarin 5 mg tablets / Pack size 28)[147]
Pneumonia	489.29	Weighted average of National Schedule of NHS Costs 2022/23, DZ22K–DZ22Q (non-elective short stay)[145]

Diarrhoea	552.32	Weighted average of National Schedule of NHS Costs 2022/23, FD01A–FD01J (non-elective short stay)[145]
Fatigue	739.05	Assumed to be the same as anaemia (as per TA850 and TA653)
Anaemia	739.05	Weighted average of National Schedule of NHS Costs 2022/23, SA01G–SA01K (non-elective short stay)[145]
Neutropenia	527.46	Weighted average of National Schedule of NHS Costs 2022/23, SA08G–SA08J (non-elective short stay)[145]
Febrile neutropenia	527.46	Weighted average of National Schedule of NHS Costs 2022/23, SA08G–SA08J (non-elective short stay)[145]
Hypertension	378.10	National Schedule of NHS Costs 2022/23, EB04Z (non-elective short stay)[145]
Platelet count decrease	615.65	Weighted average of National Schedule of NHS Costs 2022/23, SA12G–SA12K (non-elective short stay)[145]
Neutrophil count decreased	527.46	Weighted average of National Schedule of NHS Costs 2022/23, SA08G–SA08J (non-elective short stay)[145]
Thrombocytopenia	615.65	Weighted average of National Schedule of NHS Costs 2022/23, SA12G–SA12K (non-elective short stay)[145]

Abbreviations: AE: adverse event; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; TA: technology appraisal; VTE: venous thromboembolism.

The total one-off AE costs by treatment regimen were calculated based on the treatment-specific incidence rates of AEs (Table 49, Section B.3.3.3) and the unit costs (Table 66). The resulting costs are presented in Table 67.

Table 67: Total one-off adverse event costs by treatment regimen

Regimen	One-off Cost (£)
Amivantamab-lazertinib	366.60
Osimertinib	62.90

B.3.5.4 Miscellaneous unit costs and resource use

A one-time cost of £4,674.07 for terminal care was incurred at death, in accordance with assumptions used in the NICE submission for atezolizumab for treating locally advanced or metastatic NSCLC after chemotherapy.[157] The breakdown of the end-of-life costs used to calculate the one-time cost are shown in Table 68.

Table 68: 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%	5,401.84	3,014.23	National Schedule of NHS Costs 2022/23, DZ17S (non-elective long stay)[145]

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).[155]
Hospice care	1	16.9%	6,752.30	1,141.14	Assumed 25% increase on hospitalisation setting
Total cost (£):				**4,674.07**	Calculation

Abbreviations: NHS: National Health Service; PSSRU: Personal Social Services Research Unit.

B.3.6 Severity

For the severity modifier calculations, two methods were considered. The most appropriate method was where QALYs were calculated based on patients in the 'MARIPOSA-like' cohort of the NCRAS database who received 1L osimertinib monotherapy (n=126). These data represent England-specific, real-world population dataset and expert clinicians at the October 2024 advisory board confirmed that the baseline characteristics of patients in the NCRAS database are broadly aligned with the characteristics of patients seen in UK clinical practice, underscoring their relevance for consideration.[32] The quality-adjusted life expectancy (QALE) for the model severity calculations was calculated within the model workbook by using the life table and general population utility norms for England. For the RWE, the severity modifier calculation tool developed by the University of York, the Sheffield Centre for Health and Related Research (SCHARR) and Lumanity was used to calculate the quality-adjusted life expectancy (QALE) (see Appendix J.3 for further details).[158]

An alternative, less appropriate method was also explored using the data from the MARIPOSA trial. In this method, QALYs for the SoC were derived from the CEM using the total discounted QALYs calculated for patients in the osimertinib arm of the MARIPOSA trial.

When calculating the QALY shortfall, the analyses resulted in a QALY weighting of 1.00, given that the proportional shortfall was less than the NICE recommended threshold of 0.85 (Table 69).[136] However, the calculated proportional shortfalls were close to the 0.85 threshold, and the considerable unmet need associated with the currently SoC, osimertinib, should be considered. Despite advancements in treatment options for patients with untreated, advanced cEGFRm NSCLC in the UK, with the introduction of osimertinib as SoC, patients continue to experience low overall survival due to the relatively fast progression and the development of resistance mechanisms. As such, there remains a clear need for a more efficacious, well-tolerated, chemotherapy-free and targeted combination therapy that extends PFS and OS and maintains QoL. Further evidence relating to unmet need is detailed in Section B.1.3.2. Addressing these issues by introducing amivantamab-lazertinib as a treatment option could justify a higher willingness-to-pay threshold, as it aligns with the NICE framework's intent to reward treatments that address significant gaps in care.

Table 69: QALY shortfall calculation

	UK RWE: Osimertinib data from the 'MARIPOSA-like' cohort of the NCRAS database (n=126)	Trial data: Osimertinib arm of MARIPOSA (n=429)
QALE at model starting age	11.74	11.39
QALYs for SoC	1.94	2.64

Absolute shortfall	9.80	8.75
Proportional shortfall	0.83	0.77
Severity modifier	1.00	1.00

Abbreviations: QALE: quality-adjusted life expectancy; QALY: quality-adjusted life year; SoC: standard of care.

B.3.7 Uncertainty

The development of the economic model was guided by global and UK advisory boards, consulting health economics 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.

Despite this, there are unavoidable uncertainties associated with the extrapolation of long-term survival data that should be acknowledged when considering the economic evidence for amivantamab-lazertinib versus osimertinib.

The curve choices for the extrapolation for PFS, OS and TTD were made 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 October 2024 advisory board.[32] The relationship between long-term extrapolations and hazard functions is crucial in determining the reliability of the model's projections. Hazard functions describe the risk of an event occurring at a given time point, and their alignment with KM data ensures that the extrapolations accurately reflect observed trends. In addition to guidance outlined in NICE DSU Technical Support Document (TSD) 14, and as validated by key clinical and health economic experts at the October 2024 advisory board, hazard functions were considered throughout the curve selection process,[32, 159] and scenario analyses were used to explore the impact of selecting an alternative curve for each base case extrapolation. Across all of these scenarios, the cost-effectiveness conclusions remained unchanged from the base case, suggesting that this uncertainty had a low impact on the model outcomes (see Section B.3.11.3).

Long-term uncertainty in the efficacy estimates for osimertinib was also explored in a scenario analysis in which longer-term data from the FLAURA trial was incorporated into the model via a left-truncation approach. Described in more detail in Section B.3.11.3.1, this approach resulted in amivantamab-lazertinib remaining dominant over osimertinib in the scenario analysis, indicating that the model is robust in relation to this uncertainty.

In addition to the unavoidable uncertainty related to modelling long-term outcomes, the distribution of subsequent treatments that will be received in clinical practice by patients are treated with 1L amivantamab-lazertinib and osimertinib is also associated with some uncertainty. While the proportion of patients receiving 2L and 3L+ therapy was based on trial data, some of the subsequent treatments used in the MARIPOSA trial are not available in UK clinical practice. As such, the subsequent treatment distributions from MARIPOSA may not represent typical expected UK clinical practice. Instead, the distribution of treatments were based on clinical estimates from the advisory board, as this was considered to be the most relevant source for UK clinical practice.[32] To explore the impact of this uncertainty, scenario analyses were explored in which the distribution of subsequent treatments were derived from the MARIPOSA trial, or from UK-based RWE (patients in the 'MARIPOSA-like' cohort of the NCRAS database who received 1L osimertinib in UK clinical practice). These scenarios resulted in no change to the cost-

effectiveness conclusions from the base case, suggesting that the model is unlikely to be substantially affected by this uncertainty (see Section B.3.11.3).

In conclusion, the modelling approaches and assumptions used were informed by the latest available guidance in addition to clinical and health economist opinion. Throughout this submission, conservative approaches have been taken where necessary, to ensure confidence in the cost-effectiveness of amivantamab-lazertinib versus osimertinib. In addition, RWE from the NCRAS database can be considered alongside the trial data as a complementary measure. This evidence provides insights from broader clinical settings beyond controlled trial environments, capturing a more representative spectrum of patient experiences and treatment responses. While efficacy data from the RWE were not incorporated in the economic model, the evidence presented in Section B.1.3.1 supports the reliability of the economic evaluation by aligning model outcomes with real-world clinical scenarios.

B.3.8 Managed access proposal

At the 11th August 2023 DCO, the primary endpoint of the MARIPOSA trial, PFS assessed by BICR, had reached its median value in both treatment arms (HR: 0.70; 95% CI: 0.58, 0.85; p<0.001) as presented in Section B.2.6.1. Furthermore, at the 13th May 2024 DCO, the median DOR was reached as a secondary objective (Section B.2.6.2), and a clear OS benefit was observed for amivantamab-lazertinib versus osimertinib (HR: 0.77; 95% CI: 0.61, 0.96; p=0.019).[24]

While the mOS for amivantamab-lazertinib was not estimable at the 13th May 2024 DCO, the osimertinib arm reported a median of 37.3 months. However, this is not reflective of data immaturity and instead reflects the greater proportion of patients remaining alive in the amivantamab-lazertinib arm during the trial period ([redacted]/429, [redacted]%) compared to the control arm ([redacted]/429, [redacted]%). These data therefore underscore the superior efficacy of amivantamab-lazertinib as compared with osimertinib.

More recently, a press release shared by Johnson & Johnson earlier this month communicated that with a longer duration of follow-up ([redacted]), amivantamab-lazertinib has shown a statistically significant and clinically meaningful improvement in OS compared to osimertinib in the phase 3 MARIPOSA trial ([redacted]).[22, 23] This means that the combination of amivantamab-lazertinib [redacted] in the ITT population.[22, 23] The mOS was not estimable ([redacted]) in the amivantamab-lazertinib arm, while the mOS for osimertinib was reached at [redacted] months ([redacted].[22, 23] These significantly improved OS results reinforce the importance of amivantamab-lazertinib and its potential to significantly improve patient prognosis. It is noteworthy that amivantamab-lazertinib is the only chemotherapy-free treatment to demonstrate a significant survival benefit versus osimertinib in the first-line treatment of patients with EGFR-mutated lung cancer. Johnson & Johnson would be pleased to provide further analyses using the updated data once full data are available.

In light of this compelling evidence, Johnson & Johnson strongly believe that amivantamab-lazertinib addresses a critical unmet need in patients with cEGFRm advanced NSCLC. The clinical and economic data presented is not only robust but also adequately supports the routine commissioning of amivantamab-lazertinib by the NHS without necessitating a managed access program. The improved efficacy and survival data indicate that patients can and will benefit from immediate and unrestricted access to this innovative treatment.

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 70.

Table 70: 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	
Discount rate for effects	3.5%	NA	
Discount rate for costs	3.5%	NA	
Patient characteristics			
Mean starting age, years	62.3	Normal	B.3.3.1
Proportion female, %	61.3	Beta	
Mean weight, kg	[redacted]	Normal	
Patients <80kg, %	86.7	Beta	
Efficacy data			
Amivantamab-lazertinib PFS	LogLogistic	Multivariate normal	B.3.3.2
Amivantamab-lazertinib OS	Weibull	Multivariate normal	
Amivantamab TTD	Exponential	Multivariate normal	
Lazertinib TTD	Exponential	Multivariate normal	
Osimertinib PFS	LogLogistic	Multivariate normal	
Osimertinib OS	Weibull	Multivariate normal	
Osimertinib TTD	Exponential	Multivariate normal	
Drug acquisition costs for intervention (per week), £			
Amivantamab-lazertinib at list price (induction)	[redacted]	Drug Price: Gamma	B.3.5.1
		% Doses Skipped: Beta	
		% Distribution of Doses: Beta	
Amivantamab-lazertinib at list price (maintenance)	[redacted]	Drug Price: Gamma	B.3.5.1
		% Doses Skipped: Beta	
		% Distribution of Doses: Beta	
	[redacted]	Drug Price: Gamma	B.3.5.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Amivantamab-lazertinib at PAS price (induction)		% Doses Skipped: Beta % Distribution of Doses: Beta	
Amivantamab-lazertinib at PAS price (maintenance)	[redacted]	Drug Price: Gamma % Doses Skipped: Beta % Distribution of Doses: Beta	B.3.5.1
Drug costs for comparators (per week), £			
Osimertinib	[redacted]	Gamma	B.3.5.1
Administration costs (per week) for intervention, £			
Amivantamab-lazertinib (induction)	[redacted]	Gamma	B.3.5.1
Amivantamab-lazertinib (maintenance)	[redacted]	Gamma	B.3.5.1
Administration costs for comparators (per week), £			
Osimertinib	0.00	Gamma	B.3.5.1
AE management costs, £			
Amivantamab-lazertinib	366.60	Cost: Gamma Incidence: Beta	B.3.5.3
Osimertinib	62.90	Cost: Gamma Incidence: Beta	
Disease management costs (weekly), progression-free, £			
Amivantamab-lazertinib Osimertinib	95.44	Gamma	B.3.5.2
Disease management costs (weekly), PD, £			
Amivantamab-lazertinib Osimertinib	126.59	Gamma	B.3.5.2
Disease management costs, one-off cost, £			
End-of-life	4,674.07	Cost: Gamma Incidence: Beta	B.3.5.4
Subsequent treatment costs (one-off), £			
Amivantamab-lazertinib	[redacted]	Cost: Gamma Proportions: Beta	B.3.5.1
Osimertinib	[redacted]	Cost: Gamma Proportions: Beta	
Health state utility values			

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Progression-free	[redacted]	[redacted]	B.3.4.5
PD	[redacted]	[redacted]	
Grade 3+ AE disutilities			
Amivantamab-lazertinib	[redacted]	Disutility: Beta	B.3.4.4
		Duration: Normal	
Osimertinib	[redacted]	Disutility: Beta	
		Duration: Normal	

Abbreviations: AE: adverse event; NA: not applicable; OS: overall survival; PD: progressed disease; PFS: progression-free survival; TTD: time to treatment discontinuation or death.

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 71.

Table 71: Assumptions in the base case analysis model

Assumption	Justification
Model settings	
The lifetime horizon for the modelled population was 30 years	Based on the starting cohort age, 30 years was assumed to be a sufficient length to capture all important differences in costs or outcomes between the technologies being compared, per NICE guidelines.[136] A scenario analysis was conducted to explore the impact of a time horizon of 37.7 years (Section B.3.11.3).
Clinical input	
OS and PFS were modelled independently of each other. Projections of OS were the only predictor of LYs accrued in the model; PFS had no impact on this.	This is consistent with the partitioned survival approach commonly used in oncology models
Risk of mortality of patients with NSCLC in the model could not be lower than the risk of mortality of the general population at the same age	General population mortality rates were implemented in the model such that the extrapolations would be adjusted to ensure that the risk of death at each cycle did not drop below that of the general population at the same age
To ensure that proportions of the cohort in the progression-free health state and on treatment were not higher than the proportion alive, PFS and TTD were restricted to be no higher than OS (i.e., PFS and TTD curves were not allowed to cross the OS curve)	It is not plausible for PFS or TTD to be longer than OS, so adjustments were made to prevent any implausible results
HRQoL	
Apart from Grade ≤2 VTE, grade 1–2 AEs had minimal impact on HRQoL and are captured by the EQ-5D health state utility values. Grade ≤2 VTE and Grade ≥3 AEs	Patients with Grade <3 AEs are more likely to be able to complete HRQoL questionnaires, and so the Grade <3 AEs are more likely to be captured by the utility estimates of the progression-free health state

had meaningful impact on HRQoL while being less likely to be captured in health state utilities, and were therefore modelled separately by applying an AE-specific utility decrement. Only AEs that occurred in ≥5% of patients in either treatment group were included in the model.	
Costs	
Drug wastage (no vial sharing) was accounted for in drug costs	It is important to accurately calculate the true (real-world) treatment cost for an average patient
Subsequent therapy had an impact on costs but not survival outcomes and was therefore applied as a one-off cost upon 1L treatment discontinuation	The clinical impact of subsequent treatment was assumed to already be captured in the OS curves

Abbreviations: AE: adverse event; HRQoL: health-related quality of life; LY: life-years; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression-free survival; TTD: time to treatment discontinuation or death; VTE: venous thromboembolism.

B.3.10 Base case results

B.3.10.1 Base case incremental cost-effectiveness analysis results

A summary of the deterministic and probabilistic base case results (at PAS price) of the CEM of amivantamab-lazertinib versus osimertinib are presented in Table 72 and Table 74, respectively. The deterministic and probabilistic base case results at the list prices of amivantamab and lazertinib are further presented in Table 73 and Table 75, respectively.

At amivantamab and lazertinib PAS prices, amivantamab-lazertinib was found to be a cost-effective use of NHS resources when compared to osimertinib at its list price, dominating osimertinib in the probabilistic and deterministic analyses. The clinical outcomes and disaggregated base case cost-effectiveness results are presented in Appendix J.

Table 72: Base case results at amivantamab and lazertinib PAS prices (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Osimertinib	[redacted]	[redacted]	3.41	[redacted]	[redacted]	1.29	−74,090.97 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.70				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years; SoC: standard of care.

Table 73: Base case results at amivantamab and lazertinib list prices (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Osimertinib	[redacted]	[redacted]	3.41	[redacted]	[redacted]	1.29	[redacted]
Amivantamab-lazertinib	[redacted]	[redacted]	4.70				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALYs, quality-adjusted life years; SoC: standard of care.

Table 74: Base case results at amivantamab and lazertinib PAS prices (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
Osimertinib	[redacted]	[redacted]	3.40	[redacted]	[redacted]	1.27	−75,539.74 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.67				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years; SoC: standard of care.

Table 75: Base case results at amivantamab and lazertinib list prices (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	
Osimertinib	[redacted]	[redacted]	3.40	[redacted]	[redacted]	1.27	[redacted]
Amivantamab-lazertinib	[redacted]	[redacted]	4.67				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALYs, quality-adjusted life years; SoC: standard of care.

B.3.11 Exploring uncertainty

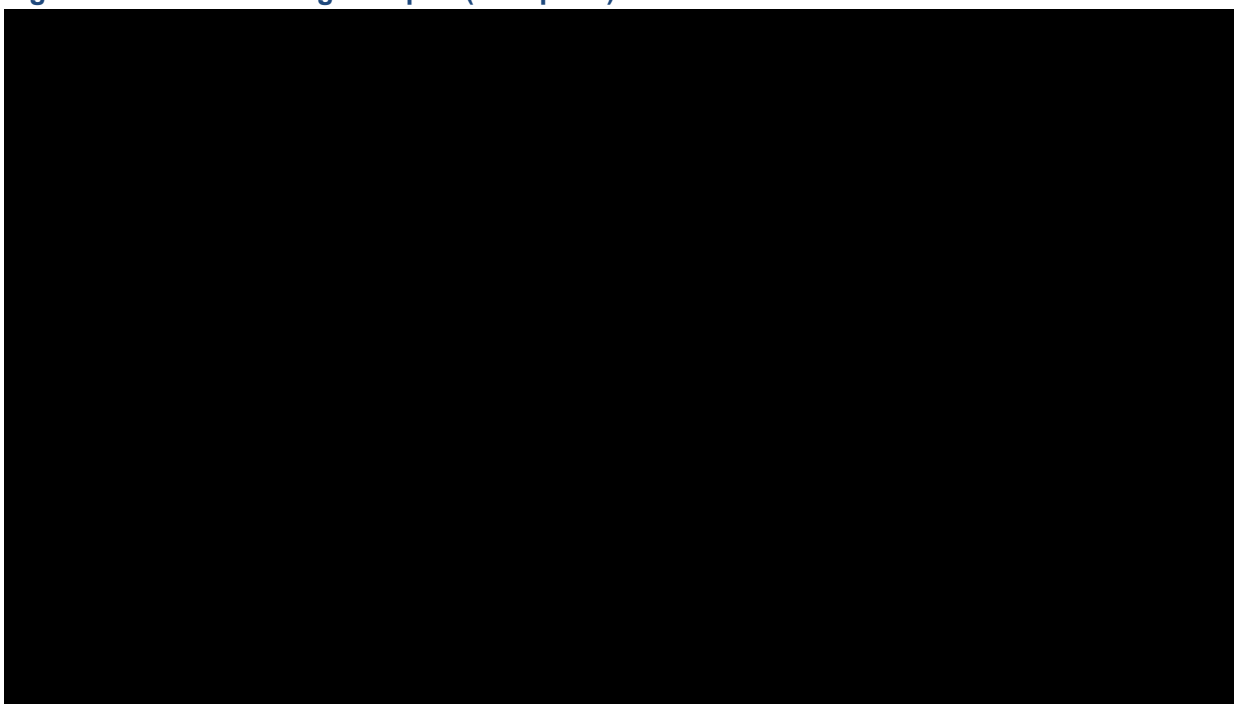
Parameter uncertainty in the model was assessed via both probabilistic and deterministic sensitivity analyses, the results of which are presented in Sections B.3.11.1 and B.3.11.2. Furthermore, key modelling approaches and assumptions were varied in scenario analyses, the results of which are presented in Section B.3.11.3.

B.3.11.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted in order 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 1,000 iterations was performed where model inputs were randomly sampled from the specified probability distributions.

The incremental net monetary benefit (INMB) convergence plot is presented in Figure 40, which incorporates the PAS discounts for amivantamab and lazertinib. Additionally, the probabilistic cost-effectiveness plane for amivantamab-lazertinib versus osimertinib is presented in Figure 41. These results indicate that at a £30,000 WTP threshold, amivantamab-lazertinib (PAS price) has a [redacted] probability of being cost-effective when compared with osimertinib, which is presented in Figure 42.

Figure 40: INMB convergence plot (PAS price)



Abbreviations: INMB: incremental net monetary benefit; PAS: patient access scheme.

Figure 41: Probabilistic cost-effectiveness plane (PAS price)

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

Figure 42: Cost-effectiveness acceptability curve (PAS price)

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

B.3.11.2 Deterministic sensitivity analysis

In order to assess the robustness of the base case cost-effectiveness results, a deterministic sensitivity analysis (DSA) was 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-lazertinib versus osimertinib is provided in Figure 43. Overall, the scale and shape of the parametric extrapolations for OS for amivantamab-lazertinib and osimertinib are the most influential parameters, followed by the TTD rate for osimertinib and amivantamab. The model is otherwise robust to variation in inputs and settings. All results generated from the DSA provide a negative ICER due to amivantamab-lazertinib (PAS price) being dominant in all instances. The tornado diagram illustrates that the parametric function for OS in the amivantamab-lazertinib 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.

Figure 43: DSA tornado diagram (PAS price)

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall 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 a 1.5% discount rate for costs and benefits
- Using an alternative time horizon of 37.7 years
- Exploring the impact of incorporating longer-term osimertinib OS data from the FLAURA trial via a left-truncation – see Section B.3.11.3.1
- Exploring the impact of using PFS as assessed by INV rather than by BICR – see Section B.3.11.3.2
- Exploring alternative survival extrapolations for PFS, OS and TTD

- Exploring the use of utility values for PD and PF states from the literature (as per TA654) – see Section B.3.11.3.3
- Using AE-specific disutilities based on literature – see Section B.3.11.3.4
- Exploring the impact of using distribution of subsequent treatments based on data from the MARIPOSA trial – see Section B.3.11.3.5
- Exploring the impact of using distribution of subsequent treatments based on RWE – See section B.3.11.3.6

Results for all scenario analyses are presented in Section B.3.11.3.7.

B.3.11.3.1 Scenario analysis: OS by left truncated approach

KM estimates of osimertinib OS in the MARIPOSA and FLAURA trials were similar up to the last observation in the former trial: at 1 and 2 years respectively, OS estimates were [redacted]% and 70% in MARIPOSA and 89% and 74% in FLAURA.[24, 34, 95] Median OS in MARIPOSA was 37.3 months (95% CI: 32.5, NE) compared to 38.6 months (95% CI: 34.5–41.8) in FLAURA.[24, 34] The OS data were more mature in FLAURA, with 58% of patients in the osimertinib arm having experienced an event by the DCO, compared with [redacted]% in MARIPOSA.[34, 95]

A scenario was explored estimating osimertinib OS by including patient data from the FLAURA trial, obtained by reconstructing individual patient data (IPD) from the published KM OS curve.[34] In the left-truncated approach, these data were included in the risk set after 3.28 years (approximately 39 months), from the time point when the number at risk in MARIPOSA dropped to 10.

The long-term OS extrapolations for osimertinib based on the left-truncated approach are presented in Figure 44, and Table 76 presents the AIC, BIC, 5- and 10-year OS, and mOS outcomes for each distribution. Generalised gamma, Weibull and Gompertz models are the most appropriate choices, according to AIC and BIC. The Weibull remained as the distribution of choice for this scenario.

Figure 44: Long-term OS projections of osimertinib based on left-truncation approach

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

Table 76: OS for osimertinib using left-truncation approach

Distribution	AIC	BIC	5-year OS	10-year OS	Median OS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Selected distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

B.3.11.3.2 Scenario analysis: PFS by INV

In the NICE appraisals of osimertinib monotherapy (TA654) and in combination with chemotherapy (ID6328), PFS was assessed by INV. PFS by INV was a secondary endpoint in the MARIPOSA trial (see Section B.2.6.1). A scenario analysis was explored in which the PFS by INV data were implemented. Given the similarity of these data with the PFS by BICR base case, the same extrapolation curve was selected as in the base case for each comparator (Log-logistic).

The KM curves for PFS by INV in the amivantamab-lazertinib and osimertinib arms are shown in Figure 45, as of the 11th August 2023 DCO.

Figure 45: MARIPOSA PFS (INV) KM curves for amivantamab-lazertinib and osimertinib (11th August 2023 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; FAS: full analysis set; INV: investigator; KM: Kaplan-Meier; OSI: osimertinib; PFS: progression-free survival.

Amivantamab-lazertinib

The long-term PFS (INV) extrapolations for amivantamab-lazertinib are presented in Figure 46 and the smoothed hazard plot is presented in Figure 47. Table 77 presents AIC, BIC, 5- and 10-year PFS, and mPFS outcomes for each distribution.

Figure 46: Long-term PFS (INV) projections of amivantamab-lazertinib

Abbreviations: INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 47: Smoothed hazard plot with parametric extrapolations for amivantamab-lazertinib for PFS (INV)

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

Table 77: PFS (INV) individual fits for amivantamab-lazertinib

Distribution	AIC	BIC	5-year PFS	10-year PFS	Median PFS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

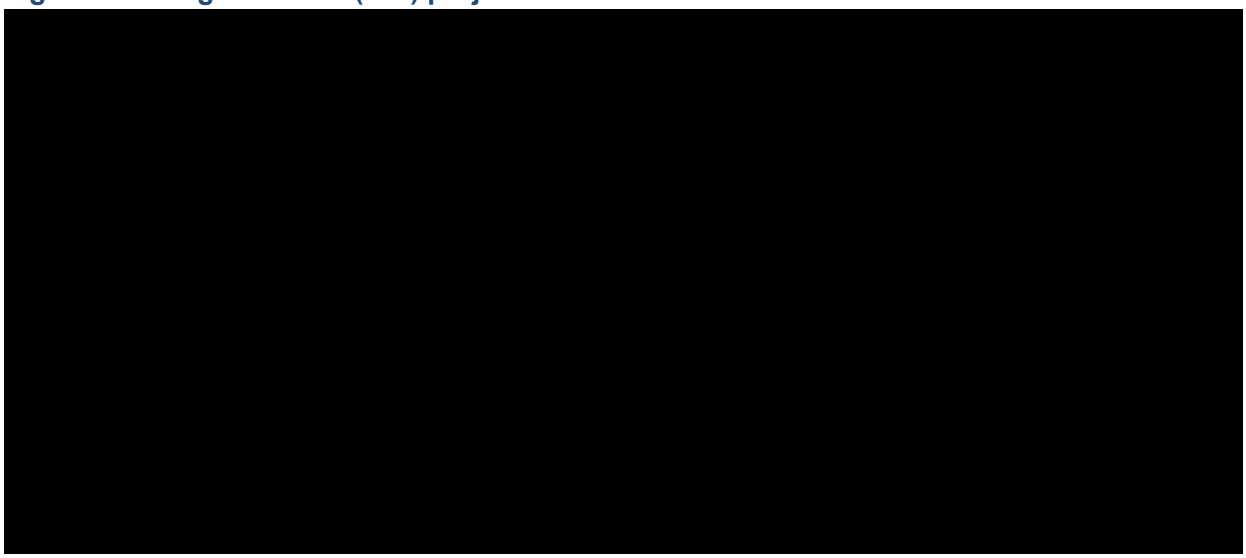
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Selected distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; INV: investigator; PFS: progression-free survival.

Osimertinib

The long-term PFS (INV) extrapolations for osimertinib are presented in Figure 48 and the smoothed hazard plot is presented in Figure 49. Table 78 presents AIC, BIC, 5- and 10-year PFS, and mPFS outcomes for each distribution.

Figure 48: Long-term PFS (INV) projections for osimertinib



Abbreviations: INV: investigator; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 49: Smoothed hazard plot with parametric extrapolations for osimertinib for PFS (INV)

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

Table 78: PFS (INV) individual fits for osimertinib

Distribution	AIC	BIC	5-year PFS	10-year PFS	Median PFS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Selected distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; INV: investigator; PFS: progression-free survival.

B.3.11.3.3 Scenario analysis: Alternative health state utility values

As noted, the MARIPOSA trial represents the most appropriate source of health state utilities. However, in the appraisals of osimertinib (monotherapy [TA654] and in combination with chemotherapy [GID-TA11408]), the Committee-preferred utility values were 0.794 and 0.678 for the progression-free and PD health states, respectively.[8, 29] Therefore, to explore alignment with previous relevant appraisals, a scenario analysis was performed in which these utility values were considered.

B.3.11.3.4 Scenario analysis: Literature disutilities

A scenario analysis was explored in which the impact of AEs on HRQoL was modelled using AE-specific disutilities sourced from literature. These disutilities are multiplied by the duration of each

AE (in years) and the probability of experiencing that AE to calculate the total QALY loss associated with each AE (i.e., AE QALYs). The disutilities and calculated QALYs for this scenario are presented in Table 79.

Table 79: Literature disutilities and calculated QALYs for each AE

AE	Disutility	Source	AE QALYs
Dermatitis acneiform	−0.032	Assumed equal to rash	−0.0026
Alanine aminotransferase increase	−0.051	NICE TA654,[8] based on assumption	−0.0030
Hypalbuminaemia	[redacted]	Assumed equal to mean disutility from pooled AEs in MARIPOSA	−0.0074
Paronychia	−0.202	NICE TA595,[135] based on assumption	−0.0223
Infusion-related reaction	−0.200	NICE TA561[160]	−0.0002
Rash	−0.032	NICE TA850,[132] based on Nafees 2008[161]	−0.0026
Pulmonary embolism	[redacted]	Assumed equal to mean disutility from pooled AEs in MARIPOSA	−0.0075
Grade ≤2 VTE	[redacted]	Analysis of MARIPOSA data on file	−0.0072
Pneumonia	[redacted]	Assumed equal to mean disutility from pooled AEs in MARIPOSA	−0.0029

Abbreviations: AE: adverse events; QALY: quality-adjusted life year; VTE: venous thromboembolism.

B.3.11.3.5 Scenario analysis: Subsequent treatment distributions based on the MARIPOSA and MARIPOSA 2

In the base case, the distribution of 2L and 3L+ treatment options were derived from clinical estimates from the advisory board meeting held by Johnson and Johnson in October 2024, as this was considered to be the most relevant source for UK clinical practice.

A scenario analysis was explored in which the distribution of subsequent therapies was based on the MARIPOSA and MARIPOSA-2 trials (see Section B.3.5.1.4). The subsequent treatment distributions following 1L treatment with amivantamab-lazertinib or osimertinib used in this scenario are presented in Table 80 and Table 81, respectively. The duration of subsequent treatments (2L and 3L+) were maintained as per the base case approach.

Table 80: Distribution of 2L and 3L+ subsequent treatments for the amivantamab-lazertinib arm implemented in the MARIPOSA-derived scenario analysis, based on the amivantamab-lazertinib treatment arm of the MARIPOSA trial

	Distribution of 2L treatments	Distribution of 3L+ treatments
Platinum-based chemotherapy	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line or beyond; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.

Table 81: Distribution of 2L and 3L+ subsequent treatments for the osimertinib arm implemented in the MARIPOSA-derived scenario analysis, based on the osimertinib treatment arm of the MARIPOSA trial

	Distribution of 2L treatments	Distribution of 3L+ treatments
Platinum-based chemotherapy	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]

Abbreviations: 2L: second-line; 3L+: third-line or beyond; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.

B.3.11.3.6 Scenario analysis: Subsequent treatment distributions based on real-world evidence

A second scenario analysis was explored in which the distribution of subsequent therapies was derived from patients in the 'MARIPOSA-like' cohort of the NCRAS database who received 1L osimertinib monotherapy and received any subsequent treatment (n=65). The subsequent treatment distributions used in this scenario are presented in Table 82. The distributions outlined in Table 82 are applied to patients treated with amivantamab-lazertinib and patients treated with osimertinib. The duration of subsequent treatments (2L and 3L+) were maintained as per the base case approach.

Table 82: Distribution of 2L and 3L+ subsequent treatments implemented in the UK RWE-derived scenario analysis

	Distribution of subsequent treatments
Platinum-based chemotherapy	[redacted]
EGFR MoA/ TKI or TKI-based regimen	35.7%
Non-platinum-based chemotherapy	1.8%
IO ± chemotherapy ± VEGFi	30.4%

Abbreviations: 2L: second-line; 3L+: third-line or beyond; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; RWE: real-world evidence; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.

B.3.11.3.7 Scenario analysis: Results

Probabilistic results for the scenario analyses carried out are presented in Table 83, with deterministic results for the scenario analyses presented in Table 84. In all analyses, amivantamab-lazertinib at PAS price remained dominant over osimertinib at list price, indicating that the cost-effectiveness of amivantamab-lazertinib versus relevant osimertinib remains robust when altering key modelling assumptions and approaches. Probabilistic and deterministic results for the scenario analyses considering the list prices of amivantamab and lazertinib are presented in Appendix N.2 for completeness.

Table 83: Summary of scenario analysis results (probabilistic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	−74,090.97 (dominant)
Discount rate				
1	1.5% discount rate	[redacted]	[redacted]	−64,965.52 (dominant)
Time horizon				
2	37.7-year time horizon	[redacted]	[redacted]	−73,942.43 (dominant)
OS modelling approach				
3	Left-truncated for osimertinib	[redacted]	[redacted]	−71,803.80 (dominant)
PFS definition				
4	PFS by INV for amivantamab-lazertinib and osimertinib	[redacted]	[redacted]	−74,186.56 (dominant)
PFS parametric extrapolation				
5	Lower PFS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−74,488.48 (dominant)
6	Higher PFS curve selections (Log-normal extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−73,943.98 (dominant)
OS parametric extrapolations				
7	Lower OS curve selections (Gompertz extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−97,759.90 (dominant)
8	Higher OS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−80,041.20 (dominant)
TTD parametric extrapolations				
9	Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	[redacted]	[redacted]	−63,939.34 (dominant)
10	Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	[redacted]	[redacted]	−62,521.41 (dominant)
Utility				

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
11	HSUV (PD: 0.678; PF: 0.794 as per TA654)	[redacted]	[redacted]	−76,290.58 (dominant)
12	AE disutilities based on literature	[redacted]	[redacted]	−74,144.15 (dominant)
Subsequent treatments				
13	Subsequent treatment distribution based on MARIPOSA trial	[redacted]	[redacted]	−71,860.37 (dominant)
14	Subsequent treatment distribution based on UK RWE	[redacted]	[redacted]	−72,676.68 (dominant)

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

Table 84: Summary of scenario analysis results (deterministic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case		[redacted]	[redacted]	−75,539.74 (dominant)
Discount rate				
1	1.5% discount rate	[redacted]	[redacted]	−66,643.24 (dominant)
Time horizon				
2	37.7-year time horizon	[redacted]	[redacted]	−75,466.39 (dominant)
OS modelling approach				
3	Left-truncated for osimertinib	[redacted]	[redacted]	−73,331.48 (dominant)
PFS definition				
4	PFS by INV for amivantamab-lazertinib and osimertinib	[redacted]	[redacted]	−75,631.03 (dominant)
PFS parametric extrapolation				
5	Lower PFS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−75,941.64 (dominant)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
6	Higher PFS curve selections (Log-normal extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−75,355.51 (dominant)
OS parametric extrapolations				
7	Lower OS curve selections (Gompertz extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−105,320.45 (dominant)
8	Higher OS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−79,423.36 (dominant)
TTD parametric extrapolations				
9	Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	[redacted]	[redacted]	−65,360.67 (dominant)
10	Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	[redacted]	[redacted]	−63,286.31 (dominant)
Utility				
11	HSUV (PD: 0.678; PF: 0.794 as per TA654)	[redacted]	[redacted]	−77,934.43 (dominant)
12	AE disutilities based on literature	[redacted]	[redacted]	−75,593.87 (dominant)
Subsequent treatments				
13	Subsequent treatment distribution based on MARIPOSA trial	[redacted]	[redacted]	−72,917.70 (dominant)
14	Subsequent treatment distribution based on UK RWE	[redacted]	[redacted]	−73,634.89 (dominant)

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

B.3.12 Subgroup analysis

The MARIPOSA trial, which forms the principal clinical evidence base for amivantamab-lazertinib in this submission, met its primary endpoint of PFS by BICR and demonstrated broadly consistent efficacy across all pre-specified endpoints (see Section B.2.7).[95] Therefore, no subgroup analyses were considered relevant in the economic analysis and were not explored.

B.3.13 Benefits not captured in the QALY calculation

The economic model presented in this submission captures many of the benefits of amivantamab-lazertinib compared with current SoC in the UK, osimertinib, including improved PFS by BICR compared with osimertinib. Furthermore, the economic model results demonstrate that amivantamab-lazertinib 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-lazertinib, there are a number of additional benefits that are not able to be captured in the model.

Amivantamab-lazertinib is an innovative, highly efficacious treatment combination that revolutionises the approach to cEGFR advanced NSCLC. This chemotherapy-free, targeted therapy uses a dual mode of action to target multiple downstream resistance mechanisms, therefore delaying subsequent progression and delivering a compelling and significant OS benefit in favour of amivantamab-lazertinib at 1L, outperforming the current SoC in patients with cEGFRm advanced NSCLC

In the management of advanced cEGFRm NSCLC, it is important for patients to receive the most effective treatment possible upfront as their 1L therapy, due to their poor prognosis and limited 2L treatment options. Although osimertinib provides initial disease control, as outlined in Section B.1.3.2, and is considered the SoC for patients with cEGFRm NSCLC in the UK, this efficacy is not consistent across high-risk patient subgroups, and disease progression on osimertinib inevitably occurs as a result of primary and acquired resistance. [11, 104] This resistance to osimertinib means that many patients either progress quickly onto 2L treatment, or die before being able to access 2L treatment, with patients treated with 1L osimertinib typically progressing in less than two years (approximately 17 to 19 months) based on RCT data.[11, 21, 71] Following disease progression due to primary or acquired resistance to osimertinib, 2L treatment options after progression on osimertinib are currently limited, consisting of non-targeted, non-specific treatments that result in poor prognosis for these patients at 2L.[7, 12-15] Clinical experts participating in an advisory board conducted by Johnson & Johnson in October 2024 noted that approximately 80% of patients receive PDC in the 2L, with the remaining 20% receiving best supportive care.[32]

Amivantamab-lazertinib is an innovative treatment combination, with results of the MARIPOSA trial demonstrating superior efficacy compared with osimertinib, with a durable clinical benefit as demonstrated by prolonged TTST (Section B.2.6.8). Additionally, through the simultaneous inhibition of both EGFR and MET, amivantamab in combination with lazertinib is anticipated to improve overall treatment efficacy, and has proven to limit the compensatory pathway activation and targeting the two major mechanisms of resistance to TKIs.[20, 21] By preventing the emergence of acquired EGFR resistance mutations and MET amplifications that could drive disease progression, amivantamab-lazertinib alters tumour biology, reducing the risk of acquired resistance compared with osimertinib.[62]

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 Section B.1.4.[37] This is particularly damaging for patients with cEGFRm NSCLC, as these mutations disproportionately affect never-smokers, as well as women and patients of Asian ethnicity.[36, 38]

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.[41] The impact of stigma on people living with lung cancer, including patients and caregivers, has been well reported, with studies demonstrating that the barrier to symptom reporting for these patients includes blame, stigma and cultural influences.[40] This perceived stigma, therefore, may have a direct impact on the timely diagnosis of disease and initiation of treatment, influencing patient outcomes.[41]

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.[162]

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-lazertinib 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.[17]

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-lazertinib to the UK NHS.

B.3.14 Validation

Clinical validation

Expert input from UK oncologists and health economists 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. Attendance at an advisory board of four clinicians and three health economists permitted alignment on key discussion points to be reached considering both clinical and technical standpoints. The advisory board was held in October 2024.[32]

As part of the advisory board, attending clinicians and health economists were asked to complete a pre-meeting survey. For the clinicians, the objective of this was:

- To validate clinical assumptions within the economic models for the MARIPOSA indication
- To validate the treatment pathway for patients with untreated cEGFRm advanced NSCLC, specifically estimating the proportion of patients receiving various SoC therapies in different treatment lines
- To elicit estimates for OS, PFS and TTD for patients with untreated cEGFRm advanced NSCLC receiving two different treatments: amivantamab-lazertinib and osimertinib

For the health economists, the objective of this was:

- To provide an overview of several key aspects of the modelling of the MARIPOSA trial indication for untreated cEGFRm advanced NSCLC
- To validate key modelling assumptions for the MARIPOSA indication, including OS, PFS and TTD extrapolations

During the advisory board, expert clinical opinion was sought to validate the following inputs:

- Generalisability of the MARIPOSA trial population to the patient population with untreated, cEGFRm advanced NSCLC in England and Wales
- The most appropriate way to model OS, PFS and TTD for both amivantamab-lazertinib and osimertinib
- Scenario analyses to be explored
- The appropriateness of utility values used in the CEM
- The potential impact that the availability of an SC formulation may have on amivantamab use in the NHS

For survival data for amivantamab-lazertinib and osimertinib 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.3.3.1.

During the advisory board, all clinicians and health economists participated fully, permitting alignment to be reached on each discussion point and ensuring that the selected approaches reflected both clinical reality and technical validity.

Technical validation

The model was developed in accordance with NICE guidelines.[136] In total, advice was sought from five health economic experts during the development of the model, including three at the October 2024 advisory board, and feedback was taken into account when developing the CEM for this submission where possible.[32]

In addition, sanity checks were performed on the model by an independent reviewer who was not involved in model development. The checklist employed incorporated the TECH-VER checklist.[163] The stress test ensured that the expected effect is observed when key inputs are varied in the model (e.g. when utilities for all health states and for AEs are set to 0, all QALYs should result equal to 0).

B.3.15 Interpretation and conclusions of economic evidence

Osimertinib represents the current 1L SoC for patients with cEGFRm NSCLC in the UK, with data from the 'MARIPOSA-like' cohort of the UK NCRAS dataset showing that between 2021 and 2023, following the introduction of osimertinib to UK clinical practice in 2020,[33] 90.5% (86/95) of patients who received 1L treatment were treated with osimertinib.[10] Osimertinib representing current SoC in the UK is supported by comprehensive clinical opinion sought by Johnson & Johnson across multiple advisory boards, and has been recently accepted as SoC by the NICE Committee in the ongoing appraisal of osimertinib with PDC for untreated cEGFRm advanced NSCLC [ID6328] in October 2024.[10, 30-32] As such, osimertinib was modelled as the sole key comparator to amivantamab-lazertinib in the *de novo* CEM developed for this submission.

However, patients treated with 1L osimertinib typically progress in less than two years (approximately 17 to 19 months) based on RCT data.[21, 71] Importantly, although osimertinib provides initial disease control, almost all patients treated with 1L osimertinib experience primary or secondary resistance, with the most common mechanisms of resistance to osimertinib related to alterations in the EGFR and MET pathways.[11, 104] In the management of advanced cEGFRm NSCLC, it is important for patients to receive the most effective treatment possible as their 1L therapy, due to their poor prognosis and limited 2L treatment options. Therefore, despite the availability of osimertinib 1L, patients with cEGFRm advanced NSCLC continue to face an urgent unmet need for a more efficacious, targeted treatment that can improve the therapeutic value for patients at 1L by delaying progression and improving survival. This unmet need is underscored by data from the 'MARIPOSA-like' cohort of the NCRAS database, which show that patients receiving osimertinib monotherapy had a mOS of 28.1 months (95% CI: 23.0, 35.7; n=126).[10] As such, the real-world survival of patients receiving osimertinib may be even lower than that reported in the MARIPOSA trial (mOS: 37.3 months; 95% CI: 32.5, NE).[95]

The economic modelling results presented in this submission demonstrate that amivantamab-lazertinib, at the amivantamab and lazertinib with-PAS prices, represents a cost-effective use of NHS resources when compared with osimertinib at its list price, dominating osimertinib in the base case and all scenario analyses (probabilistic and deterministic). These results show the model to be robust to variation in inputs, which is further 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 from ISPOR and the NICE DSU.

B.3.15.1 Strengths and limitations of the evidence base

Strengths

The MARIPOSA trial represents the primary evidence source for amivantamab-lazertinib in the population of interest to this submission: adult patients with untreated cEGFRm advanced NSCLC. The results of the quality assessment of the MARIPOSA 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 MARIPOSA trial is a registrational Phase 3 randomised trial which provides direct head-to-head comparative data for amivantamab in combination with lazertinib versus osimertinib. The trial includes a large number of patients (N=858 randomised) in the specific patient population relevant to this submission. As a result, this trial is highly generalisable to patients with cEGFRm advanced NSCLC in typical UK clinical practice. Furthermore, the MARIPOSA trial considered a

wide range of endpoints (PFS, OS, ORR, DOR, TTD, TTST, PFS2 and TTSP) that are highly clinically relevant to patients with untreated cEGFRm advanced NSCLC, and reflect outcomes assessed in prior appraisals of therapies in cEGFRm advanced NSCLC, including those of osimertinib monotherapy [TA654] and osimertinib in combination with chemotherapy [ID6328].[8, 29] In addition, RWE from the NCRAS database can provide insights from broader clinical settings beyond controlled trial environments, capturing a more representative spectrum of patient experiences and treatment responses. While clinical efficacy data from the RWE were not incorporated in the economic model, the evidence presented in Section B.1.3.1 supports the reliability of the economic evaluation by aligning model outcomes with real-world clinical scenarios.

The CEM developed for this submission leverages an established model framework frequently used in previous NICE appraisals, including for osimertinib (monotherapy [TA654] or in combination with platinum-based chemotherapy [NICE ID6328]).[8, 29] The modelling approaches and assumptions used were informed by the latest available guidance in addition to clinical and health economist opinion. Throughout this submission, conservative approaches have been taken where necessary, to ensure confidence in the cost-effectiveness of amivantamab-lazertinib versus osimertinib. The curve choices for the extrapolation for PFS, OS and TTD were made 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 October 2024 advisory board.[32] With the base case curve selection for PFS and TTD, patients are modelled to continue treatment post-progression, given that the proportion of patients modelled to have discontinued amivantamab-lazertinib was lower that the proportion modelled to have progressed on amivantamab-lazertinib treatment at 5- and 10-years (B.3.3.2.3). The continuation of treatment post-progression based on PFS and TTD curves, and the use of TTD as a measure of treatment duration, have both been previously used in NICE appraisals for oncology, including for osimertinib (TA654 and ID6328).[8, 29]

Limitations

The mOS for amivantamab-lazertinib was not estimable at the 13th May 2024 DCO, while it was 37.3 months in the osimertinib arm, thus introducing uncertainty with respect to long-term extrapolation of these data. However, mOS not being reached is not reflective of data immaturity, and instead reflects the greater proportion of patients remaining alive in the amivantamab-lazertinib arm during the trial period ([redacted]/429, [redacted]%) compared to the control arm ([redacted]/41.3, [redacted]%). These data therefore underscore the superior efficacy of amivantamab-lazertinib as compared with osimertinib. In the economic analysis, the proportion of patients modelled to be alive at 5- and 10-years ([redacted]% and [redacted]%, respectively) was closely aligned with estimates provided by UK clinical experts ([redacted]% and [redacted]%, respectively) and extrapolations presented in previous appraisals for patients with cEGFRm NSCLC (TA654). To explore the impact of any uncertainty relating to long-term estimation of outcomes, a variety of scenario analyses were explored in which alternative extrapolations were implemented for PFS, OS and TTD, and in which longer-term osimertinib OS data from the FLAURA trial were incorporated into the model via a left-truncation (Section B.3.11.3). None of these scenarios resulted in any changes to the conclusion of cost-effectiveness, with amivantamab-lazertinib at PAS price remaining dominant compared with osimertinib at list price. As such, while this uncertainty is unavoidable within the model, these results indicate its impact on cost-effectiveness conclusions to be limited.

Furthermore, Johnson & Johnson announced via a press release on 7th January 2025 that amivantamab and lazertinib have shown a statistically significant and clinically meaningful

improvement in OS compared to osimertinib in the Phase 3 MARIPOSA trial (B.2.6.2).[23] While only top-line data are currently available from this final analysis, Johnson & Johnson would be pleased to provide further analyses using the updated data once full data are available, thus reducing any remaining uncertainty still further.

A second consideration in the current evidence base is that the distribution of subsequent treatment options derived from clinician estimates from the advisory board held by Johnson & Johnson in October 2024 (base case) differ slightly from those derived from the MARIPOSA trial and from UK RWE. Given that some of the subsequent treatments used in the MARIPOSA trial are not available in UK clinical practice, the subsequent treatment distributions from MARIPOSA may not represent typical expected UK clinical practice. Instead, the distribution of treatments implemented in the base case analysis was based on clinical estimates from the advisory board, as this was considered to be the most relevant source for UK clinical practice.[32] To explore the impact of this uncertainty, scenario analyses were explored in which the distribution of subsequent treatments were derived from the MARIPOSA trial, or from UK-based RWE (patients in the 'MARIPOSA-like' cohort of the NCRAS database who received 1L osimertinib monotherapy and received any subsequent treatment (n=65)), described in B.3.11.3.5 and B.3.11.3.6, respectively.[10, 21] These scenarios resulted in no change to the cost-effectiveness conclusions from the base case, suggesting that the model is unlikely to be substantially affected by this uncertainty.

B.3.15.2 Conclusions

The registrational Phase III MARIPOSA trial is a robust and well-reported trial, with the results demonstrating the amivantamab-lazertinib achieves more durable response rates and prolongs the time until disease progression compared with osimertinib in adult patients with cEGFRm advanced NSCLC. Such benefits are expected to translate to survival benefits in patients treated with amivantamab-lazertinib versus the current SoC.

The cost-effectiveness analysis demonstrates that amivantamab-lazertinib represents value for money for the NHS. A positive NICE recommendation for amivantamab-lazertinib will improve 1L treatment options for patients with cEGFRm advanced NSCLC in the UK, providing upfront treatment efficacy and delaying disease progression and need for subsequent treatment with non-targeted, sub-optimal treatments. In conclusion, amivantamab-lazertinib is anticipated to fulfil the substantial unmet need for a more efficacious, targeted treatment option in patients with cEGFRm advanced NSCLC, improving therapeutic value for patients at 1L compared with current SoC, 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 lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256]

Addendum

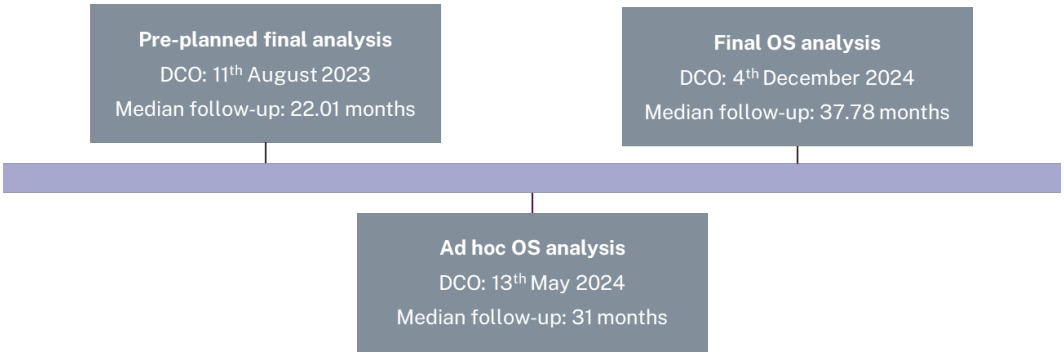
March 2025

1. Background/context

The original Company Submission (CS) presented data from the 11th August 2023 and 13th May 2024 data-cut offs (DCOs) of the MARIPOSA trial (Figure 1):[1-3]

- **11th August 2023 DCO:** The protocol-specified, pre-planned final analysis, at which point amivantamab-lazertinib met the MARIPOSA trial primary endpoint, PFS.[1] The statistical alpha spending (0.05) for the primary endpoint of PFS was exhausted at the point of this analysis, so data for this endpoint were not collected in subsequent DCOs.[2]
- **13th May 2024 DCO:** An *ad hoc* OS analysis conducted at the request of the European Medicines Authority (EMA), to assist with the assessment of overall treatment benefit.[3]
- **4th December 2024 DCO:** The protocol-specified final overall survival analysis (OS), for which only topline results were available from a press release at the time of the original CS to NICE on 15th January 2025.[4] These topline data were presented within the original CS. Additional efficacy and safety data have since become available, and are presented within this addendum document.[5] An updated model in which these longer-term data are incorporated has been provided alongside this document (see Section 3 for further details on modelling updates).

Figure 1: MARIPOSA trial DCOs



Abbreviations: DCO: data cut-off; OS: overall survival.

Therefore, this addendum presents the latest available data from the MARIPOSA trial (DCO: 4th December 2024). Alongside the associated updated economic model, it addresses Key Issue 2 raised by the EAG in their report, in which the EAG stated a preference for the most recent DCO available for all outcomes to be presented and to inform the economic model.[5] The definitions of all efficacy and safety outcomes and analysis sets presented below are as previously defined in the original CS (see Section B.2.3.2 of Document B of the original CS for definitions).[2]

Additionally, since the original CS, amivantamab-lazertinib received marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) on 5th March 2025 for the 1L treatment of advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.[6]

2. Clinical effectiveness results

The MARIPOSA trial is an ongoing, randomised, multicentre, Phase 3 trial which compares amivantamab-lazertinib to osimertinib in combination with placebo (the osimertinib arm) and lazertinib in combination with placebo (the lazertinib arm) for patients with treatment-naïve, locally advanced or metastatic cEGFRm

NSCLC. The lazertinib monotherapy arm was only included to assess the contribution of each individual component. As described in Section B.2.3.3 of the CS, the demographic and baseline characteristics were well-balanced between the three treatment arms. Given lazertinib monotherapy is not indicated for the treatment of advanced NSCLC with cEGFR mutations, efficacy and safety data for the lazertinib monotherapy arm are not presented within the submission.

Key secondary endpoint: overall survival

A comparison between OS at the 13th May 2024 DCO (as previously presented in the original CS) and at the 4th December 2024 DCO is presented in Table 1.

At the 4th December 2024 DCO, with a median study follow-up of 37.8 months, [redacted] deaths were observed in the amivantamab-lazertinib and osimertinib arms combined.[5, 7] There were [redacted] deaths in the amivantamab-lazertinib arm and [redacted] deaths in the osimertinib arm. This translated to a statistically significant and clinically meaningful [redacted] risk reduction in death in the amivantamab-lazertinib arm compared with the osimertinib arm (HR: 0.75; 95% CI: 0.61, 0.92; [redacted]).[5, 7]

The median OS (mOS) was not estimable in the amivantamab-lazertinib arm (95% CI: 42.94, NE) and 36.73 months (95% CI: 33.41, 41.03) in the osimertinib arm.[7] The results presented herein highlight a significantly greater proportion of patients surviving within the amivantamab-lazertinib arm during the trial period, in stark contrast to the osimertinib arm. This observation serves to underscore the clinically meaningful and superior efficacy of amivantamab-lazertinib when compared with osimertinib..[5] This is further supported by the 95% CIs for the two treatment arms being mutually exclusive: the lower 95% CI of the amivantamab-lazertinib arm is numerically higher than the upper 95% CI for the osimertinib arm.[5] The mOS for osimertinib of [redacted] months (median follow-up in osimertinib arm: [redacted] months) is comparable to that reported in the osimertinib arm of the FLAURA trial at a similar duration of follow-up (mOS: 38.9 months; median follow-up: 35.8 months).[8] At 42 months, the survival rate was 56% for patients in the amivantamab-lazertinib arm, versus 44% for patients in the osimertinib arm, corresponding to a significantly greater proportion of patients remaining alive in the amivantamab-lazertinib arm.[5]

The Kaplan-Meier (KM) and cumulative hazard plots for OS at the 4th December 2024 DCO are presented in Figure 2 and Figure 3, respectively. Overall, the OS curves demonstrate a clear separation occurring prior to the 12-month mark, followed by a continuous widening over time in favour of amivantamab-lazertinib, which has been confirmed by a key UK clinician during a validation of FA OS.[29] This trend corresponds to an increasingly robust HR over time. Moreover, the observed flattening of the slope for the amivantamab-lazertinib arm suggests a durable OS benefit.

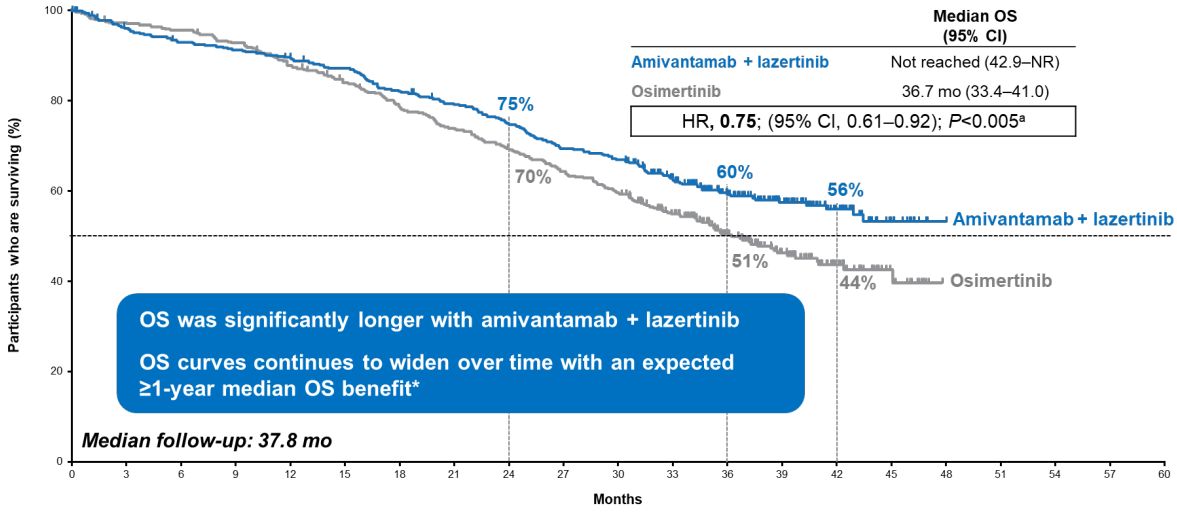
Amivantamab-lazertinib is the first and only regimen to have demonstrated a clinically meaningful and statistically significant OS benefit compared with osimertinib. These longer-term OS data, which are incorporated into the updated economic model submitted alongside this addendum (base case results presented in Section 4) directly mitigate the concerns of the EAG raised in Key Issue 4 of their report re\garding uncertainty in the l\fong-term predictions for OS.

Table 1: Summary of OS (13th May 2024 and 4th December 2024 DCOs; FAS)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	NE (NE, NE)	37.3 (32.5, NE)	NE (42.9, NE)	36.7 (33.4, 41.0)
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.75 [redacted]	0.70 [redacted]	0.75 [redacted]	0.70 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.61 [redacted]	0.53 [redacted]	0.60 [redacted]	0.51 [redacted]
42-month event-free rate (95% CI)	NR	NR	0.56 [redacted]	0.44 [redacted]
Treatment difference				
p-value[a]	0.019		[redacted]	
HR (95% CI)[b]	0.77 (0.61, 0.96)		0.75 (0.61, 0.92)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; OS: overall survival.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024).[3] Gadgeel *et al*. WCLC 2024.[9] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5] Chih-Hsin Yang et al. ELCC 2025.[7]

Figure 2: KM plot of OS (4th December 2024 DCO; FAS)



Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is predicted to exceed 1 year.

Note: Last participant was enrolled in May 2022. Clinical cutoff date was December 4, 2024. In total, 390 deaths had occurred in the amivantamab + lazertinib (173 deaths) and osimertinib (217 deaths) arms.

[a]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; NR: not reached; OS: overall survival.
Source: Chih-Hsin Yang et al. ELCC 2025.[7]

Figure 3: Cumulative hazard plot for OS (4th December 2024 DCO; FAS)

Abbreviations: ami+laz: amivantamab-lazertinib; DCO: data cut-off; OS: overall survival.

In alignment with data from the previously presented DCOs, these data continue to demonstrate that amivantamab-lazertinib offers an innovative therapeutic option of two targeted treatments that delivers a clinically meaningful difference in efficacy compared with standard of care (SoC). These OS results presented

in the latest DCO reinforce the importance of amivantamab-lazertinib and its potential to significantly improve patient survival outcomes compared with current SoC. It is noteworthy that amivantamab-lazertinib is the only chemotherapy-free treatment to demonstrate a significant and clinically meaningful survival benefit versus osimertinib in the first-line treatment of patients with EGFR-mutated lung cancer.

Key secondary endpoint: progression-free survival after first subsequent therapy

First subsequent systemic therapy

At the 4th December DCO, the use of subsequent systemic therapy after treatment discontinuation due to disease progression was recorded in [redacted] patients in the amivantamab-lazertinib arm and [redacted] patients in the osimertinib arm.[5] Table 2 summarises the most common first subsequent systemic therapy classes in the amivantamab-lazertinib and osimertinib arms. In general, first subsequent therapies were balanced between amivantamab-lazertinib and osimertinib, although a higher proportion of patients received any chemotherapy in 2L after 1L osimertinib ([redacted]) compared with those receiving 1L amivantamab-lazertinib ([redacted]).[5] In the amivantamab-lazertinib arm, a greater proportion of patients received targeted TKI therapies at 2L ([redacted]) compared with patients in the osimertinib arm ([redacted]).[5]

In the UK, treatment options for patients following disease progression due to primary or acquired resistance to osimertinib are currently limited and associated with poor patient outcomes, with the NICE lung cancer guidelines (NG122) not recommending the use of any TKIs following osimertinib use.[10-15] The clinical benefit of the dual mechanism of action of amivantamab-lazertinib is two-fold: it confers a prolonged response in the 1L setting compared with osimertinib, and has the potential to alter the biology of the disease, which may impact response to subsequent treatments. Final analysis results of the pivotal MARIPOSA trial show that use of amivantamab-lazertinib in 1L not only delays time to 2L treatment, as demonstrated by a clinically meaningful and significantly improved PFS when compared with osimertinib, but also leads to improved, and sustained, progression-free survival after first subsequent therapy (PFS2, see below), time to symptomatic progression (TTSP) and time to subsequent treatment (TTST).

Table 2: Summary of subsequent systemic therapy received by patients who discontinued treatment due to disease progression (13th May 2024 and 4th December DCOs; FAS)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Patients receiving one or more subsequent systemic therapies after treatment discontinuation due to disease progression, %	72	74	[redacted]	[redacted]
1L of subsequent systemic therapies, %				
Doublet chemotherapy	41	45	[redacted]	[redacted]
Doublet chemotherapy plus VEGFi/IO	12	20	[redacted]	[redacted]
Third-generation TKI	27	16	[redacted]	[redacted]
Other TKIs (not including third-generation)	7	5	[redacted]	[redacted]
TKI-based combination regimen	8	7	[redacted]	[redacted]

Abbreviations: 1L: first-line; DCO: data cut-off; FAS: full analysis set; INV: investigator; IO: immuno-oncology; NR: not reported; TKI: tyrosine kinase inhibitor; VEGFi: Vascular Endothelial Growth Factor inhibitors.
Source: Gadgeel *et al.* WCLC 2024.[9] Cho *et al.* 2024.[1] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Key secondary endpoint: progression-free survival after first subsequent therapy

At the 4th December 2024 DCO, patients in the amivantamab-lazertinib arm had a [redacted] reduction in the risk of progression or death after their first subsequent therapy (PFS2), compared to patients in the osimertinib arm ([redacted]).[5] In the amivantamab-lazertinib arm, the median time to PFS2 was [redacted] months (95% CI: [redacted]) compared to [redacted] months in the osimertinib arm (95% CI: [redacted]) (Table 3).[5] 30-, 36-, and 42-month event-free rates were [redacted], respectively, in the amivantamab-lazertinib arm and [redacted], respectively, in the osimertinib arm.[5] Of note, the difference between the amivantamab-lazertinib and osimertinib event-free rates at 36-months increased after a longer duration of follow-up, with a difference of 8% at the May 2024 DCO and [redacted] at the December 2024 DCO, demonstrating the durable response provided by amivantamab-lazertinb.[5, 9] The associated KM plot for PFS2 is presented in Figure 4. The plot shows a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around twelve months after randomisation.

These results suggest that, in addition to increasing time to disease progression or death (Section B.2.6.1 in Document B of the original CS), the durable response observed with amivantamab-lazertinib in 1L confers a sustained benefit in delaying patients' subsequent progression on 2L treatment, and that amivantamab-lazertinib is associated with a PFS2 benefit compared with osimertinib, regardless of the 2L treatment received. These data suggest that the prolonged sustained clinical benefit conferred with amivantamab-lazertinib compared with osimertinib may continue after disease progression.[5]

Table 3: Summary of PFS2 (13th May 2024 and 4th December DCOs; FAS)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	NE (36.0, NE)	32.4 (29.3, NE)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.73[redacted]	0.65[redacted]	0.73[redacted]	0.65[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.57[redacted]	0.49[redacted]	[redacted]	[redacted]
42-month event-free rate (95% CI)	NR	NR	[redacted]	[redacted]
Treatment difference				
Nominal p-value[a]	0.004		[redacted]	
HR (95% CI)[b]	0.73 (0.59, 0.91)		[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; PFS2: progression-free survival after first subsequent therapy.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 5, page 10.[3] Gadgeel *et al.* WCLC 2024.[9] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Figure 4: KM plot of PFS2 (4th December 2024 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib; PFS2: progression free survival after first subsequent therapy.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Key secondary endpoint: time to symptomatic progression

At the 4th December 2024 DCO, patients in the amivantamab-lazertinib arm had a statistically significant 31% reduction in the risk of symptomatic progression or death compared to patients in the osimertinib arm (HR: 0.69; 95% CI: 0.57, 0.83; Table 4).[7] Median TTSP was months in the amivantamab-lazertinib arm (95% CI: 36.0, NE) compared to 29.3 months in the osimertinib arm (95% CI: 26.4, 33.4). Of note, the difference between the amivantamab-lazertinib and osimertinib event-free rates at 36-months increased after a longer duration of follow-up, with a difference of at the May 2024 DCO and at the December 2024 DCO, demonstrating the durable response provided by amivantamab-lazertinb.[3, 5]

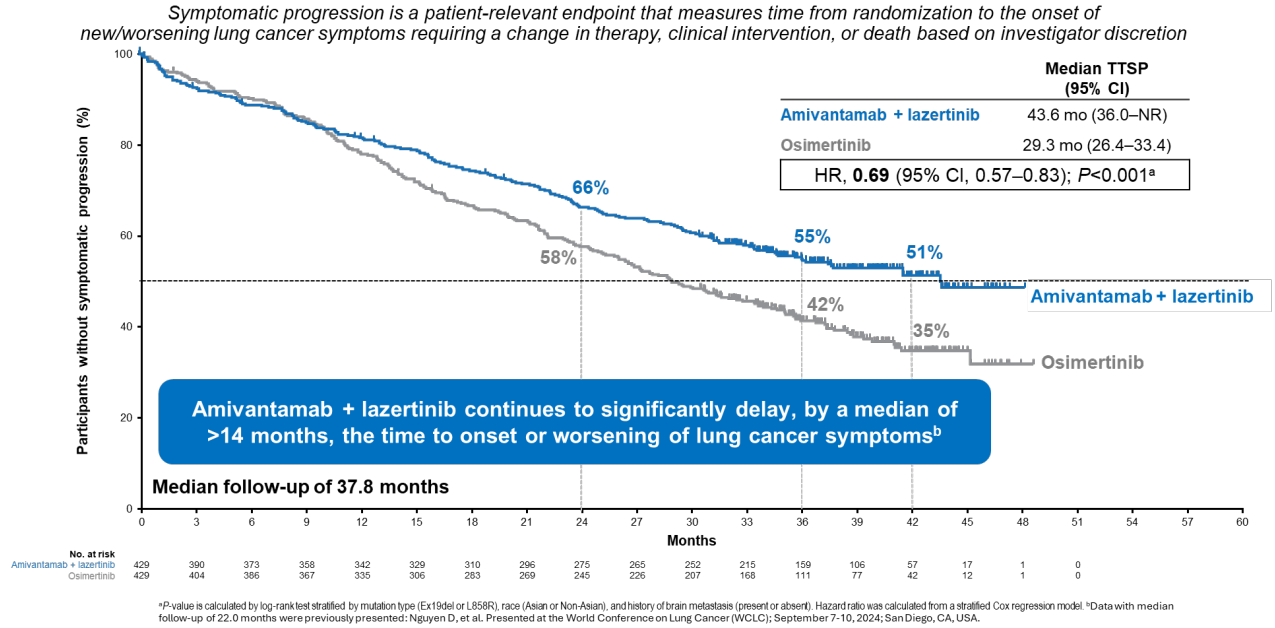
The associated KM plot for TTSP is presented in Figure 5. The plot shows a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around 12 months after randomisation.

Table 4: Summary of TTSP (13th May 2024 and 4th December 2024 DCOs; FAS)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic PD	[redacted]	[redacted]	[redacted]	[redacted]
Death without symptomatic PD	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	[redacted]	[redacted]	43.6 (36.0, NE)	29.3 (26.4, 33.4)
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	0.74[redacted]	0.67[redacted]	0.74[redacted]	0.67[redacted]
24-month event-free rate (95% CI)	0.67[redacted]	0.59[redacted]	[redacted]	[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	[redacted]	[redacted]	0.55[redacted]	0.42[redacted]
42-month event-free rate (95% CI)	NR	NR	0.51[redacted]	0.35[redacted]
Treatment difference				
p-value[a]	[redacted]		[redacted]	
HR (95% CI)[b]	[redacted]		0.69 (0.57, 0.83)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; PD: progressive disease; TTSP: time to symptomatic progression.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 6, page 12.[3] Nguyen *et al.* WCLC 2024.[16] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5] Chih-Hsin Yang et al. ELCC 2025.[7]

Figure 5: KM plot of TTSP (4th December 2024 DCO; FAS)



aP-value is calculated by log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model. bData with median follow-up of 22.0 months were previously presented: Nguyen D, et al. Presented at the World Conference on Lung Cancer (WCLC); September 7-10, 2024; San Diego, CA, USA.

Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; NR: not reached; TTSP: time to symptomatic progression.
Source: Chih-Hsin Yang et al. ELCC 2025.[7]

Exploratory endpoint: time to treatment discontinuation

TTD was investigated as an exploratory endpoint in the MARIPOSA trial. At the 4th December 2024 DCO, the median time to treatment discontinuation or death for the amivantamab-lazertinib arm was [redacted] months (95% CI: [redacted]), as compared to [redacted] months (95% CI: [redacted]) in the osimertinib arm (HR: [redacted]), as presented in Table 5.[5] The 30-, 36-, and 42-month event-free rates were [redacted]%, respectively, in the amivantamab-lazertinib arm and [redacted]%, respectively, in the osimertinib arm.[5]

The associated KM and cumulative hazard plots for TTD are presented in Figure 6 and Figure 7, respectively. The KM plot shows a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around 22 months after randomisation.

This combined TTD analysis demonstrates a prolonged median TTD in both arms as compared with median PFS. At the 4th December 2024 DCO, the median TTD in the amivantamab-lazertinib arm ([redacted] months) was longer than the median PFS (assessed by BICR) at the 11th August 2023 DCO (23.7 months), which is primarily driven by the prolonged TTD for the lazertinib component (see Figure 18).[1, 5] This difference is even more pronounced in the osimertinib arm, with a median TTD of [redacted] months compared with a median PFS of 16.6 months.[1, 5] The use of TKIs such as osimertinib post-progression is common and reflective of UK clinical practice, as confirmed by UK clinicians at an advisory board held by Johnson & Johnson in October 2024.[17] This post-progression use of TKIs is also in line with clinical opinion from the British Thoracic Oncology Group in the Committee meeting for the ongoing NICE appraisal of osimertinib in combination with pemetrexed and PBC for untreated EGFR mutation-positive advanced NSCLC (NICE ID6328), who noted that treatment with osimertinib would be continued until loss of clinical benefit or unmanageable toxicities.[18] Through delaying treatment resistance and subsequent progression, amivantamab-lazertinib addresses the unmet need for a more efficacious 1L treatment option that maximises long-term effectiveness.

Within the economic model, TTD curves were fitted separately for the amivantamab and lazertinib components of the amivantamab-lazertinib arm to ensure that the efficiency gains and costs associated with each component of the combined therapy regimen is reflective of what is reported in the MARIPOSA trial and is representative of clinical practice. The decision to model the TTD separately was informed by clinical insights and data from the MARIPOSA CSR, and is in alignment with the preferences of the EAG in their report.[3]

Table 5: Summary of TTD (13th May 2024 and 4th December 2024 DCOs; FAS)

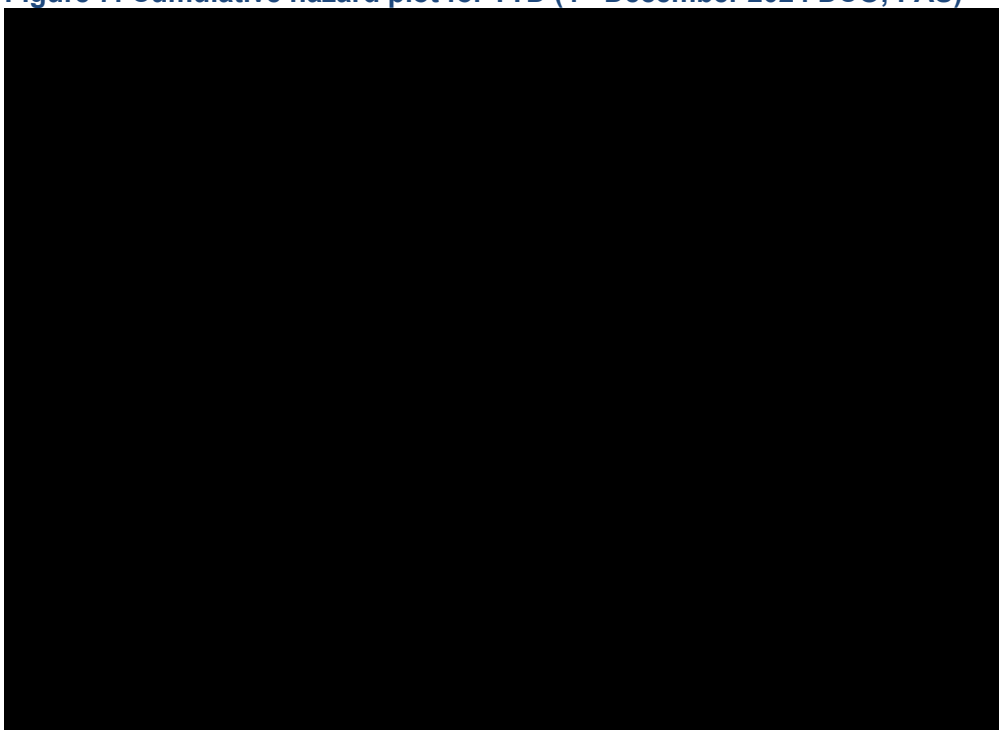
	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	26.3 (22.3, 30.4)	22.6 (20.3, 24.5)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.52[redacted]	0.46[redacted]	0.52[redacted]	0.46[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.40[redacted]	0.29[redacted]	[redacted]	[redacted]
42-month event-free rate (95% CI)	NR	NR	[redacted]	[redacted]
Treatment difference				
p-value[a]	0.014		[redacted]	
HR (95% CI)[b]	0.80 (0.68, 0.96)		[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; TTD: time to treatment discontinuation.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 10, page 19.[3] Gadgeel *et al.* WCLC 2024.[9] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Figure 6: KM plot of TTD (4th December 2024 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib; TTD: time to treatment discontinuation.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Figure 7: Cumulative hazard plot for TTD (4th December 2024 DCO; FAS)



Abbreviations: ami+laz: amivantamab-lazertinib; DCO: data cut-off.

Exploratory endpoint: time to subsequent therapy

At the 4th December 2024 DCO, the median time to initiate subsequent therapy or death for the amivantamab-lazertinib arm was [redacted] months (95% CI: [redacted]), as compared to [redacted] months (95% CI: [redacted]) in the osimertinib arm (HR: [redacted]) (Table 6).

These results demonstrate the durability of the clinical benefit offered by amivantamab-lazertinib, prolonging time until patients require a subsequent therapy as compared with osimertinib. This is also supported by the event-free rates observed for these patients; the 30-, 36-, and 42-month event-free rates were [redacted]%, respectively, in the amivantamab-lazertinib arm, compared with [redacted]%, respectively, in the osimertinib arm.

The KM curve for TTST is presented in Figure 8, showing a distinct and maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around 12 months after randomisation.

Table 6: Summary of time to subsequent systemic anti-cancer therapy (13th May 2024 and 4th December 2024 DCOs; FAS)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	30.0 (26.3, 36.0)	24.0 (22.5, 26.2)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.57[redacted]	0.50[redacted]	0.57[redacted]	0.50[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.45[redacted]	0.32[redacted]	[redacted]	[redacted]
42-month event-free rate (95% CI)	NR	NR	[redacted]	[redacted]
Treatment difference				
p-value[a]	0.005		[redacted]	
HR (95% CI)[b]	0.77 (0.65, 0.93)		[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).

[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Table 11, page 21.[3] Gadgeel *et al*. WCLC 2024.[9] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Figure 8: KM plot of time to subsequent anti-cancer therapy (4th December 2024 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Safety results

Safety data from the 4th December 2024 DCO are presented below. J&J note that not all of the safety data presented in Section B.2.10 of the original CS are available from the 4th December 2024 DCO, so cannot be provided here. However, all available safety data from this latest DCO (4th December 2024) are presented, and the economic model has been updated with these latest data (see Section 3).

Treatment disposition

At the 4th December 2024, [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) remained on treatment in the amivantamab-lazertinib and osimertinib arms, respectively (Table 7).[5] The most common reason for discontinuation of study treatment in both arms was disease progression, with a higher proportion of patients in the osimertinib arm discontinuing treatment due to disease progression [redacted] than in the amivantamab-lazertinib arm [redacted].[5] Overall, more patients discontinued all study treatment due to an AE from the amivantamab-lazertinib arm ([redacted]%) than the osimertinib arm ([redacted]%).[5]

Table 7: Summary of treatment disposition (11th August 2023 and 4th December 2024 DCOs; SAS)

Event, n (%)	11th August 2023 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)

Treatment disposition				
Patients ongoing any study treatment	230 (55)	213 (50)	[redacted]	[redacted]
Discontinued all study treatment	191 (45)	215 (50)	[redacted]	[redacted]
Interruption of amivantamab[a]	206 (49)	N/A	NR	NR
Reason for discontinuation of all study treatment				
Progressive disease	86 (20)	154 (36)	[redacted]	[redacted]
AE	86 (20)	50 (12)	[redacted]	[redacted]
Withdrawal by patient	14 (3)	10 (2)	[redacted]	[redacted]
Physician decision	2 (0.5)	1 (0.2)	[redacted]	[redacted]
Non-compliance with study drug	1 (0.2)	0	[redacted]	[redacted]
Lost to follow-up	1 (0.2)	0	[redacted]	[redacted]
Other	1 (0.2)	0	NR	NR

[a] Within the first four months.
Abbreviations: AE: adverse event; DCO: data cut-off; IRR: infusion-related reaction; N/A: not applicable; NR: not reported; SAS: safety analysis set.
Sources: Cho *et al.* 2024 (Figure S2).[1] Campelo *et al.* ELCC 2024.[19] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Overview of TEAEs

An overall summary of TEAEs for the safety population in the MARIPOSA trial at the 11th August 2023 and 4th December 2024 DCOs is presented in Table 8.[1, 2, 5] At the 4th December 2024 DCO, almost all patients experienced at least one AE: [redacted] of patients in the amivantamab-lazertinib arm and [redacted] of patients in the osimertinib arm.[5] Overall, amivantamab-lazertinib was well-tolerated and consistent with the observations from the primary analysis.[1, 5]

Grade 3 or higher TEAEs were observed with a higher incidence in the amivantamab-lazertinib arm ([redacted]) compared with the osimertinib arm ([redacted]); [redacted] and [redacted] were considered related to amivantamab-lazertinib or osimertinib treatment, respectively.[5] This difference is almost entirely driven by the incidence of Grade 3 TEAEs in the amivantamab-lazertinib and osimertinib arms ([redacted] and [redacted] respectively).[5] Grade 3 or higher TEAEs observed in the amivantamab-lazertinib arm were mostly driven by AEs related to EGFR and mesenchymal epithelial transition (MET) inhibition.[5] The most common Grade 3 or higher TEAEs (≥10% of patients in any arm) were rash (amivantamab-lazertinib: [redacted] osimertinib: [redacted]) and paronychia (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]).[5]

Incidence of SAEs was comparable between the two treatment arms, experienced by [redacted] patients ([redacted]%) and [redacted] patients ([redacted]) in the amivantamab-lazertinib and osimertinib arms, respectively.[5] The most common SAEs (≥5% of patients in any arm) were pulmonary embolism (amivantamab-lazertinib: [redacted] osimertinib: [redacted]) and pneumonia (amivantamab-lazertinib: [redacted] osimertinib: [redacted]).[5] TEAEs leading to death were reported in [redacted] patients ([redacted]) in the amivantamab-lazertinib arm and [redacted] patients ([redacted]) in the osimertinib arm. There were no specific patterns of preferred terms identified for these events.[5]

TEAEs leading to the discontinuation of any study drug was reported in [redacted] patients ([redacted]) in the amivantamab-lazertinib arm compared with [redacted] patients ([redacted]) in the osimertinib arm.[5] Overall, [redacted] and [redacted] participants from amivantamab-lazertinib and osimertinib arms, respectively, discontinued all treatments due to adverse events. TEAEs leading to dose reduction was reported in [redacted] patients ([redacted]) in

the amivantamab-lazertinib arm compared with [redacted] patients [redacted]) in the osimertinib arm, most commonly (≥5% of patients in any arm) due to rash (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]), paronychia (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]), and dermatitis acneiform (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]).[5] TEAEs leading to dose interruption was reported in [redacted] patients ([redacted]) in the amivantamab-lazertinib arm and [redacted] in the osimertinib arm.[5] As discussed in Section B.2.10.1, early dose modifications of amivantamab-lazertinib do not adversely affect the efficacy of amivantamab-lazertinib.[19]

Table 8: Overall summary of TEAEs (11th August 2023 and 4th December 2024 DCOs; SAS)

Event, n (%)	11th August 2023		4th December 2024	
	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with ≥1 AE	421 (100)	425 (99)	[redacted]	[redacted]
Related AEs[a]	414 (98)	378 (88)	[redacted]	[redacted]
AEs leading to death[b]	34 (8)	31 (7)	[redacted]	[redacted]
Serious AEs	205 (49)	143 (33)	[redacted]	[redacted]
Related serious AEs[a]	97 (23)	24 (6)	[redacted]	[redacted]
AEs leading to discontinuation of any study agent	147 (35)	58 (14)	[redacted]	[redacted]
AEs leading to discontinuation of amivantamab	145 (34)	N/A	[redacted]	N/A
Related AEs to amivantamab[a]	100 (24)	N/A	[redacted]	N/A
AEs leading to dose reduction of any study agent	249 (59)	23 (5)	[redacted]	[redacted]
AEs leading to dose reduction of amivantamab	193 (46)	N/A	[redacted]	N/A
Related AEs to amivantamab[a]	184 (44)	N/A	[redacted]	N/A
AEs leading to dose interruption of any study agent[c]	350 (83)	165 (39)	[redacted]	[redacted]
AEs leading to dose interruption of amivantamab	328 (78)	N/A	[redacted]	N/A
Related AEs to amivantamab[a,c]	282 (67)	N/A	[redacted]	N/A
Grade ≥3 AEs	316 (75)	183 (43)	[redacted]	[redacted]
Related grade ≥3 AEs[a]	252 (60)	59 (14)	[redacted]	[redacted]
Maximum toxicity grade				
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]

Event, n (%)	11th August 2023		4th December 2024	
	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]

[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.
[c] Excludes infusion related reactions.
Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set; TEAE: treatment-emergent adverse event.
Sources: Cho *et al.* 2024 (Table 3, S10, S11).[1] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 24, page 103.[2] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

AEs of special interest

AESIs were prospectively identified based upon the identified safety profile of amivantamab. Pre-defined AESIs per the protocol were IRRs, rash, and pneumonitis/interstitial lung disease.[20] VTE events were later identified as a risk for the amivantamab-lazertinib arm within the first four months of study treatment and were added as an AESI during the study.

As discussed in Section B.2.11 of Document B of the CS, the clinical trial programme PALOMA is assessing the safety and feasibility of a SC amivantamab formulation in advanced solid malignancies, including NSCLC, with the potential to reduce treatment administration durations and address AEs associated with IV delivery of amivantamab, such as IRRs and VTEs.[21, 22] The SC formulation of amivantamab is expected to receive marketing authorisation from the MHRA between [redacted]. In addition to the PALOMA trial programme, the ongoing SKIPPirr and COCOON studies are proactively assessing the prophylactic management of AEs associated with IV amivantamab.[23 24]

Infusion-related reaction (IRR)

In line with the well-established safety profile of amivantamab, IRRs were one of the most frequently occurring TEAEs in the amivantamab-lazertinib arm, reported in [redacted] patients ([redacted]).[5] Most of the IRR events were Grade 1 or 2, with only [redacted] patients ([redacted]) in the amivantamab-lazertinib arm experiencing Grade 3 IRR and [redacted] patients ([redacted]%) experiencing a Grade 4 IRR.[5] No patients experienced a Grade 5 IRR.[5]

Most IRRs occurred early in the treatment regimen, as discussed in Section B.2.10.2.5 of the CS. At the 11th August 2023 DCO, [redacted] experienced IRRs, which mostly occurred early in the treatment regimen, reported in [redacted]% of patients on Cycle 1 Day 1 ([redacted]), reducing to [redacted]% of patients in Cycle ≥2 ([redacted]).[2]

Data from the PALOMA-3 trial show that SC amivantamab is associated with a five-fold reduction in the incidence of IRRs compared with IV amivantamab (13% versus 66%, respectively) and these events were primarily mild in nature (0.5% versus 4%, respectively, were Grade ≥3).[25] The incidence of dose reductions, interruptions and discontinuations with SC amivantamab was generally consistent with the rates observed with IV amivantamab; however, notably no patients receiving SC amivantamab reported treatment discontinuation due to IRRs, whilst this was reported in 2% of patients in the IV treatment arm.[25]

In addition, preliminary data from the SKIPPirr trial, a Phase 2, open label trial investigating the use of premedication to reduce IRRs associated with IV amivantamab, suggest that prophylaxis with 8 mg oral dexamethasone results in a meaningful reduction in the incidence of IRRs and is an effective strategy to reduce IRRs.[23, 26]

Rash

Due to the on-target activity of amivantamab, lazertinib and osimertinib against the EGFR pathway, rash was commonly observed in both the amivantamab-lazertinib ([redacted]%) and osimertinib ([redacted]%) treatment arms.[5] More patients in the amivantamab-lazertinib arm experienced a Grade 3 event: [redacted]% compared with [redacted]% of patients in the osimertinib arm.[5] Grade 4 rash was reported in [redacted] patient ([redacted]) in the amivantamab-lazertinib arm, and no patients in either treatment arm experienced a Grade 5 rash.[5]

As discussed in Section B.2.11 of the CS, enhanced dermatologic care to reduce rash and paronychia is being proactively evaluated in the ongoing Phase 2 COCOON trial (NCT06120140). This trial aims to evaluate the impact of enhanced versus standard dermatologic management on the incidence of dermatological AEs among patients with cEGFRm advanced or metastatic NSCLC receiving first line IV amivantamab in combination with lazertinib (MARIPOSA population).[24] The first interim analysis of the COCOON trial demonstrated a statistically significant and clinically meaningful reduction in dermatologic reactions in patients receiving the enhanced prophylactic regimen versus standard dermatological management.[27]

Interstitial lung disease (ILD)/pneumonitis

At the 11th August 2023 DCO, the incidence of pneumonitis or interstitial lung disease was similar between treatment arms, reported in [redacted] patients in the amivantamab-lazertinib arm ([redacted]%) and [redacted] patients in the osimertinib arm ([redacted]%).[2] No additional pneumonitis or ILD events have been reported since the 11th August 2023 DCO.

Venous thromboembolism (VTE) events

During the study, VTEs were identified as a high-risk for patients in the amivantamab-lazertinib arm, largely occurring in the first four months of treatment.[2] As such, a protocol amendment was implemented, recommending that patients in the amivantamab-lazertinib arm receive prophylactic anticoagulation for the first four months of treatment.[2]

A higher proportion of patients in the amivantamab-lazertinib arm experienced at least one VTE event as compared with osimertinib ([redacted] versus [redacted]), but the same proportion of patients in each of these arms experienced VTEs leading to death ([redacted]).[5] The majority of VTE events reported were pulmonary embolism (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]) or deep vein thrombosis (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]).[5]

The majority of VTE events in both arms were Grade 1–2 (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]) and the rate of discontinuations due to VTE was low (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]).[5] The incidence of VTE at the 4th December 2024 DCO (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]) is comparable to that reported at the primary PFS analysis (DCO: 11th August 2023 [amivantamab-lazertinib: [redacted]; osimertinib: [redacted]) supporting that the risk of VTE event onset was greatest during the first 4 months of treatment, after which the risk discordance decreased.[2, 5]

To reduce the incidence of VTEs, the amivantamab SmPC recommends the use of prophylactic anticoagulants for the first four months of treatment, as data from the MARIPOSA trial demonstrated that nearly all first VTE events occurred in participants who were not receiving concomitant anticoagulants, and recurrent VTE events while on anticoagulants were uncommon (see Clarification Question A22).[2, 28] In addition, as discussed in Section B.2.11 of the CS, data from the ongoing PALOMA-3 trial has demonstrated that SC amivantamab, expected to receive marketing authorisation from the MHRA between [redacted], is associated with a reduced incidence of VTEs compared with the IV formulation (9% versus 14%,

respectively), Furthermore, results from the COCOON trial show fewer patients reporting VTE when treated with enhanced prophylactic regimen versus standard dermatological management (6% versus 7%, respectively) .[27]

Results from COCOON, SKIPPirr and PALOMA-3 underscore the advancements currently underway to minimise key aspects of the amivantamab adverse effect profile.[25]

3. Updated economic analysis inputs

The cost-effectiveness model (CEM) submitted at the Clarification Questions stage (referred to as the 'previous model') has been updated to incorporate the recent clinical data available from the 4th December 2024 DCO of the MARIPOSA trial (referred to as the 'updated model'). The updated clinical inputs and curve choices implemented in the updated model are detailed below.

Survival inputs and assumptions

OS

In the updated model base case, OS for amivantamab-lazertinib and for osimertinib were modelled using data from the respective arms of the MARIPOSA trial (December 2024 DCO), thereby directly mitigating the concerns of the EAG raised in Key Issue 4 of their report regarding uncertainty in the long-term predictions for OS.

Amivantamab-lazertinib

The OS KM curve and independently fitted extrapolations for amivantamab-lazertinib are presented in Figure 9 and Figure 10, and the smoothed hazard plots in Figure 11 and Figure 12. Table 9 presents AIC, BIC, 5- and 10-year OS, and mOS outcomes for each distribution.

The Weibull curve was maintained for the base case long-term extrapolation of amivantamab-lazertinib OS data based on its strong statistical and visual fit, and close alignment with clinical timepoint estimates (see Section B.3.3.3 of original CS). In addition, a comparison of the Weibull and 1-knot hazard spline model OS extrapolations at the 13th May 2024 and 4th December 2024 DCOs is presented in Figure 13. This demonstrates that the Weibull extrapolation represents a more conservative option at the later DCO informed by the longer-term data than at the previously submitted May 2024 DCO, which translates to a marginally reduced incremental QALY benefit versus osimertinib in the updated economic analysis (see Section 5). As such, the Weibull curve represents a realistic and appropriate curve choice to maintain in the base case. This is further supported by the 10-year survival estimations: with the final OS results (DCO: 4th December 2024), the 10-year survival estimation for the Weibull extrapolation is [redacted], which is closer to the mean of the estimates provided by clinicians in the MARIPOSA advisory board in October 2024 ([redacted]) than those estimated by the Weibull extrapolation based on the previous 13th May 2024 DCO ([redacted]) or the 1-knot hazard extrapolation at the 4th December 2023 DCO ([redacted]).[17] Overall, the available OS data are robust and the selected base case curve choice is a realistic representation of expected patient outcomes in clinical practice.

In the scenario analysis exploring the impact of a higher OS curve selection, the gamma curve was maintained (see Section 5). This curve was originally selected based on feedback from clinicians and health economists during the MARIPOSA advisory board meeting in October 2024, where it was regarded as an optimistic choice..[17] In light of the results from the final overall survival analysis (DCO: 4th December 2024), Johnson & Johnson has sought to validate the new data. During this validation, which included input from a

key clinician in the UK, the appropriate curve choices included gamma, exponential or the flexible parametric model-3 (i.e. Spline Hazard 3 Knots).[29] Moreover, the perspective on the long-term extrapolations and the selection of the curves was notably more optimistic in comparison to the earlier May DCO. The rationale provided by the clinician when making these assumptions stemmed from an appreciation that the combination of amivantamab and lazertinib provides a broader therapeutic strategy than a TKI alone by targeting both EGFR and MET, while enhancing immune cell activity. This approach seems to reduce resistance mechanisms compared to osimertinib, resulting in improved long-term survival, with 56% of patients alive at 42 months compared to 44% on osimertinib, showing clear separation that widens over time. The clinician also believed that proactive management could further improve treatment adherence and quality of life, leading to even better long-term outcomes.

Regarding the scenario analysis exploring a lower OS curve selection, this has been updated to the 1-knot hazard, in alignment with the preference of the EAG, rather than the previously explored Gompertz curve. This is also more in line with feedback received from clinicians and health economists in the MARIPOSA advisory board (October 2024), who noted that the Gompertz curve is not considered to be an appropriate choice for the OS extrapolation of amivantamab-lazertinib as it does not represent typical outcomes in UK clinical practice.[17]

As presented in Section 5, the suggested scenarios exploring the curve choice for modelling long-term OS had a minimal impact on the incremental costs, incremental QALYs, and resulting ICER.

Figure 9: Updated long-term OS projections of amivantamab-lazertinib; parametric extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival.

Figure 10: Updated long-term OS projections of amivantamab-lazertinib; spline extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival.

Figure 11: Updated smoothed hazard plot with parametric extrapolations for amivantamab-lazertinib for OS (4th December 2024 DCO; FAS)

Abbreviations: Ami+lazertinib: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; OS: overall survival.

Figure 12: Updated smoothed hazard plot with spline extrapolations for amivantamab-lazertinib for OS (4th December 2024 DCO; FAS)

Abbreviations: Ami+lazertinib: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; OS: overall survival.

Table 9: OS individual fits for amivantamab-lazertinib

Distribution	AIC	BIC	5-year OS	10-year OS	Median OS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Figure 13: Comparison between long-term OS projections of amivantamab-lazertinib (13th May and 4th December 2024 DCOs; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; OS: overall survival.

Osimertinib

The OS KM curve and independently fitted extrapolations for osimertinib are presented in Figure 14 and Figure 15, and the smoothed hazard plots in Figure 16 and Figure 17. Table 10 presents AIC, BIC, 5- and 10-year OS, and mOS outcomes for each distribution. The Weibull curve was maintained for the base case long-term extrapolation of osimertinib OS data based on its strong statistical and visual fit, and close alignment with clinical timepoint estimates (see Section B.3.3.3 of original CS). In alignment with the amivantamab-lazertinib arm, the gamma curve was maintained as a higher OS curve selection scenario analysis (see Section 5), whereas the lower OS curve selection scenario analysis updated to the 1-knot hazard. The OS curves from the final analysis (DCO: 4th December 2024) for osimertinib have also been validated. In this assessment, the Weibull and Gamma distributions were identified as the most appropriate for representing the long-term survival of osimertinib.[29] As presented in Section 5, the suggested scenarios exploring the curve choice for modelling long-term OS had a minimal impact on the incremental costs, incremental QALYs, and resulting ICER.As presented in Section 5, scenarios exploring the curve choice for modelling long-term OS had a minimal impact on the incremental costs, incremental QALYs, and resulting ICER.

Figure 14: Updated long-term OS projections of osimertinib; parametric extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival.

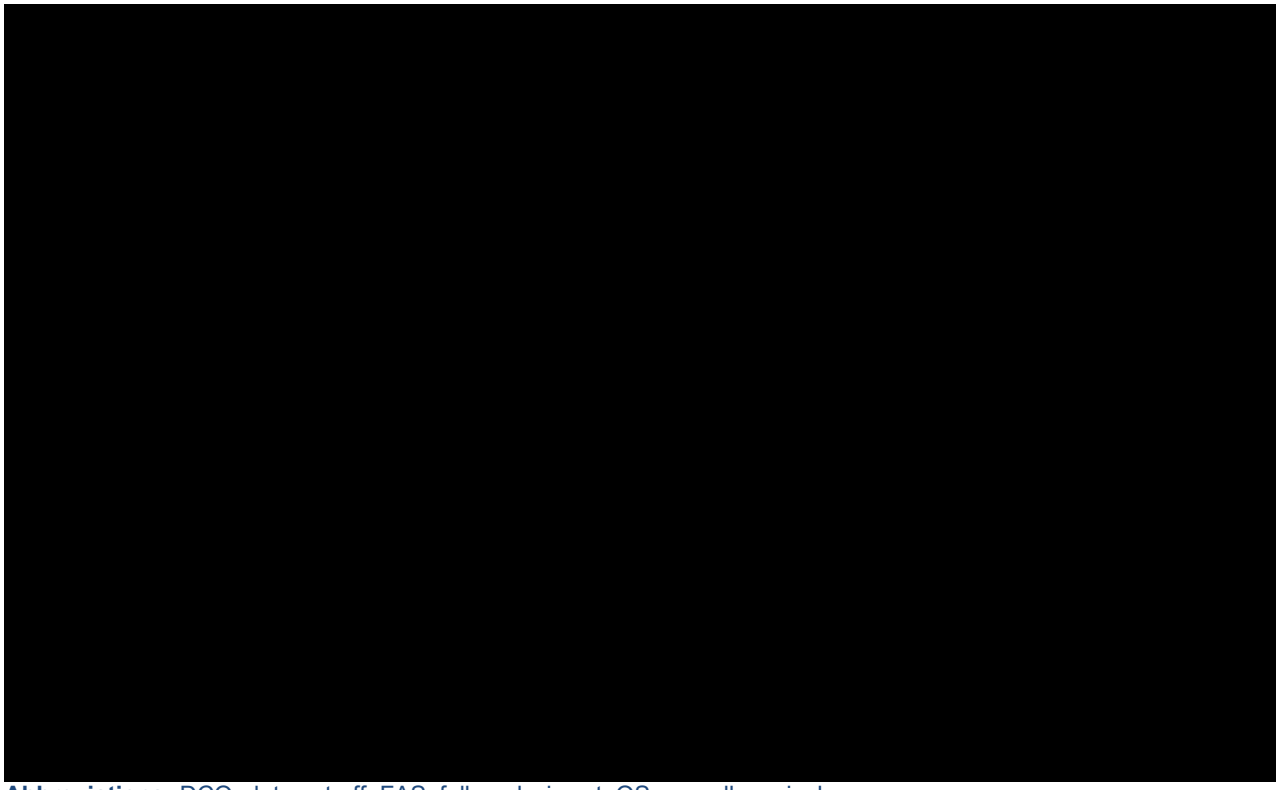
Figure 15: Updated long-term OS projections of osimertinib; spline extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; ITT: intention-to-treat; KM: Kaplan-Meier; OS: overall survival.

Figure 16: Updated smoothed hazard plot with parametric extrapolations for osimertinib for OS (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; OS: overall survival.

Figure 17: Updated smoothed hazard plot with spline extrapolations for osimertinib for OS (4th December 2024 DCO; FAS)



Abbreviations: DCO: data cut-off; FAS: full analysis set; OS: overall survival.

Table 10: OS individual fits for osimertinib

Distribution	AIC	BIC	5-year OS	10-year OS	Median OS (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

TTD

In the updated model base case, TTD for amivantamab-lazertinib and for osimertinib were modelled using data from the respective arms of the MARIPOSA trial (December 2024 DCO), thereby directly mitigating the concerns of the EAG raised in Key Issue 3 of their report regarding uncertainty in the long-term predictions for TTD and the potential benefit of a model updated with more complete, longer-term TTD data from the final trial DCO.

In the economic model, TTD was defined as the time from the date of randomisation to discontinuation of treatment for any reason, including death. In their report, the EAG considered the separate fitting of TTD models in the economic model for amivantamab and lazertinib in the amivantamab-lazertinib arm to be an appropriate approach; this approach is maintained below. Figure 18 presents the TTD KM curves for amivantamab, lazertinib and osimertinib based on the December 2024 DCO.

Figure 18: MARIPOSA TTD KM curves for amivantamab, lazertinib and osimertinib (4th December 2024 DCO; FAS)

Abbreviations: ami+laz: amivantamab-lazertinib; FAS: full analysis set; KM: Kaplan-Meier TTD: time to treatment discontinuation or death.

Amivantamab

The TTD KM curve and independently fitted extrapolations for amivantamab are presented in Figure 9 and Figure 20, and the smoothed hazard plots in Figure 11 and Figure 22. Table 9 presents AIC, BIC, 5- and 10-year TTD, and median TTD outcomes for each distribution. The exponential curve was maintained for the base case long-term extrapolation of amivantamab TTD data based on its strong statistical and visual fit, and close alignment with clinical timepoint estimates (see Section B.3.3.3 of original CS). The TTD curves from the final analysis (DCO: 4th December 2024) have also been validated with a key clinician from the UK. In this assessment the exponential and gamma were confirmed to be the most appropriate curve selections for long term TTD estimates.[29] As in the CS, the generalised gamma and gamma curves were explored in scenario analyses (see Section 5).

Figure 19: Updated long-term TTD projections of amivantamab; parametric extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; TTD: time to treatment discontinuation or death.

Figure 20: Updated long-term TTD projections of amivantamab; spline extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; TTD: time to treatment discontinuation or death.

Figure 21: Updated smoothed hazard plot with parametric extrapolations for amivantamab for TTD (4th December 2024 DCO; FAS)

Abbreviations: Ami: amivantamab; Ami+lazertinib: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; TTD: time to treatment discontinuation or death.

Figure 22: Updated smoothed hazard plot with spline extrapolations for amivantamab for TTD (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; TTD: time to treatment discontinuation or death.

Table 11: TTD individual fits for amivantamab

Distribution	AIC	BIC	5-year TTD	10-year TTD	Median TTD (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Lazertinib

The TTD KM curve and independently fitted extrapolations for lazertinib are presented in Figure 9 and Figure 24, and the smoothed hazard plots in Figure 11 and Figure 26. Table 9 presents AIC, BIC, 5- and 10-year TTD, and median TTD outcomes for each distribution. The exponential curve was maintained for the base case long-term extrapolation of lazertinib TTD data based on its strong statistical and visual fit, and close alignment with clinical timepoint estimates (see Section B.3.3.3 of original CS). In the validation of the TTD curves from the final analysis (DCO: 4th December 2024), the clinician considered the gamma, Generalised gamma, or Weibull distributions as the most appropriate long-term extrapolation for TTD.[29] This selection is closely aligned with the characteristics of the exponential curve. As in the CS, the Weibull and gamma curves were explored in scenario analyses (see Section 5).

Figure 23: Updated long-term TTD projections of lazertinib; parametric extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; TTD: time to treatment discontinuation or death.

Figure 24: Updated long-term TTD projections of lazertinib; spline extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; TTD: time to treatment discontinuation or death.

Figure 25: Updated smoothed hazard plot with parametric extrapolations for lazertinib for TTD (4th December 2024 DCO; FAS)

Abbreviations: Ami+lazertinib: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; LAZ: lazertinib; TTD: time to treatment discontinuation or death.

Figure 26: Updated smoothed hazard plot with spline extrapolations for lazertinib for TTD (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; TTD: time to treatment discontinuation or death.

Table 12: TTD individual fits for lazertinib

Distribution	AIC	BIC	5-year TTD	10-year TTD	Median TTD (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Osimertinib

The TTD KM curve and independently fitted extrapolations for osimertinib are presented in Figure 14 and Figure 28 and Figure 30, and the smoothed hazard plots in Figure 16. Table 10 presents AIC, BIC, 5- and 10-year TTD, and median TTD outcomes for each distribution. The exponential curve was maintained for the base case long-term extrapolation of osimertinib TTD data based on its strong visual fit, and close alignment with clinical timepoint estimates (see Section B.3.3.3 of original CS). In the validation of the TTD curves from the final analysis (DCO: 4th December 2024), the clinician identified either the exponential or loglogistic distributions as the most appropriate for osimertinib.[29] The proposed loglogistic curve presents a more optimistic and higher TTD for osimertinib compared to the base case. In the CS, the Weibull and gamma curves were explored in scenario analyses (see Section 5).

Figure 27: Updated long-term TTD projections of osimertinib; parametric extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; TTD: time to treatment discontinuation or death.

Figure 28: Osi TTD: Updated long-term TTD projections of osimertinib; spline extrapolations (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; TTD: time to treatment discontinuation or death.

Figure 29: Updated smoothed hazard plot with parametric extrapolations for osimertinib for TTD (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; TTD: time to treatment discontinuation or death.

Figure 30: Updated smoothed hazard plot with spline extrapolations for osimertinib for TTD (4th December 2024 DCO; FAS)

Abbreviations: DCO: data cut-off; FAS: full analysis set; TTD: time to treatment discontinuation or death.

Table 13: TTD individual fits for osimertinib

Distribution	AIC	BIC	5-year TTD	10-year TTD	Median TTD (Months)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Hazard	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3-Knot Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Base case distribution is in **boldface**.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Adverse events

The updated adverse event incidence rates and durations for 1L treatment informing the model are presented in Table 14 and Table 15, respectively.

Table 14: Incidence of AEs included in the CEM

Adverse event	Amivantamab-lazertinib (%)	Osimertinib (%)
Dermatitis acneiform	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Hypalbuminaemia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]
Grade ≤2 VTE	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

[a] Incidence of Grade ≤2 VTE in MARIPOSA includes patients with maximum Grade 1 or 2 VTE events (i.e., patients who experienced both Grade ≤2 and Grade ≥3 VTE were not counted) to avoid double-counting.
Abbreviations: AE: adverse event; CEM: cost-effectiveness model; VTE: venous thromboembolism.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[5]

Table 15: Durations for each AE

Adverse event	Mean Cumulative Duration (Days)
Dermatitis acneiform	[redacted]
Alanine aminotransferase increase	[redacted]
Hypalbuminaemia	[redacted]
Paronychia	[redacted]
IRR	[redacted]
Rash	[redacted]
Pulmonary embolism	[redacted]
Grade ≤2 VTE	[redacted]
Pneumonia	[redacted]

Abbreviations: AE: adverse events; IRR: infusion-related reaction; QALY: quality-adjusted life year; VTE: venous thromboembolism.

Health state utilities

The updated health state utility values used in the model (DCO: 4th December 2024) are presented in Table 16 (unpublished and confidential results of available PROs are provided in the reference pack).[31] The progression-free utility value implemented within the model remains similar to the average age-matched general population utility of 0.822 at 64 years.[30]

Table 16: Health state utilities

Health state	Utility value, mean (SE)
Progression-free	[redacted]
Progressed disease	[redacted]

Abbreviations: SE: standard error.

The EAG-preferred approach of using treatment-arm specific utility values was explored in the Company's response to the Clarification Questions. The resulting mean PF utility value of [redacted] for osimertinib monotherapy was higher than the expected utility value for the general population that has been accepted by the EAG in the ongoing appraisal for osimertinib with chemotherapy (ID6328). Furthermore, the same EAG noted that the Hernandez Alava et al. mapping algorithm, which has been used as a reference for the EAG's preferred assumption, results in higher-than-expected valuations for this population and therefore may lack face validity. Additionally, the EAG-preferred utility value for osimertinib monotherapy is also higher than the pooled value currently used for both arms in the model ([redacted]).

Modelling utilities based on specific health states, rather than treatment specific utilities, is the more appropriate way to not only capture variation of HRQoL over time, but to also consider the benefits offered by the forthcoming subcutaneous formulation of amivantamab. Furthermore, promising results from COCOON, SKIPPirr, and PALOMA-3, suggest that effective treatment strategies play a crucial role in enhancing outcomes for patients with cEGFR-mutant NSCLC receiving amivantamab and lazertinib.
Overall, the introduction of subcutaneous amivantamab, coupled with improved disease management methods, will significantly enhance the overall patient experience during treatment. This improvement is likely to have a positive impact on treatment-specific utilities for amivantamab-lazertinib, thereby making the health state-specific utility a more appropriate measure.

Drug acquisition costs

The proportion of doses missed, and the proportion of planned dose received for all interventions, are presented in Table 17 and Table 18. The updated total weekly drug acquisition costs for amivantamab-lazertinib, including missed doses and dose reductions, and for osimertinib, including missed doses, are presented in Table 19 and Table 20, respectively.

Table 17: Drug dosing, including doses missed and proportion of planned doses received (amivantamab)

Regimen	Component	Doses Missed	Proportion of planned doses administered (full vials)	Source
Amivantamab-lazertinib	Amivantamab (patient weight <80 kg)	[redacted]	[redacted]	MARIPOSA trial
	Amivantamab (patient weight ≥80 kg)	[redacted]	[redacted]	

Abbreviations: kg: kilogram;

Table 18: Drug dosing, including doses missed and proportion of planned doses received (lazertinib and osimertinib)

Regimen	Component	Doses Missed	Actual dose	Proportion of administrations with actual dose	Source
Amivantamab-lazertinib	Lazertinib[b]	[redacted]	80 mg	[redacted]	MARIPOSA trial
			160 mg	[redacted]	
			240 mg	[redacted]	
			320 mg	[redacted]	
			400 mg	[redacted]	

			480 mg	[redacted]	
Osimertinib[a]	Osimertinib	[redacted]	40 mg	[redacted]	MARIPOSA trial
			80 mg	[redacted]	
			160 mg	[redacted]	
			240 mg	[redacted]	
			320 mg	[redacted]	

[a] Flat pricing of osimertinib means that dose reductions (switching to 40 mg tablets) does not impact costs.
[b] For lazertinib and osimertinib there's a distribution of doses received in the trial, each with an associated cost (determined by the combination of tablet of different strengths required for that dose), and the final cost is calculated as a weighted average.
Abbreviations: kg: kilogram;

Table 19: Total weekly drug acquisition cost for amivantamab-lazertinib including missed doses and dose reductions

Component	Treatment duration	Dosing frequency per week (induction)	Dosing frequency per week (maintenance)	Cost per week of induction (£)[a]	Cost per week of maintenance (£)[a]
Amivantamab (list price)	<80 kg patients: 4 weeks (up to C2D1)	1	0.5	[redacted]	[redacted]
Amivantamab (PAS price)	<80 kg patients: 4 weeks (up to C2D1)	1	0.5	[redacted]	[redacted]
Amivantamab (list price)	≥80 kg patients: 4 weeks (up to C2D1)	1	0.5	[redacted]	[redacted]
Amivantamab (PAS price)	≥80 kg patients: 4 weeks (up to C2D1)	1	0.5	[redacted]	[redacted]
Lazertinib (list price)	Taken once daily until progression	7	0.23	[redacted]	[redacted]
Lazertinib (PAS price)	Taken once daily until progression	7	0.23	[redacted]	[redacted]
Total amivantamab-lazertinib (list price)[b]				[redacted]	[redacted]
Total amivantamab-lazertinib (PAS price)[b]				[redacted]	[redacted]

[a] Calculated accounting for doses missed and proportion of planned doses received.
[b] Weighted based on the % of patients over and under 80 kg.
Abbreviations: C2D1: Day 1 of cycle 2; kg: kilogram; mg: milligram.

Table 20: Total weekly drug acquisition cost for osimertinib including missed doses

Component	Dosing frequency per week	Cost per week (£)
Osimertinib	7	[redacted]

Subsequent treatment costs

The proportion of patients receiving treatment within each line of therapy was calculated separately for the amivantamab- lazertinib and the osimertinib arms. As outlined in the CS (Section B.3.5.1.4), the proportion of patients receiving 3L+ treatment was informed by the MARIPOSA-2 trial and, as such, has not been updated. However, the proportion of patients receiving 2L treatment was informed by the MARIPOSA trial and,

therefore, has been updated to [redacted] for amivantamab-lazertinib and [redacted] for osimertinib, in line with data from the 4th December 2024 DCO.

4. Base case economic results

As compared with the previous model submitted alongside the Company responses to Clarification Questions, the following inputs have been updated in the updated model to be informed by the 4th December 2024 DCO:

- OS
- TTD
- AE incidence and duration
- Health state utility values
- The proportion of missed doses, proportion of planned amivantamab doses received and distribution of lazertinib and osimertinib doses
- The proportion of patients receiving 2L treatments by 1L regimen

The base case results from the updated model at amivantamab and lazertinib PAS prices are presented in Table 20 (probabilistic) and Table 21 (deterministic). In line with the conclusions of the base case results presented in the original CS and following Clarification Questions, the revised base case results continue to demonstrate that, at amivantamab and lazertinib PAS prices, amivantamab-lazertinib is a cost-effective use of NHS resources when compared to osimertinib at its list price, dominating osimertinib in the probabilistic and deterministic analyses. For completeness, the base case results at list prices are presented in Table 22 (probabilistic) and Table 23 (deterministic).

Table 21: Base case results at amivantamab and lazertinib PAS prices (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Previous model							
Osimertinib	[redacted]	[redacted]	3.41	[redacted]	[redacted]	1.29	−75,200.42 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.70				
Updated model							
Osimertinib	[redacted]	[redacted]	3.36	[redacted]	[redacted]	1.16	−83,155.87 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.52				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years; SoC: standard of care.

Table 22: Base case results at amivantamab and lazertinib PAS prices (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Previous model							
Osimertinib	[redacted]	[redacted]	3.40	[redacted]	[redacted]	1.27	−76,643.31 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.67				

Updated model							
Osimertinib	[redacted]	[redacted]	3.35	[redacted]	[redacted]	1.15	−83,958.55 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.51				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years; SoC: standard of care.

Table 23: Base case results at amivantamab and lazertinib list prices (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Previous model							
Osimertinib	[redacted]	[redacted]	3.41	[redacted]	[redacted]	1.29	165,144.40
Amivantamab-lazertinib	[redacted]	[redacted]	4.70				
Updated model							
Osimertinib	[redacted]	[redacted]	3.36	[redacted]	[redacted]	1.16	188,322.41
Amivantamab-lazertinib	[redacted]	[redacted]	4.52				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years; SoC: standard of care.

Table 24: Base case results at amivantamab and lazertinib list prices (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Previous model							
Osimertinib	[redacted]	[redacted]	3.40	[redacted]	[redacted]	1.27	165,710.13
Amivantamab-lazertinib	[redacted]	[redacted]	4.67				
Updated model							
Osimertinib	[redacted]	[redacted]	3.35	[redacted]	[redacted]	1.15	186,872.98
Amivantamab-lazertinib	[redacted]	[redacted]	4.51				

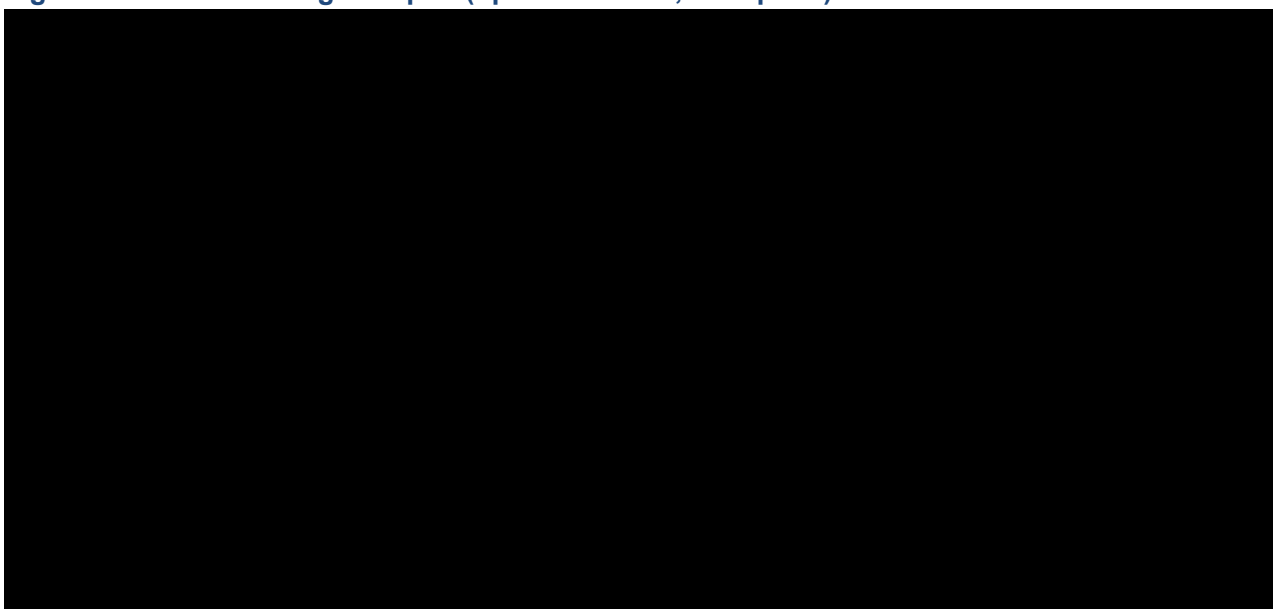
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years; SoC: standard of care.

5. Sensitivity analyses

Probabilistic sensitivity analysis

An updated probabilistic sensitivity analysis was conducted using the updated CEM. The incremental net monetary benefit (INMB) convergence plot is presented in Figure 31, which incorporates the PAS discounts for amivantamab and lazertinib. Additionally, the probabilistic cost-effectiveness plane for amivantamab-lazertinib versus osimertinib is presented in Figure 32. In line with the results from the previous model, these results indicate that at a £30,000 WTP threshold, amivantamab-lazertinib (PAS price) retains a [redacted] probability of being cost-effective when compared with osimertinib (Figure 33).

Figure 31: INMB convergence plot (updated model; PAS price)



Abbreviations: INMB: incremental net monetary benefit; PAS: patient access scheme.

Figure 32: Probabilistic cost-effectiveness plane (updated model; PAS price)

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

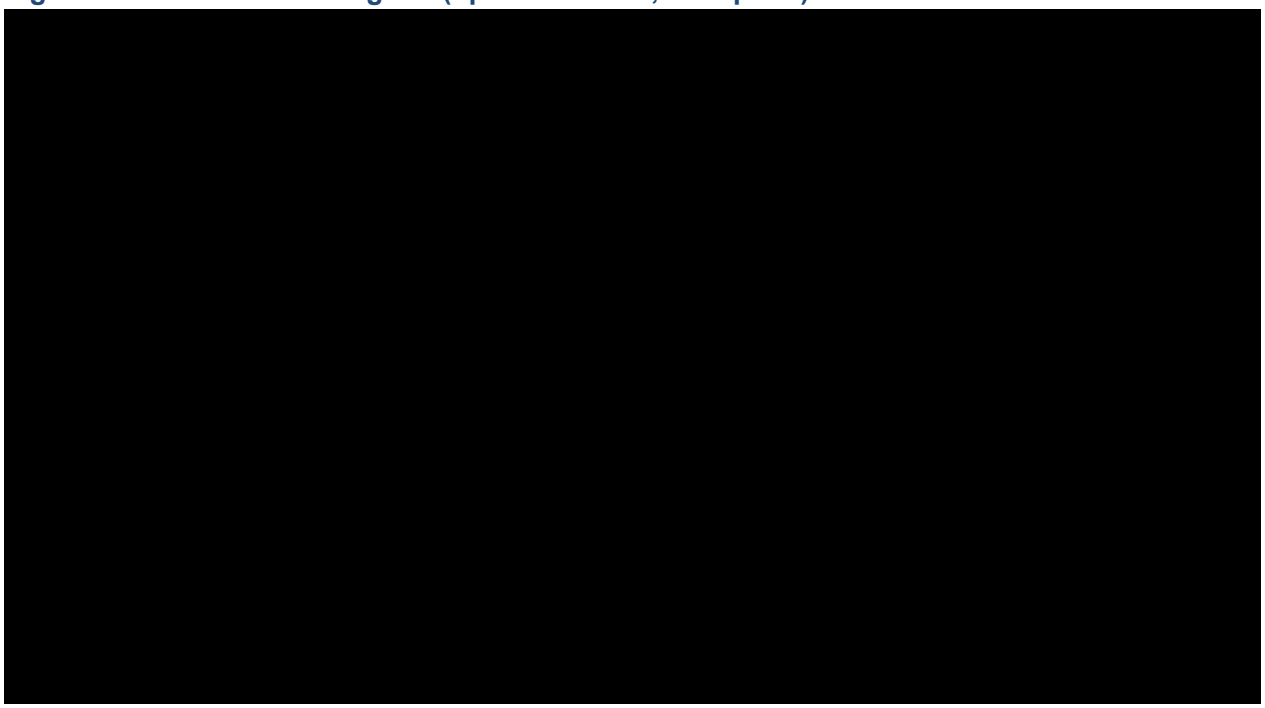
Figure 33: Cost-effectiveness acceptability curve (updated model; PAS price)

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

Deterministic sensitivity analysis

An updated tornado diagram showing the top 10 most influential parameters on the ICER for amivantamab-lazertinib versus osimertinib in the updated model is provided in Figure 34. Overall, the scale and shape of the parametric extrapolations for OS for amivantamab-lazertinib and osimertinib are the most influential parameters, followed by the TTD rate for osimertinib and amivantamab. The model is otherwise robust to variation in inputs and settings. In alignment with the results presented in the CS and the Company response to Clarification questions, all results generated from the DSA provide a negative ICER due to amivantamab-lazertinib (PAS price) being dominant in all instances.

Figure 34: DSA tornado diagram (updated model; PAS price)



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

Scenario analyses

At the 4th December 2024 DCO, with a median study follow-up of [redacted] months, [redacted] deaths were observed in the amivantamab-lazertinib and osimertinib arms combined.[5] Given the availability of longer-term osimertinib OS data from the MARIPOSA trial, the left-truncated scenario using osimertinib OS data from the FLAURA trial has been removed.

Subsequent treatment distributions based on the MARIPOSA and MARIPOSA-2 trials

In the base case, the distribution of 2L and 3L+ treatment options were derived from clinical estimates from the advisory board meeting held by Johnson and Johnson in October 2024, as this was the most relevant source for UK clinical practice. A scenario analysis was explored in which the MARIPOSA and MARIPOSA-2 trials informed the distribution of 2L and 3L+ subsequent therapies, respectively.

In this updated scenario, the 3L treatment distributions remained the same as in the CS (informed by MARIPOSA-2), and the duration of subsequent treatments (2L and 3L+) were maintained as per the base case approach. However, the updated 2L treatment distributions were updated to be informed by the 4th December 2024 DCO of the MARIPOSA trial. These distributions for patients following 1L treatment with amivantamab-lazertinib or osimertinib are presented in Table 24.

Table 25: Distribution of 2L subsequent treatments for amivantamab-lazertinib and osimertinib implemented in the MARIPOSA-derived scenario analysis, based on the amivantamab-lazertinib and osimertinib treatment arms of the MARIPOSA trial

	Distribution of 2L treatments	
	Amivantamab-lazertinib	Osimertinib
Platinum-based chemotherapy	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]

Abbreviations: 2L: second-line; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.

Scenario analyses results

Results of the updated probabilistic and deterministic scenario analyses are presented in Table 25 and Table 26, respectively. The presented scenario analyses are in line with those presented in the original CS and in the Company response to Clarification Questions, except that the pessimistic curve choice for OS for amivantamab-lazertinib and osimertinib has been updated to 1-knot hazard (Scenario 6 below), in line with the EAGs preferred pessimistic curve choice for amivantamab-lazertinib.

In all analyses, amivantamab-lazertinib at PAS price remained dominant over osimertinib at list price, in line with the results of the previous model, indicating that the cost-effectiveness of amivantamab-lazertinib versus relevant osimertinib remains robust when altering key modelling assumptions and approaches.

Table 26: Scenario analysis results (updated model; probabilistic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Previous base case		[redacted]	[redacted]	**−75,200.42 (dominant)**
Updated base case		[redacted]	[redacted]	**−83,155.87 (dominant)**
Discount rate				
1	1.5% discount rate	[redacted]	[redacted]	−73,374.19 (dominant)
Time horizon				
2	37.7-year time horizon	[redacted]	[redacted]	−83,056.41 (dominant)
PFS definition				
3	PFS by INV for amivantamab-lazertinib and osimertinib	[redacted]	[redacted]	−83,280.64 (dominant)
PFS parametric extrapolation				
4	Lower PFS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−83,629.20 (dominant)
5	Higher PFS curve selections (Log-normal extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−82,924.19 (dominant)
OS parametric extrapolations				
6	Lower OS curve selections (1-knot hazard extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−89,647.82 (dominant)
7	Higher OS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−85,522.50 (dominant)
TTD parametric extrapolations				
8	Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	[redacted]	[redacted]	−73,605.56 (dominant)
9	Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	[redacted]	[redacted]	−74,029.61 (dominant)
Utility				

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
10	HSUV (PD: 0.678; PF: 0.794 as per TA654)	[redacted]	[redacted]	−85,240.55 (dominant)
11	AE disutilities based on literature	[redacted]	[redacted]	−83,225.42 (dominant)
Subsequent treatments				
12	Subsequent treatment distribution based on MARIPOSA trial	[redacted]	[redacted]	−81,650.85 (dominant)
13	Subsequent treatment distribution based on UK RWE	[redacted]	[redacted]	−82,321.00 (dominant)

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

Table 27: Scenario analysis results (updated model; deterministic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Previous base case		[redacted]	[redacted]	**−76,643.31 (dominant)**
Updated base case		[redacted]	[redacted]	**−83,958.55 (dominant)**
Discount rate				
1	1.5% discount rate	[redacted]	[redacted]	−74,415.64 (dominant)
Time horizon				
2	37.7-year time horizon	[redacted]	[redacted]	−83,908.94 (dominant)
PFS definition				
3	PFS by INV for amivantamab-lazertinib and osimertinib	[redacted]	[redacted]	−84,086.04 (dominant)
PFS parametric extrapolation				
4	Lower PFS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−84,457.85 (dominant)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
5	Higher PFS curve selections (Log-normal extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−83,734.41 (dominant)
OS parametric extrapolations				
6	Lower OS curve selections (1-knot hazard extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−92,295.72 (dominant)
7	Higher OS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−86,019.23 (dominant)
TTD parametric extrapolations				
8	Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	[redacted]	[redacted]	−74,346.40 (dominant)
9	Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	[redacted]	[redacted]	−74,233.41 (dominant)
Utility				
10	HSUV (PD: 0.678; PF: 0.794 as per TA654)	[redacted]	[redacted]	−86,039.81 (dominant)
11	AE disutilities based on literature	[redacted]	[redacted]	−84,030.88 (dominant)
Subsequent treatments				
12	Subsequent treatment distribution based on MARIPOSA trial	[redacted]	[redacted]	−82,128.37 (dominant)
13	Subsequent treatment distribution based on UK RWE	[redacted]	[redacted]	−82,729.15 (dominant)

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

January 2025

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
ID6256_Amivantamab with lazertinib in NSCLC_SIP_[NoCON]	**V1**	**No**	**15th January 2025**

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®) and Lazertinib (Lazcluze®)

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 treat 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) Exon19 deletion mutation, or an Exon21 L858R substitution mutation, and this must be the first treatment patients receive in the advanced setting.[1] These two types of mutations are common mutations for NSCLC (approximately 86% of all patients with advanced NSCLC[2]), and will be referred to as common EGFR mutations. To avoid complexity, in the rest of the document, we will refer to the relevant patient group as *patients with common EGFR mutation-positive advanced NSCLC.* In this patient population, amivantamab (administered intravenously, meaning that the medicine is delivered directly into a vein) is given in combination with lazertinib (taken as a pill).

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.

Amivantamab in combination with lazertinib does not yet have marketing authorisation in the United Kingdom (UK). The application for marketing authorisation with the UK Medicines and Healthcare Products Regulatory Agency (MHRA) was conducted in early 2024, with anticipated approval expected in May 2025. Amivantamab is indicated: • in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).

- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

The link to the previous MHRA approvals is here:
https://www.medicines.org.uk/emc/product/13084/smpc#aboutmedicine

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 and lazertinib is detailed in Table 1.

Table 1: Engagement and financial support provided to patient groups

Patient Group	Engagement/Activity (correct as of 31/12/24)	Financial Support Provided
EGFR Positive UK	Grant towards the refresh of their website	£3,508 (2024)
	Grant to support the design, development, and running of two day-long patient information events	£8,800 (2023)
	Grant to cover two of their membership events which provide information and support to patients	£5,000 (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	£5,000 (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	£7,000 (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	£9,000 (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 lung cancer cases.[3] It is categorised based on changes in the tumour, with one type of change being an EGFR mutation, which occurs in about 10% of all incidences of advanced NSCLC.[4] Within the UK, around 45% of patients with NSCLC have a specific type of EGFR mutation called an Exon19 deletion mutation, whilst 34% of patients have a Exon21 L858R mutation.[5, 6] These proportions represent approximately 86% of patients with advanced NSCLC having common EGFR mutations in the UK.[2]

Patients living with these EGFR mutations have poor life-expectancy. This is shown in real world data (data collected from patients outside of a clinical trial, within normal clinical practice), with this patient population typically living for only a little over 2 years (24.6 months).[7] Therefore, it can be shown that this disease is particularly severe and significantly reduces life expectancy compared to that of the general population.

Impact on Patients' and Carers' Quality of Life

Patients with common EGFR mutation-positive advanced NSCLC experience many symptoms that impact their quality of life. These may include feeling tired all the time, pain in their bones, constipation and feeling sick, and get recurring and constant infections. They might also have problems with their skin and eyes. As well as the physical impact, there is also a negative impact of the disease and treatment on mental health and emotional wellbeing which impacts their quality of life. This includes the inability to think clearly and difficulty concentrating, in addition to anxiety around the results of the next scan, the mental load of planning life around NSCLC, concerns around the future and even losing their sense of identity, negatively impacting their self-esteem.[8]

There is also an impact on caregivers/supporters of patients with common EGFR mutation-positive advanced NSCLC, as it has been found that 94% of caregivers also experience an impact on their quality of life, with both an emotional impact and an effect on their ability to participate in everyday life.[9]

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 more than half of patients in England and Wales being diagnosed with NSCLC in the advanced stage.[10] To determine if someone has lung cancer, doctors can use different tests. These tests include[11]:

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 patients through appropriate treatment options once the patient's type of EGFR mutation has been identified.

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 is therefore predominately used.

This testing is important for deciding the best treatment for patients with lung cancer (known as precision medicine). With the introduction of amivantamab-lazertinib, there is no need for additional diagnostic tests as the testing for EGFR mutations is already part of routine lung cancer care in the UK.[12]

2c) Current treatment options:

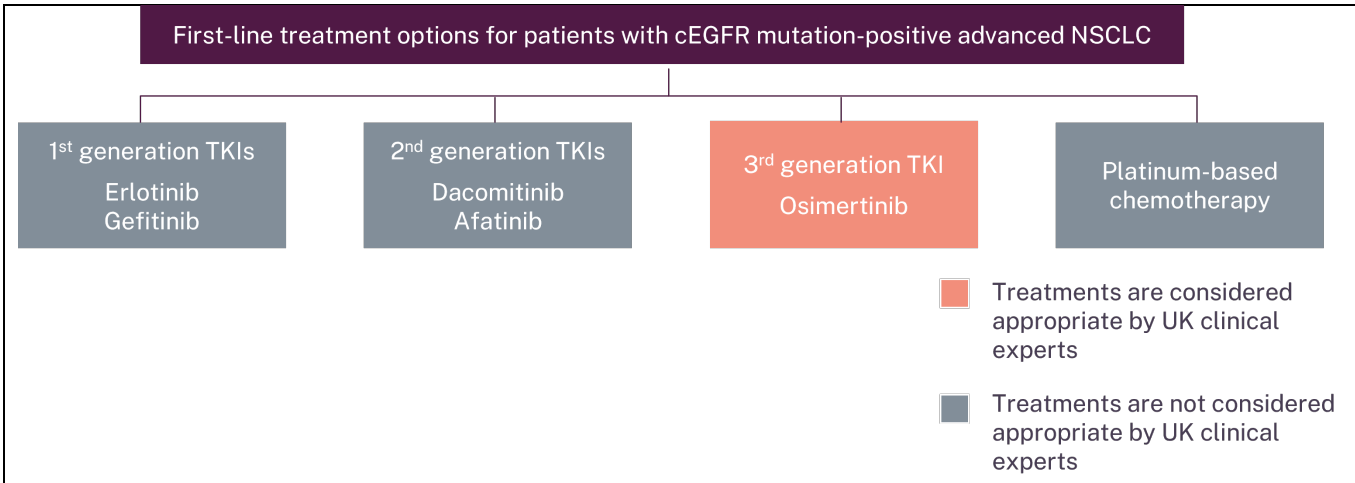
The purpose of this section is to set the scene on how the condition is currently managed:

- 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, maintain quality of life, and alleviate symptoms. For patients with common EGFR mutations in advanced NSCLC, the UK-specific treatment guidelines (NG122) published by the National Institute of Health and Care Excellence (NICE) recommend a number of treatment options.[13]

Historically, these treatment options were associated with high cases of the resistance mutation called T790M, which leads to an increased chance of disease progression.[14] Treatments associated with the T790M mutation typically involve 1st or 2nd generation TKIs. As a result, UK clinicians prefer osimertinib, a 3rd-generation TKI, as the standard of care treatment because osimertinib is a treatment option that specifically targets T790M resistance mutations and has been shown to deliver better health outcomes for patients than the previously established standard of care.[15, 16] The treatment options that patients with common EGFR mutations currently receive are shown in Figure 1.

Figure 1: Current treatment options for patients in UK clinical practice



Contraindications and drug-drug interactions

Contraindications are specific situations or conditions where a drug should not be used because it could cause harm. Drug-drug interactions occur when two or more medications affect each other's effectiveness or cause harmful side effects when taken together. No drug-drug interaction studies have been performed for amivantamab-lazertinib but the way the treatment works should not interfere with how other medications work or how they are broken down in the body.[17]

Contraindications for amivantamab include hypersensitivity to the active substance or to any of the excipients listed below[17]:

- Ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate
- L-Histidine
- L-Histidine hydrochloride monohydrate
- L-Methionine
- Polysorbate 80
- Sucrose
- Water for injection

Lazertinib does not currently hold a marketing authorisation in the UK. Anticipated contraindications for lazertinib include hypersensitivity to the active substance or to any of the excipients listed below[18, 19]:

- Silica, hydrophobic colloidal
- Croscarmellose sodium
- Cellulose, microcrystalline
- Mannitol
- Magnesium stearate
- Macrogols
- Polyvinyl alcohol
- Glycerol monocaprylocaprate type I
- Titanium dioxide
- Talc
- Yellow, red, and black iron oxide

2d) Patient-based evidence (PBE) about living with the condition

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 common EGFR 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).[8]

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, concern for the future and losing their sense of identity, negatively impacting their self-esteem. The in-depth interviews stated patients live in a constant state of 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 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 that side effects of current treatments have a negative impact on quality of life. Fatigue was a common symptom, 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 on quality of life and experiences of stigma was conducted in 2021. This found the physical and emotional impact of NSCLC 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.[9] See *Section 3k) Equalities* for further details on stigma.

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, which is a special kind of protein that can stick to two different targets at the same time. Amivantamab 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[17, 20, 21]:

1) It blocks certain substances that make cancer grow and proliferate (extend to other parts of the body).
2) It helps block attachment to receptors that are already present in the body and enable cancer growth and proliferation, which further reduces the growth of cancer cells.

3) It works with the immune system to identify and help destroy cancer cells.

How lazertinib works
Lazertinib is a new type of third-generation TKI medicine that helps treat lung cancer by specifically and selectively targeting mutations in the EGFR protein. It works on certain mutations in this protein that make cancer grow and can also overcome a common form of resistance (T790M resistance mutation) that develops when using older cancer treatments. Lazertinib is suitable for use in combination therapy due to its selectivity towards EGFR mutations and its safety profile.[22]

Mutations in the MET gene are a frequent cause of resistance to EGFR-TKIs.[23] Amivantamab targets both, EGFR and MET genes and works with lazertinib to effectively target both major (resistance) pathways, rather than just one. This is anticipated to improve the overall treatment efficacy of patients with common EGFR mutation-positive advanced NSCLC by targeting both major resistance pathways, rather than just one.[22]

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.

No – amivantamab and lazertinib are not indicated to be used in combination with any other medicines.

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. The combination therapy is given on a 21 day cycle and the impact of this schedule for patients is explained below.[17]

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 (700mg) 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 1,050mg once weekly.
- From week 5 onwards, the patient will be given 1,050mg of amivantamab every two 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 (1,050mg) 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 1,400mg once weekly.

- From week 5 onwards, the patient will be given 1,400mg of amivantamab every two weeks.

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.

Lazertinib, irrespective of the weight of the patient, is administered as a once-daily oral tablet, at a strength of 240mg (3 tablets of 80 mg or 1 tablet of 240 mg).[18]

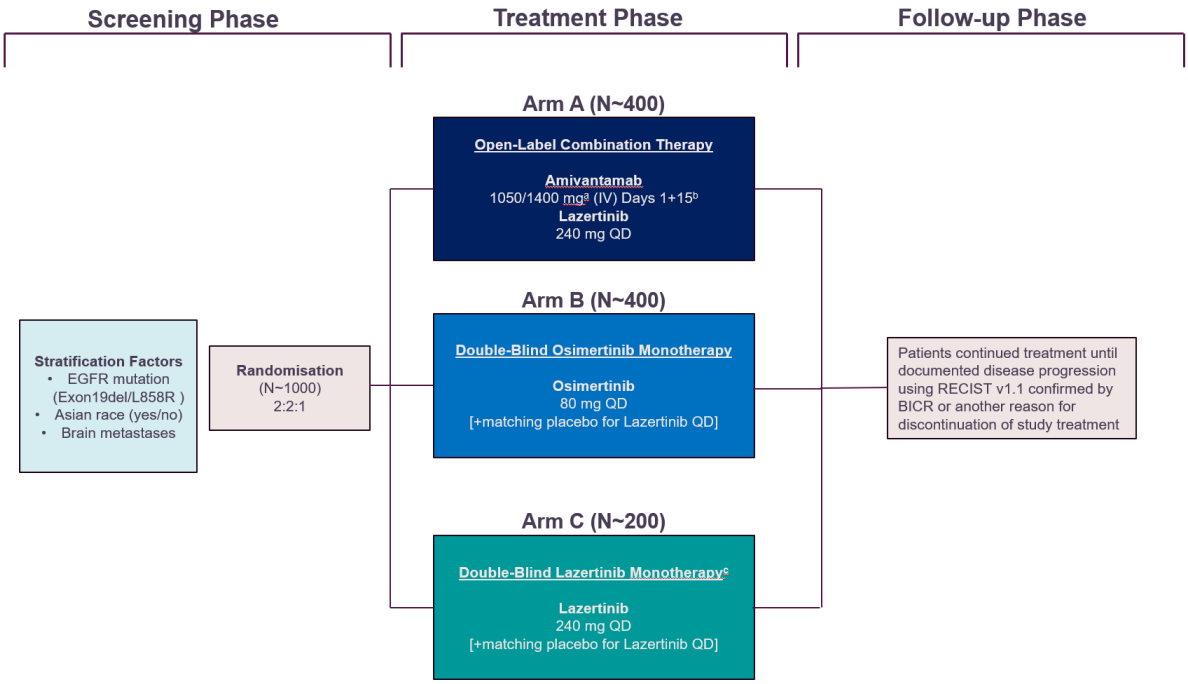
3d) Current clinical trials

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.

MARIPOSA

Amivantamab in combination with lazertinib is anticipated to receive a license for this setting in the UK in May 2025. The license will be informed by a clinical trial called 'MARIPOSA' (clinical trial number NCT04487080).[24] This is a phase 3 registrational clinical trial where patients were randomised, referring to a method used in trials to ensure that participants are randomly assigned to different groups in a fair and unbiased way, to receive either a) amivantamab and lazertinib combination, b) osimertinib, or c) lazertinib alone. The lazertinib alone arm was included to evaluate the contribution of the components in the combination treatment arm. A phase 3 trial means the trial tests the clinical effectiveness and safety of a new treatment. The amivantamab and lazertinib group was open label, meaning patients knew the treatment they were receiving (as amivantamab is administered via IV and osimertinib and lazertinib as given as a tablet). The osimertinib and lazertinib groups were blinded, meaning the patients did not know which treatment they were receiving (as they are both tablets). The trial recruited 1,047 patients who were split in a 2:2:1 ratio between each group (429 to amivantamab and lazertinib, 429 to osimertinib, and 216 to lazertinib). The study was conducted in North America, Asia, Australasia and Europe (including 7 sites in the UK). Figure 2 below demonstrates the study design.[25]

Figure 2: Overview of MARIPOSA study design



Abbreviations: EGFR: epidermal growth factor receptor; IV: intravenous; NSCLC: non-small cell lung cancer; PFS: progression free survival; QD: once daily.
Footnotes: Arm A=amivantamab + lazertinib arm; Arm B=osimertinib arm; Arm C=lazertinib arm. *Weight-based dosing: <80 kg/≥80 kg. †Cycle 1: Days 1/2 (split dose), 8, 15, 22; Cycles 2+: Days 1, 15.

Source: J&J Data on File. MARIPOSA CSR (DCO: 11th August 2023).[25]

Some key criteria for participants being included in the trial include: patients aged 18 years and older, histologically (tissue) or cytologically (cells) confirmed (referring to the term in medicine to describe how doctors determine whether a person has a specific disease, often cancer), newly diagnosed locally advanced or metastatic non-squamous NSCLC with documented primary EGFR Exon19 deletion mutations, or Exon21 L858R substitution mutations, an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 (the ECOG score is a system used by doctors to measure how well a cancer patient is doing and how much they can carry out daily activities. A score of 0 or 1 indicates that the patient is in a relatively good shape and can manage daily tasks without significant issues) and adequate organ and bone marrow function.

Some of the key exclusion criteria included: patients who had received prior systemic treatment for locally advanced or metastatic disease, has an uncontrolled illness, has symptomatic brain metastases (refers to cancer that has spread to the brain and is currently still growing or causing symptoms), or has active or past medical history of leptomeningeal disease, or interstitial lung disease / pneumonitis. Further details can be found on the clinical trial website.

The MARIPOSA 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 in 2024. The study is still ongoing, and its estimated completion date is in June 2027.

Further information about the trial can be found using the following links:

- Clinical trial: https://clinicaltrials.gov/study/NCT04487080
- Publication: https://www.nejm.org/doi/full/10.1056/NEJMoa2403614

Other amivantamab trials

PALOMA-2 clinical trial (NCT05388669);[26] this is a global, parallel-cohort, phase 2 study evaluating the efficacy, safety, and pharmacokinetics (how drugs are absorbed, distributed, metabolised, and excreted by the body) of subcutaneous (SC) injection of amivantamab plus oral lazertinib. Cohorts 1 and 6 included patients *with common EGFR mutation-positive advanced NSCLC*. The primary endpoint was the rate at which patients responded to treatment.

There are other additional trials investigating amivantamab; however, these are in different patient populations and in combination with different therapies.

A single arm trial, 'CHRYSALIS', investigating amivantamab as monotherapy in the second-line setting (after platinum based chemotherapy) for EGFR Exon20 insertion mutations was previously conducted with a marketing authorisation granted by the MHRA in November 2021.[27] The indication for that population is:

- amivantamab as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

Additionally, a Phase 3, randomised controlled trial, 'PAPILLON', investigating amivantamab in combination with chemotherapy in the front-line setting for EGFR Exon20 insertion mutations was also conducted with a marketing authorisation granted by the MHRA in July 2024.[27] The indication for that population is:

- amivantamab in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations.

Further, a Phase 3, randomised controlled trial, 'MARIPOSA-2', is investigating amivantamab and lazertinib in combination with platinum-based chemotherapy in patients with EGFR-mutated metastatic non-small cell lung

cancer after osimertinib failure. This indication was granted a marketing authorisation by the MHRA in November 2024.[27] The indication for this population is:

- amivantamab in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).

Amivantamab is also being investigated as a SC injection (a type of injection that is given just below the skin) in several clinical trials: the PALOMA-3 study (the clinical trial numbers is NCT05498428, a non-inferiority study comparing SC vs IC amivantamab plus lazertinib in patients with locally advanced or metastatic NSCLC with EGFR Ex19del or L858R after progression on or after osimertinib and platinum-based chemotherapy, irrespective of order).[28] Based on the results of these trials, amivantamab may in future be available as a SC injection, SC license currently pending. This means that patients would need to spend less time in hospital as the SC injection will reduce the administration time and overall time spent in hospital 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.

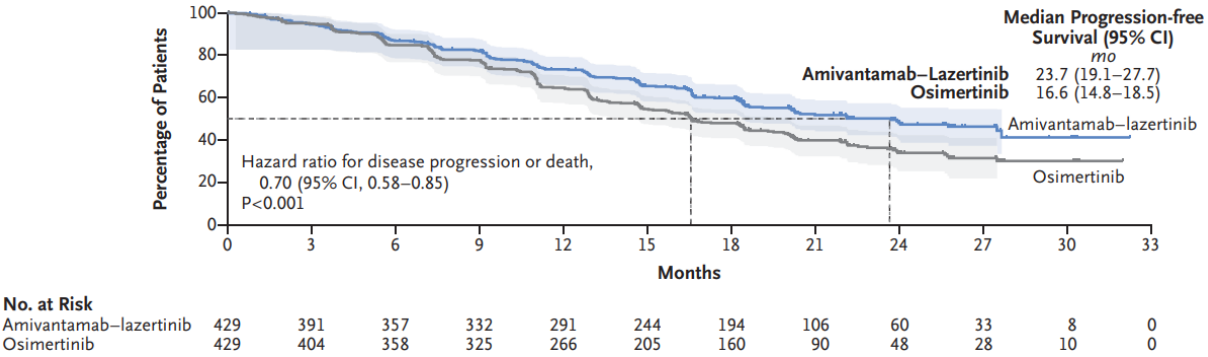
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect 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 MARIPOSA trial were published by Cho BC et al. in the New England Journal of Medicine in 2024.[22]

Progression Free Survival (by blinded, independent, central review (BICR))

PFS was the primary endpoint in the MARIPOSA trial. At a median follow up time of 22.0 months, the median PFS by BICR was 23.7 months for amivantamab and lazertinib versus 16.6 months for osimertinib (hazard ratio (HR, the HR is a way to compare the risk of an event happening between two groups over time): 0.70; 95% Confidence Interval (CI, the CI is a term that shows the range of values that likely contains the true value): 0.58, 0.85; p<0.001). This shows that amivantamab and lazertinib increased the amount of time before the cancer got worse by 7.1 months compared with osimertinib alone and resulted in a 30% reduction in the risk of disease progression or death compared to osimertinib. This benefit was shown to be consistent when looking at different subgroups (e.g., age, sex, race, weight). Figure 3 details the PFS rates within the MARIPOSA trial.

Figure 3: Progression Free Survival in the MARIPOSA trial

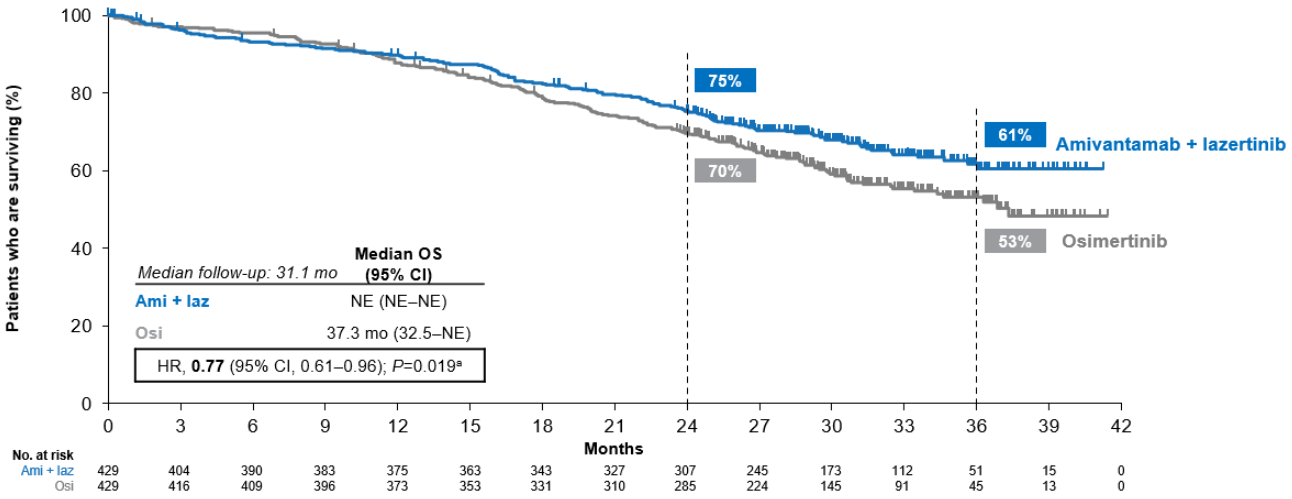


Overall Survival

Overall survival (OS) is the length of time patients remain alive after starting treatment. With median follow up of 31 months, the amivantamab and lazertinib arm had not yet reached median OS, but the osimertinib arm did, with a median OS of 37.3 months.[29] After 36-months, 61% of patients were alive in amivantamab and lazertinib group and 53% in the osimertinib group.[29] This represents a hazard ratio (HR) of 0.77 (95% CI: 0.61 – 0.96).[29]

Figure 4 details the overall survival rates from the MARIPOSA trial. On January 7th, Johnson & Johnson announced, via a press release, that amivantamab and lazertinib has shown a statistically significant and clinically meaningful improvement in overall survival compared to osimertinib in the phase 3 MARIPOSA trial. With the final analysis featuring an extended follow-up, the median overall survival improvement of this chemotherapy-free combination is anticipated to exceed one year compared to osimertinib.[30] These significant overall survival results reinforce the importance of amivantamab-lazertinib and its potential to significantly improve patient prognosis. It is noteworthy that amivantamab-lazertinib is the only chemotherapy-free treatment to demonstrate a significant survival benefit versus osimertinib in the first-line treatment of patients with EGFR-mutated lung cancer. Johnson & Johnson are not yet able to include this data in the submission as currently only top line data are available. Johnson & Johnson would be pleased to provide further analyses using the updated data once full data are available.

Figure 4: Overall Survival from the MARIPOSA trial



Abbreviations: Ami + laz: amivantamab-lazertinib; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; NE: not estimable; No.: number; OS: overall survival; Osi: osimertinib.
Footnotes: [a]P-value was calculated from a log-rank test stratified by mutation type (Ex19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified proportional hazards model.
Source: Johnson & Johnson Data on File, Clinical Study Report[31]; Cho et al., 2024[22]

Objective Response Rate

The objective response rate (ORR) is the total number of patients whose cancer has either gone away or shrunk after treatment. Amivantamab and lazertinib provides a rapid objective response rate, as does osimertinib, with approximately 85% of patients having an objective response across all treatments.[25] This means that there is a similar proportion of patients within each group which experienced their tumours completely or partially shrinking after starting treatment.

Duration of Response

The duration of response (DoR) is, for patients whose cancer has either gone away or shrunk, the time it takes for the disease to progress. The median DoR for patients treated with amivantamab and lazertinib was 9 months longer compared to those treated with osimertinib.[25] This means amivantamab and lazertinib has a more durable, meaningful delay in disease progression, as opposed to a more temporary response.

Progression Free Survival After First Subsequent Therapy (PFS2)

Given progression with either amivantamab and lazertinib or osimertinib is likely, exploring progression-free survival on treatments after the first line can show how a patient's disease progresses further into the future.[29] With a median follow up of 31 months, patients treated with amivantamab and lazertinib had a 27% reduction in the risk of second progression or death after their first subsequent therapy compared with participants in the osimertinib arm.[29] This further demonstrates durability of response whereby, even after receiving subsequent therapy, the reduction in the risk of disease progression is sustained for amivantamab and lazertinib.

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.

The MARIPOSA trial evaluated the quality of life of patients who received treatment.[25] Quality of life, symptoms, and functioning were captured using three patient-reported outcome measures: the EORTC Core Quality of Life (EORTC-QLQ-C30) questionnaire, the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), and the EuroQol 5-Dimension 5-level (EQ-5D-5L) questionnaire.

The 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 and lazertinib compared to osimertinib were similar, indicating that there are few differences between the two treatments. The exact scores are confidential but can be found in Section B.2.6.9 of the company submission.

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 and lazertinib maintained the patient's HRQoL functioning without adding lung cancer related symptoms compared to osimertinib. Coupled with enhanced efficacy, these results underscore the significance of amivantamab and lazertinib as a new treatment combination for patients.

Patient preference information

Patient preference information was sought in market research led by Johnson & Johnson in 2023 and showed the desire amongst patients for treatments that increase life or keep the disease stable with minimal impact on their everyday life. Patients generally expect some manageable side effects, which are predictable and within their control. These side effects have a limited impact on quality of life, meaning the patient is not frequently hospitalised 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.[8]

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 and lazertinib was similar with the safety profile of the separate individual treatments based on the data from the MARIPOSA trial.[22] Adverse events (AEs) are side effects that occur during treatment. The MARIPOSA trial showed that all patients (100%) in the amivantamab and lazertinib group experienced an AE and 99% of patients had an AE in the osimertinib group.[22]

The occurrence of serious AEs was similar between treatment arms with 205 patients (49%) experiencing a serious AE in the amivantamab and lazertinib group and 143 patients (33%) in the osimertinib arm reporting them.[22] AEs which led to discontinuation were seen in 147 patients (35%) in the amivantamab and lazertinib arm compared to 58 patients (14%) in the osimertinib arm.[22] Dose reductions also occurred in both arms with 249 patients (59%) in the amivantamab and lazertinib arm receiving a dose reduction and 23 patients (5%) in the osimertinib arm.[22] Dose interruptions were reported in 350 patients (83%) in the amivantamab and lazertinib

arm compared to 165 patients (39%) in the osimertinib arm. AEs which led to death occurred in 34 patients (8%) in the amivantamab and lazertinib arm compared to 31 patients (7%) in the osimertinib arm.[29]

Despite the increased discontinuation rate with amivantamab in the MARIPOSA trial, the observed side effects are consistent with what is expected for a bispecific monoclonal antibody targeting both EGFR and MET, which are known to cause immune-related reactions such as infusion-related reactions, paronychia (nail toxicity) and skin rashes.[32] These side effects, are generally manageable with appropriate monitoring and management, as seen in clinical practice with current therapies.[32] Additionally, the combination of amivantamab-lazertinib may have contributed to a higher incidence of side effects due to the cumulative toxicity often associated with combined therapies, but these reactions can be managed through dose adjustments, supportive care, and close monitoring.[21]

Table 2 presents the most commonly reported AEs in the MARIPOSA trial.[22] The AEs are graded according to severity, with Grade ≥3 AEs being more serious. The total number of Grade ≥3 AEs was 316 (75%) in the amivantamab and lazertinib arm compared to 183 (43%) in the osimertinib arm.[22] The Grade ≥3 AEs associated with amivantamab and lazertinib were manageable with dose reductions and interruptions.

Table 2: Adverse events reported in ≥15% of patients in either group

	Amivantamab and lazertinib (n = 421)		**Osimertinib (n = 428)**	
Adverse events reported in ≥15% of patients in either group	**All grades**	**Grade ≥3**	**All grades**	**Grade ≥3**
Paronychia	288 (68)	46 (11)	121 (28)	2 (<1)
Infusion-related reaction	265 (63)	27 (6)	0	0
Rash	260 (62)	65 (15)	131 (31)	3 (1)
Hypoalbuminemia	204 (48)	22 (5)	26 (6)	0
Increased alanine aminotransferase	152 (36)	21 (5)	57 (13)	8 (2)
Peripheral edema	150 (36)	8 (2)	24 (6)	0
Constipation	123 (29)	0	55 (13)	0
Diarrhea	123 (29)	9 (2)	190 (44)	3 (1)
Dermatitis acneiform	122 (29)	35 (8)	55 (13)	0
Stomatitis	122 (29)	5 (1)	90 (21)	1 (<1)
Increased aspartate aminotransferase	121 (29)	14 (3)	58 (14)	5 (1)
Covid-19	111 (26)	8 (2)	103 (24)	9 (2)
Decreased appetite	103 (24)	4 (1)	76 (18)	6 (1)
Pruritus	99 (24)	2 (<1)	73 (17)	1 (<1)
Anemia	96 (23)	16 (4)	91 (21)	7 (2)
Nausea	90 (21)	5 (1)	58 (14)	1 (<1)
Hypocalcemia	88 (21)	9 (2)	35 (8)	0
Asthenia	78 (19)	12 (3)	46 (11)	4 (1)
Pulmonary embolism	73 (17)	35 (8)	20 (5)	10 (2)
Fatigue	70 (17)	6 (1)	42 (10)	4 (1)
Muscle spasms	70 (17)	2 (<1)	32 (7)	0
Dry skin	67 (16)	1 (<1)	60 (14)	1 (<1)
Thrombocytopenia	66 (16)	1 (<1)	84 (20)	5 (1)
Cough	65 (15)	0	88 (21)	0
Pain in extremity	64 (15)	1 (<1)	22 (5)	0
Dyspnea	51 (12)	6 (1)	68 (16)	17 (4)
Leukopenia	26 (6)	1 (<1)	66 (15)	0

Source: *Cho et al. 2024*[22]

Initial results from the PALOMA-3 trial demonstrate a reduction in infusion-related reactions (IRRs) and venous thromboembolism (VTE) for patients treated with lazertinib and SC amivantamab versus IV amivantamab. While this population differs from the population investigated in the MARIPOSA trial, results from the PALOMA-3 clinical trial are considered informative, as they demonstrate the potential for both IV and SC formulations of

amivantamab to enhance the treatment process for patients with EGFR-mutated NSCLC compared with current SoC.[33]

In the PALOMA-3 trial, SC amivantamab was shown to be associated with a five-fold reduction in the incidence of IRRs (13%) compared with IV amivantamab (66%) and these events were primarily mild in nature (0.5% versus 4%, respectively, were Grade ≥3).[33] Additionally, no patients receiving SC amivantamab reported treatment discontinuation due to IRRs, whilst this was reported in 2% of patients in the IV treatment arm. Furthermore, PALOMA-3 trial identified that the incidence of venous thromboembolisms (VTEs) was lower in the SC amivantamab-lazertinib arm (9%) compared with the IV amivantamab-lazertinib arm (14%).[33]

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 and lazertinib has demonstrated several benefits to patients when compared to osimertinib. This includes:

- A dual mechanism of action (a bispecific antibody that targets two key receptors, EGFR and MET), reducing resistance and facilitating improved outcomes.[20, 21]
- A clinically meaningful and statistically significant improvement in overall survival compared to osimertinib.[29-31]
- Delaying the cancer progression by an additional 7.1 months compared to osimertinib.[22]
- Demonstrating consistent benefit regardless of gender, ethnicity and type of common EGFR mutation.[22]
- Achieving an improved durability of response even after receiving subsequent therapy.[29]
- Quality of life being similar between both amivantamab and lazertinib and osimertinib arms at different points in time when patients are receiving treatment.[25]
- Safety profile consistent with the individual treatments without new adverse events.[17, 22]

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 and lazertinib sees more grade ≥3 AEs (75% vs 43%) and serious AEs (49% vs 33%) compared to osimertinib, although the AEs associated with amivantamab and lazertinib were manageable with dose reductions and interruptions. Specific adverse events related to the treatment with IV are notable, with the rate of infusion-related reactions at 63%, although most of these were grade 1-2 AEs (therefore considered not too serious) and associated with the first infusion on the first day of treatment.

In addition to the MARIPOSA trial, other studies are proactively addressing the pre-emptive management of AEs associated with IV amivantamab, SKIPPirr (NCT05663866) and COCOON (NCT06120140).[34, 35] These study results are due to be reported in mid-2025, with a continuous effort to explore ways in which patient safety can be improved with amivantamab and lazertinib as well as effective management to ensure the best experience for patients during treatment.

Amivantamab and lazertinib has an administrative burden due to amivantamab being administered via IV, rather than as an oral therapy, which is relevant for lazertinib and osimertinib. Patients require weekly visits to hospital

for the first 4 weeks of treatment (with the first dose needing to be split over 2 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 2 weeks from week 4 onwards, and a subcutaneous formulation is in development which could, depending on the results of the relevant trials, replace the IV formulation.

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 and lazertinib versus the main comparator of osimertinib. 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.

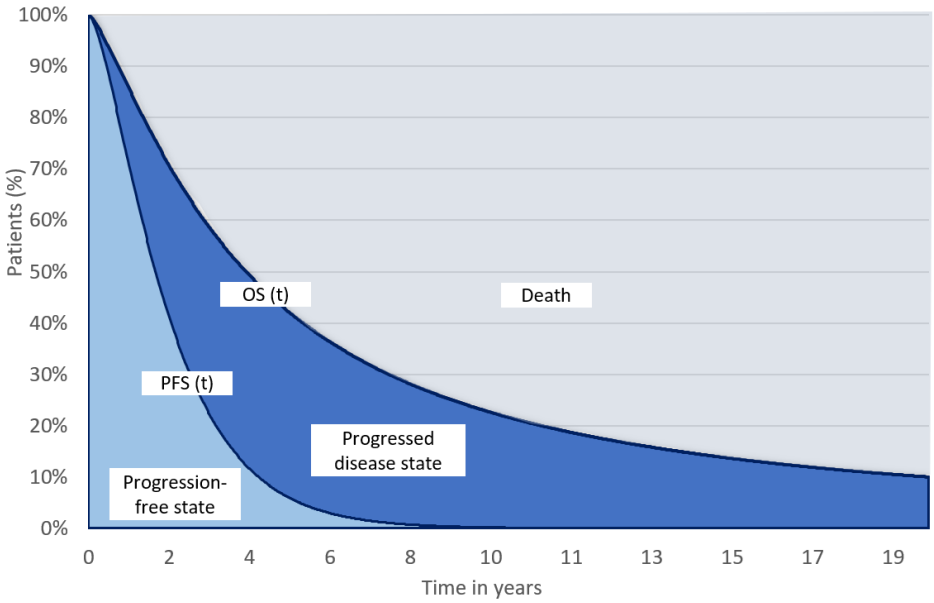
The model simulates a patient's progression over a 30-year time horizon through a set of different health states (before disease progression, after disease progression, and death). Each health state is associated with relevant costs and a specific quality-of-life benefit.

The following health states were used in this cost-effectiveness model (shown diagrammatically in Figure 5):

- **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.

Figure 5: Cost-Effectiveness Model: Partitioned survival model approach



Abbreviations: OS: overall survival; PFS: progression-free survival; TTNT: time to next treatment.

The model uses PFS, time to next treatment, treatment discontinuation, OS, AE and QoL data (the EQ-5D questionnaire) from the MARIPOSA trial for amivantamab, lazertinib and osimertinib. 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 include 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.

The model demonstrates that amivantamab and lazertinib results in more life years (LYs) and QALYs compared to osimertinib. This is mainly from the improvement in both PFS and OS compared with the comparator in the model. Without the incorporation of discounts applied to the drug list prices, the model also shows higher overall costs with the introduction of amivantamab and lazertinib compared with osimertinib alone due to the drug costs of treatment and the time spent on treatment being higher with amivantamab and lazertinib. When comparing the costs and the estimated health benefits (in the form of QALYs) between amivantamab and lazertinib and osimertinib, the model demonstrates amivantamab and lazertinib 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 a median follow-up of 22.0 months for progression free survival, and 31.1 months for all other endpoints, and are used to model outcomes over 30 years. Therefore, there is some uncertainty as to whether the modelled outcomes follow exactly what will happen in the trial. To address this uncertainty, Johnson & Johnson has gathered long-term data on osimertinib, along with extensive real-world information. The company have also consulted clinical experts who possess valuable insights and experience regarding the long-term outcomes of patients with common EGFR mutation-positive advanced NSCLC.

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 in combination with lazertinib represents a step-change in treatment for patients with common EGFR mutation-positive advanced NSCLC by offering an innovative treatment option that leverages a dual mode of action to improve efficacy and survival outcomes, whilst maintaining patients' quality of life. Simultaneous inhibition of both EGFR and MET by amivantamab in combination with lazertinib is anticipated to delay disease progression by limiting the compensatory pathway activation and targeting the two major mechanisms of resistance to TKIs (mutations in EGFR and MET pathways). In addition to delaying disease progression in the first-line setting, with a consistent benefit observed across patient groups (regardless of gender, ethnicity and type of common EGFR mutation), amivantamab-lazertinib is shown to maintain an improved durability of clinical benefit even after subsequent treatment. The significance of this for patients is a broader range of first-line treatment options extending the time to progression in the first-line setting compared with the current standard of care, osimertinib monotherapy.

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. Patients with lung cancer often face stigma due to people associating smoking with lung cancer, therefore blaming the patient for their disease. Common EGFR 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 common EGFR mutations specifically which makes it especially difficult for these patients.[36-38] There is also evidence that symptoms of lung cancer are stigmatised in communities of Asian ethnicity, which could reinforce the treatment delaying behaviour seen in lung cancer more generally.[9] If amivantamab and lazertinib is made available on the NHS, patients with common EGFR mutations will have an opportunity to receive a more efficacious targeted combination therapy. This is paramount for patients with this severe disease due to the limited life expectancy with current treatments (24.6 months).[7]

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://www.clinicaltrials.gov/study/NCT04487080 • Amivantamab SmPC: https://www.medicines.org.uk/emc/product/13084/smpc • Lazertinib SmPC draft documents are included within the reference pack as they are not yet published.

- Amivantamab plus Lazertinib in NSCLC with common EGFR mutations publication: https://www.nejm.org/doi/full/10.1056/NEJMoa2403614

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.
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.
Contraindications: specific circumstances or conditions under which a particular treatment should not be used because it may be harmful to the patient.
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.
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.
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.
Life expectancy: the average number of years a person is expected to live.
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.
Subcutaneous (SC): a method of delivering medication or injections just beneath the skin's surface, usually in the fatty tissue.
Symptoms: the signs or indicators of a disease that a person experiences or reports.
Tyrosine Kininase Inhibitor: a type of cancer medication that helps fight cancer by blocking specific proteins that help cancer cells grow and multiply. Think of these proteins as "signals" that tell the cancer cells to grow. By stopping these signals, TKIs can slow down or even stop the cancer from growing, making them a crucial option in the treatment of certain types of cancer.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

February 2025

File name	Version	Contains confidential information?	Date
ID6256_Amivantamab with lazertinib in NSCLC_Clarification Questions Response Document_[CON]_Redacted	1.0	Yes	18th February 2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision Problem

A1. PRIORITY: The EAG notes the reasons stated by the company for not including osimertinib with chemotherapy as a comparator. However, the appraisal of osimertinib with chemotherapy for first-line treatment (ID6328) is currently ongoing. Final guidance will not be published before the company submits their clarification response but should be published before the first committee meeting for ID6256. Please provide clinical and cost-effectiveness evidence comparing amivantamab with lazertinib against osimertinib with chemotherapy for the committee to consider should osimertinib with chemotherapy receive positive guidance.

Johnson & Johnson acknowledges that osimertinib with chemotherapy for untreated advanced common epidermal growth factor receptor mutated (cEGFRm) non-small cell lung cancer (NSCLC) is currently undergoing the NICE appraisal process. However, based on the conclusion of a lack of cost-effectiveness for osimertinib with chemotherapy, a draft non-recommendation guidance was issued in October 2024 (NICE ID6328).[1] As such, osimertinib with chemotherapy is not currently recommended by NICE and does not represent an established treatment option in clinical practice in the NHS in England.

This is further supported by real-world UK-based data from the NCRAS database, which show that of the 95 patients with cEGFRm NSCLC and similar baseline

characteristics to patients in the MARIPOSA trial (the 'MARIPOSA-like' cohort) who received first-line (1L) treatment in the UK between 2021 and 2023, the vast majority (90.5%; n=86/95) received osimertinib monotherapy.[2] The predominance of osimertinib monotherapy as current standard of care (SoC) in the UK was further supported by insight provided by expert clinicians working in current UK clinical practice, who stated that first- and second-generation TKIs are no longer routinely used in UK clinical practice due to the availability of osimertinib, and confirmed the osimertinib represents the sole SoC for patients with cEGFRm NSCLC.[3]

The NICE manual on health technology evaluations states that relevant comparators should be treatments that are established practice in the National Health Service (NHS), including those regarded as current best practice.[4] Therefore, in line with NICE guidance on the selection of relevant comparators, UK clinical expert opinion, and UK-based real world evidence, osimertinib monotherapy remains the only comparator considered relevant to this submission.

As outlined in the NICE manual, this submission concentrates on the current care pathway utilised within the NHS, which also forms the basis for the parallel appraisal of osimertinib with chemotherapy (ID6328). J&J contend that parallel appraisals should be conducted equitably. Introducing osimertinib with chemotherapy as an additional comparator after the submission has been made would only serve to introduce additional uncertainty into this appraisal, creating disparities between the appraisals. The fact that both this appraisal and ID6328 compare interventions against a common standard of care—osimertinib—should be a sufficient basis for informed decision-making Consequently, clinical and cost-effectiveness evidence for osimertinib in combination with chemotherapy is not provided.

Clinical effectiveness systematic review methods

A2. According to Appendix D.1.1.3, searches were conducted of ClinicalTrials.gov. Please clarify if the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) was also searched as part of the clinical systematic literature review (SLR)?

The WHO ICTRP platform was not searched as part of the clinical SLR as supplementary searches of ClinicalTrials.gov were considered sufficient to capture any trial records which were not identified through electronic database searches.

A3. In Appendix D.1.1.5., the text states that search terms to capture economic studies are based on the validated Scottish Intercollegiate Network (SIGN) filter set. However, Appendix D is describing the search for clinical studies and not economic

studies, please confirm whether this is a typo/error and provide the relevant corrected sentence.

Johnson & Johnson thanks the EAG for flagging this inconsistency and confirms that this was an error. The corrected sentence should read "*For all applicable searches (i.e., of databases with complex search functionality) the search terms to capture RCTs and observational studies are based on the validated Scottish Intercollegiate Guidelines Network (SIGN) filter sets.*[5]"

A4. Regarding the use of search filters in the clinical SLR, the submission states that the study design filters used were adapted from filters published by the Scottish Intercollegiate Guidelines Network [SIGN], and that safety outcome terms were adapted from the adverse effects 'Special Ovid Filters' for MEDLINE/Embase (Appendix D.1.1.5). Please provide a) details of the modifications made where applicable, and b) justification for the changes made to the published filters.

The adaptations to the SIGN filter for RCTs are minor, including the addition of some additional subject heading terms to maximise sensitivity of the strategy (such as Controlled Clinical Trial/; Adaptive Clinical Trial/) and updating the ".tw." field limit to "ti,ab,kf.".[5]

The original 'Special Ovid Filter' contains various search terms that were not anticipated to apply to this SLR, such as 'drug overdose', 'pregnancy', 'wound and injuries'.[6] As such, terms deemed irrelevant to this SLR were removed, whilst the core search strategy of terms relevant to this review was retained to capture any potentially eligible studies reporting safety data.

A5. For the clinical SLR, the database search strategy is broad, and the search terms do not include terms for the main interventions (e.g. amivantamab, lazertinib) or comparators (e.g. osimertinib) of interest. Please explain the rationale behind this search approach.

This approach was taken to ensure that sensitivity was prioritised over specificity, maximising the chances that all potentially relevant articles were identified in the searches.

A6. Given that studies of first-line treatments are of interest, please explain the rationale behind including search terms for mutations or Tyrosine Kinase Inhibitor (TKI) resistance (e.g. in lines 10 and 11 of the search in Table 1, Appendix D.1.1.5), which seem more relevant to second-line treatments and beyond.

As noted in the footnote of the eligibility criteria table for the clinical SLR (cSLR; Table 28, Appendix D.1.2.1), treatments in the first-line setting, as well as treatments

in the second-line (or later) settings, were eligible for inclusion in the global SLR, as the aim was to capture evidence across all treatment lines. As such, terms for TKI resistance were included in the search strategy. However, studies reporting exclusively on patients in the second-line (or later) settings were not considered or presented within this submission, as they are not relevant to the decision problem.

A7. In Appendix D.1.2.1. In the paragraph above Table 28, it is stated, "*Only RCTs and observational studies including patients previously treated with osimertinib were included."* However, in Table 28 of Appendix D, one of the inclusion criteria is given as, "*Studies where participants have not received any prior systemic treatment*." These two statements appear to contradict each other. Please clarify if the SLR was restricted to first-line studies.

The global SLR was not restricted to first-line studies, and instead captured evidence across all treatment lines; as such, studies in the second-line (or later) were also eligible for inclusion. Given a paucity of evidence in the second or later-line setting, observational studies and RCTs were both acceptable study designs, whereas RCTs were the only study design eligible for inclusion in the first-line setting – please refer to the updated eligibility criteria presented in Table 1.

As the cSLR evidence relevant to this submission is in the first-line setting, only RCTs where participants have not received prior systemic therapy are presented within this submission. As such, the statement in Table 28 (Appendix D.1.2.1) "*Studies where participants have not received any prior systemic treatment*" should be linked to footnote 'b', which notes that studies reporting exclusively on patients in the second-line (or later) were not considered or presented within this submission, as they are not relevant to the decision problem.

A8. Please confirm if the SLR for this submission was developed a prior or post hoc.

The original SLR for this submission was developed and conducted prior to submission, with the most recent SLR update conducted within six months of the submission.

A9. Company submission (CS) B.2.2 page 40 and Appendix D.1 Table 28, Figure 1. Identification and selection of relevant studies provided appears for a broader review question. Please could you provide further details on how the MARIPOSA trial was identified and selected for inclusion in the SLR. For clarity please provide detailed inclusion/exclusion criteria, PRISMA flow diagram and brief reason of excluded studies for the SLR of this submission – The Systematic review of Amivantamab with

lazertinib for untreated Epidermal Growth Factor Receptor (EGFR) mutation-positive advanced non-small-cell lung cancer (NSCLC).

As noted above, the global cSLR encompassed a broader review question than that required for this submission. Specifically, studies in the first-line, second-line or later were considered eligible for inclusion. However, in line with the decision problem, only studies in the first-line setting (i.e., for untreated advanced EGFRm NSCLC), were considered and presented within this submission. The table below reflects the eligibility applied to the global cSLR, with the *yellow highlighted text* relating to the criteria used to consider whether studies were relevant to present within this submission (Table 1).

Furthermore, the PRISMA flow diagram presented in Figure 1 of Appendix D.1.3 relates to the global cSLR, and the subset of first-line studies presented in this submission. The 167 records included in the SLR refer to studies in the first-line, second-line or later, of which 85, including the MARIPOSA trial, were in the first-line setting.

The Included and Excluded Studies list provided in the accompanying reference pack; please refer to column N in the 'All Included Records' tab for a list of studies not presented in this submission (i.e., studies which can be considered 'excluded' from the SLR for this submission). The PRISMA flow diagram has been updated (Figure 1).

Table 1: Eligibility criteria in the clinical SLR

	Inclusion	Exclusion
Population	Adult (≥18 years old) patients with locally advanced or metastatic cEGFR-mutated NSCLC that is not amenable to curative therapy including surgical resection or chemoradiation, specifically: • Patient populations where at least 85% of the cohort has adenocarcinoma[a] **Treatment setting:** • *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) – in line with PAPILLON and MARIPOSA indications*[b]	• 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 • Patients with ex20ins NSCLC • 1L+: Studies where the patient population consists of a mixture of patients, with some receiving 1L but

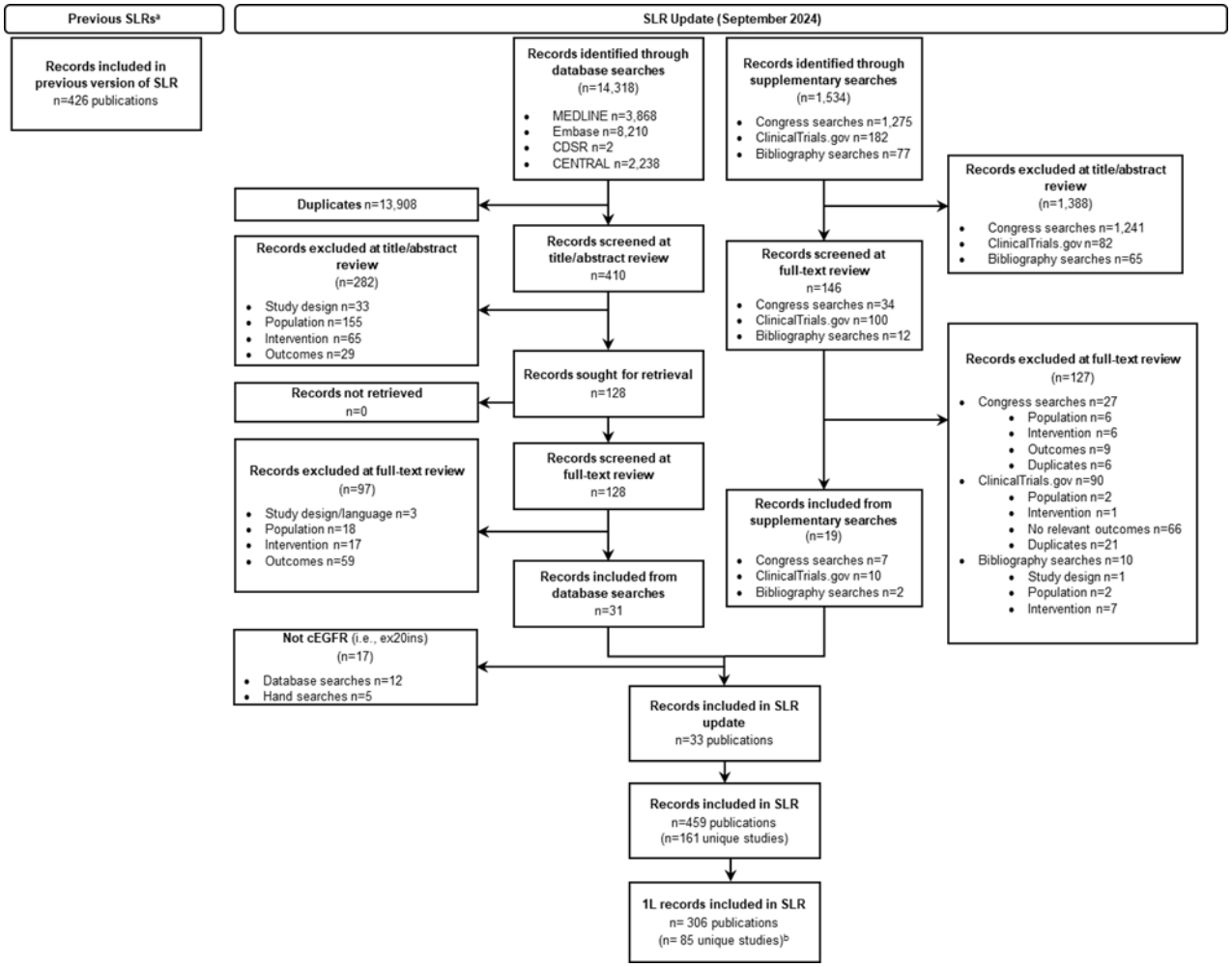
	Inclusion	Exclusion
		others receiving 2L or later, unless outcomes are presented separately for a subgroup of 1L alone • *Patients receiving 2L or later treatment*[b]
Intervention	• Any therapeutic or palliative intervention administered within the healthcare system	• Non-therapeutic or palliative interventions
Comparator	• Placebo or SoC • Any comparator if also an intervention of interest	N/A
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	**1L, 2L+ treatment settings** • RCTs (phase I, II, III, IV) ***2L+ post-osimertinib (or any 3G TKI) setting***[b] • 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)

	Inclusion	Exclusion
		• 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
Other considerations	• Any location, focused on OECD countries or Europe if necessary • Human subjects • English language (abstract or full text)	• Not in human subjects • Not in English language

Footnote: [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] Studies of patients receiving 2L treatment were included in the SLR but are not relevant for the MARIPOSA indication. As such, these studies are not considered or presented in this submission.

Abbreviations: 1L, first-line; 1L+, first-line or later; 2L, second-line; 3G: third generation; AE, adverse event; AESI, adverse event of special interest; CBR, clinical benefit rate; cEGFR, common epidermal growth factor receptor mutation; 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)MA, (network) meta-analysis; NSCLC, non-small cell lung cancer; NSCLS-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, PROMIS 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; TTNT, time to next treatment; TTP, time to progression; TTSP, time to symptomatic progression; WDAE, withdrawals due to adverse event.

Figure 1: PRISMA flow diagram for 1L studies identified in the SLR update (September 2024)



Footnotes: [a]Original SLR (conducted in May 2020) and subsequent SLR updates (July 2022, September 2023 and March 2024). [b]Within the 85 included studies, 69 enrolled exclusively patients with cEGFR-mutated NSCLC, while the other 16 studies included planned or unplanned subgroup analyses for cEGFR. **Abbreviations**: 1L, first-line; CDSR, Cochrane Database of Systematic Reviews; cEGFR, common epidermal growth factor receptor; CENTRAL, Cochrane Controlled Register of Trials; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial; SLR, systematic literature review.

A10. CS Appendix D page 44. States “In cases where the publication did not give enough information to be sure it met the eligibility criteria, it was excluded at this stage, to ensure that only relevant articles were ultimately included in the SLR.” Please clarify how many studies were excluded due to this reason and if the study authors were contacted to seek clarification before exclusion.

During the full-text review stage, studies which did not contain enough information to confirm relevance in line with the eligibility criteria were assigned exclusion labels according to the criterion they lacked sufficient detail for (i.e., Population, Intervention, Comparator, Outcome). As such, it is not possible to retrieve studies that were specifically excluded due to lack of information on a specific criterion. For example, if it was unclear whether patients with NSCLC in a study had EGFR mutations, the study would be excluded under the ‘Population’ exclusion category – this category also contains studies which definitely did not meet the Population inclusion criteria, such as those conducted in early-stage NSCLC. It should be noted that all records were screened by two independent reviewers, with any disagreements resolved by discussion, and arbitrated by a third independent reviewer, if necessary, until a consensus was met. As such, the lack of sufficient information in a study would be verified by two individuals.

Given the volume of evidence screened, it was not feasible to contact study authors to seek clarification before exclusion.

A11. CS Appendix D.1.2.1 Page 45 Table 28. Please provide rationale for only including Conference abstracts published in or after 2020.

Johnson & Johnson apologises for a typographical error here, as conferences abstracts published in or after 2018, rather than 2020, were considered eligible for inclusion. The justification for this threshold is outlined below.

For the original SLR conducted in 2020, conference abstracts were included if they were published in the last two years (i.e. 2018). Only recent conference abstracts were considered eligible for inclusion as it was expected that any abstracts published over two years prior that presenting high-quality research would have been published as a peer-reviewed journal article by the time of the SLR searches. As such, conference abstracts were included in the SLR to capture relevant data from studies that present high-quality research, but have yet to be published. The two-year threshold for conference abstracts applied in the original SLR was retained at each SLR update, for consistency; as such, abstracts published from 2018 onwards were included.

A12. CS Appendix D.1.3 Figure 1 page 48. Please confirm if the total number of records included from database searches is n=31 as (128-96) = 32

Johnson & Johnson thanks the EAG for raising this inconsistency. There was a typographical error in the number of studies excluded at the full-text review. The PRISMA has now been updated (see Figure 1 above).

A13. CS Appendix D.1.3 Figure 1 page 48. Please confirm if the "Not cEGFR records (n=14)" was removed from records included in the SLR update (n=50) as (31+19 = 50)-14 = 34. Also 34+424=458 not 474.

The "Not cEGFR records" were removed from the records included in the SLR update. The PRISMA flow diagram has been updated to correct any errors and is now accurate (see Figure 1 above).

A14. CS Appendix D.1.2.1 Table 28. The SLR eligibility criteria was limited to randomised controlled trials (RCTs). Whilst CS B.2.5 page 56 and Appendix D.3 page 50 mention using ROBINS-1 QA checklist for assessing non-RCT studies. Please clarify.

Within the global cSLR, RCTs were eligible in the first-line and second-line or later setting. Non-RCT studies were considered eligible only if they were conducted in the second-line or later setting specifically in patients who had received prior therapy with a third-generation TKI (please refer to the updated eligibility criteria presented in Table 1 above). Therefore, the use of ROBINS-1 quality assessment (QA) is not relevant to the evidence supporting this submission. Johnson & Johnson apologises for any confusion caused.

Clinical effectiveness studies

A15. CS, B.2.5, page 56 Table 11. Please could you undertake the quality assessments of the MARIPOSA trial using the Cochrane risk of bias 2 tool and provide a narrative summary of the critical appraisal of the included studies.

A quality assessment of the MARIPOSA trial has been conducted using the Cochrane Risk of Bias 2 tool (Table 2).

The MARIPOSA trial has an overall low risk of bias. Across all five domains of the Cochrane Risk of Bias 2.0 tool, the risk of bias being introduced to results was judged to be low. Firstly, the trial conducted randomisation in an appropriate manner and concealed treatment allocation. Participants, carers and healthcare professionals administering treatment were blinded for two of the three treatment arms (osimertinib monotherapy and lazertinib monotherapy), with blinding deemed to be unfeasible in the amivantamab-lazertinib arm due to the IV route of administration

required for amivantamab, compared with oral administration of lazertinib and osimertinib. However, no deviations from the intended intervention were reported, and an intent-to-treat (ITT) analysis was employed for analysis of intervention efficacy. Outcomes were measured using appropriate methods, which were consistent between treatment arms; a blinded independent central review was employed, meaning outcome assessors were unaware of, and uninfluenced by, the intervention received by participants. Finally, all outcomes were analysed and reported in line with the pre-specified trial protocol and statistical analysis plan.

Table 2: Cochrane Risk of Bias 2.0 Assessment for MARIPOSA trial

Signalling questions	Comments	Response
Domain 1: Risk of bias arising from the randomisation process		
1.1 Was the allocation sequence random?	Computer-generated randomisation (using blocks and stratification); interactive web response system to conceal treatment allocation	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Baseline characteristics were well-balance between treatment arms	N
Risk of bias judgement	Randomisation achieved successfully, with allocation sequence concealment	**Low**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)		
2.1 Were participants aware of their assigned intervention during the trial?	Osimertinib and lazertinib monotherapy arms administered in double-blinded manner. Blinding for amivantamab-lazertinib not feasible due to administration route	PY
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PY
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No deviations from allocated study drug reported	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	-	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	-	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All randomised patients included in efficacy analyses, classified according to their assigned treatment arm rather than actual treatment received (i.e., ITT)	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of	-	NA

the failure to analyse participants in the group to which they were randomized?		
Risk of bias judgement	Participants and carers aware of intervention but no deviations from intended interventions	**Low**
Domain 3: Missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	ITT analyses used for all efficacy outcomes	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	-	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	-	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk of bias judgement	Data available for all participants across efficacy outcomes	**Low**
Domain 4: Risk of bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	Appropriate measurement of outcomes, according to RECIST v1.1 assessment	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Identical methods of outcome measurement between intervention groups	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	All efficacy outcomes performed by blinded independent central review	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	-	NA

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	-	NA
Risk of bias judgement	Appropriate methods of measuring outcomes, comparable between intervention groups; outcome assessors unaware of intervention received	**Low**
Domain 5: Risk of bias in selection of the reported result		
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Reported results aligned with pre-specified analysis plan in study protocol/statistical analytical plan	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	All pre-specified outcome measurements reported on	N
5.3 ... multiple eligible analyses of the data?	All eligible analyses of data appear to be reported on across outcomes	N
Risk of bias judgement	Data analysed in line with pre-specified protocol/statistical analytical plan	**Low**
Overall risk of bias judgement		
Risk of bias judgement	Trial involved successful randomisation and treatment allocation; appropriate outcome measurement methods, ITT and blinded outcome assessors; data analysed in line with pre-specified protocol	**Low**

Abbreviations: ITT: intent-to-treat; N: No; NI: no information; PN: partly no; PY: partly yes; RECIST: Response Evaluation Criteria in Solid Tumors; Y: yes.

A16. CS, B.2.5, page 56 Table 11. Please could you provide a rationale for assessing patient/care provider blinding as medium risk of bias when the trial was open labelled for amivantamab plus lazertinib.

Despite the amivantamab-lazertinib trial arm being open-label, a medium, rather than high, risk of bias was assigned to take into consideration blinding of the comparator arms (osimertinib monotherapy and lazertinib monotherapy). Furthermore, the University of York Centre for Reviews and Dissemination (CRD) QA guidance acknowledges that "the feasibility and/or success of blinding will partly depend on the intervention in question. There are situations where blinding is not possible owing to the nature of the intervention".[7] As such, a medium risk of bias reflects that blinding was employed where possible throughout the MARIPOSA trial.

A17. PRIORITY: Please clarify why the CS does not include progression-free survival (PFS) data from the 13th May 2024 data cut-off (DCO) of the MARIPOSA trial. Please provide results tables equivalent to Tables 13 and 14 and plots equivalent to Figure 8, 9 and 10 for the 13th May 2024 DCO.

The primary endpoint of the MARIPOSA trial, PFS assessed by blinded independent central review (BICR), was met at the 11th August 2023 DCO, where amivantamab-lazertinib demonstrated a 30% reduction on the risk of disease progression by BICR or death compared with osimertinib.[8, 9] The 13th May 2024 DCO was requested by the European Medicines Agency (EMA) to assess interim OS data only; as such, PFS data are not available from the 13th May 2024 DCO, and the most up-to-date data for PFS (from the 11th August 2023 DCO) have been provided within the submission. Updated final analysis data for relevant outcomes will be provided as an addendum, as discussed and agreed with NICE.

A18. CS, p44 states, "*Continuation of study treatment after confirmed disease progression was allowed in accordance with local practice, after consultation with the Medical Monitor, if the investigator believed the patient was deriving clinical benefit*". Please provide information on the proportion of patients in each trial arm who continued treatment beyond confirmation of disease progression?

The proportion of patients who discontinued treatment before and after confirmed disease progression is presented in Table 3. In both arms, a high proportion of patients discontinued treatment, or were censored for TTD, after disease progression (amivantamab-lazertinib: [redacted]; osimertinib: [redacted]). This reflects the combined TTD analysis presented in Section B.2.6.7 of Document B of the company submission, which demonstrated a prolonged median TTD in both arms as compared with median PFS. At the 13th May 2024 DCO, the median TTD in the amivantamab-lazertinib arm (26.3 months) was longer than the median PFS (assessed by BICR) at the 11th August 2023 DCO (23.7 months).[8, 10] This difference

is even more pronounced in the osimertinib arm, with a median TTD of 22.6 months compared with a median PFS of 16.6 months.[8, 10]

As further discussed in Question B14, the use of osimertinib post-progression is common and reflective of UK clinical practice, as confirmed by UK clinicians at an advisory board held by Johnson & Johnson in October 2024.[3] This post-progression use of osimertinib is also in line with clinical opinion from the British Thoracic Oncology Group in the Committee meeting for the ongoing NICE appraisal of osimertinib in combination with pemetrexed and PBC for untreated EGFR mutation-positive advanced NSCLC (NICE ID6328), who noted that treatment with osimertinib would be continued until loss of clinical benefit or unmanageable toxicities.[1]

Overall, based on trial data and what is seen in RWE, treatment discontinuation post-progression is common in both treatment arms, amivantamab-lazertinib and osimertinib. Although from a clinical effectiveness perspective, the TTD data for amivantamab-lazertinib is combined; in order to most accurately estimate treatment duration in the model, the TTD curves have been analysed separately for each treatment component (please see Question B14).

Table 3: The proportion of patients in each trial arm who discontinued treatment before and after confirmed disease progression (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Discontinued or censored for TTD after progression	[redacted]	[redacted]
Discontinued before or at the time of progression	[redacted]	[redacted]

Abbreviations: DCO: data cut off; PFS: progression-free survival; SAS: safety analysis set; TTD: time to treatment discontinuation.

A19. CS B.2.3 page 52. Although the decision problem and draft Summary of Product Characteristics (SmPC) states amivantamab-lazertinib will be indicated for first-line treatment of advanced untreated NSCLC with EGFR exon19del or exon 21 L858R substitution mutations – the trial included approximately 25% of patients with prior therapy for lung cancer (Systemic, radiotherapy, Cancer-related surgery). Please clarify.

In the MARIPOSA trial, participants who had received any prior systemic treatment at any time for locally advanced Stage III or metastatic Stage IV disease were excluded from participation in the study.[11] However, adjuvant or neo-adjuvant therapy for Stage I or II disease was permitted, if administered more than 12 months prior to the development of locally advanced or metastatic disease.[11] Overall, [redacted] patients ([redacted]) received any prior therapy for lung cancer: [redacted] patients ([redacted]%) received prior

systemic therapy, all of which were administered in the adjuvant/neo-adjuvant setting, [redacted] patients received prior radiotherapy ([redacted]%) and [redacted] patients received prior cancer-related surgery ([redacted]%). The percentage of patients receiving these prior therapies was balanced across treatment arms.[11]

A20. CS, Section B.2.3.9 page 75. Please provide all patient reported outcome (PRO) measures reported in the MARIPOSA trial including EORTC-QLQ-C30 and NSCLC-SAQ utility scores.

Changes in EORTC-QLQ-C30 global health status scores from baseline across the two treatment arms at key trial timepoints from the 11th August 2023 DCO are presented in Table 4, with physical functioning scores presented in Table 5. Across both treatment arms, scores on the EORTC-QLQ-C30 indicated that high levels of functioning and global health status were maintained on treatment.

Changes in NSCLC-SAQ total scores from baseline across the two treatment arms at key trial timepoints from the 11th August 2023 DCO are presented in Table 6. The NSCLC-SAQ total score showed that participants had a low burden of disease symptoms at baseline that improved slightly on treatment for both treatment arms.

Table 4: Analysis of EORTC-QLQ-C30 global health status scores (11th August 2023 DCO; FAS)

Global health status	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Initiation of Q2W dosing (Cycle 2 Day 1)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]

Abbreviations: DCO: data cut-off; FAS: full analysis set; SD: standard deviation; Q2W: once every two weeks.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). TPROQLQ02, page 301.[11]

Table 5: Analysis of EORTC-QLQ-C30 physical functioning scores (11th August 2023 DCO; FAS)

Physical functioning	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Baseline		
n	[redacted]	[redacted]

Physical functioning	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Mean (SD)	[redacted]	[redacted]
Initiation of Q2W dosing (Cycle 2 Day 1)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]

Abbreviations: DCO: data cut-off; FAS: full analysis set; SD: standard deviation; Q2W: once every two weeks.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). TPROQLQ02, page 303.[11]

Table 6: Analysis of NSCLC-SAQ total scores (11th August 2023 DCO; FAS)

Total scores	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Baseline		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Initiation of Q2W dosing (Cycle 2 Day 1)		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]
End of treatment		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]

Abbreviations: DCO: data cut-off; FAS: full analysis set; SD: standard deviation; Q2W: once every two weeks.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). TPROSAQ02, page 340.[11]

A21. Please provide safety data from DCO of 13th May 2024 or the most recent DCO available.

Safety data from the 13th May 2024 DCO are provided in Table 7.[12] Grade ≥3 TEAEs were reported in [redacted] patients ([redacted] in the amivantamab-lazertinib arm and [redacted] patients ([redacted] in the osimertinib arm.[12]

The incidence rates and durations of AEs for 1L treatment implemented within the economic model were sourced from these updated data from the MARIPOSA trial (Table 8).[12] Grade 3 or higher TEAEs were included if they occurred in ≥5% of patients in one of the modelled treatment arms, as informed by the MARIPOSA

Phase 3 trial.[12] Additionally, Grade ≤2 VTE was included given that this is a clinically relevant consideration for amivantamab treatment.

Table 7: Number of patients with Grade ≥3 TEAEs with frequency of at least 5% in either relevant treatment group by system organ class and preferred term (13th May 2024 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more Grade ≥3 AEs	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Dermatitis acneiform	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Hypoalbuminaemia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
IRR	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]

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. AEs were coded using MedDRA Version 25.0.
The event experienced by the patient with the worst toxicity is used.
Abbreviations: AE: adverse event; DCO: data cut-off; IRR: infusion-related reaction; SAS: safety analysis set; TEAE: treatment-emergent adverse event.
Source: Johnson & Johnson Data on File. MARIPOSA Updated Safety Data (DCO: 13th May 2024).[12]

Table 8: Incidence of AEs included in the CEM (13th May 2024 DCO; SAS)

Adverse event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Dermatitis acneiform	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]
Hypalbuminaemia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Infusion related reaction	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]
Grade ≤2 VTE	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]

Abbreviations: AE: adverse event; CEM: cost-effectiveness model; DCO: data cut-off;; SAS: safety analysis set; VTE: venous thromboembolism.
Source: Johnson & Johnson Data on File. MARIPOSA Updated Safety Data (DCO: 13th May 2024).[12]

A22. In the Multi-disciplinary Review and Evaluation conducted by the US Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) it states that, '*Although the risk of VTE is described in the product labeling, data provided in the application incompletely characterize the safety signal including whether prophylactic anticoagulation for the first four months of therapy is adequate…*' Please provide additional data describing the incidence of venous thromboembolism (VTEs) in patients with and without prophylactic anticoagulation, as well as the need for treatment-level anticoagulation.
[https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/219008Orig1s000MultidisciplineR.pdf]

A protocol amendment was implemented to address an Urgent Safety Measure regarding an imbalance in the overall incidence of VTE events associated with amivantamab-lazertinib compared with osimertinib or lazertinib, largely occurring in the first four months of therapy. The amendment added the recommendation that patients receiving the combination of amivantamab-lazertinib receive prophylactic anticoagulation for the first four months of treatment; at the time of this Urgent Safety Measure, enrollment in MARIPOSA had completed and only 12 participants were eligible for prophylactic anticoagulation per the recommendation. Data regarding the incidence of VTEs in patients with and without prophylactic anticoagulation are not available.

A summary of first VTE events by anticoagulation status (unrelated to prophylaxis) is presented in Table 9. Nearly all first VTE events occurred in participants who were not receiving concomitant anticoagulants, and recurrent VTE events while on

anticoagulants were uncommon. The most frequently reported VTE TEAEs were pulmonary embolism and deep vein thrombosis. Although there was a higher incidence of all-grade VTE events in the amivantamab-lazertinib arm ([redacted]) compared with the osimertinib arm ([redacted]), this difference was due primarily to a higher incidence of participants with Grade 1 or Grade 2 VTE events. The incidence of Grade 4 and Grade 5 VTE events was ≤0.5% in both arms.

Table 9: Overall summary of TEAE VTEs by anticoagulation status (11th August 2023 DCO; SAS)

Event, n (%)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more VTEs	[redacted]	[redacted]
First VTE started while on anticoagulants	[redacted]	[redacted]
First VTE started while off anticoagulants	[redacted]	[redacted]
Recurrent VTE started while on anticoagulants[a]	[redacted]	[redacted]
Patients with 1 or more DVT or PE	[redacted]	[redacted]
First DVT or PE started while on anticoagulants	[redacted]	[redacted]
First DVT or PE started while off anticoagulants	[redacted]	[redacted]

Footnotes: a Recurrent VTE includes any VTE that started at least 30 days after the start of first VTE.
Abbreviations: DCO: data cut-off; DVT: deep vein thrombosis; PE: pulmonary embolism; SAS: safety analysis set; TEAE: treatment-emergent adverse event; VTE: venous thromboembolism.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 39, page 138.[11]

Supporting real-world evidence studies

A23. The CS describes real-world evidence (RWE) provided by the National Cancer Registration and Analysis Service (NCRAS) dataset and refers to two cohorts described as the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts (N=617 and N=1469 respectively). Please provide tables of baseline characteristics for each of these cohorts.

The baseline characteristics for the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts are presented in Table 10.[2]

Table 10: Summary of patient demographics and baseline characteristics of patients in the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts of the NCRAS dataset

Characteristic	'MARIPOSA-like' (N=617)	'MARIPOSA-expanded' (N=1,469)
Age in years, n (%)		
18–55	159 (26)	274 (19)
56–60	87 (14)	168 (11)
61–65	86 (14)	185 (13)
>65	285 (46)	842 (57)
Sex, n (%)		
Female	431 (70)	984 (67)
Male	186 (30)	485 (33)
Race, n (%)		
Asian	61 (9.9)	146 (10)
White	492 (80)	1,184 (81)
Black	25 (4.1)	60 (4.1)
Other or unknown	39 (6.3)	79 (5.4)
Weight, kg		
Mean (SD)	69.3 (15.1)	71.1 (16.1)
Median (range)	66.7 (40.2, 123.1)	NR
Body mass index, kg/m^2		
Mean (SD)	25.1 (4.6)	26.0 (5.1)
Median (range)	24.5 (14.1, 42.9)	NR
EGFR mutation, n (%)		
Exon19del	533 (86)	1,243 (85)
Exon 21 L858R substitution	84 (14)	226 (15)
Initial diagnosis NSCLC subtype, n (%)		
Adenocarcinoma	581 (94)	1,376 (94)
Carcinoid	1 (0.2)	1 (0.1)
Squamous cell carcinoma	7 (1.1)	16 (1.1)
Other	23 (3.7)	56 (3.8)
Unspecified	5 (0.8)	20 (1.4)
Cancer stage at initial diagnosis, n (%)		
IIIB	29 (4.7)	68 (4.6)
IIIC	2 (0.3)	9 (0.6)
IV	220 (36)	558 (38)
IVA	186 (30)	408 (28)
IVB	180 (29)	426 (29)

Abbreviations: EGFR: epidermal growth factor receptor; FAS: full analysis set; NSCLC: non-small cell carcinoma; SD: standard deviation.
Source: Johnson & Johnson Data on File. RWE NCRAS IPD Analysis, 2024.[2]

A24. The CS also makes some statements regarding the subgroups of the MARIPOSA-like and MARIPOSA-expanded cohorts from the NCRAS who were treated with first-line osimertinib. Please provide baseline characteristics for these osimertinib treated subgroups of the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts (N=126 and N=278 respectively).

The baseline characteristics for patients in the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts who received first-line osimertinib are presented in Table 11.[2]

Table 11: Summary of patient demographics and baseline characteristics of patients in the 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts of the NCRAS dataset who received first-line osimertinib

Characteristic	'MARIPOSA-like' (N=126)	'MARIPOSA-expanded' (N=278)
Age in years, n (%)		
18–55	35 (27.8)	56 (20.1)
56–60	17 (13.5)	33 (11.9)
61–65	14 (11.1)	36 (12.9)
>65	60 (47.6)	153 (55.0)
Sex, n (%)		
Female	95 (75.4)	193 (70.5)
Male	31 (24.6)	82 (29.5)
Race, n (%)		
Asian	12 (9.5)	26 (9.4)
White	98 (77.8)	219 (78.8)
Black	5 (4.0)	11 (4.0)
Other or unknown	11 (8.7)	22 (7.9)
Weight, kg		
Mean (SD)	65.7 (12.8)	69.7 (16.1)
Median (range)	63.7 (40.2, 103.2)	67.0 (40.2, 156.0)
Body mass index, kg/m^2		
Mean (SD)	24.1 (3.7)	25.7 (5.0)
Median (range)	23.6 (16.1, 32.5)	24.4 (16.1, 49.8)
EGFR mutation, n (%)		
Exon19del	120 (95.2)	261 (93.9)
Exon 21 L858R substitution	6 (4.8)	17 (6.1)
Initial diagnosis NSCLC subtype, n (%)		
Adenocarcinoma	120 (95.2)	261 (93.9)
Squamous cell carcinoma	2 (1.6)	4 (1.4)
Other	4 (3.2)	9 (3.2)
Unspecified	0 (0)	4 (1.4)

Characteristic	'MARIPOSA-like' (N=126)	'MARIPOSA-expanded' (N=278)
Cancer stage at initial diagnosis, n (%)		
IIIB	4 (3.2)	10 (3.6)
IV	6 (4.8)	19 (6.8)
IVA	61 (48.4)	114 (41.0)
IVB	55 (43.7)	133 (47.8)

Abbreviations: EGFR: epidermal growth factor receptor; FAS: full analysis set; NSCLC: non-small cell carcinoma; SD: standard deviation.
Source: Johnson & Johnson Data on File. RWE NCRAS IPD Analysis, 2024.[2]

A25. The NCRAS report (CS, ref 90) states, "The target cohort population excludes patients who were flagged as being in receipt of a CDF-listed drug indicated for NSCLC but developed by a different manufacturer." Does this mean that patients in receipt of first-line osimertinib would have been excluded from the NCRAS cohort if they were treated after osimertinib entered the Cancer Drugs Fund (CDF) for this indication. Please describe the rationale for excluding patients receiving CDF listed drugs.

The NCRAS observational standing cohort study excluded patients who were in receipt of a CDF-listed drug developed by a different manufacturer under evaluation for NSCLC at the time of analysis. This is because, during the two-year CDF managed access period, data collection is undertaken by the systemic anti-cancer therapy dataset (SACT) team and provided to NICE as part of their HTA function, but NHS England embargoes the release of data that concern the treatment and health outcomes of patients in receipt of CDF-funded treatments for the duration of the evaluation. As such, patients in receipt of first-line osimertinib were necessarily excluded from the NCRAS cohort if they were treated after osimertinib entered the CDF for this indication; this was not an optional exclusion criterion selected by Johnson & Johnson.

A26. CS Table 1. It is stated that "*From 2021 (following the introduction of osimertinib to UK clinical practice in 2020) to 2023, 95 patients in the 'MARIPOSA-like' cohort received 1L treatment, of whom 90.5% (86/95) were treated with osimertinib, demonstrating the preferential use of osimertinib as a third-generation TKI as compared with earlier-generation TKIs*"**.** This cohort is smaller than the cohort of MARIPOSA-like patients described previously (N=617) presumably because of the time period restriction. Please describe the numbers of patients contributing to both the numerator and denominator of years 2021, 2022 and 2023. Does exclusion of patients on CDF listed drugs explain the drop in first-line osimertinib usage in 2022

and 2023 vs 2021 in the NRAS database (CS, ref 10)? Comment on how this may bias the assessment of treatment usage when assessed using the NCRAS MARIPOSA-like cohort receiving first-line osimertinib. Please consider whether a less biased assessment of treatment usage could be achieved using a different range of years or whether this data source is not suitable for this purpose due to the exclusion of data on patients treated within the CDF.

Of patients with registered NSCLC diagnoses between 2016 and 2024 in England, 617 patients met the criteria for analysis as part of the 'MARIPOSA-like' cohort.[2] The 'MARIPOSA-like' cohort closely matched the inclusion criteria of the MARIPOSA trial (adult patients with locally advanced or metastatic cEGFRm NSCLC, with an ECOG PS of 0 or 1, with no untreated CNS metastases). When limiting the time period to 2021–2023, 95 patients met the criteria for the 'MARIPOSA-like' cohort (2021: 91 patients; 2022: 3 patients; 2023: 1 patient), of which 86 received osimertinib in 1L (2021: 83 patients; 2022: 3 patients; 2023: no patients).[2]

The NCRAS dataset intends to capture all patients receiving osimertinib monotherapy who fit the selection criteria specified in the trial. Limited data were available for 2023 due to the small number of patients meeting the 'MARIPOSA-like' criteria, and 2024 was excluded from consideration given a full years' worth of data was yet available at the time of the data analysis, resulting in extremely small patient numbers. In addition, the NCRAS cohort population excluded patients who were flagged as being in receipt of a CDF-listed drug indicated for NSCLC but developed by a different manufacturer. As explained in response to Question A25, this was necessary because the data for patients receiving CDF-listed drugs were collected by SACT and under strict embargo by NHS England.

Despite limiting patient numbers, the considerations outlined above do not represent a source of bias in the assessment of treatment usage within the dataset, which is a reliable, full record of patients using osimertinib monotherapy after its NICE recommendation in the appropriate setting and indication as specified in this submission. This is supported by the proportion of patients identified to be receiving 1L osimertinib in the 'MARIPOSA-like' cohort between 2021 and 2023 (90.5%) closely aligning with the estimate reported in the most recent draft guidance for osimertinib in combination with pemetrexed and PBC for untreated EGFR mutation-positive advanced NSCLC (NICE ID6328), in which 86% of patients were reported to receive 1L osimertinib monotherapy.

Section B: Clarification on cost-effectiveness data

Economic literature review

B1. For the economic SLRs, please confirm whether the EconLit database was searched in the original SLR and/or any of the search updates.

The EconLit database was not searched as part of the original SLR or subsequent updates.

B2. Please provide details of which platform was used to search the NHS EED database during the original economic SLR (the database is mentioned in Appendix G.1.1.1 and Table 32).

The NHS EED database was searched during the original economic SLR via the University of York CRD platform.

Data informing health state occupancy

B3. PRIORITY: Please explain why data up to the 13 May 2024 DCO of the MARIPOSA trial were not incorporated in the model for the PFS outcome. Please update the model to reflect the most recent DCO available for all outcomes informed by the MARIPOSA trial.

As noted in response to Question A17 above, the primary endpoint of the MARIPOSA trial, PFS assessed by BICR, was met at the 11th August 2023 DCO, where amivantamab-lazertinib demonstrated a 30% reduction on the risk of disease progression by BICR or death compared with osimertinib.[8, 9] The 13th May 2024 DCO was a regulatory request in order to assess interim OS data only; as such, PFS data are not available from the 13th May 2024 DCO, and the most up-to-date data for PFS (from the 11th August 2023 DCO) have been provided within the submission.

B4. Please provide the unsmoothed hazard plots for PFS, overall survival (OS) and time to treatment discontinuation (TTD) separately.

The unsmoothed hazard plots for PFS by BICR, PFS by INV, OS and TTD for the amivantamab-lazertinib and osimertinib arms are presented in Figure 2 to Figure 10.

Figure 2: Unsmoothed hazard plot for PFS assessed by BICR in the amivantamab-lazertinib arm (11th August 2023 DCO; full analysis set)

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

Figure 3: Unsmoothed hazard plot for PFS assessed by BICR in the osimertinib arm (11th August 2023 DCO; full analysis set)

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

Figure 4: Unsmoothed hazard plot for PFS assessed by INV in the amivantamab-lazertinib arm (11th August 2023 DCO; full analysis set)

Abbreviations: DCO: data cut-off; INV: investigator; PFS: progression-free survival.

Figure 5: Unsmoothed hazard plot for PFS assessed by INV in the osimertinib arm (11th August 2023 DCO; full analysis set)

Abbreviations: DCO: data cut-off; INV: investigator; PFS: progression-free survival.

Figure 6: Unsmoothed hazard plot for OS in the amivantamab-lazertinib arm (13th May 2024 DCO; full analysis set)

Abbreviations: DCO: data cut-off; OS: overall survival.

Figure 7: Unsmoothed hazard plot for OS in the osimertinib arm (13th May 2024 DCO; full analysis set)

Abbreviations: DCO: data cut-off; OS: overall survival.

Figure 8: Unsmoothed hazard plot for TTD for amivantamab (13th May 2024 DCO; full analysis set)

Abbreviations: DCO: data cut-off; PFS: progression-free survival; TTD: time to treatment discontinuation.

Figure 9: Unsmoothed hazard plot for TTD for lazertinib (13th May 2024 DCO; full analysis set)

Abbreviations: DCO: data cut-off; PFS: progression-free survival; TTD: time to treatment discontinuation.

Figure 10: Unsmoothed hazard plot for TTD for osimertinib (13th May 2024 DCO; full analysis set)

Abbreviations: DCO: data cut-off; PFS: progression-free survival; TTD: time to treatment discontinuation.

B5. PRIORITY Please fit spline models on different scales (hazard, odds, and normal) with up to three knots (one, two and three) for each arm of the MARIPOSA trial for the outcomes of PFS, OS and TTD. Please provide the estimated parameters, AIC/BIC, Kaplan-Meier (KM) plots with long-term predictions, and hazard plots with estimated hazards from spline models. Please adapt the model to include the option to select the fitted spline models.

The outcomes of PFS, OS and TTD using spline models with up to three knots (one, two and three) have been outlined below, alongside the estimated parameters from the long-term extrapolations and AIC/BIC outcomes, in addition to hazard plots with estimated hazards from spline models. The spline model using the 'hazard' scale with three knots is used as an example for the extrapolation curves for each parameter presented in this section. Long-term extrapolations using other spline models can be extracted by changing the settings in the clinical inputs tab of the model. Please note that some of the rows required to change these settings may be hidden in the current version of the model.

The data presented within this section is contained within the previously submitted version of the model; no further updates to the model have been made in this regard. These data can be extracted by selecting spline fits as an option to replace standard fits for each parameter in the 'Clinical inputs' tab. Further details surrounding the spline model parameters and statistical fit values can be found in the 'Spline Fits' tab of the model, and in Appendix D below.

PFS

Amivantamab-lazertinib

The long-term PFS (BICR) extrapolations for amivantamab-lazertinib are presented in Figure 11, and the hazard plot with estimated hazards from spline models is presented in Figure 12.

Table 12 presents AIC and BIC for each distribution.

Figure 11: Long-term PFS (BICR) projections of amivantamab-lazertinib with spline model included

Abbreviations: BICR: blinded independent committee review; IRC: independent review committee; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 12: Hazard plot for amivantamab-lazertinib PFS (BICR) with estimated hazards from spline models

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Table 12: PFS (BICR) spline fits for amivantamab-lazertinib

Scale	Knots (internal)	AIC	BIC
Hazard	1	[redacted]	[redacted]
Hazard	2	[redacted]	[redacted]
Hazard	3	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]
Odds	2	[redacted]	[redacted]
Odds	3	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]
Normal	2	[redacted]	[redacted]
Normal	3	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BICR: blinded independent central review; PFS: progression-free survival.

Osimertinib

The long-term PFS (BICR) extrapolations for osimertinib are presented in Figure 13, and the hazard plot with estimated hazards from spline models is presented in Figure 14. Table 13 presents AIC and BIC for each distribution.

Figure 13: Long-term PFS (BICR) projections of osimertinib with spline model included

Abbreviations: BICR: blinded independent committee review; IRC: independent review committee; KM: Kaplan-Meier; PFS: progression-free survival.

Figure 14: Hazard plot for osimertinib PFS (BICR) with estimated hazards from spline models

Abbreviations: BICR: blinded independent committee review; PFS: progression-free survival.

Table 13: PFS (BICR) spline fits for osimertinib

Scale	Knots (internal)	AIC	BIC
Hazard	1	[redacted]	[redacted]
Hazard	2	[redacted]	[redacted]
Hazard	3	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]
Odds	2	[redacted]	[redacted]
Odds	3	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]
Normal	2	[redacted]	[redacted]
Normal	3	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BICR: blinded independent central review; PFS: progression-free survival.

OS

Amivantamab-lazertinib

The long-term OS extrapolations for amivantamab-lazertinib are presented in Figure 15, and the hazard plot with estimated hazards from spline models is presented in Figure 15. Table 14 presents AIC and BIC for each distribution.

Figure 15: Long-term OS projections of amivantamab-lazertinib with spline model included

Abbreviations: KM: Kaplan-Meier; ITT: intention-to-treat; OS: overall survival.

Figure 16: Hazard plot for amivantamab-lazertinib OS with estimated hazards from spline models

Abbreviations: OS: overall survival.

Table 14: OS spline fits for amivantamab-lazertinib

Scale	Knots (internal)	AIC	BIC
Hazard	1	[redacted]	[redacted]
Hazard	2	[redacted]	[redacted]
Hazard	3	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]
Odds	2	[redacted]	[redacted]
Odds	3	[redacted]	[redacted]

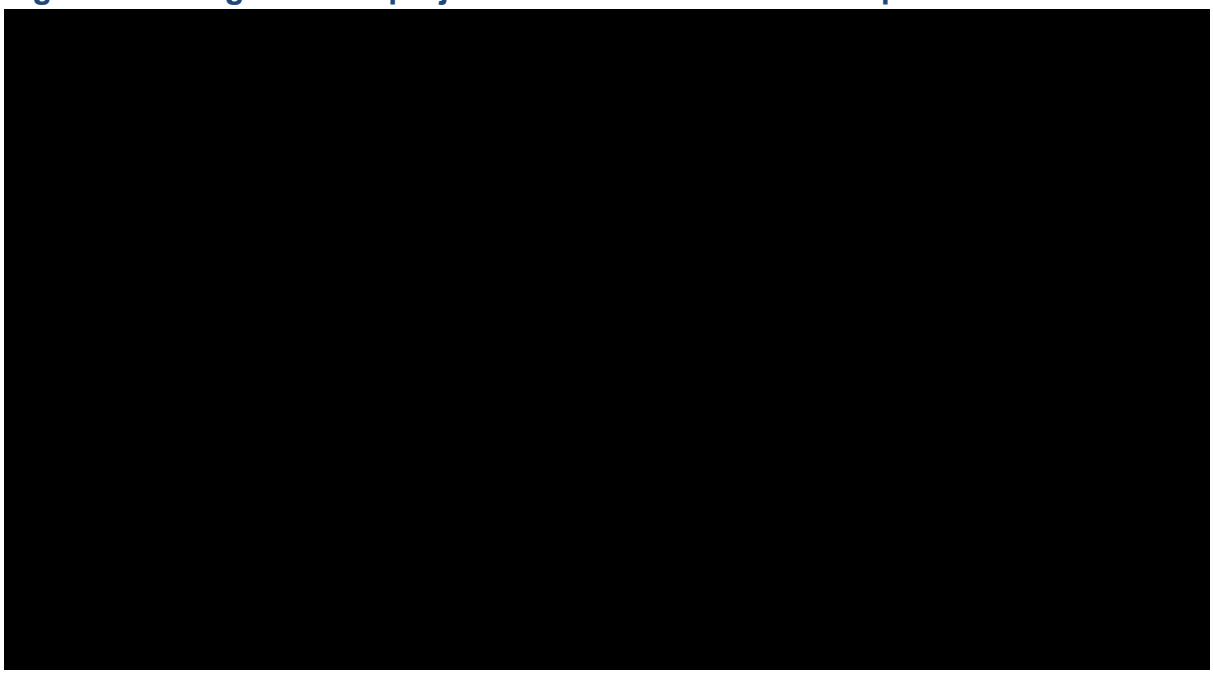
Normal	1	[redacted]	[redacted]
Normal	2	[redacted]	[redacted]
Normal	3	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

Osimertinib

The long-term OS extrapolations for osimertinib are presented in Figure 17, and the hazard plot with estimated hazards from spline models is presented in Figure 18. Table 15 presents AIC and BIC each distribution.

Figure 17: Long-term OS projections of osimertinib with spline model included



Abbreviations: KM: Kaplan-Meier; ITT: intention-to-treat; OS: overall survival.

Figure 18: Hazard plot for osimertinib OS with estimated hazards from spline models

Abbreviations: OS: overall survival.

Table 15: OS spline fits for osimertinib

Scale	Knots (internal)	AIC	BIC
Hazard	1	[redacted]	[redacted]
Hazard	2	[redacted]	[redacted]
Hazard	3	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]
Odds	2	[redacted]	[redacted]
Odds	3	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]
Normal	2	[redacted]	[redacted]
Normal	3	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: overall survival.

TTD

Amivantamab

The long-term TTD extrapolations for amivantamab are presented in Figure 19, and the hazard plot with estimated hazards from spline models is presented in Figure 20. Table 16 presents AIC and BIC for each distribution.

Figure 19: Long-term TTD projections of amivantamab with spline model included

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

Figure 20: Hazard plot for amivantamab TTD with estimated hazards from spline models

Abbreviations: TTD: time to treatment discontinuation or death.

Table 16: TTD spline fits for amivantamab

Scale	Knots (internal)	AIC	BIC
Hazard	1	[redacted]	[redacted]
Hazard	2	[redacted]	[redacted]
Hazard	3	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]
Odds	2	[redacted]	[redacted]
Odds	3	[redacted]	[redacted]

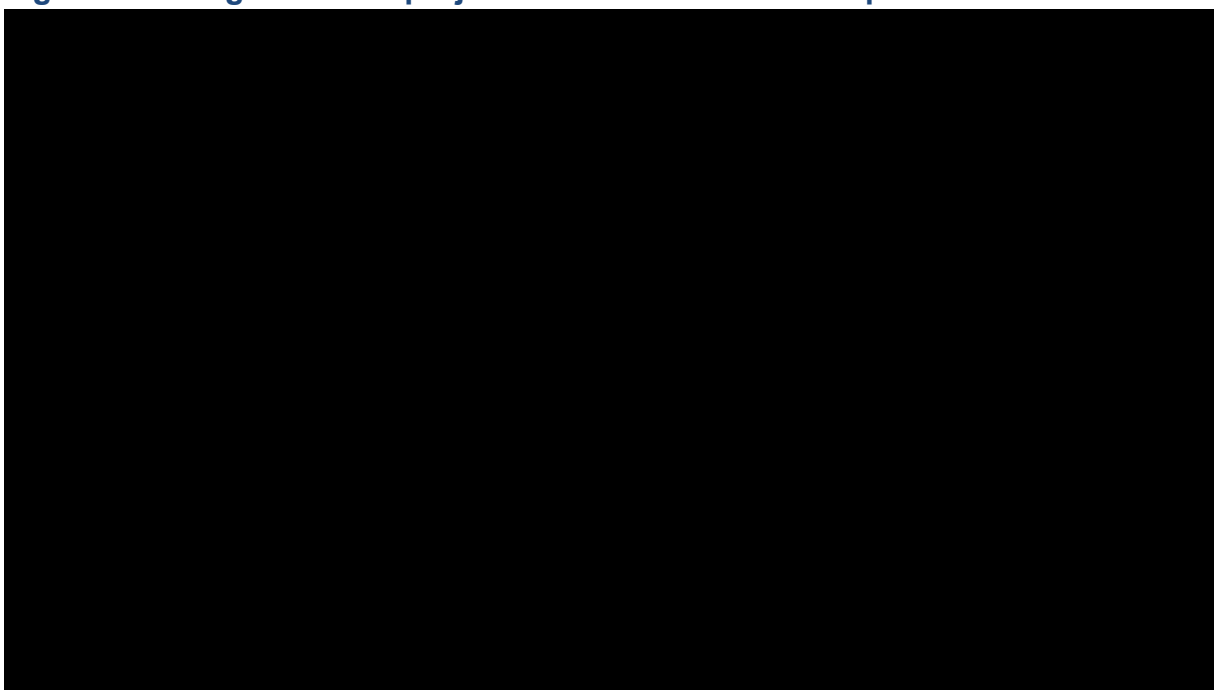
Normal	1	[redacted]	[redacted]
Normal	2	[redacted]	[redacted]
Normal	3	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Lazertinib

The long-term TTD extrapolations for lazertinib are presented in Figure 21, and the hazard plot with estimated hazards from spline models is presented in Figure 22. Table 17 presents AIC and BIC for each distribution.

Figure 21: Long-term TTD projections of lazertinib with spline model included



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

Figure 22: Hazard plot for lazertinib TTD with estimated hazards from spline models

Abbreviations: TTD: time to treatment discontinuation or death.

Table 17: TTD spline fits for lazertinib

Scale	Knots (internal)	AIC	BIC
Hazard	1	[redacted]	[redacted]
Hazard	2	[redacted]	[redacted]
Hazard	3	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]
Odds	2	[redacted]	[redacted]
Odds	3	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]
Normal	2	[redacted]	[redacted]
Normal	3	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

Osimertinib

The long-term TTD extrapolations for osimertinib are presented in Figure 23, and the hazard plot with estimated hazards from spline models is presented in Figure 24. Table 18 presents AIC and BIC for each distribution.

Figure 23: Long-term TTD projections of osimertinib with spline model included

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

Figure 24: Hazard plot for osimertinib TTD with estimated hazards from spline models

Abbreviations: TTD: time to treatment discontinuation or death.

Table 18: TTD spline fits for osimertinib

Scale	Knots (internal)	AIC	BIC
Hazard	1	[redacted]	[redacted]
Hazard	2	[redacted]	[redacted]
Hazard	3	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]
Odds	2	[redacted]	[redacted]
Odds	3	[redacted]	[redacted]

Normal	1	[redacted]	[redacted]
Normal	2	[redacted]	[redacted]
Normal	3	[redacted]	[redacted]

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTD: time to treatment discontinuation or death.

B6. PRIORITY Please clarify if there is available data from external sources on long term survival probability for PFS, OS and TTD of each treatment, such as five-year overall survival probability for patients receiving first-line osimertinib. If such data exist, please provide them with justifications on the similarity to the current trial population.

External long-term data were used in the original company submission to supplement the data available from the MARIPOSA trial.

First, real-world OS data from the NCRAS database between 2016–2024 were included. The cohort for this study is referred to as the 'MARIPOSA-like' cohort, which included UK population-based patients who had cEGFRm NSCLC and similar baseline characteristics to patients in the MARIPOSA trial. This is the latest up-to-date data from patients in UK clinical practice, and therefore the best external long-term data available.

Second, long-term data on mOS, mPFS and mTTD available from the FLAURA trial have been referenced in the submission, and the inclusion of these OS data in the economic model has been explored in a scenario analysis (modelling OS by left truncated approach, see Section B.3.11.3 of Document B of the company submission).

Finally, real-world evidence from other countries have been leveraged in the submission where relevant, including mOS and mPFS data from Pérol et al. (2024) which reported similar results in a retrospective study using secondary data from the Epidemiological Strategy and Medical Economics (ESME; France) and the Rigshospitalet (RH; Denmark) databases on 757 patients with locally advanced or metastatic cEGFRm NSCLC, treated with first- or 2L osimertinib.

Johnson & Johnson consider that the previous presentation and exploration of these external data sources fully and appropriately captures all relevant and up to date long-term survival data that are currently available. Johnson & Johnson are unaware of any further relevant data sources to explore.

B7. Please add the OS Kaplan-Meier curve from FLAURA osimertinib arm to CS Figure 31 to facilitate a comparison between the FLAURA osimertinib arm and long-

term OS predictions for MARIPOSA. Please also provide the digitised KM data for FLAURA osimertinib OS.

The long-term OS projections for osimertinib, including the MARIPOSA and FLAURA KM curves represented as black and pink dashed lines, respectively, are presented in Figure 25. The KM data have also been provided within the reference pack.[13]

Figure 25: Long-term OS projections for osimertinib, based on MARIPOSA OS KM data, amended to include the osimertinib FLAURA OS KM curve for reference

Abbreviations: KM: Kaplan-Meier; ITT: intention-to-treat; OS: overall survival.

B8. CS Section B.3.11.3.1. For the scenario analysis incorporating the data from the FLAURA osimertinib arm, please clarify if CS Figure 44 is showing the combined KM data incorporating the left-truncated data from FLAURA or just the MARIPOSA KM data. If the latter, please provide an updated Figure 44 showing the combined KM data incorporating the FLAURA data, i.e. the KM data to which the curves were fitted.

Johnson & Johnson thanks the EAG for noting this and confirm that Figure 44 of Document B of the company submission displays MARIPOSA KM data only. The longer-term OS projections of osimertinib based on the combined approach, in which the available FLAURA data were incorporated into the MARIPOSA data, are presented in Figure 26.

Figure 26: Long-term OS projections of osimertinib, based on left-truncation approach, amended to include the combined KM data

Abbreviations: KM: Kaplan-Meier; OS: overall survival.

B9. Please provide a table of baseline characteristics for the FLAURA trial similar to those presented for the MARIPOSA trial (CS Tables 7 and 8) so we can assess the comparability of the populations as this influences the generalisability of the scenario analysis incorporating the FLAURA data.

The baseline characteristics for patients in the osimertinib arm of the FLAURA trial are presented in Table 19, alongside data for patients in the osimertinib arm of the MARIPOSA trial.[14, 15] The characteristics are broadly similar between the MARIPOSA and FLAURA trials in terms of median age (63 years versus 64 years, respectively), proportion of female patients (59% versus 64%, respectively), and proportion of patients being of Asian ethnicity (59% versus 62%, respectively).[8] Furthermore, the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) was similar for patients treated with osimertinib in the MARIPOSA (0: 35%; 1: 65%) and FLAURA trials (0: 40%; 1: 60%).[8, 14] The proportion of patients with central nervous system (CNS) metastases in the FLAURA trial was lower than the proportion of patients with brain metastases in the MARIPOSA trial (19% versus 40%, respectively).[8, 14] However, this is attributed to the difference in requirements for baseline brain magnetic resonance imaging (MRI): the MARIPOSA trial mandated a brain MRI for all patients at screening, whereas the FLAURA trial required baseline brain imaging only for patients with known or suspected brain metastases, which likely resulted in fewer patients being identified.[11, 14]

Table 19: Summary of patient demographics and baseline characteristics of patients in the osimertinib arms of the MARIPOSA and FLAURA trials

Characteristic	MARIPOSA Osimertinib (N=429)	FLAURA Osimertinib (N=279)
Age, years		
Median (range)	63 (28, 88)	64 (26, 85)
Sex, n (%)		
Male	178 (41)	101 (36)
Female	251 (59)	178 (64)
Race, n (%)[a]		
Asian	251 (59)	174 (62)
White	165 (38)	101 (36)
Other or unknown	13 (3)	4 (1)
Smoking status, n (%)		
Never	295 (69)	182 (65)
Current	[redacted]	8 (3)
Former	[redacted]	89 (32)
WHO/ECOG performance status[b]		
0	149 (35)	112 (40)
1	280 (65)	167 (60)
Missing data	NR	0
EGFR mutation type at randomisation, n (%)		
Exon19del	257 (60)	175 (63)
Exon 21 L858R substitution	172 (40)	104 (37)
Histologic type, n (%)		
Adenocarcinoma	415 (97)	275 (99)
Other	9 (2)	4 (1)[c]
Overall disease classification, n (%)		
Metastatic	NR	264 (95)[d]
Locally advanced	NR	14 (5)[e]
Missing data	NR	1 (0.4)
Metastases, n (%)		
Visceral metastases	NR	94 (34)[f]
CNS metastases	[redacted]	53 (19)[g]

[a] Race was reported by the patient. The category of "other" includes black, American Indian, and Alaska Native.
[b] The WHO performance status of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a WHO performance status of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work.
[c] Two patients had large-cell carcinoma; one patient had adenosquamous carcinoma; and one patient had a carcinoid tumour.
[d] The patient had any metastatic site of disease.

[e] The patient had only locally advanced sites of disease.
[f] Visceral metastases were determined programmatically from baseline data for which the disease site was described as adrenal, ascites, brain or CNS, gastrointestinal, genitourinary, hepatic (including gallbladder), liver, other CNS, pancreas, peritoneum, or spleen. Also included were other metastatic sites, such as those occurring in the eye and thyroid, as identified as extrathoracic visceral sites by AstraZeneca physicians.
[g] CNS metastases were determined programmatically from baseline data for the CNS lesion site, medical history, surgery, or radiotherapy.
Abbreviations: CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; Exon19del: exon 19 deletion mutations; FAS: full analysis set; NSCLC: non-small cell carcinoma; SD: standard deviation; WHO: World Healht Organisation.
Sources: Cho *et al.* (2024), (Table 1, Page 10; Table S2, Page 32).[8] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). (Table 9, Page 53).[11] Soria *et al*. 2018.[14] NICE (TA654) 2020.[15]

B10. Please clarify whether patients were allowed to permanently discontinue one component of the amivantamab-lazertinib combination and continue the other component in the study. Could this be done for either component or was amivantamab always discontinued first? Is there any guidance in the draft SmPC on whether patients can discontinue one component of the combination and which component this should be?

Throughout the MARIPOSA trial, patients were permitted to permanently discontinue amivantamab for reasons other than disease progression, but continue open-label lazertinib.[16] This is due to the different mechanisms of action of amivantamab compared with lazertinib. In the event of VTE recurrence, patients were able to continue receiving study treatment with either amivantamab or lazertinib (but not both), at the discretion of the treating physician. In the trial, [redacted] patients discontinued lazertinib first, [redacted] of whom did not subsequently receive any amivantamab doses.

The amivantamab summary of product characteristics (SmPC) provides guidance on the discontinuation of study treatment due to AEs, and in most cases recommends either discontinuing both components or discontinuing amivantamab only.[17] As with the MARIPOSA trial, in the event of VTE recurrence despite appropriate anticoagulation, either amivantamab or lazertinib can be discontinued.[17] Treatment is allowed to continue with one component, but not both, at the discretion of the treating physician.[17] This is aligned with the guidance provided in the lazertinib SmPC on discontinuation of treatment.[18]

B11. CS Figure 17. Please clarify how the TTD for the combination treatment was defined in the study. Was it defined as time until both components of the combination were discontinued (or death if death proceeded discontinuation)?

As outlined in Section B.2.3.2 (Table 6) of Document B of the company submission, in the MARIPOSA trial, TTD for amivantamab-lazertinib was defined as the time from randomisation to discontinuation of all study treatment for any reason, including disease progression, treatment toxicity and death.[11]

B12. CS Figure 33. Please clarify how TTD for the individual components of the amivantamab-lazertinib combination was defined in the study and whether this was a pre-planned study outcome. The numbers at risk for the amivantamab-lazertinib combination in Figure 17 and the number at risk for the lazertinib component in Figure 33 appear to be the same and the KM data in the model for the lazertinib component appear to match the data reported in Table 21 for TTD for the combination treatment. Please confirm if the TTD for lazertinib in Figure 33 is equivalent to the TTD for the combination of amivantamab-lazertinib shown in Figure 17.

TTD for amivantamab and for lazertinib was defined as the time from randomisation to discontinuation of study treatment for any reason, including disease progression, treatment toxicity and death.[11] Analysis of TTD for these individual components was not a pre-planned outcome of the trial. As described in the CS, TTD models were fitted separately in the economic model for amivantamab and lazertinib in the amivantamab-lazertinib arm. This ensures that the efficiency gains and costs associated with each component of the combined therapy regimen is reflective of what is reported in the MARIPOSA trial and is representative of clinical practice. The decision to model the TTD separately was informed by clinical insights and data from the MARIPOSA CSR.[3, 11]

The analysis of TTD by individual components was validated to be relevant by three UK clinicians during an advisory board held by Johnson & Johnson in October 2024, who noted that they would expect treatment with amivantamab to be discontinued earlier than lazertinib due to their differential safety profiles and how they are administered (IV amivantamab versus oral lazertinib).[3]

While similar, Johnson & Johnson note that the TTD data for the amivantamab-lazertinib combination are not identical to the TTD data for lazertinib. For example, the number at risk at 27 months was 178 for the amivantamab-lazertinib combination (Document B of company submission, Figure 17) versus [redacted] for lazertinib (Document B of company submission, Figure 33).[10] This similarity is attributable to most patients discontinuing the amivantamab component before lazertinib, with the minor difference reflecting that some patients discontinued the lazertinib component before amivantamab (see response to Question B10).

B13. Please conduct a scenario analysis using the combined TTD (CS Figure 17) to estimate TTD for the combination therapy in the model. For this scenario analysis, please provide all equivalent data to that provided for the base-case analysis using

TTD for the separate components (unless these are equivalent to the data for the lazertinib component of the combination, in which case please simply confirm this).

The separate modelling of amivantamab and lazertinib TTD is informed by data from the MARIPOSA trial, in which TTD associated with amivantamab is shorter on average than the TTD associated with either lazertinib or osimertinib, despite amivantamab-lazertinib being associated with longer median PFS than osimertinib (23.7 months versus 16.6 months, respectively).[8] This suggests more patients discontinue amivantamab for reasons other than disease progression, which can be explained by the increased toxicity of amivantamab compared with the other treatments.

As outlined above, this difference in TTD is expected to reflect UK clinical practice, in which treatment durations for amivantamab and lazertinib individually are anticipated to differ. This is supported by clinical expert opinion provided by three UK clinicians during an advisory board held by Johnson & Johnson in October 2024 who agreed that modelling TTD separately was the most appropriate approach to reflect expected clinical reality.[3]

As per the amivantamab SmPC, patients are permitted to continue lazertinib monotherapy after discontinuing amivantamab for reasons other than disease progression.[17] As such, Johnson & Johnson do not consider modelling treatment durations based on combined amivantamab-lazertinib TTD to be an appropriate reflection of expected treatment durations in UK clinical practice. As such, the requested scenario analysis is not presented.

B14. CS Table 12. The median TTD for osimertinib is longer than the median PFS. However, the clinician estimates (mid-point) for the proportion of patients remaining at 5 years and 10 years is higher for PFS than TTD (comparing Table 38 with Table 48). Please justify if it is a common practice in the UK for osimertinib to be used beyond progression or whether this is behaviour that is specific to the trial protocol which may lead to overestimating the cost of the comparator.

Osimertinib is licensed for use for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations, until disease progression or unacceptable toxicity.[19] However, UK clinicians at an advisory board held by Johnson & Johnson in October 2024 confirmed that they would expect that patients in UK clinical practice with cEGFR-mutated NSCLC who are receiving first-line osimertinib would continue osimertinib post-progression provided they were still deriving a clinical benefit.[3] The post-progression use of osimertinib is supported by clinical opinion from the British Thoracic Oncology Group in the Committee meeting for the ongoing NICE appraisal of osimertinib in combination with pemetrexed and PBC for untreated EGFR mutation-positive advanced NSCLC (NICE ID6328), who noted that treatment with osimertinib would be continued until loss of clinical benefit

or unmanageable toxicities. Furthermore, the modelling of TTD as greater than PFS was accepted as appropriate in ID6328 and in the previous NICE appraisal of osimertinib monotherapy (TA654).[1, 15]

The clinical expert input and previously accepted modelling approaches outlined above acknowledge the value of continuing osimertinib for symptom control or long-term management, which is expected to be aligned with UK clinical practice.[1, 15] In further support of this, the modelling of treatment continuation post-progression corroborates data that are available from the MARIPOSA trial, which provided a structured environment for the estimation of PFS and TTD. These data show that patients receiving osimertinib and lazertinib had a longer median TTD than median PFS (discussed in Question A18), and thus that any discrepancy in the clinician estimates of TTD versus PFS is observed for both osimertinib and lazertinib and does not specifically affect the estimation of comparator cost. As both trial and real-world data show that patients often stay on osimertinib after progression due to its long-term efficacy, the modelling of TTD as longer than PFS for osimertinib, as well as lazertinib, is expected to reflect typical UK clinical practice.

With respect to the clinician estimates for TTD being slightly lower than the corresponding estimates for PFS at each timepoint (except for 8 years which is slightly higher for TTD), this is likely due to clinicians unconsciously basing TTD estimates on the licensed indication for osimertinib, continuing treatment until disease progression. As such, these estimates may not take into account the use of osimertinib post-progression in UK clinical practice. Additionally, clinicians may have been focused on progression status as the main driver for treatment decisions, with a focus on disease management for any decision made about whether a patient remains on a particular treatment or not. Clinicians might therefore assume a more direct relationship between PFS and TTD and give more weighting in their estimations for how long patients can live without progression than to the rate of treatment discontinuation, potentially marginally overestimating PFS in relation to TTD. In addition, the ranges for both PFS and TTD overlap at all time points (Table 20).

Table 20: PFS and TDD estimates from clinicians (October 2024 advisory board)

Time-point	PFS midpoint (min, max)	TTD midpoint (min, max)
4-years	0.20 (0.15 – 0.25)	0.15 (0.10 – 0.20)
6-years	0.13 (0.10 – 0.15)	0.10 (0.05 – 0.15)
8-years	0.05 (0.00 – 0.10)	0.06 (0.02 – 0.10)

As such, differences exist between available clinical data and expected clinical practice and the estimates derived from the advisory board, but these differences do

not undermine the reliability of the advisory board estimates, which were based on real-world clinical assumptions where treatment is usually stopped after progression. However, both trial data and real-world evidence show that patients often stay on osimertinib after progression, making longer TTD a reasonable expectation.

B15. PRIORITY Please adapt the model to allow capping of TTD by PFS as an option.

As discussed above, the capping of TTD by PFS is not considered an accurate reflection of treatment duration. TTD is longer than PFS, based on the MARIPOSA trial data for osimertinib and lazertinib. Moreover, feedback from UK clinicians have confirmed that in UK clinical practice, patients may continue treatment with osimertinib after progression, provided they are experiencing clinical benefit. [3] Furthermore, it would not be in line with previous NICE appraisals in this indication, in which TTD has been modelled as greater than PFS.[1] As such, adapting the model to allow capping of TTD by PFS is not appropriate since this would not be representative of clinical practice; therefore, this change has not been implemented.

Utility analysis

B16. Please provide a plot of progression-free (PF) utility scores over time by trial arm and comment on whether this supports the model assumption of equivalent utilities for the PF health-state across both arms of the model (If Figure 44 of the Cost-effectiveness Model Technical Report would be suitable for this purpose, please provide this with appropriate confidentiality marking). Please provide a scenario analysis in which trial arm-specific utilities are applied in the PF state to test the sensitivity of the model to this assumption.

Johnson & Johnson thank the EAG for the additional time to provide responses to questions related to utility analysis and will provide these in a subsequent document.

B17. B3.4.5. Please clarify the data and the models, including covariates, used to estimate health state utilities in CS Table 51 and the disutilities for adverse events (AEs) (pooled AE disutility for grade 3+ AEs of [redacted] and VTE disutility of [redacted]). If the health state utility for the PF health-state was not adjusted for the presence of adverse events (Grade 3 or higher AE), please provide the adjusted PF health state utility. Please present all estimated coefficients (treatment arm, presence of AE of grade 3 or higher, and presence of a VTE event) and an intercept from the mixed

model for repeated measures (MMRM), which was modelled for the disutility of adverse events.

Johnson & Johnson thank the EAG for the additional time to provide responses to questions related to utility analysis and will provide these in a subsequent document.

B18. PRIORITY Please consider model selection starting with a full MMRM model for utility that includes progression status, treatment arm, presence of AE of grade 3 or higher, presence of a VTE and the possible interaction terms (e.g. treatment arm and progression status) using all the data. Please provide the details of the model selection process including the estimated coefficients for each model.

Johnson & Johnson thank the EAG for the additional time to provide responses to questions related to utility analysis and will provide these in a subsequent document.

B19. PRIORITY Please adapt the model so that treatment arm specific utilities can be applied to both pre- and post-progression as doing so will allow the EAG to explore alternative assumptions should these be supported by the analysis of utility data requested in question B18.

Johnson & Johnson thank the EAG for the additional time to provide responses to questions related to utility analysis and will provide these in a subsequent document.

Adverse events

B20. Please confirm whether the AE rates in the model are correct. The data in the model, which match CS Table 49, do not match the figures in CS Table 27.

Johnson & Johnson thanks the EAG for raising this inconsistency. The updated safety data from the 13th May 2024 DCO used to inform AE incidence in the model are provided in response to Question A21.[12]

B21. Please clarify whether the inclusion of pulmonary embolism (PEs) at grade ≥3 and VTEs at grade ≤ 2 excludes any deep vein thromboses (DVTs) recorded in MARIPOSA which were grade ≥3. If so, please amend the model to include all VTE at grade ≥3 with an appropriate distribution of DVTs and PEs. Please ensure that cost applied to these are specific to DVT and PE. Please also clarify if all VTEs at

grade ≤ 2 were DVTs. If not, please ensure that the cost for grade ≤ 2 VTEs captures the distribution of PEs and DVTs and relevant unit costs for these events.

Johnson & Johnson can confirm that the description outlined above is correct: the inclusion of PEs at Grade ≥3 and VTEs at Grade ≤2 does exclude any DVTs recorded in the MARIPOSA trial that were Grade ≥3. This is because TEAEs were included in the model only if they occurred in ≥5% of patients in one of the modelled treatment arms, as informed by the MARIPOSA Phase 3 trial.[12] However, in the trial, only [redacted] patients in the amivantamab-lazertinib arm ([redacted]) and [redacted] patients in the osimertinib arm ([redacted]) experienced Grade ≥3 DVTs, so these events did not pass the threshold for inclusion.[12] Due to these low proportions, the exclusion of these Grade ≥3 DVTs is expected to have a negligible impact on the economic results. As such, Johnson & Johnson have not amended the model to include all Grade ≥3 VTEs.

Furthermore, not all VTEs at Grade ≤2 were DVTs. For amivantamab-lazertinib, [redacted] ([redacted]%) patients had PEs, and [redacted] ([redacted]%) patients had DVT. This breakdown is [redacted] ([redacted]%) and [redacted] ([redacted]%) for the osimertinib arm.

Johnson & Johnson can further confirm that the costs applied are relevant for VTEs, DVTs and PEs.

B22. CS, Table 50. Please comment on whether it is realistic to assume that the disutility for PE lasts only [redacted] days but the disutility for VTE lasts [redacted] days? Disutility for PE is usually assumed to be longer lasting than disutility for DVT and both require 90 days of treatment (https://bmjmedicine.bmj.com/content/3/1/e000408). The EAG is concerned that the duration of PE is underestimated either due to the small sample size for PE versus the VTE outcome, or possibly due to a proportion of the PE events being fatal. Please amend the model to apply the VTE duration to PE adverse events.

The duration of AEs is specific to their toxicity grade: [redacted] days is the duration of Grade ≥3 PE, while [redacted] days is the duration of VTE at Grade ≤2. This is consistent with patients spending more time with AEs of lower toxicity grade.

In order to test the impact of fatal PE events, Johnson & Johnson estimated the duration of Grade 3–4 PE (i.e., excluding fatal events). The resulting estimate was [redacted] days, which was not meaningfully different from the value of [redacted] days used in the model. As such, Johnson & Johnson have not amended the model to apply the VTE duration to PE adverse events.

Resource use and costs

B23. PRIORITY CS, Table 55. Please clarify how the proportion of missed doses and the proportion of planned dose were derived exactly from the outcomes collected in the MARIPOSA trial. Does the proportion of planned dose refer to a dose reduction rather than a missed dose? Please clarify whether different wastage assumptions were applied for missed doses versus dose reductions and what these were in each case. The company has stated that the model assumes no vial sharing. In keeping with this assumption, the EAG would prefer to see no cost reduction when patients receive a proportion of a vial for amivantamab due to dose reductions.

Acquisition and administration costs of amivantamab, lazertinib and osimertinib were corrected for the proportion of missed doses estimated from MARIPOSA trial data. The correction was based on a ratio of administered doses to the expected number of doses for each patient based on their duration of treatment. An additional correction for dose reductions was also applied to account for the fact that dose modifications could occur in the course of treatment. It is included in the CEM as a proportion of the planned dose received, based on the MARIPOSA trial.[11] "Planned dose" in this context refers to the cumulative dose that a patient would have received if there had been no dose modifications, while dose received was calculated as a sum of doses prepared for each administration that took place in the trial.

For amivantamab, missed doses and the proportion of planned doses were estimated separately for patients in different weight categories (<80 kg and ≥80 kg). Amivantamab dose changes in the MARIPOSA trial corresponded to multiples of the full vial contents (350 mg), which means that there was no drug wastage associated with dose modifications. The model assumed no vial sharing, and dose reductions only affected drug acquisition costs, and not administration costs.

B24. The data for lazertinib in Table 53 appear to have been adjusted to account for the average dose in mg of lazertinib received, but the data for amivantamab have not been adjusted similarly. Please clarify why this is the case.

The proportion of administrations at different doses of lazertinib has been adjusted for the average dose in mg of lazertinib received to account for dose modifications, which correspond to different number of units at different strengths (80 mg or 240 mg), reflecting the difference in pack cost. For amivantamab, planned dose reductions are accounted for similarly using the proportion of planned dose administered. The model assumes no vial sharing, and therefore, doses are reduced by the number of full vials. Since there is only one unit strength for amivantamab

(350 mg) a more granular calculation is not necessary, and a percentage representing the proportion of planned doses is used instead.

B25. CS Table 52 and Table 56. Please clarify why the drug acquisition costs for amivantamab say “up to C2D1.” Does cycle 1 cover 4 weeks of treatment or does 1 cycle refer to 1 week as in the model? Please clarify drug costs for cycles 2 and beyond.

Johnson & Johnson understand this question to relate to Table 53 (instead of Table 52) and Table 56 of the original Company submission. Johnson & Johnson apologise for a typographical error within these tables: “<80 kg patients: 4 weeks (up to C2D1)” in the treatment duration column should say “until progression”. To clarify, the treatment duration of amivantamab is until progression; amivantamab is administered once weekly during the four-week induction period, and once every two weeks for the remainder of the treatment duration. Corrected versions of Tables 53 and 56 from the company submission are presented below in Table 21 and Table 22 respectively. Note that one cycle in the model refers to one week, whereas one treatment cycle as per the MARIPOSA trial relates to the four-week treatment cycle described above.

Table 21: Drug acquisition cost per dose for amivantamab-lazertinib (amended version of Table 53 from Document B of the company submission)

Component	Dose (mg)	Treatment duration	Units (vials/caps) per admin	Cost per average dose required (£)
Amivantamab <80 kg patients (list price)	1,050	Until progression	3	[redacted]
Amivantamab <80 kg patients (PAS price)	1,050	Until progression	3	[redacted]
Amivantamab ≥80 kg patients (list price)	1,400	Until progression	4	[redacted]
Amivantamab ≥80 kg patients (PAS price)	1,400	Until progression	4	[redacted]
Lazertinib (list price)	240	Taken once daily until progression	1	[redacted]
Lazertinib (PAS price)	240	Taken once daily until progression	1	[redacted]

Abbreviations: kg: kilogram; mg: milligram; PAS: patient access scheme.

Table 22: Total weekly drug acquisition cost for amivantamab-lazertinib including missed doses and dose reductions (amended version of Table 56 from Document B of the company submission)

Component	Treatment duration	Dosing frequency per week (induction)	Dosing frequency per week	Cost per week of induction (£)[a]	Cost per week of maintenance (£)[a]

			(maintenance)		
Amivantamab <80 kg patients (list price)	Until progression	1	0.5	[redacted]	[redacted]
Amivantamab <80 kg patients (PAS price)	Until progression	1	0.5	[redacted]	[redacted]
Amivantamab ≥80 kg patients (list price)	Until progression	1	0.5	[redacted]	[redacted]
Amivantamab ≥80 kg patients (PAS price)	Until progression	1	0.5	[redacted]	[redacted]
Lazertinib (list price)	Taken once daily until progression	7	7	[redacted]	[redacted]
Lazertinib (PAS price)	Taken once daily until progression	7	7	[redacted]	[redacted]
Total amivantamab-lazertinib (list price)[b]				[redacted]	[redacted]
Total amivantamab-lazertinib (PAS price)[b]				[redacted]	[redacted]

[a] Calculated accounting for doses missed and proportion of planned doses received.
[b] Weighted based on the % of patients over and under 80 kg.
Abbreviations: kg: kilogram; mg: milligram.

B26. Please clarify which of the drug administration costs in Table 58 apply to which treatments in the model.

The complex IV administration cost (SB14Z) is applied in the model for the subsequent treatment cost for platinum-based chemotherapy during the induction weeks (pemetrexed, carboplatin and cisplatin) and IO ± chemotherapy ± VEGFi during both induction and maintenance weeks (atezolizumab, bevacizumab, carboplatin and paclitaxel).

The simple IV administration cost (SB12Z) is used to calculate the administration costs for all other treatments that are administered intravenously, including amivantamab.

The oral therapy one-off cost (SB11Z) is applied to lazertinib and osimertinib at the start of treatment, and to nintedanib when administered with docetaxel as a subsequent treatment.

B27. CS, Table 58. The EAG is concerned that the HRG codes applied for treatment administration of amivantamab do not adequately capture the expected duration of

infusion. CS, page 88 states that the median infusion time for amivantamab in PALOMA-3 was 5 hours.

a) Please comment on whether the average infusion time is likely to be similar for patients receiving amivantamab for this first-line indication with reference to the infusion rates specified in the draft SmPC and the time required for any pre-medications.

The five-hour infusion time reported in PALOMA-3 was reported for Day 1 of Cycle 1 only; for Cycle 3 onwards, a median duration of 2.25 hours was reported. Therefore, the HRG code applied in this submission for treatment administration is considered reflective of the average infusion time for amivantamab. As such, no changes have been made to the model.

b) Please comment on whether the HRG applied in the model (SB12Z) is the most appropriate HRG given that SB12Z is recommended for treatments with an overall chair time of up to 60 minutes. [see Table 1 of this document for information on HRGs for chemotherapy: https://www.england.nhs.uk/wp-content/uploads/2021/02/20-21NT_Annex_B_Currencies_with_national_prices.pdf]

Johnson & Johnson consider this HRG code (SB12Z) to be the most appropriate code to use, since it most closely reflects expected clinical practice. As such, no changes have been made to the model.

c) If necessary, please update the HRG codes in the economic model to ensure that the minimum infusion times for each treatment are within the maximum infusion time for the applied HRG.

As outlined above, the HRG code included in the model are considered to be most relevant for consideration, so the unit cost for IV administration in the model has not been changed.

d) Please justify why SB15Z (Deliver subsequent elements of a chemotherapy cycle) is not the most relevant HRG code for the second part of the split dose given on day 2 of week 1

The suggested HRG code, SB15Z, refers to subsequent elements of a chemotherapy cycle. Whilst amivantamab is administered in a split dose in Cycle 1, this refers to a single dose only. As such, SB15Z is considered inappropriate to use, and use of SB12Z has instead been maintained.

e) Please clarify if the cost of the second administration of amivantamab in week 1 is accounted for in the model and if not please amend the model to correct this including the most appropriate HRG code.

In order to simplify the calculation of administration costs, the model uses an assumption that the first dose of amivantamab is not split. This is considered an appropriate simplifying assumption, given that the same dose is being administered. As such, no changes have been made to the model.

B28. In Table 60, the duration of treatment for dexamethasone is given as '2 cycles', but the frequency is given as C1D1, C1D2 and the costing appears to account for only two 10mg doses. Please clarify the dosing schedule for dexamethasone with reference to the draft SmPC, specifying both the days on which doses of dexamethasone are required and the dosages required on those days. If necessary, please amend the model to match the recommendations in the draft SmPC.

As per the amivantamab SmPC, dexamethasone should be given twice in total: 20 mg on C1D1 and 10 mg C1D2.[17] As such, the cost of 10 mg dexamethasone has been multiplied by three in the model to account for the full cost of dexamethasone comedication (30 mg total).

B29. The protocol amendment for adding VTE prophylaxis said it was to be given for the first 4 months, but the duration for rivaroxaban in Table 60 is only 12 weeks. Please increase this to 4 months (~17 weeks) or justify why this is not appropriate. Please also justify why rivaroxaban is the presumed prophylaxis rather than LMWH or an alternative direct oral anticoagulant (DOAC). In responding, please consider any relevant guidance on choice of DOACs when combined with TKIs.

The model has been updated to replace rivaroxaban with low molecular weight heparin (LMWH), specifically enoxaparin sodium, for VTE prophylaxis. In addition, treatment duration has been increased to 17 weeks, as requested. Costs were sourced from the BNF.[20] This is in line with the licensed indication for enoxaparin sodium and is therefore considered reflective of UK clinical practice.[21]

B30. In Table 60, the dosing frequency of rivaroxaban is "once daily," but the cost per induction week is only £5.40, equivalent to 3 doses of 10mg. The EAG suspects that there is an error in this calculation in that the 12 weeks of treatment assumed by the company have been allocated across the 4 induction weeks, but only a single dose per week has been accounted for. Please describe how the number is calculated and correct if required. In doing so please ensure that the full 4 months of

prophylaxis covered by the protocol amendment and [redacted] is accounted for in the model.

Johnson & Johnson thanks the EAG for raising this discrepancy. As noted above, the model has now been updated to include enoxaparin sodium (LMWH) instead of rivaroxaban for VTE prophylaxis, and to account for daily dosing in the cost calculations. In the updated model, the full cost of VTE management is accounted for in the induction period, irrespective of the duration of VTE, corresponding to a total co-medication cost per week for enoxaparin sodium of £15.89.

B31. Please clarify why the costs of Grade ≤2 VTE is limited to drug costs. Diagnosis of DVTs requires clinical examination and an ultrasound scan. Please update the costs to include at a minimum a HRG cost for a non-admitted Accident and Emergency attendance and an unbundled ultrasound scan e.g. RD40Z.

The model has now been updated to include the HRG cost RD40Z to account for DVT diagnosis costs in patients with Grade ≥2 VTE.

B32. For PE AEs please include costs for assessment and diagnosis e.g. an Accident and Emergency Attendance leading to admission, and unbundled cost for a computerised tomography pulmonary angiography (CTPA).

Within the model, the management of PE has been costed based on a weighted average of HRG codes DZ09J–DZ09Q (non-elective short stay). As a weighted average of all PE-related HRG codes, Johnson & Johnson maintained that this is the most appropriate costing approach to reflect the average cost for pulmonary embolism accurately. As such, no changes have been made to the model.

B33. Please clarify whether warfarin is the preferred anticoagulant treatment for VTE, given that the draft SmPC specifies that [redacted] and the study protocol states that [redacted]. Please also include costs for regular INR monitoring if warfarin is the assumed VTE treatment (e.g. Anticoagulant service - service 324). If an alternative treatment regimen is preferred then please cost accordingly considering both drug costs and any monitoring required.

Johnson & Johnson thanks the EAG for raising this. In line with the study protocol, NICE guidelines and the amivantamab SmPC, warfarin has now been replaced within the model by rivaroxaban as the preferred treatment for the management of Grade ≤2 VTE in the model.[16, 17, 22] A per-administration unit cost has been applied in the model, informed by the NICE guideline on VTE diseases (NG158).[22] As noted in response to Question B31, the model has also been updated to include the HRG cost RD40Z to account for DVT diagnosis costs.

B34. Please clarify why usage of chest x-rays is so high in Table 65. Our clinical expert indicated that chest x-rays are only used to investigate patients with suspected complications and are not used for routine monitoring of disease progression. In ID6328, the EAG preferred to assume 2 MRI scans per year (4 for those with central nervous system metastases), 2 chest CT scans per year and 2 other CT scans per year for both the PF and progressed-disease (PD) health states. Please amend the model to incorporate these assumptions or explain why the company's current assumptions are preferable.

The usage of chest x-rays was based on the resource use frequency quoted in NICE TA531 for pembrolizumab in untreated programmed death-ligand 1 (PD-L1) positive metastatic NSCLC.[23] However, to align with EAG preference, the resource use in the updated economic model has now been updated to account for 2 MRI scans per year, 2 chest CT scans per year and 2 other CT scans per year (in the PF and PD health states). The update resource use is shown in Table 23.

Table 23: Resource use and costs for routine follow-up care by health state (amended version of Table 65 from the Company Submission)

Resource	Unit Cost (£)	Source	PF (number of visits)	PD (number of visits)	Source
Oncology outpatient visit	192.95	National Schedule of NHS Costs 2023/24, WF01A. Consultant Led, Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology Service[24]	9.61	7.91	NICE TA531[23]
Clinical nurse specialist (hours)	88.00	PSSRU 2023, Cost per hour Band 8B nurse P.61 (as per TA705)[25]	12.00	12.00	NICE TA584[26]
GP surgery visit	49.00	PSSRU 2023, Unit costs for a GP Per surgery consultation lasting 10 minutes including direct care staff costs & qualifications p.64[25]	12.00	0.00	NICE TA584[26]
Therapist visit	52.00	PSSRU 2023, Cost per hour for a community occupational therapist (local authority), incl. qualification p.77 (as per TA705)[25]	0.00	26.09	NICE TA584[26]
GP home visit	49.00	PSSRU 2023, Unit costs for a GP. Assumed the same costs as per surgery consultation lasting 10 minutes incl. direct	0.00	26.09	NICE TA584[26]

		care staff costs & qualifications p.64[25]			
Community nurse home visit (20 minutes)	76.00	PSSRU 2023, Cost per hour Band 8A nurse P.61 (as per TA705)[25]	8.70	8.70	NICE TA584[26]
Chest radiography	101.10	National Schedule of NHS Costs 2023/24, IMAGCDC Plain Film (as per TA654)[24]	0	0	EAG recommendation, ID6328[1]
CT scan (chest)	121.71	National Schedule of NHS Costs 2023/24, RD24Z, IMAG Computerised Tomography Scan of Two Areas, with Contrast[24]	2.00	2.00	EAG recommendation, ID6328[1]
CT scan (other)	123.03	National Schedule of NHS Costs 2023/24, RD26Z, IMAG Computerised Tomography Scan of Three Areas, with Contrast[24]	2.00	2.00	EAG recommendation, ID6328[1]
ECG	176.40	National Schedule of NHS Costs 2023/24, EY51Z, Outpatient, Electrocardiogram Monitoring or Stress Testing (as per TA705)[24]	1.04	2.00	EAG recommendation, ID6328[1]
MRI	161.19	National Schedule of NHS Costs 2023/24, RD01A, Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over)[24]	2	2	EAG recommendation, ID6328[1]
Average annual cost by health state (£)			5,154.74	7,043.16	Calculation
Average weekly cost by health state (£)			98.79	134.98	Calculation

Abbreviations: CG: clinical guideline; CT: computed tomography; ECG: electrocardiogram; 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; TA: technology appraisal.

B35. Please clarify why usage of ECG is lower for patients with progressed disease and consider amending the frequency to twice per year as per the EAG preferences in ID6328. Please clarify if any of the drugs included at first, second or third-line in the model have a specific requirement for regular ECG monitoring.

The ECG usage was based on the resource use frequency quoted in NICE TA531 for pembrolizumab in untreated programmed death-ligand 1 (PD-L1) positive metastatic NSCLC.[23] However, treatments included at the first, second and third-line

do not have specific requirements for regular ECG monitoring; as such, the ECG resource frequency has been updated within the model to be twice per year. This is in line with the preferences of the EAG within the ongoing NICE appraisal of osimertinib with chemotherapy for untreated advanced cEGFRm NSCLC (NICE ID6328).[1] The updated resource use is shown in Table 23 above.

B36. Please clarify if the resource use in Table 65 for the progressed disease state applies only to those receiving active second or third-line treatment or whether it is also relevant to those receiving best supportive care (BSC). Please clarify in particular what frequency of outpatient oncology visits are assumed for those on and off active treatment in the PD state. Please also clarify if the frequency of GP home visits, therapists visits a community nurse home visits are appropriate for those on active treatment or whether they would apply only to those receiving BSC.

The resource use for the progressed diseased state presented in Table 65 of Document B of the company submission, and now updated as presented in Table 23 above, is applied within the model to all patients with progressed disease. As such, the frequency of outpatient oncology visits is assumed to be equal for all patients with progressed disease, regardless of whether they are currently receiving active treatment or not, and the same frequency of GP home visits, therapist visits and community nurse home visits is modelled for progressed patients receiving active treatment as those receiving BSC.

B37. In the Economic model, costs and life-years were discounted on a yearly basis, while QALY was discounted on a cycle basis. Please use the same approach consistently across model outcomes.

Johnson & Johnson can confirm that the same approach to discounting was applied to all model outcomes within the original submitted model: life years, QALYs and costs were all discounted on a cycle basis. This discounting is applied in the engine tabs for each treatment group by calculating and applying a discounting factor for each cycle. As such, no changes have been made to the model.

B38. Please update the model with the latest drug prices from eMIT and 2023/24 National Cost Collection data.

The model has now been updated with the latest drug prices.

B39. Please confirm whether drug prices were fixed when analysing the probabilistic sensitivity analysis (PSA). If so, amend Table 70.

Drug prices, including for amivantamab, lazertinib and osimertinib, were fixed for the PSA as these are known costs. An amended version of Table 70 from the original company submission is presented below in Table 24, where the ‘measurement of

uncertainty (distribution)' column has been updated to not applicable (NA) for drug prices. Table 24 also presents the updated costs used in the base case.

Table 24: Summary of variables applied in the economic base case (amended version of Table 70 from Document B of the company submission)

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	
Discount rate for effects	3.5%	NA	
Discount rate for costs	3.5%	NA	
Patient characteristics			
Mean starting age, years	62.3	Normal	B.3.3.1
Proportion female, %	61.3	Beta	
Mean weight, kg	[redacted]	Normal	
Patients <80kg, %	86.7	Beta	
Efficacy data			
Amivantamab-lazertinib PFS	LogLogistic	Multivariate normal	B.3.3.2
Amivantamab-lazertinib OS	Weibull	Multivariate normal	
Amivantamab TTD	Exponential	Multivariate normal	
Lazertinib TTD	Exponential	Multivariate normal	
Osimertinib PFS	LogLogistic	Multivariate normal	
Osimertinib OS	Weibull	Multivariate normal	
Osimertinib TTD	Exponential	Multivariate normal	
Drug acquisition costs for intervention (per week), £			
Amivantamab-lazertinib at list price (induction)	[redacted]	Drug Price: NA	B.3.5.1
		% Doses Skipped: Beta	
		% Distribution of Doses: Beta	
	[redacted]	Drug Price: NA	B.3.5.1
		% Doses Skipped: Beta	

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
Amivantamab-lazertinib at list price (maintenance)		% Distribution of Doses: Beta	
Amivantamab-lazertinib at PAS price (induction)	[redacted]	Drug Price: NA % Doses Skipped: Beta % Distribution of Doses: Beta	B.3.5.1
Amivantamab-lazertinib at PAS price (maintenance)	[redacted]	Drug Price: NA % Doses Skipped: Beta % Distribution of Doses: Beta	B.3.5.1
Drug costs for comparators (per week), £			
Osimertinib	[redacted]	NA	B.3.5.1
Administration costs (per week) for intervention, £			
Amivantamab-lazertinib (induction)	[redacted]	Gamma	B.3.5.1
Amivantamab-lazertinib (maintenance)	[redacted]	Gamma	B.3.5.1
Administration costs for comparators (per week), £			
Osimertinib	0.00	Gamma	B.3.5.1
AE management costs, £			
Amivantamab-lazertinib	430.54	Cost: Gamma Incidence: Beta	B.3.5.3
Osimertinib	79.06	Cost: Gamma Incidence: Beta	
Disease management costs (weekly), progression-free, £			
Amivantamab-lazertinib	98.79	Gamma	B.3.5.2
Osimertinib			
Disease management costs (weekly), PD, £			
Amivantamab-lazertinib	134.98	Gamma	B.3.5.2
Osimertinib			
Disease management costs, one-off cost, £			
End-of-life	4,862.63	Cost: Gamma	B.3.5.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty (distribution)	Reference to section in submission
		Incidence: Beta	
Subsequent treatment costs (one-off), £			
Amivantamab-lazertinib	[redacted]	Cost: Gamma	B.3.5.1
		Proportions: Beta	
Osimertinib	[redacted]	Cost: Gamma	
		Proportions: Beta	
Health state utility values			
Progression-free	[redacted]	[redacted]	B.3.4.5
PD	[redacted]	[redacted]	
Grade 3+ AE disutilities			
Amivantamab-lazertinib	[redacted]	Disutility: Beta	B.3.4.4
		Duration: Normal	
Osimertinib	[redacted]	Disutility: Beta	
		Duration: Normal	

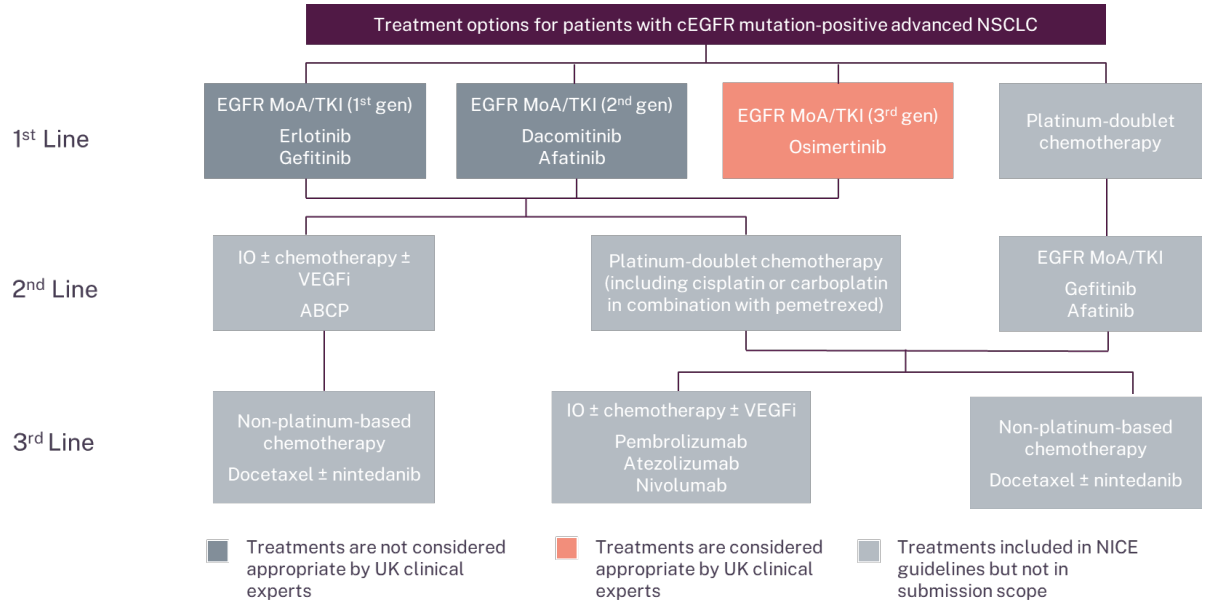
Abbreviations: AE: adverse event; NA: not applicable; OS: overall survival; PD: progressed disease; PFS: progression-free survival; TTD: time to treatment discontinuation or death.

Subsequent treatments

B40. CS, Figure 6. This treatment pathway only covers first-line treatment. Please provide a diagram showing the current treatment pathway covering first, second and third-line treatment. Please indicate all licensed options and indicate which fall within each category shown in Table 62.

The updated treatment pathway, covering first-, second- and third-line treatment options, is presented in Figure 27. Within the figure, these have been annotated with “platinum-based chemotherapy”, “EGFR MoA/TKI”, “Non-platinum-based chemotherapy” and “IO ± chemotherapy ± VEGFi” categories, aligned with Table 62 in the original company submission.

Figure 27: Current treatment options for patients with untreated cEGFRm advanced NSCLC in UK clinical practice (updated Figure 6 from Document B of the company submission)



Abbreviations: ABCP: atezolizumab and bevacizumab, carboplatin and paclitaxel; gen: generation; *EGFR*, epidermal growth factor receptor; IO: immunotherapy; MoA: mechanism of action; NSCLC, non-small cell lung cancer; TKI: tyrosine kinase inhibitors; VEGFi: vascular endothelial growth factor inhibitor.
Sources: NICE. Lung cancer: diagnosis and management: NICE guideline (NG122). 2019;[27] Johnson & Johnson Data on File. MARIPOSA Advisory Board (October 2024).[3]

B41. CS, Tables 62, 63, 80, 81 and 82. For each of these Tables, please clarify which exact treatments/treatment combinations are included as second and third line treatments within the model. (This can be done once, if the answer is the same for all five tables.) For example which treatments are referred to by 'EGFR MoA', 'IO', and 'VEGFi'. If each row refers to a single treatment option then please list this. If more then one treatment option is possible within each row then please give each and their relative frequency (for example please specify the split between carboplatin/pemetrexed, cisplatin/pemetrexed and any other platinum-based chemotherapy options in the first row of Table 62).

All treatments are distributed evenly within each group, and the same treatments are included for each table. The treatments included are outlined below:

- Platinum chemotherapy: pemetrexed, carboplatin and cisplatin
- EGFR MoA/TKI or TKI-based regimen: osimertinib
- Non-platinum chemotherapy: docetaxel and nintedanib (see response to Question B42 below)

- IO ± chemotherapy ± VEGFi: atezolizumab, bevacizumab, carboplatin and paclitaxel

B42. The EAG can find no reference to nintedanib within the economic model even though docetaxel with nintedanib is recommended by TA347. The EAG notes the clinical expert advice provided in the October 2024 Advisory Board (CS reference 32) that "[redacted]." Please clarify why docetaxel with nintedanib does not feature in the non-platinum based chemotherapy options included in the model. Please amend the model to allow this treatment combination to be included as a third-line treatment option.

Johnson & Johnson can confirm that while docetaxel was included in the model under the non-platinum-based chemotherapy regimen, nintedanib was not included. In the updated version of the model provided alongside these responses, nintedanib has been added (in combination with docetaxel) to the non-platinum-based chemotherapy options in the model (Table 25). Given that non-platinum-based chemotherapy was already included in the subsequent treatments in the economic model, the overall proportion of patients receiving non-platinum-based chemotherapy, and therefore any other regimen, remains unchanged.

Table 25: Dosing schedule and cost details for nintedanib as included in the non-platinum-based chemotherapy regimen for subsequent treatment

Regimen	Component	Treatment duration	Dose (mg)	Dosing frequency
Non-platinum-based chemotherapy	Nintedanib	Until progression	150	Twice daily

Abbreviations: mg: milligram.

B43. Please clarify why the model assumes that platinum-based chemotherapy will be offered third-line when it also assumed that 100% of patients will receive platinum-based chemotherapy at second-line.

The distribution of subsequent treatments was based on an average of responses from two out of three KOLs that responded to the advisory board pre-meeting survey. Johnson & Johnson consider that this result is an artifact of the data, and do not feel that it is appropriate to alter the clinical experts estimates.

B44. Table 82 describes the distribution of subsequent treatments based on the NCRAS MARIPOSA-like cohort. It is described as being informed by N=65 patients who received osimertinib 1L in the MARIPOSA-like cohort and who received any

subsequent treatment. Please clarify if this is a typo and the proportions in Table 82 are based on 56 patients (20 EGFR-based, 18 platinum-based chemotherapy, 1 non-platinum chemotherapy and 17 atezolizumab-based combinations).

Johnson & Johnson can confirm that this was a typographical error and that these distributions were informed by N=56 patients from the NCRAS MARIPOSA-like cohort who received osimertinib 1L and any subsequent treatment.

Severity modifier calculation

B45. Please justify that PFS can be replaced with time to next treatment (TTNT) from NRAS RWE for the severity modifier calculations. In doing so, please explain how TTNT is defined in NRAS and whether using TTNT as a proxy for PFS is likely to under or overestimate PFS. A comparison of PFS and time to subsequent therapy (TTST) from MARIPOSA may be helpful in indicating the potential direction of any bias.

TTNT was reported as a proxy for PFS in the NCRAS study, in lieu of routine administrative data detailing the progression of disease over time. Time at risk was equal to the period in days between the index data and the end of follow-up (movement to a new line of therapy, death or censoring, whichever came first). Failure for the estimation of TTNT was defined as the earliest of movement to a new line of therapy or death during the time at risk).[28]

A comparison of PFS by BICR and TTST from the MARIPOSA trial is shown in Table 26; please note the data are derived from different data cuts, given that TTST at the 11th August 2023 DCO was [redacted] (95% CI: [redacted]) in the amivantamab-lazertinib arm, and [redacted] months ([redacted]) in the osimertinib arm.[11] The KM plots for PFS by BICR and TTST from the MARIPOSA trial are shown in Figure 28 and Figure 29, respectively.

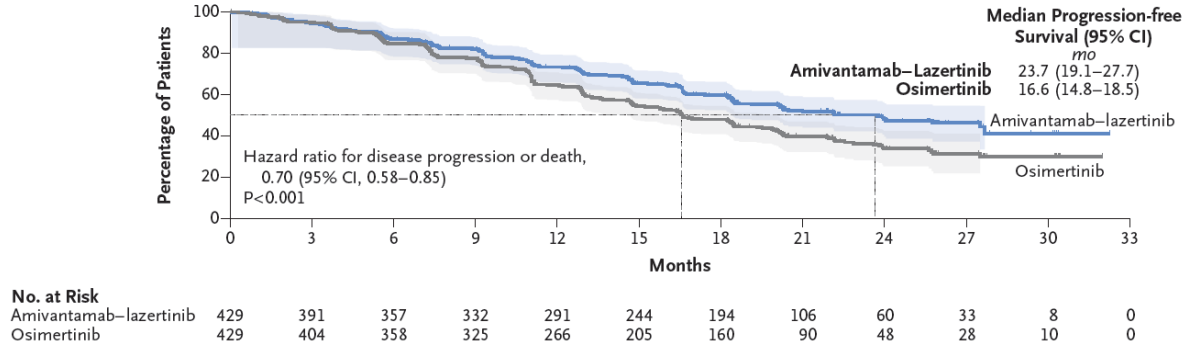
This side-by-side comparison illustrates that TTST overestimated PFS in the MARIPOSA trial. In line with this, the use of TTNT from NCRAS as a proxy for PFS is considered to be a conservative approach in the absence of direct PFS data, given that TTNT in the NCRAS study is similarly likely overestimates PFS, thereby underestimating the QALY shortfall. Given the threshold for application of a severity modifier has not been reached, Johnson & Johnson consider use of this simplifying assumption to be appropriate in order to provide additional context on the unmet need that is maintained with osimertinib.

Table 26: Comparison of PFS by BICR (11th August 2023 DCO) and TTST (13th May 2024 DCO) in the MARIPOSA trial

	PFS by BICR (11th August 2023 DCO)		TTST (13th May 2024 DCO)	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)	30.0 (26.3, 36.0)	24.0 (22.5, 26.2)
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate, % (95% CI)	73 (69, 77)	65 (60, 69)	[redacted]	[redacted]
18-month event-free rate, % (95% CI)	60 (55, 64)	48 (43, 53)	[redacted]	[redacted]
24-month event-free rate, % (95% CI)	48 (42, 54)	34 (28, 39)	57[redacted]	50[redacted]
Treatment difference				
p-value[a]	<0.001		0.005	
HR (95% CI)[b]	0.70 (0.58, 0.85)		0.77 (0.65, 0.93)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable.
Sources: Cho *et al.* 2024.[8] Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 11th August 2023). Table 12, page 60; Table 11, page 21.[11] Gadgeel et al. WCLC 2024.[10]

Figure 28: KM plot of PFS assessed by BICR (11th August 2023 DCO; FAS)



Abbreviations: BICR: blinded independent central review; CI: confidence interval; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; mo: months; PFS: progression-free survival.
Source: Cho *et al.* 2024. Figure 1A.[8]

Figure 29: KM plot of TTSP (13th May 2024 DCO; FAS)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; Osi: osimertinib; TTSP: time to symptomatic progression.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 13th May 2024). Figure 4, page 13.[29]

Section C: Textual clarification and additional points

C1. CS page 92. Is there a typo in this sentence. "*Fewer patients discontinued all study treatment due to an AE in the amivantamab-lazertinib arm (86/421, 20%) than the osimertinib arm (50/428, 12%)"*

This was a typographical error. The sentence should read "Overall, more patients discontinued all study treatment due to an AE from the amivantamab-lazertinib arm (86/421, 20%) than the osimertinib arm (50/428, 12%)."

C2. Please clarify what the bold in Table 48 of Appendix G signifies?

The bold text signifies the primary publication, where there are secondary publications associated with the same study.

C3. Appendix G, Table 55. For each study in this table, please clarify what the health state utility measurement tool was (e.g. EQ-5D, HUI, SF-6D etc)

An updated version of Table 55, specifying the health state utility measurement tool in the final column, is presented below (Table 27).

Table 27: Summary of the results of published HSUV studies included in the economic SLR (EFGRm NSCLC population)

Study and country	Treatment line	Intervention and comparator	HSUV description/ health state	Timepoint	HUV	Measurement tool; value set
1L/1L+						
CARMA-BROS Canada	Advanced/metastatic disease (mixture of cEGFR and ex20ins mutations) 1L	Any TKI (>70 years, n=57)	At TKI initiation	NR	0.78	EQ-5D-5L; Canadian value set
		Any TKI (<70 years, n=82)			0.72	
		Gefitinib (>70 years, n=25)			0.79	
		Gefitinib (<70 years, n=31)			0.79	
		Osimertinib (>70 years, n=32)			0.77	
		Osimertinib (<70 years, n=31)			0.68	
		Any TKI (>70 years, n=20)	At progression on TKI		0.58	
		Any TKI (<70 years, n=16)			0.77	
		Gefitinib (>70 years, n=15)			0.54	
		Gefitinib (<70 years, n=15)			0.81	
		Osimertinib (>70 years, n=5)			0.70	
		Osimertinib (<70 years, n=11)			0.71	
		Any TKI (>70 years, n=80)	Stable on TKI		0.82	
		Any TKI (<70 years, n=145)			0.81	
		Gefitinib (>70 years, n=64)			0.83	
		Gefitinib (>70 years, n=97)			0.84	
		Osimertinib (>70 years, n=16)			0.78	
		Osimertinib (>70 years, n=48)			0.77	
Labbe 2017 Canada	Metastatic disease (EGFR and ALK mutations) 1L+	Osimertinib (n=14)	Stable disease on most appropriate treatment[a]	Mean for all follow-up visits (number of visits NR)	0.84	EQ-5D-3L; Canadian value set
		Erlotinib (n=7)			0.81	
		Afatinib (n=4)			0.78	
		Gefitinib (n=71)			0.80	
		Rociletinib (n=8)			0.78	

Study and country	Treatment line	Intervention and comparator	HSUV description/ health state	Timepoint	HUV	Measurement tool; value set
		Nazartinib (n=8)			0.84	
		N/A	Stable disease with treatment (n=112)		0.81	
			Stable disease without treatment (n=8)		0.80	
			Progressed disease (n=81)		0.70	
O'Kane 2019 Canada	Stage IV disease (EGFR or ALK mutations) 1L+	Patients undergoing treatment but specific intervention not specified	EGFRm or ALKm	Mean for all outpatient visits (number of visits NR)	0.79	Canadian value set
			Other NSCLC		0.75	
			EGFRm or ALKm with brain metastases		0.78	
			Other NSCLC with brain metastases		0.74	
Verduyn 2012 (IPASS) Netherlands	Advanced disease 1L	All EGFR mutation-positive patients (n=251)	Progression-free	Baseline	0.736	EQ-5D-3L; FACT-L scores converted into Dutch utilities by applying the unequal distribution algorithm
		Gefitinib (n=NR)	Weighted mean for CfB (Progression-free)	Change from baseline (treatment at week 42)	0.0528	
		Carboplatin and paclitaxel (n=NR)			0.0011	
Yang 2020 Taiwan	Advanced disease 1L	Afatinib (n=48)	HSUV for specific treatment (health states NR, assumed stable/ progression-free)	Mean for all follow-up visits (follow-up from May 2017 until September 2018)	0.80	EQ-5D (unspecified); utility scoring function from Taiwan
		Erlotinib (n=48)			0.85	
		Gefitinib (n=96)			0.81	
2L						

Study and country	Treatment line	Intervention and comparator	HSUV description/ health state	Timepoint	HUV	Measurement tool; value set
Hirsh 2013 (LUX-Lung1) International	Stage IIIB–IV disease 2L	Afatinib (n=380)	HSUV for treatment or comparator arm (health states NR, assumed stable/ progression-free)	At specific timepoint (Median follow-up time: Week 13)	0.71	EQ-5D (unspecified); UK preference weights
		Placebo (n=195)			0.67 (p=0.006 vs afatinib)	
Any treatment line						
Jiang 2018 Canada	Advanced disease Any treatment line	Osimertinib (n=33)	HSUV for specific treatment (health states NR, assumed stable/ progression-free)	Mean for all 782 follow-up visits (over 2014–2017)	0.85 (114 visits)	EQ-5D (unspecified); Canadian preference weights
		Gefitinib (n=147)			0.8 (351 visits)	
		Chemotherapy (n=32)			0.72 (76 visits)	
		Other TKIs (unspecified; n=49)			0.79 (133 visits)	
Jiang 2019 Canada	Stage IV disease Any treatment line	Osimertinib (n=54)	Stable disease while on specific treatment[a]	Mean for all follow-up visits (number of visits NR)	0.815 (p=0.86 vs gefitinib)	EQ-5D (unspecified); Canadian preference weights
		Gefitinib (n=121)			0.81	
		Chemotherapy (n=25)			0.756 (p=0.04 vs gefitinib)	
		Other TKIs (unspecified; n=42)			0.795 (0.61 vs gefitinib)	
		All; N=242	Stable disease while on chemotherapy or TKI		0.803	

Study and country	Treatment line	Intervention and comparator	HSUV description/ health state	Timepoint	HUV	Measurement tool; value set
		All; N=163	Progressing disease while on chemotherapy or TKI		0.771	
		Any 1L	Overall utility (specific health state[s] NR)		0.79	
		Any 2L			0.77	
		Any 3L+			0.77	
Sari 2020 Indonesia	Stage IIIB–IV disease Treatment line NR	Patients undergoing treatment but specific intervention not specified	Progressive free disease (n=29)	Mean for all follow-up visits (follow-up period NR)	0.824	EQ-5D (unspecified); Indonesian value set
			Disease progression before and while diagnosed with NSCLC (n=21)		0.528	
			Disease progression after diagnosis with NSCLC (n=24)		0.544	
Molife 2023a International	Advanced disease 1L/2L/3L	Chemotherapy; targeted therapy (1st/2nd generation EGFR-TKI; 3rd generation EGFR-TKI; EGFR-TKI and anti-VEGF; other targeted therapy); immunotherapy; other or best supportive care	1L (n=764)	NR	0.7	EQ-5D-5L
			2L (n=138)		0.7	
			3L (n=32)		0.8	
			1L/2L/3L (n=934)		0.7	

Footnotes: [a]TKIs for EGFRm population.[b] HSUVs for several other heath states were reported in the publication. The trend was the same in all health states so HSUVs are only included here for stable disease as p-values were not reported for other health states.
Abbreviations: 1L: first-line; 2L: second-line; 3L: third-line; ALK: anaplastic lymphoma kinase; CfB; change from baseline, EGFR**,** epidermal growth factor receptor; EQ-5D(-3L/-5L): EuroQol 5-Dimensions (3 levels/5 levels); FACT-L: Functional Assessment of Cancer Therapy-Lung; HSUV, health state utility value; N/A: not applicable; NR, not reported; NSCLC, non-small cell lung cancer; TKIs, tyrosine kinase inhibitors; UK: United Kingdom; VEGF: Vascular endothelial growth factor.

C4. Please explain why the smoothed hazard plots in CS Figures 25, 27 and 37 differ from the empirical hazard plots in Figures 23, 24 and 41 of the technical model report.

Johnson & Johnson thanks the EAG for highlighting this inconsistency. This is a result of inconsistent settings used to generate different hazard plots in the two documents. Please consider the smoothed hazard plots presented below as correct and final. All were generated using the *muhaz* R package with default settings and left boundary correction.

Figure 30. Smoothed hazard plot with parametric extrapolations for amivantamab-lazertinib for PFS (BICR)

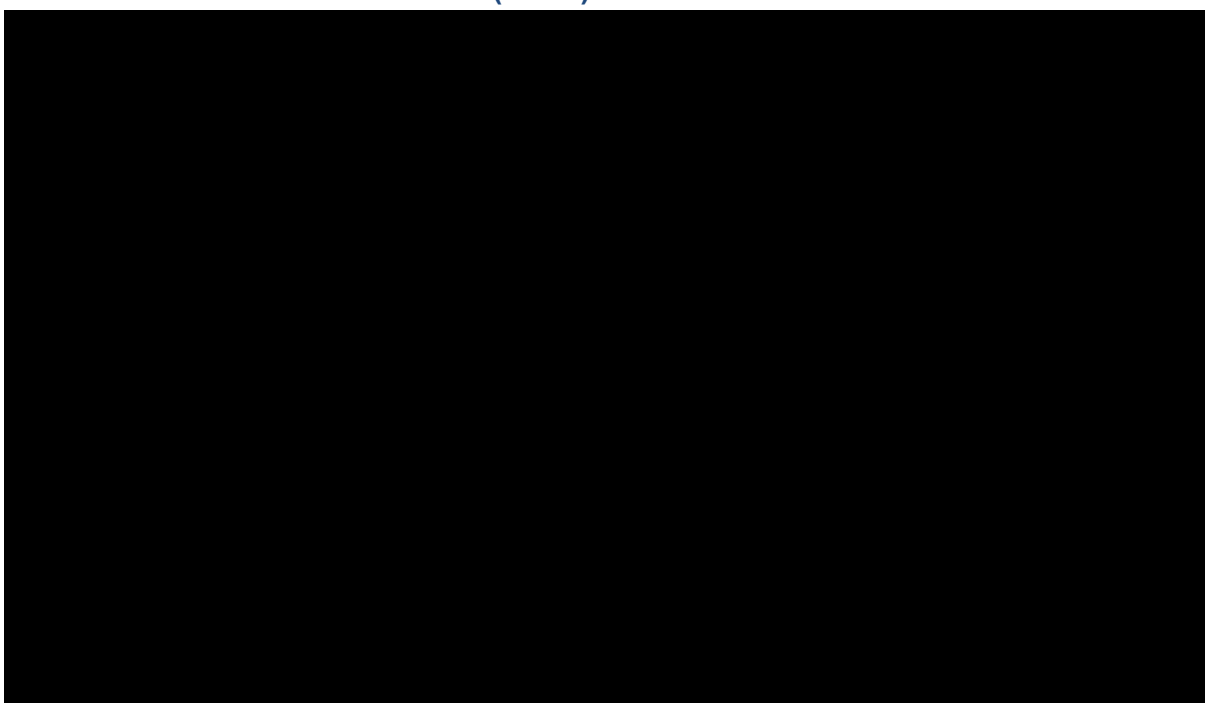


Figure 31. Smoothed hazard plot with parametric extrapolations for osimertinib PFS (BICR)

Figure 32. Smoothed hazard plot with parametric extrapolations for amivantamab-lazertinib for OS

Figure 33. Smoothed hazard plot with parametric extrapolations for osimertinib for OS

Figure 34. Smoothed hazard plot with parametric extrapolations for amivantamab for TTD

Figure 35. Smoothed hazard plot with parametric extrapolations for lazertinib for TTD

Figure 36. Smoothed hazard plot with parametric extrapolations for osimertinib for TTD

C5. Please clarify if the following submitted files are related to this appraisal, as they appear to refer specifically to the Exon20 mutation subgroup. 1) “J&J Advisory Board

June 2023 Pre-meeting Responses.pdf"; 2) "J&J Advisory Board Report May 2024", 3) "J&J Advisory Board Report August 2024"

These files were submitted as additional supporting evidence for the EAG's consideration, if wanted.

Appendix A: Updated base case

Appendix A.1: Updates to economic base case

As compared with the economic model submitted alongside the original company submission, the economic model submitted alongside this response document has been updated as follows:

- To include enoxaparin sodium (LMWH) instead of rivaroxaban for VTE prophylaxis, with the formulas updated to account for daily dosing in the cost calculations (Question B30)
- To include HRG code RD40Z (ultrasound scan) in the AE unit cost for Grade ≤2 VTE, to account for diagnosis costs (Question B31)
- To replace the use of warfarin for the management of Grade ≤2 VTE with the use of rivaroxaban (Question B33)
- To account for 2 MRI scans per year, 2 chest CT scans per year and 2 other CT scans per year (PF and PD health states) (Question B34)
- Inclusion of MRI scan cost from the 2023/24 National Cost Collection data, RD01A (Question B34)
- To update ECG resource use frequency to twice per year for the progressed disease state (Question B35)
- To use the latest drug prices from eMIT and 2023/24 National Cost Collection data (Question B38)
- To include nintedanib into the subsequent treatment input sheet (Question B42)

Appendix A.2: Updated base case incremental cost-effectiveness analysis results

A summary of the deterministic and probabilistic base case results (at PAS price) from the original and the updated CEM of amivantamab-lazertinib versus osimertinib are presented in Table 28 and Table 29, respectively.

At amivantamab and lazertinib PAS prices, amivantamab-lazertinib was found to be a cost-effective use of NHS resources when compared to osimertinib at its list price, dominating osimertinib in the probabilistic and deterministic analyses. These results are highly consistent with the results from the original model.

Table 28: Base case results at amivantamab and lazertinib PAS prices (probabilistic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Original model							
Osimertinib	[redacted]	[redacted]	3.41	[redacted]	[redacted]	1.29	−74,090.97 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.70				
Updated model							
Osimertinib	[redacted]	[redacted]	3.41	[redacted]	[redacted]	1.29	−75,200.42 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.70				

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years.

Table 29: Base case results at amivantamab and lazertinib PAS prices (deterministic)

	Total			Incremental			ICER (£/QALY)
	Costs (£)	QALYs	LYs	Costs	QALYs	LYs	
Original model							
Osimertinib	[redacted]	[redacted]	3.40	[redacted]	[redacted]	1.27	−75,539.74 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.67				
Updated model							
Osimertinib	[redacted]	[redacted]	3.40	[redacted]	[redacted]	1.27	−76,643.31 (dominant)
Amivantamab-lazertinib	[redacted]	[redacted]	4.67				

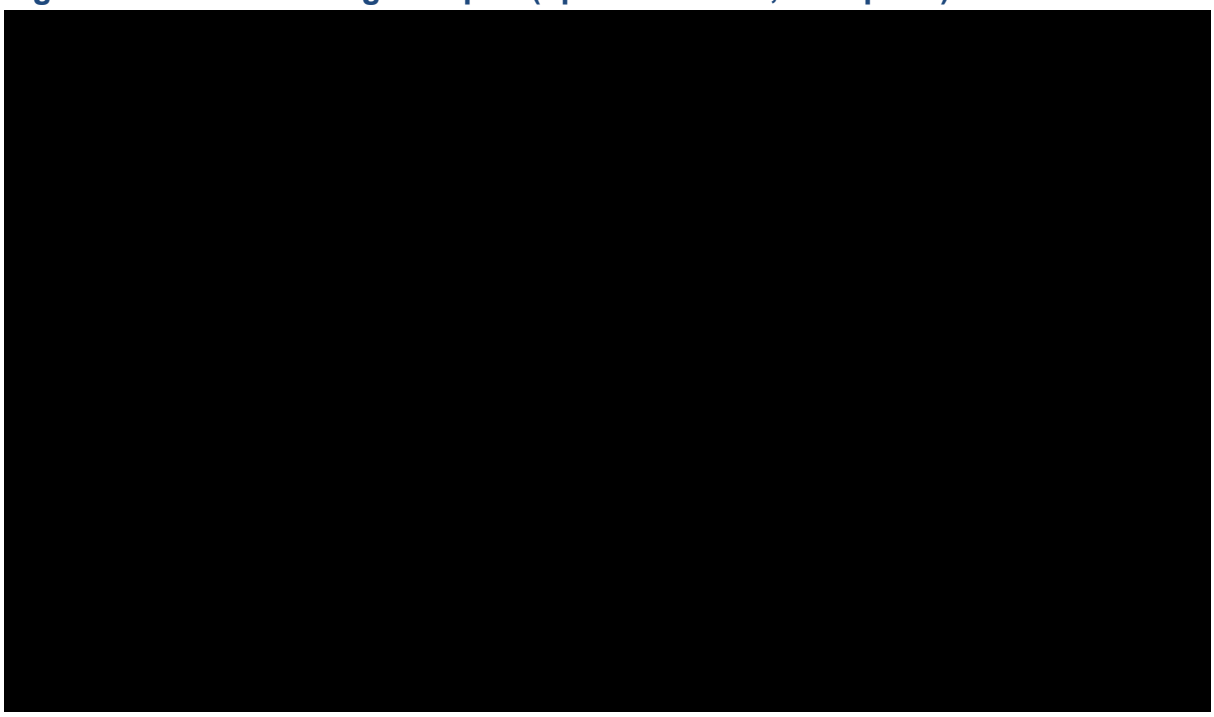
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; PAS: patient access scheme; QALYs, quality-adjusted life years.

Appendix A.3 Updated probabilistic sensitivity analysis

An updated probabilistic sensitivity analysis was conducted using the updated CEM; results are presented in Table 28 above.

The incremental net monetary benefit (INMB) convergence plot is presented in Figure 30, which incorporates the PAS discounts for amivantamab and lazertinib. Additionally, the probabilistic cost-effectiveness plane for amivantamab-lazertinib versus osimertinib is presented in Figure 31. These results indicate that at a £30,000 WTP threshold, amivantamab-lazertinib (PAS price) has a [redacted] probability of being cost-effective when compared with osimertinib, which is presented in Figure 32. This is in line with the results from the original model.

Figure 37: INMB convergence plot (updated model; PAS price)



Abbreviations: INMB: incremental net monetary benefit; PAS: patient access scheme.

Figure 38: Probabilistic cost-effectiveness plane (updated model; PAS price)

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

Figure 39: Cost-effectiveness acceptability curve (updated model; PAS price)

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

Appendix A.4 Updated deterministic sensitivity analysis

An updated tornado diagram showing the top 10 most influential parameters on the ICER for amivantamab-lazertinib versus osimertinib in the updated model is provided in Figure 33. Overall, the scale and shape of the parametric extrapolations for OS for amivantamab-lazertinib and osimertinib are the most influential parameters, followed by the TTD rate for osimertinib and amivantamab. The model is otherwise robust to variation in inputs and settings. All results generated from the DSA provide a negative ICER due to amivantamab-lazertinib (PAS price) being dominant in all

instances. The tornado diagram illustrates that the parametric function for OS in the amivantamab-lazertinib 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. These results are in line with the DSA conducted for the original CEM.

Figure 40: DSA tornado diagram (updated model; PAS price)

Abbreviations: ICER: incremental cost-effectiveness ratio; OS: overall survival; TTDD: time to treatment discontinuation or death.

Appendix B: Updated scenario analyses

Probabilistic results from the updated model for the scenario analyses previously presented in Section B.3.11.3 of Document B of the company submission are presented in Table 30, with the deterministic results presented in Table 31. In all analyses, amivantamab-lazertinib at PAS price remained dominant over osimertinib at list price, in line with the results of the original model, indicating that the cost-effectiveness of amivantamab-lazertinib versus relevant osimertinib remains robust when altering key modelling assumptions and approaches.

Table 30: Summary of original scenario analysis results (updated model; probabilistic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case		[redacted]	[redacted]	−75,200.42 (dominant)
Discount rate				
1	1.5% discount rate	[redacted]	[redacted]	−65,878.44 (dominant)
Time horizon				
2	37.7-year time horizon	[redacted]	[redacted]	−75,049.23 (dominant)
OS modelling approach				
3	Left-truncated for osimertinib	[redacted]	[redacted]	−72,852.55 (dominant)
PFS definition				
4	PFS by INV for amivantamab-lazertinib and osimertinib	[redacted]	[redacted]	−75,279.46 (dominant)
PFS parametric extrapolation				
5	Lower PFS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−75,504.71 (dominant)
6	Higher PFS curve selections (Log-normal extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−75,086.18 (dominant)
OS parametric extrapolations				
7	Lower OS curve selections (Gompertz extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−99,893.80 (dominant)
8	Higher OS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−81,300.61 (dominant)
TTD parametric extrapolations				
9	Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	[redacted]	[redacted]	−65,185.61 (dominant)
10	Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	[redacted]	[redacted]	−63,842.73 (dominant)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Utility				
11	HSUV (PD: 0.678; PF: 0.794 as per TA654)	[redacted]	[redacted]	−77,432.97 (dominant)
12	AE disutilities based on literature	[redacted]	[redacted]	−75,254.40 (dominant)
Subsequent treatments				
13	Subsequent treatment distribution based on MARIPOSA trial	[redacted]	[redacted]	−73,102.67 (dominant)
14	Subsequent treatment distribution based on UK RWE	[redacted]	[redacted]	−73,939.88 (dominant)

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

Table 31: Summary of original scenario analysis results (updated model; deterministic)

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Updated base case		[redacted]	[redacted]	−76,643.31 (dominant)
Discount rate				
1	1.5% discount rate	[redacted]	[redacted]	−67,555.87 (dominant)
Time horizon				
2	37.7-year time horizon	[redacted]	[redacted]	−76,568.71 (dominant)
OS modelling approach				
3	Left-truncated for osimertinib	[redacted]	[redacted]	−74,379.96 (dominant)
PFS definition				
4	PFS by INV for amivantamab-lazertinib and osimertinib	[redacted]	[redacted]	−76,717.91 (dominant)
PFS parametric extrapolation				

Scenario		WITH PAS		
		Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
5	Lower PFS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−76,951.25 (dominant)
6	Higher PFS curve selections (Log-normal extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−76,499.10 (dominant)
OS parametric extrapolations				
7	Lower OS curve selections (Gompertz extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−107,707.55 (dominant)
8	Higher OS curve selections (Gamma extrapolation for amivantamab-lazertinib and osimertinib)	[redacted]	[redacted]	−80,662.55 (dominant)
TTD parametric extrapolations				
9	Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	[redacted]	[redacted]	−66,597.24 (dominant)
10	Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	[redacted]	[redacted]	−64,628.66 (dominant)
Utility				
11	HSUV (PD: 0.678; PF: 0.794 as per TA654)	[redacted]	[redacted]	−79,072.99 (dominant)
12	AE disutilities based on literature	[redacted]	[redacted]	−76,698.23 (dominant)
Subsequent treatments				
13	Subsequent treatment distribution based on MARIPOSA trial	[redacted]	[redacted]	−74,178.91 (dominant)
14	Subsequent treatment distribution based on UK RWE	[redacted]	[redacted]	−74,926.07 (dominant)

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

Appendix C: Requested scenario analyses

Johnson & Johnson thank the EAG for the additional time to provide responses to questions related to utility analysis and will provide the requested scenario analyses in a subsequent document.

Appendix D: Spline parameters

Table 32: Spline parameters for amivantamab-lazertinib OS

Scale	Knots (internal)	P1	P2	P3	P4	P5	K1	K2	K3	K4	K5
Hazard	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Hazard	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Hazard	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Odds	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Odds	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Normal	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Normal	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: K: knot; OS: overall survival; P: parameter.

Table 33: Spline parameters for osimertinib OS

Scale	Knots (internal)	P1	P2	P3	P4	P5	K1	K2	K3	K4	K5
Hazard	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Hazard	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Hazard	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Odds	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Odds	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Normal	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Normal	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: K: knot; OS: overall survival; P: parameter.

Table 34: Spline parameters for amivantamab-lazertinib PFS (BICR)

Scale	Knots (internal)	P1	P2	P3	P4	P5	K1	K2	K3	K4	K5
Hazard	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Hazard	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Hazard	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Odds	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Odds	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Normal	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Normal	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BICR: blinded independent central review; K: knot; P: parameter; PFS: progression-free survival.

Table 35: Spline parameters for osimertinib PFS (BICR)

Scale	Knots (internal)	P1	P2	P3	P4	P5	K1	K2	K3	K4	K5
Hazard	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Hazard	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Hazard	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Odds	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Odds	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Normal	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Normal	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BICR: blinded independent central review; K: knot; P: parameter; PFS: progression-free survival.

Table 36: Spline parameters for amivantamab TTD

Scale	Knots (internal)	P1	P2	P3	P4	P5	K1	K2	K3	K4	K5
Hazard	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Hazard	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Hazard	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Odds	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Odds	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Normal	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Normal	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: K: knot; P: parameter; TTD: time to treatment discontinuation or death.

Table 37: Spline parameters for lazertinib TTD

Scale	Knots (internal)	P1	P2	P3	P4	P5	K1	K2	K3	K4	K5
Hazard	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Hazard	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Hazard	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Odds	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Odds	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Normal	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Normal	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: K: knot; P: parameter; TTD: time to treatment discontinuation or death.

Table 38: Spline parameters for osimertinib TTD

Scale	Knots (internal)	P1	P2	P3	P4	P5	K1	K2	K3	K4	K5
Hazard	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Hazard	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Hazard	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Odds	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Odds	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Odds	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Normal	1	[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		
Normal	2	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
Normal	3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: K: knot; P: parameter; TTD: time to treatment discontinuation or death

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

February 2025

File name	Version	Contains confidential information?	Date
ID6256_Amivantamab with lazertinib in NSCLC_Clarification Questions Response Document_B16-19_[CON]_Redacted	1.0	Yes	21st February 2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section B: Clarification on cost-effectiveness data

Utility analysis

B16. Please provide a plot of progression-free (PF) utility scores over time by trial arm and comment on whether this supports the model assumption of equivalent utilities for the PF health-state across both arms of the model (If Figure 44 of the Cost-effectiveness Model Technical Report would be suitable for this purpose, please provide this with appropriate confidentiality marking). Please provide a scenario analysis in which trial arm-specific utilities are applied in the PF state to test the sensitivity of the model to this assumption.

PF utility scores over time by trial arm of the MARIPOSA trial are presented in Figure 27. At each timepoint, the mean utility values for each trial arm are close in value with many showing overlapping 95% confidence levels. This supports the Company submission model assumption of equivalent utilities, in which a pooled utility value is used for the PF health state across both arms, is appropriate.

To explore the impact of different utility values on model results, a scenario was conducted in the original submission using utilities based on literature (PD: 0.678; PF: 0.794; as per TA654).[1] As shown in the original company submission (Section B.3.11.3 of Document B) and in the updated scenario analysis results presented alongside these responses to reflect the company's revised base case (Appendix B), amivantamab-lazertinib remains dominant over osimertinib in this scenario analysis, with an ICER that only marginally differs from the base case ICER. These scenario

results indicate that utility values are not significant model drivers and do not impact overall conclusions of cost-effectiveness.

However, as requested by the EAG in Question B18 below, Johnson & Johnson have fitted a mixed model for repeated measures (MMRM) that includes progression status, Grade 3+ AEs, VTE Grade 1–2, treatment, time, and treatment and time interaction to MARIPOSA-1 EQ-5D-5L. The MMRM model is provided in response to question B18 in this document.

In the per-cycle MMRM, which followed the same methodology used to estimate the mean PF utility in the CEM, applied only on the osimertinib arm, the osimertinib-specific mean PF utility estimate derived was [redacted].

In addition to this PF utility value being higher than the pooled value currently used for both arms in the model ([redacted]), it is also higher than the average utility of the general population for the age group of interest (age 55–64 years: 0.799).[2] Furthermore, it is higher than the value previously accepted by the NICE Committee in appraisals in advanced EGFR-mutated NSCLC (0.794 [TA654 and ID6328]).[1, 2] As such, a scenario analysis exploring the impact of applying trial arm-specific utilities in the PF state has not been conducted.

Figure 1: Progression-free utility scores over time in MARIPOSA (13th May 2024 DCO; ITT)

Abbreviations: Ami+La: amivantamab-lazertinib; CL: confidence limit; EQ-5D-5L: EuroQoL five-dimensional descriptive system (five level version); ITT: intention-to-treat; Osi: osimertinib; PD: progressed disease.

B17. B3.4.5. Please clarify the data and the models, including covariates, used to estimate health state utilities in CS Table 51 and the disutilities for adverse events (AEs) (pooled AE disutility for grade 3+ AEs of [redacted] and VTE disutility of [redacted]

[redacted]). If the health state utility for the PF health-state was not adjusted for the presence of adverse events (Grade 3 or higher AE), please provide the adjusted PF health state utility. Please present all estimated coefficients (treatment arm, presence of AE of grade 3 or higher, and presence of a VTE event) and an intercept from the mixed model for repeated measures (MMRM), which was modelled for the disutility of adverse events.

As requested, Johnson & Johnson have provided a table summarising the covariates used to inform the health state utilities used in CS Table 51 and the disutilities for adverse events. The adjusted PF health state utility is provided as part of the MMRM requested in question B18 below, based on data from progression-free patients (Table 1).

Table 1. Covariates used to estimate health state utilities in CS Table 51

Variable	Mean (95% CI)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: VTE: venous thromboembolism; AE: adverse events

B18. PRIORITY Please consider model selection starting with a full MMRM model for utility that includes progression status, treatment arm, presence of AE of grade 3 or higher, presence of a VTE and the possible interaction terms (e.g. treatment arm and progression status) using all the data. Please provide the details of the model selection process including the estimated coefficients for each model.

As discussed in response to Question B16 above, Johnson & Johnson have fitted an MMRM as requested by the EAG. However, the resulting mean PF utility value of [redacted] is higher than the expected utility value for the general population (age 55–64 years: 0.799), the pooled value currently used in both arms of the model ([redacted]), and the value previously accepted by the NICE Committee in appraisals in advanced EGFR-mutated NSCLC (0.794 [TA654 and ID6328]).[1, 2] As such, the use of this value within the model is considered clinically and technically inappropriate, so no updates have been made to the model base case.

Details of the model selection process, starting with a full MMRM with progression status, treatment arm, presence of AE of grade 3 or higher, presence of a VTE, and an interaction of treatment with progression status, are provided below.

Step 1: Covariance structures

Three covariance structures were tested: unstructured, Autoregressive(1), and compound symmetry. The unstructured model did not converge and was therefore not considered when fitting the full MMRM. The statistical fit of the compound symmetry and Autoregressive(1) covariance structures were explored, with the AIC score indicating that the Autoregressive(1) structure was a better fit and therefore used to model the full MMRM (Table 2).

Table 2. Statistical fit of covariance structures explored when fitting MMRM

Fit Statistics	Compound Symmetry	Autoregressive(1)
AIC	[redacted]	[redacted]

Step 2: Coefficient estimates from the full MMRM and the selecting of appropriate parameters based on statistical significance

Coefficient estimates from the model with Autoregressive(1) covariance structure are presented in Table 3.

Type 3 Tests of Fixed Effects was computed to explore the significance of all the parameters in the full MMRM (Table 4). The parameters that were not statistically significant were removed from the MMRM (Table 5). For the purpose of this exercise, the interaction term (treatment*PD status) was removed as it was not statistically significant, but the PD status parameter was included in the final MMRM in order to inform the progression-free utility values. The coefficient estimates of the updated MMRM are presented in Table 5.

Table 3. Coefficient estimates of the full MMRM using the Autoregressive(1) covariance structure

Solution for Fixed Effects							
Effect	**Planned Treatment for Period 01**	**Status progression**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]					
	[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]				

Table 4. Results of Type 3 Tests of Fixed Effects

Type 3 Tests of Fixed Effects						
Effect	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
[redacted]						

Table 5. Coefficient estimates of parameters that were statistically significant based on Type 3 Tests of Fixed Effects

Solution for Fixed Effects							
Effect	Planned Treatment for Period 01	Status progression	Estimate	Standard Error	DF	t Value	Pr > |t|
[redacted]							

Step 3: Type 3 Tests of Fixed Effects for final selected parameters for inclusion in MMRM

The p-value results of the Type 3 Tests of Fixed Effects for the final selected parameters informing the MMRM model are presented in Table 6.

Table 6. Results of Type 3 Tests of Fixed Effects for final selected MMRM

Type 3 Tests of Fixed Effects						
Effect	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
[redacted]						

The mean PF utility estimate without AEs (the health economic model already accounts for adverse event related disutility) for osimertinib monotherapy, based on the model, is [redacted], versus [redacted] for amivantamab-lazertinib, and utility difference between both treatments of [redacted]. Based on a systematic literature review conducted by Cheng et al., 2024, the difference reported in the selected MMRM (Table 5) is likely to be considered below the EQ-5D MID for non-surgical

patients.[3] Therefore, the results suggest that the difference reported in the MMRM presented here are not clinically meaningful.

Furthermore, as explained in response to question B16, the PF utility for osimertinib monotherapy is higher than the pooled value currently used for both arms in the model ([redacted]) and it is also higher than the average utility of the general population for the age group of interest (age 55–64 years: 0.799).[2] Additionally, it is higher than the value previously accepted by the NICE Committee in appraisals in advanced EGFR-mutated NSCLC (0.794 [TA654 and ID6328]).[1, 2]

Another consideration is the difference in utility values between pre- and post-progression states in the selected MMRM model. The difference of <0.01 further demonstrates that the utility values derived from this model are not clinically plausible and therefore do not appropriately capture the true impact of disease progression for patients eligible for treatment within this indication.

B19. PRIORITY Please adapt the model so that treatment arm specific utilities can be applied to both pre- and post-progression as doing so will allow the EAG to explore alternative assumptions should these be supported by the analysis of utility data requested in question B18.

As outlined in response to Questions B16 and B18, an MMRM was run as requested and is provided above. However, given the resulting mean PF utility estimate was higher than the expected utility value for the general population (age 55–64 years: 0.799), the pooled value currently used in both arms of the model ([redacted]), and the value previously been accepted by the NICE Committee in appraisals in advanced EGFR-mutated NSCLC (0.794 [TA654 and ID6328]), altering the model base case is inappropriate, not considered clinically meaningful and therefore not explored as an alternative scenario.[1, 2]

References

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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 920 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 12 months we have received £3,508 from Janssen to cover some of our patient support activities.

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. 920 members we are able to present a representative view of the experience of living with EGFR mutation positive lung cancer. We also ran two surveys with our membership exploring the experiences of EGFR+ patients in the UK in terms of their diagnosis, treatment, surveillance and wellbeing (*n*s for both were > 200). For this submission I have drawn on the experiences of our EGFR patient members, 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?	A diagnosis of EGFR-positive non-small cell lung cancer (NSCLC) has a profound and multifaceted impact on patients and their families, affecting them physically, emotionally, socially, and economically. This type of lung cancer is often diagnosed in younger individuals who are non-smokers, many of whom are still working and have dependent children, making the diagnosis particularly devastating. **Emotional and Psychological Effects** Patients often describe feelings of shock, fear, and isolation upon diagnosis. One patient, diagnosed at 39, shared, *"When I was diagnosed, I felt like my world crashed down around me. I was terrified, and completely overwhelmed – I just didn't know what to do."* Another patient (aged 43) said *"I was completely shocked and devastated. It's strange… if someone has said I had breast cancer, I'm not sure it would have been so shocking. But as someone who has never smoked, being told I had lung cancer just blind-sided me completely. I just feel so scared and so alone."* Patients and their families also often describe feelings of immense sadness and guilt, while grappling with the uncertainty of the future. For example, one patient reflected on the potential loss of milestones with their children: *"I feel like my future has been ripped away from me. I was supposed to watch my children grow up, to watch them go to school, and university, to fall in love, get married, maybe have children of their own. How is it that I'm not going to be there for all of that?? And worse than that – I'm supposed to be here to protect them. How is it that I am going to be the one that causes them pain? I just don't have words…"* These quotes highlight the magnitude of the impact of a lung cancer diagnosis on psychological wellbeing. This impact is reflected in our annual survey of EGFR+ UK members (n=234), which showed Anxiety and depression are common amongst patients. In this 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 is associated with 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. **Disease status, treatment and distress** Common sources of distress for EGFR patients is the status of their disease, and the limited number of treatment lines available to them. For example, the fear of progression and/or recurrence of disease is enormous, and has a significant psychological burden on the patient and their families. One patient said:

	"I know my treatment is keeping the cancer cells sleeping, but I can't help but wonder when they are going to wake up. I feel like I'm a ticking timebomb – it's only a matter of time before it progresses… and then what? I just want more time." The uncertainty and limitations around treatment options is also commonly talked about by members, with one patient saying: *"I am struggling with my diagnosis at the moment. I keep reading that the average time on treatment is about 18 months – what happens next? Is there anything else available, or is it just chemo? It's so stressful knowing there isn't really anything else to help me."* These quotes highlight the worry patients and loved ones have as a result of the limited number of treatment lines that are available in the UK, and the longevity of those available. It is our hope that more NICE approved treatment lines will become available in the UK, so that patients will be able to live longer and longer, while still maintaining active lives. **Impact on family life:** The disease also disrupts family and work life, and places a significant financial burden on households. Normal activities, such as holidays, are curtailed, and family income often decreases. Family members often bear the brunt of caregiving responsibilities, which can affect their employment, education, and mental health. For younger family members, the strain can influence their life choices and affect their education, which may have a long-lasting impact. For patients who are carers themselves, the implications are particularly severe. One patient, a full-time carer for her husband, highlighted that if her cancer recurs, her husband would require residential care, significantly impacting both their family and healthcare costs. Additionally, brain metastases are common with EGFR mutations, which often leads to patients needing to surrender their driving license. This means they may be less able to able to support family activities, and often feel like a burden on others, which impacts hugely on patient quality of life. For example, one patient said: *"Losing my license has honestly been one of the hardest things I've had to deal with since my diagnosis. It hasn't just impacted me, but it's impacted our whole family. I can't take our children to parties and clubs and things. I*

	have to rely on my partner to drive them everywhere – and me, which makes me feel like a massive burden. It feels like my freedom has been stripped away from me." Having treatment options that can impact on brain metastases, in addition to the primary cancer, is often seen as a priority for EGFR patients.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Our abovementioned survey showed that the majority of our members are diagnosed with Exon 19 or 21 mutations, and that 77.7% of respondents were being treated with a TKI – most commonly Osimertinib (which is the current standard of care). Osimertinib is generally viewed extremely positively amongst our membership, and it is very well tolerated. Taking a single tablet once a day is seen as convenient and does not disrupt day-to-day life. However, side effects are common. In a recent survey exploring the impact of side effects of TKIs among our members (n=204), we found some of the most common side effects were: dry skin, fatigue, diarrhoea, muscle cramps, rashes/acne, difficulty sleeping, sexual issues, paronychia. Additionally, many of these side effects were seen as significantly distressing. However, patients and carers overwhelmingly view Osimertinib in a positive light (many referring to is as their "magic medicine") and feel these side effects are worth it, given the extra time and quality of life it affords them. The main concerns that patients and loved ones have (as highlighted above) are in relation to the relatively few treatment options/lines available to them, and the longevity of treatment. May patients worry that the median time on Osimertinib is only around 18 months. There is an overwhelming fear about the limited time TKIs give them, knowing that their cancer is likely to develop a resistance mechanism and progress. They hope for more treatment lines, and more choice about options that can potentially help to prolong their lives – however, quality of life (not just quantity) is a key priority for patients.
8. Is there an unmet need for patients with this condition?	Yes. As mentioned above, there are limited treatment options available to EGFR patients, and those that do exist only work for a limited amount of time. 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.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	On our patient forums we often summarise results of recent research. Since reporting on the results of the MARIPOSA trial which showed a significantly improved PFS with the combination of Amivantamab and Lazertinib (median = 23.7 months) compared to Osimertinib (median = 16.6 months), we have had a considerable number of 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 effects, patients' main priority seems to be the existence of efficacious treatment options, which are currently lacking. Patients are also particularly positive about the fact that the addition of Lazertinib adds protection to the brain, and potential treatment of brain mets – which is a particular concern for EGFR patients. From our patient support forums, we already know that some of our patients are receiving Amivantamab (with or without Lazertinib) either through trials, or through expanded access programs. Generally, this treatment is well received by patients who are taking it (albeit with dose reduction in some cases) – 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 availability. For example, in the last week one patient contacted us to say: *"Why is the UK so behind? I can see that this is already approved by the FDE and in the EU. How can we get it here too?"*

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The main disadvantages of this treatment relate to the mode of delivery (i.e. in hospital, via IV) and the side effects associated with the combination treatment. EGFR patients often comment on how IV treatments are more disruptive to day-to-day life than taking TKIs: *"With osi on its own, I can just take it at home every day – I'm really glad I don't have to be tied to a hospital all of the time."* *"Going to hospital makes me feel like a cancer patient – taking tablets at home almost allows me to forget. Not that you can ever **really** forget."* However, in a recent online discussion about the MARIPOSA trial, patients discussed whether or not (given the choice) they would opt to take it, most patients felt that the inconvenience and side effects would be both manageable and worth it. *"I would definitely take AmiLaz. I know it looks to be a bit more toxic than Osi and it is a pain to go into hospital sometimes, but if it would buy me more time with my kids (without having to take chemo) I would 100% do it."* One major disadvantage of this treatment is that is only being considered in a first line setting. Many of our members are desperate to have further lines available to them after Osimertinib and want this treatment option to be considered in subsequent line settings – particularly as results from the Phase 1 Chrysalis trial (Cohort E) showed a durable clinical response to Amivantamab and Lazertinib (with an overall response rate of 36%, and median duration of response of 9.6 months) in patients who had progressed on Osimertinib. There is also some concern about what this combination treatment might mean for treatment options further down the line: *"If you have Amivantamab and Lazertinib as first line, will you still be able to have Osimertinib afterwards? And will it still work as well?"* As this demonstrates, there is a general feeling that more work needs to be done to improve access to treatments and to establish the best sequencing of treatment lines.

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 Amivantamab and Lazertinib 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. EGFR affects certain groups more than others (for example, it is more prevalent in women, and in Asian populations). Ensuring access to treatment and information about the treatment is relevant and understandable to these groups is essential. In addition, only untreated patients are included in the current appraisal, however there is a huge unmet need amongst patients who have previously received TKIs.

Other issues

13. Are there any other issues that you would like the committee to consider?	Please see above statements about the unmet need in subsequent treatment lines.
14. What would you consider to be the benefits and limitations of treatments that have different modes of administration?	While oral drugs (such as TKIs) have minimal impact on the day-to-day lives of patients and their loved ones, resistance inevitably occurs. Drugs administered by IV involve more time toxicity (which is the amount of time a person spends dealing with cancer treatment, time spent travelling, in clinics, hospitals and waiting rooms, receiving treatment and other time-related burdens). They are also often associated with more drug toxicity and side effects. These toxicities inevitably impact on quality of life. However, when side effects can be well managed and their use is associated with significant improvements in PFS and OS, patients often report that these additional burdens are worth it.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• EGFR is associated with significant psychological distress (including anxiety and depression), some of which is related to the lack of longevity associated with the current standard treatment, and the limited number of treatment options available. • Having a new treatment line, which has proven efficacy, is likely to have a positive impact on patients' wellbeing and quality of life. • Patients would welcome a new treatment that increased PFS (and likely OS) beyond that which is currently available. • Amivantamab and Lazertinib should also be considered for use in pre-treated patients • Some questions were raised about what subsequent treatment options would be available if a patient had taken Amivantamab and Lazertinib as first line treatment.

Thank you for your time.

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Single Technology Appraisal

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

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
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) - 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; £1820 Advisory board Honoraria) - Roche (1 year funding of GLCC project; £10,000 for Lung cancer Awareness Month initiative) - Novartis (£30,000 for 1 year funding of GLCC project); £3656.50 for 4 Advisory Boards and Quarterly Consultations) - Novocure (£30,000 for1 year funding of GLCC project) - Pfizer (£30,000 for 1 year funding of GLCC project) - Astra Zeneca (£30,000 for 1 year funding of GLCC project; £500 for Meeting Honorarium) - Daiichi Sankyo (£30,000 for 1 year funding of GLCC project; £131.50 for Advisory Board Honorarium)

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	- Takeda (£30,000 for 1 year funding of GLCC project; £260 Speaker honorarium) - Regeneron (£30,000 for 1 year funding of GLCC project) - Gilead (£30,000 for 1 year funding of GLCC project; £460 speaker honorarium) - Merck (£30,000 for 1 year funding of GLCC project) - J &J (£20,000 for Lung Cancer Awareness Month initiative)
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. We do not have any additional data, beyond n

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?	EGFR mutation is found in about 10 to15% of US/European lung cancer patients. These patients tend to be younger and more likely to be light/non-smokers, as compared to the general lung cancer population. With that in mind, it is our observation that, though a younger, fitter patient group (fewer co-morbidities), EGFR mutation patients tend to be diagnosed later, as they do not fit the 'typical' lung cancer patient profile. Symptoms of advanced lung cancer, such as breathlessness, cough and weight loss are often difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. Recent years, with the development of Targeted Therapies for this EGFR mutation group has resulted in very much improved treatments. From a carer's perspective, it is, of course difficult to have a loved one diagnosed with advanced lung cancer.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The third generation EGFR TKI, osimertinib, is NICE approved in several indications, including in first line treatment of EGFR mutation positive lung cancer. The development of such targeted therapies has been a major step forward in the treatment of lung cancer. These oral therapies have been much better tolerated than traditional chemotherapy, with less time spent in hospital. Despite the high response rate, however, disease progression is likely to occur eventually. There is therefore a need for therapies with better outcomes.
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?	In the Phase III study, patents with previously untreated EGFR mutated locally advanced or metastatic NSCLC were randomly assigned to receive amivantamab-lazertinib or osimertinib. The median progression free survival was significantly longer in the amivantamab-lazertinib group than in the osimertinib group (23.7 months versus 16.6 months). 48% of patients in the amivantamab-lazertinib group were alive and free from disease progression at 24 months, compared with 34% in the osimertinib group.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Amivantamab was administered intravenously and osimertinib and lazertinib orally. Obvious disadvantages with intravenous administration. Disadvantages are with the side effects of the treatment. From the Study, it is noted that adverse events of grade 3 or higher were reported more often in the amivantamab-lazertinib group.

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 would you consider to be the benefits and limitations of treatments that have different modes of administration?	Ultimately this comes down to patient preference. There are obviously patients who would prefer to spend as little time as possible in the clinical environment. However, for some patients, the trade off of potential outcome benefits would be certainly worth more time at hospital and intravenous administration.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission.	• Despite the use of target specific EGFR TKIs, there is a need to improve therapies in this patient population. • In the study, progression free survival was significantly prolonged with the amivantamab-lazertinib combination, as compared with osimertinib.

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Single Technology Appraisal

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

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.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	British Thoracic Oncology Group
3. Job title or position	Consultant Medical Oncologist
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).	The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK. Funded by sponsorship and registration fees.
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.**	BTOG 2024 Platinum Sponsorship £30,000
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 delay progression and improve survival in patients with metastatic / advanced lung cancer. This should improve quality of life through control of cancer.
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.)	To improve progression free survival by 3 months Stabilisation or shinkage of the tumour
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Front line EGFR-targeted therapy. Most frequently 3rd generation EGFR inhibitor Osimertinib.
9a. Are any clinical guidelines used in the	European Society of Medical Oncology Guidelines for Oncogenic-addicted non-small cell lung cancer: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-lung-and-chest-tumours/clinical-practice-guideline-oncogene-addicted-metastatic-non-small-cell-lung-cancer

treatment of the condition, and if so, which?	
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.)	Yes, until this point the pathway of care is well defined.
9c. What impact would the technology have on the current pathway of care?	Rather than starting an oral targeted therapy, they would start an oral therapy in addition to an intravenous bispecific antibody. This is different as it requires chemotherapy / SACT chair time on chemotherapy units. Previously these patients would only require intravenous anti-cancer therapies after 1st line treatment.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is not currently in use in NHS clinical practice.
10a. How does healthcare resource use differ between the technology and current care?	+ The first cycle of amivantimab (intravenous) is delivered over 2 long days due to the risk of infusion reactions. In some units, for some patients (depending on travelling arrangements) may require an overnight stay on inpatient unit. + This is an intravenous therapy delivered alongside an oral therapy in a cohort of patients that typically in the first line setting only previously had an oral based therapy. This has impact on chemotherapy unit capacity / resource. + The combination of treatments means the toxicity profile is increased and as such may require additional clinical input and appointments to treat these toxicities + The intravenous therapy is delivered more frequently than the oral current standard of care. This requires additional outpatient appointments.

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care under the supervision of an oncologist.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Chemotherapy unit capacity Outpatient capacity (for toxicity reviews and clinical checks while on treatment)
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, in a cohort of patients.
11a. Do you expect the technology to increase length of life more than current care?	Overall survival data is not mature.
11b. Do you expect the technology to increase health-related quality of life more than current care?	An improvement in PFS should see an improvement in health-related quality of life due to the delay in deterioration of health due to progressive disease. This may be at the up-front expense of increased toxicity profile of this combination approach / technology.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Utilisation of this technology may offer a chemotherapy-free approach (reserving the need for chemotherapy to 2nd line treatment) and may be desirable for some patients. High risk patients with brain mets / liver mets / ctDNA positive disease with high burden of disease may benefit from a combination approach with improved depth of response. However, the increased toxicitiy profile and commitment to hospital attendences (compared to current standard of care of oral Osimertinib) may see a group of frail or elderly patients that may be less effective for due to the impact in quality of life.

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.)	It is more difficult than current standard of care due to requirement of intravenous administration of therapy on a chemotherapy unit. This has time and resource implications. Furthermore there is a delay to starting treatment due to the wait for treatment suites to start. This is compared to current standard of care oral Osimertinib that can often be started the same day as the clinical consultation / consenting. There are additional toxicities, as such supportive medications (particularly skin toxicity, infusion reactions and risk of VTE) and subsequent specialty input for more complex / higher grade toxicities (eg dermatologists, haematologists) may be required.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Regular CT scans to track disease and toxicities under control Nothing in addition to standard of care.
15. 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?	No

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?	I think the technology should be an option to control high burden disease / high risk disease that requires rapid disease control. It is innovative in this way in its potential to make a significant impact on health-related benefits. Rapid control of disease should result in improvement in quality of life.
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?	Chemotherapy-free option for high risk / high disease burden EGFR mutant lung cancer
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?	As previous: Skins toxicities – requiring prophylactic supportive medications Increased risk of infusion reactions – requires a long 2 day infusion for cycle 1 (+/- overnight stay) Increased risk of venous thromboembolism All are at risk of impacting the patient's quality of life.

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?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Progression free survival, Overall Survival, response rate and quality of life – yes all measured
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	PFS was used as primary outcome. Unclear if this is suitable surrogate as OS, which was measured as a secondary endpoint.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. Mains AEs noted above. Note 10% discontinuation rate due to AEs reflective of these higher grade toxicities
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Use of amivantimab as a subcutaneous formation. This has desirable toxicity, resource and quality of life features.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of	Use of first line Osimertinib in combination with platinum doublet chemotherapy (FLAURA2 trial)

NICE technology appraisal guidance [TA654]?	
21. How do data on real-world experience compare with the trial data?	Not aware of any real-world evidence / experience. However, in real world will need close tracking of toxicity profiles, as these are often higher in real-world experiences

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. What treatments would amivantamab with lazertinib displace if it were recommended? *If possible would you be able to estimate market shares of any treatments displaced*	This would be a treatment option as front line therapy for EGFR mutant lung cancer. Aim to delay progression / resistance generation. It wouldn't replace front line oral TKI (Osimertinib) but be an option for those with high risk / burdern disease at baseline who have a suitable performance status / co-morbidity profile. I suspect this could be used in up to 30 – 40% of current EGFR mutant disease (compared to current comparator Osimertinib, not accounting for FLAURA2 data).

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• A new chemotherapy-free up-front option for patients with high risk EGFR mutant lung cancer. This will not be an option for every patient • Extended PFS / delayed PFS may confer to improvement in quality of life for some patients through delaying development of resistance through a combination approach • Increased resource requirements compared to current SOC due to intravenous nature of this combination (chemotherapy unit, clinic reviews) • Increased toxicity profile also means careful patient selection and pro-active toxicity management • Consideration also needs to taken with the FLAURA2 data

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Single Technology Appraisal

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

Professional organisation submission

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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.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of Respiratory Nurses
3. Job title or position	Lung Cancer Specialist Nurse
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).	The Association of Respiratory Nurses (ARNS) was established in 1997 as a nursing forum to champion the specialty respiratory nursing community, promote excellence in practice, and influence respiratory health policy. ARNS also works to influence the direction of respiratory nursing care.
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.**	No
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.)	Improve progression free survival, improve quality of life, improve symptoms
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.)	Reduction of disease burden, no further progression of disease following commencement of treatment.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are a number of treatment options for this patient group but a further option will provide an alternative.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Erlotinib, afatinib, Osimertinib, gefitinib, dacomitinib, chemotherapy
9a. Are any clinical guidelines used in the	654, 595, 310, 258, 192

treatment of the condition, and if so, which?	
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.)	Yes, some professionals choose different options but largely well defined plan of care
9c. What impact would the technology have on the current pathway of care?	More treatment options
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes
10a. How does healthcare resource use differ between the technology and current care?	No difference
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Training of oncology nurses to administer the drug. Education to oncologists and pharmacists to understand the regime and protocol. Resource in pharmacy to produce the correct drug mix for patients.

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	EGFR mutation dependent

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	Should be comparable to administering current medications.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	EGFR mutation status
15. 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?	Progression free survival may also bring increased quality of life
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
16a. Is the technology a 'step-change' in the management of the condition?	No

16b. Does the use of the technology address any particular unmet need of the patient population?	No
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?	Similar side effect profile to other TKIs

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?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Life expectancy, progression free survival quality of life
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical	n/a

trials but have come to light subsequently?	
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 comparator treatment(s) since the publication of NICE technology appraisal guidance [TA654]?	No
21. How do data on real-world experience compare with the trial data?	n/a

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.	No

Topic-specific questions

23. What treatments would amivantamab with lazertinib displace if it were recommended? *If possible would you be able to estimate market shares of any treatments displaced*	unsure

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Additional option for EGFR positive patients • Trial shows improvement in survival • • •

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Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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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.

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 **14 April 2025.** 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.

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Part 1: Treating previously untreated EGFR positive 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	Adam Januszewski
2. Name of organisation	British Thoracic Oncology Group
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 lung cancer? ☒ A specialist in the clinical evidence base for 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
8. What is the main aim of treatment for untreated EGFR positive non-small-cell lung cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To delay progression and improve survival in patients with metastatic / advanced lung cancer. This should improve quality of life through control of cancer. Delay intracranial progression (a significant issue in patients with EGFR mutant lung cancer)

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)	To improve progression free survival by 3 months Improved Overall survival by >3 months Stabilisation or shinkage of the tumour
10. In your view, is there an unmet need for patients and healthcare professionals in untreated EGFR positive non-small-cell lung cancer?	Yes
11. How is untreated EGFR positive non-small-cell lung cancer 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?	Front line EGFR-targeted therapy (typically Osimertinib) vs. recently NICE approved Osimertinib in combination of chemotherapy NICE ID3628 Most frequently 3rd generation EGFR inhibitor Osimertinib. NICE guidelines: NG122 Until recently there was a well defined pathway. The recent publication of NICE ID3628 gives option of combination chemo with Osimertinib in the first line setting. This improves outcomes, but it is unclear which population in reality will derive most benefit from this regimen given its increased toxicity profile. This technology gives an additional first line option for patients with EGFR mutant lung cancer that is a chemotherapy-free option. In terms of impact of pathway, this is now less so since the introduction of Osimertinib with chemotherapy – as they are both oral and intravenous formulations. While it is a significant impact compared to historical standard of care (front line single agent oral Osimertinib) this is less different compared to NICE 3628 Note this is for common (L858R and exon19 deletion) EGFR mutations

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)	This is not currently being used in the NHS. This would be an additional option in the front line setting. With the recent approval of Chemo-osi, this technology will have reduced impact on healthcare resource as they both require chemotherapy chair time. The difference between osi (single agent) and this technology is – intravenous chair time for D1 and D2 of C1 and then 2 weekly intravenous chair time ongoing. There are increased toxicities (infusion related reactions) and dermatology toxicities. This means increased outpatient clinic attendances (prior to each cycle) and also management of these toxicities. Compared to the recent approval of chemo-osi, which is delivered every 3 weekly – there is increase chemo chair time compared to this. For this technology: additional OP appointments, additional chair time
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 – compared to single agent Osimertinib. There is clear benefit in survival / PFS across all sub-groups of patients with EGFR mutant lung cancer. There is no head to head trial comparing the chemo-osi combination with this technology. It provides a treatment intensification with improved outcomes that is chemotherapy-free

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The data demonstrates that across all sub-groups there is benefit in OS and PFD. Whether all patients will be suitable for treatment intensification (with associated toxicities) may be dependent on performance status and co-morbidities. It will be a balance of toxicity profile, patient preference and effectiveness. Clinicians may opt for intensification of treatment with this technology in patients with higher risk of poor outcomes (eg brain mets, liver mets, TP53 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 patient acceptability or ease of use or additional tests or monitoring needed)	2 day infusion for C1 with risk of infusion reactions increases complexity of treatments and resources. Infusion is then weekly until week 5 and then 2 weekly beyond that time. Dermatological toxicities are recognised, although pro-active management with supportive medications (demonstrated in the CACOON trial) should mitigate this to some degree. Increased frequency of infusions will require increased chair time.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
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. Increasingly oncogenic mutant lung cancer with oligo-progression are managed with loco-ablative therapies (such as radiotherapy) to enable patients to remain on treatment that is controlling the remaining of their disease for longer. This could have an impact on patients duration on treatment (whether that be this technology or other treatments in this space) and may be reflected in patients who are treated 'beyond progression'.

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 condition? • Does the use of the technology address any particular unmet need of the patient population?	This, along with NICE 3628, together will make a significant and substantial improvement in outcomes for this cohort 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?	Dermatological toxicities are recognised, although pro-active management with supportive medications (demonstrated in the CACOON trial) should mitigate this to some degree. Infusion related reactions (IRR) are a recognised complication, particularly in the 1st cycle. This in part is the reason for splitting the dose across 2 days on C1. Pre-medications are required to prevent this in addition to those required in response to an IRR. Recognised increased risk of VTEs These toxicities should be reduced through the use of preventative medications.
20. Do the clinical trials on the technology reflect current UK clinical practice? • 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?	Yes. Most important outcome: Overall Survival and Quality of Life measures – yes they were measured.

• 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?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	CACOON trial (data presented at ELCC) looking at prophylactic dermatological management
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA654]?	No
23. How do data on real-world experience compare with the trial data?	It will be important to consider patients fitness and co-morbidities. As is clear across all trials (not exclusive to this trial) that patients have better performance status and fewer co-morbidities in trials when compared to real-world experience. This will be important in this technology to enable to right selection of patients with a regimen that has increased toxicities compared to historical control of Osimertinib (although this doesn't account for the new Chemo-Osi observed in NICE 3628 that also has increased toxicities)
24. NICE considers whether there are any equalities 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	No

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 • 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.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

An important step-wise improvement in outcomes for patients with common EGFR mutant lung cancer when compared to historical control of single agent osimertinib

Increased resources required through delivery of intravenous component and management of toxicity profile

It provides a chemotherapy free treatment intensification. It will not be suitable for all patients in the front line setting and there is still debate amongst the clinical community around who will be the most appropriate patients for this technology. This revolves around fitness of patients, risk of disease and toxicity profile.

In the frontline setting the option of this technology and Chemo-IO remains an open question with no head-to-head comparisons

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

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

In part 1 we are asking you about living with untreated EGFR positive non-small-cell lung cancer or caring for a patient with untreated EGFR positive non-small-cell lung cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **14 April 2025.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with lung cancer

Table 1 About you, lung cancer, current treatments and equality

1. Your name	Virginia (Gini) Harrison
2. Are you (please tick all that apply)	☒ A patient with lung cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with lung cancer? ☒ A patient organisation employee or volunteer? ☐ 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)	☐ 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: discussions with friends with EGFR lung cancer, and researcher into patient wellbeing ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

Patient expert statement

	☒ 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 lung cancer? **If you are a carer (for someone with lung cancer) 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. When I was first diagnosed, I was shocked and terrified by the lack of treatment options for EGFR+ Lung Cancer in the UK – and I still am. This uncertainty has caused an immense stress and upset, which can dramatically impact my quality of life, and that of my family. 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.
7a. What do you think of the current treatments and care available for untreated EGFR positive non-small-cell lung cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Current treatment for EGFR+ lung cancer involves taking the tyrosine kinase inhibitor (TKI) Osimertinib. Most of us view this treatment very positively as it is pretty well tolerated, and the convenience of taking a single tablet once daily allows many of us to maintain a degree of normalcy in our daily lives. A big advantage is less time in hospital being 'done to' i.e. the clinical staff administering the treatment at a time and in a way that fits with their workload and schedule. The side effects of Osimertinib are much less than the older generation TKI's and certainly less than Chemo.

8. If there are disadvantages for patients of current NHS treatments for untreated EGFR positive non-small-cell lung cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	In terms of disadvantages, there are a number of side effects that TKIs can cause. Fatigue can be one of the toughest side effects-it's more than just tiredness, it's a deep, dragging exhaustion. Patients also often get dry skin, a persistent rash, sore nails, digestive issues, and changes to their hair and taste… which can really affect confidence and self esteem. The emotional toll is real too—managing all these side effects while trying to live life can feel overwhelming. There is also considerable anxiety about the future. One of the most worrying issues is that resistance to Osi is likely to happen - and most of us have seen the research that suggests this is (on average) after only 16-18 months. This doesn't feel like enough time and uncertainty around this is a deep source of worry. Not knowing what comes next is also a huge concern – there just aren't enough treatment lines in the UK. However, we can see from the US and other countries that other treatment options are available which can be sequenced, or which have longer effectiveness. Knowing that there are other treatments that may be more effective than the one you are on can be very upsetting. And seeing that there are other treatment lines available in other countries but not here leads to a sense of unfairness and can make you feel utterly helpless. We are hopeful for more treatment lines and greater choice in therapies that can extend life while preserving its quality. For patients, it is not simply about having more time — it is about ensuring that time is lived well.
9a. If there are advantages of amivantamab with lazertinib 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?**	The main advantages are that it has a longer progression free survival, and adds another treatment option to those available. This gives a lot of hope that patients might be able to continue to live their lives for longer, and make more memories with loved ones. This is likely to dramatically improve quality of life.

9c. Does amivantamab with lazertinib 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	Yes – it makes a more efficacious treatment available to EGFR patients.
10. If there are disadvantages of amivantamab with lazertinib over current treatments on the NHS please describe these. For example, are there any risks with amivantamab with lazertinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The main issues are that (1) patients will need to go into hospital to receive IV treatment, rather than simply taking a daily tablet at home, which will cause more disruption to their lives. And (2) that the drugs are likely to be more toxic than Osi alone. I'm quite worried about the scalp rashes that seem difficult to manage.
11. Are there any groups of patients who might benefit more from amivantamab with lazertinib 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	Given this drug combo is more toxic, there might be some people who are too frail to take it.
12. Are there any potential equality issues that should be taken into account when considering lung cancer and amivantamab with lazertinib? 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	See EGFR's submission

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.	
13. Are there any other issues that you would like the committee to consider?	Patients have some questions about sequencing of treatments – that is, what happens if they take this option first. Will they be allowed Osi after that? And does this have any effect on efficacy? It's a question that matters a lot when you're trying to plan for the unknown.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Living with EGFR-positive lung cancer can be really tough mentally—partly because we know there aren't many treatment options out there, and what's currently available doesn't always give us long-term stability or hope for the future. Having something else that might help can lift a huge emotional weight.
- A treatment that can help patients stay stable for longer means more time living lives without things getting worse, which is so important.
- There is some uncertainty about what impact this treatment option will have on subsequent treatment options and efficacy.

Thank you for your time.

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Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer [ID6256].
A Single Technology Appraisal

Produced by: Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield

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

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Rider on responsibility for report

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

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Contributions of authors

Sarah Davis was project lead. Emily Pulsford critiqued the company's search strategy. Munira Essat critiqued the clinical effectiveness evidence reported within the company's submission. Sarah Ren critiqued the statistical aspects of the submission. Sarah Davis and Sunhong Kwon critiqued the health economic analysis submitted by the company and undertook additional exploratory analyses. All authors were involved in drafting and commenting on the final report.

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ABBREVIATIONS

2L	Second-line
3L+	Third-line or later
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike information criterion
ALK	Anaplastic lymphoma kinase
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BSA	Body surface area
cEGFR	Common epidermal growth factor receptor
CI	Confidence interval
CNS	Central nervous system
CS	Company submission
CR	Complete response
CT	Computed tomography
CTPA	Computerised tomography pulmonary angiography
DCO	Data cut-off
DOR	Duration of response
DVT	Deep vein thrombosis
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFRm	Epidermal growth factor receptor -mutated
eMIT	Electronic market information tool
ESMO	European Society for Medical Oncology
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life questionnaire
EQ-5D-3L/5L	Euroqol 5-Dimensions 3 Level / 5 Level
FAS	Full analysis set
GP	General practitioner
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

ILD	Interstitial lung disease
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LYs	Life years
MET	Mesenchymal-epithelial transition factor
MMRM	Mixed-effects model for repeated measures
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analysis Service
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PE	Pulmonary embolism
PF	Progression-free
PFS	Progression-free survival
PR	Partial response
PRO	Patient reported outcome
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PS	Performance status
PSA	Probabilistic sensitivity analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RECIST	Response evaluation criteria in solid tumours
RCT	Randomised controlled trial
RWE	Real-world evidence
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal

TA	Technology Appraisal
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TTNT	Time to next therapy
TTSP	Time to symptomatic progression
TTST	Time to subsequent therapy
VTE	Venous thromboembolism

1 EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses amivantamab with lazertinib for untreated epidermal growth factor receptor (EGFR) mutation-positive (exon 19 deletion or exon 21 L858R substitution) advanced non-small-cell lung cancer (NSCLC). The company submission (CS) states that the most relevant comparator is osimertinib, which is recommended for this population under Technology Appraisal (TA) 654.[1] Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI). First-generation and second-generation TKIs are also recommended for the first-line treatment of EGFR mutation-positive advanced NSCLC (gefitinib in TA192, erlotinib in TA258, afatinib in TA310, dacomitinib in TA595). However, the company does not consider these to be relevant comparators as they state that osimertinib is the preferred first-line treatment in current clinical practice. The National Institute for Health and Care Excellence (NICE) scope also listed osimertinib with chemotherapy as a potential comparator.[2] This treatment combination is subject to an ongoing NICE appraisal, the outcome of which was unknown at the time of the CS. However, the company did not consider this to be a relevant comparator as the draft guidance for osimertinib with chemotherapy available at the time of the CS was negative and the company did not consider it to be an established treatment option within clinical practice.[1] The key evidence presented in the CS was the MARIPOSA trial which was a randomised controlled trial (RCT) comparing amivantamab with lazertinib against osimertinib,[3] which the company considers to the be only relevant comparator. No evidence was presented in the CS comparing amivantamab with lazertinib to any of the other comparators listed in the NICE scope.

This executive summary provides a brief overview of the key issues identified by the EAG as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) which are specified in terms of cost per quality-adjusted life-year (QALY). The results presented in this report include the patient access scheme (PAS) prices for amivantamab and lazertinib and the list prices for comparator technologies, as the PAS prices for comparator technologies are confidential and cannot be shared with the company. The cost-effectiveness results when using confidential comparator PAS prices are included in a separate confidential appendix. The company has provided an assessment of the proportional and absolute QALY shortfall, which is used to determine the appropriate severity modifier for decision making. However, the company's assessment of QALY shortfall supported a QALY weighting of 1.0. Therefore, all ICERs are presented without any modification for severity.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest impact on the ICER. Sections 1.3 to 1.6

explain these key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main report (Sections 2 to 6).

The EAG notes that the company provided additional data in an addendum at the time of the factual accuracy check. These are critiqued in a separate addendum to this EAG report and this EAG report is based only on the information provided by the company in its original submission and in its clarification response. However, the EAG has indicated in this report where substantial sections are superseded by the additional data provided in the company addendum.

All issues identified represent the view of the EAG, and do not necessarily reflect the opinion of NICE.

1.1 Overview of the EAG's key issues

Key issues identified by the EAG that impact on the incremental costs and QALYs are summarised in Table 1. A fuller description of each issue, together with potential alternative approaches, the expected impact on the ICER of such approaches and additional evidence that would resolve the issue are contained in Sections 1.3 to 1.5.

Table 1: Overview of the EAG's key issues

ID 6256	Summary of issue (More detail is provided in Sections 1.3, 1.4 and 1.5)
Issue 1	The company has not presented a comparison against osimertinib with chemotherapy
Issue 2	Progression-free survival (PFS) and the majority of the safety data are only reported for the interim data cut-off (DCO)
Issue 3	Uncertainty around the modelling of time to treatment discontinuation (TTD)
Issue 4	Uncertainty in the long-term predictions for overall survival (OS)
Issue 6	Potential underestimation of administration costs for amivantamab
Issue 7	Use of treatment-independent utilities for the progression-free state

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers to apply alternative TTD curves that it considers provide a better statistical fit

- The EAG prefers to use treatment-specific utility values in the progression-free health state, whereas the company has applied the same utility for both arms based on a pooled estimate across both arms of the MARIPOSA trial

- The EAG prefers to apply a reference cost for intravenous (IV) administration of amivantamab that reflects an anticipated infusion time of greater than 2 hours, whereas the company's preferred reference cost is suitable only if the treatment delivery time is less than 60 minutes.

1.2 Overview of key model outcomes

NICE technology appraisals estimate how much a new technology improves length of life (OS) and quality of life, using QALYs. In the company's model, amivantamab with lazertinib increases QALYs compared with osimertinib by increasing expected OS. This results in additional life-years and additional QALYs being gained both pre- and post-progression, although the overall QALY gain is marginally reduced in size by an increased risk of adverse events (AEs). The company's model estimates that amivantamab with lazertinib will result in additional administration costs compared with osimertinib, and that the additional survival will be associated with additional costs for disease management, with smaller cost differences for AEs, subsequent treatments and end-of-life care. Overall, the company's model estimates that amivantamab with lazertinib will result in substantial cost savings, due to drug acquisition costs being much lower. However, this is because the PAS prices are applied for both amivantamab and lazertinib, but the list price is applied for osimertinib.

The modelling assumptions that have the greatest effect on the cost-effective estimates are:

- the choice of curve to extrapolate TTD
- the administration costs applied for intravenous (IV) infusion of amivantamab
- whether or not treatment-specific utilities are applied for the progression-free health state or the same pooled utilities are applied for both treatments.

The assumptions within the company's base-case modelling that the EAG believes are either incorrect, or uncertain, and that impact most on the incremental cost and QALY estimates, are discussed in more detail in Sections 1.3 to 1.5.

1.3 The decision problem: summary of the EAG's key issues

The key issues related to the decision problem are described here, with other issues discussed in Section 2.3. The EAG's only key issue relating to the decision problem, was the fact that the company did not provide a comparison against osimertinib with chemotherapy, which was described as a comparator in the NICE Final Scope but is subject to an ongoing NICE appraisal (Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced NSCLC ID6328). However, the importance of this omission will depend on the final outcome of that appraisal and the degree of uptake of that treatment option in future, if the appraisal results in positive guidance. The EAG's clinician advisers considered that osimertinib monotherapy was the comparator that most reflected current clinical practice.

Issue 1. The company has not presented a comparison against osimertinib with chemotherapy

Report section	2.3.3
Description of issue and why the EAG has identified it as important	The company has not presented a comparison against osimertinib with chemotherapy despite this being listed as a comparator 'subject to NICE appraisal' in the NICE final scope. The company argues that osimertinib with chemotherapy is not a relevant comparator because the appraisal of osimertinib with chemotherapy for untreated EGFR mutation-positive advanced NSCLC (ID6328) is still ongoing, and the draft guidance was negative and therefore this treatment combination is not part of current clinical practice.
What alternative approach has the EAG suggested?	The EAG would have preferred the company to have submitted evidence comparing amivantamab with lazertinib against osimertinib with chemotherapy which the committee would then be able to consider if the final guidance for osimertinib with chemotherapy were to be positive. However, the EAG acknowledges that the relevance of such a comparison is dependent on the outcome of ID6328.
What is the expected effect on the cost-effectiveness estimates?	The cost-effectiveness of amivantamab with lazertinib relative to osimertinib with chemotherapy is unknown.
What additional evidence or analyses might help to resolve this key issue?	The company could provide an indirect comparison to estimate the relative clinical effectiveness of amivantamab with lazertinib versus osimertinib with chemotherapy and an updated model to estimate the relative cost-effectiveness.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The key issues related to the clinical effectiveness evidence are described here, with other issues discussed in Section 3.

Issue 2. PFS and the majority of the safety data are only reported for the interim DCO

Report section	2.3.4 & 4.3.3.2
Description of issue and why the EAG has identified it as important	PFS and the majority of the AE outcomes are only reported for the 11th August 2023 interim DCO, despite data being available from a later DCO (13th May 2024) for the majority of the other outcomes reported including OS, TTD and the AEs informing the model.
What alternative approach has the EAG suggested?	The EAG would have preferred the company to have presented data from the most recent DCO available for all outcomes informing the submission. Whilst the AE data informing the economic model did reflect the 13th May 2024 DCO, the use of PFS data from the interim DCO (11th August 2023) in the economic analysis is considered to be a significant limitation.
What is the expected effect on the cost-effectiveness estimates?	The EAG analyses suggest that the cost-effectiveness estimates are not particularly sensitive to different long-term extrapolations for PFS, therefore, the impact on the cost-effectiveness estimates of including data from a more recent DCO for PFS may be small. However, changes in the within-trial PFS estimates may have a greater impact than changes in the long-term extrapolation, so the impact of incorporating the most recent PFS data remains uncertain.
What additional evidence or analyses might help to resolve this key issue?	The company indicated in its clarification response that it was working to provide an addendum to NICE with an updated final analysis for 'relevant outcomes'. The EAG welcomes this, and notes that ideally the cost-effectiveness evidence presented to the committee should be informed by the most recent DCO available for all outcomes informing the economic model (OS, PFS, TTD and AEs) as these all have the potential to influence cost-effectiveness.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The key issues related to the cost-effectiveness evidence are summarised in this section, with a focus on those issues that are most likely to affect decision making. In addition to these key issues, the EAG also identified and corrected some errors in the model which are not described in detail here (see Section 4.3.3.1). The EAG also had some concerns related to the resource use data applied in the model and to the modelling of venous thromboembolism (VTE) AEs. However, neither of these were considered to be key issues as they had a limited impact on the cost-effectiveness estimates in the EAG's exploratory analyses. These are further described in Sections 4.3.3.5 and 4.3.3.6 respectively. The EAG also had concerns regarding the use of PFS data from the 11th August 2023 DCO in the economic analysis. Whilst the EAG considers this to be a significant limitation that impacts the economic analysis, this issue has been previously described in Section 1.4, and is therefore not discussed further in this section.

Issue 3. Uncertainty around the modelling of TTD

Report section	4.2.4.2 & 4.3.3.2
Description of issue and why the EAG has identified it as important	The company has fitted individual TTD curves for the individual components of the amivantamab with lazertinib combination treatment and for the osimertinib monotherapy treatment. The EAG considers that the company's choice of curves to model TTD do not accurately capture the hazards of treatment discontinuation for amivantamab, lazertinib or osimertinib. This is because the company has chosen an exponential model which assumes constant hazards, which does not reflect the observed data for any of the three treatments.
What alternative approach has the EAG suggested?	The EAG prefers to use spline models (2-knots normal) to capture the complex shape for the hazards of discontinuation for amivantamab and lazertinib and a Weibull model for the non-constant hazards of discontinuation for osimertinib.
What is the expected effect on the cost-effectiveness estimates?	The company's choice of using an exponential TTD for each of the drugs leads to the costs of osimertinib being potentially overestimated and the costs of amivantamab with lazertinib being potentially underestimated. This results in the cost savings, predicted in the company's base-case analysis being potentially over-estimated (incremental costs of [redacted] for the company's base-case versus [redacted] when using the EAG's preferred TTD curves).
What additional evidence or analyses might help to resolve this key issue?	Although the company has fitted curves to the data from the later 13th May 2024 DCO for the TTD outcomes, the EAG believes that more complete TTD data will be available from the final trial DCO for which only headline OS results are currently available. The EAG would like to see the model updated with the more complete TTD data from the final trial DCO, as this would allow the curve selection to be refined. Although the EAG acknowledges that this may not be possible before the first committee meeting.

Issue 4. Uncertainty in the long-term predictions for OS

Report section	4.2.4.2 & 4.3.3.2
Description of issue and why the EAG has identified it as important	There is considerable uncertainty regarding the gain in long-term OS expected for amivantamab with lazertinib compared with osimertinib. This is in part due to the company's economic model not yet being updated to reflect the company's analysis of OS data from the final trial DCO. It is also due to the inherent uncertainty in the long-term OS predictions that results from the finite duration of the MARIPOSA trial, which will not be addressed by the updated OS analysis from the final DCO.
What alternative approach has the EAG suggested?	The EAG has explored alternative curves that assess the sensitivity of the cost-effectiveness estimates to uncertainty in the long-term OS. Whilst it has not incorporated these into its preferred base-case, the EAG considers that these represent plausible alternative extrapolations which are in keeping with the predictions of long-term survival provided by the company's clinical experts. The EAG has explored using a gamma distribution for OS for osimertinib and a 1-knot hazard spline model for OS for amivantamab with lazertinib, instead of the company's preference for a Weibull distribution in both arms. The EAG's alternative choices provide a higher 10-year OS prediction for osimertinib and a lower prediction for amivantamab with lazertinib.
What is the expected effect on the cost-effectiveness estimates?	The EAG's alternative curves for OS result in a large reduction in the incremental QALYs compared with the EAG's base-case ([redacted] versus [redacted]), demonstrating the sensitivity of the cost-effectiveness estimates to the long-term OS predictions.
What additional evidence or analyses might help to resolve this key issue?	Updating the model to reflect the OS outcomes from the final DCO of the MARIPOSA trial should reduce uncertainty in the long-term predictions of OS, although some uncertainty is likely to remain unless further data are collected.

Issue 5. Potential underestimation of administration costs for amivantamab

Report section	4.3.3.4
Description of issue and why the EAG has identified it as important	The company has applied a reference cost for amivantamab administration that assumes a total time for drug administration of under 60 minutes. However, information from a study comparing IV infusion to subcutaneous administration suggests an infusion time of greater than 2 hours for amivantamab. The company has also excluded any additional costs in the first week arising from the need for the first dose to be split over two days.
What alternative approach has the EAG suggested?	The EAG prefers to apply a reference cost that reflects an infusion time of over 2 hours for amivantamab. In addition, it has included an administration cost for the second half of the initial dose occurring on day 2 of cycle. 1.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analyses indicate that the company's assumption that amivantamab can be administered within 60 minutes, and at no addition cost when given as a split dose, has a large impact on the cost savings (incremental cost of [redacted] for EAG's preferred approach versus [redacted] for the company's base-case). This difference is mainly driven by the choice of reference cost with the additional administration cost for the split dose having minimal impact.
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider it necessary for the company to provide any additional information as there is already a study reporting administration duration for IV amivantamab.

Issue 6. Use of treatment-independent utilities for the progression-free state

Report section	4.2.4.3 & 4.3.3.3
Description of issue and why the EAG has identified it as important	The company has assumed equivalent utility values for patients in the progression-free state despite their regression analysis finding a statistically significant coefficient for treatment arm in their analysis of pre-progression utility data from the MARIPOSA trial. This regression analysis also accounted for the presence of grade ≥ 3 AEs and VTE AEs of any grade. Therefore, the EAG considers it likely that patients taking amivantamab with lazertinib have lower utility than those taking osimertinib even after accounting for the AEs which are accounted for separately in the model. This may be due to other lower grade AEs or due to the requirement for frequent hospital attendance for IV infusions for the amivantamab component of treatment.
What alternative approach has the EAG suggested?	The EAG prefers to use the utility values obtained from the company's regression analysis in the progression-free health state. It maintains the company's preferred utility value for progressed disease.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analysis demonstrates that using treatment specific utility values significantly reduces the incremental QALY gains estimated in the company's base-case analysis ([redacted] for the EAG's preferred utility values versus [redacted] in the company's base-case).
What additional evidence or analyses might help to resolve this key issue?	The EAG does not consider it likely that this uncertainty will be reduced by further evidence as the model is already informed by utility data from the 13th May 2024 DCO. The company indicates that AEs and treatment burden for amivantamab may be reduced if amivantamab can be given subcutaneously in future, but this is not the formulation put forward by the company in their CS for consideration by NICE.

1.6 Other key issues: summary of the EAG's key issues

No other key issues were identified.

1.7 Summary of EAG's preferred exploratory analyses

Table 2 provides the results from the EAG's exploratory analyses for amivantamab with lazertinib compared with osimertinib. Whilst amivantamab with lazertinib dominates osimertinib (provides higher QALY gains at lower cost) in all of the exploratory analysis presented (EA1 to EA6 and the EAG's preferred base-case), the analyses demonstrate that the cost-effectiveness estimates are sensitive to the uncertainties highlighted by the EAG in the company's calculation of drug administration costs, the company's choice of utility values for the progression-free health state, and the company's choice of curves for TTD extrapolation. The scenario analyses presented in Table 2 (ASA 1 to ASA5 which use the EAG's base-case as their starting point), also demonstrate, in particular, the sensitivity of the cost-effectiveness estimates to uncertainty in the long-term extrapolation of OS. The EAG notes that whilst all of the analyses presented in Table 2 indicate that amivantamab with lazertinib dominates osimertinib (i.e. has lower costs and higher QALYs), the analyses do not incorporate the confidential PAS discount for osimertinib and the EAG directs the committee to the confidential appendix for analyses incorporating all confidential drug prices (see Appendix 1, Table 66, for sources of prices applied in the confidential appendix).

Table 2: Results of the EAG's exploratory analyses

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Company's base-case, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
EAG EA1: Correction of model errors, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
EAG EA2: EA1 + Use of alternative TTD curves (two-knots normal spline models for amivantamab and lazertinib; Weibull model for osimertinib)							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
EAG EA3: EA1 + Applying treatment-specific utility							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
EAG EA4: EA1 +Applying administration cost with prolonged chair time							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Osimertinib	3.73	[redacted]	[redacted]				Amivantamab with lazertinib dominates
EAG EA5: EA1 + Applying frequencies of resource use from ID6328							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
EAG EA6: EA1 + Including the incidence of grade ≥ 3 DVT, account for proportion of Grade ≤2 VTE that are pulmonary embolism and EAG preferences for VTE costs, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
EAG base-case applying analyses 1-6, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
EAG base-case applying analyses 1-6, probabilistic							
Amivantamab with lazertinib	5.50	[redacted]	[redacted]	1.75	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.76	[redacted]	[redacted]				
ASA1: Use of the company's preferred administration cost							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
ASA2: Use of treatment independent utility values from TA654							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
ASA3: Use of two-knots normal spline model for TTD in osimertinib							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				
ASA4: Use of alternative distributions for OS (1-knot hazard for amivantamab with lazertinib, gamma for osimertinib)							
Amivantamab with lazertinib	4.88	[redacted]	[redacted]	0.79	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	4.10	[redacted]	[redacted]				
ASA5: Use of alternative distributions for PFS (gamma for all)							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Osimertinib	3.73	[redacted]	[redacted]				Amivantamab with lazertinib dominates

Abbreviations: ASA - additional sensitivity analysis; EA - exploratory analysis; DVT - deep vein thrombosis; ICER - incremental cost-effectiveness ratio LYG - life year gained; OS – overall survival; PFS – progression-free survival; TTD – time to discontinuation; QALY - quality-adjusted life year; VTE - venous thromboembolism

*Undiscounted

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

This Single Technology Appraisal (STA) focuses on the use of amivantamab with lazertinib as a first-line treatment for epidermal growth factor receptor (EGFR) mutation-positive (exon 19 deletion or exon 21 L858R substitution) advanced non-small-cell lung cancer (NSCLC). NSCLC is the most common form of lung cancer, accounting for 85% of all lung cancer cases.[4] In 2022, 66% of NSCLC cases were classed as advanced disease at diagnosis.[5] This means that the primary tumour is large or the disease has spread beyond the lungs to the lymph nodes or other organs in the chest (locally advanced; stage 3) or it has spread to other parts of the body (metastatic; stage 4).[6] Histological classification can also be used to describe NSCLC as either squamous-cell carcinoma, adenocarcinoma or large-cell carcinoma, with adenocarcinoma being the most common form across all lung cancers.[4] However, the emergence of treatments targeting specific mutations, such as tyrosine kinase inhibitors (TKIs) activating targeting EGFR mutations, means that patients are often classified based on the presence of particular mutations in their tumours. Patients with EGFR mutation-positive NSCLC make up approximately 10% of all UK cases of advanced NSCLC.[7] The two most common mutations are exon 19 deletion or exon 21 L858R substitution accounting for 85% of EGFR mutations.[7] Collectively, patients with either of these two common mutations are referred to as having common EGFR mutation (cEGFRm) NSCLC.

The EAG considers that Section B.1.3 of the CS provides a broadly accurate description of the underlying health problem. In this section, the EAG provides only a brief summary of the details from CS Section B.1.3, highlighting any inconsistencies identified from the cited sources or any limitations in the generalisability of the sources to the population addressed in the CS.

The CS states correctly states that lung cancer is, *"the leading cause of cancer death in the UK, with approximately 39,097 patients diagnosed with lung cancer in 2022 in England and Wales."*[1] However, the EAG disagrees with the company's statement that "*lung cancer is the most common malignancy,"*[1] as the sources identified by the EAG indicate that lung cancer is the second most common malignancy in both males and females, and the third most common cancer overall.[8, 9] NSCLC with cEGFR mutations is more commonly seen in people of Asian ethnicity, women and never-smokers.[10] The CS states that cEGFRm NSCLC is more common in younger patients and supports this statement through reference to a study that describes the median age for all lung cancer as being "*close to 70 years*",[11] and a study reporting the median age at baseline for the FLAURA trial as being 64 years.[12] The CS also describes the population with cEGFRm NSCLC as being generally younger than patients with other types of lung cancer, citing a mean age of 63.1 years (interquartile range 54.6-72.8 years). Although the EAG had some difficultly identifying the source of this latter figure, the EAG's clinical advisers confirmed that NSCLC patients with common EGFR mutations tend to be younger than other lung cancer populations.

The CS describes patients with cEGFRm advanced NSCLC as having a poor prognosis with a 5-year survival of 24%.[13] It also provides estimates of median overall survival (OS) from the National Cancer Registration and Analysis Service (NCRAS) real-world evidence (RWE) dataset. The CS notes that median OS in the NCRAS 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts receiving first-line osimertinib (28.1 months and 26.2 months, respectively) was considerably lower than median OS in the population recruited to the FLAURA RCT (38.6 months), which was the pivotal trial for first-line osimertinib use. The CS notes that median survival for patients with cEGFRm advanced NSCLC is lower than median survival for patient with other mutations.[14-16]

The CS describes how central nervous system (CNS) metastases, which are predictive of a worse prognosis,[17, 18] are common in patients with cEGFRm NSCLC, citing that 40% of patients had CNS metastases at baseline in the MARIPOSA trial.[3] A study examining the risk of developing CNS metastases in patients with locally advanced disease identified that patients with EGFR-mutated (EGFRm) NSCLC were at higher risk of developing CNS metastases than patients with EGFR wild type NSCLC (i.e. without EGFR mutations) independent of their lower competing risk of death.[19]

The CS describes NSCLC as having an impact on day-to-day activities in 84% of patients and an impact on emotional wellbeing in 60% of patients (CS, Figure 5), based on a survey of 43 patients conducted by the company.[20] The CS describes the humanistic burden of NSCLC in terms of patients experiencing reduced health-related quality-of-life (HRQoL) compared with the general population and those with other advanced cancers.[21] In a European survey of 1,030 patients with NSCLC, the majority of whom were receiving first-line therapy (70.5%), the utility calculated from the Euroqol 5-Dimensions 3 Level (EQ-5D-3L) was 0.84 and 0.74 in patients with performance status (PS) scores of 0 and 1, respectively, but was lower at 0.57 and 0.29 for those with PS scores of 2 and 3-4, respectively.[22] The main symptoms reported in patients with cEGFRm advanced NSCLC having first-line treatment are described as cough (61%), fatigue (61%) and pain in areas other than the chest (74%). However, this was based on a small qualitative study conducted by the company (N=36, of whom 23 were having first-line treatment).[20, 23]

The CS describes the impact of NSCLC on caregivers, stating that the mean time spent caring was 29.5 hours per week.[21] This was based on the same European survey which examined 427 informal caregivers of the 1,030 NSCLC patients recruited. However, the EAG notes that this estimate was based on a study conducted in France, Germany and Italy; the hours of care provided varied significantly between countries (15 hours in Germany to 46 hours in Italy) and it is unclear if the caregiving burden would be similar in the UK.[22] The same survey also identified that 69% of caregivers were classified as being at risk of depression, with the risk of depression being higher for people caring for patients who had progressed to later lines of therapy.[21] The CS describes how people with lung cancer are affected by the stigma that results from the general public's perception that lung cancer diagnosis is associated

with smoking behaviours,[24] and how this stigma applies to patients with cEGFRm NSCLC, even though this mutation is more common in patients who have never smoked.[10]

2.2 Critique of company's overview of current service provision

The summary of the clinical pathway of care, summarised in CS, Figure 6, was restricted to the first-line treatment options available.[1] At the clarification stage, the EAG requested that the company provide an updated summary of the clinical pathway showing all lines of therapy; the updated clinical pathway diagram provided in the company's clarification response is reproduced in Figure 1.[25]

The CS describes the first-line treatment options as consisting of platinum-doublet chemotherapy and TKI inhibitors which it separates into first-generation (erlotinib and gefitinib), second-generation (dacomitinib and afatinib) and third-generation (osimertinib).[1] It describes osimertinib as the preferred first-line treatment option based on both the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines.[26, 27] It also provides information from the NCRAS RWE dataset to support its argument that osimertinib is the mostly commonly used first-line treatment in current clinical practice.[28, 29] The CS states that 90.5% of patients (=86/95) in the NCRAS 'MARIPOSA-like' cohort (i.e., those identified as being similar to the population enrolled in the MARIPOSA trial) received first-line osimertinib in the years 2021 to 2023.[29] It also states that osimertinib monotherapy was accepted as the only relevant comparator in the ongoing appraisal of osimertinib with chemotherapy for patients with untreated EGFR mutation-positive advanced NSCLC.[5]

The EAG broadly agrees with the company that osimertinib is the most commonly used first-line treatment for cEGFRm advanced NSCLC in current clinical practice. The EAG's clinical advisers did identify that an alternative TKI, may be used instead of osimertinib in patients who have an Eastern Cooperative Oncology Group (ECOG) PS of > 1, who would not meet the Cancer Drugs Fund (CDF) criteria for osimertinib, especially if their performance status is disease related and they are expected to respond well to a TKI and have an improved performance status once on treatment. However, this group of patients may not be considered well enough to receive amivantamab with lazertinib and therefore osimertinib would remain the main comparator in the population most likely to receive amivantamab with lazertinib. In addition, one of the EAG's clinical advisers stated that patients who were contraindicated to osimertinib due to pre-existing interstitial lung disease (ILD) may be considered for first-line platinum-doublet chemotherapy instead of TKIs. The other clinical adviser stated that they may still offer TKIs to some patients with ILD despite the increased risk of pneumonitis as there is also an increased risk of pneumonitis with pemetrexed, which is offered as part of platinum-doublet chemotherapy. However, any patient contraindicated for osimertinib due to ILD would be likely to be also contraindicated for amivantamab with lazertinib. Overall, the EAG's clinical advisers were

satisfied that osimertinib was the most appropriate comparator in the population likely to be offered amivantamab with lazertinib.

The EAG also notes that osimertinib is also now recommended for adjuvant treatment following complete tumour resection in adults with stage IB to IIIA NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (TA1043). The EAG's clinical advisers stated that re-treatment with osimertinib would be offered to those patients who present with advanced disease after receiving adjuvant osimertinib only if they had been progression-free for more than 12 months since completing adjuvant therapy. The impact of prior adjuvant treatment with osimertinib on the effectiveness of TKIs offered for advanced disease is not currently known. Although patients having prior adjuvant treatment with systemic therapies for early-stage NSCLC (stage I and II) more than 12 months previously could be recruited to the MARIPOSA trial, prior treatment with any EGFR TKI was an exclusion criterion. However, the EAG's clinical advisers stated that experience from other diseases suggest that re-treatment for advanced disease with a treatment used for adjuvant treatment can still be effective when used in those who have not progressed during adjuvant treatment.

The company's clinical pathway (see Figure 1) shows two treatment options for patients who have received a TKI at first-line. The first option is platinum-doublet chemotherapy including either cisplatin or carboplatin combined with pemetrexed. Cisplatin with pemetrexed is recommended in TA181, but the EAG's clinical advisers noted that carboplatin with pemetrexed is the preferred option in current clinical practice due to the improved side effect profile and the shorter infusion duration required. The second option is the combination of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP) recommended in TA584. This treatment combination is labelled as 'immunotherapy (IO) ± chemotherapy ± vascular endothelial growth factor inhibitor (VEGFi)' in the CS. However, in the company's economic model, it is assumed that [redacted]% of patients receive platinum-doublet chemotherapy at second-line with [redacted] between cisplatin-pemetrexed and carboplatin-pemetrexed. At third-line, the company's clinical pathway shows two options, the first being a non-platinum based chemotherapy consisting of docetaxel with or without nintedanib. Docetaxel with nintedanib is recommended in TA347 and the EAG's clinical advisers stated that docetaxel with nintedanib is the most common third-line treatment in current clinical practice, although nintedanib is only given if the patient is fit enough. The alternative option shown at third-line in Figure 1 appears to be mislabelled, as it is labelled as 'IO ± chemotherapy ± VEGFi' (i.e., the same as ABCP), but then three individual IO agents are listed (pembrolizumab, atezolizumab and nivolumab). These IO agents are all recommended as single agent IOs after chemotherapy under TA428, TA520 and TA713, respectively, suggesting that single agent IO is the alternative option being described as third-line in Figure 1. The company's economic model assumes that a platinum rechallenge is offered at third-line to [redacted]% of those receiving a systematic anticancer therapy (SACT), whilst docetaxel with nintedanib is

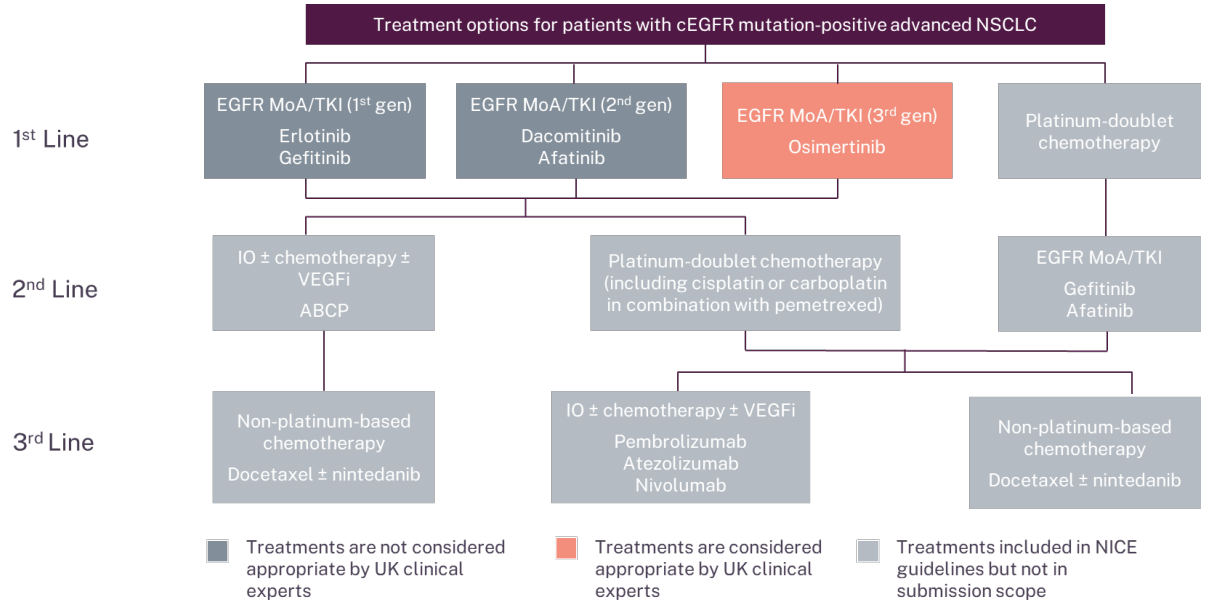
offered to the remaining [redacted]%, but the option for a platinum-rechallenge is not included in the company's clinical pathway diagram. The EAG's clinical advisers stated that a platinum rechallenge would be offered third-line if patients had responded well previously to platinum-based chemotherapy and had been progression-free for a significant period since their last treatment with platinum-based chemotherapy. It should be noted that the company's economic analysis assumes that best supportive care is offered to approximately [redacted]% of patients at both second-line and third-line who are not considered suitable candidates for SACT. However, this usage of best supportive care, is not reflected in the company's clinical pathway diagram.

In terms of unmet need, the CS describes how there is a need for first-line treatments that reduce the risk of patients developing treatment-resistant mutations, thereby delaying relapse on first-line TKI therapy, and which reserve chemotherapy options for later lines of treatment (CS, p24).[1] The EAG notes that reserving chemotherapy options for later lines of treatment would only be a benefit of amivantamab with lazertinib if the comparator was either chemotherapy or osimertinib with chemotherapy, neither of which are considered relevant comparators by the company. If the only relevant first-line comparator is osimertinib monotherapy, as the company argues, then this treatment option already reserves chemotherapy for later lines of treatment.

The CS also provides some information on treatments received at second-line and third-line in the NHS from the NCRAS RWE dataset. It provided information from both the MARIPOSA-like cohort and a broader 'MARIPOSA-expanded' cohort, which was similar to MARIPOSA-like cohort but not restricted by PS. It states that the most common subsequent treatments in the MARIPOSA-expanded cohort in patients who received first-line osimertinib were platinum-based chemotherapy regimens (38%) or osimertinib (34.3%).[29] The EAG notes that the third most common regimen in this cohort was ABCP (18.5%). These were also the three most common second-line regimens in the smaller cohort of MARIPOSA-like patients who received first-line osimertinib (CS, Table 82),[1] although the EAG notes that in the MARIPOSA-like cohort, similar percentages received ABCP (30.4%), osimertinib (35.7%) and platinum-based chemotherapies ([redacted]).[29] The EAG did however have concerns about the generalisability of the results from the NCRAS database presented by the company. These concerns relate to the exclusion of patients from this dataset receiving treatments funded via the CDF. This was due to a strict embargo by NHS England on data for patients receiving CDF-listed drugs developed by a different manufacturer. This exclusion meant that there were minimal data available on patients receiving first-line osimertinib from 2022 onwards (see response to clarification question A25).[25] For example, there were data on 91 patients in the MARIOSA-like cohort who received first-line osimertinib in 2021, but data on only 3 similar patients in 2022 and 1 similar patient in 2023. This means that any data on second- and third-line treatments in NCRAS reflect the population treated before

osimertinib became widely available through the CDF and may therefore not reflect the current treatment pathway for patients receiving first-line osimertinib.

Figure 1: Summary of clinical pathway of care for patients with untreated cEGFRm advanced NSCLC in UK clinical practice (reproduced from company's clarification response, Figure 27)



Abbreviations: ABCP - atezolizumab and bevacizumab, carboplatin and paclitaxel; gen - generation; EGFR, epidermal growth factor receptor; IO - immunotherapy; MoA - mechanism of action; NSCLC - non-small cell lung cancer; TKI - tyrosine kinase inhibitors; VEGFi - vascular endothelial growth factor inhibitor
Sources: NICE. Lung cancer: diagnosis and management: NICE guideline (NG122). 2019;[30] Johnson & Johnson Data on File. MARIPOSA Advisory Board (October 2024)[31]

2.3 Company's definition of the decision problem

A summary of the company's adherence to the decision problem set out in the NICE scope is provided in Table 3. The EAG's critique of the company's deviations from the NICE scope are discussed in Section 2.3.

Table 3: Decision problem (adapted from Table 1 of the CS)

	Scope issued by NICE	Decision problem addressed in the CS and company's rationale if different from the final NICE scope	EAG comments
Population	People with untreated advanced NSCLC which has an EGFR exon 19 deletion or exon 21 L858R substitution mutation	First-line treatment of adult patients with advanced NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. This population is in alignment with the anticipated licensed indication and with the population included within the pivotal MARIPOSA trial (NCT04487080)	Whilst the NICE scope did not restrict the population to adults, the EAG considers this narrowing of the population reasonable, given that the pivotal MARIPOSA trial was restricted to adults. The EAG notes that the MARIPOSA trial was restricted to patients with an ECOG PS of 0 to 1 and therefore the evidence from this trial may not be generalisable to patients with a poorer ECOG score.
Intervention	Amivantamab with lazertinib	Amivantamab with lazertinib	In line with NICE scope.
Comparators	• Osimertinib monotherapy • Dacomitinib • Afatinib • Erlotinib • Gefitinib • Osimertinib with chemotherapy (subject to NICE appraisal)	• Osimertinib monotherapy Osimertinib monotherapy was identified to be the only relevant comparator in the ongoing appraisal of osimertinib with platinum-doublet chemotherapy for untreated cEGFRm advanced NSCLC (ID6328), given that 86% of patients with EGFRm NSCLC in the UK currently receive it.[5] Advisory boards with UK oncologists (held in January 2023, June 2023 and October 2024) and UK RWE (collected from the NCRAS dataset) further support that osimertinib, a third generation TKI, represents the current standard of care in the UK for patients in the population considered in this appraisal.[29, 31-33] **First- and second-generation TKIs** First- (erlotinib and gefitinib) and second- (dacomitinib and afatinib) generation TKIs are	The EAG's clinical advisers stated that osimertinib monotherapy is the most commonly used first-line treatment in this patient population. They also noted that some patients with an ECOG > 1 would be unable to receive osimertinib first-line through the CDF and in these patients an alternative TKI may be offered. The EAG therefore agrees that dacomitinib, afatinib, erlotinib and gefitinib would not be relevant comparators if the population is restricted to patients with an ECOG PS score of 0 to 1, which was the group recruited to the MARIPOSA trial. The company declined to provide a comparison of amivantamab with lazertinib against osimertinib with chemotherapy in response to the EAG's clarification request.[25] The EAG would have preferred the company to have presented a comparison against osimertinib with

	Scope issued by NICE	Decision problem addressed in the CS and company's rationale if different from the final NICE scope	EAG comments
		recommended by NICE for use in the population of interest to this appraisal. However, clinical expert opinion, gathered from advisory boards held in January 2023, June 2023, and October 2024, informed Johnson & Johnson that these treatments have very limited use in patients with untreated advanced NSCLC who have EGFR exon 19 deletion or exon 21 (L858R) substitution mutations, following the reimbursement of osimertinib monotherapy in 2020 (TA654).[34] This is supported by evidence from the NCRAS dataset, which provides data for patients in the UK with cEGFRm NSCLC who had similar baseline characteristics to patients in the MARIPOSA trial (the 'MARIPOSA-like' cohort, N=617). From 2021 (following the introduction of osimertinib to UK clinical practice in 2020) to 2023, 95 patients in the 'MARIPOSA-like' cohort received first-line treatment, of whom 90.5% (86/95) were treated with osimertinib, demonstrating the preferential use of osimertinib as a third-generation TKI as compared with earlier-generation TKIs.[29] This is further supported by the results of the FLAURA trial, which found patients treated with osimertinib to have statistically significantly longer OS than patients treated with gefitinib or erlotinib (mOS: 38.6 months versus 31.8 months, respectively).[35] Clinical experts also support that osimertinib is a beneficial treatment option compared with first- and second-generation TKIs, as it is better tolerated with fewer side effects.[5]	chemotherapy that could be used to inform the committee's decision should osimertinib with chemotherapy receive positive guidance in ID6328. However, the EAG acknowledges that the relevance of such a comparison is dependent on the outcome of ID6328.

	Scope issued by NICE	Decision problem addressed in the CS and company's rationale if different from the final NICE scope	EAG comments
		In this appraisal, erlotinib, gefitinib, dacomitinib, and afatinib are therefore not regarded as relevant comparators, as they do not align with the current standard of care in the UK. Therefore, osimertinib monotherapy is considered the only relevant comparator for this appraisal. **Osimertinib with chemotherapy** Given that at the time of submission, this proposed indication is currently undergoing NICE appraisal and is not an established treatment option in clinical practice, osimertinib with chemotherapy does not represent current standard of care. Furthermore, draft guidance issued in October 2024 does not recommend osimertinib with chemotherapy for this proposed indication (ID6328).[5] As such, it does not represent a relevant comparator in this appraisal.	
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • time to treatment discontinuation • time to subsequent therapy • adverse effects of treatment • health-related quality of life.	Outcomes addressed in the submission include: • progression-free survival (PFS) • overall survival (OS) • objective response rate (ORR) • duration of response (DOR) • time to treatment discontinuation (TTD) • time to symptomatic progression (TTSP) • time to subsequent therapy (TTST) • adverse events (AEs) • health-related quality of life (HRQoL).	The CS addresses all of the outcomes specified in the NICE scope. However, the EAG had some concerns regarding the completeness of the reporting. In the original CS, outcome data for PFS and AEs were only reported for the 11th August 2023 interim DCO, which was the DCO used to evaluate the primary endpoint of PFS.[1] Data from the more recent DCO of 13th May 2024, which was used to inform all other outcomes in the CS,[1] were provided at clarification for the AEs informing the economic analysis, but the company stated that they were unable to provide updated PFS data.[25]

	Scope issued by NICE	Decision problem addressed in the CS and company's rationale if different from the final NICE scope	EAG comments
			The EAG also notes that the original CS only presented data on HRQoL using the EQ-5D-5L, whilst the MARIPOSA trial also collected data using two other HRQoL measures (see Section 2.3.4).[1] However, data on these additional HRQoL outcomes were provided in response to a clarification request (company response to clarification question A20).[25]
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: • Type of EGFR mutation • Co-mutation (e.g. TP-53) • Disease stage • Histology • Treatments had at previous stages (surgery, radiotherapy, previous systemic therapies) • Presence of CNS metastases	Analyses are presented for PFS for the following subgroups: type of EGFR mutation, presence of CNS metastases, age, sex, race, weight, ECOG performance and history of smoking. Subgroups based on disease stage, co-mutation (e.g. TP-53), histology (squamous or non-squamous), and treatments had at previous stages are not available and therefore could not be explored.	The company states that analyses exploring the impact of co-mutations are not available, but does report results for a high-risk subgroup in which TP53 co-mutation is one of the indicators of high-risk (CS, page 76).[1] The EAG notes that the cited paper describing the high-risk subgroup also reports an analysis for the subgroup with TP53 co-mutations but this analysis is not highlighted in the CS (Felip 2024). [1, 36] No subgroup analyses were provided for the economic analysis.
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	• Amivantamab with lazertinib is presented within its anticipated marketing authorisation for the treatment of untreated common (exon 19 deletion and exon 21 L858R substitution) EGFR mutation-positive NSCLC. • The impact of stigma on people living with lung cancer, including patients and caregivers, is also of relevance to this submission and is	The EAG does not consider that access to treatment with amivantamab with lazertinib is likely to reduce inequalities that are driven by disease prevalence or diagnostic delay.

	Scope issued by NICE	Decision problem addressed in the CS and company's rationale if different from the final NICE scope	EAG comments
	underpinned the marketing authorisation granted by the regulator.	not inherently captured in the cost/QALY measure. The United Kingdom Lung Cancer Coalition (UKLCC) report on health inequalities in lung cancer highlights the crucial fact that lung cancer has the biggest deprivation gap compared to any other cancer in the UK.[37] Deaths associated with socio-economic variation are shown to be most commonly reported in lung cancer and as such, there is an ever growing need not only to acknowledge the health inequality associated with this disease, but also to identify drivers of health inequality in order to ensure all patients have equal access to life changing treatments. Health inequality associated with stigma is a major concern for lung cancer patients as it is largely driven by a perception that it is 'self-inflicted' due to the public recognising the link between lung cancer and smoking. This is particularly damaging for patients with cEGFRm NSCLC as these mutations disproportionately affect never-smokers, women and people of Asian ethnicity.[10, 37, 38] Specifically in communities of Asian ethnicity, there is evidence that symptoms of lung cancer are stigmatised, which could reinforce treatment delaying behaviour.[39, 40] A recent study assessing differences in screening, diagnosis, and initial care between people with newly diagnosed lung cancer of Asian and White ethnicity reported that,	

	Scope issued by NICE	Decision problem addressed in the CS and company's rationale if different from the final NICE scope	EAG comments
		compared with people of White ethnicity, people of Asian ethnicity were more likely to be diagnosed with later-stage lung cancer and had a longer median time to treatment initiation.[41] The impact of stigma on people living with lung cancer, including patients and caregivers has been well-reported. In one qualitative study, barriers to symptom reporting for people with lung cancer included blame, stigma and cultural influences.[39] Additionally, an observational, cross-sectional study has shown that some patients report feeling uncomfortable communicating their symptoms leading, to delay in presentation, diagnosis and treatment (or low uptake of treatment).[40] The effects of stigma associated with lung cancer should be included within the decision-making process and are not inherently captured within the cost per QALY framework. Stigma is included in the NICE social value judgements principles document and as such, should be considered when deciding whether amivantamab with lazertinib is cost-effective in this population.	

2.3.1 *Population*

The EAG is broadly satisfied that the population addressed in the CS falls within the population specified in the NICE scope. It notes that the MARIPOSA trial was restricted to adult participants with an ECOG PS score of 0 to 1 and therefore the evidence from the trial will have limited generalisability to paediatric patients or patients with a higher ECOG PS score. The EAG's clinical advisers indicated that osimertinib is currently restricted to ECOG PS 0 to 1 via the CDF criteria and that a similar restriction for amivantamab with lazertinib would be reasonable as patients with a ECOG PS score of > 1 may not be well enough to tolerate amivantamab with lazertinib.

2.3.2 *Intervention*

Amivantamab is described in the CS as a novel, fully human antibody that targets both EGFR and mesenchymal-epithelial transition (MET) receptors.[1] Lazertinib is described as a highly selective, CNS-penetrant, third-generation EGFR TKI that targets both activating EGFR mutations and T790M resistance mutations. The proposed marketing indication for the combination of amivantamab with lazertinib is for the first-line treatment of adult patients with advanced untreated NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations (CS, page 11).[1] The wording in the draft Summary of Product Characteristics (SmPC) for lazertinib and amivantamab that relates to this combination treatment states that EGFR mutation-positive status should be established prior to treatment initiation and that the recommended duration of treatment should be until progression or unacceptable toxicity.[42,43]

Lazertinib is available as an oral formulation (given by mouth) and the dosing of lazertinib is 240 mg once daily.[43] Draft SmPCs are provided by the company for both a 240 mg and an 80 mg tablet strength.

Amivantamab is given by intravenous (IV) infusion at a dose of 1,050 mg for patients weighing up to 80 kg and 1,400 mg for patients weighing 80 kg or more.[42] Each 7 mL vial contains 350 mg of amivantamab at a concentration of 50 mg/mL and the treatment should be diluted prior to infusion (see SmPC Section 6.6 for details).[42] There is a treatment initiation phase whereby the required dose (1,050 mg or 1,400 mg depending on the patient's weight) is split over days 1 and 2 in week 1, and then the required dose is given weekly as a single dose on day 1 for weeks 2 to 4.[42] In the long-term, the required dose is given once every 2 weeks, starting from week 5.[42] The infusion rate is gradually increased over the initiation phase, up to a target infusion rate of 125 mL/hr. Please see the draft SmPC for further details on the infusion rate required for the treatment initiation and maintenance phases.[42] Due to the risk of infusion related reactions (IRRs), amivantamab should be administered in an environment suitable to support and treat patients experiencing IRRs.[42] Prophylactic treatment with antihistamines, antipyretics and glucocorticoids should be administered to reduce the risk of IRRs in the first week.[42]

Pre-medication with antihistamines and antipyretics should be continued for subsequent administrations, with glucocorticoid pre-medication being optional from week 2 onwards.[42]

It should be noted that the CS also indicates that an application has been submitted for an extension to the marketing authorisation for the use of subcutaneous amivantamab in combination with oral lazertinib (CS, page 19).[1] However, the bulk of the evidence presented in the CS relates to the IV administration of amivantamab in combination with oral lazertinib and the EAG has prepared their report assuming that this is the treatment combination which the committee will be asked to consider at the first meeting.

Due to venous thromboembolism (VTE) AEs, including fatal events, being reported in patients receiving this treatment combination, patients are recommended to receive prophylactic anticoagulants (e.g., low-molecular weight heparin [LMWH]; vitamin K antagonists are not recommended) for the first 4 months of treatment.[42, 43] Special precautions regarding skin and nail reactions are described in the draft SmPCs for the treatment combination of amivantamab with lazertinib.[42, 43] Patients are instructed to limit sun exposure during treatments and for 2 months after treatment and to use emollient creams on areas of dry skin. A prophylactic approach should be adopted to reduce the risk of skin reactions. The use of chlorhexidine solution to wash hands and feet should be considered for the first 12 months of treatment and topical and/or oral antibiotics and topical corticosteroids should be available to minimise any delay in treatment should rash be observed. Both amivantamab and lazertinib have been associated with an increased risk of ILD or ILD-like adverse reactions, including fatal events.[42, 43] Patients should therefore be monitored for symptoms indicative of ILD or pneumonitis and treatment should be stopped in patients with confirmed ILD or ILD-like AEs.[42,43]

Details on the dose reductions recommended for specific AEs in patients receiving the treatment combination of amivantamab with lazertinib can be found in Section 4.2 of the lazertinib draft SmPC.[42, 43] There is no dose adjustment required for lazertinib in patients with mild to severe renal impairment or mild to moderate hepatic impairment, but the pharmacokinetics of lazertinib in patients with end stage renal disease or severe hepatic impairment is unknown.[43] For amivantamab, no dose adjustment is required for patients with mild to moderate renal impairment or mild hepatic impairment, but caution should be exercised in patients with severe renal impairment or moderate to severe hepatic impairment as amivantamab has not been studied in these populations.[42] Section 4.6 of the draft SmPCs for amivantamab and lazertinib provides additional advice related to fertility, pregnancy and lactation.[42, 43] Both of the draft SmPCs state that there is no relevant use of amivantamab or lazertinib in paediatric populations for the treatment of NSCLC.[42, 43]

The list price per pack containing one 350 mg vial of amivantamab is £1,079.[44] The company has an agreed PAS which takes the form of a simple price discount of [redacted]%; the discounted cost per pack of amivantamab is therefore £[redacted]. The list price for lazertinib 80 mg (56 tablets) is £4,128.50 per pack, and the list price for lazertinib 240 mg (28 tablets) is £6,192.75 per pack. The PAS price of lazertinib included in the analysis is £[redacted] for 80 mg and £[redacted] for 240 mg, equivalent to a discount of [redacted]% for both preparations.

2.3.3 *Comparators*

The CS argues that osimertinib monotherapy is the only relevant comparator because this is used in preference to other TKIs in current clinical practice.[1] The EAG's clinical advisers agreed that osimertinib monotherapy is the treatment of choice in current clinical practice for patients with an ECOG PS of 0 to 1. They stated that alternative TKIs, may be offered to patients with an ECOG PS > 1 and platinum-doublet chemotherapy may be offered to those who are contraindicated to osimertinib due to the presence of known ILD. However, amivantamab with lazertinib is also likely to be contraindicated in patients contraindicated to osimertinib due to ILD and the EAG's clinical advisers considered it unlikely that patients with an ECOG PS > 1 would be considered well enough to be offered amivantamab with lazertinib.

The NICE scope also describes osimertinib with chemotherapy as a comparator subject to the ongoing appraisal of this treatment combination in untreated cEGFRm advanced NSCLC (ID6328). At the time of the CS, the outcome of ID6328 was not known. Therefore, the EAG requested that the company provide information on the relative clinical effectiveness and cost-effectiveness of amivantamab with lazertinib versus osimertinib with chemotherapy in their clarification response. However, the company declined to provide this information, as the company considered that osimertinib with chemotherapy did not represent an established treatment option in current clinical practice, as draft guidance for osimertinib with chemotherapy was negative.[25] At the time of the final EAG report being prepared the outcome of ID6328 was still unknown and for this reason, the EAG would have preferred this information to be available to the committee, for its consideration, should the outcome of ID6328 be positive guidance for osimertinib with chemotherapy. However, the EAG acknowledges that the relevance of osimertinib with chemotherapy as a comparator for amivantamab with lazertinib is dependent on the outcome of the ongoing appraisal. It also notes the advice from its clinical experts that osimertinib with chemotherapy is not part of current clinical practice.

2.3.4 *Outcomes*

Outcome data for all of the key outcomes included in the NICE scope, as listed in Table 3, were available from the pivotal MARIPOSA trial. The trial outcomes of OS, PFS, the time to treatment

discontinuation (TTD), HRQoL (Euroqol 5-Dimensions - 5 level [EQ-5D-5L]) and treatment emergent adverse events (TEAEs) were used to inform the economic analysis.

The definition of progression used when assessing PFS for the primary outcome in MARIPOSA was progression assessed by blinded independent central review (BICR) using the Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 guidelines. PFS based on investigator assessment is also reported in the CS as a secondary outcome. PFS by BICR was included in the base-case economic analysis with PFS by investigator assessment included as a scenario analysis.

Additional outcomes reported only in the clinical section of the CS included objective response rate (ORR), duration of response (DOR), time to subsequent therapy (TTST), time to symptomatic progression (TTSP) and intracranial PFS. The ORR was based on partial or complete response assessed by BICR using RECIST v1.1 guidelines, in patients having measurable disease at baseline (CS, page 65).[1] Duration of time from first documented response to subsequent progression or death was used to define DOR. The CS also reported PFS2, which is defined as the time from randomisation to 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.

The EAG had some concerns regarding the completeness of the reporting within the original CS, with the major concern relating to the lack of PFS or AE outcome data beyond the interim DCO (11th August 2023).[1] The EAG requested at clarification that the company provide updated PFS and AE data from the more recent 13th May 2024 DCO, which was used to inform all other outcome data reported in the CS. The company did not provide updated AE data for all safety data tabulated in CS Section B.2.10. However, it did clarify that the AEs in the model were already based on data from the 13th May 2024 DCO, and it provided additional tables summarising these AEs (company response to A21, Table 7 and 8). In response to the clarification request (question A17), the company stated that analysis of data from the 13th May 2024 DCO was requested by the European Medicines Agency (EMA) to assess interim OS data only.[25] As such, PFS data from the 13th May 2024 DCO were not requested by the EMA and therefore these data are not available for the company to provide. In addition, the company clarified during the factual accuracy check that, *"the statistical alpha (0.05) for PFS was spent at [the 11th August 2023 DCO], so data for this endpoint could not be, and were not, collected in any subsequent DCOs."* The company did indicate that it was working to provide an addendum to NICE with an updated final analysis for 'relevant outcomes'. The EAG considers the lack of PFS data beyond the interim 11th August 2023 DCO to be a key limitation of the evidence presented by the company.

The EAG also had a minor concern that the company only reported data for one of the three HRQoL tools collected in MARIPOSA, with data from the European Organization for Research and Treatment

of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) and Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) not being reported in the CS.[1] However, these data were later provided by the company in response to a clarification request (company response to A20, Tables 4 to 6), although only data from the interim DCO were provided (11th August 2023).[25]

2.3.5 *Subgroups*

Subgroup analyses are presented for PFS for the following pre-specified subgroups: type of EGFR mutation (exon 19 deletions versus exon 21 L858R), presence of CNS metastases, age (< 65 versus ≥ 65 years and < 75 versus ≥ 75 years), sex (male versus female), race (Asian versus non-Asian), weight (< 80 kg versus ≥ 80 kg) , ECOG PS (0 versus 1) and history of smoking (yes versus no). Randomisation was stratified by mutation type, race and history of brain metastases and subgroup analysis for OS was only presented for these three subgroups.

The following subgroups were defined as being subgroups of interest in the NICE scope but were not addressed in the CS: disease stage, co-mutation (e.g. TP-53), histology (squamous or non-squamous), and treatments had at previous stages. The company stated that subgroup analyses could not be presented for these characterises as these data were not available. However, the EAG notes that one of the articles cited in the CS included an analysis of PFS for the subgroup of patients with TP53 co-mutations which is not highlighted in the CS (see Section 3.2 for further details).[1, 36]

2.3.6 *Special considerations*

The CS states that cEGFRm NSCLC disproportionately affects women, people of Asian ethnicity and people who have never smoked (CS, page 28).[1] It also describes how lung cancer has the biggest deprivation gap compared to any other cancer in the UK. The CS cites a paper describing how patients of Asian ethnicity were more likely than patients of White ethnicity to present with later stage lung cancer and were more likely to experience treatment delays.[41] However, the EAG notes that this study was conducted in the US and it is unclear whether these findings are applicable to the UK. The CS cites two studies as supporting its assertion that, "*specifically in communities of Asian ethnicity, there is evidence that symptoms of lung cancer are stigmatised, which could reinforce treatment delaying behaviour*".[1] Whilst both of these studies were conducted in the UK, one of these papers was a qualitative analysis that included no patients from minority ethnic groups,[39] and the other paper was a cross-sectional survey in which only 1% of the cohort were from a non-White ethnic groups and ethnicity was not one of the variables explored as a predictor of stigma.[40] The EAG considers that any positive or negative recommendation for treatment would be unlikely to address any differences in the incidence of diseases, or in patient experiences related to diagnosis and treatment delay, as these occur prior to patients being assessed as eligible for amivantamab with lazertinib.

3 CLINICAL EFFECTIVENESS

This chapter presents a summary and critical appraisal of the methods and results of the clinical effectiveness review and evidence synthesis presented within the CS.[1]

3.1 Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify all clinical evidence regarding the efficacy and safety of amivantamab with lazertinib and comparator treatments as first-line treatment in adults with untreated cEGFRm advanced NSCLC which has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. The methods for the company's SLR of clinical evidence are detailed in CS, Appendix D.[1]

3.1.1 *Searches*

CS Appendix D presents the search strategy for the SLR conducted to identify efficacy, safety, HRQoL and patient-related outcome evidence associated with treatment options for patients with metastatic or surgically unresectable cEGFRm NSCLC. An initial SLR was conducted in May 2020, which has been updated five times, most recently in September 2024. Unless otherwise stated, this critique refers to the search strategy and strings for the latest update (September 2024).

A comprehensive range of bibliographic databases were searched: MEDLINE, including MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print; Embase; Cochrane Database of Systematic Reviews (CDSR) and The Cochrane Central Register of Controlled Trials (CENTRAL). The Database of Abstracts of Reviews of Effects (DARE) was searched for the original 2020 SLR, but not in subsequent updates because this database has not been updated since 2015 so no new records would have been identified.

Database searching was supplemented by searches of relevant conference proceedings and the trial register ClinicalTrials.gov. In addition, hand searching was conducted of the bibliographies of relevant reviews and (network) meta-analyses to identify further relevant studies. One notable omission from the list of supplementary searches was the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) (clarification response, question A2). It is usual practice to search both of these sources for trials, although coverage is also provided via CENTRAL, which has been searched, so it is unlikely that trial evidence has been missed.

Reporting of the search strings for all updates is comprehensive, with search results presented by line for each database search, with all updates presented to the same level of detail. The supplementary

searches have also been reported transparently, in line with the methods set out by Stansfield *et al.* (2016)[45] for conducting and reporting website searching and other online sources systematically.

Despite the individual searches being reported in detail, the EAG's greatest concern with the overall search strategy for the clinical SLR is in the lack of transparency in reporting in other areas. The company has re-purposed an existing search strategy for a wider population that is relevant to this submission, without transparently reporting how the results from earlier iterations of the searches were incorporated into the most recent (September 2024) SLR results. The submission states that relevant results from previous search updates were carried forward and combined with new results retrieved in the latest update, leaving a high number of duplicates according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram (Appendix D, Figure 1). Although the search strategies from each iteration have been presented in detail, a PRISMA diagram has only been provided for the latest iteration, with an indication that 424 publications fed into the final results total from previous iterations of the search. What is not clear, however, is how those previous results were screened and included, given that the searches were designed for a global SLR and were not bespoke searches developed for this submission. The EAG generally considers it to be sub-optimal to use an existing search strategy rather than designing one that matches more closely the decision problem for an individual submission. This approach and the lack of transparency in the reporting described above, and subsequent lack of reproducibility, undermines confidence in the overall search approach and strategy. This leaves the EAG unable to confidently exclude the possibility that evidence has not been missed in the clinical SLR.

3.1.2 *Inclusion criteria*

The inclusion criteria for the company's SLR are described in CS Appendix D.1.2.1, page 45, Table 28.[1] The specified inclusion and exclusion criteria appear to relate to a broader SLR than the information given in the decision problem and the NICE scope.[2] The EAG requested the eligibility criteria for the present submission clarification (question A9),[25] the company provided the eligibility criteria for the broader SLR (clarification response, questions A7, A8 and A9, Table 1)[25] and stated the following: "*the global cSLR encompassed a broader review question than that required for this submission. Specifically, studies in the first-line, second-line or later were considered eligible for inclusion. However, in line with the decision problem, only studies in the first-line setting (i.e., for untreated advanced EGFRm NSCLC), were considered and presented within this submission. The table below reflects the eligibility applied to the global cSLR, with the yellow highlighted text relating to the criteria used to consider whether studies were relevant to present within this submission..*"[25]

The company's decision problem and the marketing authorisation states that amivantamab in combination with lazertinib is indicated for the first-line treatment of adults people with advanced

untreated NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation. This is slightly different to the NICE scope,[2] which states that the population for the appraisal relates to people with untreated advanced NSCLC which has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. The CS restricted this to adult patients only, which the EAG acknowledged was reasonable. In addition, the company's SLR allowed the inclusion of studies which recruited participants who had received prior adjuvant or neoadjuvant therapy for Stage I or II disease, if administered more than 12 months prior to the development of locally advanced or metastatic disease. Furthermore, only studies with at least 85% of the cohort with adenocarcinoma were included.[1] The EAG's clinical advisers did not consider these issues to be of key concern. Further discussion on the impact of prior adjuvant treatment with osimertinib on treatment choice for advanced disease is provided in Section 2.2.

The intervention of interest listed in the NICE scope[2] and in the company's decision problem was amivantamab with lazertinib,[1] however, the company's SLR inclusion and exclusion criteria used a broader criteria allowing for the inclusion of any therapeutic or palliative intervention administered within the healthcare system.[1] Similarly, in the broader SLR, the comparator included placebo or standard of care or any comparator if also an intervention of interest.[1] The NICE scope included osimertinib monotherapy, dacomitinib, afatinib, erlotinib, gefitinib and osimertinib with chemotherapy (subject to NICE appraisal) as comparators [2] whilst in the decision problem presented in the CS, the company restricted the comparator to osimertinib monotherapy only. The company explained that osimertinib monotherapy is considered the only relevant comparator for this appraisal as other comparators do not align with the current standard of care in the UK.[1] The EAG's clinical advisers stated that osimertinib monotherapy is the most commonly-used first-line treatment patient population with an ECOG PS score of 0 to 1 (which corresponds to the population recruited in the MARIPOSA trial). Therefore, the EAG agrees that dacomitinib, afatinib, erlotinib and gefitinib would not be relevant comparators in this patient group. During the clarification round, the EAG requested information on the relative clinical effectiveness of amivantamab with lazertinib versus osimertinib with chemotherapy, but the company did not provide any data (see clarification response, question A1).[25] The company's rationale was that the draft guidance for osimertinib with chemotherapy available at the time of the CS was negative and the company did not consider it to be an established treatment option within clinical practice. The EAG acknowledges that the relevance of osimertinib with chemotherapy as a comparator for amivantamab with lazertinib is dependent on the outcome of the ongoing appraisal (ID6328). It also notes the advice from its clinical experts that osimertinib with chemotherapy is not part of current clinical practice. However, the EAG would have preferred the company to have submitted evidence comparing amivantamab with lazertinib against osimertinib with chemotherapy, which the committee would then be able to consider if the final guidance for osimertinib with chemotherapy were to be positive. Further details are provided in Section 2.3.3 and Table 1.

The EAG was unclear why the company only included conference abstracts published in or after 2020. In response to clarification question A11,[25] the company noted that this was a typographical error and that conferences abstracts published in or after 2018 were considered eligible for inclusion. This was because the original SLR was conducted in 2020 and would have included conference abstract prior to this date. The EAG agrees with the company's rationale. In addition, study eligibility was restricted to English language publications, which introduces the risk that relevant data not published in the English language may have been missed; however, the EAG does not anticipate that key studies would have been missed due to the above restrictions.

3.1.3 *Critique of study selection, data extraction and quality assessment*

The company used appropriate methods for study selection. Titles, abstracts and full-texts were reviewed against the eligibility criteria by two independent reviewers and any disagreements were resolved by discussion, and arbitrated by a third independent reviewer.[1] However, the CS states that in cases where the publication did not give enough information to be sure whether the study met the review eligibility criteria, it was excluded, to ensure that only relevant articles were ultimately included in the SLR. In response to clarification question A10,[25] the company stated: "*During the full-text review stage, studies which did not contain enough information to confirm relevance in line with the eligibility criteria were assigned exclusion labels according to the criterion they lacked sufficient detail for (i.e., Population, Intervention, Comparator, Outcome). As such, it is not possible to retrieve studies that were specifically excluded due to lack of information on a specific criterion. For example, if it was unclear whether patients with NSCLC in a study had EGFR mutations, the study would be excluded under the 'Population' exclusion category – this category also contains studies which definitely did not meet the Population inclusion criteria, such as those conducted in early-stage NSCLC. It should be noted that all records were screened by two independent reviewers, with any disagreements resolved by discussion, and arbitrated by a third independent reviewer, if necessary, until a consensus was met. As such, the lack of sufficient information in a study would be verified by two individuals. Given the volume of evidence screened, it was not feasible to contact study authors to seek clarification before exclusion."*[25]

CS Appendix D.1.2.2 states that data from the included studies were extracted into a pre-defined data extraction grid in Microsoft Excel® by a single individual and were independently verified by a second reviewer to check that no relevant information was missed. Any discrepancies or missing information were discussed by both individuals until a consensus was reached; if necessary, a third individual arbitrated the final decision.[1] The EAG regards this approach to be appropriate.

The CS[1] used the University of York Centre for Reviews and Dissemination (CRD) quality assessment tool[46] to assess the quality of the included studies. The EAG considers this be an appropriate quality

assessment tool for the included RCTs. However, the use of Cochrane Risk of Bias 2 tool[47] is recommended by the Cochrane Collaboration and is generally considered to be more comprehensive and structured compared to other tools, particularly when evaluating the potential for bias across the different domains of a study design, conduct and reporting process (see Section 3.2.1.2). The CS[1] also stated that 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.[48] Although EAG acknowledges this is an appropriate tool for non-randomised studies, the EAG was unclear about the need for its inclusion since the company's SLR eligibility criteria were restricted to RCTs only. The company's clarification response (question A15 and A14) states that " *.....the use of ROBINS-1 quality assessment (QA) is not relevant to the evidence supporting this submission…".*[25] The quality assessment was completed by one individual and verified by a second individual. If necessary, a third individual arbitrated the final decision. The EAG considers the methods used for the quality assessment process to be appropriate.

3.1.4 *Results of the company's SLR*

The company presented an SLR of the clinical effectiveness and safety of amivantamab with lazertinib as a treatment for adult patients with untreated cEGFRm advanced NSCLC. The company's PRISMA flow diagram (CS, Appendix D, page 48, Figure 1)[1] was for the broader global SLR and the EAG found it difficult to follow. After addressing minor discrepancies (clarification questions A12 and A13),[25] the company provided an updated PRISMA flow diagram for first-line therapy (see clarification response, question A9, Figure 1).[25] The identification and selection of relevant studies for the treatment of cEGFRm advanced NSCLC in adults as first-line treatment appears to be an adequate record of the literature searching and screening process.

The main primary clinical evidence included in the CS[1], Section B.2.2 was from the MARIPOSA (NCT04487080) RCT[49] that examined the efficacy and safety of amivantamab with lazertinib in adult patients with advanced NSCLC with activating cEGFR mutations. A summary of the characteristics of the MARIPOSA trial are presented in Table 4.

Table 4: Summary of the MARIPOSA study (reproduced from CS, page 32, Table 3)

Study	MARIPOSA (NCT04487080)
Study design	Phase 3, open-label, randomised, multicentre study
Population	Adult patients (aged ≥ 18 years) with treatment-naïve locally advanced or metastatic NSCLC with cEGFR mutations
Intervention(s)	Amivantamab intravenous (IV) in combination with lazertinib (open-label; treatment blinding was not feasible in this trial, due to differences in administration, pre-medication requirements and safety profiles of the two regimens). **Amivantamab:**

Study	MARIPOSA (NCT04487080)
	• Body weight at baseline < 80 kg: o Weeks 1–4: 1,050 mg weekly (total of 4 doses) Week 1 – split infusion on Day 1 and 2 Weeks 2 to 4 – infusion on Day 1 o Week 5 onwards: 1,050 mg every 2 weeks • Body weight at baseline ≥ 80 kg: o Weeks 1–4: 1,400 mg weekly (total of 4 doses) Week 1 – split infusion on Day 1 and 2 Weeks 2 to 4 – infusion on Day 1 o Week 5 onwards: 1,400 mg every 2 weeks **Lazertinib:** • 240 mg QD (oral)
Comparator(s)	• Osimertinib 80 mg QD (oral) plus matching placebo for lazertinib QD (blinded) • Lazertinib 240 mg QD (oral) plus matching placebo for osimertinib QD (blinded)
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> • OS • ORR • DoR • TTSP • Incidence and severity of AEs <u>Exploratory outcomes:</u> • TTD <u>HRQoL outcomes:</u> EQ-5D-5L
All other reported outcomes	<u>Secondary outcomes:</u> • Complete response (CR), partial response (PR), stable disease (SD) and progressed disease (PD) • PFS2 • Intracranial PFS (see Appendix M.1.1) <u>Exploratory outcomes:</u> • TTST • Dose interruption • Intracranial ORR (see Appendix M.1.2) • Intracranial DOR (see Appendix M.1.3)

AE - adverse event; AUC - area under the concentration-time curve; CR - complete response; DOR - duration of response; EGFR - epidermal growth factor receptor; EQ-5D-5L - EuroQoL five-dimensional descriptive system (five level version); HRQoL - health-related quality of life; N/A - not applicable; NSCLC - non-small cell lung cancer; ORR - objective response rate; OS - overall survival; PD - progressed disease; PR - partial response; PROMIS-PF - Patient-Reported Outcomes Measurement Information System – Physical Function; PFS - progression-free survival; PFS2 - PFS after subsequent therapy; SD - stable disease; QD - once daily; TTSP - time to symptomatic progression; TTST - time to subsequent therapy.

3.1.4.1 *Main evidence (MARIPOSA study)*

The MARIPOSA study (NCT04487080) is an ongoing registrational Phase 3, randomised, international, multicentre clinical trial[49] designed to evaluate the effect of amivantamab with lazertinib compared with osimertinib monotherapy and lazertinib monotherapy in adult (aged ≥ 18 years) patients with untreated cEGFRm locally advanced or metastatic NSCLC. The MARIPOSA study[49] recruited patients at 267 sites across 28 countries, including seven UK sites. The trial started in September 2020 and is anticipated to complete in June 2027. The trial is comprised of three phases: (i) a screening phase; (ii) a treatment phase; and (iii) a follow-up phase. Further details are provided below and a detailed overview is provided in the CS[1], page 43, Figure 7. The screening phase was performed 28 days before randomisation. Patients were randomised in a 2:2:1 ratio to receive amivantamab with lazertinib (N=429), osimertinib (N=429) or lazertinib (N=216). The amivantamab with lazertinib arm of the study was open-label due to differences in routes of administration. The osimertinib and lazertinib monotherapies were administered in a double-blind manner. The CS[1] noted that the lazertinib monotherapy arm was only included to assess the contribution of each individual component. Randomisation was stratified according to mutation type (exon 19 deletion or exon 21 L858R), Asian race (yes or no) and history of brain metastases (yes or no).

The treatment phase started at Cycle 1, Day 1 and continued in 28-day cycles until the 'end of treatment' visit (approximately 30 days after disease progression, unacceptable toxicity, or another reason for discontinuation of study treatment). Patients who discontinued their assigned study treatment for any reason were followed for survival and symptomatic progression in the follow-up phase. The follow-up phase started after the last dose of study treatment or disease progression, whichever occurred first. Survival, subsequent anticancer treatment, and disease status were assessed at least every 12 weeks (±14 days) until the end of study, death, loss to follow-up, or withdrawal of consent from participation by the patient, whichever occurred first.

As per the study protocol, patients underwent regular disease assessments to monitor their underlying disease, including imaging of the chest, abdomen, pelvis and any other disease locations. Patients had brain magnetic resonance imaging (MRI) at screening, followed by serial post-baseline brain MRIs for the evaluation of CNS outcomes.

Patients

Eligibility criteria for the MARIPOSA trial[49] are presented in the CS[1], page 44. The population met the specifications of the NICE final scope[2] which included patients with advanced NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation. However, the NICE scope[2] does not restrict the population by age, whilst the MARIPOSA trial included adult patients only. Clinical advisers to the EAG confirmed that the eligibility criteria for the study are reasonable.

Adult patients (≥ 18 years of age) with newly diagnosed, histologically or cytologically confirmed locally advanced or metastatic NSCLC that is treatment-naïve and not amenable to curative therapy, including surgical resection or chemoradiation, were included. Only participants with a confirmed diagnosis of EGFR exon 19 deletion or exon 21 L858R substitution, as detected by a Food and Drug Administration (FDA) approved or other validated test in an accredited local laboratory, in accordance with standard of care, were included. Patients had to have at least one measurable lesion, according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, that had not been previously irradiated. In addition, patients were included only if they had an ECOG PS of 0 or 1 and adequate organ and bone marrow function, without history of red blood cell transfusion, platelet transfusion, or granulocyte colony-stimulating factor.

The key exclusion criteria were

- Any prior systemic treatment at any time for locally advanced or metastatic disease; however, adjuvant or neoadjuvant therapy for Stage I or II disease was allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease.
- Symptomatic brain metastases. However, those with asymptomatic or stable brain metastases, including those treated with radiation or surgery for symptomatic or unstable brain metastases if they had been clinically stable and off corticosteroids or on low-dose corticosteroids (≤ 10 mg/day prednisone or equivalent) for at least two weeks prior to randomisation, were eligible.
- Received prior EGFR TKI treatment; or an investigational drug within 12 months before randomisation or is currently enrolled in an investigational study
- Active or past medical history of leptomeningeal disease, ILD/pneumonitis, including drug-induced ILD, or radiation ILD/pneumonitis
- History of spinal cord compression that has not been treated definitively with surgery or radiation
- Uncontrolled tumour-related pain or uncontrolled inter-current illness
- Concurrent or prior malignancy other than the disease under study.
- Have active cardiovascular disease, positive hepatitis B, C, or other clinically active infectious liver disease at screening.

The EAG notes that the MARIPOSA trial included only adult patients with ECOG PS of 0 or 1; hence, the evidence from the trial may not be generalisable to patients with ECOG PS of higher than 1.

Intervention

The intervention group in the MARIPOSA trial[49] received amivantamab with lazertinib. Amivantamab was administered intravenously and dosing was dependent on patient weight. In those with a body

weight at baseline of < 80 kg, amivantamab was dosed at 1,050 mg weekly during weeks 1 to 4 (in Week 1 infusion was split between Day 1 and Day 2, between Weeks 2 to 4 infusion was done on Day 1) and every two weeks from Week 5 onwards (infusion done on Day 1). For those with a body weight of ≥ 80 kg, amivantamab was dosed at 1,400 mg weekly in Weeks 1 to 4 (in Week 1 infusion was split between Day 1 and Day 2, between Weeks 2 to 4 infusion was done on Day 1) and every two weeks from Week 5 onwards (infusion done on Day 1). Lazertinib was dosed orally at 240 mg once daily. The dosage and formulation are consistent with the proposed licensed dose in the draft SmPC.[43]

Treatment started at Cycle 1, Day 1 and continued in 28-day cycles until disease progression using RECIST v1.1 (confirmed by BICR), unacceptable toxicity or another reason for discontinuation of study treatment. Although the draft SmPC,[43] recommends stopping treatment when there is disease progression or unacceptable toxicity, continuation of study treatment after confirmed disease progression was allowed in the MARIPOSA trial, if the investigator believed the patient was deriving clinical benefit.[1]

Dose modification or dosing interruptions were mandated in patients who did not tolerate the protocol-specified dosing schedule to allow patients to continue the study treatment. Guidelines regarding management of and dose reductions for AEs are provided in the draft SmPC.[43]

Permitted and non-permitted concomitant treatments are presented in the CS[1], page 46, Table 4 and in the MARIPOSA protocol.[50] Clinical advisers to the EAG confirmed that these are reasonable.

Comparator

The MARIPOSA trial[49] has two comparator arms: the osimertinib arm and the lazertinib arm. In the osimertinib arm, participants were prescribed one 80 mg capsule of osimertinib orally once daily, along with three placebo tablets, also taken orally once a day. In addition, for dose reduction osimertinib 40 mg was used as needed. In the lazertinib arm, lazertinib 3x80 mg tablets and one placebo capsule were dosed orally once daily. In both arms, the treatment started at Cycle 1, Day 1 and continued in 28-day cycles. Patients continued treatment for the prescribed number of cycles, as tolerated or until unacceptable toxicity, or until disease progression.

Outcomes

Patients were screened 28 days before randomisation and underwent regular disease assessments including imaging of the chest, abdomen, pelvis and any other disease locations as per the study protocol. Brain MRI was performed at screening, followed by serial post-baseline brain MRIs. Survival, subsequent anticancer treatment, and disease status were assessed at least every 12 weeks (±14 days)

until the end of the study, death, loss to follow-up, or withdrawal of consent from participation by the patient, whichever occurred first.

Outcomes were only reported for the amivantamab with lazertinib versus the osimertinib arm in the CS.[1] The company stated that the lazertinib monotherapy arm was only included to assess the contribution of each individual component; as such, results for this treatment arm are not presented in the CS.[1]

The primary efficacy outcome was PFS, defined as the time from randomisation until the date of objective disease progression as assessed by BICR using RECIST v1.1 or death, whichever occurred first. 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. PFS assessed by investigator assessor (INV) was used for sensitivity analysis.

A number of secondary and exploratory outcomes were listed in the CS[1] see page 46, Table 4. Only outcomes that were reported in the CS are detailed below.

Secondary outcomes included:

- OS, defined as the time from the date of randomisation to death due to any cause. 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, defined as the proportion of patients who achieved either a complete response (CR) or partial response (PR) as defined by BICR using RECIST v1.1.
- DOR, defined as the time from the first documented response (CR or PR) until the date of documented progression or death, whichever occurred first.
- TTSP, defined as the time from randomisation to documentation in the electronic case report form (eCRF) of any of the following (whichever occurred 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.
- PFS2, defined as time from randomisation to 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 occurred first.
- Intracranial PFS, defined as the time from randomisation until the date of objective intracranial disease progression or death, whichever occurred first, based on BICR using RECIST v1.1 in participants who had a history of brain metastasis at screening in the Full Analysis Set (FAS).
- HRQoL, assessed using the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire

(NSCLC-SAQ) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) patient reported outcome (PRO) measures.
- TEAEs, including adverse events of special interests (AESIs), defined as any AE occurring at or after the initial administration of study treatment through to the day of the last dose plus 30 days, or until the start of subsequent anticancer therapy (if earlier).

Exploratory outcomes included:

- TTD, defined as the time from randomisation to discontinuation of all study treatments for any reason.
- TTST, defined as the time from randomisation to the start date of the subsequent anticancer therapy, following study treatment discontinuation or death, whichever occurred first.
- Intracranial ORR, DOR and time to intracranial disease progression.
- HRQoL, assessed using the European Quality of Life 5 Dimensions 5 Level (EQ-5D-5L) questionnaire

The CS[1] also reports data on the following 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
- Weight: < 80 kg and ≥ 80 kg
- Baseline ECOG PS: 0 versus 1
- History of smoking: yes versus no
- History of brain metastasis: yes versus no
- EGFR mutation: exon 19 deletion versus exon 21 L858R substitution.

The CS[1] (Table 1, page 14) states that data for subgroups based on disease stage, co-mutation (e.g. TP-53), histology (squamous or non-squamous), and treatments received at previous stages are not available and therefore could not be explored.[1] However, the company does report analyses for a high-risk subgroup including a TP53 co-mutation in the CS[1], page 76 and Felipe *et al.* 2024.[36] Further details are provided in Section 3.2.1.3.

3.2 Clinical effectiveness results

3.2.1 *Summary and critique of results*

This section presents the results (as reported by the company) from the MARIPOSA trial,[49] which forms the pivotal evidence in the CS[1] for the efficacy and safety of amivantamab with lazertinib compared with osimertinib as first-line treatment in adult (aged > 18 years) patients with advanced NSCLC with

EGFR exon 19 deletion or exon 21 L858R substitution mutations. Further information which was not reported in the CS[1] was provided by the company in its response to the clarification questions raised by the EAG. This additional data has been included in the results below. Where applicable, data have been re-tabulated by the EAG to ensure clarity.

3.2.1.1 *Demographic and baseline characteristics*

A total of 1,375 patients were screened for entry into the MARIPOSA trial. Of these, 1,074 patients were recruited upon completion of the screening phase and randomised in a 2:2:1 ratio to the amivantamab with lazertinib arm (N=429), the osimertinib arm (N=429) and the lazertinib arm (N=216). A total of 1,062 patients received at least one dose of trial treatment. Most of the patient characteristics were well balanced between the amivantamab with lazertinib arm and osimertinib arm at baseline (see Table 5). As noted in Section 3.1.4.1, the lazertinib monotherapy arm was only included to allow for a descriptive comparison with the other treatment arms for an evaluation of the contribution of components of the amivantamab with lazertinib combination regimen.

In the MARIPOSA trial, the median age of patients in the amivantamab with lazertinib arm, the osimertinib arm and the lazertinib arm was 64 years (range: 25–88 years), 63 years (range: 28–88 years) and 63 years (range: 31–87 years), respectively, and 55% of the patients were aged < 65 years in all the treatment arms and only 12% of the patients were aged ≥ 75 years in both the amivantamab with lazertinib and the osimertinib arm. As noted in Section 2.1, the typical median age for lung cancer diagnosis is around 70 years.[11] However, the EAG's clinical advisers confirmed that NSCLC patients with common EGFR mutations tend to be younger than other NSCLC populations. The majority of patients in the amivantamab with lazertinib arm, the osimertinib arm and the lazertinib arm weighed < 80 kg (88%, 86% and 91%, respectively). Most patients were Asian (58% in the amivantamab with lazertinib arm and 59% in both the osimertinib and lazertinib arms) followed by White patients (38% in both the amivantamab with lazertinib arm and the osimertinib arm). However, Black patients were underrepresented and comprised only 1% of patients in the amivantamab with lazertinib and osimertinib arms.. There were more female than male patients across all arms and a slightly higher proportion of female patients in the amivantamab with lazertinib arm (64%) and the lazertinib arm (63%) compared with the osimertinib arm (59%). Thirty percent of patients in the amivantamab with lazertinib arm, 31% in the osimertinib arm and 34% in the lazertinib arm had a history of smoking.

The baseline lung cancer characteristics were generally balanced between the treatment arms. In both the amivantamab with lazertinib arm and the osimertinib arm, 60% of patients had an exon 19 deletion EGFR mutation and 40% had an exon 21 L858R substitution EGFR mutation. The majority of the patients had an ECOG PS of 1 (67% vs 33% in the amivantamab with lazertinib arm and 65% vs 35% in both the osimertinib arm and the lazertinib arm). At initial diagnosis, the main NSCLC diagnosis in

patients was adenocarcinoma, ranging between 97 to 98% in treatment arms and history of brain metastases was reported in 40 to 41% of the cohort. At screening, over [redacted]% of patients across all three treatment arms had Stage IVA or Stage IVB cancer. There was a number of metastasis at screening at different locations with the highest number of metastases in all arms was found in the lymph nodes followed by lungs.

In the MARIPOSA trial, patients were not allowed to have received previous systemic treatment for cEGFRm locally advanced or metastatic NSCLC, except for the use of adjuvant or neoadjuvant therapy for Stage I or II disease if administered more than 12 months prior to disease progression to locally advanced or metastatic disease. Some patients across the treatment arms had received prior therapies for lung cancer ([redacted] in the amivantamab with lazertinib arm, [redacted] in the osimertinib arm and [redacted] in the lazertinib arm). Prior therapy included systemic therapy, radiotherapy, and cancer related surgery. Further details are provided in Table 5. The company's clarification response (question A19)[25] states that all prior systemic therapies received by patients in any treatment arm (N=21 [2.0%]) were received in an adjuvant/neoadjuvant setting. The mean time since initial lung cancer diagnosis to randomisation was [redacted] months in the amivantamab with lazertinib arm, [redacted] months in the osimertinib arm and [redacted] months in the lazertinib arm. The mean time since metastatic disease diagnosis and randomisation was [redacted] months in the amivantamab with lazertinib arm, [redacted] months in the osimertinib arm and [redacted] months in the lazertinib arm.

Although the population in the MARIPOSA trial were younger (median age 63) and had lower ECOG PS score (0 or 1) compared with typical lung cancer patients,[11] the clinical advisers to the EAG agreed that the study population demographic characteristics are generally representative of the patients with cEGFRm locally advanced or metastatic NSCLC seen in UK routine clinical practice. It was also highlighted that although there is a much higher population of Asians in the trial than that would be seen in the UK routine clinical practice, it is unlikely that this would have an impact on the relative treatment effect.

Table 5: Demographics and baseline disease characteristics in the MARIPOSA trial, FAS; N=858 (reproduced from CS, page 50, Table 7, 8 and 9)

Characteristic	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Age, years			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	64 (25, 88)	63 (28, 88)	63 (31, 87)
< 65, n (%)	235 (55)	237 (55)	119 (55)
65 to < 75, n (%)	143 (33)	139 (32)	79 (37)
≥ 75, n (%)	51 (12)	53 (12)	18 (8)
Female Sex, n (%)	275 (64)	251 (59)	136 (63)
Race, n (%)[a]			
Asian	250 (58)	251 (59)	128 (59)
White	164 (38)	165 (38)	79 (37)
American Indian or Alaska Native	7 (2)	7 (2)	4 (2)
Black	4 (1)	3 (1)	4 (2)
Native Hawaiian or Pacific Islander	1 (< 1)	1 (< 1)	0
Multiple	1 (< 1)	1 (< 1)	0
Unknown	2 (< 1)	1 (< 1)	1 (< 1)
Body Weight, kg			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	62.5 (32, 118)	62 (35, 109)	60.5 (41, 118)
< 80, n (%)	376 (88)	368 (86)	197 (91)
≥ 80, n (%)	53 (12)	61 (14)	19 (9)
Body mass index, kg/m^2			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
History of smoking, n (%)			
No	299 (70)	295 (69)	143 (66)
Yes	130 (30)	134 (31)	73 (34)
EGFR mutation, n (%)[b]			
Exon 19 deletion	258 (60)	257 (60)	131 (61)
Exon 21 L858R substitution	172 (40)	172 (40)	85 (39)
History of brain metastasis, n (%)	178 (41)	172 (40)	86 (40)
ECOG PS, n (%)[c]			
0	141 (33)	149 (35)	76 (35)
1	288 (67)	280 (65)	140 (65)
Initial diagnosis NSCLC subtype, n (%)			
Adenocarcinoma	417 (97)	415 (97)	212 (98)
Large cell carcinoma	3 (1)	0	0
Squamous cell carcinoma	6 (1)	5 (1)	2 (1)
Other[d]	2 (< 1)	9 (2)	2 (1)
Not reported	1 (< 1)	0	0

Characteristic	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Histology grade at initial diagnosis, n (%)			
Poorly differentiated	[redacted]	[redacted]	[redacted]
Moderately differentiated	[redacted]	[redacted]	[redacted]
Well differentiated	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]
Cancer stage at initial diagnosis, n (%)			
IA	[redacted]	[redacted]	[redacted]
IB	[redacted]	[redacted]	[redacted]
IIA	[redacted]	[redacted]	[redacted]
IIB	[redacted]	[redacted]	[redacted]
IIIA	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]
Cancer stage at screening, n (%)			
IIIA	[redacted]	[redacted]	[redacted]
IIIB	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]
Location of metastasis at screening, n (%)[e]			
N	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Brain	[redacted]	[redacted]	[redacted]
Lymph Node	[redacted]	[redacted]	[redacted]
Adrenal Gland	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Time from initial lung cancer diagnosis to randomisation, months			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	1.5 (0.2, 207.9)	1.4 (0.3, 162.8)	1.3 (0.2, 197.3)
Time from metastatic disease diagnosis to randomisation, months			
N	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median (range)	1.3 (0.2, 24.1)	1.2 (0.1, 11.7)	1.2 (0.2, 9.2)
Prior therapy, n (%)			
Any prior therapy for lung cancer	[redacted]	[redacted]	[redacted]
Systemic therapy	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]

Characteristic	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Cancer-related surgery	[redacted]	[redacted]	[redacted]

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

All study withdrawals were adequately described, and all patients were accounted for in the MARIPOSA trial. As of the DCO (11th August 2023), 230/421 patients (55%) in the amivantamab with lazertinib arm and 213/428 patients (50%) in the osimertinib arm remained on treatment. In the amivantamab with lazertinib arm, 86/421 patients (20%) discontinued treatment due to disease progression and 86/421 patients (20%) discontinued due to AEs. In the osimertinib arm, 154/428 patients (36%) discontinued treatment due to disease progression and 50/428 patients (12%) discontinued due to AEs. Further details are available in CS[1], Appendix, page 49, Figure 2.

3.2.1.2 *Summary and critique of the company's quality assessment*

The CS presented a table of methodological quality assessment of the MARIPOSA trial based on the York CRD quality assessment checklist for RCTs. Following the clarification round, the company undertook a further quality assessment of the MARIPOSA trial using the Cochrane Risk of Bias 2 tool and provided an accompany narrative summary (see clarification response A15).[25] A summary of the RoB2 quality assessment undertaken by the company and the EAG is presented in Table 6. The EAG is mostly satisfied with the company's critical assessment of the study but disagrees that the overall risk of bias is low. Since the amivantamab with lazertinib arm of the MARIPOSA study is open-label, blinding of participants was not possible; however, outcome assessments were undertaken by blinded independent central review (BICR) to minimise detection bias. In addition, no detailed information was provided in the CS[1] regarding deviations from the intended intervention, adherence to the intervention and use of any concomitant medication. Hence the EAG, considers the overall bias to be of some concern.

No attempt has been made in the CS[1] to integrate the assessment of study quality into the findings reported.

Table 6: Cochrane Risk of Bias 2.0 Assessment for MARIPOSA trial (reproduced from clarification response, question A15, Table 2)

Signalling questions	Comments	Company Response	EAG Response
Domain 1: Risk of bias arising from the randomisation process			
1.1 Was the allocation sequence random?	Computer-generated randomisation (using blocks and stratification); interactive web response system to conceal treatment allocation	Y	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Baseline characteristics were well-balance between treatment arms	N	N
Risk of bias judgement	Randomisation achieved successfully, with allocation sequence concealment	**Low**	**Low**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)			
2.1 Were participants aware of their assigned intervention during the trial?	Osimertinib and lazertinib monotherapy arms administered in double-blinded manner. Blinding for amivantamab with lazertinib not feasible due to administration route	PY	Y
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PY	Y
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No deviations from allocated study drug reported	N	N
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	-	NA	NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	-	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All randomised patients included in efficacy analyses, classified according to their assigned treatment arm rather than actual treatment received (i.e., ITT)	Y	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	-	NA	NA

Signalling questions	Comments	Company Response	EAG Response
Risk of bias judgement	Participants and carers aware of intervention but no deviations from intended interventions	**Low**	**Some concern**
Domain 3: Missing outcome data			
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	ITT analyses used for all efficacy outcomes	Y	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	-	NA	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	-	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA	NA
Risk of bias judgement	Data available for all participants across efficacy outcomes	**Low**	**Low**
Domain 4: Risk of bias in measurement of the outcome			
4.1 Was the method of measuring the outcome inappropriate?	Appropriate measurement of outcomes, according to RECIST v1.1 assessment	N	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Identical methods of outcome measurement between intervention groups	N	N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	All efficacy outcomes performed by BICR	N	N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	-	NA	NA

Signalling questions	Comments	Company Response	EAG Response
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	-	NA	NA
Risk of bias judgement	Appropriate methods of measuring outcomes, comparable between intervention groups; outcome assessors unaware of intervention received	**Low**	**Low**
Domain 5: Risk of bias in selection of the reported result			
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Reported results aligned with pre-specified analysis plan in study protocol/statistical analytical plan	Y	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...			
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	All pre-specified outcome measurements reported on	N	N
5.3 ... multiple eligible analyses of the data?	All eligible analyses of data appear to be reported on across outcomes	N	N
Risk of bias judgement	Data analysed in line with pre-specified protocol/statistical analytical plan	**Low**	**Low**
Overall risk of bias judgement			
Risk of bias judgement	Trial involved successful randomisation and treatment allocation; appropriate outcome measurement methods, ITT and blinded outcome assessors; data analysed in line with pre-specified protocol	**Low**	**Some concern**

ITT - intent-to-treat; N - No; NI - no information; PN - partly no; PY - partly yes; RECIST - Response Evaluation Criteria in Solid Tumors; Y - yes.

3.2.2.2 *Efficacy results*

The statistical methods used for the analysis of the MARIPOSA trial are reported in CS,[1] page 53, Table 10; these are summarised below. Unless otherwise stated, all efficacy results are presented for amivantamab with lazertinib (N=429) versus osimertinib (N=429) based on the FAS.

PFS data are presented for the interim DCO (11th August 2023) and for all other efficacy endpoints, data are presented for the most recent DCO (13th May 2024), with a median duration of follow-up across both treatment arms of 31.1 months. In response to the EAG's clarification request for PFS data from the 13th May 2024 DCO (question A17),[25] the company stated the following: "*The primary endpoint of the MARIPOSA trial, PFS assessed by blinded independent central review (BICR), was met at the 11th August 2023 DCO, where amivantamab-lazertinib demonstrated a 30% reduction on the risk of disease progression by BICR or death compared with osimertinib. The 13th May 2024 DCO was requested by the European Medicines Agency (EMA) to assess interim OS data only; as such, PFS data are not available from the 13th May 2024 DCO, and the most up-to-date data for PFS (from the 11th August 2023 DCO) have been provided within the submission*."[25] The company also provided additional clarification on this issue during the factual accuracy check stating, "*the statistical alpha (0.05) for PFS was spent at [the 11th August 2023 DCO], so data for this endpoint could not be, and were not, collected in any subsequent DCOs."*

Primary endpoint

Progression-free survival

The primary endpoint analysis in the MARIPOSA trial was PFS assessed by BICR. The treatment differences of the amivantamab with lazertinib arm with the osimertinib arm were compared based on log-rank test stratified by mutation type (exon 19 deletion vs exon 21 L858R substitution), race (Asian vs non-Asian) and history of brain metastases (present vs absent). The median PFS and 95% confidence interval (CI) was estimated using the Kaplan-Meier (KM) method. The final analysis of PFS was based on the 11th August 2023 DCO, with a median follow-up across both treatment arms of 22.0 months and median follow-up of [redacted] and [redacted] months in the amivantamab with lazertinib arm and osimertinib arm, respectively. BICR-assessed median PFS showed an improvement of 7.1 months in the amivantamab with lazertinib (23.7 months; 95% confidence interval [CI]: 19.1, 27.7 months) compared with the osimertinib arm (16.6 months; 95% CI: 14.8, 18.5 months). Hazard ratio (HR) for disease progression or death was 0.70 (95% CI: 0.58, 0.85, p<0.001), indicating a 30% reduction in the risk of disease progression or death, see Table 7 and Figure 2.

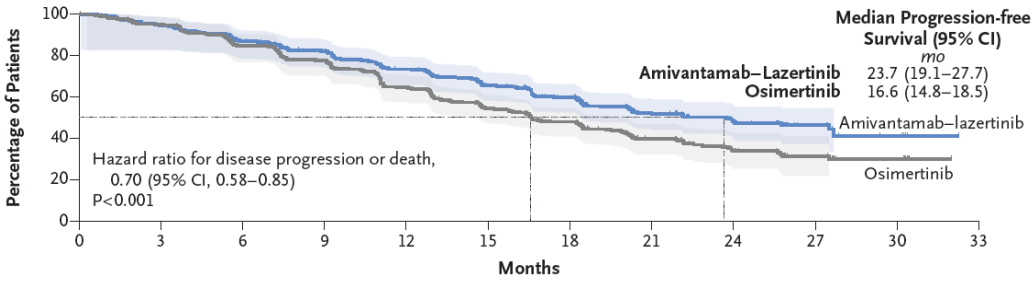
The analysis of PFS based on INV was conducted as a sensitivity analysis. The median PFS as assessed by INV was [redacted] months (95% CI: [redacted] months) in the amivantamab with lazertinib arm

and [redacted] months ([redacted] months) in the osimertinib arm, improving median PFS by [redacted] months. A [redacted] reduction in the risk of disease progression or death in patients receiving amivantamab with lazertinib compared with patients receiving osimertinib (HR: [redacted]) was observed, see Table 7. Results of PFS per INV and per BICR both indicated superiority of amivantamab with lazertinib compared with osimertinib.

The difference in PFS between amivantamab with lazertinib and osimertinib increased at later time points, from 8% at 12 months to 14% at 24 months as assessed by BICR and from [redacted] at 12 months to [redacted]% at 24 months, respectively, as assessed by INV, indicating that the benefit provided by amivantamab with lazertinib is durable over time. However, in the INV assessment at 30 months, the difference in the event-free rate between the two treatment groups reduced to 5%. As the 30 month PFS data by BICR were not reported in the CS[1], EAG is unclear on the durability of the treatment effect of amivantamab with lazertinib beyond 24 months, but the EAG notes that there are limited number of patients at risk at 30 months, with 8 and 10 patients for amivantamab with lazertinib and osimertinib respectively.

The KM and cumulative hazard plots for PFS by BICR in both treatment arms are presented in CS[1] Figure 8 (reproduced below as Figure 2) and CS Figure 9, respectively and PFS by INV are presented in CS[1] Figure 10 and CS Figure 11, respectively.

Figure 2: KM plot of PFS assessed by BICR (11th August 2023 DCO; FAS; reproduced from CS, Figure 8)



Abbreviations: BICR - blinded independent central review; CI - confidence interval; DCO - data cut-off; FAS - full analysis set; KM - Kaplan-Meier; mo - months; PFS - progression-free survival.
Source: Cho *et al.* 2024. Figure 1A.[3]

Table 7: Analysis of the primary endpoint of PFS in MARIPOSA study assessed by BICR and INV on the Full Analysis Set at DCO 11th August 2023 (reproduced from CS, Table 13 and 14)

	Blinded Independent Central Reviewer Assessment		Investigator Reviewer Assessment	
	Amivantamab with lazertinib (N=429)	**Osimertinib (N=429)**	**Amivantamab with lazertinib (N=429)**	**Osimertinib (N=429)**
PFS events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median PFS (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate, % (95% CI)	73 (69, 77)	65 (60, 69)	[redacted]	[redacted]
18-month event-free rate, % (95% CI)	60 (55, 64)	48 (43, 53)	[redacted]	[redacted]
24-month event-free rate, % (95% CI)	48 (42, 54)	34 (28, 39)	[redacted]	[redacted]
30-month event-free rate, % (95% CI)			[redacted]	[redacted]
Treatment difference				
p-value[a]	< 0.001		[redacted]	
HR (95% CI)[b]	0.70 (0.58, 0.85)		[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon 19 deletion or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).[redacted] [b] HR is from stratified proportional hazards model. HR < 1 favours amivantamab with lazertinib treatment.
+ censored observation
Abbreviations: CI - confidence interval; HR - hazard ratio; NE - not estimable.

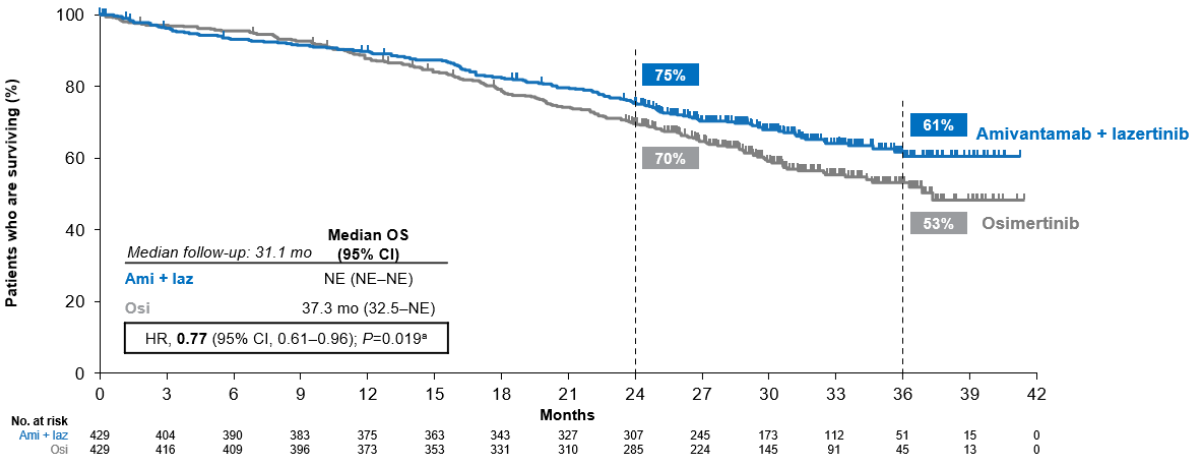
Secondary endpoints - OS, ORR, DOR, PFS2 and TTSP

Overall survival

The secondary endpoints analysis in the MARIPOSA trial was OS, based on FAS (13th May 2024 DCO).[3] [redacted] out of 429 patients [redacted] in the amivantamab with lazertinib arm and [redacted]/429 [redacted] in the osimertinib arm had died, with a survival benefit of 23% for amivantamab with lazertinib (HR: 0.77; 95% CI: 0.61, 0.96; p=0.019) (Table 8). The OS rate at 30 months and 36 months was [redacted] and 61%, respectively, for patients in the amivantamab with lazertinib arm versus [redacted] and 53%, respectively for patients treated with osimertinib. The median OS for amivantamab with lazertinib remained not estimable, while it was 37.3 months in the osimertinib arm. The CS[1] states that the OS analysis at 13th May 2024 DCO was unplanned and a p-value of ≤ 0.00001 is required to achieve statistical significance. The FDA stated that amivantamab with lazertinib appears to indicate no obvious detrimental effect on OS and has required a final OS analysis at May 2025 DCO.[51]

The KM and cumulative hazard plots for OS at the 13th May 2024 DCO are presented in CS[1] Figure 12 (reproduced below as Figure 3) and CS Figure 13, respectively.

Figure 3: KM plot of OS (13th May 2024 DCO; FAS; reproduced from CS, Figure 12)



Abbreviations: Ami + laz - amivantamab with lazertinib; CI - confidence interval; DCO - data cut-off; FAS - full analysis set; HR - hazard ratio; KM - Kaplan-Meier; mo - months; NE - not estimable; No. - number; OS - overall survival; Osi - osimertinib.
Footnotes: [a]p-value was calculated from a log-rank test stratified by mutation type (ex19del or exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified proportional hazards model.
Source: Gadgeel *et al.* WCLC 2024.[52]

The MARIPOSA study is ongoing and a pre-specified final OS analysis with formal statistical testing is planned; however, the company reported in the CS[1] that on January 7 2025, Johnson and Johnson announced an improvement in OS in the amivantamab with lazertinib arm compared with osimertinib arm at the final analysis median follow-up of [redacted] months ([redacted]). The median OS was not estimable

([redacted]) in the amivantamab with lazertinib arm, while the median OS for osimertinib was reached at [redacted] months ([redacted]). The company was not able to include these data in the submission as currently only top-line data are available.

Table 8: Analysis of secondary endpoints for the MARIPOSA study assessed by BICR on the Full Analysis Set at DCO 13th May 2024 (reproduced from CS, Table 15, 16, 17, 19 and 20)

	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)
Overall Survival		
Events, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	NE (NE, NE)	37.3 (32.5, NE)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.75 [redacted]	0.70 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.61 [redacted]	0.53 [redacted]
Treatment difference		
p-value[a]	0.019	
HR (95% CI)[b]	0.77 (0.61, 0.96)	
ORR based on RECIST v1.1 criteria in patients with measurable disease at baseline by BICR		
Patients with measurable disease at baseline, n	[redacted]	[redacted]
ORR, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Treatment difference		
p-value[a]	[redacted]	
Odds ratio (95% CI)[c]	[redacted]	
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE	[redacted]	[redacted]
DOR in confirmed responders based on patients with measurable disease at baseline by BICR		
Confirmed responders (CR+PR), n	[redacted]	[redacted]

	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)[d]		
Median (95% CI)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
DOR ≥ 6 months, n (%)	[redacted]	[redacted]
DOR ≥ 12 months, n (%)	[redacted]	[redacted]
DOR ≥ 18 months, n (%)	[redacted]	[redacted]
DOR ≥ 24 months, n (%)	[redacted]	[redacted]
DOR ≥ 30 months, n (%)	[redacted]	[redacted]
DOR ≥ 36 months, n (%)	[redacted]	[redacted]
PFS2: Progression-free survival after first subsequent therapy		
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	NE (36.0, NE)	32.4 (29.3, NE)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	[redacted]	[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	[redacted]	[redacted]
Treatment difference		
Nominal *p*-value[a]	0.004	
HR (95% CI)[b]	0.73 (0.59, 0.91)	

	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)
TTSP Time to symptomatic progression		
Event, n (%)	[redacted]	[redacted]
Symptomatic PD, n (%)	[redacted]	[redacted]
Death without symptomatic PD, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	0.74[redacted]	0.67[redacted]
24-month event-free rate (95% CI)	0.67[redacted]	0.59[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	[redacted]	[redacted]
Treatment difference		
p-value[a]	[redacted]	
HR (95% CI)[b]	[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (exon 19 deletion or exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no). [b] HR is from stratified proportional hazards model. HR < 1 favours amivantamab with lazertinib treatment.

[c] Odds ratio > 1 favours amivantamab with lazertinib treatment.
[d] Quartiles and 95% CIs are estimated with Kaplan-Meier method.
+ censored observation
Note: In ORR, CR and PR do not have to be confirmed. Percent of Responder is based on the number of subjects with measurable disease at baseline
In DOR, Percentages are based on the number of subjects who achieved Confirmed CR or Confirmed PR.
Abbreviations: BICR - blinded independent central review; BOR - best overall response; CI - confidence interval; CR - complete response; DCO - data cut-off; DOR - duration of response; FAS - full analysis set; HR - hazard ratio; NE - not estimable; ORR - objective response rate; OS - overall survival; PD - progressive disease; PFS2 - progression-free survival after first subsequent therapy; PR - partial response; RECIST - Response Evaluation Criteria in Solid Tumours; SD - stable disease; TTSP - time to symptomatic progression

Objective response rate

The descriptive analysis of the secondary endpoint of ORR was assessed in patients with measurable disease at baseline ([redacted]/429 patients in the amivantamab with lazertinib arm and [redacted]/429 patients in the osimertinib arm) and responders were defined as patients achieving either a CR or PR, as assessed by BICR assessment per RECIST v1.1 criteria. At the 13th May 2024 DCO, the ORR rate was [redacted] in the amivantamab with lazertinib arm and [redacted] in the osimertinib arm, with an odds ratio (OR) of [redacted] showing numerically similar results between the two treatment arms. This indicates that patients receiving amivantamab with lazertinib have 19% higher odds to achieve an ORR compared with patients receiving osimertinib. A [redacted] proportion of patients in the amivantamab with lazertinib arm achieved a CR ([redacted]) compared with the osimertinib arm ([redacted]) and there were [redacted] patients in

the amivantamab with lazertinib arm with progressive disease compared with the osimertinib arm (and , respectively); see Table 8. The EAG notes that these numbers are small and may not be clinically meaningful. As noted by the FDA, ORR was included as a secondary endpoint but was not part of the pre-specified testing plan.[51]

Duration of response

In the descriptive analysis of the secondary endpoint of DOR, the median DOR was longer in the amivantamab with lazertinib arm, months (95% CI:), compared with months (95% CI:) in the osimertinib arm. Patients treated with amivantamab with lazertinib had a median DOR that was months longer than patients treated with osimertinib. The percentages of patients in the amivantamab with lazertinib arm remaining in confirmed response at 18- and 24-months were and , respectively, compared with and , respectively, for patients receiving osimertinib. A KM plot for DOR in both treatment arms is presented in CS[1], Figure 14. In the CS, ORR and DOR analyses were conducted only in the subgroup of patients with measurable disease at baseline, but ideally, as highlighted in the FDA, ORR and DOR analyses should be based on confirmed responses in the intention-to-treat (ITT) population.[51]

Progression-free survival after first subsequent therapy

As of the 13th May 2024 DCO, the proportion of patients who went on to receive a subsequent anticancer therapy after treatment discontinuation due to disease progression was similar between the two treatment arms: 72% (80/111) in the amivantamab with lazertinib arm and 74% (128/173) in the osimertinib arm. In both the amivantamab with lazertinib arm and the osimertinib arm, the most commonly received subsequent systemic therapy was doublet chemotherapy (41% and 45%, respectively). A greater proportion of patients in the amivantamab with lazertinib arm (27%) received a third-generation TKI than in the osimertinib arm (16%) whilst more patients in the osimertinib arm (20%) received chemotherapy plus a VEGFi and IO than in the amivantamab with lazertinib arm (12%). Further details are provided in CS[1], Table 18, page 68.

A higher proportion of patients experienced progression after first subsequent therapy in the osimertinib arm ( ) compared with the amivantamab with lazertinib arm ( ). The CS reports a statistically significant reduction in the risk of second disease progression or death in the amivantamab with lazertinib arm compared with the osimertinib arm (HR: 0.73 [95% CI: 0.59, 0.91]; nominal p=0.004) (Table 8). Median PFS2 was 32.4 months (95% CI:29.3, NE) in the osimertinib arm and not estimable in the amivantamab with lazertinib arm (95% CI: 36.0, NE). At 36 months, 43% of patients treated with amivantamab with lazertinib and 51% of patients in the osimertinib group had progressed after their first subsequent therapy. The associated KM plot for PFS2 is presented in CS, Figure 15. The FDA notes that results of PFS2 are solely exploratory and hypothesis-generating.[51]

Time to symptomatic progression

Symptomatic progression or death was experienced in fewer patients in the amivantamab with lazertinib arm than the osimertinib arm ([redacted] versus [redacted]). The CS indicates a reduction in the risk of symptomatic progression or death in the amivantamab with lazertinib arm (HR: [redacted]; 95% CI: [redacted], [redacted], nominal *p*=[redacted]; Table 8).

Median time to symptomatic progression (TTSP) was [redacted] in the amivantamab with lazertinib arm, compared with [redacted] months in the osimertinib arm. At 24- and 36-months, [redacted] patients had experienced symptomatic progression in the amivantamab with lazertinib arm (event-free rates of [redacted] and [redacted], respectively) compared with patients in the osimertinib arm (event-free rates of [redacted] and [redacted], respectively). In agreement with the FDA,[51] the EAG considers TTSP to be exploratory; hence, these outcomes should be viewed with caution.

Exploratory endpoints

Time to treatment discontinuation

TTD was investigated as an exploratory endpoint in the MARIPOSA trial. At the 13th May 2024 DCO, a higher proportion of patients in the osimertinib arm had discontinued treatment or died compared with the amivantamab with lazertinib arm ([redacted] versus [redacted]); see Table 9. Median TTD in the amivantamab with lazertinib arm was 26.3 months; (95% CI: 22.3 to 30.4 months) and 22.6 months; 95% CI: 20.3 to 24.5 months) in the osimertinib arm (HR: 0.80; 95% CI: 0.68, 0.96; *p*=0.014). At three years, more patients in the amivantamab with lazertinib arm remained on treatment compared with the osimertinib arm (40% versus 29%, respectively). However, as reported in response to clarification question A18,[25] at the 11th August 2023 DCO, [redacted] patients in the amivantamab with lazertinib arm versus [redacted] patients in the osimertinib arm discontinued or were censored after progression and [redacted] in the amivantamab with lazertinib arm versus [redacted] in the osimertinib arm discontinued before or at the time of progression.

Time to subsequent therapy

At the 13th May 2024 DCO, [redacted] of patients in the amivantamab with lazertinib arm and [redacted] of patients in the osimertinib arm had initiated subsequent systemic therapy (see Table 9)**.** The median time to initiation of any subsequent anticancer therapy was longer in the amivantamab with lazertinib arm (30.0 months; 95% CI: 26.3 to 36.0 months) compared with the osimertinib arm (24.0 months; 95% CI: 22.5 to 26.2 months). A [redacted] reduction in risk (HR: 0.77; 95% CI: 0.65, 0.93; nominal *p*=0.005) for time to subsequent therapy (TTST) in the amivantamab with lazertinib arm compared with the osimertinib arm was observed, which was statistically significant. The EAG noted that since both TTD and TTST are exploratory analyses, it should be used with caution.

Table 9: Exploratory analyses for the MARIPOSA Study assessed by BICR on the Full Analysis Set at DCO 13th May 2024 (reproduced from CS, Table 21 and 22)

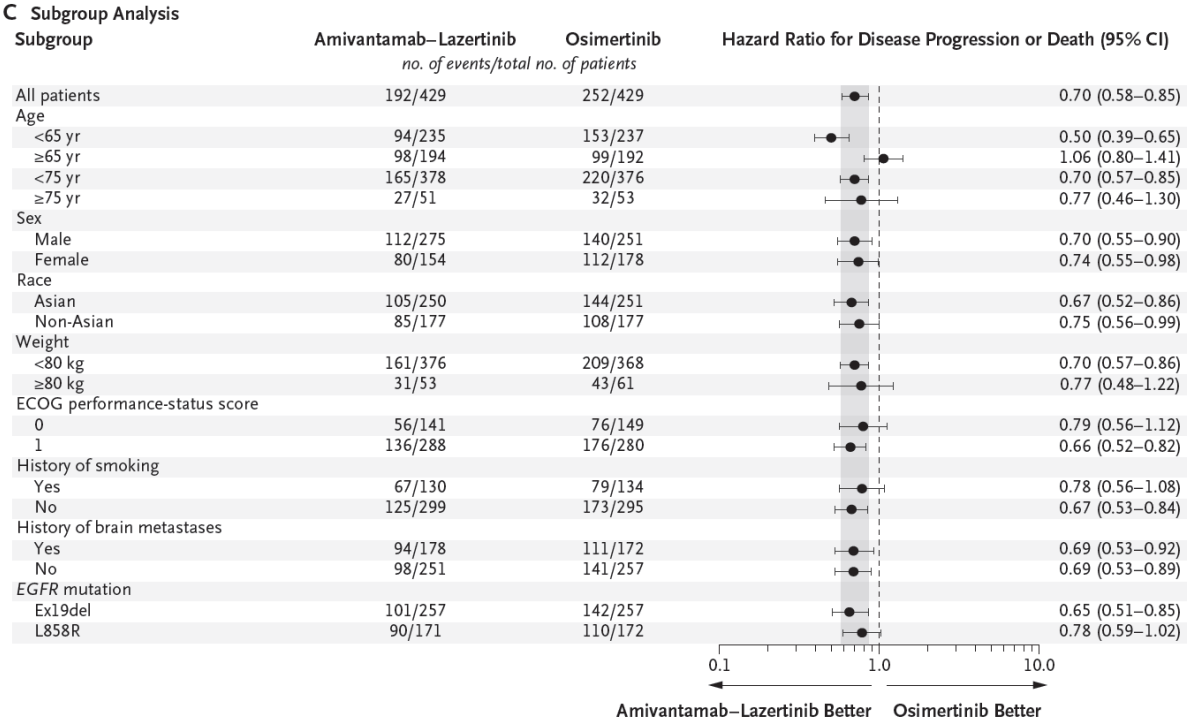
	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)
TTD: Time to treatment discontinuation		
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	26.3 (22.3, 30.4)	22.6 (20.3, 24.5)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.52 [redacted]	0.46 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.40 [redacted]	0.29 [redacted]
Treatment difference		
p-value[a]	0.014	
HR (95% CI)[b]	0.80 (0.68, 0.96)	
TTST: time to subsequent systemic anti-cancer therapy		
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	30.0 (26.3, 36.0)	24.0 (22.5, 26.2)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.57 [redacted]	0.50 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.45 [redacted]	0.32 [redacted]
Treatment difference		
p-value[a]	0.005	
HR (95% CI)[b]	0.77 (0.65, 0.93)	

[a] p-value is from a log-rank test stratified by mutation type (exon 19 deletion or exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR < 1 favours amivantamab with lazertinib treatment.
+ censored observation
Abbreviations: CI - confidence interval; DCO - data cut-off; FAS - full analysis set; HR - hazard ratio; NE - not estimable; TTD - time to treatment discontinuation.

Subgroup analysis in MARIPOSA trial

PFS assessed by BICR per RECIST 1.1 for subgroups defined by baseline disease characteristics at the 11th August 2023 DCO using the FAS is presented in Figure 4. Subgroups were analysed by age, sex, race, weight, ECOG PS, history of smoking, history of brain metastases and EGFR mutation. A broadly consistent benefit with amivantamab with lazertinib was observed across most pre-specified subgroups, except for patients who were aged 65 or older, with the HR being 1.06 (95% CI: 0.80, 1.41). In addition, beneficial effects were not statistically significant for EGFR mutation L858R, those with history of smoking, ECOG PS of 0, weight ≥ 80 kg and in patients aged ≥ 75 years.

Figure 4: Forest plot of PFS assessed by BICR for subgroups defined by baseline disease characteristics (11th August 2023 DCO; FAS), reproduced from CS, Figure 20



Footnotes: The shaded area indicates the 95% confidence interval for the overall hazard ratio among all the patients (primary end point). Except for the primary end point, 95% confidence intervals in the subgroup analysis were not adjusted for multiplicity, with the hazard ratios for progression or death obtained from an unstratified proportional-hazards model, and should not be used to infer definitive treatment effects. Race was reported by the patient. ECOG performance-status scores range from 0 to 5, with higher scores indicating greater disability.
Abbreviations: BICR - blinded independent central review; CI - confidence interval; DCO - data cut-off; ECOG - Eastern Cooperative Oncology Group; EGFR - epidermal growth factor receptor; Ex19del - exon 19 deletion; FAS - full analysis set; HR - hazard ratio; L858R - exon 21 L858R substitution mutations; PFS - progression-free survival; PS - performance status; yr - years.

A secondary analysis in the MARIPOSA trial was undertaken in patients (N=636) with biomarkers of high-risk disease (amivantamab with lazertinib, N=320; osimertinib, N=316), including detectable ctDNA, TP53 co-mutations or metastases in the liver or brain. PFS benefit was observed with amivantamab with lazertinib compared with osimertinib (mPFS: 20.3 months (95% CI: 18.2 to 24.0 months) versus 15.0 months (95% CI: 13.0-16.8 months), respectively; HR: 0.72; 95% CI: 0.58, 0.90; p=0.004). As reported in Felip *et al.* 2024,[36] amivantamab with lazertinib improved mPFS versus osimertinib for patients with TP53 co mutations, (18.2 versus 12.9 months; HR 0.65 [95% CI: 0.48-

0.87]); and for patients with wild-type TP53, (22.1 versus 19.9 months; HR 0.75 [95% CI 0.52-1.07]). In patients with EGFR-mutant, ddPCR-detectable baseline ctDNA, amivantamab with lazertinib significantly prolonged mPFS versus osimertinib (20.3 versus 14.8 months; HR 0.68 [95% CI 0.53-0.86]; *p*=0.002). Amivantamab with lazertinib significantly improved mPFS versus osimertinib in patients without ctDNA clearance at C3D1 (16.5 versus 9.1 months; HR 0.49 [95% CI 0.27-0.87]; *p*=0.015) and with clearance (24.0 versus 16.5 months; HR 0.64 [95% CI 0.48-0.87]; *p*=0.004). Amivantamab with lazertinib significantly prolonged mPFS versus osimertinib among randomised patients with (18.2 versus 11.0 months; HR 0.58 [95% CI 0.37-0.91]; *p*=0.017] and without baseline liver metastases (24.0 versus 18.3 months; HR 0.74 [95% CI 0.60-0.91]; *p*=0.004).

OS by subgroup demonstrated a [redacted], across subgroups of history of brain metastases, EGFR mutation type and race (see Figure 5). EAG notes that the MARIPOSA trial is ongoing and these are only exploratory endpoints.

Figure 5: Forest plot of OS for subgroups defined by baseline disease characteristics (13th May 2024 DCO; FAS), reproduced from CS, Figure 21

Abbreviations: CI - confidence interval; DC - data cut; EGFR - epidermal growth factor receptor; exon 19del - exon 19 deletion; FAS - full analysis set; HR - hazard ratio; exon 21 L858R - exon 21 L858R substitution mutations; OS - overall survival; strat - stratification.

Analysis of intracranial endpoints in patients with a history of brain metastases in the MARIPOSA trial

Secondary endpoint: Intracranial PFS

At the 13th May 2024 DCO, among patients with a history of brain metastases, [redacted] patients in the amivantamab with lazertinib arm had BICR-assessed intracranial disease progression or had died, compared with those in the osimertinib arm ([redacted] versus [redacted], respectively), HR=0.82 (95% CI: 0.62, 1.09; nominal *p*=0.165) (see Table 10). The median intracranial PFS was comparable between the two treatment arms with 24.9 months (95% CI: 20.1 to 34.7 months) in the amivantamab with lazertinib arm compared with 22.2 months (95% CI: 18.4 to 26.1 months) in the osimertinib arm.

At 24 months, the proportion of patients remaining progression-free was similar between treatment arms (51% in the amivantamab with lazertinib arm and 48% in the osimertinib arm) whereas by 36 months, 38% of patients in the amivantamab with lazertinib arm remained progression-free compared with 18% of patients in the osimertinib arm. A KM plot for intracranial PFS assessed by BICR in both treatment arms is presented in CS Appendix M,[1] Figure 6. The FDA noted that the company's intracranial PFS analysis does not account for events of extra-cranial progression; hence, it considers these analyses as exploratory.[51]

Exploratory endpoint: Intracranial ORR

The exploratory analysis of intracranial ORR was based on RECIST v1.1 criteria in patients with intracranial disease at baseline by BICR and responders were defined as patients achieving either intracranial CR or PR, but CR and PR did not have to be confirmed. The percentage of responders was based on the number of subjects with measurable disease at baseline. The EAG notes that the FDA[51] considered that the use of confirmed responses would have been more appropriate for characterising the treatment effect on intracranial ORR.

At the 13th May 2024 DCO, there were no major differences in confirmed intracranial ORR between the amivantamab with lazertinib arm and the osimertinib arm ([redacted] versus [redacted], respectively) with an OR of [redacted] (95% CI: [redacted]; nominal *p*=[redacted]). A higher proportion of patients in the amivantamab with lazertinib arm achieved a intracranial CR [redacted] compared with the osimertinib arm ([redacted]), whilst a lower proportion of patients in the amivantamab with lazertinib arm achieved a intracranial PR ([redacted]) compared with the osimertinib arm ([redacted]) (see Table 10).

Among the 139 responding patients (those achieving CR or PR), [redacted] of patients in the amivantamab with lazertinib arm had intracranial disease progression or died, compared with [redacted] of the 144 responding patients in the osimertinib arm. Median intracranial DOR was 24.4 months (95% CI: 22.1 to 31.2 months) in the osimertinib arm and was not estimable in the amivantamab with lazertinib arm

(Table 10). In the amivantamab with lazertinib arm, [redacted] and [redacted] had an intracranial DOR of at least 18 months and 24 months, respectively, compared with [redacted] and [redacted] at these timepoints in the osimertinib arm, which suggests improved intracranial DOR in the amivantamab with lazertinib arm compared with osimertinib. The KM plot of intracranial DOR is presented in CS[1], Appendix M, Figure 7.

Table 10: Summary of efficacy results for the MARIPOSA trial by BICR, based on RECIST v1.1 criteria in patients with history of brain metastasis at baseline (reproduced from CS, Appendix M, Table 70, 71 and 72)

	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)
iPFS (11th August 2023 DCO; FAS)		
Patients with history of brain metastasis[a], n (%)	178 (41)	172 (40)
PFS Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)		
Median (95% CI)	24.9 (20.1, 34.7)	22.2 (18.4, 26.1)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.51[redacted]	0.48[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.38[redacted]	0.18[redacted]
Treatment difference		
p-value[b]	0.165	
HR (95% CI)[c]	0.82 (0.62, 1.09)	
iORR based on RECIST v1.1 criteria in patients with intracranial disease at baseline by BICR-(13th May 2024 DCO; FAS)		

	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)
Patients with intracranial disease at baseline, n	[redacted]	[redacted]
iORR, n (%)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Treatment difference		
p-value[d]	[redacted]	
Odds ratio (95% CI)[d,e]	[redacted]	
Intracranial DOR, n (%)		
Intracranial CR	[redacted]	[redacted]
Intracranial PR	[redacted]	[redacted]
Intracranial SD[f]	[redacted]	[redacted]
Intracranial PD	[redacted]	[redacted]
Intracranial NE	[redacted]	[redacted]
DOR in responders based on patients with intracranial disease at baseline by BICR (13th May 2024 DCO; FAS)		
Responders (CR+PR), n	[redacted]	[redacted]
Event, n (%)	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]
Time to event (months)[g]		
Median (95% CI)	NE (21.4, NE)	24.4 (22.1, 31.2)
25th percentile (95% CI)	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]
Range	[redacted]	[redacted]
DOR ≥ 6 months, n (%)	[redacted]	[redacted]
DOR ≥ 12 months, n (%)	[redacted]	[redacted]
DOR ≥ 18 months, n (%)	[redacted]	[redacted]
DOR ≥ 24 months, n (%)	[redacted]	[redacted]
DOR ≥ 30 months, n (%)	[redacted]	[redacted]
DOR ≥ 36 months, n (%)	[redacted]	[redacted]

[a] History of brain metastasis is based on investigator reported data recorded on electronic case report form.
[b] p-value is from a log-rank test stratified by mutation type (exon 19 deletion or exon 21 L858R) and Asian race (yes or no). [redacted] HR is from stratified proportional hazards model. HR < 1 favours amivantamab with lazertinib treatment.
[d] *p*-value and odds ratio are from a logistic regression model stratified by mutation type (exon 19 deletion or exon 21 L858R) and Asian race (yes or no).
[e] Odds ratio > 1 favours amivantamab with lazertinib treatment.
[f] Includes non-CR/non-PD in subjects with only non-target lesions at baseline.
[g] Quartiles and 95% CIs are estimated with Kaplan-Meier method.
+ censored observation
Note: In iORR, CR and PR do not have to be confirmed. Percent of Responder is based on the number of subjects with measurable disease at baseline In DOR, Percentages are based on the number of subjects who achieved Confirmed CR or Confirmed PR.
Abbreviations: BICR - blinded independent central review; BOR - best overall response; CI - confidence interval; CR - complete response; DCO - data cut-off; DOR - duration of response; FAS - full analysis set; HR - hazard ratio; iORR - intracranial objective response rate; iPFS - intracranial progression-free survival; NE - not estimable; PD - progressive disease; PR - partial response; PS - performance status; RECIST - Response Evaluation Criteria in Solid Tumours; SD - stable disease.

Health-related quality of life

The MARIPOSA trial included three PRO measures: the EORTC-QLQ-C30, the NSCLC-SAQ, and the EQ-5D-5L. However, the CS only reports data for the EQ-5D-5L based on the 13th May 2024 DCO. Following a request for clarification from the EAG (see clarification response, question A20),[25] the company provided data from the EORTC-QLQ-C30 and the NSCLC-SAQ from the 11th August 2023 DCO. The scores from all three PRO measures are based on the FAS and presented in Table 11. There was [redacted] in the scores between the three PRO measures and overall scores were [redacted] in the osimertinib arm than the amivantamab with lazertinib arm at start of Q2W dosing schedule and end of treatment. EAG notes that these data are exploratory and should be interpreted with caution. In addition, given the safety profile of amivantamab with lazertinib, patient-generated data informing tolerability should have been more comprehensively collected. Specifically dermatologic and visual symptoms would have added valuable information regarding the patient experience in the MARIPOSA study.

Table 11: Analysis of patient reported outcome measures in the MARIPOSA Study (reproduced from CS, Table 23 and clarification response A20)

	EORTC-QLQ-C30 score (11th August 2023 DCO; FAS)				NSCLC-SAQ total scores (11th August 2023 DCO; FAS)		EQ-5D-5L utility scores (13th May 2024 DCO; FAS)	
	Global health status scores		Physical functioning scores					
	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)	Amivantamab with lazertinib (N=429)	Osimertinib (N=429)
Baseline								
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initiation of Q2W dosing (Cycle 2 Day 1)								
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment								
N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean change from baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

n for measured value is the number of patients with a non-missing value at the specified time point.
Abbreviations: DCO - data cut-off; FAS - full analysis set; SD - standard deviation; Q2W - once every two weeks.

3.3 Safety

This section presents the main safety evidence for the use of amivantamab with lazertinib in patients with untreated cEGFRm advanced NSCLC available from the ongoing MARIPOSA trial. The safety of amivantamab with lazertinib compared with osimertinib monotherapy was evaluated using the Safety Analysis Set (SAS), which includes randomised patients who received at least one dose of study treatment. This included 421 patients in the amivantamab with lazertinib arm and 428 patients in the osimertinib arm. The CS[1] notes that results for the lazertinib arm are not relevant to the decision problem for this appraisal and are therefore not presented here. The CS[1] reports safety data from the 11th August 2023 DCO. The EAG requested safety data from the 13th May 2024 DCO or later. In response to clarification question A21,[25] the company only provided data for Grade ≥ 3 TEAEs for the 13th May 2024 DCO. Since the MARIPOSA trial is still ongoing, the long-term effects of using amivantamab with lazertinib on safety are not yet clear.

A summary of the TEAEs from the SAS in the MARIPOSA trial at the 11th August 2023 DCO is presented in Table 12; further details are provided in CS[1], page 79, Table 25. Most patients experienced at least one AE in both treatment arms. A greater number of AEs related to study treatment as assessed by INV was found in the amivantamab with lazertinib arm (98%) compared with the osimertinib arm (88%). In both the amivantamab with lazertinib arm and the osimertinib arm, the most commonly observed AEs of any grade reflected inhibition of EGFR receptors and included: rash (62% versus 31%, respectively); dermatitis acneiform (29% versus 13%, respectively); stomatitis (29% versus 21%, respectively) and diarrhoea (29% versus 44%, respectively). Common TEAEs associated with MET inhibition activity of amivantamab included hypoalbuminemia (48%) and peripheral oedema (36%). Grade ≥ 3 TEAEs were observed with a higher incidence in the amivantamab with lazertinib arm compared with the osimertinib arm. Similarly, the incidence of serious adverse events (SAEs) was greater in the amivantamab with lazertinib (49%) arm than the osimertinib arm (33%). SAEs reported in ≥ 2% of patients in either arm (amivantamab with lazertinib versus osimertinib) were: pulmonary embolism ([redacted] versus [redacted]); pneumonia ([redacted] versus [redacted]; pleural effusion ([redacted] versus [redacted]); dyspnoea ([redacted] versus [redacted]); COVID-19 ([redacted] versus [redacted]); deep vein thrombosis (DVT) ([redacted] versus [redacted]). Infusion-related reactions (IRRs) were reported in [redacted] of patients in the amivantamab with lazertinib arm (CS[1], page 82, Table 28). While the incidence of SAEs was similar for most types of events across both treatment arms, VTEs occurred more frequently in the amivantamab with lazertinib arm.

In the amivantamab–lazertinib group, AEs leading to a dose interruption of any trial agent were reported in 350 (83%) patients, AEs leading to any dose reduction were reported in 249 (59%) patients, and AEs leading to any discontinuation of treatment were reported in 147 (35%) patients. The corresponding numbers in the osimertinib group were 165 (39%), 23 (5%), and 58 (14%). The most common AEs

leading to the discontinuation of any trial agent were IRRs and paronychia. AEs leading to death occurred in 34 (8%) patients in the amivantamab with lazertinib arm and 31 (7%) patients in the osimertinib arm.

Table 12: Overall summary of TEAEs (11th August 2023 DCO; SAS), reproduced from CS, page 79, Table 25 and Table 26

Event, n (%)	Amivantamab with lazertinib (N=421)	Osimertinib (N=428)
Patients with ≥ 1 AE	421 (100)	425 (99)
Related AEs[a]	414 (98)	378 (88)
AEs leading to death[b]	34 (8)	31 (7)
SAEs	205 (49)	143 (33)
AEs leading to discontinuation of any study agent	147 (35)	58 (14)
AEs leading to dose reduction of any study agent	249 (59)	23 (5)
AEs leading to dose interruption of any study agent[c]	350 (83)	165 (39)
AEs leading to dose interruption of amivantamab	328 (78)	N/A
Related AEs to amivantamab[a,c]	282 (67)	N/A
Grade ≥ 3 AEs	316 (75) [redacted]	183 (43) [redacted]
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
AEs reported in ≥ 15% of the patients in either group		
Skin and subcutaneous tissue disorders		
Rash	260 (62)	131 (31)
Dermatitis acneiform	122 (29)	55 (13)
Dry skin	67 (16)	60 (14)
Pruritus	99 (24)	73 (17)
Peripheral oedema	150 (36)	24 (6)
Stomatitis	122 (29)	90 (21)
Gastrointestinal disorders		
Constipation	123 (29)	55 (13)
Nausea	90 (21)	58 (14)
Diarrhoea	123 (29)	190 (44)
Infections and infestations		
Paronychia	288 (68)	121 (28)
COVID-19	111 (26)	103 (24)
Metabolism and nutrition disorders		

Event, n (%)	Amivantamab with lazertinib (N=421)	Osimertinib (N=428)
Hypoalbuminaemia	204 (48)	26 (6)
Decreased appetite	103 (24)	76 (18)
Hypocalcaemia	88 (21)	35 (8)
Blood and lymphatic system disorders		
Anaemia	96 (23)	91 (21)
Leukopenia	26 (6)	66 (15)
Thrombocytopenia	66 (16)	84 (20)
General disorders and administration site conditions		
Asthenia	78 (19)	46 (11)
Fatigue	70 (17)	42 (10)
Muscle spasms	70 (17)	32 (7)
Pain in extremity	64 (15)	22 (5)
Investigations		
Alanine aminotransferase increased	152 (36)	57 (13)
Aspartate aminotransferase increased	121 (29)	58 (14)
Injury, poisoning and procedural complications		
Infusion related reaction	265 (63)	0
Respiratory, thoracic and mediastinal disorders		
Cough	65 (15)	88 (21)
Dyspnoea	51 (12)	68 (16)
Pulmonary embolism	73 (17)	20 (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.
[c] Excludes infusion related reactions
[d] Data from 13th May 2024 DCO
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.
SAEs were defined in the MARIPOSA 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
Abbreviations: AE - adverse event; DCO - data cut-off; SAS - safety analysis set; SAEs, serious adverse events; TEAE - treatment-emergent adverse event

Grade ≥ 3 TEAEs in the CS were reported from the 11th August 2023 DCO. In response to clarification question A21,[25] the company provided data from the 13th May 2024 DCO, which is summarised below. Grade ≥ 3 TEAEs occurred more frequently in the amivantamab with lazertinib arm ([redacted]) compared with the osimertinib arm ([redacted]). Grade ≥ 3 AEs with a frequency of ≥ 5% are presented in Table 13. These included (amivantamab with lazertinib versus osimertinib): rash ([redacted] versus [redacted]); paronychia ([redacted] versus [redacted]); dermatitis acneiform ([redacted] versus [redacted]); IRR ([redacted] versus [redacted]); pulmonary embolism ([redacted] versus [redacted]) and hypoalbuminemia ([redacted] versus [redacted]). The EAG notes that as expected, the number of AE slightly increased in both treatment arms at the later DCO.

Table 13: Number of patients with Grade ≥ 3 TEAEs with frequency of > 5% in either relevant treatment group by system organ class and preferred term (SAS) (reproduced from CS, page 81, Table 27 and clarification response A21)

	11th August 2023 (DCO; SAS)		13th May 2024 (DCO; SAS)	
Event, n (%)	**Amivantamab with lazertinib (N=421)**	**Osimertinib (N=428)**	**Amivantamab with lazertinib (N=421)**	**Osimertinib (N=428)**
Patients with 1 or more Grade ≥ 3 AEs	316 (75)	183 (43)	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Rash	65 (15)	3 (1)	[redacted]	[redacted]
Dermatitis acneiform	35 (8)	0	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Paronychia	46 (11)	2 (< 1)	[redacted]	[redacted]
Pneumonia	NR	NR	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	35 (8)	10 (2)	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hypoalbuminaemia	22 (5)	0	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	21 (5)	8 (2)	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]	[redacted]
IRR	27 (6)	0	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac disorders	NR	NR	[redacted]	[redacted]
Gastrointestinal disorders	NR	NR	[redacted]	[redacted]
General disorders and administration site conditions	NR	NR	[redacted]	[redacted]
Nervous system disorders	NR	NR	[redacted]	[redacted]
Vascular disorders	NR	NR	[redacted]	[redacted]

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.
The event experienced by the patient with the worst toxicity is used.
Abbreviations: AE - adverse event; DCO - data cut-off; IRR - infusion-related reaction; NR – not reported; SAS - safety analysis set; TEAE - treatment-emergent adverse event.

AEs of special interest

AESIs were prospectively identified based upon the identified safety profile of amivantamab. Pre-defined AESIs per the protocol were IRRs, rash, and pneumonitis/ILD. VTE events were later identified as a risk for the amivantamab with lazertinib arm within the first four months of study treatment and were added as an AESI during the study. Overall, [redacted] patients ([redacted]) in the amivantamab with lazertinib arm and [redacted] patients ([redacted]) in the osimertinib arm had at least one AESI.

IRRs were most common TEAE in the amivantamab with lazertinib arm, occurring in [redacted] patients ([redacted]), with the majority of events occurring on Cycle 1, Day 1 ([redacted]), reducing to [redacted] of patients in cycle ≥ 2 ([redacted]). Most of the IRR events were Grade 1 or 2, with 27 patients (6%) experiencing Grade 3 IRR and [redacted] patients ([redacted]) experiencing a Grade 4 IRR. The FDA[51] reported a total of 54% of patients had dose interruptions, 0.7% had dose reductions, and 4.5% of patients had permanently discontinued amivantamab due to IRRs. Rash was commonly observed in both treatment arms (amivantamab with lazertinib [redacted] versus osimertinib [redacted]). More patients in the amivantamab with lazertinib arm experienced a Grade 3 event compared with the osimertinib arm ([redacted] versus [redacted]). Serious TEAEs of rash were only observed in the amivantamab with lazertinib arm ([redacted] versus [redacted]). Rash events leading to discontinuation of any study treatment occurred in [redacted] of participants in the amivantamab with lazertinib arm (amivantamab discontinuation: [redacted] patients; lazertinib discontinuation: [redacted] patients) compared with [redacted] patients in the osimertinib arm. The incidence of pneumonitis or ILD was similar between treatment arms ([redacted] ([redacted], N=[redacted]) in the amivantamab with lazertinib arm and the osimertinib arm, respectively, with Grade ≥ 3 events occurring in 1% in each group. VTEs were identified as a high-risk AE for patients during the trial in the amivantamab with lazertinib arm, occurring in [redacted] of the patients in the amivantamab with lazertinib arm and in [redacted] of patients in the osimertinib group. Among the VTE AEs, 62% of events occurred in the first four months of treatment compared with 33% in the osimertinib group.[3] As such, a protocol amendment was implemented, recommending that patients in the amivantamab with lazertinib arm receive prophylactic anticoagulation for the first four months of treatment. The EAG asked the company to provide additional data describing the incidence of VTEs in patients with and without prophylactic anticoagulation, as well as the need for treatment-level anticoagulation, to clarify whether prophylactic anticoagulation for the first four months of therapy is adequate (see clarification response, question A22).[25] The company's response states: "*at the time of this Urgent Safety Measure, enrolment [sic] in MARIPOSA had completed and only 12 participants were eligible for prophylactic anticoagulation per the recommendation. Data regarding the incidence of VTEs in patients with and without prophylactic anticoagulation are not available."* The company provided a summary of first VTE events by anticoagulation status (unrelated to prophylaxis) in Table 14 and stated that: "*Nearly all first VTE events occurred in participants who were not receiving concomitant anticoagulants, and recurrent VTE events while on anticoagulants were uncommon.*"[25]

The most common VTE events were pulmonary embolism and DVT. Overall, [redacted] ([redacted]) patients in the amivantamab with lazertinib arm required hospitalisation or prolongation of hospitalisation due to a VTE, with the main reason for hospitalisation being the initiation of anticoagulation treatment ([redacted]). In contrast, a higher proportion of patients in the osimertinib arm required hospitalisation or prolongation of hospitalisation due to a VTE ([redacted]), with management of symptoms

representing the most common reason for hospitalisation ([redacted]). VTEs leading to death occurred in [redacted] of patients in both arms.

Table 14: Overall summary of TEAE VTEs by anticoagulation status (11th August 2023 DCO; SAS) (reproduced from CS, page 84, Table 29, Table 30 and clarification response A22)

Event, n (%)	Amivantamab with lazertinib (N=421)	Osimertinib (N=428)
Patients with 1 or more VTEs	[redacted]	[redacted]
VTEs leading to death[a]	[redacted]	[redacted]
Serious VTEs	[redacted]	[redacted]
VTEs leading to discontinuation of any study agent	[redacted]	[redacted]
VTEs requiring hospitalisation or prolongation of hospitalisation	[redacted]	[redacted]
Reason for hospitalisation[b]		
Initiation of anti-coagulation treatment	[redacted]	[redacted]
Management of symptoms	[redacted]	[redacted]
Required by local standard of care	[redacted]	[redacted]
Other	[redacted]	[redacted]
Maximum toxicity grade		
Grade 1	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]
First VTE started while on anticoagulants	[redacted]	[redacted]
First VTE started while off anticoagulants	[redacted]	[redacted]
Recurrent VTE started while on anticoagulants[c]	[redacted]	[redacted]
Patients with 1 or more DVT or PE	[redacted]	[redacted]
First DVT or PE started while on anticoagulants	[redacted]	[redacted]
First DVT or PE started while off anticoagulants	[redacted]	[redacted]

[a] VTEs leading to death are based on AE outcome of Fatal.
[b] Patients can be counted in more than one category.
[c] Recurrent VTE includes any VTE that started at least 30 days after the start of first VTE.
Abbreviations: DCO - data cut-off; DVT - deep vein thrombosis; PE - pulmonary embolism; SAS - safety analysis set; TEAE - treatment-emergent adverse event; VTE - venous thromboembolism.

Summary of treatment disposition

Rates of discontinuation (including dose interruption) for all participants at the 11th August 2023 DCO are presented in CS[1], page 78, Table 24. The median follow-up was 22.0 months the median duration of treatment was 18.5 months (range, 0.2 to 31.4 months) in the amivantamab with lazertinib group and 18.0 months (range, 0.2 to 32.7 months) in the osimertinib group. Overall, 230/421 patients (55%) and 213/428 patients (50%) remained on treatment in the amivantamab with lazertinib and osimertinib arms, respectively. More people in the amivantamab with lazertinib arm discontinued treatment due to AE

(20% vs 12%) and more people in the osimertinib discontinued treatment due to disease progression, (36% vs. 20%). In addition, dose interruptions and dose reduction occurred more frequently in the amivantamab with lazertinib arm than the osimertinib arm. Almost half of the patients (49%) in the intervention group had a dose interruption with amivantamab within the first 4 months of treatment, highlighting the lack of tolerability of amivantamab with lazertinib at the recommended dosage. The CS[1] suggested that early dose modifications did not adversely affect the efficacy of amivantamab with lazertinib as the corresponding mPFS for those who had an early dose interruption was [redacted], compared with [redacted] for those who did not.

Deaths

A summary of deaths that occurred at any time during the MARIPOSA trial up until the 11th August 2023 DCO in the SAS is presented in Table 15. Ninety-six patients ([redacted]) in the amivantamab with lazertinib arm and [redacted] patients ([redacted]) in the osimertinib arm died. The most frequent cause of death in both treatment arms was progressive disease with [redacted] ([redacted]) in the amivantamab with lazertinib arm and [redacted] ([redacted]) in the osimertinib arm, followed by AEs, 9.3% (39/421) in the amivantamab with lazertinib arm and 6.8% (29/428) in the osimertinib arm. TEAEs leading to death are summarised in CS[1], page 86, Table 32. Cardiopulmonary, cerebrovascular, and infection-related deaths predominated in these two groups,[3] and death due to AESIs occurred in [redacted] patients ([redacted]) in the amivantamab with lazertinib arm.

Table 15: Summary of death and cause of death (11th August 2023 DCO; SAS), reproduced from CS, page 85, Table 31

Event, n (%)	Amivantamab with lazertinib (N=421)	Osimertinib (N=428)
Deaths during study	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
AE	[redacted]	[redacted]
Other	[redacted]	[redacted]
Deaths within 90 days of first dose	[redacted]	[redacted]
AE	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Deaths within 30 days of last dose	[redacted]	[redacted]
AE	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Other	[redacted]	[redacted]

AE - adverse event; DCO - data cut-off; SAS - safety analysis set.

3.4 Ongoing studies

As reported in the CS,[1] page 87, the MARIPOSA trial is ongoing. The final analysis is anticipated to be available in the second or third quarter of 2025. Additionally, the CS,[1] reports five ongoing studies that are examining ways to enhance patient safety and implement effective management strategies for individuals undergoing treatment with amivantamab with lazertinib for EGFR mutation-positive advanced NSCLC (Table 16).

Table 16: Ongoing studies of amivantamab with lazertinib in patients with EGFR mutation-positive advanced NSCLC

Study number	Study objective	Study design	Estimated completion
SKIPPirr NCT05663866	To investigate the use of premedication to reduce IRRs associated with IV amivantamab. The study enrolled patients with EGFR exon 19 deletion or L858R-mutated advanced or metastatic NSCLC whose disease progressed on prior osimertinib and platinum-based chemotherapy	Phase 2, open-label trial	October 2025
COCOON trial NCT06120140	To evaluate the impact of enhanced versus standard dermatologic management on the incidence of dermatological AEs among patients with cEGFRm advanced or metastatic NSCLC receiving first line IV amivantamab in combination with lazertinib (MARIPOSA population).	Phase 2, open-label RCT	March 2026
PALOMA programme To assess the safety and feasibility of a subcutaneous amivantamab formulation in advanced solid malignancies, including NSCLC, with the potential to reduce treatment administration durations and address AEs associated with IV delivery of amivantamab, such as IRRs and VTEs			
PALOMA NCT04606381	To assess the safety and pharmacokinetics of SC delivery of amivantamab, a human bispecific EGFR and cMet antibody for the treatment of advanced solid malignancies	Phase 1b, open-label	October 2025
PALOMA-2 NCT05498428	To confirm that amivantamab subcutaneous formulation has similar anti-cancer activity similar to what is seen in amivantamab as an injection in a vein in combination regimens In patients including with cEGFR-mutated NSCLC	Phase 2, open-label, parallel cohort study	August 2026
PALOMA-3 NCT05388669	To assess the non-inferiority of pharmacokinetics, efficacy and safety of SC amivantamab versus	Phase 3, open-label RCT	December 2025

Study number	Study objective	Study design	Estimated completion
	IV amivantamab, both in combination with oral lazertinib, in patients with cEGFRm NSCLC whose disease has progressed on or after osimertinib and platinum-based chemotherapy irrespective of order		

Abbreviations: AEs - adverse events; cEGFRm - epidermal growth factor receptor-mutated; IRRs - infusion-related reactions; IV - intravenous; NSCLC - non-small cell lung cancer; RCT - randomised control trial; SC - subcutaneous; VTEs - venous thromboembolisms

3.5 Meta-analysis

As the submission reports results from a single RCT, a meta-analysis was not conducted.

3.6 Indirect treatment comparison (ITC)

As the MARIPOSA trial provides a direct comparison between the amivantamab with lazertinib and osimertinib, which the company considers to be the only relevant comparator, an indirect treatment comparison (ITC) was not conducted. The EAG notes that an ITC would be required if the company were to provide a comparison against osimertinib with chemotherapy.

3.7 Additional work on clinical effectiveness undertaken by the EAG

No additional work on clinical effectiveness was undertaken by the EAG.

3.8 Conclusions of the clinical effectiveness section

3.8.1 *Summary of principle findings*

The clinical evidence base supporting amivantamab with lazertinib for first-line treatment of adults with untreated cEGFRm advanced NSCLC which has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation was based on the MARIPOSA trial. In this study, amivantamab with lazertinib demonstrated a statistically significant improvement in PFS compared to osimertinib (HR 0.70; 95% CI: 0.58, 0.85; $p<0.001$). The median PFS was 23.7 months (95% CI: 19.1, 27.7) in the amivantamab with lazertinib arm and 16.6 months (95% CI: 14.8, 18.5) in the osimertinib arm. At the DCO (13th May 2024), an *ad hoc* analysis showed a trend favouring amivantamab with lazertinib with a HR of 0.77 (95% CI 0.61, 0.96; $p=0.019$) for OS. A higher incidence of AEs related to EGFR TKI inhibitors and MET TKI inhibitors and a higher incidence of VTEs was reported in the amivantamab with lazertinib arm than the osimertinib arm. TEAEs resulting in treatment discontinuation were reported in 10% of patients on amivantamab with lazertinib and 3% of patients on osimertinib.[3] Longer follow-up is needed to reduce uncertainty around OS benefit of amivantamab with lazertinib and monitor for the development of any new safety issues. Further RWE studies are needed to assess whether the

administration of prophylactic anticoagulation during the first four months of therapy reduces the incidence of VTEs.

3.8.2 *Uncertainties surrounding the reliability of the clinical effectiveness*

The main uncertainties in the clinical evidence primarily relate to the duration of treatment and follow-up to assess the survival and safety profile of amivantamab with lazertinib. As the MARIPOSA trial is ongoing, the analyses are mainly exploratory. As noted in the CS, it is recommended that treatment with amivantamab with lazertinib should continue until disease progression or until the development of unacceptable toxicity. As a result, the long-term efficacy and safety of amivantamab with lazertinib is unknown, especially with regards to impacts on VTEs. Another uncertainty is around the generalisability of the MARIPOSA trial. The study only included adult patients and the age distribution of patients enrolled in the MARIPOSA trial (55% of patients < 65 years old) reflected the fact that the population with cEGFRm NSCLC are younger than the overall population with NSCLC, who have a median age of 70 years.[11] Although this broadly reflects the age distribution in the MARIPOSA-like cohort of the NCRAS, where 54% had an age ≤ 65 years,[29] the subgroup analyses from MARIPOSA were less favourable for the subgroup with age ≥ 65 years.[1] In addition, the MARIPOSA trial only enrolled patients who had an ECOG PS of 0 or 1 and therefore patients offered the treatment in clinical practice may need to have a similar level of fitness to be able to tolerate the toxicity associated with treatment.

4 COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of amivantamab with lazertinib for the first-line treatment of adult patients with cEGFRm advanced NSCLC. Section 4.1 presents a critique of the company's review of existing health economic analyses. Section 4.2 summarises the methods and results of the company's model. Sections 4.3 and 4.4 present the critique of the model and additional exploratory analyses undertaken by the EAG, respectively. Section 4.5 presents a brief discussion of the key drivers of the ICER.

The two key components of the economic evidence presented in the CS are: (i) a systematic review of the relevant literature, (ii) a report of the company's economic evaluation which provides estimates of the ICER reported as the cost per quality-adjusted life year (QALY) gained for amivantamab with lazertinib versus osimertinib. The company also provided an electronic version of their economic model developed in Microsoft Excel®. Following the clarification process, the company submitted a revised version of the model that included updated estimates of the cost-effectiveness of amivantamab with lazertinib following some minor changes to resource use assumptions. For brevity, this report will only refer to the model received in response to the clarification request, unless explicitly stated otherwise.

The EAG notes that the company provided an addendum at the time of the factual accuracy check which included updated data from the 4th December 2024 DCO. These data and updated cost-effectiveness results which are dependent on these updated data are discussed in a separate EAG report addendum.

4.1 EAG's comment on company's review of cost-effectiveness evidence

4.1.1 *Company's search objective and methods*

Search strategies for the economic evaluation SLRs are presented in CS Appendices G (cost-effectiveness), H (health-state utility values) and I (cost and healthcare resource use). Databases and supplementary sources were searched simultaneously using the search terms presented in CS Appendix G.1.1.5, and then screened for inclusion in any of the three SLRs. Searches were first conducted in May 2020, with five updates being undertaken since then, with the latest being October 2024.

The search strategy was designed for a wider population than for the clinical SLR (all patients with EGFR mutations and not limited to the cEGFRm population), which increases the sensitivity of the search.

The relevant bibliographic databases were searched: MEDLINE, including MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print; Embase; NHS EED (in the original SLR, but not in the updates as records only go up to 2015); Health Technology Assessment database (HTA), including in the most recent SLR update in October 2024. One notable omission from the database sources is

EconLit (clarification response B1), although this is unlikely to result in a large number of studies being missed.

In addition, relevant conference proceedings (dating back to 2018 in the original SLR, with subsequent years covered in the search updates), HTA websites and other grey literature sources were searched. The bibliographies of relevant reviews, network meta-analyses and HTAs were also searched to identify further relevant studies.

As with the clinical SLR, reporting of the search strings for all updates is comprehensive, with search results presented by line for each database search. The supplementary searches have also been reported transparently and thoroughly in line with Stansfield *et al.* (2016).[45] This includes details of the search strategy and keywords used for each website source and how many of the retrieved results were included in the review after screening.

For the MEDLINE and Embase searches, search filters for the study design types of interest have been used. The submission states that these are adapted from filters published by Scottish Intercollegiate Guidelines Network (SIGN),[53] but they have been used in a modified form. However, as with the clinical SLR, these modifications have been made with sensitivity in mind, and are unlikely to result in crucial evidence being missed.

Overall, the search strategy for the economic SLR is adequate to retrieve economic studies relating to treatments for patients with advanced NSCLC, which were then screened for relevance to this particular submission.

4.1.2 *Findings of the cost effectiveness review*

Reviews were conducted originally in May 2020, with five updates since then, the latest being October 2024. The company has provided only the process of the latest review. The review identified 53 unique studies that were relevant to the broader population of patients with EGFR mutation positive (exon 19 deletion, exon 21 L858R substitution or exon 20 insertion) advanced NSCLC.

The company tabulates information on the methods used in these published cost-effectiveness studies and their results (CS Appendix G, Tables 49 and 50).[1] It also tabulates the findings of its quality appraisal using the Drummond *et al.* checklist (CS, Appendix G, Table 51 and 52).[1, 54] However, the CS does not provide a narrative summary of the methods, results or quality assessment and does not explain how the results of the SLR informed the development of the company's *de novo* cost-effectiveness model. The CS does provide a comparison between the features of their *de novo* economic evaluation and the features of the model used to inform the appraisal of osimertinib for untreated EGFR

mutation-positive NSCLC (TA654), implying that they used this model to inform their *de novo* analysis. Key differences include the use of a 1-week cycle length versus a 30-day cycle length, a longer time horizon (30 years versus 20 years) and the use of utility data from the MARIPOSA trial rather than the FLAURA trial (see CS, Table 33).[1] They also state that the partition survival modelling approach chosen in the *de novo* analysis is in keeping with the approach used in previous appraisals for similar indications (TA654, TA595 and ongoing appraisal ID6328). No reference is made in CS, Document B, to any published models other than those informing previous NICE appraisals. For example, no comment is made regarding the 24 published cost-effectiveness analyses that used a model structure other than a partitioned survival model. In its description of the company's *de novo* analysis in Section 4.2, the EAG has noted where the company has drawn on assumptions and estimates from previous appraisals.

4.1.3 *Conclusions of the cost effectiveness review*

Based on an absence of published estimates examining the cost-effectiveness of amivantamab with lazertinib for the first-line treatment of cEGFRm advanced NSCLC, the company concludes that a *de novo* analysis is required. The EAG agrees with this conclusion. However, the company could have provided a better explanation of how the review of published cost-effectiveness analyses informed its model development.

4.2 Summary of the company's submitted economic analysis

As part of the company's submission to NICE, it submitted a fully executable health economic model of amivantamab with lazertinib. As part of the clarification process, the company submitted a set of responses to the questions raised by the EAG, an updated version of the model and new descriptions of the economic analysis undertaken. This section reflects the updated version of the submitted model. The scope of the company's economic analysis is summarised in Table 17.

Table 17: Scope of the company's economic analyses

Population	First-line treatment of adult patients with advanced NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations
Time horizon	Lifetime (maximum of 30 years)
Intervention	Amivantamab with lazertinib
Comparator	Osimertinib
Economic analysis approach	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum for both health outcomes and costs
Price year	2023/24, with exception of drugs which were valued at current prices

Abbreviations: QALY - quality-adjusted life year; NHS - National Health Service; PSS - Personal Social Services

4.2.1 *Population*

The population within the model relates to first-line treatment of adult patients with advanced NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations. This population is in alignment with the anticipated licensed indication and with the population included within the pivotal MARIPOSA trial.[3]

4.2.2 *Interventions and comparators*

The intervention included in the company's economic analyses is amivantamab used in combination with lazertinib. The dose of amivantamab is 1,050 mg for patients weighing less than 80 kg at baseline and 1,400 mg for patients weighing ≥ 80 kg. Within the model, amivantamab is assumed to be administered as an IV infusion at the dose required according to patient weight on days 1 (split infusion on days 1 and 2), 8, 15 and 22 over the first four weeks (total of 4 doses across 5 administrations); and on day 1 for subsequent two-week periods. The company's model assumes that partially used vials are wasted with dose reductions being modelled based on the MARIPOSA trial. Lazertinib is an oral medication, and the dose is 240 mg once daily. Within the model, the actual dose of lazertinib is taken from the MARIPOSA trial. Information on the distribution of the dosing of amivantamab and lazertinib in MARIPOSA trial is presented in Table 18.

The comparator, evaluated within the company's model, is osimertinib monotherapy. While osimertinib is an oral medication and the licensed dose for this indication is 80 mg taken once daily, the model also considered the actual dose of osimertinib, which patients received in the MARIPOSA trial (see Table 18).

Drug acquisition costs for both arms over the patient's lifetime are based on the probability of patients remaining on each treatment based on TTD functions without a cap for PFS. Although the draft SmPC,[43] recommends stopping treatment when there is disease progression or unacceptable toxicity, continuation of study treatment after confirmed disease progression was allowed in the MARIPOSA trial, if the investigator believed the patient was deriving clinical benefit.[1] The EAG's clinical advisers confirmed that this was aligned with how TKIs are currently used in UK clinical practice. In the NICE draft guidance for osimertinib with chemotherapy for untreated cEGFRm advanced NSCLC (ID6328),[5] it is stated that clinical expert advice was that osimertinib might be used beyond progression, so PFS and TTD curves did not necessarily need to be precisely aligned. Therefore, the EAG deems it to be acceptable that the PFS curves have not been used to cap TTD in the company's model.

For amivantamab with lazertinib, the TTD for each individual drug was used to calculate the treatment costs. This was considered reasonable by the EAG as it reflected the treatment usage within the MARIPOSA trial where TTD was shorter for amivantamab compared with lazertinib (CS Figure 33).[1]

This may have been because the trial protocol stated that, "[redacted]". [50] The EAG's clinical advisers also agreed that this was likely to reflect how the treatment combination would be used in clinical practice.

For the amivantamab with lazertinib combination, the TTD for lazertinib was used to determine when patients were deemed to have discontinued all first-line treatment and become eligible for subsequent treatments. This was because very few patients discontinued lazertinib whilst continuing amivantamab in the trial and the TTD for lazertinib was similar to the TTD for the treatment combination as a whole (see clarification responses to B10 and B12).[1]

Table 18: Actual dose, measured in MARIPOSA trial

Regimen	Component	Dosing frequency	Actual dose administered in MARIPOSA trial *
Amivantamab with lazertinib	Amivantamab	Once weekly for the first 4 weeks and then once every 2 weeks (IV)	< 80 kg: [redacted][a] of 1050 mg (3 vials) ≥ 80 kg: [redacted][a] of 1400 mg (4 vials)
	Lazertinib	Once daily (PO)	[redacted]
Osimertinib monotherapy	Osimertinib	Once daily (PO)	[redacted]

[a] the proportion of planned dose
Abbreviations: IV – intravenous; PO – per os (by mouth/oral administration)
*** Data points updated in the company's addendum – please refer to the addendum to the EAG report**

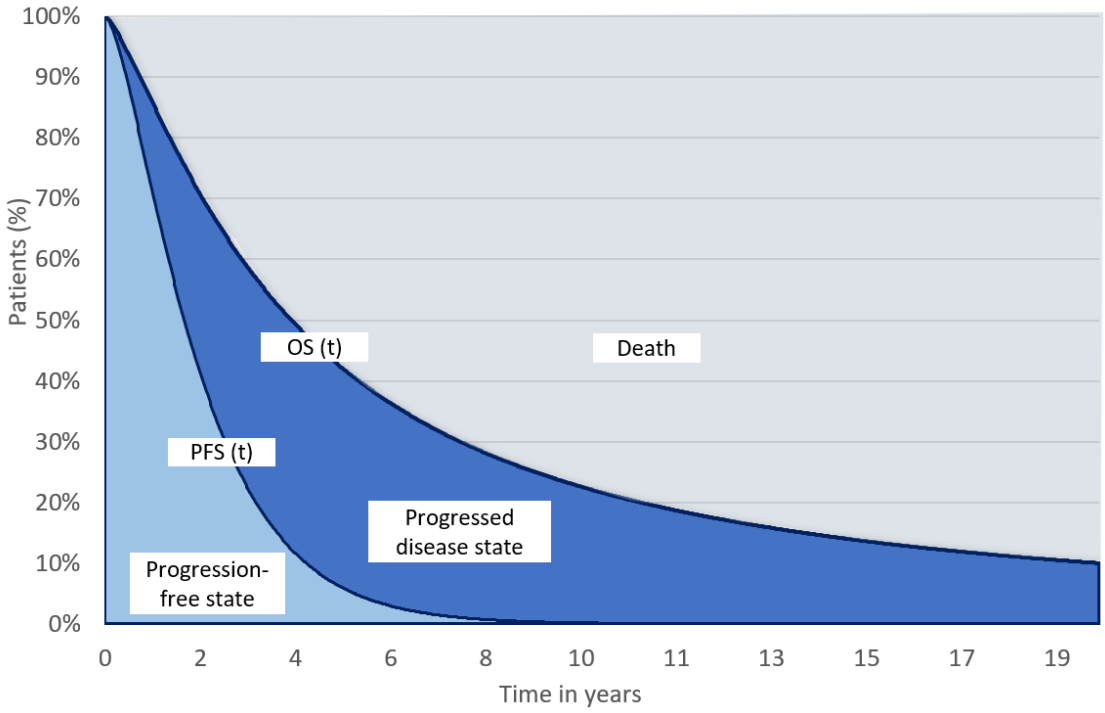
4.2.3 *Model structure and logic*

The company employed a partitioned survival model (PSM) to evaluate both costs and health outcomes from the start of first-line treatments over the time horizon. This approach aligns with previous NICE appraisals of TKIs for cEGFRm NSCLC, including assessments of osimertinib (TA654) and dacomitinib (TA595).[55, 56] Additionally, it is consistent with the company's model for the ongoing NICE evaluation of osimertinib combined with chemotherapy (ID6328),[5] which the Appraisal Committee described as being appropriate in its draft guidance.

The PSM includes three mutually exclusive and jointly exhaustive health states: progression-free, progressed disease, and dead. All individuals begin in the progression-free state, with their movement through the states depending on whether their disease remains stable or worsens. The model determines the patient distribution across these states over time using parametric survival models fitted to data on PFS and OS, with health state occupancy calculated using an area under the curve (AUC) method (Figure 6). The proportion of patients in the progression-free state is calculated based on survival curves for PFS, while the occupation of the post-progression state is determined by the difference between the OS and PFS survival curves. The proportion of patients in the dead state is 1-OS.

A one-week cycle length was chosen to accommodate the differing dosing schedules of the comparators. A half-cycle correction was applied. Costs and health utility values were assigned to each alive health state and weighted based on state occupancy to calculate overall costs and QALYs.

Figure 6: Illustration of partitioned survival model (reproduced from CS, Figure 22)



Abbreviations: OS: overall survival; PFS: progression-free survival.

Key structural assumptions

The key structural assumptions employed within the company's model are presented in CS Table 71, with key points presented here:

Assumption 1. The PAS discount was applied to amivantamab and lazertinib. List prices were used for all other drugs.

Assumption 2. It is assumed that a lifetime horizon of 30 years was sufficient to significantly capture outcomes.

Assumption 3. In the base-case analysis, log-logistic distributions were used for modelling PFS, Weibull distributions were used for OS; and exponential distributions were used for TTD; Parametric survival models were fitted separately to data for each trial arm (amivantamab-lazertinib and osimertinib) for PFS and OS, and were fitted separately to data for amivantamab, lazertinib and osimertinib for TTD.

Assumption 4. OS in the model was adjusted to ensure that the risk of death did not fall below that experienced in the general population; PFS was capped to ensure it remained lower than adjusted OS.

Assumption 5. It was assumed that patients who progressed could continue any study treatment if the clinician considered they were still deriving clinical benefit and therefore TTD was not capped by PFS.

Assumption 6. Drug acquisition costs for amivantamab, lazertinib and osimertinib are modelled separately using the TTD survival functions for each individual drug administered.

Assumption 7. The frequency of follow-up and monitoring interventions (physician visits, complete blood tests and biochemistry) were assumed independent of treatment.

Assumption 8. Grade ≤ 2 AEs (with the exception of VTEs) or which occurred in less than 5% of patients in either arm of the MARIPOSA trial were assumed not to have a sufficient impact on patient HRQoL and were excluded from the economic model.

Assumption 9. The utility decrement attributable to AEs is assumed to occur at the start of treatment and is accounted for as a one-off QALY loss, taking into account both the utility decrement and the duration of the AE.

Assumption 10. Vial sharing of amivantamab is not permitted and dose reductions were assumed to always consist of a reduction by a whole number of complete vials meaning that they were not associated with any drug wastage.

Assumption 11. An outpatient attendance is required for each IV administration of amivantamab, and a single outpatient attendance is required to initiate oral medication (lazertinib and osimertinib). These are in addition to regular outpatient attendance for follow-up.

Assumption 12. Drug administration costs for amivantamab were adjusted for missed doses and it is assumed that no additional administration cost is incurred due to the need for a split dose in week 1

Assumption 13. Patients who do not receive subsequent anticancer therapy are assumed to receive best supportive care, with no associated costs.

Assumption 14. In the base-case, the distributions of subsequent therapies are assumed to be the same for both arms, while the proportion of patients receiving subsequent treatments differs depending on the arms.

Assumption 15. The proportion of patients receiving best supportive care at second-line and later lines was informed by an analysis of the MARIPOSA and MARIPOSA-2 trials respectively.

Assumption 16. The mix of treatments received at second and third lines in the company's base-case was informed by clinical expert opinion and any differences between the treatments modelled and those received in the MARIPOSA trial were assumed not to affect OS; the treatment mix from MARIPOSA trial and RWE sources were explored in scenario analyses.

Assumption 17. Subsequent treatment costs were assumed to occur when patients discontinued first-line treatment. The discontinuation of the amivantamab with lazertinib combination treatment was assumed to be the same as that of the lazertinib arm rather than amivantamab of that arm.

Assumption 18. When calculating the proportion of patients receiving subsequent treatments, deaths prior to progression were assumed to occur proportionally among patients undergoing and not undergoing first-line treatment.

Assumption 19. End-of-life costs are assumed to arise from: (1) hospital admission and excess bed days, (2) Macmillan nurse support in a home setting, and (3) hospice care. Hospice care costs are assumed to be 25% higher than those of hospital admission based on an assumption from TA520.[57]

4.2.4 *Evidence used to inform the company's model parameters*

The sources of evidence used to inform company's model parameters are summarised in Table 19. These are discussed in detail in the subsequent sections.

This report describes the data in the version of the model submitted in response to the clarification request. However, the EAG notes that the company provided additional data in an addendum at the time of the factual accuracy check. These updated data are discussed in a separate EAG report addendum, but the EAG has tried to indicate where specific data inputs have been superseded using footnotes on the relevant tables so the reader can refer to the updated tables in the EAG critique of the company's addendum. The EAG notes in particular that **substantive parts of Section 4.2.4.2 describing the survival analysis for OS and TTD are superseded** by the updated data and would refer the reader to the EAG's critique of the company's addendum for a discussion of the most relevant OS and TTD survival curves based on the updated data provided in the company's addendum.

Table 19: Summary of evidence sources used to inform the model parameters for the company's base-case

Parameter type	Amivantamab with lazertinib	Osimertinib
Patient characteristics	Baseline characteristics across both arms of the MARIPOSA trial[3]	
PFS	Log-logistic model fitted to PFS data for amivantamab with lazertinib arm of MARIPOSA (DCO 11th August 2023)[58]	Log-logistic model fitted to PFS data for osimertinib arm of MARIPOSA (DCO 11th August 2023)[58]
OS	Weibull model fitted to PFS data for amivantamab with lazertinib arm of MARIPOSA (DCO 13th May 2024)[59]	Weibull model fitted to PFS data for osimertinib arm of MARIPOSA (DCO 13th May 2024)[59]
TTD	Exponential model fitted to TTD data for amivantamab and lazertinib informed by MARIPOSA (DCO 13th May 2023)[59]	Exponential model fitted to TTD data for osimertinib arm of MARIPOSA (DCO 13th May 2024)[59]
AE frequency	Grade ≥ 3 TEAEs and Grade ≤ 2 VTE from the MARIPOSA trial[59]	
Health state utility values	Progression-free/progressed utility value based on EQ-5D estimates using MMRM fitted to EQ-5D-5L data collected from progression-free/progressed patients in the MARIPOSA trial (mapped to EQ-5D-3L using Hernandez *et al.*[60])	
HRQoL age-adjustment	Age- and sex-matched general population EQ-5D-3L based on published UK population norms from Hernandez Alava *et al.*[61]	
AE disutility values	Disutility for Grade ≥ 3 AEs and Grade ≤ 2 VTE estimated from the MMRM fitted to EQ-5D-5L data collected from progression-free patients in the MARIPOSA trial (mapped to EQ-5D-3L using Hernandez *et al.*[60])	
Drug acquisition costs	Treatment duration based on MARIPOSA; drug prices taken from NHS dictionary,[62] Electronic Market Information Tool (eMIT)[63] and British National Formulary (BNF);[44] PAS for amivantamab and lazertinib provided by the company	
Drug administration costs	Unit costs taken from the 2023/24 National Schedule of NHS Costs[64]	
Health state costs	Resource use based on TA531 and ID6328;[65, 66] unit costs taken from the 2023/24 National Schedule of NHS Costs;[64] the 2023 Personal Social Services Research Unit (PSSRU) report on unit costs of health care[67]	
AE costs	Cost for infusion related reaction – costs in TA651, inflated to 2021/22 prices using the NHS Cost Inflation Index; cost for VTE – one dose of rivaroxaban plus one ultrasound scan; others - costed by taking a weighted average of non-elective short stay admissions from the 2023/24 National Schedule of NHS Costs[64]	
Subsequent-line therapy use and costs	The proportion of subsequent active treatments informed by MARIPOSA and MARIPOSA-2; The distribution of subsequent treatments derived from clinical estimates from the advisory board meeting;[31] duration of subsequent treatments informed by MARIPOSA-2, IMPOWER150[68] and AURA3[69] trials and Park *et al.*[70]	
End-of-life costs	Assumptions from atezolizumab submission to NICE (TA520),[57] updated with the 2023/24 National Schedule of NHS Costs[64] and the 2023 PSSRU costs[67]	

Abbreviations: DCO - data cut-off; AE - adverse event;; HR - hazard ratio; HRQoL - health-related quality of life; ITC - indirect treatment comparison; ITT - intention-to-treat; KM - Kaplan Meier; OS - overall survival; PFS - progression-free survival; TTD - time to discontinuation; VTE - venous thromboembolism; MMRM - mixed-effects model for repeated measures; PAS - Patient Access Scheme; eMIT - electronic Market Information Tool; BNF - British National Formulary; NHS - National Health Service;

4.2.4.1 Patient characteristics at model entry

The model assumes that patients enter the model aged 62.3 years and 61.3% of the modelled cohort is assumed to be female (Table 20). These characteristics reflect the ITT population of patients who received either amivantamab with lazertinib or osimertinib in the MARIPOSA trial.[3]

Table 20: Baseline characteristics (adapted from CS Table 34)

Characteristic	Base-case value	Source
Mean age, years (SD)	62.3 ([redacted])	Pooled data for amivantamab with lazertinib or osimertinib arms in the MARIPOSA trial
Female, %	61.3	
Mean weight, kg (SD)	[redacted]	
Patients < 80 kg, %	86.7%	
Body surface area, m^2 (SD)	[redacted]	

Abbreviations: SD: standard deviation

4.2.4.2 Survival curves – PFS, OS, and TTD

The company fitted standard parametric survival models and spline models for each of the treatments separately, using individual patient data (IPD) from the MARIPOSA trial. PFS by BICR has an earlier DCO of 11th August 2023 (median trial follow-up of 22 months). OS and TTD have a later DCO of 13th May 2024 (median trial follow-up of 31.1 months). Seven standard parametric models were considered including exponential, Gompertz, log-logistic, log-normal, Weibull, gamma, and generalised gamma distributions. In response to clarification question B5, nine spline models were also fitted on three different scales (hazard, odds, and normal) and with three different numbers of knots (one, two or three).

The CS states that the company's model selection process included: (1) visual inspection of the fitted survival models against the observed KM survival curves and the model-predicted hazard plots against the smoothed empirical hazard plots; (2) examination of goodness of fit statistics using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), and (3) assessment of clinical plausibility and face validity of the extrapolated survival curves.

(a) Progression-free survival

Amivantamab with lazertinib PFS

Standard parametric models and spline models were fitted to data on PFS by BICR for the amivantamab with lazertinib arm. The AIC and BIC values for the standard parametric models and spline models are shown in Table 21 and Table 22, respectively. Comparisons of the observed KM curve and predicted PFS are presented in Figure 7 and Figure 8, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 9 and Figure 10, respectively. Clinicians' estimates of expected PFS are presented in Table 23.

The log-logistic model was selected as the company's preferred base-case model for PFS for amivantamab with lazertinib. Amongst all of the fitted standard parametric models, the gamma distribution has the lowest AIC and BIC, with values within one point difference to the log-logistic and Weibull distributions. All parametric models appear to fit the observed KM data well. In terms of hazard plots, the smoothed hazard function appears to increase initially, and then decrease at around 16 months, followed by an increasing tail at the end, which is likely due to the uncertainty associated with high censoring at the end of trial. The gamma and Weibull models predict the initial increase phase of the hazard function well. The hazard function from the log-logistic model first increases and then decreases, but the turning point is at around 12 months, which is earlier than the empirical hazard function.

All spline models provide a good visual fit to the KM curve. The AIC values for the spline models are similar, with a four-point difference between the best- and worst-fitting models. The one-knot normal spline model has the lowest AIC, followed by one-knot odds, one-knot hazard, two-knot normal, two-knot odds and two-knot hazard models, of which the one-knot normal, one-knot odds, two-knot normal, two-knot odds models predict an increasing and decreasing hazard; the one-knot hazard and two-knot hazards models predict a monotonically increasing hazard.

Clinicians' estimates of expected PFS provided by the company are presented in Table 23. The mean of clinicians' 8-year PFS estimates is [redacted]%. The 8-year prediction from the log-logistic distribution is 11.5% and the 8-year prediction from the gamma distribution is 2.8%. The spline models that provide a good statistical fit and close predictions to the clinicians' estimates are the one-knot normal (9.6%), one-knot odds (11%), two-knot odds (10%), two-knot normal (8.4%), three-knot normal models (10.4%).

Overall, the EAG agrees with use of the log-logistic model in the company's preferred base-case model and considers both the log-logistic and gamma distributions to be appropriate as they provide a good statistical fit and reasonable hazard shape. The log-logistic model represents a scenario with higher predictions than the clinicians' estimates, whereas the gamma distribution represents a scenario with lower predictions than clinicians' estimates. The EAG acknowledges the increased complexity associated with the spline models and considers the use of standard parametric models to be adequate for fitting amivantamab with lazertinib PFS (BICR).

Table 21: AIC and BIC statistics for amivantamab with lazertinib PFS (BICR) with standard parametric models (reproduced from CS Table 35)

Models	AIC (rank)	BIC (rank)
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic (Company's base-case)	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; BICR - blinded independent central review; PFS - progression-free survival

Table 22: AIC and BIC statistics for amivantamab with lazertinib PFS (BICR) with spline models (reproduced from clarification response Table 12)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; BICR - blinded independent central review; PFS - progression-free survival

Table 23: Clinician estimates for amivantamab with lazertinib PFS (reproduced from Advisory board report, Table 27)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS - progression-free survival

Figure 7: Long-term predictions for amivantamab with lazertinib PFS (BICR) with standard parametric models

Abbreviations: BICR - blinded independent central review; PFS - progression-free survival

Figure 8: Long-term predictions for amivantamab with lazertinib PFS (BICR) with spline models

Abbreviations: BICR - blinded independent central review; PFS - progression-free survival

Figure 9: Hazard plot for amivantamab with lazertinib PFS (BICR) with standard parametric models (reproduced from clarification response Figure 30)

Abbreviations: BICR - blinded independent central review

Figure 10: Hazard plot for amivantamab with lazertinib PFS (BICR) with spline models (reproduced from clarification response Figure 12)

Osimertinib PFS

Standard parametric models and spline models were fitted to data on PFS by BICR for the osimertinib arm. The AIC and BIC values from the standard parametric models and spline models are shown in Table 24 and Table 25, respectively. Comparisons of the observed KM curve and predicted PFS are

presented in Figure 11 and Figure 12, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 13 and Figure 14, respectively. Clinician estimates of expected PFS are presented in Table 26.

The log-logistic model was selected as the company's preferred base-case model for PFS for osimertinib. Amongst all of the fitted standard parametric models, the log-logistic model has the lowest AIC and BIC, with differences of less than two points compared to the gamma and Weibull distributions. All models other than the exponential distribution appear to provide good visual fit to the observed KM curves. In terms of hazard plots, the smoothed hazard function first increases and then decreases at about 16 months. The gamma and Weibull distributions predict the increase phase of the hazard function well. The hazard function of the log-logistic model first increases and then decreases, but the turning point is at around 10 months, which is earlier than the empirical hazard function.

All nine spline models appear to fit the KM curve well. AIC values do not vary much across the fitted spline models, with a four-point difference between the best- and worst-fitting models. The one-knot odds model has the lowest AIC, followed by the one-knot normal, two-knot odds, two-knot hazard and two-knot normal models. Apart from the one-knot hazard model which has a monotonically increasing hazard, all of other splines models have at least one turning point.

Clinicians' estimates of expected PFS provided by the company are presented in Table 26. The mean of clinician's 8-year PFS estimates is [redacted]%, which is very similar to the 8-year prediction from the log-logistic model (5.2%) and is higher than the 8-year prediction from the gamma model (0.4%). 8-year PFS predictions from the one-knot and two-knot spline models are listed as follows: two-knot odds (5.2%), one-knot odds (4.4%), two-knot normal (3.3%), one-knot normal (2.6%), two-knot hazard (1.3%), and one-knot hazard (0.3%).

Overall, the EAG agrees with the use of the log-logistic model as the company's preferred base-case model and considers both the log-logistic and gamma models to be appropriate as they provide a good statistical fit and reasonable hazard shape. The log-logistic model represents a scenario with higher predictions than the clinicians' estimates, whereas the gamma distribution represents a scenario with lower predictions than clinicians' estimates. The EAG acknowledges the increased complexity with spline models and considers the use of standard parametric models to be adequate for fitting osimertinib PFS (BICR).

Table 24: AIC and BIC statistics for osimertinib PFS (BICR) with standard parametric models (reproduced from CS Table 37)

Models	AIC (rank)	BIC (rank)
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic (company's base-case)	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; BICR - blinded independent central review; PFS - progression-free survival

Table 25: AIC and BIC statistics for osimertinib PFS (BICR) with spline models (reproduced from clarification response Table 13)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; BICR - blinded independent central review; PFS - progression-free survival

Table 26: Clinician estimates for osimertinib PFS (reproduced from Advisory board report, Table 29)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS - progression-free survival

Figure 11: Long-term predictions for osimertinib PFS (BICR) with standard parametric models

Abbreviations: BICR - blinded independent central review; PFS - progression-free survival

Figure 12: Long-term predictions for osimertinib PFS (BICR) with spline models

Abbreviations: BICR - blinded independent central review; PFS - progression-free survival

Figure 13: Hazard plot for osimertinib PFS (BICR) with standard parametric models (reproduced from clarification response Figure 31)

Abbreviations: BICR - blinded independent central review

Figure 14: Hazard plot for osimertinib PFS (BICR) with spline models (reproduced from clarification response Figure 14)

Abbreviations: BICR - blinded independent central review

(b) Overall survival

The EAG notes that the company submitted additional data on OS in an addendum provided during the factual accuracy check. Therefore the **information provided here on OS is superseded** and the reader may wish to refer instead to the EAG's critique of the addendum.

Amivantamab with lazertinib OS

Standard parametric models and spline models were fitted to data on OS for amivantamab with lazertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 27 and Table 28, respectively. Comparisons of the observed KM curve and predicted OS are presented in Figure 15 and Figure 16, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 17 and Figure 18, respectively. Clinicians' estimates of expected OS are presented in Table 29.

The Weibull model was selected as the company's preferred base-case model for OS for amivantamab with lazertinib. Amongst all the fitted standard parametric models, the Gompertz model has the lowest AIC, followed by generalised gamma and Weibull distributions, with differences of less than three points. The exponential model has the lowest BIC, followed by Gompertz and Weibull models, with differences of less than three points. All standard parametric models appear to underestimate the KM curve between approximately 0.5 and 2 years. The smoothed empirical hazard plot has a complex shape. It has an overall increasing trend with a dip between 0.5 and 2 years and a decrease at the end. The dip was not predicted by any of the standard parametric models.

All spline models provide a good visual fit to the KM curve. The three-knot odds model has the lowest AIC, followed by three-knot normal, three-knot hazard, one-knot hazard and two-knot normal models. The one-knot hazard model has the lowest BIC, followed by the one-knot odds and one-knot normal models. The one-knot and two-knot spline models have an overall increasing trend, with tails either increasing or decreasing. The three-knot spline models have a dip at around 10 months, and a peak at around 23 months, while the tail of the empirical hazard function only decreases from around 28 months.

Clinicians' estimates of expected OS provided by the company are presented in Table 29. The mean of the clinician's estimates of 10-year OS is [redacted]%, with two clinician's estimates being 5% and 10%. Amongst the standard parametric models, the Weibull distribution provides the closest 10-year estimation (15%) to the clinicians' estimates. The other standard parametric models either have 10-year OS predictions which are higher than 15% or close to 0. For the spline models, the one-knot hazard model has a 10-year prediction of 12%, and the two-knot hazard model has a 10-year prediction of 7.2%. The remaining seven spline models all have a 10-year prediction of higher than 15%.

Overall, the EAG considers the Weibull model to be the most appropriate standard parametric model as it provides a good statistical fit and closely aligns with the clinician's estimates of 10-year OS. The EAG considers that the spline models offer a better visual fit than the standard parametric models, and that the one-knot hazard model is appropriate due to its good statistical fit and closeness to the clinician estimates of 10-year OS. However, the EAG notes that neither the Weibull model nor the one-knot hazard model provides a great representation of the hazard function.

Table 27: AIC and BIC statistics for amivantamab with lazertinib OS with standard parametric models (reproduced from CS Table 39)

Models	AIC (rank)	BIC (rank)
Exponential	[redacted]	[redacted]
Weibull (company's base-case)	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; OS – overall survival

Table 28: AIC and BIC statistics for amivantamab with lazertinib OS with spline models (reproduced from clarification response Table 14)

Models	**AIC (rank)**	**BIC (rank)**
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; OS – overall survival

Table 29: Clinician estimates for amivantamab with lazertinib OS (reproduced from Advisory board report, Table 18)

Timepoints	**Clinician 1**	**Clinician 2**	**Clinician 3**	**Mean**	**Midpoint**
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS – overall survival

Figure 15: Long-term predictions for amivantamab with lazertinib OS with standard parametric models

Abbreviations: OS – overall survival

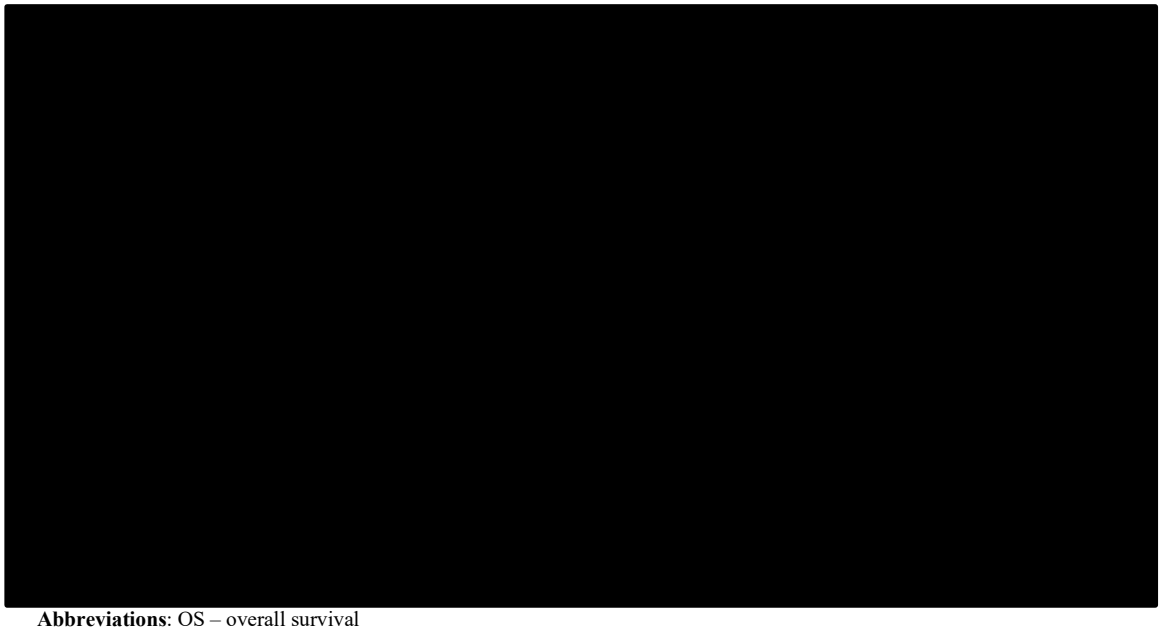
Figure 16: Long-term predictions for amivantamab with lazertinib OS with spline models

Abbreviations: OS – overall survival

Figure 17: Hazard plot for amivantamab with lazertinib OS with standard parametric models (reproduced from clarification response, Figure 32)

Abbreviations: OS – overall survival

Figure 18: Hazard plot for amivantamab with lazertinib OS with spline models (reproduced from clarification response Figure 16)



Abbreviations: OS – overall survival

Osimertinib OS

Standard parametric models and spline models were fitted to data on OS for osimertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 30 and Table 31, respectively. Comparisons of the observed KM curve and predicted OS are presented in Figure 19 and Figure 20, respectively. Empirical hazard plots and hazard plots from the fitted models are presented in Figure 21 and Figure 22, respectively. Clinician's estimates of expected OS are presented in Table 32.

The Weibull model was selected as the company's preferred base-case model for OS for osimertinib. Amongst all the standard parametric models, the Gompertz distribution has the lowest AIC/BIC, followed by Weibull, gamma and generalised gamma models. The standard parametric models generally provide a good visual fit, with the exception of log-normal and exponential distributions. The empirical hazard function appears to increase from the month 0 until about 27 months and decreases in the tail. The hazard functions for the Weibull, gamma, generalised gamma and Gompertz models align with the empirical hazard during the increasing phase.

All spline models provide a good visual fit to the KM curve and have similar AIC values with a five-point difference between the best- and worst-fitting models. The one-knot odds model has the smallest AIC, followed by the one-knot hazard, two-knot hazard, two-knot odds and one-knot normal models, with differences in AIC within three points. The one-knot odds model also has the smallest BIC, followed by the one-knot hazard and one-knot normal models, with differences in BIC within three points. All spline models predict an increasing hazard until around 30 months, with different predictions in the tails of the curves.

Clinicians' estimates of expected OS provided by the company are presented in Table 32. The mean of clinician's estimates of 10-year OS is [redacted]%. The 10-year OS prediction from the company's base-case Weibull model is 3.1%, which is slightly lower than clinicians' estimates. The standard parametric model that has the closest 10-year estimation to the clinicians' estimates is the gamma model, with a prediction of 6.3%. The Gompertz and generalised gamma models both give a 10-year OS prediction which is close to 0. For the spline models, the 10-year OS predictions from the one-knot and two-knot spline models are listed in order as follows: one-knot normal (11.2%), two-knot odds (10.8%), one-knot odds (10.6%), two-knot normal (8.6%), two-knot hazard (3.1%), and one-knot hazard (1.4%).

Overall, the EAG considers the use of standard parametric models to be adequate for fitting osimertinib OS. Of all the fitted standard parametric models, both the Weibull and gamma models are appropriate as they provide good statistical fit and reasonable hazard shape. The gamma model is associated with higher predictions than the clinician estimates, and the Weibull model is associated with lower predictions than clinician estimates.

Table 30: AIC and BIC statistics for osimertinib OS with standard parametric models (reproduced from CS Table 41)

Models	AIC (rank)	BIC (rank)
Exponential	[redacted]	[redacted]
Weibull (company's base-case)	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; OS – overall survival

Table 31: AIC and BIC statistics for osimertinib OS with spline models (reproduced from clarification response Table 15)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; OS – overall survival

Table 32: Clinician estimates for osimertinib OS (reproduced from Advisory board report, Table 20)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS – overall survival

Figure 19: Long-term predictions for osimertinib OS with standard parametric models

Abbreviations: OS – overall survival

Figure 20: Long-term predictions for osimertinib OS with spline models

Abbreviations: OS – overall survival

Figure 21: Hazard plot for osimertinib OS with standard parametric models (reproduced from clarification response Figure 33)

Abbreviations: OS – overall survival

Figure 22: Hazard plot for osimertinib OS with spline models (reproduced from clarification response Figure 18)

Abbreviations: OS – overall survival

(c) Time to discontinuation

The EAG notes that the company submitted additional data on TTD in an addendum provided during the factual accuracy check. Therefore the **information provided here on TTD is superseded** and the reader may wish to refer instead to the EAG's critique of the addendum.

Amivantamab TTD

Standard parametric models and spline models were fitted to data on TTD for amivantamab. The AIC and BIC values for the standard parametric models and spline models are shown in Table 33 and Table 34, respectively. Comparisons of the observed KM curve and predicted PFS are presented in Figure 23 and Figure 24, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 25 and Figure 26, respectively. Clinicians' estimates of expected TTD for amivantamab are presented in Table 35.

The exponential model was selected for use in the company's base-case. Amongst all the fitted standard parametric models, the generalised gamma model has the lowest AIC, which is five points lower than the next-best fitting model (exponential). The exponential distribution has the lowest BIC, followed by the generalised gamma distribution, with a two-point difference. The AIC/BIC values for the log-normal and log-logistic models are more than 30 points higher than the generalised gamma. All models other than the log-logistic and log-normal distributions appear to provide a good visual fit to KM curve. The smoothed empirical hazard plot appears to decrease, increase and then decrease, while the exponential model predicts a constant hazard.

All spline models appear to fit the KM curve well. Excluding the one-knot odds and one-knot normal models, the other seven spline models have similar AIC values, with differences of less than two points. The two-knot odds model has the lowest AIC, with less than one point difference compared to the two-knot normal, three-knot normal and three-knot odds models. All two-knot and three-knot spline models provide a good fit to the empirical hazard function.

Clinicians' estimates of expected TTD for amivantamab provided by the company are presented in Table 35. The mean of the clinicians' estimates of 8-year TTD is [redacted]%. The 8-year TTD prediction from the company's preferred exponential model is 2.4%. The 8-year TTD predictions from the two-knot spline models are listed as follows: two-knot normal (2.9%), two-knot odds (4.4%) and two-knot hazard (10%).

Overall, the EAG does not consider the use of the exponential model to be appropriate as it cannot reflect the complex hazard shape in the observed data. The EAG prefers the use of spline models as they provide a better fit to the empirical hazard function. Of all the fitted spline models, the EAG

considers the two-knot normal and two-knot odds models to be appropriate as they provide a good statistical fit to the KM estimates and good predictions to the hazard function, as well as closer predictions to clinicians' estimates of 8-year TTD.

Table 33: AIC and BIC statistics for amivantamab TTD with standard parametric models (reproduced from CS Table 43)

Models	AIC (rank)	BIC (rank)
Exponential (company's base-case)	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; TTD – time to discontinuation

Table 34: AIC and BIC statistics for amivantamab TTD with spline models (reproduced from clarification response Table 16)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; TTD – time to discontinuation

Table 35: Clinician estimates for amivantamab TTD (reproduced from Advisory board report, Table 31)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD – time to discontinuation

Figure 23: Long-term predictions for amivantamab TTD with standard parametric models

Abbreviations: TTD – time to discontinuation

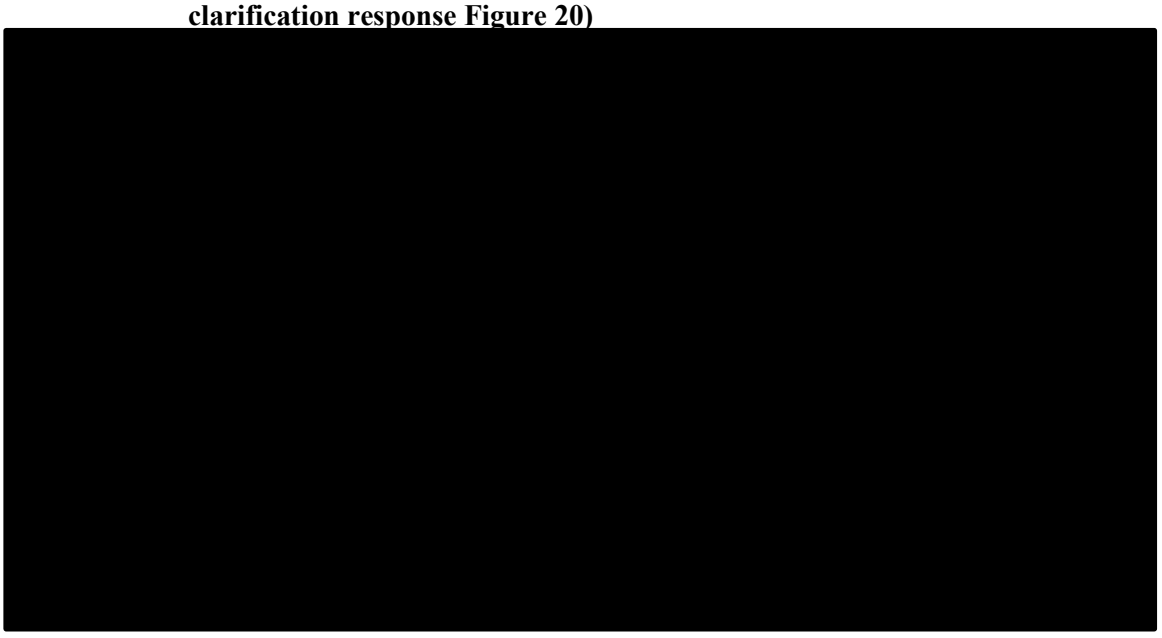
Figure 24: Long-term predictions for amivantamab TTD with spline models

Abbreviations: TTD – time to discontinuation

Figure 25: Hazard plot for amivantamab TTD with standard parametric models (reproduced from clarification response Figure 34)

Abbreviations: TTD – time to discontinuation

Figure 26: Hazard plot for amivantamab TTD with spline models (reproduced from clarification response Figure 20)



Abbreviations: TTD – time to discontinuation

Lazertinib TTD

Standard parametric models and spline models were fitted to data on TTD for lazertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 36 and Table 37, respectively. Comparisons of the observed KM curve and predicted PFS are presented in Figure 27 and Figure 28, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 29 and Figure 30, respectively. Clinicians' estimates of expected TTD for lazertinib are presented in Table 38.

The exponential model was selected for use in the company's base-case. Amongst all the fitted standard parametric models, the exponential model has the lowest AIC, and the Gompertz, Weibull and gamma distributions are within three points. The exponential distribution also has the lowest BIC, followed by the Gompertz which has a six point difference. All models other than the log-logistic and log-normal distributions appear to provide a good visual fit to KM curve. The smoothed empirical hazard function appears to decrease, plateau and then decrease. None of the standard parametric models can provide hazard plots with such a shape.

All of the spline models appear to fit the KM curve well. The three-knot normal model has the lowest AIC, followed by the three-knot odds, three-knot hazard and two-knot normal models, all with a difference in AIC within five points. The three-knot spline models do not seem to predict the empirical hazard plot well, while all the two-knot spline models predict the empirical hazard plot better.

Clinicians' estimates of expected TTD provided by the company are presented in Table 38. The mean of the clinicians' 8-year TTD estimates is [redacted]%. The 8-year TTD prediction from the company's preferred exponential model is 8.4%. The 8-year TTD predictions from the two-knot spline models are: two-knot hazard (9.3%), two-knot normal (13%) and two-knot odds (14.3%). The remaining six spline models all have 8-year predictions that are higher than 10%.

Overall, the EAG does not consider the use of exponential model to be appropriate as this model cannot predict the complex hazard shape in the observed data. The EAG prefers the use of spline models as they provide a better fit to the empirical hazard plot. Of all the fitted spline models, the EAG prefers the two-knot normal model as it provides good statistical fit to KM data and good predictions to the hazard function.

Table 36: AIC and BIC statistics for lazertinib TTD with standard parametric models (reproduced from CS Table 45)

Models	AIC (rank)	BIC (rank)
Exponential (company's base-case)	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; TTD – time to discontinuation

Table 37: AIC and BIC statistics for lazertinib TTD with spline models (reproduced from clarification response Table 17)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; TTD – time to discontinuation

Table 38: Clinician estimates for lazertinib TTD (reproduced from Advisory board report, Table 33)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD – time to discontinuation

Figure 27: Long-term predictions for lazertinib TTD with standard parametric models

Abbreviations: TTD – time to discontinuation

Figure 28: Long-term predictions for lazertinib TTD with spline models

Abbreviations: TTD – time to discontinuation

Figure 29: Hazard plot for lazertinib TTD with standard parametric models (reproduced from clarification response Figure 35)

Abbreviations: TTD – time to discontinuation

Figure 30: Hazard plot for lazertinib TTD with spline models (reproduced from clarification response Figure 22)

Abbreviations: TTD – time to discontinuation

Osimertinib TTD

Standard parametric models and spline models were fitted to data on TTD for osimertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 39 and Table 40, respectively. Comparisons of the observed KM curve and predicted PFS are presented in Figure 31 and Figure 32, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 33 and Figure 34, respectively. Clinician estimates of expected TTD for osimertinib are presented in Table 41.

The exponential model was selected for use in the company's base-case. Amongst all the fitted standard parametric models, the Weibull model has the lowest AIC and BIC, followed by the gamma, generalised gamma and Gompertz distributions. The EAG notes that the AIC for the exponential model is 16 points higher than that of the Weibull model. The hazard plot appears to increase from month 0 until around 29 months and decrease in the tail. The hazard functions for the Weibull, gamma and generalised gamma distributions closely align with the empirical hazard during the increasing phase.

All spline models appear to fit the KM curve well. AIC values do not vary much between the different spline models, with a four-point difference between the best- and worst-fitting models. The one-knot normal model has the lowest AIC, followed by the one-knot odds and one-knot hazard models. All spline models closely align with the empirical hazard during the increasing phase, from month 0 until about 30 months.

Clinician's estimates of TTD for osimertinib provided by the company are presented in Table 41. The mean of the clinicians' estimates of 8-year TTD is [redacted]%. The 8-year model-predicted TTD based on the exponential and Weibull distributions are 4.7% and 1.3%, respectively. The 8-year TTD predictions from the one-knot and two-knot spline models are listed in order as follows: one-knot odds (7.4%), two-knot odds (6.3%), one-knot normal (5.6%), two-knot normal (4.6%), two-knot hazard (2.2%), and one-knot hazard (1.6%).

The EAG acknowledges that the exponential model provides a closer estimation to the mean of clinicians' estimates, but does not consider it to be appropriate as it provides a poor statistical fit. The EAG considers the Weibull model to be the most appropriate standard parametric model as it has the lowest AIC and BIC, as well as a reasonable hazard shape. The EAG also considers two-knot normal and two-knot odds model to be appropriate as they provide close estimation to clinicians' 8-year estimates, albeit with worse statistical fit compared to the Weibull model.

Table 39: AIC and BIC statistics for osimertinib TTD with standard parametric models (reproduced from CS Table 47)

Models	AIC (rank)	BIC (rank)
Exponential **(company's base-case)**	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; TTD – time to discontinuation

Table 40: AIC and BIC statistics for osimertinib TTD with spline models (reproduced from clarification response Table 18)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - akaike information criterion; BIC - bayesian information criterion; TTD – time to discontinuation

Table 41: Clinician estimates for osimertinib TTD (reproduced from Advisory board report, Table 35)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD – time to discontinuation

Figure 31: Long-term predictions for osimertinib TTD with standard parametric models

Abbreviations: TTD – time to discontinuation

Figure 32: Long-term predictions for osimertinib TTD with spline models

Abbreviations: TTD – time to discontinuation

Figure 33: Hazard plot for osimertinib TTD with standard parametric models (reproduced from clarification response Figure 36)

Abbreviations: TTD – time to discontinuation

Figure 34: Hazard plot for osimertinib TTD with spline models (reproduced from clarification response Figure 24)

Abbreviations: TTD – time to discontinuation

4.2.4.3 Health-related quality of life

HRQoL data used in the company's model are based on data collected in MARIPOSA using the EQ-5D-5L questionnaire. Within the study, the questionnaire was administered at the following times: day 1 of the first and second cycles; every other subsequent cycle (i.e., every 28 days) during treatment; 30 days after the last treatment administration; and every 12 weeks during the post-treatment follow-up period (1-year). The company mapped the EQ-5D-5L data to the EQ-5D-3L using the algorithm reported by Hernandez Alava *et al.*[60] In the CS and the clarification response, the company provided three estimates of utility for the progression-free state based on three approaches. The utility for progressed status was estimated by a mixed-effects model for repeated measures (MMRM) using data from progressed patients.

Approach 1 (the company's base-case): In the CS, the mean utility per health state was calculated independently of the treatment group. The mean utility for progression-free status was calculated as the mean of the per-cycle utility predicted by a cycle-specific MMRM (Table 42). The cycle-specific MMRM was fitted for each cycle using data from patients who stayed progression-free until that cycle with all information from the start of the trial until that cycle (18 models).

Table 42: Health state utilities used for the company's base-case (adapted from CS, Table 51)

	Value	Source
Progression-free (SE)	[redacted]	Multiple MMRM from the pooled cohort of progression-free patients in MARIPOSA trial
Progressed disease (SE)	[redacted]	A single MMRM from the pooled patients who progressed in MARIPOSA

Abbreviations: MMRM - mixed model for repeated measures; SE – standard error
*** Data point updated in the company's addendum – please refer to the addendum to the EAG report**

Approach 2: In their response to clarification question B18, the company explored fitting a full MMRM using all available data. The full MMRM includes progression status, treatment arm, interaction between progression status and treatment arm, presence of Grade ≥ 3 AEs, and presence of a VTE event as covariates. The results (see Table 3 of the company's later clarification response to B18) suggest that the coefficients for progression status and treatment arm are statistically significant ($p<0.0001$ and $p=0.0005$ respectively), after adjusting for the presence of Grade ≥ 3 AEs, and presence of a VTE. As the interaction term was not statistically significant ($p=0.5808$), it was not included in the final selected model. The EAG notes that this model is worth reviewing to determine whether the appropriate variables were selected. However, such a model would also suggest a treatment-specific post-progression utility, which is likely due to the limited data collection after progression. The EAG prefers to analyse each health state separately instead of using the pooled data, as the company did, because the company's selected model assumes the equivalent differences in utilities between treatment arms for progression-free patients and progressed patients.

Approach 3: The company also fitted an MMRM including treatment arm, presence of Grade ≥ 3 AEs, and presence of a Grade ≤ 2 VTE event as covariates using all progression-free EQ-5D scores. The coefficients for Grade ≥ 3 AEs and Grade ≤ 2 VTE were used as a utility decrement for AEs. The estimated coefficients are presented in Table 43, with the coefficient for treatment arm being statistically significant, meaning that there is significant difference between mean progression-free utility scores for different treatments.

Table 43: Coefficients from the MMRM fitted to all progression-free EQ-5D scores (reproduced from Table 1 of the company's later clarification response to B16)

Variable	Mean (95% CI)
Intercept	[redacted]
Treatment: osimertinib	[redacted]
Grade ≤ 2 VTE	[redacted]
Grade ≥ 3 AEs	[redacted]

Abbreviations: AE - adverse events; CI – confidence interval; MMRM - mixed model for repeated measures; VTE - venous thromboembolism

The company used progression-free utility estimated using Approach 1 in their base-case model (see Table 42). That is, the utility values for the progression-free and progressed disease are assumed to be independent of treatment group. These values used in the model are applied in all cycles of the model. The model applies age-adjustment to the health state utilities based on UK general population norms reported by Hernandez Alava *et al*.[61]

Table 44: Summary of all estimated progression-free utilities in the CS

	Estimated utility for the progression-free state		
	Approach 1: multiple MMRM without the treatment term – used in the CS	**Approach 2: a single MMRM, all patients (adjusted by the progression status)**	**Approach 3: a single MMRM, progression-free patients only**
Amivantamab with lazertinib	[redacted]	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]	[redacted]

Abbreviations: MMRM - mixed model for repeated measures

[redacted] *QALY loss due to adverse events*

The model incorporates the decrement in QALYs resulting from Grade ≥ 3 AEs and Grade ≤ 2 VTEs for both treatment arms. By utilising the incidence of AEs and the cumulative duration observed in the MARIPOSA trial, a QALY loss was calculated based on disutility values for these AEs (Table 45). The disutility values were derived from a MMRM fitted to EQ-5D data of progression-free patients from the MARIPOSA (described above as Approach 3; Table 43). The company also conducted a scenario analysis using disutility values obtained from the literature. The utility values applied in the base-case and scenario analysis are summarised in Table 46.

Table 45: Loss of QALYs for each adverse event (adapted from CS, Tables 49, 50 and 79)

AE category	Incidence of AE[a] (%)*		Mean cumulative duration [a] (days)*	QALY loss[b]*	
	Amivantamab with lazertinib	Osimertinib		Base-case	Scenario analysis
Grade ≥ 3					
Dermatitis acneiform	[redacted]	[redacted]	[redacted]	[redacted]	−0.0026
Alanine aminotransferase increase	[redacted]	[redacted]	[redacted]	[redacted]	−0.0030
Hypalbuminaemia	[redacted]	[redacted]	[redacted]	[redacted]	−0.0074
Paronychia	[redacted]	[redacted]	[redacted]	[redacted]	−0.0223
Infusion related reaction	[redacted]	[redacted]	[redacted]	[redacted]	−0.0002
Rash	[redacted]	[redacted]	[redacted]	[redacted]	−0.0026
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]	−0.0075
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]	−0.0029
Grade ≤ 2					
VTE	[redacted]	[redacted]	[redacted]	[redacted]	−0.0072

[a] from the MARIPOSA trial
[b] QALY loss = Incidece of AEs × Mean duration × disutilities for AEs
Abbreviations: AE - adverse events; QALY - quality-adjusted life year; VTE - venous thromboembolism.
*** Data were updated in the company's addendum - please refer to the addendum to the EAG report**

Table 46: Disutility for adverse events

	Value	Source
Disutility for a base-case analysis (95% CI)		
Grade ≥ 3 TEAEs	[redacted]	A MMRM from pooled data for both arms in MARIPOSA trial
Grade ≤ 2 VTE		
Disutility for a company's scenario analysis (adapted from CS, Table 79)		
Dermatitis acneiform	−0.032	Assumed equal to rash
Alanine aminotransferase increase	−0.051	NICE TA654[55] for untreated EGFR mutation-positive NSCLC
Hypalbuminaemia	[redacted]	Assumed equal to mean disutility from pooled AEs in MARIPOSA
Paronychia	−0.202	NICE TA595[56] for untreated EGFR mutation-positive NSCLC
Infusion related reaction	−0.200	NICE TA561,[71] referring to NICE TA344,[a] for previously treated chronic lymphocytic leukaemia
Rash	−0.032	Nafees *et al.*[72]
Pulmonary embolism	[redacted]	Assumed equal to mean disutility from pooled AEs in MARIPOSA

	Value	Source
Disutility for a base-case analysis (95% CI)		
Pneumonia	[redacted]	Assumed equal to mean disutility from pooled AEs in MARIPOSA
Grade ≤ 2 VTE	[redacted]	Assumed equal to mean disutility from pooled AEs in MARIPOSA

[a]TA344 was withdrawn so EAG was not able to check the original source.
Abbreviations: CI - confidence interval; SE - standard error; VTE - venous thromboembolism.

4.2.4.4 Resource use and costs

This section provides a description of the resource costs included in the company's model. The model includes costs associated with: (i) drug acquisition and administration; (ii) disease management; (iii) treatments following disease relapse/progression; (iv) management of AEs, and (v) end-of-life care.

(i) Drug acquisition and administration costs for first-line treatments

Drug acquisition costs are modelled as a function of the planned treatment schedule, actual dose/vials, unit costs and the proportion of dose missed. Based on its list price, the cost per 350 mg vial of amivantamab is £1,079. The company has an agreed PAS which takes the form of a simple price discount of [redacted]; the discounted cost per pack of amivantamab is therefore [redacted]. The PAS price of lazertinib included in the analysis is [redacted] for 80 mg tablet and [redacted] for 240 mg tablet. Drug prices were taken from the BNF[44] for osimertinib. Drug acquisition costs were adjusted to reflect the actual doses administered in the MARIPOSA trial, accounting for both missed doses and dose modifications. The company stated in the clarification response (question B23) that, *"Amivantamab dose changes in the MARIPOSA trial corresponded to multiples of the full vial contents (350 mg), which means that there was no drug wastage associated with dose modifications."*

Administration costs for each treatment are calculated assuming that all drugs are given in an outpatient setting. The unit costs were taken from the National Schedule of NHS Costs 2023/24 (codes SB11Z and SB12Z).[64] An outpatient attendance to initiate oral treatment was assumed to occur once at model entry for patients starting treatment with either osimertinib or lazertinib. An outpatient procedure is assumed to be required for each IV administration of amivantamab. The treatment costs for amivantamab with lazertinib are higher in the first four weeks due to the higher dosing frequency for amivantamab in the treatment initiation phase. Total costs for drug acquisition and administration are presented in Table 47.

Concomitant medication costs, defined as drugs used alongside active treatments, were included in the model based on the MARIPOSA trial, where they were administered with amivantamab (Table 48). The company's response to clarification question B28 states that: "*the cost of 10 mg dexamethasone has been multiplied by three in the model to account for the full cost of dexamethasone comedication (30 mg total).*" This is described as being in accordance with the SmPC recommending 20 mg dexamethasone for the first dose and 10 mg for the second dose. However, the EAG notes that

company's model was set to administer a total of 60 mg of dexamethasone, which differs from their explanation provided above. Also, the cost of enoxaparin sodium for thromboprophylaxis was included only for the first four weeks in the model even though it should be continued until 17 weeks (the clarification response B29). No additional administration costs were assumed for concomitant medications.

Table 47: Drug acquisition costs for subsequent treatment

Drug	Dose*	Drug acquisition					Drug administration		Proportion of doses missed*	Cost per week (£)
		Strength per unit (mg)	Unit per pack	Price per pack (£)	Price per unit (£)	Unit per admin, reflecting actual dose*	Dosing frequency	Unit cost (£)		
Amivantamab (inc. PAS)	Required dose: - < 80 kg - 1,050 mg - ≥ 80 kg - 1,400 mg	350	1	[redacted]	[redacted]	< 80 kg: [redacted] vials[a] ≥ 80 kg: [redacted] vials[a]	IV, once weekly for the first 4 weeks and then once every 2 weeks	152.13[b]	< 80 kg: [redacted]% ≥ 80 kg: [redacted]%	First 4 weeks: [redacted][d] After 4 weeks: [redacted][d]
Lazertinib (inc. PAS)	Actual dose: - 80 mg - 160 mg - 240 mg - 320 mg - 480 mg	80	56	[redacted]	[redacted]	Weighted mean of unit: - 80 mg [redacted] - 240 mg [redacted]	PO, once daily	247.13[b]	[redacted]%	One-off: 247.13
		240	28	[redacted]	[redacted]					
Osimertinib	Actual dose: - 40 mg - 80 mg - 160 mg - 240 mg - 320 mg	40	30	5770[e]	192.33	Weighted mean of unit: - 40 mg [redacted] - 80 mg [redacted]	PO, once daily	247.13[c]	[redacted]%	[redacted] One-off: 247.13
		80	30	5770[e]	192.33					

[a]Calculated by EAG using the proportion of planned does administered, provided by the company; the planned number of vials * the proportion of planned dose administered (full vials)
[b]National Schedule of NHS Costs 2023/24,[64] SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; Outpatient; Medical Oncology Service
[c]National Schedule of NHS Costs 2023/24,[64] SB11Z - Deliver Exclusively Oral Chemotherapy; Medical Oncology Service
[d] Drug acquisition cost + IV administration cost; Weighted mean of drug costs by the distribution of weight (< 80 kg or ≥ 80 kg); The proportion of dose missed was applied to the unit cost for administration
[e]Taken from the British National Formulary (BNF)[44]
Abbreviations: IV - intravenous; PAS - Patient Access Scheme; PO - per os (by mouth/oral administration)
*** Data points updated in the company's addendum – please refer to the addendum to the EAG report**

Table 48: Comedication drug acquisition costs (adapted from CS Tables 59 and 60)

Drug	Dose (mg)	Drug acquisition					Dosing frequency	Proportion of doses missed	Cost per week (£)	
		Strength per unit (mg)	Unit per pack	Price per pack (£)	Price per unit (£)	Unit per admin			First 4 weeks	Week 5 onwards
Dexamethasone	Day 1: 20 Day 2: 10	10	1	30.80[a]	30.80	Day 1: 2 Day2: 1	IV, week 1 day 1 and 2	< 80 kg: [redacted]% ≥ 80 kg: [redacted]%	[redacted]	-
Paracetamol	825	500	100	0.79[a]	0.01	2.0	PO, once weekly for the first 4 weeks and then once every 2 weeks	Weighted mean: [redacted]%	[redacted]	[redacted]
Diphenhydramine	37.5	25	20	1.50[b]	0.08	2.0			[redacted]	[redacted]
Enoxaparin sodium	40	100	10	22.70[c]	2.27	1.0	SC, once daily until 17 weeks		[redacted]	-

[a] Taken from eMIT[63]
[b] Taken from NHS dictionary of medicines and devices (DM&D) indicative price (generic from Flamingo Pharma) [62]
[c] Taken from the British National Formulary (BNF)[44]
Abbreviations: IV - intravenous; PO - per os (by mouth/oral administration)

(ii) Disease management costs

The model captures health-state-specific costs associated with routine monitoring and follow-up care (Table 49). In the original CS, the types and frequencies of resources were based on previous HTA submissions (TA531, referred to by TA584).[65, 66] The EAG had difficultly verifying the original sources cited in these appraisals and had concerns that some of the original data sources are over 15 years old. According to the committee papers for NICE TA531, the resource use estimates quoted were based on Brown *et al.*[73] which published in 2013. Brown *et al.*[73] mainly referred to Maslove *et al.* (published in 2005),[74] NICE Guideline CG121 (2009) and the Marie Curie report (2004).[75] The EAG could not find the original values from the Marie Curie report and could not retrieve NICE Guideline CG121 because that has been updated and replaced with NICE Guideline NG121. Through the clarification process, the company updated some figures to match the values used in ID6328, which is an ongoing NICE appraisal of osimertinib with chemotherapy for untreated cEGFRm advanced NSCLC.[5] The resource use from ID6328 referenced Brown *et al.*[73] but were revised based on advice from clinical experts.

The values used in the model are presented in Table 49. Unit costs (Table 50) were based on the 2023/24 National Schedule of NHS Costs[64] or the 2023 PSSRU report on unit costs of health care.[67]

Table 49: Resource use per year and aggregated costs for disease management (adapted from CS, Table 65 and clarification response, Table 23)

	Company's original submission[ab]		ID6328 committee preferred[c]		Company's model submitted with the clarification response[c]	
	PF	**PD**	**PF**	**PD**	**PF**	**PD**
Resource use per year						
Oncology outpatient visit	9.61	7.91	9.61	7.91	9.61	7.91
Chest radiography	6.79	6.50	-	-	-	-
MRI scans	-	-	2	2	2	2
CT scan (chest)	0.62	0.24	2	2	2	2
CT scan (other)	0.36	0.42	2	2	2	2
ECG	1.04	0.88	2	0	1.04	2
Community nurse home visit (20 mins)	8.7	8.7	-	-	8.7	8.7
Clinical nurse specialist	12.0	12.0	12	12	12	12
GP surgery visit	12.0	-	-	-	12.0	-
GP home visit	-	26.09	-	-	-	26.09
Therapist visit	-	26.09	-	-	-	26.09
Annual cost by health state (£)	4,980.06	6,605.17	4,074.88	3,394.07	5,154.74	7,043.16
Weekly cost by health state (£)	95.44	126.59	78.09	65.05	98.79	134.98

[a]NICE TA531, referring to Brown *et al.* [73]
[b]Annual costs were calculated based on National Schedule of NHS Costs 2022/23[76]
[c]Annual costs were calculated based on National Schedule of NHS Costs 2023/24[64]
Abbreviations: ECG – Electrocardiogram; GP – General Practitioner; PF – progression-free; PD – progressed disease

Table 50: Unit costs associated with disease management (adapted from Table 23 in company's response to clarification question B34)

	Unit cost		
	Value (£)	**Source**	
Oncology outpatient visit	192.95	National Schedule of NHS Costs 2023/24[64]	WF01A. Consultant Led, Non-Admitted Face-to-Face Attendance, Follow-up, Medical Oncology Service
MRI scans	161.19		RD01A, Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over
CT scan (chest)	121.71		RD24Z, IMAG Computerised Tomography Scan of Two Areas, with Contrast
CT scan (other)	123.03		RD26Z, IMAG Computerised Tomography Scan of Three Areas, with Contrast
ECG	176.40		EY51Z, Outpatient, Electrocardiogram Monitoring or Stress Testing
Community nurse home visit	76.00	PSSRU 2023[67]	Cost per hour Band 8a nurse
Clinical nurse specialist	88.00		Cost per hour Band 8b nurse
GP surgery visit	49.00		Unit costs for a GP, per surgery consultation lasting 10 minutes incl. direct care staff costs with qualifications
GP home visit	49.00		Assumed the same costs as GP surgery visit
Therapist visit	52.00		Cost per hour for a community occupational therapist, incl. qualification

Abbreviations: CT – computed tomography; ECG – Electrocardiogram; GP – General Practitioner; MRI -Magnetic resonance imaging; NHS - National Health Service; PSSRU - personal social services research unit

(iii) Cost for treatments following disease progression (subsequent treatment)

The costs associated with subsequent treatments are considered as a one-off cost at the point of discontinuing first-line treatment. These include drug acquisition, administration, co-medications, monitoring, and management of AEs (Table 51). Subsequent treatments are categorised into second-line and third-line therapies. One-off costs are calculated based on the percentage of patients who receive each line, the types of treatments within each line, and the duration allocated to each treatment. The proportion of patients receiving second-line therapy, as opposed to best supportive care, was derived from an analysis of MARIPOSA, while the estimates for patients on the third-line and beyond treatment came from MARIPOSA-2 data. The MARIPOSA-2 trial, is a Phase III RCT that assessed the efficacy and safety of amivantamab-chemotherapy in patients with EGFR-mutated advanced NSCLC whose disease had progressed on or after osimertinib monotherapy.

The proportion of patients receiving subsequent therapy was calculated by dividing the number of patients who received any subsequent systemic therapy by the number of patients who discontinued their first-line treatment for reasons other than death. Deaths were assumed to occur proportionally among patients undergoing and not undergoing first-line treatment. For amivantamab with lazertinib, it was assumed that the number of patients on first-line treatment reflected the number of patients treated

with lazertinib. Costs for patients receiving best supportive care (not receiving any active treatments) for each line of subsequent treatment were assumed to be £0.

Table 51: One-off costs for subsequent treatment (adapted from CS, Table 61 and clarification response, Table 24)

	Cost[a] (£)	Patients receiving treatment[b]	
		Amivantamab with lazertinib*	Osimertinib*
Second-line costs			
Drug	592	[redacted]	[redacted]
Administration	1,727		
Co-medication	41		
Monitoring	36		
Managing AEs	294		
Best supportive care	0	[redacted]	[redacted]
Third-line and beyond costs			
Drug	2,210	[redacted]	[redacted]
Administration	2,760		
Co-medication	6		
Monitoring	6		
Managing AEs	397		
Best supportive care	0	[redacted]	[redacted]
One-off costs for subsequent treatments (£)		[redacted]	[redacted]

[a] aggregated costs reflecting the distribution of patients receiving treatment within each therapy
[b] second-line from MARIPOSA, Third-line or later from MARIPOSA-2; calculated by dividing the number of patients receiving any subsequent systemic therapy by those who discontinued their first-line treatment for reasons other than death; proportion of patients with best supportive care = 1- % patients receiving active treatment
*** Data points updated in the company's addendum – please refer to the addendum to the EAG report**

The distribution of patients receiving treatment within each therapy line was informed by clinical estimates from an advisory board meeting held by the company (Table 52). [redacted] use of platinum-based chemotherapy was assumed for second-line treatment. In the company's base-case, the distributions are independent of first-line treatment received, while the trial-arm specific distributions from the MARIPOSA and MARIPOSA-2 trials were tested in the company's scenario analysis. An additional analysis using subsequent treatments based on RWE from the NCRAS data was also conducted (see CS, Table 82).

Table 52: Distribution of subsequent treatments and durations on treatment (adapted from CS, Tables 80 and 81)

	Base-case	Scenario analysis using trial-based estimates of subsequent treatments	
	Both arms	Amivantamab with lazertinib	Osimertinib
Second-line		MARIPOSA*	
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]	[redacted]
Third-line and beyond		MARIPOSA-2	
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]	[redacted]

Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.
*** Data points updated in the company's addendum – please refer to the addendum to the EAG report**

To estimate one-off costs for subsequent treatment (Table 51), the costs of each treatment (Table 53) were aggregated with the distribution of patients receiving each treatment (Table 52). The company used the weight/body surface area obtained from the MARIPOSA trial for dose of chemotherapy. Osimertinib represents "EGFR MoA or TKI-based regimen" while the combination of atezolizumab and bevacizumab, carboplatin and paclitaxel represents 'IO ± chemotherapy ± VEGFi.' In the post-clarification model, non-platinum-based chemotherapy was assumed to consist of docetaxel given in combination with nintedanib; the original model included only docetaxel, but this was updated in response to clarification question B42.[25] A more detailed discussion of the current treatment pathway is provided in Section 2.2. However, the EAG's clinical advisers were broadly satisfied with the assumptions on second-line and third-line treatments made by the company. This included the potential for rechallenge with platinum-based chemotherapy at third-line in patients who had responded well previously to platinum-based chemotherapy and who had been progression-free for a significant period since their last treatment with platinum-based chemotherapy.

Co-medication costs were considered for platinum-based chemotherapy (until progression; vitamin B12, folic acid, and dexamethasone) and 'IO ± chemotherapy ± VEGFi' (when administered; famotidine, diphenhydramine, and dexamethasone). Monitoring costs were incurred for platinum-based chemotherapy only (every three weeks; full blood count, liver function, and renal function). These are not described in further detail as they account for a small proportion (< 5%) of the costs for subsequent treatments.

Table 53: Drug acquisition and administration costs for subsequent treatment

Regimen/ drug	Drug acquisition				Administration		Duration on treatment (weeks)		Drug acquisition cost (£)		Administration cost (£)	
	Dose	Strength per unit (mg)	Price per unit (£)	Unit per admin	Dosing frequency	Unit cost	2L	3L+[i]	2L	3L+	2L	3L+
Platinum-based chemotherapy												
Pemetrexed	500 mg/m²	500	28.76	2	IV, every three weeks	First 4 cycles: 352.31[b] Later: 152.13[c]	[redacted][e]	11.3	592	445	1,727	1,328
Platinum (Carboplatin [redacted]%, Cisplatin [redacted]%)												
Carboplatin[a]	5 AUC	450	23.18	2								
Cisplatin[a]	75 mg/m²	100	37.34	2								
Non-platinum-based chemotherapy												
Docetaxel[a]	75 mg/m²	80	9.73	2	IV, every three weeks	152.13[c]	[redacted][f]	10.9	3,089	2,799	3,574	3,238
Nintedanib	150 mg	150	35.85	1	PO, twice daily	247.13[d]						
EGFR MoA/TKI or TKI-based regimen												
Osimertinib[a]	80 mg	40	192.33	1	PO, daily	247.13[d]	43.9[g]	12.6	57,752	16,582	247	247
IO ± chemotherapy ± VEGFi												
Atezolizumab	1,200 mg	1200	3807.69	1	IV, every three weeks	352.31[b]	36.1[h]	18.3	75,484	38,414	4,238	2,145
Bevacizumab	15 mg/kg	400	810.10	3								
Carboplatin[a]	6 AUC	450	23.18	2								
Paclitaxel[a]	200 mg/m²	300	31.89	2								

[a] maximum of 4 cycles
[b] National Schedule of NHS Costs 2023/24,[64]SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; Outpatient; Medical Oncology Service
[c] National Schedule of NHS Costs 2023/24,[64] SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; Outpatient; Medical Oncology Service
[d] National Schedule of NHS Costs 2023/24,[64] SB11Z - Deliver Exclusively Oral Chemotherapy; Medical Oncology Service
[e] From the MARIPOSA-2
[f] Assumed same as platinum-based chemotherapy
[g]Median progression-free survival from the AURA3 trial[69]
[h]Median progression-free survival from the IMPOWER150 trial[68]
[i] Park *et al*.[70]
Abbreviations: 2L – second-line; 3L+ – third-line and latter lines; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor; IV - intravenous; PO - per os (by mouth/oral administration);

(iv) Management of AEs

The aggregated one-off costs of managing AEs were calculated by multiplying the estimates of AE incidence (Table 54) and their unit costs (Table 55) for first-line treatments and subsequent-line treatments. At first-line, Grade ≥ 3 AEs were included if they occurred in 5% or more of patients in any of the modelled treatment arms in each line and the incidence of AEs were obtained from the MARIPOSA trial. Additionally, the company included Grade ≤ 2 VTEs for first-line treatments as an AESI. For later lines of treatment, estimates of AEs incidence were obtained from NICE TA850,[77] and Mark *et al.* (the IMPOWER 150 trial).[78]

Table 54: Adverse events of subsequent treatments and one-off costs

	First line		Subsequent line			
			Chemotherapy			
	Amivantamab with lazertinib	Osimertinib	Platinum	Non-platinum	EGFR MoA/ TKI or TKI-based regimen	IO ± chemotherapy ± VEGFi
AE incidence (%)						
Dermatitis acneiform	[redacted]	[redacted]				
Alanine aminotransferase increase	[redacted]	[redacted]				
Hypalbuminaemia	[redacted]	[redacted]				
Paronychia	[redacted]	[redacted]				
Infusion related reaction	[redacted]	[redacted]				
Rash	[redacted]	[redacted]	0.0	0.0	5.9	1.3
Pulmonary embolism	[redacted]	[redacted]				
Grade ≤2 VTE	[redacted]	[redacted]				
Pneumonia	[redacted]	[redacted]				
Anaemia			11.8	3.8	0.0	6.1
Diarrhoea			11.0	24.4	69.9	2.8
Fatigue			0.7	3.5	1.3	3.1[a]
Febrile neutropenia			0.0	9.4	0.0	8.4
Neutropenia			11.8	14.6	0.0	13.7
Neutrophil count decreased			0.0	11.1	0.0	8.7
Thrombocytopenia			7.4	0.0	0.0	4.1
Hypertension			0.0	0.0	0.0	6.4
Platelet count decrease			0.0	0.0	0.0	5.1
Source for AE incidence	MARIPOSA trial		NICE TA850[77]	NICE TA850[77]	NICE TA850[77]	IMpower150[78]
One-off costs for managing AEs (£)	430.54	79.06	294.14	456.00	430.72	389.46

[a]The EAG note that the original value from IMpower150 trial is 3.3.
EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor; AE - adverse event; VTE - venous thromboembolism.

The company took the cost for an IRR from the AE costs used in TA561 and inflated it to 2021/22 prices using the NHS Cost Inflation Index (NHSCII).[76] The cost for a Grade ≤ 2 VTE was assumed to reflect the cost of rivaroxaban plus a diagnostic scan. The EAG notes that the company included only one dose of rivaroxaban. Others were costed by taking a weighted mean of non-elective short-stay admissions from the 2023/24 National Schedule of NHS Costs.[64]

Table 55: Unit cost for managing adverse events (adapted from CS, Table 66; includes updated reference costs applied post-clarification)

AE (Grade ≥ 3 unless otherwise stated)	Unit Cost (£)	Source	
Alanine aminotransferase increased	767.65	Mean of GC01F (liver failure disorder), non-elective inpatient – short stay	National Schedule of NHS Costs 2023/24[64]
Hypoalbuminaemia	767.65	Assumed same as alanine aminotransferase increased	
Hypertension	404.67	Mean of EB04Z, non-elective inpatient – short stay	
Dermatitis acneiform	511.89	Weighted mean of JD07A–JD07K (skin disorder), non-elective inpatient – short stay	
Rash	511.89		
Paronychia	511.89	Assuming same as rash	
Pulmonary Embolism	921.75	Weighted mean of DZ09J–DZ09Q (pulmonary embolus), non-elective inpatient – short stay	
Pneumonia	520.41	Weighted mean of DZ22K–DZ22Q (unspecified acute lower respiratory Infection), non-elective inpatient – short stay	
Diarrhoea	594.90	Weighted mean of FD01A–FD01J (gastrointestinal infections), non-elective inpatient – short stay	
Anaemia	766.57	Weighted mean of SA01G–SA01K (acquired pure red cell aplasia or other aplastic anaemia), non-elective inpatient – short stay	
Fatigue	766.57	Assumed same as anaemia	
Neutropenia	654.14	Weighted mean of SA08G–SA08J (other haematological or splenic disorders), non-elective inpatient – short stay	
Febrile neutropenia	654.14		
Neutrophil count decreased	654.14		
Platelet count decrease	752.52	Weighted mean of SA12G–SA12K (thrombocytopenia), non-elective inpatient – short stay	
Thrombocytopenia	752.52		
Grade ≤ 2 VTE	64.60	Weighted mean of RD40Z (ultrasound scan with duration of less than 20 minutes), diagnostic imaging	
	1.80	Cost of rivaroxaban	BNF[44]
Infusion related reaction	443.83	Cost used in TA561, inflated to 2021/2022 prices using the NHS Cost Inflation Index[76]	

Abbreviations: AE - adverse event; NHS - National Health Service; NICE - National Institute of Health and Care Excellence; TA - technology appraisal; VTE - venous thromboembolism; BNF - British National Formulary

(v) End-of-life care

A one-off cost of £4,862.63 was applied for terminal care upon death, estimated following the assumptions from NICE TA520.[57] Details of the contributing end-of-life costs are in Table 56.

Table 56: End of life costs (adapted from CS, Table 68)

	Patients receiving care[a] (%)	Cost (£)	Reference
Hospital admission and excess bed days	55.8%	5,646.97	National Schedule of NHS Costs 2023/24,[64] DZ17S (non-elective long stay)
Home setting - Macmillan nurse	27.3%	50*57*2/3 hours (40mins)	50 times of a community nurse (band 6) for 40 mins, PSSRU 2023[67]
Hospice care	16.9%	7,058.71	Assumed 25% increase on hospitalisation setting
Total one-off cost (£)		4,862.63	Weighted mean

[a] Obtained from TA520[57]
Abbreviations: NHS - National Health Service; PSSRU - Personal Social Services research unit

4.2.5 *Model evaluation methods*

The CS base-case presents ICERs for amivantamab with lazertinib versus osimertinib. Results are presented using the deterministic and probabilistic versions of the model. The probabilistic ICERs are based on 1,000 Monte Carlo simulations. Within the probabilistic sensitivity analysis (PSA), the company used beta distributions for utility/disutility values and proportions/probabilities, gamma distributions for costs, normal distributions for AE durations, and multivariate normal distributions for survival distributions. The results of the PSA were presented in the CS as a cost-effectiveness plane and as cost-effectiveness acceptability curves for amivantamab with lazertinib versus osimertinib.

Deterministic sensitivity analyses (DSAs) are presented using tornado plots, showing the top 10 most influential parameters on the ICER. Some of these analyses involve varying parameters according to their 95% CIs where available or using +/- 10% of the expected value where 95% CIs were not available.

4.2.6 *Model validation and face validity check*

The CS reports that expert advice from both clinical and health economic experts was sought at an advisory board meeting (October 2024) to validate the model.[31] Topics covered included;

- Generalisability of the MARIPOSA trial population to the population in England and Wales with untreated cEGFRm advanced NSCLC
- The current treatment pathway, in particular, the proportion of patients receiving standard of care treatments at different treatment lines in the current practice
- Choice of extrapolations for OS, PFS and TTD including a comparison against estimates elicited from clinical experts

- Appropriateness of utility data
- Validation of key model assumptions.

A technical validation of the model by an independent health economics review was also conducted and the TECH-VER checklist was utilised.[79]

4.2.7 *Company's cost effectiveness results*

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process. The company provided an analysis with list prices and the PAS discount associated with amivantamab and lazertinib. The results presented in this section incorporate the PAS discount for amivantamab and lazertinib but exclude the PAS discounts for any other drug.

Table 57 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of amivantamab with lazertinib versus osimertinib. The probabilistic version of the model suggests that compared to osimertinib, amivantamab with lazertinib generates an additional [redacted] QALYs per patient and a cost saving of [redacted]. The deterministic version of the model produces an additional [redacted] QALYs and a cost saving [redacted].

Table 57: Company's base-case results (generated by the EAG based on the company's post clarification model)

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs	LYGs	QALYs	Costs	
Probabilistic model (1000 iterations)							
Amivantamab with lazertinib	5.50	[redacted]	[redacted]	1.75	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.76	[redacted]	[redacted]	-	-	-	
Deterministic model							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73	[redacted]	[redacted]				

*Undiscounted
Abbreviations: ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year

The scatter plot (Figure 35), generated by the EAG running the probabilistic analysis for the company's base-case, showed that all PSA iterations resulted in lower costs for amivantamab with lazertinib versus osimertinib and > 99% resulted in greater QALYs. The cost-effectiveness acceptability curve (the company's clarification response, Figure 32) suggests that the probability that amivantamab with lazertinib generates more net benefit than osimertinib at willingness-to-pay thresholds below £30,000 is [redacted]%.

Figure 35: Cost-effectiveness plane, amivantamab with lazertinib versus osimertinib, with PAS prices

Generated by the EAG based on the company's post clarification model, 1000 iterations
Abbreviations: PAS - patient access scheme; PSA - probabilistic sensitivity analyses

4.2.8 *Company's deterministic sensitivity analyses*

All of the deterministic analyses provided in the updated tornado diagram show that amivantamab with lazertinib dominates osimertinib (Figure 36).

Figure 36: Tornado diagram for deterministic sensitivity analyses with PAS prices

Generated by the EAG based on the company's post clarification model
Abbreviations: ICER - incremental cost-effectiveness ratio; OS - overall survival; TTDD - time to treatment discontinuation or death.

4.2.9 *Company's scenario analyses*

All of the deterministic scenario analyses provided by the company had a ICER below [redacted] with the choice of OS and TTD distributions having the greatest impact on the magnitude of incremental costs and the choice of OS having the greatest impact on the incremental QALYs.

Table 58: Company's scenario analyses, deterministic (adapted from clarification response, Table 31)

Scenario description	Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs[a]	QALYs	Costs (£)	
Company's base-case (deterministic)	1.71	[redacted]	[redacted]	Dominant[b]
1.5% discount rate	1.71	[redacted]	[redacted]	Dominant[b]
37.7-year time horizon	1.71	[redacted]	[redacted]	Dominant[b]
Left-truncated for osimertinib	1.75	[redacted]	[redacted]	Dominant[b]
PFS by INV for amivantamab with lazertinib and osimertinib	1.71	[redacted]	[redacted]	Dominant[b]
Lower PFS curve selections (Gamma extrapolation for amivantamab with lazertinib and osimertinib)	1.71	[redacted]	[redacted]	Dominant[b]
Higher PFS curve selections (Log-normal extrapolation for amivantamab with lazertinib and osimertinib)	1.71	[redacted]	[redacted]	Dominant[b]
Lower OS curve selections (Gompertz extrapolation for amivantamab with lazertinib and osimertinib)	0.91	[redacted]	[redacted]	Dominant[b]
Higher OS curve selections (Gamma extrapolation for amivantamab with lazertinib and osimertinib)	1.69	[redacted]	[redacted]	Dominant[b]
Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	1.71	[redacted]	[redacted]	Dominant[b]
Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	1.71	[redacted]	[redacted]	Dominant[b]
HSUV (PD: 0.678; PF: 0.794 as per TA654)	1.71	[redacted]	[redacted]	Dominant[b]
AE disutilities based on literature	1.71	[redacted]	[redacted]	Dominant[b]
Subsequent treatment distribution based on MARIPOSA trial	1.71	[redacted]	[redacted]	Dominant[b]
Subsequent treatment distribution based on UK RWE	1.71	[redacted]	[redacted]	Dominant[b]

[a] Undiscounted

[b] Amivantamab with lazertinib dominates osimertinib (has higher costs and lower QALYs)

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

4.3 Critique of company's submitted economic evaluation by the EAG

4.3.1 *Model verification*

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Cell-checking to ensure integrity of programming in the company's model
- Examination of the correspondence between the company's executable models and their description in the CS and the company's clarification response.
- Replication of the base-case results, PSA, DSAs and scenario analyses presented within the CS using the company's executable model.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- Comparison of the model structure and data sources against the model used to inform TA654.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

A few minor errors in the post-clarification updated model were identified by the EAG. These are described in Section 4.3.3.1. The EAG considers the company's updated version of the model to be generally well programmed despite these errors, and that the version of the model used by the EAG after correcting these errors is appropriate for informing decision-making.

4.3.2 *Adherence of the company's model to the NICE reference case*

The extent to which the company's submission adhere to the NICE Reference Case is summarised in Table 59.

Table 59: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	EAG comments (a ✓ denotes the company's analyses are in line with the reference case)
Population	The scope developed by NICE	Restricted to patients with an ECOG PS of 0 or 1 which is narrower than the population listed in the scope, but consistent with the population recruited to the pivotal MARIPOSA
Intervention	As listed in the scope developed by NICE	✓

Element	Reference case	EAG comments (a ✓ denotes the company's analyses are in line with the reference case)
Comparator(s)	As listed in the scope developed by NICE	A comparison against osimertinib with chemotherapy is not provided (see Section 2.3.3)
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓
Perspective on costs	NHS and PSS	✓ The company's analysis excludes the cost of testing for EGFR mutations (CS, Table 1), but the EAG considers this to be reasonable as their clinical advisers stated that testing for EGFR mutations is already part of routine care.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	✓
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓
Synthesis of evidence on health effects	Based on systematic review	✓
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	✓ Utility values for the progression-free and progressed disease health states, and the utility decrements attributable to AEs are estimated from the EQ-5D-5L data collected in the MARIPOSA trial. The company has mapped from EQ-5D-5L to EQ-5D-3L using the algorithm reported by Hernandez Alava *et al.* Carer HRQoL is not included.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQOL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓ A severity modifier is not applied by the company (see Section 5)
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	✓
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	✓

4.3.3 *EAG Critique of the modelling performed by the company*

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's economic analyses.

Box 1: Summary of the main issues identified within the company's health economic model

- *Model errors and other minor issues*
- *Uncertainty around the survival analysis* (Key Issues 3 and 4)
- *Potential underestimation of administration costs for amivantamab* (Key Issue 5)
- *Use of treatment-independent utilities for the progression-free state* (Key Issue 6)
- *Uncertainty around resource use*
- *Uncertainty around VTE cost*

4.3.3.1 *Model errors and other minor issues*

(a) Discrepancies in unit cost estimates

The EAG found that some of the unit costs (Table 60), which were taken from the 2023/24 National Schedule of NHS Costs[64] by the company, were not matched with figures taken by the EAG (accessed on the 20th of February 2025) whilst verifying the model.

Table 60: Unit costs from the 2023/24 National Schedule of NHS Costs

Category	Item	Definition	CS	EAG's base-case
AE cost	Pulmonary embolism	Weighted mean of DZ09J–DZ09Q (pulmonary embolus), non-elective inpatient – short stay	921.75	663.63
	Neutropenia	Weighted mean of SA08G–SA08J (other haematological or splenic disorders), non-elective inpatient – short stay	654.14	560.68
Administration cost	Oral therapy one-off cost	SB11Z - Deliver Exclusively Oral Chemotherapy; Medical Oncology Service	247.13	240.44
	IV administration, simple	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; Outpatient; Medical Oncology Service	152.13	133.39
	IV administration, complex	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance; Outpatient; Medical Oncology Service	352.31	337.16

Abbreviations: CS – company submission; EAG – external assessment group

(b) Programming error leading to the shorter duration of rivaroxaban for managing VTE

The company's model assumes that patients suffering from VTE (Grade ≤ 2) have rivaroxaban for one day instead of the duration of VTE ([redacted] days). The EAG believes that this is a programming error.

(c) Minor error in adverse events

The EAG verified the incidence of AEs from the original sources which the company cited and found a minor error in fatigue for 'IO ± chemotherapy ± VEGFi'. The proportion of patients who had fatigue

in the IMpower150 trial was 3.3% rather than the 3.1% applied in the company's model.[78] All other AEs obtained from IMpower150 correlated with those reported in the trial and therefore the EAG considers this is likely to be a transcription error.

(d) Programming errors related to the administration of co-medication of amivantamab

The model includes the cost of enoxaparin sodium for thromboprophylaxis (£15.59 per week) only for the first four weeks rather than 17 weeks. Additionally, the cost calculations for dexamethasone assumed that it is given at twice the recommended dose in the SmPC during the first four weeks. The EAG deemed these to be programming errors.

(e) Adjusting the cost of infusion-related reactions to current value

The company stated that *"IRR costs included in TA651, inflated to 2021/2022 prices using the NHS Cost Inflation Index."* The EAG was unsure how this was done and could not replicate the estimate applied in the company's model. Also, the EAG notes that the company inflated the cost to 2021/22 rather than 2022/2023 prices. The EAG assumes that the cost taken by the company is £401.01 from TA561. Using the NHSCII (pay and prices) reported in PSSRU 2023,[67] the estimated cost inflated to 2022/23 values is £474.03.

(f) The treatment duration of second-line IO ± chemotherapy ± VEGFi

The company reported that the treatment duration for second-line therapy, which includes 'IO ± chemotherapy ± VEGFi', was 8.3 months, based on the IMpower150 trial.[68] This duration represents the median PFS in the ITT population, which includes patients with EGFR mutations or anaplastic lymphoma kinase (ALK) genetic alterations. The EAG believes that the subgroup of patients with sensitising EGFR mutations, specifically exon 19 deletion or the exon 21 L858R mutation, is the most relevant population for evaluation. In this subgroup of the Impower150 trial, the median PFS is reported to be 10.3 months.[68]

4.3.3.2 Uncertainty around the survival analysis

The EAG has several concerns regarding the company's survival analysis presented in the CS[1] These concerns are discussed below based on the general considerations around model fitting and selection set out in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[80, 81]

(a) Appropriateness of the data used

IPD from the MARIPOSA trial were used to inform survival extrapolation. The EAG notes that PFS (DCO 11th August 2023) has an earlier data cut than OS and TTD (DCO 13th May 2024). In their response to the EAG's clarification questions, the company states that there is no later data cut for PFS but there will be a new data cut based on the final analysis for 'relevant outcomes' which will be

provided after the EAG submits its final report. The EAG notes that if only OS is updated based on the final analysis DCO this would mean that there will be three different data cuts for PFS, OS and TTD.

(b) Suitability of the joint models

The company investigated the appropriateness of fitting combined models by assessing the proportional hazard assumption based on log cumulative hazard plot of PFS and OS and concluded that fitting separate models to each arm is more appropriate than using jointly fitted models. The EAG agrees with the company that fitting separate models is a reasonable approach.

(c) Range of candidate models assessed

The company fitted seven standard parametric survival models to the data for each treatment arm separately. In response to clarification question B5, the company also fitted nine spline models with three different scales (hazard, odds, and normal) for up to three knots. After assessing all of the fitted models, the EAG concludes that the standard parametric models are adequate for PFS, but the spline models provide better fit for OS and TTD. For TTD, the spline models capture the shape of the empirical hazard function better, while for OS in amivantamab with lazertinib, the spline models provide a better visual fit than standard parametric models.

(d) Statistical and visual goodness-of-fit

Amongst other factors, the company's model selection process included consideration of statistical goodness-of-fit (AIC and BIC) and visual inspection. The company's preferred base-case models all have reasonable AIC/BIC values, apart from the exponential model for osimertinib TTD, which has high AIC and BIC values, 16 points higher than the model with the lowest AIC and 12 points higher than the model with the lowest BIC.

(e) Consideration of hazard plots The company has taken into account the smoothed empirical hazard plots in the process of selecting curves. Hazard plots from PFS and OS of both arms are reasonably captured in the company's preferred base-case models, but hazard plots for TTD have more complex shapes that are not captured by the company's preferred base-case models. For both amivantamab and lazertinib TTD, there are noticeable decreases at the beginning of the hazard curves. The EAG prefers the two-knot spline models as they provide a hazard function with a reasonable shape, while the company's preferred base-case exponential model predicts a constant hazard. For osimertinib TTD, the hazard function first increases and then decreases, which is well predicted by the Weibull model and the spline models but not by the exponential model.

In addition, the company provided unsmoothed empirical hazard plots in response to clarification question B4, but the unsmoothed plots are too noisy, due to the plotting method used. The EAG is unable to assess the shape of the unsmoothed hazard function based on these plots.

(f) Consideration of long-term clinical plausibility

Three clinicians were consulted at an advisory board meeting held in October 2024 to inform long-term survival extrapolation assumptions. The estimates obtained from each of the three clinicians are presented at Section 4.2.4.2. The EAG notes that the estimates from Clinician 1 are noticeably higher than those of Clinicians 2 and 3 across all endpoints. The EAG's clinical advisers consider the company's clinicians' estimates to be reasonable and their estimates are more closely aligned with those of Clinicians 2 and 3.

In the CS, the company presented the midpoint of the clinicians' estimates, which is the mean between the lowest and highest estimates. The EAG prefers to use the mean of all three clinicians' estimates instead of the midpoint, as the midpoint ignores part of the data and is sensitive to outliers. Due to the uncertainty associated with long-term predictions, the EAG has explored different potentially plausible survival curves in the scenario analysis.

(g) Additional scenario including OS data from the FLAURA trial

The CS included a scenario analysis in which they used data from the osimertinib arm of the FLAURA study to supplement the data used when fitting the OS curves for the osimertinib arm (CS, B.3.11.3.1). The EAG did not consider this scenario to be preferable to the company's base-case approach because the addition of the FLAURA data does not provide much additional longer-term data and it introduces the complication of combining data across multiple sources, thereby reducing the internal validity of the OS comparison provided by the MARIPOSA trial.

EAG conclusions on the company's survival analysis

Overall, the EAG considers the company's base-case selections (PFS - log-logistic; OS – Weibull) to be reasonable. For TTD, the EAG prefers the use of two-knot normal spline models for amivantamab and lazertinib as they provide a good fit to the hazard functions, and the use of the Weibull model for osimertinib as it has a good statistical fit. The EAG has incorporated these alternative TTD curves in its preferred base-case analysis (see Sections 4.4.2 and 4.4.3). As the long-term OS, PFS and TTD predictions are uncertain, the EAG has also explored some alternative OS, PFS and TTD curves in scenario analyses to assess the extent to which the choice of parametric survival model impacts on the cost-effectiveness estimates.

4.3.3.3 *Use of treatment-independent utilities for the progression-free state*

The EAG notes that the coefficient for treatment arm (presented in Table 43) is statistically significant in the regression that also included coefficients for both Grade ≥ 3 AEs and Grade 1-2 VTEs. This would support a conclusion that the utility is significantly different between trial arms for reasons other than the rate of these AEs being different.

The company's response to clarification question B16 states that: *"at each timepoint, the mean utility values for each trial arm are close in value with many showing overlapping 95% confidence levels. This supports the Company submission model assumption of equivalent utilities, in which a pooled utility value is used for the PF health state across both arms, is appropriate."* However, the EAG notes that the [redacted] (Figure 37). Amongst the AEs included in the utility regression, the longest duration of AEs was [redacted] days for VTE (Grade 1–2), with all Grade ≥ 3 AEs having a duration of under [redacted] days. Therefore, the EAG considers that the differences in utilities showing in Figure 37 are unlikely to be explained by AEs that occur mostly at the start of treatment and resolve within [redacted] days.

Figure 37: Progression-free utility scores over time (reproduced from Figure 27 of the company's later clarification response covering questions B16 to B19)

The EAG is concerned that using the pooled utility values for patients in the progression-free state may underestimate the difference between the two treatment arms. The company responded that they deemed

it inappropriate to use treatment-specific utility because mean progression-free utility value of osimertinib when using this approach ([redacted]; Approach 2 in Table 44) is higher than

- the expected utility value for the general population (age 55–64 years: 0.799),
- the pooled value currently used in both arms of the model ([redacted]), and
- the value previously accepted by the NICE Committee in appraisals in advanced EGFR-mutated NSCLC (0.794 [TA654[55] and ID6328[5]]).

The EAG notes that the expected EQ-5D-3L for a 62.3 years old is 0.826 based on UK general population norms reported by Hernandez Alava *et al*.[61] Meanwhile, the progression-free utility used in TA654 and ID6328 (0.794) is a mapped value to EQ-5D-3L from the pooled data in FLAURA patients. The estimated progression-free health-state utility in the osimertinib arm of the FLAURA trial was 0.803, as presented in TA621 (TA654 was the review of TA621). Overall, the EAG would prefer to use the treatment arm-specific utility values, shown in Table 44 (0.813; Approach 3), as the company's regression analysis shows a statistically significant difference in utility between arms after taking into account the impact of AEs already captured separately in the model.

4.3.3.4 Potential underestimation of administration costs for amivantamab

In the PALOMA-3 trial, which is comparing the subcutaneous and IV formulations of amivantamab (see Table 16), Leigh *et al.* reported that the median infusion time for IV amivantamab on day 1 of cycle 1 was 5 hours (range: 0.2 to 9.9) and the median infusion time on day 1 of cycle 3 was 2.3 hours (range: 0.5 to 4.4)..[82] In response to clarification question B27, the company stated that: "*For cycle 3 onwards, a median duration of 2.25 hours was reported. Therefore, the HRG code applied in this submission for treatment administration is considered reflective of the average infusion time for amivantamab."* The EAG notes that the company has been using two terms interchangeably for the infusion time and duration that it planned to measure in the PALOMA-3 trial (participant chair time and the duration of treatment administration). The EAG is unsure how long the expected chair time would be for amivantamab administration based on the information provided, although none of the information provided by the company supports a chair time of less than 60 minutes. The draft SmPC for amivantamab describes an infusion rate of 125 mL/hr from week 4 onwards which would require a minimum of 2 hours to administer the 250 mL infusion volume recommended. The EAG is concerned that the HRG code (SB12Z) applied for the treatment administration of amivantamab does not adequately capture the expected duration of infusion because SB12Z is for 30 to 60 minutes of chair time (Table 61). Given the information provided by the company, and the estimates from Leighl *et al.,* the EAG prefers to apply SB14Z which allows for over 2 hours of chair time.

Also, the company did not include the administration cost for the second part of the split dose given on day 2 of week 1. The EAG believes that the company should include it in the model and SB15Z (deliver subsequent elements of a chemotherapy cycle) is the most relevant HRG code for delivery of the second part of the split dose, which is a one-off occurrence.

Table 61: Chemotherapy delivery HRGs

HRG Code	Definition	Explanation
SB12Z	Deliver simple parenteral chemotherapy	Overall time of 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.
SB13Z	Deliver more complex parenteral chemotherapy	Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.
SB14Z	Deliver complex chemotherapy, including prolonged infusional treatment	Overall time of 60 minutes nurse time and over two hours chair time for the delivery of a complete cycle.
SB15Z	Deliver subsequent elements of a chemotherapy cycle	Delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance, for example day 8 of a day 1 and 8 regimen or days 8 and 15 of a day 1, 8 and 15 regimen.

Source: 2020/21 National Tariff Payment System Annex B: Guidance on currencies with national prices[83]

4.3.3.5 Uncertainty around resource use

As noted in Section 4.2.4.4, the EAG expressed concerns that some of the original data sources are over 15 years old, and the EAG cannot verify certain figures, particularly those from NICE Guideline CG121 (2009) and the Marie Curie report (2004).[75] To ensure consistency with recent appraisals, the EAG prefers to use the figures used in ID6328, which were revised with input from clinical experts based on the work of Brown *et al*.[73]

4.3.3.6 *Uncertainty around VTE cost*

The EAG notes that the resource use for Grade ≥ 3 pulmonary embolisms (PEs) is limited to non-elective short stay admission costs. These do not account for any unbundled diagnostic costs, such as the costs of a computerised tomography pulmonary angiography (CTPA) to diagnose PE (RD21A; £114). In addition, the company's approach may underestimate the cost of PE in some patients requiring a long-stay admission or admission to critical care. The EAG would prefer the company to include unbundled diagnostic costs and the costs of outpatient drug treatment as a minimum, in addition to the short-stay admission. This would increase the cost of a Grade ≥ 3 PEs from £664 (the EAG's estimate from Table 60) to £819.

The EAG notes that the company's model assumes limited resource use for managing Grade ≤ 2 VTEs. Firstly, only drug costs and costs for diagnostic scans were included. Secondly, the resource use

included effectively assumes that the VTE event is a DVT and not a PE as the diagnostic scan included is a leg ultrasound, whereas chest imaging (e.g. CTPA) would be required to diagnose a PE. The data provided in response to clarification question B21 suggest that approximately 45% of Grade ≤ 2 VTEs are PEs when estimated across both arms. Therefore, the costs of diagnosis should be based on 66% of patients requiring a leg vein ultrasound (RD40Z) and 45% requiring a CTPA (RD21A). Finally, no costs are included for emergency department attendance. Whilst the EAG accepts that only events not leading to admission would usually be classified as Grade ≤ 2, the diagnosis of these events would usually occur in an emergency department. Therefore, it would have preferred the company to have included the cost for an emergency department attendance for this category of AE (VB05Z as used by Pandor *et al.*).[84]

The EAG notes that the company's approach of only including Grade ≥ 3 AEs occurring in ≥ 5% patients in either trial arm has resulted in Grade ≥ 3 DVTs being excluded from the model, despite all Grade ≤ 2 VTE events being included which would include both PEs and DVTs. The EAG considers that this is inconsistent and would prefer to see resource use associated with all VTEs, including Grade ≥ 3 DVTs ([redacted]% for amivantamab with lazertinib and [redacted]% for osimertinib; see clarification response B21), included in the model. The EAG's preferred resource use for these Grade ≥ 3 DVTs would be a non-elective short-stay admission (YQ51A to YQ51E; weighted average cost £477), in addition to applying the drug and diagnostic costs applied to Grade ≤ 2 DVTs.

Table 62 summarises the costs on average across both DVTs and PEs for Grade ≥ 3 VTEs and Grade ≤ 2 VTEs under the EAG's preferences.

The EAG's clinical advisers also noted that they would be more likely to prescribe an oral anticoagulant for thromboprophylaxis instead of the company's choice of enoxaparin sodium which requires daily subcutaneous injections. However, the EAG has not amended the model to reflect this preference because the daily costs are similar (£2.27 per day for enoxaparin sodium versus £1.80 per day for rivaroxaban), meaning that the change would be unlikely to have a large impact on the cost-effectiveness estimates.

Table 62: Costs of VTE preferred by the EAG

Resource use category	DVT Grade ≤ 2	PE Grade ≤ 2	DVT Grade ≥ 3	PE Grade ≥ 3
Anticoagulant treatment for 3 to 6 months ([redacted] days rivaroxaban)	£277	£277	£277	£277
Leg vein ultrasound (RD40Z)	£65	NA	£65	NA
Diagnostic scan for PE - CTPA (RD21A)	NA	£114	NA	£114
Emergency department attendance without admission (VB05Z)	£511	£511	NA	NA
Short stay admission for PE (see EAG's estimate Table 60)	NA	NA	NA	£664
Short stay admission for DVT (YQ51A to YQ51E)	NA	NA	£477	NA
Average cost by VTE category and grade	£853	£902	£819	£1055
Distribution of DVT and PE [a]	55%	45%	23%	77%
Average cost for VTE by grade	£875		£1002	

[a]Based on information provided in clarification response B21 using average across both arms
Abbreviations: CTPA - computerised tomography pulmonary angiography; DVT - deep vein thrombosis; NA – not applicable; PE - pulmonary embolism

4.4 Exploratory analyses undertaken by the EAG

4.4.1 *Overview of EAG's exploratory analyses*

The exploratory analyses performed by the EAG are described in Section 4.4.2. The results of the EAG's analyses are provided in Section 4.4.3.

4.4.2 *EAG's exploratory analyses - methods*

The EAG's base-case analysis is comprised of six amendments to the company's model: EAG exploratory analysis (EA) 1-6; these are detailed below.

EA1: Correcting programming and implementation errors in the company's economic model

The EAG corrected the company's implementation errors mentioned in Section 4.3.3.1 as follows:

- Unit costs that the EAG derived from the 2023/24 National Schedule of NHS Costs[64] were used (Table 60).
- For the management of VTE, it was assumed that rivaroxaban would be administered for [redacted] days, which aligned with the duration of VTE observed in the MARIPOSA trial.
- The dose of dexamethasone was changed from 60 mg to 30 mg during the first treatment cycle.
- Enoxaparin sodium is scheduled to be administered for 17 weeks.
- The cost of IRRs was adjusted for inflation to 2022/23 values using the NHSCII (pay and prices).
- The duration of 'IO ± chemotherapy ± VEGFi' in second-line treatment was revised to 10.3 months, instead of 8.3 months.

- The incidence of fatigue for 'IO ± chemotherapy ± VEGFi' was revised to 3.3%, based on a sample size of 13 out of 393 patients.

As these were considered to be error corrections, these changes were maintained in all subsequent EAG analyses.

EA2: Using spline models for TTD

The EAG changed the distribution for TTD to the two-knots normal model for amivantamab and lazertinib, and the Weibull model for osimertinib.

EA3: Applying treatment-specific utility

The EAG applied treatment-specific utility for progression-free (see Approach 3 in Table 44).

EA4: Applying administration cost with prolonged chair time

The EAG utilised the unit cost associated with SB14Z (chair time exceeding two hours) for administration costs in the amivantamab arm, rather than using the unit cost of SB12Z (chair time of 30 to 60 mins). Additionally, the EAG included the administration cost for subsequent administration on Week 1, Day 2 (SB15Z: delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance) to account for the need for a split dose in the first week.

EA5: Applying frequencies of resource use which the committee preferred in ID6328

The EAG utilised the resource use frequencies that were favoured by the committee of ID6328 (see Table 49).

EA6: Applying consistent category of VTE

To align with the company's approach of including Grade ≤ 2 VTE, the EAG applied the incidence of Grade ≥ 3 VTE (covering PE and DVT) rather than Grade ≥ 3 PE alone. The costs for managing VTEs were also re-estimated to account for outpatient drug costs for Grade ≥ 3 VTE, diagnostic costs for all and emergency department costs for Grade ≤ 2 VTE which is assumed not to require admission. The costs presented in Table 62 were used for EA7.

The following additional sensitivity analyses (ASA) were undertaken using the EAG's base-case as the starting point.

ASA1: Use of the company's preferred administration cost

The EAG assessed the impact on the ICER when the company's choice for administration unit cost was used (SB12Z).

ASA2: Use of treatment independent utility

The EAG evaluated the impact on the ICER of using the utility values from TA654 for both arms (progression-free: 0.794; progressed disease: 0.678).

ASA3: Use of alternative distribution for TTD in osimertinib

The EAG changed the distribution of TTD for osimertinib to the two-knots normal model. All distributions for amivantamab, lazertinib and osimertinib are two-knots normal in this scenario as the EAG preferred two-knots normal for amivantamab and lazertinib in its base-case.

ASA4: Use of alternative distributions for OS

The EAG changed the distributions for OS: to a one-knot hazard model for amivantamab with lazertinib and to a gamma model for osimertinib. This scenario aimed to assess whether the cost-effectiveness estimates were sensitive to alternative survival curve choices that provided a good statistical fit but different long-term predictions. The EAG's alternative distributions provide a lower 10-year survival prediction for amivantamab with lazertinib (10.4% one-knot hazard model versus 15.0% for Weibull) and a higher prediction for osimertinib (6.3% for gamma versus 3.1% for Weibull) than the company's preferred Weibull distributions. The EAG considers that these alternative distributions provide 10-year OS predictions that are better matched to the clinical expert estimates presented by the company (means of [redacted]% and [redacted]% for amivantamab with lazertinib and osimertinib respectively).

ASA5: Use of alternative distributions for PFS

The EAG used gamma distributions for PFS for both arms to explore whether the cost-effectiveness estimates were sensitive to an alternative choice of survival curves with a good statistical fit but lower long-term PFS predictions in both arms.

4.4.3 *EAG's exploratory analyses – results*

The results of the EAG's preferred analyses are shown in Table 63, which provides the impact of each individual change and the results for the EAG's preferred base-case. Across all these scenarios, amivantamab with lazertinib was found to dominate osimertinib consistently, with cost savings ranging from [redacted] to [redacted]. Using alternative TTD curves had the greatest impact on incremental costs, followed by accounting for longer chair time for IV infusion of amivantamab. Applying treatment-specific utility values was the only analysis that impacted QALYs and this decreased the incremental QALY gains in the deterministic analysis from [redacted] to [redacted].

Table 63: EAG exploratory analysis results

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Company's base-case, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG EA1: Correction of model errors, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG EA2: EA1 + Use of alternative TTD curves (two-knots normal spline models for amivantamab and lazertinib; Weibull model for osimertinib)							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG EA3: EA1 + Applying treatment-specific utility for progression-free state, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG EA4: EA1 + Applying administration cost with prolonged chair time, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG EA5: EA1 + Applying frequencies of resource use from ID6328, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG EA6: EA1 + Including the incidence of grade ≥ 3 DVT, account for proportion of Grade ≤ 2 VTE that are pulmonary embolism and EAG preferences for VTE costs, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG base-case applying analyses 1-6, deterministic							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
EAG base-case applying analyses 1-6, probabilistic							
Amivantamab with lazertinib	5.50	[redacted]	[redacted]	1.75	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.76						

*Undiscounted

Abbreviations: EA - exploratory analysis; DVT - deep vein thrombosis; ICER - incremental cost-effectiveness ratio LYG - life year gained; TTD – time to discontinuation; QALY - quality-adjusted life year; VTE - venous thromboembolism

The results for the EAG's preferred base-case scenario when using the mean costs and QALYs obtained from the probabilistic analysis are consistent to those obtained in the deterministic analysis. The scatter plot (Figure 38) shows that all PSA iterations resulted in lower costs for amivantamab with lazertinib versus osimertinib and > 99% resulted in additional QALYs. The range of incremental costs was -£[redacted] to -£[redacted] and the range of incremental QALYs was [redacted] to [redacted].

Figure 38: Cost-effectiveness plane, amivantamab with lazertinib versus osimertinib, with PAS prices, 1000 iterations

[redacted]

Abbreviations: PAS - patient access scheme; PSA - probabilistic sensitivity analyses

Additional sensitivity analyses exploring individual changes using the EAG preferred base-case as the starting point are shown in Table 64. The sensitivity analyses applied to the EAG-preferred base-case resulted in an incremental gain for amivantamab with lazertinib compared with osimertinib ranging from [redacted] to [redacted] QALYs. The higher incremental QALY value was obtained by using the treatment-independent utility values from TA654, and this estimate of QALY gained is similar to that obtained in the company's base-case. The lower value of the range was obtained in the scenario analysis exploring plausible alternative extrapolations for OS. This analysis demonstrates that the incremental QALYs gained are highly sensitive to uncertainty in the long-term OS predictions. The cost-effectiveness estimates are less sensitive to changes in the selected model for extrapolating PFS, but the incremental costs are sensitive to alternative models for extrapolating TTD.

Table 64: EAG additional sensitivity analyses results

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
EAG base-case							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
ASA1: Use of the company's preferred administration cost							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
ASA2: Use of treatment independent utility values from TA654							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
ASA3: Use of two-knots normal spline model for TTD in osimertinib							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						
ASA4: Use of alternative distributions for OS (1-knot hazard for amivantamab with lazertinib, gamma for osimertinib)							
Amivantamab with lazertinib	4.88	[redacted]	[redacted]	0.79	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	4.10						
ASA5: Use of alternative distributions for PFS (gamma for all)							
Amivantamab with lazertinib	5.44	[redacted]	[redacted]	1.71	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.73						

*Undiscounted
Abbreviations: ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio;

4.5 Discussion

The EAG's exploratory analyses indicate that the company's base-case potentially underestimates the costs of amivantamab with lazertinib due to the application of an administration cost that reflects a shorter chair time for IV administration of amivantamab than is likely to be needed. The company's model also potentially overestimates the cost of osimertinib treatment due to the company's preferred exponential curve for TTD being a poor fit to the hazards of discontinuation for osimertinib.

The EAG's analyses demonstrate that the company's decision to apply equivalent utility values across treatment arms for the progression-free state potentially overestimates the QALY gains for

amivantamab with lazertinib. The EAG does not consider that assuming equivalent utility values is supported by either the company's regression analysis for PFS utility (see Table 43), which found treatment arm to be a statistically significant covariate, or the company's plot of utility over time (see Figure 37), which showed [redacted]

The EAG's scenario analyses indicate that the model is sensitive to uncertainty in OS and TTD, suggesting that additional long-term data would be beneficial, although the final analysis of the OS data from the MARIPOSA trial is unlikely to resolve long-term uncertainty in the predicted OS at 10 years. Whilst the cost-effectiveness estimates were not particularly sensitive to different long-term extrapolations for PFS in the EAG's exploratory analyses, it is possible that changes in the within-trial PFS estimates from using data from a more recent DCO may have a greater impact than changes in the long-term extrapolation.

Overall, the EAG's exploratory analyses indicate that the company's base-case analysis is likely to overestimate both QALY gains and cost-savings. However, amivantamab with lazertinib was still found to dominate osimertinib in all of the EAG's exploratory analyses. The EAG also notes that the cost savings presented in this report, for both the company and the EAG's analyses, do not account for the confidential PAS for osimertinib and it directs the committee to the confidential appendix for analyses which take into account all confidential discounts on drug prices.

5 SEVERITY OF THE CONDITION

The NICE Methods Manual states that the committee will consider the severity of the condition, based on the absolute and proportional QALY shortfall. It may then choose to apply QALY weightings for severity if the proportionate QALY shortfall is greater than 0.85 or the absolute QALY shortfall is greater than 12.[85] The QALY shortfall is the difference in expected lifetime discounted QALYs between patients with the condition receiving the current standard of care and members of the general population living without the condition. The CS presents a QALY shortfall calculation using two alternative sources of information to estimate the discounted lifetime expected QALYs for patients receiving standard of care. The company's preferred approach uses the OS data from the MARIPOSA-like cohort of the NCRAS database who received first-line osimertinib (N=126) to estimate life-expectancy for patients receiving current standard of care. As PFS data were not available from the NCRAS database, the company used time to next therapy (TTNT) as a proxy for PFS. The company applied the pre-progression and post-progression utility values from their economic model to estimate discounted lifetime expected QALYs for patients receiving the current standard of care. This resulted in an estimate of 1.94 QALYs for patients receiving current standard of care treatment (osimertinib) based on the NCRAS RWE data source.

In the company's alternative approach, the OS and PFS extrapolations for the osimertinib arm of the company's base-case cost-effectiveness analyses were used to generate an estimate of 2.64 QALYs for patients receiving current standard of care. This higher estimate of QALYs is due to the patients in the RWE data source having lower median OS than patients in the MARIPOSA trial (28.1 versus 37.3 months).

The company calculates the lifetime expected QALYs for patients in the general population with the same characteristics (63 years, 75% female for MARIPOSA-like NCRAS cohort and 62 years with 61% female for MARIOPOSA trial cohort) who do not have NSCLC. The CS states that this is estimated using an online calculator tool developed by Schneider *et al.*[86] The EAG believes that the company has used the 'reference case' utilities in the Schneider *et al.* tool, based on a reference to the "*ALDVVMM model for general population utility in England (Hernández Alava, 2022)*" in the economic model. This 'reference case' utility source uses the Measurement and Value of Health (MVH) Group's value set for the Health Survey for England (HSE) 2014 health state profiles, the adjusted limited dependent variable mixture model (ALDVMM) by Hernandez *et al.,* and the 2017 to 2019 lifetables for England.[86] The EAG considers this to be an acceptable approach.

The company's QALY shortfall calculation is summarised in Table 65. It can be seen that the implied QALY multiplier is 1 in both cases presented by the company, although the company argues that the

considerable unmet need in patients currently eligible to receive first-line osimertinib should be taken into account as the proportional shortfall calculation is close to the 0.85 required when using the estimate based on the RWE.

The EAG notes that the two approaches adopted by the company provide quite different estimates of lifetime expected QALYs for patients receiving osimertinib. The company considers that the estimates of lifetime QALY gains from the RWE are more appropriate than the estimates from the economic model, because the RWE dataset better reflects the characteristics of patients seen in UK clinical practice. However, this raises the question of whether the predictions of OS for osimertinib in the cost-effectiveness analysis should have been adjusted to better reflect the OS predictions from the RWE.

The EAG was able to replicate the estimate of 11.74 QALYs for the general population when using the baseline characteristics of the MARIPOSA-like cohort receiving osimertinib (63 years and 75% female). However, it was unable to replicate the 11.39 QALYs estimate when using the online tool and the baseline characteristics for the MARIPOSA trial (62 years with 61% female) and instead obtained a value of 12.05. The company's figure of 11.39 QALYs appears to have been derived from calculations within the economic model itself, and these use lifetables from 2020-2022, whereas the Schneider *et al.* tool uses lifetables from 2017-2019, which may account for this discrepancy. However, amending the QALY shortfall calculation to use lifetime QALYs from the Schneider *et al.* tool had no impact on the implied severity modifier as it gave an absolute shortfall of 9.41 and a proportional short fall of 78% versus the company's estimate of 77%.

The EAG had some concern regarding the appropriateness of using TTNT as a proxy for PFS as TTNT may overestimate PFS if patients remain on first-line treatment following progression while they are still deriving clinical benefit. However, the EAG estimates that the QALY shortfall would remain under 0.85 even if all remaining survival was in the progressed health state (expected lifetime QALYs of 1.87 instead of 1.94). Therefore, any bias introduced by using TTNT as a proxy for PFS is not expected to alter the conclusion that the proportionate QALY shortfall is under 0.85.

Using the EAG's preferred base-case to estimate the QALY shortfall from the comparator arm of the cost-effectiveness model, did not result in a QALY shortfall exceeding 0.85. Applying the EAG's preferred utilities ([redacted] for osimertinib pre-progression) to the RWE of PFS also did not result in a QALY shortfall exceeding 0.85. Therefore, despite some uncertainties in the estimates of the QALY shortfall provided by the company, the EAG is satisfied that the QALY shortfall is likely to be below 0.85.

Table 65: QALY shortfall calculation (reproduced from CS, Table 69)

	UK RWE: Osimertinib data from the 'MARIPOSA-like' cohort of the NCRAS database (n=126)	Trial data: Osimertinib arm of MARIPOSA (n=429)
QALE at model starting age	11.74	11.39
QALYs for standard of care	1.94	2.64
Absolute shortfall	9.80	8.75
Proportional shortfall	0.83	0.77
Severity modifier	1.00	1.00

Abbreviations: QALY - quality-adjusted life year; RWE – real-world evidence

6 OVERALL CONCLUSIONS

The main clinical evidence assessing the use of amivantamab with lazertinib for first-line treatment of adults with untreated advanced NSCLC which has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation was derived from the MARIPOSA trial. Overall, amivantamab with lazertinib demonstrated a statistically significant improvement in PFS compared to osimertinib, and an *ad hoc* OS analysis showed a positive trend favouring amivantamab with lazertinib. Higher incidences of AEs related to EGFR TKI inhibitors and MET TKI inhibitors, as well as VTEs, were reported in the amivantamab with lazertinib arm compared to the osimertinib arm. TEAEs leading to treatment discontinuation were higher in patients treated with amivantamab with lazertinib than in those treated with osimertinib.

The main uncertainties in the clinical evidence relate primarily to the duration of treatment and follow-up in the MARIPOSA trial. Since the MARIPOSA trial is ongoing, the analyses are mainly exploratory, and the long-term efficacy and safety of amivantamab with lazertinib are unknown. As a result, longer follow-up is needed to reduce uncertainty around the OS benefit of amivantamab with lazertinib and monitor for the development of any new safety issues. Further RWE studies are needed to assess whether the administration of prophylactic anticoagulation during the first four months of therapy reduces the incidence of VTEs.

In the company's cost-effectiveness analysis, amivantamab with lazertinib results in additional QALYs gained versus osimertinib due to an increase in life-years gained both pre- and post-progression. Overall, the company's base-case model estimates that amivantamab with lazertinib will result in substantial cost savings, mainly driven by lower drug acquisition costs.

In the EAG's preferred base-case, amivantamab with lazertinib still provides a cost saving and a QALY gain relative to osimertinib, however, both of these estimates are smaller in magnitude. These differences are mainly driven by: (i) the administration costs applied for amivantamab; (ii) the TTD curves applied for first-line treatments; and (iii) the use of treatment-specific utilities for PFS. However, the EAG notes that whilst both the company and the EAG's preferred base-case analyses indicate that amivantamab with lazertinib results in cost-savings relative to osimertinib, these analyses do not incorporate the confidential PAS discount for osimertinib and the EAG directs the committee to the confidential appendix for analyses incorporating all confidential drug prices.

The EAG's exploratory analyses indicate that alternative plausible long-term extrapolations for OS result in substantial changes in the estimates of incremental QALYs. Updating the model to reflect the

OS outcomes from the final DCO of the MARIPOSA trial should reduce uncertainty in the long-term predictions of OS, although some uncertainty is likely to remain unless further data are collected.

The company's regression analysis for utilities measured in patients who were progression-free during the MARIPOSA trial, suggests that patients taking amivantamab with lazertinib have lower utility than those taking osimertinib, even after accounting for disutility related to those AEs included in the economic model. This may be due to other lower grade AEs or due to the requirement for frequent hospital attendance for IV infusions for the amivantamab component of treatment. The company indicates that AEs and treatment burden for amivantamab may be reduced if amivantamab can be given subcutaneously in future, but this is not the formulation put forward by the company in their CS for consideration by NICE.

There were several areas of uncertainty that could not be explored in the EAG's analyses. The EAG considers that the cost-effectiveness evidence presented to the committee should be informed by the most recent DCO available for all outcomes informing the economic model (OS, PFS, TTD and AEs) as these all have the potential to influence cost-effectiveness. It notes that the company's use of PFS data from the interim DCO (11th August 2023) is a significant limitation, especially when data from the later DCO (13 May 2024 DCO) have been provided for other outcomes. Whilst the cost-effectiveness estimates were not particularly sensitive to different long-term extrapolations for PFS in the EAG's exploratory analyses, it is possible that changes in the within-trial PFS estimates may have a greater impact than changes in the long-term extrapolation. Therefore, the impact of incorporating the most recent PFS data remains uncertain. The EAG would also like to see the model updated with more complete TTD data from the final trial DCO, as this would allow the curve selection for TTD to be refined.

Finally, the EAG would have preferred the company to have submitted evidence comparing amivantamab with lazertinib against osimertinib with chemotherapy which the committee would then be able to consider if the final guidance for osimertinib with chemotherapy were to be positive. However, the EAG acknowledges that the relevance of such a comparison is dependent on the outcome of ID6328.

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APPENDIX 1: Price sources used when running the analyses for the confidential appendix

Sources for the prices used when running the analyses for the confidential appendix are provided in Table 66. Bold text indicates where the source differs from that used in the analyses presented in the main EAG report.

Table 66: Price sources used when running the analyses for the confidential appendix

Treatment	Price in company's analysis	Source for price in company's model	Source for price used in the confidential appendix
Amivantamab 350 mg (pack of 1)	[redacted]	CS	CS
Lazertinib 240 mg (pack of 28)	[redacted]	CS	CS
Lazertinib 80 mg (pack of 56)	[redacted]	CS	CS
Osimertinib 80mg (pack of 30)	£5770.00	BNF[1]	**CAA**
Osimertinib 40mg (pack of 30)	£5770.00	BNF[1]	**CAA**
Atezolizumab 1,200mg (pack of 1)	£3807.69	BNF[1]	**CAA**
Bevacizumab 400 mg (pack of 1)	£810.10	BNF[1]	**MPSC (low)**
Pemetrexed 500 mg (pack of 1)	£28.76	eMIT[2]	**MPSC (low)**
Nintedanib 150 mg (pack of 60)	£2151.10	BNF[1]	**PAS**
Paclitaxel 300 mg (pack of 1)	£31.89	eMIT[2]	eMIT[2]
Docetaxel 80 mg (pack of 1)	£9.73	eMIT[2]	eMIT[2]
Cisplatin 100 (pack of 1)	£37.34	eMIT[2]	eMIT[2]
Carboplatin 450 mg (pack of 1)	£23.18	eMIT[2]	eMIT[2]
Rivaroxaban 10 mg (pack of 100)	£180	BNF[1]	BNF[1]
Enoxaparin sodium 40 mg (pack of 10)	£22.70	BNF[1]	BNF[1]
Diphenhydramine 25 mg (pack of 20)	£1.50	DM&D	DM&D
Dexamethasone 10 mg (pack of 1)	£30.80	eMIT[2]	eMIT[2]
Paracetamol 500 mg (pack of 100)	£0.79	eMIT[2]	eMIT[2]

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

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

A Single Technology Appraisal

Addendum: EAG critique of the company's additional evidence

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
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Date completed	24th April 2025

Rider on responsibility for report addendum

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

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Contributions of authors

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

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Abbreviations

2L	Second-line
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike information criterion
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
cEGFRm	Common epidermal growth factor receptor mutation
CI	Confidence interval
CS	Company submission
DCO	Data cut-off
DVT	Deep vein thrombosis
EAG	External Assessment Group
EGFR	Epidermal growth factor receptor
eMIT	Electronic market information tool
EQ-5D	Euroqol 5-Dimensions
Exon19del	Exon 19 Deletions
FAS	Full analysis set
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ILD	Interstitial lung disease
IRR	Infusion related reaction
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LYG	Life years gained
MET	Mesenchymal-epithelial transition factor
MMRM	Mixed-effects model for repeated measures
NA	Not applicable
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer

OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PE	Pulmonary embolism
PF	Progression-free
PFS	Progression-free survival
PSA	Probabilistic sensitivity analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RWE	Real world evidence
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TEAE	Treatment emergent adverse event
TKI	Tyrosine kinase inhibitor
TTD	Time to treatment discontinuation
TTSP	Time to symptomatic progression
TTST	Time to subsequent therapy
VTE	Venous thromboembolism

1 Introduction

The main clinical effectiveness and safety evidence for the appraisal of amivantamab with lazertinib, compared with osimertinib as a first-line treatment in adults (aged >18 years) with advanced non-small cell lung cancer (NSCLC) and epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations, was derived from the ongoing MARIPOSA trial (NCT04487080). The original company submission (CS)[1] presented efficacy and safety data from the MARIPOSA trial based on the data cut-offs (DCOs) of 11th August 2023 and/or 13th May 2024. These data are reported and discussed in the main External Assessment Group (EAG) report, along with any additional information provided by the company in response to the EAG's clarification questions.

During the clarification process for this appraisal, the National Institute for Health and Care Excellence (NICE) agreed to allow the company to submit additional evidence, related to the 4th December 2024 DCO of the MARIPOSA trial, at the time of the factual accuracy and confidentiality (FAC) check, after the main EAG report had been submitted. This addendum to the EAG report provides a critique of the additional evidence submitted by the company at that time.

2 Summary and critique of the additional clinical effectiveness evidence

2.1 Scope of the additional clinical effectiveness evidence

This section presents the latest results from the MARIPOSA trial (DCO: 4th December 2024), as reported by the company in its addendum, which became available after the submission of the EAG report. The MARIPOSA trial forms the pivotal evidence in the CS[1] for the efficacy and safety of amivantamab with lazertinib compared with osimertinib as a first-line treatment in adults (aged >18 years) with advanced NSCLC and EGFR exon 19 deletion or exon 21 L858R substitution mutations.

In the addendum, the company provided updated results from the 4th December 2024 DCO of the MARIPOSA trial for the following outcomes:

Secondary endpoints:
- Overall survival
- Progression-free survival after first subsequent therapy
- Time to symptomatic progression

Exploratory endpoints:
- Time to treatment discontinuation
- Time to subsequent therapy

All other outcome data are discussed in the main EAG report and are based on the 11th August 2023 or 13th May 2024 DCOs, unless stated otherwise.

The statistical methods used for the analysis of the MARIPOSA trial are reported in CS[1] page 53, Table 10. Unless otherwise stated, all efficacy results are presented for amivantamab with lazertinib (N=429) versus osimertinib (N=429), based on the full analysis set (FAS).

2.2 Clinical effectiveness results

2.2.1 *Secondary Endpoint: Overall Survival*

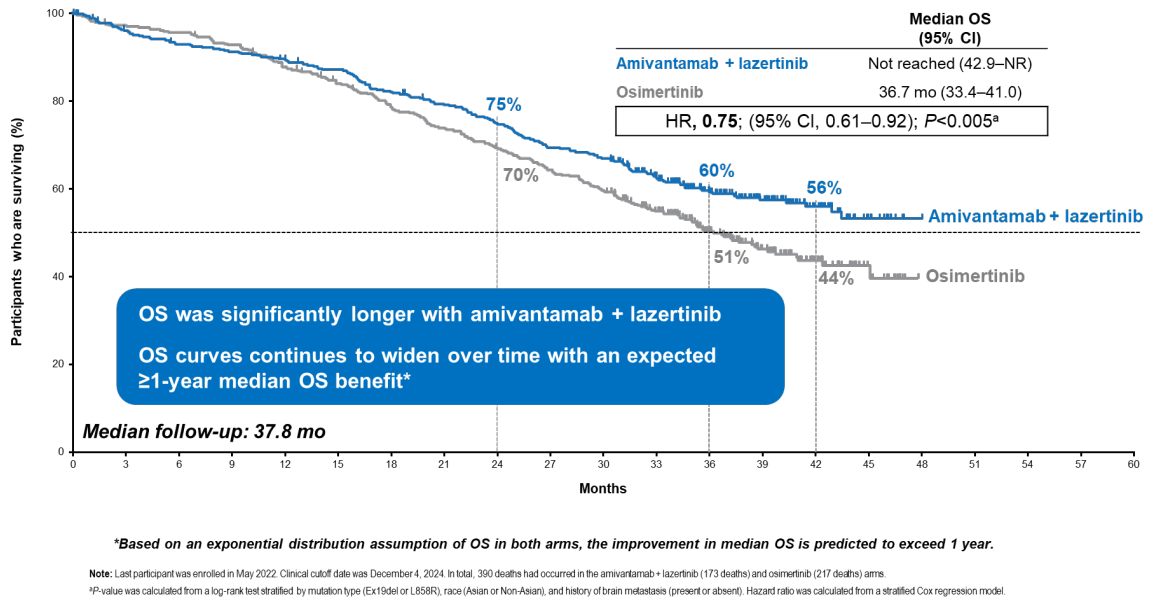
The secondary endpoint analysis in the MARIPOSA trial was overall survival (OS), based on the FAS. A comparison between OS at the 13th May 2024 DCO (as previously presented in the EAG report, Section 3.2.2.2) and the new data from 4th December 2024 DCO (the protocol-specified final OS analysis) provided by the company as an addendum is presented in Table 1.

At the 4th December 2024 DCO, with a median study follow-up of 37.8 months, there were [redacted] deaths in the amivantamab with lazertinib arm and [redacted] deaths in the

osimertinib arm. A statistically significant and clinically meaningful [redacted] risk reduction in death in the amivantamab with lazertinib arm compared with the osimertinib arm (hazard ratio [HR]: 0.75; 95% CI: 0.61, 0.92; [redacted]) was observed. The median OS for amivantamab with lazertinib remained not estimable (95% CI: 42.94, NE), while it was [redacted] months (95% CI: 33.41, 41.03) in the osimertinib arm. At 42 months, a significantly greater proportion of patients remained alive in the amivantamab with lazertinib arm compared with osimertinib arm with a survival rate of 56% in the amivantamab with lazertinib arm, compared with 44% in the osimertinib arm. Overall, the EAG noted that the results from DCO 13th May 2024 and DCO 4th December 2024 were comparable with slightly more events occurring at the later DCO which would be expected.

The Kaplan-Meier (KM) and cumulative hazard plots for OS at the 4th December 2024 DCO are presented in CS Addendum, Figure 2 (reproduced below as Figure 1) and CS Addendum, Figure 3, respectively.

Figure 1: KM plot of OS (4th December 2024 DCO; FAS, reproduced from addendum Figure 2)



Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; NR: not reached; OS: overall survival
Source: Chih-Hsin Yang et al. ELCC 2025.[2]

Table 1: Summary of OS for the MARIPOSA study on the Full Analysis Set at DCO 13th May 2024 and 4th December 2024 (reproduced from addendum Table 1)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	**Osimertinib (N=429)**	**Amivantamab-lazertinib (N=429)**	**Osimertinib (N=429)**
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	NE (NE, NE)	37.3 (32.5, NE)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.75 [redacted]	0.70 [redacted]	0.75 [redacted]	0.70 [redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.61 [redacted]	0.53 [redacted]	0.60 [redacted]	0.51 [redacted]

42-month event-free rate (95% CI)	NR	NR	0.56[redacted]	0.44[redacted]
Treatment difference				
p-value[a]	0.019		[redacted]	
HR (95% CI)[b]	0.77 (0.61, 0.96)		[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).[redacted] [b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; OS: overall survival.

2.2.2 *Secondary Endpoint: Progression-free survival after first subsequent therapy*

At the 4th December DCO, the use of subsequent systemic therapy after treatment discontinuation due to disease progression was similar between the two arms: [redacted] in the amivantamab with lazertinib arm and [redacted] in the osimertinib arm. Table 2 summarises the most common first subsequent systemic therapy classes in the amivantamab with lazertinib and osimertinib arms. In general data from DCO 13th May 2024 and DCO 4th December 2024 are comparable. A greater proportion of patients in the amivantamab with lazertinib arm ([redacted]) received a third-generation tyrosine kinase inhibitor (TKI) than in the osimertinib arm ([redacted]) whilst more patients in the osimertinib arm ([redacted]) received chemotherapy plus a vascular endothelial growth factor inhibitor. (VEGFi) or an immuno-oncology (IO) agent than in the amivantamab with lazertinib arm [redacted]). In general, first subsequent therapies were balanced between amivantamab with lazertinib and osimertinib, although a higher proportion of patients received any chemotherapy in second-line after first-line osimertinib ([redacted]) compared with those receiving first-line amivantamab with lazertinib ([redacted]).[3] A greater proportion of patients received targeted TKI therapies at second-line ([redacted]) in the amivantamab with lazertinib arm compared with patients in the osimertinib arm ([redacted]).

Table 2: Summary of subsequent systemic therapy received by patients who discontinued treatment due to disease progression (13th May 2024 and 4th December DCOs; FAS, reproduced from addendum Table 2)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Patients receiving one or more subsequent systemic therapies after treatment discontinuation due to disease progression, %	72	74	[redacted]	[redacted]
First-line of subsequent systemic therapies, %				
Doublet chemotherapy	41	45	[redacted]	[redacted]
Doublet chemotherapy plus VEGFi/IO	12	20	[redacted]	[redacted]
Third-generation TKI	27	16	[redacted]	[redacted]
Other TKIs (not including third-generation)	7	5	[redacted]	[redacted]
TKI-based combination regimen	8	7	[redacted]	[redacted]

Abbreviations:DCO: data cut-off; FAS: full analysis set; INV: investigator; IO: immuno-oncology; NR: not reported; TKI: tyrosine kinase inhibitor; VEGFi: Vascular Endothelial Growth Factor inhibitors.

Patients in the amivantamab with lazertinib arm had a [redacted] reduction in the risk of progression or death after their first subsequent therapy (PFS2) compared with patients in the osimertinib arm ([redacted]).[3] Median time to PFS2 was [redacted] months (95% CI: [redacted]) in the amivantamab with lazertinib arm, compared with [redacted] months in the osimertinib arm (95% CI: [redacted]) [3] At 30-, 36-, and 42-month event-free rates were [redacted], respectively, in the amivantamab with lazertinib arm and [redacted], respectively, in the osimertinib arm.[3] The difference between the amivantamab with lazertinib and osimertinib event-free rates at 36-months increased slightly after a longer duration of follow-up, with a difference of 8% at the 13th May 2024 DCO and [redacted] at the 4th December 2024 DCO, further details are provided in Table 3. The associated KM plot for PFS2 is presented in Figure 2. The plot shows a maintained separation of the treatment arms, favouring treatment with amivantamab with lazertinib, beginning around 12 months after randomisation. As highlighted in the EAG report, the FDA notes that results of PFS2 are solely exploratory and hypothesis-generating.[4]

Table 3: Summary of PFS2 (13th May 2024 and 4th December DCOs; FAS, reproduced from addendum Table 3)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	**Osimertinib (N=429)**	**Amivantamab-lazertinib (N=429)**	**Osimertinib (N=429)**
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	NE (36.0, NE)	32.4 (29.3, NE)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.73[redacted]	0.65[redacted]	0.73[redacted]	0.65[redacted]

30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.57[redacted]	0.49[redacted]	[redacted]	[redacted]
42-month event-free rate (95% CI)	NR	NR	[redacted]	[redacted]
Treatment difference				
Nominal p-value[a]	0.004		[redacted]	
HR (95% CI)[b]	0.73 (0.59, 0.91)		[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).[redacted] [b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; PFS2: progression-free survival after first subsequent therapy.

Figure 2: KM plot of PFS2 (4th December 2024 DCO; FAS, reproduced from addendum Figure 4)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib; PFS2: progression free survival after first subsequent therapy.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[3]

2.2.3 *Secondary Endpoint: Time to symptomatic progression*

At the 4th December 2024 DCO, time to symptomatic progression (TTP) or death was experienced in fewer patients in the amivantamab with lazertinib arm than the osimertinib arm ([redacted] versus [redacted]). Patients in the amivantamab with lazertinib arm had a statistically significant 31% reduction in the risk of symptomatic progression or death compared to patients in the osimertinib arm (HR: 0.69; 95% CI: 0.57, 0.83;[redacted]Table 4).[2] Median TTSP was [redacted] months in the amivantamab-lazertinib arm (95% CI: 36.0, NE) compared to 29.3 months in the osimertinib arm (95% CI: 26.4, 33.4). In the CS addendum it was noted that the difference between the amivantamab with lazertinib and osimertinib event-free rates at 36-months increased after a longer duration of follow-up, with a difference of [redacted] at the 13th May 2024 DCO and [redacted] at the 4th December 2024 DCO, demonstrating the durable response provided by amivantamab with lazertinib. The associated KM plot for TTSP is presented in Figure 3. However, as previously stated in the EAG report, in agreement with the FDA,[4] the EAG considers TTSP to be exploratory; hence, these outcomes should be viewed with caution.

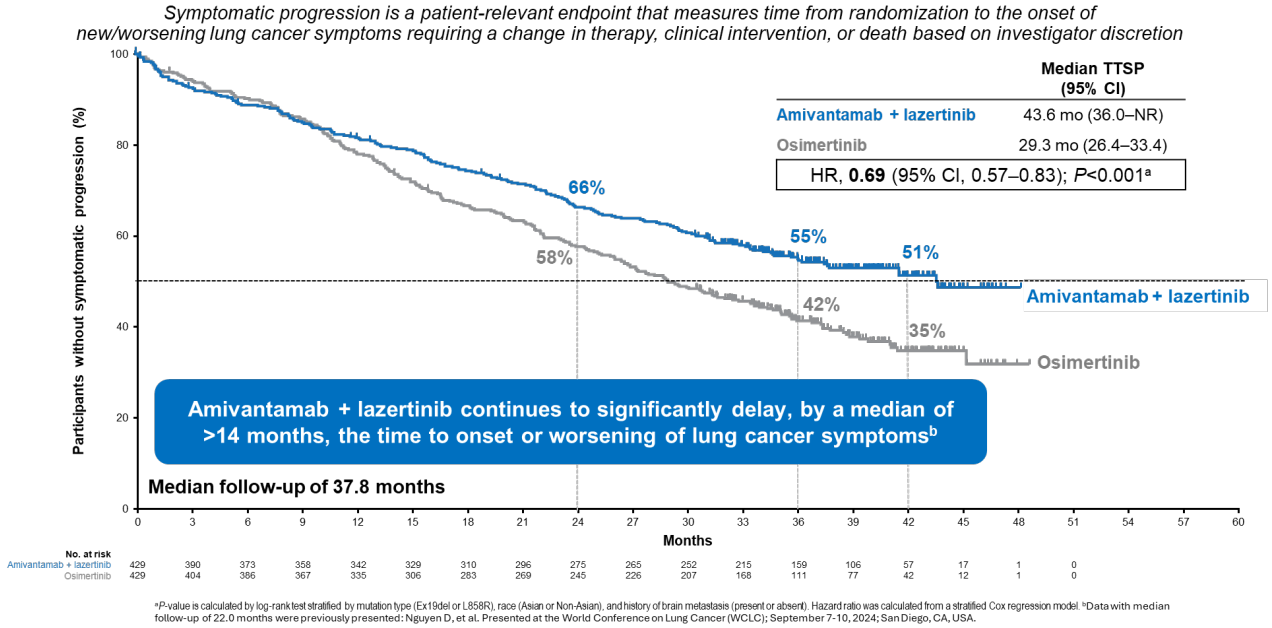
Table 4: Summary of TTSP (13th May 2024 and 4th December 2024 DCOs; FAS, reproduced from addendum Table 4)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)	Amivantamab-lazertinib (N=429)	Osimertinib (N=429)
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic PD	[redacted]	[redacted]	[redacted]	[redacted]
Death without symptomatic PD	[redacted]	[redacted]	[redacted]	[redacted]
Censored	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	[redacted]	[redacted]	43.6 (36.0, NE)	29.3 (26.4, 33.4)
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	0.74[redacted]	0.67[redacted]	0.74[redacted]	0.67[redacted]
24-month event-free rate (95% CI)	0.67[redacted]	0.59[redacted]	[redacted]	[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	[redacted]	[redacted]	0.55[redacted]	0.42[redacted]

42-month event-free rate (95% CI)	NR	NR	0.51[redacted]	0.35[redacted]
Treatment difference				
p-value[a]	[redacted]		[redacted]	
HR (95% CI)[b]	[redacted]		0.69 (0.57, 0.83)	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).[redacted] [b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; PD: progressive disease; TTSP: time to symptomatic progression.

Figure 3: KM plot of TTSP (4th December 2024 DCO; FAS, reproduced from addendum Figure 5)



Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; KM: Kaplan-Meier; mo: months; NR: not reached; TTSP: time to symptomatic progression.
Source: Chih-Hsin Yang et al. ELCC 2025.[2]

2.2.4 *Exploratory endpoint: Time to treatment discontinuation*

Time to treatment discontinuation (TTD) was investigated as an exploratory endpoint in the MARIPOSA trial. At the 4th December 2024 DCO, the median TTD or death for the amivantamab with lazertinib arm was [redacted] months (95% CI: [redacted]), and [redacted] months (95% CI: [redacted]) in the osimertinib arm (HR: [redacted]), see Table 5.[3] The 30-, 36-, and 42-month event-free rates were [redacted]%, respectively, in the amivantamab with lazertinib arm and [redacted]%, respectively, in the osimertinib arm. The KM plot shows a maintained separation of the treatment arms, favouring treatment with amivantamab-lazertinib, beginning around 22 months after randomisation. The associated KM plot is presented in Figure 4 and the cumulative hazard plots are presented in the CS Addendum, Figure 7. As mentioned in the EAG report, the EAG notes that since TTD is an exploratory analysis, these findings should be used with caution.

Table 5: Summary of TTD (13th May 2024 and 4th December 2024 DCOs; FAS, reproduced from CS addendum Table 5)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	**Osimertinib (N=429)**	**Amivantamab-lazertinib (N=429)**	**Osimertinib (N=429)**
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	26.3 (22.3, 30.4)	22.6 (20.3, 24.5)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.52[redacted]	0.46[redacted]	0.52[redacted]	0.46[redacted]
30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

36-month event-free rate (95% CI)	0.40	0.29		
42-month event-free rate (95% CI)	NR	NR		
Treatment difference				
p-value[a]	0.014			
HR (95% CI)[b]	0.80 (0.68, 0.96)			

[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported; TTD: time to treatment discontinuation.

Figure 4 KM plot of TTD (4th December 2024 DCO; FAS, reproduced from addendum Figure 6)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib; TTD: time to treatment discontinuation.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[3]

2.2.5 *Exploratory endpoint: Time to subsequent therapy*

At the 4th December 2024 DCO, the median time to initiate subsequent therapy or death was longer in the amivantamab with lazertinib arm (months; 95% CI:), compared with osimertinib arm (months; 95% CI:). A reduction in risk (HR:) for time to subsequent therapy (TTST) in the amivantamab with lazertinib arm compared with the osimertinib arm was observed. The event-free rates observed at 30-, 36-, and 42-month were %, respectively, in the amivantamab with lazertinib arm, compared with %, respectively, in the osimertinib arm. A summary of TTST at both DCO (4th December 2024 and 13th May 2024) are presented in Table 6. The KM curve for TTST is presented in Figure 5.

Although these results demonstrate the durability of the clinical benefit offered by amivantamab with lazertinib, prolonging time until patients require a subsequent therapy as compared with osimertinib, the EAG noted these analyses are exploratory and should be used with caution.

Table 6: Summary of time to subsequent systemic anti-cancer therapy (13th May 2024 and 4th December 2024 DCOs; FAS, reproduced from addendum Table 6)

	13th May 2024 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=429)	**Osimertinib (N=429)**	**Amivantamab-lazertinib (N=429)**	**Osimertinib (N=429)**
Event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Censored, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Time to event (months)				
Median (95% CI)	30.0 (26.3, 36.0)	24.0 (22.5, 26.2)	[redacted]	[redacted]
25th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
75th percentile (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]	[redacted]
6-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
12-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
18-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
24-month event-free rate (95% CI)	0.57[redacted]	0.50[redacted]	0.57[redacted]	0.50[redacted]

30-month event-free rate (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
36-month event-free rate (95% CI)	0.45[redacted]	0.32[redacted]	[redacted]	[redacted]
42-month event-free rate (95% CI)	NR	NR	[redacted]	[redacted]
Treatment difference				
p-value[a]	0.005		[redacted]	
HR (95% CI)[b]	0.77 (0.65, 0.93)		[redacted]	

[a] p-value is from a log-rank test stratified by mutation type (Exon19del or Exon 21 L858R), Asian race (yes or no), and history of brain metastasis (yes or no).
[b] HR is from stratified proportional hazards model. HR <1 favours amivantamab-lazertinib treatment.
+ censored observation
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; HR: hazard ratio; NE: not estimable; NR: not reported.

Figure 5: KM plot of time to subsequent anti-cancer therapy (4th December 2024 DCO; FAS, reproduced from addendum Figure 8)

Abbreviations: A+L: amivantamab-lazertinib; DCO: data cut-off; FAS: full analysis set; KM: Kaplan-Meier; OSI: osimertinib.
Source: Johnson & Johnson Data on File. MARIPOSA CSR (DCO: 4th December 2024).[3]

2.3 Safety results

The main safety evidence for the use of amivantamab with lazertinib in patients with untreated common EGFR mutation (cEGFRm) advanced NSCLC was derived from the ongoing MARIPOSA trial. The safety of amivantamab with lazertinib compared with osimertinib monotherapy was evaluated using the Safety Analysis Set (SAS), which includes randomised patients who received at least one dose of study treatment. This comprised 421 patients in the amivantamab with lazertinib arm and 428 patients in the osimertinib arm.

The safety data provided by the company in the CS from the 11th August 2023 DCO, as well as additional data on Grade ≥3 treatment-emergent adverse events (TEAEs) from the 13 May 2024 DCO (submitted in response to clarification question A21), have been evaluated in Section 3.3 of the EAG report. After the EAG report was submitted, the company provided further safety data from the 4th December 2024 DCO, which were included as an addendum. Only these new safety data are presented here. The company noted that not all safety data originally reported in Section B.2.10 of the CS were available from the 4th December 2024 DCO and, therefore, have not been included in the addendum.

2.3.1 *Treatment disposition*

At the 4th December 2024 DCO, [redacted] patients ([redacted]%) and [redacted] patients ([redacted]%) remained on treatment in the amivantamab with lazertinib and osimertinib arms, respectively.[3] The most common reason for discontinuation of study treatment in both arms was disease progression, with a higher proportion of patients in the osimertinib arm discontinuing treatment due to disease progression [redacted] than in the amivantamab with lazertinib arm [redacted].[3] Overall, more patients discontinued all study treatment due to an AE from the amivantamab with lazertinib arm ([redacted]%) than the osimertinib arm ([redacted]%). Table 7 summarises treatment disposition from 11th August 2023 and 4th December 2024 DCOs. As expected the number of patients ongoing any study treatment in both arms has fallen.

Table 7: Summary of treatment disposition (11th August 2023 and 4th December 2024 DCOs; SAS' reproduced from addendum Table 7)

Event, n (%)	11th August 2023 DCO		4th December 2024 DCO	
	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Treatment disposition				
Patients ongoing any study treatment	230 (55)	213 (50)	[redacted]	[redacted]
Discontinued all study treatment	191 (45)	215 (50)	[redacted]	[redacted]
Interruption of amivantamab[a]	206 (49)	N/A	NR	NR
Reason for discontinuation of all study treatment				
Progressive disease	86 (20)	154 (36)	[redacted]	[redacted]
AE	86 (20)	50 (12)	[redacted]	[redacted]
Withdrawal by patient	14 (3)	10 (2)	[redacted]	[redacted]
Physician decision	2 (0.5)	1 (0.2)	[redacted]	[redacted]
Non-compliance with study drug	1 (0.2)	0	[redacted]	[redacted]
Lost to follow-up	1 (0.2)	0	[redacted]	[redacted]
Other	1 (0.2)	0	NR	NR

[a] Within the first four months.
Abbreviations: AE: adverse event; DCO: data cut-off; IRR: infusion-related reaction; N/A: not applicable; NR: not reported; SAS: safety analysis set.

2.3.2 *Overview of TEAEs*

An overall summary of TEAEs for the safety population in the MARIPOSA trial at the 11th August 2023 and 4th December 2024 DCOs is presented in Table 8;[3, 5, 6] further details are provided in CS[1], page 79, Table 25 and EAG report Section 3.3. At the 4th December 2024 DCO, almost all patients experienced at least one AE: [redacted] of patients in the amivantamab with lazertinib arm and [redacted] of patients in the osimertinib arm. Incidence of serious adverse events (SAEs) was experienced by [redacted]

patients ([redacted]%) in the amivantamab with lazertinib and by [redacted]patients ([redacted]) in the osimertinib arm.[3] The most common SAEs (≥5% of patients in any arm) were pulmonary embolism (amivantamab with lazertinib: [redacted] osimertinib: [redacted]) and pneumonia (amivantamab with lazertinib: [redacted] osimertinib: [redacted]).[3] TEAEs leading to death were reported in [redacted] patients ([redacted]) in the amivantamab with lazertinib arm and [redacted] patients ([redacted]) in the osimertinib arm. Grade ≥3 TEAEs were observed with a higher incidence in the amivantamab with lazertinib arm ([redacted]) compared with the osimertinib arm ([redacted]); of these [redacted] and [redacted] were considered related to amivantamab with lazertinib or osimertinib treatment, respectively.[3] This difference is almost entirely driven by the incidence of Grade 3 TEAEs in the amivantamab with lazertinib and osimertinib arms ([redacted] and [redacted] respectively).[3] Grade ≥3 TEAEs observed in the amivantamab with lazertinib arm were mostly driven by AEs related to EGFR and mesenchymal epithelial transition (MET) inhibition.[3] The most common Grade ≥3 TEAEs (≥10% of patients in any arm) were rash (amivantamab with lazertinib: [redacted] osimertinib: [redacted]) and paronychia (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]). Although overall, TEAEs were comparable from both DCOs (11th August 2023 and 4th December 2024), the incidence of SAE had increased with time. Data for AEs reported in ≥ 15% of the patients in either group for DCO 4th December 2024 DCOs was not reported, however data from DCO 11th August 2023 is provided in the EAG report, Section 3.3 Table 12.

TEAEs leading to the discontinuation of any study drug was reported in [redacted] patients ([redacted]) in the amivantamab-lazertinib arm compared with [redacted] patients ([redacted]) in the osimertinib arm.[3] Overall, [redacted] and [redacted] participants from amivantamab with lazertinib and osimertinib arms, respectively, discontinued all treatments due to AEs. TEAEs leading to dose reduction was reported in [redacted] patients ([redacted]) in the amivantamab with lazertinib arm compared with [redacted] patients ([redacted]) in the osimertinib arm, most commonly (≥5% of patients in any arm) due to rash (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]), paronychia (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]), and dermatitis acneiform (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]).[3] TEAEs leading to dose interruption was reported in [redacted]patients ([redacted]) in the amivantamab with lazertinib arm and [redacted] in the osimertinib arm.[3]

Table 8: Overall summary of TEAEs (11th August 2023 and 4th December 2024 DCOs; SAS reproduced from addendum Table 8)

Event, n (%)	11th August 2023		4th December 2024	
	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)	Amivantamab-lazertinib (N=421)	Osimertinib (N=428)
Patients with ≥1 AE	421 (100)	425 (99)	[redacted]	[redacted]
Related AEs[a]	414 (98)	378 (88)	[redacted]	[redacted]
AEs leading to death[b]	34 (8)	31 (7)	[redacted]	[redacted]
Serious AEs	205 (49)	143 (33)	[redacted]	[redacted]
Related serious AEs[a]	97 (23)	24 (6)	[redacted]	[redacted]
AEs leading to discontinuation of any study agent	147 (35)	58 (14)	[redacted]	[redacted]
AEs leading to discontinuation of amivantamab	145 (34)	N/A	[redacted]	N/A
Related AEs to amivantamab[a]	100 (24)	N/A	[redacted]	N/A
AEs leading to dose reduction of any study agent	249 (59)	23 (5)	[redacted]	[redacted]
AEs leading to dose reduction of amivantamab	193 (46)	N/A	[redacted]	N/A
Related AEs to amivantamab[a]	184 (44)	N/A	[redacted]	N/A
AEs leading to dose interruption of any study agent[c]	350 (83)	165 (39)	[redacted]	[redacted]
AEs leading to dose interruption of amivantamab	328 (78)	N/A	[redacted]	N/A
Related AEs to amivantamab[a,c]	282 (67)	N/A	[redacted]	N/A
Grade ≥3 AEs	316 (75)	183 (43)	[redacted]	[redacted]
Related grade ≥3 AEs[a]	252 (60)	59 (14)	[redacted]	[redacted]
Maximum toxicity grade				
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
Grade 5	[redacted]	[redacted]	[redacted]	[redacted]

[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.
[c] Excludes infusion related reactions.
Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set; TEAE: treatment-emergent adverse event.

2.3.3 *Adverse events of special interest*

The company has discussed ongoing clinical trials in both CS[1] Section B.2.11 and the company addendum, which assess the safety and feasibility of a subcutaneous (SC) amivantamab formulation in advanced solid malignancies. These trials have the potential to reduce treatment administration time and address adverse events (AEs) associated with intravenous (IV) delivery of amivantamab, such as infusion-related reactions (IRRs) and venous thromboembolism (VTEs). However, as this appraisal is based solely on the IV formulation of amivantamab, details of trials assessing the SC formulation will not be discussed here. Further details of ongoing studies using the SC formulation are provided in Section 3.4 of the EAG report.

As noted in the EAG report, adverse events of special interest (AESIs) were prospectively identified based upon the identified safety profile of amivantamab. Pre-defined AESIs per the protocol were IRRs, rash, and pneumonitis/interstitial lung disease (ILD). VTE events were later identified as a risk for the amivantamab with lazertinib arm within the first four months of study treatment and were added as an AESI during the study. Evaluation of the AEIS from DCO 11th August 2023 is discussed in the EAG report Section 3.3. Only AESI data provided from DCO 4th December 2024 in the CS addendum is discussed below.

IRRs were one of the most common TEAE in the amivantamab with lazertinib arm, occurring in [redacted] patients ([redacted]). Most of the IRR events were Grade 1 or 2, with [redacted] patients ([redacted]) in the amivantamab with lazertinib arm experiencing Grade 3 IRR and [redacted] patients ([redacted]) experiencing a Grade 4 IRR. No patients experienced a Grade 5 IRR. These results are comparable with the findings from 11th August 2023 DCO, where [redacted] patients ([redacted]) experienced IRRs, and most experienced Grade 1 or 2 IRRs events. The CS addendum also mentioned that the preliminary data from the ongoing SKIPPirr trial, a Phase 2, open label trial investigating the use of premedication to reduce IRRs associated with IV amivantamab. suggested that prophylaxis with 8 mg oral dexamethasone results in a meaningful reduction in the incidence of IRRs and is an effective strategy to reduce IRRs.[7, 8] However, no further data was provided. Details of the ongoing SKIPPirr trial are reported in Section 3.4 of the EAG report.

Rash was commonly observed in both treatment arms due to the on-target activity of amivantamab, lazertinib and osimertinib against the EGFR pathway (amivantamab with lazertinib [redacted] versus osimertinib [redacted]). More patients in the amivantamab with lazertinib arm experienced a Grade 3 event compared with the osimertinib arm ([redacted] versus [redacted] Grade 4 rash was reported in [redacted] patient ([redacted]) in the amivantamab with lazertinib arm, and no patients in either treatment arm experienced a Grade 5 rash.[3] These AE data are very similar to that observed at 11th August 2023 DCO; further details are available in the EAG report, Section 3.3. The CS addendum stated that the first interim analysis of the

ongoing Phase 2 COCOON trial evaluating the impact of enhanced versus standard dermatologic management on the incidence of dermatological AEs among patients with cEGFRm advanced or metastatic NSCLC receiving first line IV amivantamab in combination with lazertinib demonstrated a statistically significant and clinically meaningful reduction in dermatologic reactions in patients receiving the enhanced prophylactic regimen versus standard dermatological management.[9] The company did not provide any further data. Details of the COCOON trial is provided in the EAG report Section 3.4.

At the 11th August 2023 DCO, the incidence of pneumonitis or ILD was similar between treatment arms ([redacted], N=[redacted]) in the amivantamab with lazertinib arm and the osimertinib arm, respectively, with Grade ≥ 3 events occurring in 1% in each group. No additional pneumonitis or ILD events were reported since the 11th August 2023 DCO.

As mentioned in the EAG report and CS[1], VTEs were identified as a high-risk for patients in the amivantamab with lazertinib arm, largely occurring in the first four months of treatment. A higher proportion of patients in the amivantamab with lazertinib arm experienced at least one VTE event as compared with osimertinib ([redacted] versus [redacted]; DCO 4th December 2024). The incidence of VTE at the 4th December 2024 DCO is comparable to that reported at the 11th August 2023 DCO [amivantamab-lazertinib: [redacted]; osimertinib: [redacted]). VTEs leading to death occurred in [redacted] of patients in both arms, this data was same for both 4th December 2024 and 11th August 2024 DCO. Similarly, the rate of discontinuations due to VTE was low in both arms (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]). The majority of VTE events reported were pulmonary embolism (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]) or deep vein thrombosis (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]). Although the addendum states, "*the majority of VTE events in both arms were Grade 1–2 (amivantamab with lazertinib: [redacted]; osimertinib: [redacted]) and the rate of discontinuations due to VTE was low (amivantamab-lazertinib: [redacted]%; osimertinib: [redacted]%)* (Dec 2024 DCO),[3] this statement appears to be a transcription error. The original text in the CSR for the Dec 2024 DCO states, "*VTE events are common among patients with NSCLC. The majority of VTE events seen were Grade 1-2 and the rate of discontinuation due to VTE was low (ami+laz: [redacted]%; osi: [redacted]%)*". In addition, the EAG notes that data from 11th August 2203 DCO, CS Table 29 and EAG report, Table 14 suggests that the majority of VTE events in both arms were Grade 2 to 3.

The company notes that, to reduce the incidence of VTEs, the amivantamab summary of product characteristics (SmPC) recommends the use of prophylactic anticoagulants during the first four months of treatment. It also suggests that preliminary data from the ongoing COCOON trial indicate fewer patients reported VTEs when treated with an enhanced prophylactic regimen compared with standard dermatological management (6% vs. 7%, respectively). Although the EAG acknowledges that work is underway to minimise key aspects of amivantamab's adverse effect profile, it should be noted that the

PALOMA-3, COCOON, and SKIPPirr trials are ongoing, and only top-line data have been provided by the company, without full datasets or detailed analyses. Therefore, these results should be interpreted with caution. In addition, PALOMA-3 is evaluating the use of the SC formulation of amivantamab, whereas this appraisal is based on the IV formulation. As such, the EAG believes the safety data should be assessed according to the indicated formulation and dosage.

The EAG has provided details of the COCOON, SKIPPirr, and PALOMA-3 trials as ongoing studies in Section 3.4 of the EAG report.

2.4 Conclusions of the clinical effectiveness section

2.4.1 *Summary of principle findings*

This conclusion is based on the updated data from the MARIPOSA trial (DCO: 4th December 2024), provided by the company in its addendum for the assessment of the clinical effectiveness of amivantamab with lazertinib for first-line treatment of adults with untreated cEGFRm advanced NSCLC which has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. The protocol-specified final analysis demonstrated that amivantamab with lazertinib resulted in a statistically significant improvement in OS compared with osimertinib, showing a [redacted] reduction in the risk of death (HR: 0.75; 95% CI: 0.61–0.92; [redacted]). The median OS was not estimable in the amivantamab with lazertinib arm (95% CI: 42.94, NE), while it was [redacted] months (95% CI: 33.41–41.03) in the osimertinib arm. PFS2, TTSP, TTTD and TTST all showed a trend favouring amivantamab with lazertinib compared with osimertinib; however, these analyses are exploratory. A higher incidence of AEs related to EGFR TKI inhibitors and MET TKI inhibitors, as well as a higher incidence of VTEs, was reported in the amivantamab with lazertinib arm compared with the osimertinib arm. TEAEs leading to the discontinuation of any study drug occurred in [redacted] of patients in the amivantamab with lazertinib arm and in [redacted] of patients in the osimertinib arm.[3]

2.4.2 *Uncertainties surrounding the reliability of the clinical effectiveness*

The main uncertainties regarding the clinical evidence from the latest data (DCO: 4th December 2024), provided by the company in its addendum, primarily relate to the safety profile of amivantamab with lazertinib. To address these concerns, the company has highlighted preliminary positive findings from the ongoing SKIPPirr and COCOON studies, which are investigating prophylactic strategies to manage AEs associated with IV amivantamab, and enhanced dermatologic care to reduce rash and paronychia. However, as these studies are still ongoing, only top-line data are currently available.

3 Summary and critique of the additional cost-effectiveness evidence

The company's addendum presented an updated base-case cost-effectiveness analysis for amivantamab with lazertinib versus osimertinib. This section provides a summary and EAG critique of the company's updated cost-effectiveness analysis. The EAG's additional analyses incorporating the updated data are provided in Section 4.

3.1 Updated inputs to the cost-effectiveness analysis

This section replicates those parts of Section 4.2.4 of the main EAG report that are impacted by the updated data provided in the addendum submitted by the company at the time of the FAC check. They incorporate the latest available data from the MARIPOSA trial (DCO: 4th December 2024), which became available after submission of the main EAG report. The sources of evidence used to inform company's model parameters are summarised in Table 9 (supersedes Table 19 in the EAG's main report).

Table 9: Summary of evidence sources used to inform the model parameters for the company's base-case

Parameter type	Amivantamab with lazertinib	Osimertinib	Updated
Patient characteristics	Baseline characteristics across both arms of the MARIPOSA trial[6]		✗
PFS	Log-logistic model fitted to PFS data for amivantamab with lazertinib arm of MARIPOSA (DCO 11th August 2023)[10]	Log-logistic model fitted to PFS data for osimertinib arm of MARIPOSA (DCO 11th August 2023)[10]	✗
OS	Weibull model fitted to PFS data for amivantamab with lazertinib arm of MARIPOSA (DCO 4th December 2024)[3]	Weibull model fitted to PFS data for osimertinib arm of MARIPOSA (DCO 4th December 2024)[3]	✓
TTD	Exponential model fitted to TTD data for amivantamab and lazertinib informed by MARIPOSA (DCO 4th December 2024)[3]	Exponential model fitted to TTD data for osimertinib arm of MARIPOSA (DCO 4th December 2024)[3]	✓
AE frequency	Grade ≥ 3 TEAEs and Grade ≤ 2 VTE from the MARIPOSA trial (DCO 4th December 2024)[3]		✓ Incidence of AEs; durations for each AE
Health state utility values	Progression-free/progressed utility value based on EQ-5D estimates using MMRM fitted to EQ-5D-5L data collected from progression-free/progressed patients in the MARIPOSA trial (mapped to EQ-5D-3L using Hernandez *et al.*[11])		✓ Progressed disease utility
HRQoL age-adjustment	Age- and sex-matched general population EQ-5D-3L based on published UK population norms from Hernandez Alava *et al.*[12]		✗
AE disutility values	Disutility for Grade ≥ 3 AEs and Grade ≤ 2 VTE estimated from the MMRM fitted to EQ-5D-5L data collected from progression-		✗

Parameter type	Amivantamab with lazertinib	Osimertinib	Updated
	free patients in the MARIPOSA trial (mapped to EQ-5D-3L using Hernandez *et al.*[11])		
Drug acquisition costs	Treatment duration based on MARIPOSA; drug prices taken from NHS dictionary,[13] Electronic Market Information Tool (eMIT)[14] and British National Formulary (BNF);[15] PAS for amivantamab and lazertinib provided by the company		✓ Doses missed; proportion of planned doses received
Drug administration costs	Unit costs taken from the 2023/24 National Schedule of NHS Costs[16]		✗
Health state costs	Resource use based on TA531 and ID6328;[17, 18] unit costs taken from the 2023/24 National Schedule of NHS Costs;[16] the 2023 Personal Social Services Research Unit (PSSRU) report on unit costs of health care[19]		✗
AE costs	Cost for infusion related reaction – costs in TA651, inflated to 2021/22 prices using the NHS Cost Inflation Index; cost for VTE – one dose of rivaroxaban plus one ultrasound scan; others - costed by taking a weighted average of non-elective short stay admissions from the 2023/24 National Schedule of NHS Costs[16]		✗
Subsequent-line therapy use and costs	The proportion of subsequent active treatments informed by MARIPOSA and MARIPOSA-2; The distribution of subsequent treatments derived from clinical estimates from the advisory board meeting;[20] duration of subsequent treatments informed by MARIPOSA-2, IMPOWER150[21] and AURA3[22] trials and Park *et al*.[23]		✓ The proportion of subsequent active treatments informed by MARIPOSA
End-of-life costs	Assumptions from atezolizumab submission to NICE (TA520),[24] updated with the 2023/24 National Schedule of NHS Costs[16] and the 2023 PSSRU costs[19]		✗

Abbreviations: DCO - data cut-off; AE - adverse event;; HR - hazard ratio; HRQoL - health-related quality of life; ITC - indirect treatment comparison; ITT - intention-to-treat; KM - Kaplan Meier; OS - overall survival; PFS - progression-free survival; TTD - time to discontinuation; VTE - venous thromboembolism; MMRM - mixed-effects model for repeated measures; PAS - Patient Access Scheme; eMIT - electronic Market Information Tool; BNF - British National Formulary; NHS - National Health Service;

3.1.1 *Survival analysis*

The company fitted standard parametric survival models and spline models for each of the treatments separately, using individual patient data (IPD) from the MARIPOSA trial. PFS by BICR has an earlier DCO of 11th August 2023, the description of which was presented in the EAG report; OS and TTD have been updated with a later DCO of December 2024 in the addendum.

The CS states that the company's model selection process included: (1) visual inspection of the fitted survival models against the observed KM survival curves and the model-predicted hazard plots against the smoothed empirical hazard plots; (2) examination of goodness of fit statistics using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), and (3) assessment of clinical plausibility and face validity of the extrapolated survival curves.

3.1.1.1 Overall survival

Amivantamab with lazertinib OS

Standard parametric models and spline models were fitted to data on OS for amivantamab with lazertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 10 and Table 11, respectively. Comparisons of the observed KM curve and predicted OS are presented in Figure 6 and Figure 7, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 8 and Figure 9, respectively. Clinicians' estimates of expected OS are presented in Table 12.

The Weibull model was selected as the company's preferred base-case model for OS for amivantamab with lazertinib. Amongst all the fitted standard parametric models, the Gompertz model has the lowest AIC, followed by Weibull, generalised gamma and gamma distributions, with differences of less than three points. The Gompertz model also has the lowest BIC, followed by exponential, Weibull and gamma models, with differences of less than three points. All standard parametric models appear to underestimate the KM curve between approximately 0.5 and 2 years. The smoothed empirical hazard plot has a complex shape. It has an overall increasing trend with a dip between around 4 and 14 months and a decrease from around 28 months. The dip was not predicted by any of the standard parametric models.

All spline models provide a good visual fit to the KM curve. The three-knot normal model has the lowest AIC, followed by three-knot odds, three-knot hazard, one-knot hazard, one-knot odds and two-knot hazard models. The one-knot hazard model has the lowest BIC, followed by the one-knot odds and one-knot normal models. In terms of hazard plots, the one-knot and two-knot spline models have an overall increasing trend, with tails either increasing or decreasing. The three-knot hazard and three-knot odds spline models have a dip at around 10 months, and a peak at around 26 months, which do not match with the turning points observed in the empirical hazard function. The hazard plot for three-knot normal spline model was not presented.

Clinicians' estimates of expected OS provided by the company are presented in Table 12. The mean of the clinician's estimates of 10-year OS is [redacted]%, with two clinician's estimates being 5% and 10%. Amongst the standard parametric models, the Weibull distribution provides the closest 10-year estimation (13.4%) to the clinicians' estimates. The gamma model has a 10-year prediction of 15.6%. The other standard parametric models either have 10-year OS predictions which are higher than 19% or lower than 5%. For the spline models, the one-knot hazard model has a 10-year prediction of 9.8%, and the two-knot hazard model has a 10-year prediction of 11.0%. The remaining seven spline models all have a 10-year prediction of higher than 15%.

Overall, the EAG considers the Weibull model to be the most appropriate standard parametric model as it provides a good statistical fit and aligns with the clinician's estimates of 10-year OS. The EAG also considers that the spline models offer a better visual fit than the standard parametric models, and that the one-knot hazard model and two-knot hazard model are also appropriate due to their good statistical fit and closeness to the clinician estimates of 10-year OS. However, the EAG notes that neither the Weibull model, the one-knot hazard model nor the two-knot hazard model provides a great representation of the hazard function. The EAG has maintained the company's choice of Weibull survival curve in its preferred base-case analysis but has explored the impact of choosing the one-knot hazard model as a plausible alternative in its scenario analysis.

Table 10: AIC and BIC statistics for amivantamab with lazertinib OS with standard parametric models (reproduced from addendum Table 9)

Models	AIC (rank)	BIC (rank)
Exponential	[redacted]	[redacted]
Weibull (company's base-case)	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; OS – overall survival

Table 11: AIC and BIC statistics for amivantamab with lazertinib OS with spline models (reproduced from addendum Table 9)

Models	**AIC (rank)**	**BIC (rank)**
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

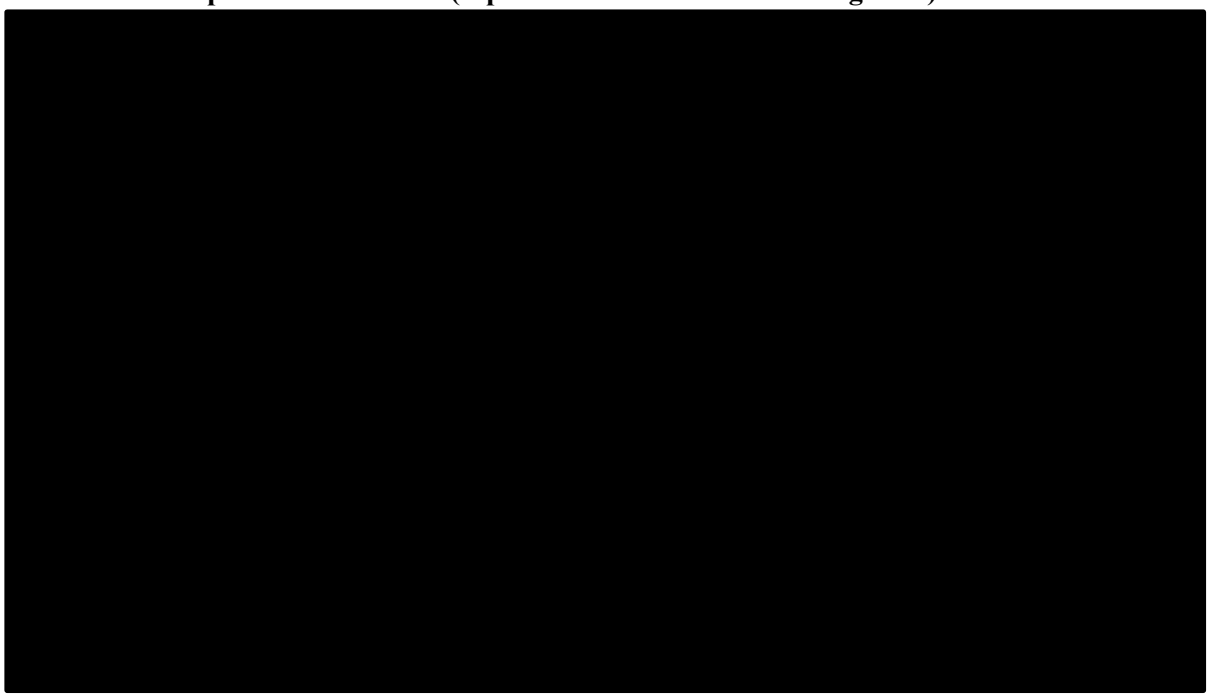
Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; OS – overall survival

Table 12: Clinician estimates for amivantamab with lazertinib OS (reproduced from Advisory board report, Table 18)

Timepoints	**Clinician 1**	**Clinician 2**	**Clinician 3**	**Mean**	**Midpoint**
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS – overall survival

Figure 6: Long-term predictions for amivantamab with lazertinib OS with standard parametric models (reproduced from addendum Figure 9)



Abbreviations: OS – overall survival

Figure 7: Long-term predictions for amivantamab with lazertinib OS with spline models (reproduced from addendum Figure 10)

Abbreviations: OS – overall survival

Figure 8: Hazard plot for amivantamab with lazertinib OS with standard parametric models (reproduced from addendum Figure 11)

Abbreviations: OS – overall survival

Figure 9: Hazard plot for amivantamab with lazertinib OS with spline models (reproduced from addendum Figure 12)

Abbreviations: OS – overall survival

Osimertinib OS

Standard parametric models and spline models were fitted to data on OS for osimertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 13 and Table 14, respectively. Comparisons of the observed KM curve and predicted OS are presented in Figure 10 and Figure 11, respectively. Empirical hazard plots and hazard plots from the fitted models are presented in Figure 12 and Figure 13, respectively. Clinician's estimates of expected OS are presented in Table 15.

The Weibull model was selected as the company's preferred base-case model for OS for osimertinib. Amongst all the standard parametric models, the Gompertz distribution has the lowest AIC/BIC, followed by Weibull, generalised gamma and gamma models. The standard parametric models generally provide a good visual fit, with the exception of log-normal and exponential distributions. The empirical hazard function appears to increase from the month 0 until about 34 months and decreases in the tail. The hazard functions for the Weibull, gamma, generalised gamma and Gompertz models align with the empirical hazard during the increasing phase.

All spline models provide a good visual fit to the KM curve and have similar AIC values with a six-point difference between the best- and worst-fitting models. The one-knot odds model has the smallest AIC, followed by the one-knot hazard, two-knot hazard, two-knot odds and one-knot normal models, with differences in AIC within three points. The one-knot odds model also has the smallest BIC, followed by the one-knot hazard and one-knot normal models, with differences in BIC within three points. All spline models predict an increasing hazard until around 30 months, with different predictions in the tails of the curves. The hazard plot for three-knot normal spline model was not presented.

Clinicians' estimates of expected OS provided by the company are presented in Table 15. The mean of clinician's estimates of 10-year OS is [redacted]%. The 10-year OS prediction from the company's base-case Weibull model is 2.8%, which is slightly lower than clinicians' estimates. The standard parametric model that has the closest 10-year estimation to the clinicians' estimates is the gamma model, with a prediction of 5.4%. The Gompertz and generalised gamma models both give 10-year OS predictions that are close to 0. For the spline models, the 10-year OS predictions from the one-knot and two-knot spline models are listed in order as follows: two-knot odds (9.3%), one-knot normal (8.4%), one-knot odds (8.9%), two-knot normal (7.0%), two-knot hazard (3.2%), and one-knot hazard (1.2%).

Overall, the EAG considers the use of standard parametric models to be adequate for fitting osimertinib OS. Of all the fitted standard parametric models, the EAG considers both the Weibull and gamma models are appropriate as they provide good statistical fit, reasonable hazard shape and close estimation to clinicians' estimates. The Weibull model has better AIC/BIC compared to the gamma model but the gamma model has predictions that are closer to clinician's estimates; the Weibull model is associated with lower predictions than clinician estimates and the gamma model is associated with higher and

closer predictions compared with the clinician estimates. The EAG has maintained the company's choice of Weibull survival curve in its preferred base-case analysis but has explored the impact of choosing the gamma model as a plausible alternative in its scenario analysis.

Table 13: AIC and BIC statistics for osimertinib OS with standard parametric models (reproduced from addendum Table 10)

Models	AIC (rank)	BIC (rank)
Exponential	[redacted]	[redacted]
Weibull (company's base-case)	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; OS – overall survival

Table 14: AIC and BIC statistics for osimertinib OS with spline models (reproduced from addendum Table 10)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; OS – overall survival

Table 15: Clinician estimates for osimertinib OS (reproduced from Advisory board report, Table 20)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: OS – overall survival

Figure 10: Long-term predictions for osimertinib OS with standard parametric models (reproduced from addendum Figure 14)

Abbreviations: OS – overall survival

Figure 11: Long-term predictions for osimertinib OS with spline models (reproduced from addendum Figure 15)

Abbreviations: OS – overall survival

Figure 12: Hazard plot for osimertinib OS with standard parametric models (reproduced from addendum Figure 16)

Abbreviations: OS – overall survival

Figure 13: Hazard plot for osimertinib OS with spline models (reproduced from addendum Figure 17)

Abbreviations**: OS – overall survival**

3.1.1.2 TTD

Amivantamab TTD

Standard parametric models and spline models were fitted to data on TTD for amivantamab. The AIC and BIC values for the standard parametric models and spline models are shown in Table 16 and Table 17, respectively. Comparisons of the observed KM curve and predicted PFS are presented in Figure 14 and Figure 15, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 16 and Figure 17, respectively. Clinicians' estimates of expected TTD for amivantamab are presented in Table 18.

The exponential model was selected for use in the company's base-case. Amongst all the fitted standard parametric models, the generalised gamma model has the lowest AIC, followed by gamma, Weibull and exponential models, with differences of less than three points. The exponential distribution has the lowest BIC, followed by gamma distribution, with a three-point difference. The AIC/BIC values for the log-normal and log-logistic models are more than 20 points higher than the generalised gamma. All models other than the log-logistic and log-normal distributions appear to provide a good visual fit to KM curve. The smoothed empirical hazard plot appears to decrease, increase and then decrease, while the exponential model predicts a constant hazard.

All spline models appear to fit the KM curve well. The three-knot normal spline model has the lowest AIC, followed by three-knot odds, three-knot hazard, two-knot odds, one-knot hazard, and two-knot normal spline models, with differences of less than six points. The one-knot hazard spline model has the lowest BIC, followed by one-knot odds spline model, with a difference of less than three points. The two-knot odds and two-knot normal spline models best capture the shape of the empirical hazard function. In contrast, the three-knot hazard and three-knot odds model predict two smooth turns that are not reflected in the empirical hazard function; the one-knot hazard and two-knot hazard models predict an increasing tail that is unlikely to be observed; the one-knot odds and one-knot normal model fail to capture the middle increasing phase of the empirical hazard function. The hazard plot for three-knot normal spline model was not presented.

Clinicians' estimates of expected TTD for amivantamab provided by the company are presented in Table 18. The mean of the clinicians' estimates of 8-year TTD is [redacted]%. The 8-year TTD prediction from the company's preferred exponential model is 2.8%. The 8-year TTD predictions from the one-knot and two-knot spline models are listed as follows: one-knot odds (8.1%), one-knot normal (6.9%), two-knot odds (5.6%), two-knot normal (4.2%), two-knot hazard (2.8%), and one-knot hazard (2.5%).

Overall, the EAG does not consider the use of the exponential model to be appropriate as it cannot reflect the complex hazard shape in the observed data. The EAG prefers the use of spline models as

they provide a better fit to the empirical hazard function. Of all the fitted spline models, the EAG considers the two-knot normal and two-knot odds models to be appropriate as they provide a good statistical fit to the KM estimates and good predictions to the hazard function, as well as closer predictions to clinicians' estimates of 8-year TTD. The EAG has implemented the two-knot normal in its preferred base-case scenario.

Table 16: AIC and BIC statistics for amivantamab TTD with standard parametric models (reproduced from addendum Table 11)

Models	AIC (rank)	BIC (rank)
Exponential (company's base-case)	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; TTD – time to discontinuation

Table 17: AIC and BIC statistics for amivantamab TTD with spline models (reproduced from addendum Table 11)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; TTD – time to discontinuation

Table 18: Clinician estimates for amivantamab TTD (reproduced from Advisory board report, Table 31)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD – time to discontinuation

Figure 14: Long-term predictions for amivantamab TTD with standard parametric models (reproduced from addendum Figure 19)

Abbreviations: TTD – time to discontinuation

Figure 15: Long-term predictions for amivantamab TTD with spline models (reproduced from addendum Figure 20)

Abbreviations: TTD – time to discontinuation

Figure 16: Hazard plot for amivantamab TTD with standard parametric models (reproduced from addendum Figure 21)

Abbreviations: TTD – time to discontinuation

Figure 17: Hazard plot for amivantamab TTD with spline models (reproduced from addendum Figure 22)

Abbreviations: TTD – time to discontinuation

Lazertinib TTD

Standard parametric models and spline models were fitted to data on TTD for lazertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 19 and Table 20, respectively. Comparisons of the observed KM curve and predicted PFS are presented in Figure 18 and Figure 19, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 20 and Figure 21, respectively. Clinicians' estimates of expected TTD for lazertinib are presented in Table 21.

The exponential model was selected for use in the company's base-case. Amongst all the fitted standard parametric models, the exponential model has the lowest AIC, followed by Gompertz, Weibull, gamma and generalised gamma models with differences of less than three points. The exponential distribution also has the lowest BIC, followed by the Gompertz model with a five-point difference. All models other than the log-logistic and log-normal distributions appear to provide a good visual fit to KM curve. The smoothed empirical hazard function appears to decrease at the start, then slowly increase and then decrease in the end. None of the standard parametric models can provide hazard plots with such a shape.

All of the spline models appear to fit the KM curve well. The three-knot normal model has the lowest AIC, followed by the three-knot odds, three-knot hazard, one-knot normal, two-knot normal and one-knot hazard models, all with a difference in AIC within six points. The one-knot normal model has the lowest BIC, followed by the one-knot hazard and one-knot odds spline models, with differences of less than three points. The three-knot hazard and three-knot odds spline models do not seem to fit the empirical hazard function well, as they provide three smooth turning points that are not observed in the empirical hazard plots. The hazard plot for three-knot normal spline model was not presented. The one-knot and two-knot spline models capture the shape of the empirical hazard plot better.

Clinicians' estimates of expected TTD provided by the company are presented in Table 21. The mean of the clinicians' 8-year TTD estimates is [redacted]%. The 8-year TTD prediction from the company's preferred exponential model is 8.8%. The 8-year TTD predictions from the spline models are high, one-knot hazard (10.8%), two-knot hazard (10.9%), two-knot normal (13.5%), three-knot hazard (14.4%) two-knot odds (14.7%), while the remaining four models have 8-year predictions that higher than 15%.

The EAG prefers the use of spline models as they provide a better fit to the empirical hazard plot. Of all the fitted spline models, the EAG prefers the one-knot hazard model as it captures the hazard shape well, provides good statistical fit to KM data and reasonable predictions. The EAG has implemented the one-knot hazard it is preferred base-case scenario. The EAG also considers the two-knot normal spline model to be appropriate as it captures the hazard shape well and provides a good statistical fit to KM data, albeit with a 8-year prediction that is further from the clinician estimates. The impact of choosing this curve is explored in the EAG scenario analysis. Although the exponential model does not

capture the shape of the hazard function well, it does provide closest 8-year predictions to clinician's estimates and it is also considered in the scenario analysis.

Table 19: AIC and BIC statistics for lazertinib TTD with standard parametric models (reproduced from addendum Table 12)

Models	AIC (rank)	BIC (rank)
Exponential (company's base-case)	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; TTD – time to discontinuation

Table 20: AIC and BIC statistics for lazertinib TTD with spline models (reproduced from addendum Table 12)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; TTD – time to discontinuation

Table 21: Clinician estimates for lazertinib TTD (reproduced from Advisory board report, Table 33)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD – time to discontinuation

Figure 18: Long-term predictions for lazertinib TTD with standard parametric models (reproduced from addendum Figure 23)

Abbreviations: TTD – time to discontinuation

Figure 19: Long-term predictions for lazertinib TTD with spline models (reproduced from addendum Figure 24)

Abbreviations: TTD – time to discontinuation

Figure 20: Hazard plot for lazertinib TTD with standard parametric models (reproduced from addendum Figure 25)

Abbreviations: TTD – time to discontinuation

Figure 21: Hazard plot for lazertinib TTD with spline models (reproduced from addendum Figure 26)

Abbreviations: TTD – time to discontinuation

Osimertinib TTD

Standard parametric models and spline models were fitted to data on TTD for osimertinib. The AIC and BIC values for the standard parametric models and spline models are shown in Table 22 and Table 23, respectively. Comparisons of the observed KM curve and predicted PFS are presented in Figure 22 and Figure 23, respectively. Smoothed empirical hazard plots and hazard plots from the fitted models are presented in Figure 24 and Figure 25, respectively. Clinician estimates of expected TTD for osimertinib are presented in Table 24.

The exponential model was selected for use in the company's base-case. Amongst all the fitted standard parametric models, the gamma model has the lowest AIC and BIC, followed by the Weibull and generalised gamma distributions. The EAG notes that the AIC for the exponential model is 13 points higher than that of the gamma model. The hazard plot appears to increase from month 0 until around 29 months and decrease in the tail. The hazard functions for the gamma, Weibull and generalised gamma distributions closely align with the empirical hazard during the increasing phase.

All spline models appear to fit the KM curve well. AIC values do not vary much between the different spline models, with a difference of less than five points between the best- and worst-fitting models. The one-knot odds model has the lowest AIC, followed by the one-knot normal, two-knot odds, two-knot normal, one-knot hazard and two-knot hazard spline models, with differences of less than three points. The one-knot odds model has the lowest BIC, followed by the one-knot normal and one-knot hazard spline models, with differences of less than three points. All spline models align with the empirical hazard during the increasing phase, from month 0 until about 29 months. The hazard plot for three-knot normal spline model was not presented.

Clinician's estimates of TTD for osimertinib provided by the company are presented in Table 24. The mean of the clinicians' estimates of 8-year TTD is [redacted]%. The 8-year model-predicted TTD based on the exponential and gamma distributions are 4.8% and 2.6%, respectively. The 8-year TTD predictions from the one-knot and two-knot spline models are listed in order as follows: one-knot odds (6.9%), two-knot odds (6.6%), one-knot normal (5.2%), two-knot normal (5.0%), two-knot hazard (3.2%), and one-knot hazard (2.1%).

The EAG acknowledges that the exponential model provides a close estimation to the mean of clinicians' estimates, but does not consider it to be appropriate as it provides a poor statistical fit. The EAG considers one-knot normal and two-knot normal spline models to be appropriate as they provide close estimation to clinicians' 8-year estimates, good statistical fit and reasonable hazard shapes. The EAG has implemented the one-knot normal in its base-case and explores the impact of using the two-knot normal in scenario analysis.

Table 22: AIC and BIC statistics for osimertinib TTD with standard parametric models (reproduced from addendum Table 13)

Models	AIC (rank)	BIC (rank)
Exponential (company's base-case)	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; TTD – time to discontinuation

Table 23: AIC and BIC statistics for osimertinib TTD with spline models (reproduced from addendum Table 13)

Models	AIC (rank)	BIC (rank)
Hazard (one-knot)	[redacted]	[redacted]
Hazard (two-knot)	[redacted]	[redacted]
Hazard (three-knot)	[redacted]	[redacted]
Odds (one-knot)	[redacted]	[redacted]
Odds (two-knot)	[redacted]	[redacted]
Odds (three-knot)	[redacted]	[redacted]
Normal (one-knot)	[redacted]	[redacted]
Normal (two-knot)	[redacted]	[redacted]
Normal (three-knot)	[redacted]	[redacted]

Models with lowest AIC/BIC values as well as those with differences of less than three points are shown in bold.
Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; TTD – time to discontinuation

Table 24: Clinician estimates for osimertinib TTD (reproduced from Advisory board report, Table 35)

Timepoints	Clinician 1	Clinician 2	Clinician 3	Mean	Midpoint
4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TTD – time to discontinuation

Figure 22: Long-term predictions for osimertinib TTD with standard parametric models (reproduced from addendum Figure 27)

Abbreviations: TTD – time to discontinuation

Figure 23: Long-term predictions for osimertinib TTD with spline models (reproduced from addendum Figure 28)

Abbreviations: TTD – time to discontinuation

Figure 24: Hazard plot for osimertinib TTD with standard parametric models (reproduced from addendum Figure 29)

Abbreviations: TTD – time to discontinuation

Figure 25: Hazard plot for osimertinib TTD with spline models (reproduced from addendum Figure 30)

Abbreviations: TTD – time to discontinuation

3.1.2 *Health-related quality of life*

The changes in utility values resulting from the 4th December 2024 DCO update are presented in Table 25 (supersedes Table 42 in the EAG's main report).

Table 25: Health state utilities used for the company's base-case

	Utility used in the company's original model	Utility used in the company's updated model	Source
Progression-free (SE)	[redacted]		Multiple MMRM from the pooled cohort of progression-free patients in MARIPOSA trial
Progressed disease (SE)	[redacted]	[redacted]	A single MMRM from the pooled patients who progressed in MARIPOSA

Abbreviations: MMRM - mixed model for repeated measures; SE – standard error

The company updated incidence rates and durations of adverse events from the 4th December 2024 DCO. Following updates to the incidence rates and mean cumulative durations of adverse events, the associated QALY losses have also been revised accordingly. A corrected version of Table 45 in the EAG's main report is Table 26.

Table 26: Loss of QALYs for each adverse event

AE category	Incidence of AE[a] (%)		Mean cumulative duration [a] (days)	QALY loss[b]	
	Amivantamab with lazertinib	Osimertinib		Base-case	Scenario analysis
Grade ≥ 3					
Dermatitis acneiform	[redacted]				−0.0026
Alanine aminotransferase increase	[redacted]				−0.0029
Hypalbuminaemia	[redacted]				−0.0071
Paronychia	[redacted]				−0.0230
Infusion related reaction	[redacted]				−0.0002
Rash	[redacted]				−0.0026
Pulmonary embolism	[redacted]				−0.0083
Pneumonia	[redacted]				−0.0028
Grade ≤ 2					
VTE	[redacted]				−0.0074

[a] from the MARIPOSA trial

[b] QALY loss = Incidece of AEs × Mean duration × disutilities for AEs

Abbreviations: AE - adverse events; QALY - quality-adjusted life year; VTE - venous thromboembolism.

3.1.3 *Resource use and costs*

(i) Drug acquisition and administration costs for first-line treatments

In line with the 4th December 2024 DCO update, actual doses administered in the MARIPOSA trial were updated as well as the proportion of doses missed for both arms (Table 27 and Table 28 supersede Table 18 and Table 47 in the EAG's main report). Accordingly, costs per week were updated.

Table 27: Actual dose, measured in MARIPOSA trial

Regimen	Component	Dosing frequency	Actual dose administered in MARIPOSA trial
Amivantamab with lazertinib	Amivantamab	Once weekly for the first 4 weeks and then once every 2 weeks (IV)	< 80 kg: [redacted][a] of 1050 mg (3 vials) ≥ 80 kg: [redacted][a] of 1400 mg (4 vials)
	Lazertinib	Once daily (PO)	- 80 mg [redacted]% - 160 mg [redacted]% - 240 mg [redacted]% - 320 mg [redacted]% - 400 mg [redacted]% - 480 mg [redacted]%
Osimertinib monotherapy	Osimertinib	Once daily (PO)	- 40 mg [redacted]% - 80 mg [redacted]% - 160 mg [redacted]% - 240 mg [redacted]% - 320 mg [redacted]%

[a] the proportion of planned dose

Abbreviations: IV – intravenous; PO – per os (by mouth/oral administration)

Table 28: Drug acquisition costs for subsequent treatment

Drug	Dose	Drug acquisition					Drug administration		Proportion of doses missed	Cost per week (£)
		Strength per unit (mg)	Unit per pack	Price per pack (£)	Price per unit (£)	Unit per admin, reflecting actual dose	Dosing frequency	Unit cost (£)		
Amivantamab (inc. PAS)	Required dose: - < 80 kg - 1,050 mg - ≥ 80 kg - 1,400 mg	350	1	[redacted]	[redacted]	< 80 kg: [redacted] vials[a] ≥ 80 kg: [redacted] vials[a]	IV, once weekly for the first 4 weeks and then once every 2 weeks	152.13[b]	< 80 kg: [redacted]% ≥ 80 kg: [redacted]%	First 4 weeks: [redacted][d] After 4 weeks: [redacted][d]
Lazertinib (inc. PAS)	Distribution of actual dose (%) - 80 mg - 160 mg - 240 mg - 320 mg - 400 mg - 480 mg	80	56	[redacted]	[redacted]	Weighted mean of unit: - 80 mg [redacted] - 240 mg [redacted]	PO, once daily	247.13[b]	[redacted]%	One-off: 247.13
		240	28	[redacted]	[redacted]					
Osimertinib	Distribution of actual dose (%) - 40 mg - 80 mg - 160 mg - 240 mg - 320 mg	40	30	5770[e]	192.33	Weighted mean of unit: - 40 mg [redacted] - 80 mg [redacted]	PO, once daily	247.13[c]	[redacted]%	[redacted] One-off: 247.13
		80	30	5770[e]	192.33					

[a]Calculated by EAG using the proportion of planned does administered, provided by the company; the planned number of vials * the proportion of planned dose administered (full vials)
[b]National Schedule of NHS Costs 2023/24,[16] SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance; Outpatient; Medical Oncology Service
[c]National Schedule of NHS Costs 2023/24,[16] SB11Z - Deliver Exclusively Oral Chemotherapy; Medical Oncology Service
[d] Drug acquisition cost + IV administration cost; Weighted mean of drug costs by the distribution of weight (< 80 kg or ≥ 80 kg); The proportion of dose missed was applied to the unit cost for administration
[e]Taken from the British National Formulary (BNF)[15]
Abbreviations: IV - intravenous; PAS - Patient Access Scheme; PO - per os (by mouth/oral administration)

(ii) Cost for treatments following disease progression (subsequent treatment)

The proportion of patients receiving the second-line treatment, informed by the MARIPOSA trial, has been updated to [redacted]% for amivantamab-lazertinib and [redacted]% for osimertinib (Table 29). In the updated scenario analysis, while the third-line and beyond treatment distributions remained the same as in the original submission, the second-line treatment distributions were updated (Table 30). Table 29 and Table 30 are updated versions of Table 51 and Table 52 in the EAG report, respectively.

Table 29: One-off costs for subsequent treatment

	Cost[a] (£)	Patients receiving treatment[b]	
		Amivantamab with lazertinib	Osimertinib
Second-line costs			
Drug	592	[redacted]	[redacted]
Administration	1,727		
Co-medication	41		
Monitoring	36		
Managing AEs	294		
Best supportive care	0	[redacted]	[redacted]
Third-line and beyond costs			
Drug	2,210	[redacted]	[redacted]
Administration	2,760		
Co-medication	6		
Monitoring	6		
Managing AEs	397		
Best supportive care	0	[redacted]	[redacted]
One-off costs for subsequent treatments (£)		[redacted]	[redacted]

[a] aggregated costs reflecting the distribution of patients receiving treatment within each therapy
[b] second-line from MARIPOSA, Third-line or later from MARIPOSA-2; calculated by dividing the number of patients receiving any subsequent systemic therapy by those who discontinued their first-line treatment for reasons other than death; proportion of patients with best supportive care = 1- % patients receiving active treatment

Table 30: Distribution of subsequent treatments and durations on treatment

	Base-case	Scenario analysis using trial-based estimates of subsequent treatments	
	Both arms	Amivantamab with lazertinib	Osimertinib
Second-line		MARIPOSA (DCO 4th December 2024)[3]	
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]	[redacted]
Third-line and beyond		MARIPOSA-2	
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]	[redacted]

Abbreviations: EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor.

3.2 Results of the company's updated economic analysis

3.2.1 *Company's base-case results*

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in the company's addendum at the time of the FAC check. The company provided base-cases analyses using both the list prices and the prices incorporating the PAS discounts for amivantamab and lazertinib. The results presented in this section incorporate the PAS discount for amivantamab and lazertinib. However they exclude the PAS discounts for any other drugs as these are confidential and cannot be disclosed. Analyses incorporating confidential prices for all drugs are provided in a separate confidential appendix to this EAG report addendum.

Table 31 presents the central estimates of cost-effectiveness generated using the company's model for the comparison of amivantamab with lazertinib versus osimertinib. The probabilistic version of the model suggests that compared to osimertinib, amivantamab with lazertinib generates an additional [redacted] QALYs per patient and a cost saving of [redacted]. The deterministic version of the model produces an additional [redacted] QALYs and a cost saving [redacted]. The incremental costs are similar to those presented for the company base-case in the main EAG report. However, the incremental QALYs are smaller ([redacted] versus [redacted]). This appears to be due to the incorporation of the updated survival data from the 4th December 2024 DCO as the incremental life-years are also smaller (1.56 versus 1.75).

Table 31: Company's base-case results (generated by the EAG using the model submitted by the company at the time of the FAC check)

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs	LYGs	QALYs	Costs	
Probabilistic model (1000 iterations)							
Amivantamab with lazertinib	5.26	[redacted]	[redacted]	1.56	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.69	[redacted]	[redacted]	-	-	-	
Deterministic model							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68	[redacted]	[redacted]				

*Undiscounted
Abbreviations: ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year

The scatter plot (Figure 26), generated by the EAG running the probabilistic analysis for the company's base-case, showed that all probabilistic sensitivity analysis (PSA) iterations resulted in lower costs for amivantamab with lazertinib versus osimertinib and > 99% resulted in greater QALYs. The cost-effectiveness acceptability curve (company's addendum, Figure 33) suggests that the probability that

amivantamab with lazertinib generates more net benefit than osimertinib at willingness-to-pay thresholds below £30,000 is [redacted]%.

Figure 26: Cost-effectiveness plane, amivantamab with lazertinib versus osimertinib, with PAS prices

Generated by the EAG based on the company's FAC model, 1000 iterations
Abbreviations: PAS - patient access scheme; PSA - probabilistic sensitivity analyses

3.2.2 *Company's deterministic sensitivity analyses*

All of the deterministic analyses provided in the updated tornado diagram show that amivantamab with lazertinib dominates osimertinib (Figure 27).

Figure 27: Tornado diagram for deterministic sensitivity analyses with PAS prices

Generated by the EAG based on the company's FAC model
Abbreviations: ICER - incremental cost-effectiveness ratio; OS - overall survival; TTDD - time to treatment discontinuation or death.

3.2.3 *Company's scenario analyses*

All of the deterministic scenario analyses provided by the company had a ICER below [redacted] with the choice of OS and TTD distributions having the greatest impact on the magnitude of incremental costs and the choice of OS having the greatest impact on the incremental QALYs.

Table 32: Company's scenario analyses, deterministic

Scenario description	Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs[a]	QALYs	Costs (£)	
Company's base-case (deterministic)	1.54	[redacted]	[redacted]	Dominant[b]
1.5% discount rate	1.54	[redacted]	[redacted]	Dominant[b]
37.7-year time horizon	1.54	[redacted]	[redacted]	Dominant[b]
PFS by INV for amivantamab with lazertinib and osimertinib	1.54	[redacted]	[redacted]	Dominant[b]
Lower PFS curve selections (Gamma extrapolation for amivantamab with lazertinib and osimertinib)	0.96	[redacted]	[redacted]	Dominant[b]
Higher PFS curve selections (Log-normal extrapolation for amivantamab with lazertinib and osimertinib)	1.55	[redacted]	[redacted]	Dominant[b]
Lower OS curve selections (Gompertz extrapolation for amivantamab with lazertinib and osimertinib)	1.54	[redacted]	[redacted]	Dominant[b]
Higher OS curve selections (Gamma extrapolation for amivantamab with lazertinib and osimertinib)	1.54	[redacted]	[redacted]	Dominant[b]
Lower TTD curve selections (Generalised Gamma extrapolation for amivantamab, Weibull extrapolation for lazertinib and osimertinib)	1.54	[redacted]	[redacted]	Dominant[b]
Higher TTD curve selections (Gamma extrapolation for amivantamab, lazertinib, and osimertinib)	1.54	[redacted]	[redacted]	Dominant[b]
HSUV (PD: 0.678; PF: 0.794 as per TA654)	1.54	[redacted]	[redacted]	Dominant[b]
AE disutilities based on literature	1.54	[redacted]	[redacted]	Dominant[b]
Subsequent treatment distribution based on MARIPOSA trial	1.54	[redacted]	[redacted]	Dominant[b]
Subsequent treatment distribution based on UK RWE	1.54	[redacted]	[redacted]	Dominant[b]

Generated by the EAG based on the company's model

[a] Undiscounted

[b] Amivantamab with lazertinib dominates osimertinib (has higher costs and lower QALYs)

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

3.3 Critique of company's updated economic evaluation

3.3.1 *Model verification*

To verify no undisclosed changes by the company, the EAG applied the updated parameters from the company's addendum (see Section 3.1), which were informed by data from the 4th December 2024 DCO, into the model used to generate the EAG results for the main EAG report and replicated the company's base case. The EAG found that there were no undisclosed changes.

3.3.2 *EAG Critique of the modelling performed by the company*

3.3.2.1 *EAG's preferences maintained from main EAG report*

All critical appraisal, written in Section 4.3.3 in the EAG's main report, remains relevant for the updated cost-effectiveness analysis presented in the company's addendum except Section 4.3.3.2 in the EAG's main report. Section 4.3.3.2 in the EAG's main report is superseded by Section 3.3.2.2 of this addendum.

3.3.2.2 Uncertainty around the survival analysis

The EAG has several concerns regarding the company's survival analysis presented in the CS[1] These concerns are discussed below based on the general considerations around model fitting and selection set out in NICE Decision Support Unit (DSU) Technical Support Documents (TSDs) 14 and 21.[25, 26]

(a) Appropriateness of the data used

IPD from the MARIPOSA trial were used to inform survival extrapolation. Data for OS and TTD has been updated (DCO 4th December 2024) in the addendum but data for PFS (DCO 11th August 2023) remains the same as in the CS.

(b) Suitability of the joint models

The company investigated the appropriateness of fitting combined models by assessing the proportional hazard assumption based on log cumulative hazard plot of PFS and OS and concluded that fitting separate models to each arm is more appropriate than using jointly fitted models. The EAG agrees with the company that fitting separate models is a reasonable approach.

(c) Range of candidate models assessed

The company fitted seven standard parametric survival models and spline models to the data for each treatment arm separately. After assessing all the fitted models, the EAG concludes that the standard parametric models are adequate for PFS, but the spline models provide better fit for OS and TTD. For TTD, the spline models capture the shape of the empirical hazard function better, while for OS in amivantamab with lazertinib, the spline models provide a better visual fit than standard parametric models.

(d) Statistical and visual goodness-of-fit

Amongst other factors, the company's model selection process included consideration of statistical goodness-of-fit (AIC and BIC) and visual inspection. The company's preferred base-case models all have reasonable AIC/BIC values, apart from the exponential model for osimertinib TTD, which has high AIC and BIC values, 13 points higher than the model with the lowest AIC and 9 points higher than the model with the lowest BIC.

(e) Consideration of hazard plots The company has taken into account the smoothed empirical hazard plots in the process of selecting curves. Hazard plots from PFS and OS of both arms are reasonably captured in the company's preferred base-case models, but hazard plots for TTD have more complex shapes that are not captured by the company's preferred base-case models. For both amivantamab and lazertinib TTD, there are noticeable decreases at the beginning of the hazard curves. The EAG prefers spline models as they provide a hazard function with a better shape, while the company's preferred base-case exponential model predicts a constant hazard. For osimertinib TTD, the hazard function first increases and then decreases, but the company's preferred base-case exponential model predicts a constant hazard.

(f) Consideration of long-term clinical plausibility

Three clinicians were consulted at an advisory board meeting held in October 2024 to inform long-term survival extrapolation assumptions. The estimates obtained from each of the three clinicians are presented in Section 4.2.4.2 of the main EAG report (for OS and TTD, these are also provided for reference in Sections 3.1.1 of this addendum). The EAG notes that the estimates from Clinician 1 are noticeably higher than those of Clinicians 2 and 3 across all endpoints. The EAG's clinical advisers consider the company's clinicians' estimates to be reasonable and their estimates are more closely aligned with those of Clinicians 2 and 3.

In the CS, the company presented the midpoint of the clinicians' estimates, which is the mean between the lowest and highest estimates. The EAG prefers to use the mean of all three clinicians' estimates instead of the midpoint, as the midpoint ignores part of the data and is sensitive to outliers. Due to the uncertainty associated with long-term predictions, the EAG has explored different potentially plausible survival curves in the scenario analysis.

EAG conclusions on the company's survival analysis

Overall, the EAG considers the company's base-case selections for PFS and OS (log-logistic for PFS; Weibull for OS) to be reasonable. For TTD, the EAG prefers the use of two-knot normal spline model for amivantamab, one-knot hazard spline model for lazertinib and the one-knot normal spline model for osimertinib as they provide a good fit to the hazard functions. The EAG has incorporated these

alternative TTD curves in its preferred base-case analysis (see Section 4.1). As the long-term OS, PFS and TTD predictions are uncertain, the EAG has also explored some alternative OS, PFS and TTD curves in scenario analyses to assess the extent to which the choice of parametric survival model impacts on the cost-effectiveness estimates (see Section 4.1).

4 Exploratory analyses undertaken by the EAG

4.1 Methods of the EAG's exploratory analyses

The exploratory analyses (EAs) and additional sensitivity analyses (ASA) conducted by the EAG are described in Section 4.4.2 of the EAG's main report. EA1 to EA6 were retained in the updated analyses; however, a minor change was applied to the alternative TTD distributions used in EA2.

EA2: Using spline models for TTD

The EAG implemented a two-knot normal model for amivantamab, a one-knot hazard model for lazertinib, and a one-knot normal model for osimertinib.

The EAG's updated base-case combined EA1 to EA6, including the updated curve choices for EA2. The ASA were undertaken using the EAG's base-case as the starting point. ASA1, ASA2, and ASA5 were maintained unchanged from the main EAG report. After critiquing the company's addendum describing the updated survival analysis, the EAG changed the choice of alternative distributions for TTD and OS which were tested through ASA3 and ASA4.

ASA3: Use of alternative distribution for TTD in lazertinib and osimertinib

The EAG changed the distributions of TTD for lazertinib and osimertinib to the two-knots normal models. All distributions for amivantamab, lazertinib and osimertinib are two-knots normal models in this scenario as the EAG already preferred a two-knots normal model for amivantamab (see EA2).

ASA4: Use of alternative distributions for OS

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

4.2 Results of the EAG's exploratory analyses

The results of the EAG's preferred analyses are shown in Table 33, which provides the impact of each individual change and the results for the EAG's preferred base-case. It supersedes Table 63 in the EAG's report.

Across all these scenarios, amivantamab with lazertinib was found to dominate osimertinib consistently, with cost savings ranging from [redacted] to [redacted]. Accounting for longer chair time for IV infusion of amivantamab had the greatest impact on incremental costs. Applying resource use estimates from from ID6328 marginally increased the cost savings. Implementation of the EAG's preferred TTD curves had a smaller impact here than in the results presented in the main EAG report. This is mainly because the EAG's choice of alternative TTD curve for osimertinib in EA2 provides predictions that are closer to the company's preferred curve in these analyses; 8-year predictions of 5.2% for EAG's preference versus 4.8% for company's preference in this analysis whereas in the analyses presented in the main EAG report it was 1.3% versus 4.7% respectively. Applying treatment-specific utility values was the only analysis that impacted QALYs and this decreased the incremental QALY gains in the deterministic analysis from [redacted] to [redacted]. For the EAG's preferred base-case analysis, the incremental QALYs gained are smaller here than in the analyses presented in the main EAG report ([redacted] versus [redacted]). However, this was also true in the company's updated base-case ([redacted] versus [redacted]), and appears to be due to the implementation of the updated OS data from the 4th December 2024 DCO, as the EAG has not changed the OS curve choice in its base-case and the life-years gained for the deterministic analysis are identical to the company's estimate (1.54 life-years).

Table 33: EAG exploratory analysis results

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Company's base-case, deterministic							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG EA1: Correction of model errors, deterministic							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG EA2: EA1 + Use of alternative TTD curves from spline models (two-knot normal for amivantamab; one-knot hazard for lazertinib; one-knot normal for osimertinib)							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG EA3: EA1 + Applying treatment-specific utility for progression-free state, deterministic							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG EA4: EA1 + Applying administration cost with prolonged chair time, deterministic							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG EA5: EA1 + Applying frequencies of resource use from ID6328, deterministic							

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG EA6: EA1 + Including the incidence of grade ≥ 3 DVT, account for proportion of Grade ≤ 2 VTE that are pulmonary embolism and EAG preferences for VTE costs, deterministic							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG base-case applying analyses 1-6, deterministic							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
EAG base-case applying analyses 1-6, probabilistic							
Amivantamab with lazertinib	5.26	[redacted]	[redacted]	1.56	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.69						

*Undiscounted
Abbreviations: EA - exploratory analysis; DVT - deep vein thrombosis; ICER - incremental cost-effectiveness ratio LYG - life year gained; TTD – time to discontinuation; QALY - quality-adjusted life year; VTE - venous thromboembolism

The results for the EAG's preferred base-case scenario when using the mean costs and QALYs obtained from the probabilistic analysis are consistent to those obtained in the deterministic analysis. The scatter plot (Figure 28) shows that all PSA iterations resulted in lower costs for amivantamab with lazertinib versus osimertinib and > 99% resulted in additional QALYs. The range of incremental costs was -£[redacted] to -£[redacted] and the range of incremental QALYs was [redacted] to [redacted].

Figure 28: Cost-effectiveness plane, amivantamab with lazertinib versus osimertinib, with PAS prices, 1000 iterations

Abbreviations: PAS - patient access scheme; PSA - probabilistic sensitivity analyses

ASAs exploring individual changes using the EAG preferred base-case as the starting point are shown in Table 34 (supersedes Table 64 in the EAG main report). The sensitivity analyses applied to the EAG-preferred base-case resulted in an incremental gain for amivantamab with lazertinib compared with osimertinib ranging from [redacted] to [redacted] QALYs. The higher incremental QALY value was obtained by using the treatment-independent utility values from TA654, and this estimate of QALY gained is similar to that obtained in the company's base-case. The lower value of the range was obtained in the scenario analysis exploring plausible alternative extrapolations for OS. This analysis demonstrates that the incremental QALYs gained are highly sensitive to uncertainty in the long-term OS predictions. The cost-effectiveness estimates are less sensitive to changes in the selected model for extrapolating PFS. The incremental costs are less sensitive to the EAG's choice of alternative models for extrapolating TTD than they were in the analyses presented in the main EAG report.

Table 34: EAG additional sensitivity analyses results

Option	Absolute outcomes by treatment arm			Incremental outcomes for amivantamab with lazertinib versus osimertinib			ICER (£/QALY)
	LYGs*	QALYs	Costs (£)	LYGs	QALYs	Costs (£)	
EAG base-case							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
ASA1: Use of the company's preferred administration cost							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
ASA2: Use of treatment independent utility values from TA654							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
ASA3: Use of two-knots normal distribution for TTD in osimertinib and lazertinib							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						
ASA4: Use of alternative distributions for OS (one-knot hazard for amivantamab with lazertinib, gamma for osimertinib)							
Amivantamab with lazertinib	4.79	[redacted]	[redacted]	0.83	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.96						
ASA5: Use of alternative distributions for PFS (gamma for all)							
Amivantamab with lazertinib	5.21	[redacted]	[redacted]	1.54	[redacted]	[redacted]	Amivantamab with lazertinib dominates
Osimertinib	3.68						

*Undiscounted

Abbreviations: ASA - additional sensitivity analysis; LYG - life year gained; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

4.3 Discussion of the updated cost-effectiveness analyses

The results presented in the company's addendum demonstrate that incorporation of the updated OS data from the 4th December 2024 DCO results in a reduction in the incremental life-years gained for amivantamab with lazertinib versus osimertinib. This in turn results in smaller QALYs gained in both the EAG's and the company's preferred base-case analyses relative to the results presented in the main EAG report. In addition, the EAG's preferred choice of TTD curves had a smaller impact in the analyses presented here, mainly due to the EAG choosing a TTD curve for osimertinib that provides TTD predictions that are closer to the company's preferred TTD curve. However, the additional TTD follow-up data provided in the latest DCO have also resulted in a set of fitted TTD curves that provide a narrower range of TTD predictions. This demonstrates how using a more complete dataset from a later DCO has the potential to reduce uncertainty in the cost-effectiveness estimates.

The EAG notes that the company has not updated the PFS data used to inform the economic model to reflect any additional data collected between the 11th August 2023 DCO and the 4th December 2024 DCO. The EAG acknowledges the company's statement in the addendum that, *"the statistical alpha spending (0.05) for the primary endpoint of PFS was exhausted at the point of this analysis [based on the 11th August 2023 DCO], so data for this endpoint were not collected in subsequent DCOs*." However, even if the company considers it inappropriate to conduct a hypothesis test on PFS using the most recent DCO, due to the statistical alpha having been spent, the EAG does not understand why this would stop the company providing updated PFS KM curves to allow PFS in the economic model to be based on more a complete set of PFS outcomes from the MARIPOSA trial. Whilst the cost-effectiveness estimates were not particularly sensitive to different long-term extrapolations for PFS in the EAG's exploratory analyses, it is possible that fitting a new set of survival curves to an updated PFS KM dataset may have a greater impact than changes in the long-term extrapolation based on alternative curves fitted to the same KM data. Therefore, the potential impact of updating the economic analysis to reflect a more complete PFS dataset remains uncertain and the EAG considers this to be a significant limitation of the evidence provided by the company in its addendum.

Whilst both the company's and the EAG's preferred base-case analyses suggest that amivantamab with lazertinib dominates osimertinib, the EAG's preferred analyses result in smaller incremental QALY gains and smaller cost savings compared with the company's base-case. As previously noted in the main EAG report, these differences are mainly due to the EAG's preference to use a treatment-specific utility value for the progression-free health state and the EAG's preference for using a reference cost for amivantamab administration that reflects the need for an infusion time greater than 2 hours. The EAG's exploratory analyses demonstrate that the incremental QALYs gained are also sensitive to the choice of long-term extrapolation curves for OS with plausible alternative curves providing much lower estimates of incremental QALYs for amivantamab with lazertinib versus osimertinib.

Overall, the EAG's exploratory analyses indicate that the company's base-case analysis is likely to overestimate both QALY gains and cost-savings. However, amivantamab with lazertinib was still found to dominate osimertinib in all of the EAG's exploratory analyses, with cost savings being driven mainly by lower drug acquisition costs. Although, the EAG notes that in these analyses the PAS prices are applied for both amivantamab and lazertinib, but the list price is applied for osimertinib.

5 Conclusions

The company has provided updated data from the MARIPOSA trial that relate to the 4th December 2024 DCO. The protocol-specified final analysis demonstrated that amivantamab with lazertinib resulted in a statistically significant improvement in OS compared with osimertinib, showing a [redacted] reduction in the risk of death (HR: 0.75; 95% CI: 0.61–0.92; [redacted]). The safety findings for this latest DCO were generally consistent with those previously reported for earlier DCOs, with higher incidences of AEs related to EGFR TKI inhibitors and MET TKI inhibitors, a higher incidence of VTEs and a higher incidence of TEAEs leading to the discontinuation of any study drug for amivantamab with lazertinib versus osimertinib. The main uncertainties regarding the clinical evidence from the latest DCO of the MARIPOSA trial primarily relate to the safety profile of amivantamab with lazertinib. Whilst the company has highlighted findings from ongoing studies which may address these concerns, the EAG considers that results from these studies should be interpreted with caution as they are ongoing and only top-line data are currently available.

The main impact of the updated data from the 4th December 2024 DCO in the cost-effectiveness analysis is to reduce the estimates of incremental life-years gained in the company's base-case analysis which also results in a reduced estimate of QALYs gained. However, amivantamab with lazertinib is still found to dominate (have greater QALYs and lower costs) than osimertinib in both the company and the EAG's preferred analysis. The EAG also notes that the analyses presented here do not include any confidential price discounts for comparator treatments and it refers the reader to the confidential appendix to this addendum which reports analyses that include price discounts for all treatments.

6 REFERENCES

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Single Technology Appraisal

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

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 31 March 2025** 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 response
Section 1.2, Page 6, states: "In the company's model, amivantamab with lazertinib increases QALYs compared with osimertinib by increasing expected OS."	Please could this wording be amended as follows: "In the company's model, amivantamab with lazertinib increases QALYs compared with osimertinib by increasing expected OS **and by increasing time spent in the progression-free health state**."	In the model, the progression-free health state is associated with a higher utility value than the progressed disease health state. As such, in addition to increasing overall lifespan, amivantamab-lazertinib is associated with higher QALY gains compared with osimertinib by increasing the time for which patients remain progression-free.	Not factually inaccurate. However, the EAG have amended the subsequent sentence to say, " This results in additional **life-years and additional** QALYs being gained both pre- and post-progression.."
Section 1.3, Page 6, states: "The EAG's only key issue relating to the decision problem, was the fact that the company did not provide a comparison against osimertinib with chemotherapy, which was described as a comparator in the NICE Final Scope but is subject to an ongoing NICE appraisal (Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced NSCLC ID6328). However, the importance of this omission will	Please remove the word "omission".	Use of the word "omission" is factual inaccurate in this case because it could indicate that this represents an oversight on the part of the Company, whereas it is a decision that has been justified by the Company in the original Company Submission (Section B.1.1) and in the Company responses to EAG Clarification Questions (Question A.1), and that is in line with the NICE manual, which recommends comparators should	Not a matter of factual inaccuracy. No amendment necessary.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
depend on the final outcome of that appraisal and the degree of uptake of that treatment option in future, if the appraisal results in positive guidance."		represent the current care pathway utilised within the NHS.	
Issue 1 table in Section 1.3, Page 8, states: "However, the EAG acknowledges that the relevance of such a comparison is dependent on the outcome of ID6328." Similar wording relating to the relevance of the outcome of ID6328 is presented in: • Table 3 in Section 2.3, row "Comparators", Page 23 • Section 6, Page 159	Please amend as follows: "However, the EAG acknowledges that the relevance of such a comparison is dependent on the outcome of ID6328. **In addition, it notes the advice from its clinical experts that osimertinib with chemotherapy is not part of current clinical practice.**"	The relevance of osimertinib with chemotherapy is not solely dependent upon the outcome of its ongoing appraisal, but its lack of representation of standard clinical practice in the NHS, as acknowledged by the EAG's clinical advisors. This wording should be added alongside each instance of wording relating to whether this treatment is relevant for consideration, as has already been provided in Section 2.3.3 (Page 31) and Section 3.1.2 (Page 35).	Not a matter of factual accuracy. As noted by the company, the EAG already makes reference to the advice from its clinical experts that osimertinib with chemotherapy is not part of current clinical practice when discussing the comparators in both Sections 2.3.3 and Sections 3.1.2. Adding this statement each time the issue is discussed is not necessary.
Table caption in Section 1.4, Page 8, states: "Issue 2. PFS and the majority of the safety data are only reported for the DCO."	Please amend this as follows: "Issue 2. PFS and the majority of the safety data are only reported for the **interim** DCO **(11th August 2023)**"	It is unclear to which DCO the current wording is referring.	The EAG has amended the title of Issue 2 to match the text in Table 1 so it now says, "… for the interim DCO" The exact date is provided in the Issue 2 box.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Issue 2 table in Section 1.4, Page 8, states: "Whilst the AE data informing the economic model did reflect the 13th May 2024 DCO, the use of PFS data from the interim DCO (11th August 2023) in the economic analysis is considered to be a significant limitation." Table 3 in Section 2.3, row "Outcomes", Page 23, states: "Data from the more recent DCO of 13th May 2024, which was used to inform all other outcomes in the CS, were provided at clarification for the AEs informing the economic analysis, but the company stated that they were unable to provide updated PFS data." Section 2.3.4, Page 32, states: "PFS data from the 13th May 2024 DCO were not requested by the EMA and therefore these data are not available for the company to provide… The EAG would have preferred the company to have	Throughout the document at all places where it occurs, please remove all wording that indicates that the use of PFS data from the 11th August 2023 DCO is a key or significant limitation and/or awaits or requires an update. Furthermore, please remove any wording which indicates that lack of provision of updated PFS data represents a choice of the Company, or is due to it not being requested by the EMA.	The MARIPOSA trial met its primary endpoint, PFS, at the 11th August 2023 DCO. The statistical alpha (0.05) for PFS was spent at this analysis, so data for this endpoint could not be, and were not, collected in any subsequent DCOs. This does not represent a significant or key limitation of the analyses, and no further PFS data are or will be available for presentation by the Company. It is inaccurate to state that this is the case.[1] Furthermore, the data from the 11th August 2023 DCO are mature and reached the study primary endpoint. Consequently, regardless of availability, PFS does not drive the model and has a negligible impact on cost-effectiveness, as acknowledged by the EAG: "the cost-effectiveness estimates were not particularly sensitive to different long-term extrapolations for PFS in the EAG's exploratory	The EAG does not consider this to be a matter of factual accuracy. Even if the company considers it inappropriate to conduct a statistical hypothesis test on PFS using the most recent DCO, the EAG does not understand why this would stop them providing updated PFS Kaplan-Meier curves to allow PFS in the model to be based on more complete data. Therefore, the EAG still considers it a key issue that the company's economic analysis is not informed by PFS data from a more recent DCO. The company's response to clarification question A17 stated, "*The 13th May 2024 DCO was requested by the European Medicines Agency (EMA) to assess interim OS data*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
based their NICE submission on the most recent PFS data available and considers the lack of PFS data beyond the interim 11th August 2023 DCO to be a key limitation of the evidence presented by the company." Similar wording relating to lack of PFS data at later DCOs is presented throughout the document, including: • Section 1.5, Page 9 • Section 4.3.3.2, Page 140 • Section 6, Page 159		analyses" (Section 4.5, Page 154). Therefore, the absence of additional follow-up data for PFS should not presented or discussed as a key or significant limitation, as this is factually inaccurate.	*only; as such, PFS data are not available from the 13th May 2024 DCO.*" The EAG report accurately represents the company's response to this clarification question so no amendment is required for factual accuracy. However, the EAG has added the information provided by the company in this factual accuracy check on its rationale for not re-analysing the PFS outcome to its discussion in Section 2.3.4 (page 31) and to its description of PFS data on page 52. The EAG has reviewed text on the other pages indicated by the company and considers these to be factually accurate.
Issue 5 table in Section 1.5, Page 12, states: "However, the EAG believes that the company's calculation of the	This is a misunderstanding on the part of the EAG; missed doses have not been double counted within the Company model.	This definition provided by the EAG as to how the proportion of planned doses has been captured (cumulative dose received in the MARIPOSA trial	Thank you for providing the additional information explaining your calculation methods in more detail. In response to this we have

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
'proportion of planned doses' which the company assumes reflects only dose reductions, is likely to also capture missed doses. This is because it is based on the cumulative dose received in the MARIPOSA trial dived by the number of doses planned based on the average time on treatment within the MARIPOSA trial." Similar wording and/or economic analyses relating to the EAG's understanding that missed doses have been double-counted within the Company model are presented throughout the document, including: • Section 1.1, Page 5 • Section 1.2, Page 6 • Section 1.7, Tabe 2, Page 15 • Section 4.2.3, Page 86 • Section 4.2.4.4 (i), Page 121 • Section 4.3.3.3, Page 142	All wording, analyses and EAG base case changes related to Key Issue 5 should be removed from the report. In addition, all costing calculations performed by the EAG in which missed doses have been excluded (such as the "calculation of unit per admin" column of Table 47, and all downstream calculations) should be adjusted to reflect values where missed doses are included.	divided by the number of doses planned based on the average time on treatment within the MARIPOSA trial) is incorrect. As outlined in response to Clarification Question B.23, the correction of acquisition and administration costs for amivantamab, lazertinib and osimertinib to account for the proportion of missed doses and reduced doses was based on the following calculations: 1. **Adjustment for missed doses**: The adjustment for missed doses was calculated by taking the number of doses actually administered in the trial and dividing it by the expected number of doses based on the patient's duration of treatment (time to discontinuation, TTD). 2. **Adjustment for dose reductions**: In parallel to the adjustment for missed	removed this key issue from the EAG report. Key changes include: Table 1 – removal of issue and renumbering of remaining issues Removal of related bullet points on pages 5 and 6 Removal of key issue box on page 12 and renumbering of subsequent key issue boxes. Text summarising EAG analyses edited on pages 14, 146, 148, 149 & 154. Removal of this analysis and updating of EAG base case in Tables 2 and 63 and Figure 63. Updating EAG scenario analyses in Tables 2 and 64. Removal of this issue from Box 1.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
• Section 4.4.2, Page 149 • Section 4.4.3, Page 150 and Table 63 • Section 4.5, Page 154 • Section 6, Page 158		doses, a separate calculation was also done to adjust for dose reductions specifically on the doses that were administered. This involved calculating the proportion of the planned cumulative drug amount that was actually used. To do this, the Company divided the total cumulative amount of the drug prepared for the administration that took place in the trial by the cumulative amount that would have been prepared if there had been no dose modifications. This calculation was based solely on amivantamab injections patients actually received in the trial. 3. **Incorporation into the cost-effectiveness model**: Both adjustments—one for	Removal of section 4.3.3.3 and renumbering of subsequent sections. Removal of description of this analysis in Section 4.4.2 and renumbering of subsequent analyses. Updating of the EAG analyses presented in the confidential appendix including the comparator patient access scheme (PAS) prices. Text in Section 4.2.4.4 (i) has also been amended to provide a simplified description of the company's approach.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		missed doses and one for dose reductions—must be included in the model as they represent separate factors affecting dosing. There is no risk of double-counting missed doses in this process. As such, wording relating to this issue should be removed throughout the report. Likewise, adjustment for it in the EAG preferred base case should be removed. A more detailed explanation, along with an example of the calculations for missed doses and dose reductions is provided in an appendix at the end of this document.	
Table 3 in Section 2.3, row "Comparators", Page 23, states: "The EAG therefore agrees that dacomitinib, afatinib, erlotinib and gefitinib would not be relevant comparators if the population is restricted to patients with an	Please amend this wording as follows: "The EAG therefore agrees that dacomitinib, afatinib, erlotinib and gefitinib would not be relevant comparators if the population is restricted to patients with an ECOG	The current wording is misleading given that it suggests that treatments other than osimertinib could represent relevant comparators for consideration if amivantamab-lazertinib were recommended unrestricted by	Not a matter of factual accuracy. If the company is proposing a recommendation unrestricted by ECOG status, with the implication being that those with an ECOG score >1 may be fit

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ECOG PS score of 0 to 1, which was the group recruited to the MARIPOSA trial"	PS score of 0 to 1, which was the group recruited to the MARIPOSA trial. **If these patients were included, the EAG's clinical advisors confirmed that this group of patients may not be considered well enough to receive amivantamab with lazertinib and therefore osimertinib would remain the main comparator in the population most likely to receive amivantamab with lazertinib**."	ECOG status, as is proposed by the Company. In Section 2.2 of the EAG report, additional context is provided, stating that the EAG's clinical advisors confirmed that osimertinib represents the sole relevant comparator, regardless of ECOG status. This wording should be added for clarity and accuracy.	enough to receive amivantamab with lazertinib, then first and second generation TKIs would be relevant comparators in these patients as they do not currently quality for osimertinib under the CDF.
Section 2.3.1, Page 29, states: "The EAG is broadly satisfied that the population addressed in the CS falls within the population specified in the NICE scope. It notes that the MARIPOSA trial was restricted to adult participants with an ECOG PS score of 0 to 1 and therefore the evidence from the trial **will** have limited generalisability to paediatric patients or patients with a higher ECOG PS score."	Please adjust this wording as follows: "The EAG is broadly satisfied that the population addressed in the CS falls within the population specified in the NICE scope. It notes that **amivantamab-lazertinib is licensed in adults only, so restriction of the decision problem under consideration to adult patients is appropriate. It further notes that** the MARIPOSA trial was restricted to ~~**adult**~~ participants with an ECOG PS score of 0 to 1 and therefore the evidence from the trial **may** ~~**will**~~ have limited generalisability to ~~**paediatric patients or**~~ patients with a higher	Amivantamab-lazertinib is licensed for use in an adult population only.[2] As such, restriction of the appraisal to consider an adult population only is necessary and appropriate. This wording should be edited to clarify this. Reference to a paediatric population is inappropriate and should be removed. In addition, clinical experts consulted by the Company confirmed that the results of the MARIPOSA trial are expected to be generalisable to the	This is not a matter of factual inaccuracy. It is a statement about the generalisability of the trial data. Not a statement about the license. The NICE Scope did not specify that the population was restricted to adults. Therefore it is reasonable for the EAG to comment that the trial data would have limited generalisability to paediatric patients.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	ECOG PS score, **although acknowledges that UK-based clinicians at an advisory board conducted by the Company in October 2024 confirmed that overall, the baseline characteristics observed in the MARIPOSA trial are generalisable to the patient population in the UK and do not affect the impression of the trial outcomes**."	population of patients expected to receive amivantamab-lazertinib, should it be recommended for use in UK clinical practice. As such, it is not factually accurate to state that generalisability will be limited, and this clinician expert input should be acknowledged.	
Section 3.1.2, Page 35, states: "Despite the EAG requesting the eligibility criteria for the present submission clarification (question A9), the company only provided the eligibility criteria for the broader SLR (clarification response, questions A7, A8 and A9, Table 1)"	Please amend this wording as follows: "~~**Despite**~~ The EAG **requested** ~~**requesting**~~ the eligibility criteria for the present submission clarification (question A9) **and** the company ~~**only provided**~~ **stated that** the eligibility criteria for the broader SLR **were used, and then the evidence collated during the global SLR was prioritised for the submission to focus on studies of relevance by narrowing to RCT studies only, and first-line studies only (see Company response to Clarification Questions A.7, A.8 and A.9, Table 1).**"	The Company apologise for any confusion around the eligibility criteria of the SLR and can confirm that the eligibility criteria provided in response to the EAG clarification questions represent the full eligibility criteria applied for this submission. As such, this section of the report should be reworded for clarity, and to avoid suggestion that the Company failed to specify some criteria when asked.	This is not a factual error, however, the EAG has amended it as relevant for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.1.4.1, Page 40, states: "Eligibility criteria for the MARIPOSA trial are presented in the CS, page 44, and CS, Appendix M1."	Please amend as follows: "Eligibility criteria for the MARIPOSA trial are presented in the CS, page 44**~~, and CS, Appendix M1~~**."	Appendix M of the CS does not include the eligibility criteria for the MARIPOSA trial, so reference to it should be removed.	This has been amended
Section 3.3, Page 74, states: "Among the VTE AEs, [redacted] of events occurred in the first four months of treatment compared with [redacted] in the osimertinib group."	This sentence should be updated to reference the source of these data. In addition, these data should be marked as confidential, as presented here.	The source is not currently specified so the accuracy of these data cannot be determined. These data are currently unpublished and therefore should be marked with confidentiality highlighting.	Source now provided (Cho et al. NEJM 2024). No further changes made.
Section 3.3, Page 76, states: "Cardiopulmonary, cerebrovascular, and infection-related deaths predominated in these two groups,"	Please amend as follows: "The only causes of death experienced by ≥1% of patients in either treatment arm were pneumonia, respiratory failure and myocardial infarction."	This is in line with Cho et al. NEJM 2024, Supplementary Appendix, Table S12.	This is not a factual error. This information was reported in Cho et al. NEJM 2024. For clarity, the source reference has been added.
Section 3.8.2, Page 79, states: "The main uncertainties in the clinical evidence primarily relate to the duration of treatment and follow-up to assess the survival and safety profile of amivantamab with lazertinib. As the MARIPOSA	Please amend the final sentence as follows: "As a result, the long-term efficacy and safety of amivantamab with lazertinib is unknown, especially with regards to impacts on VTEs**~~, and the~~**	Amivantamab-lazertinib is positioned for use patients with incurable disease. In this setting, and for a treatment such as amivantamab-lazertinib that has a mechanism of action distinct from immunotherapy, it is	This has been amended as requested

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
trial is ongoing, the analyses are mainly exploratory. As noted in the CS, it is recommended that treatment with amivantamab with lazertinib should continue until disease progression or until the development of unacceptable toxicity. As a result, the long-term efficacy and safety of amivantamab with lazertinib is unknown, especially with regards to impacts on VTEs, and the optimum duration of therapy remains unclear."	~~**optimum duration of therapy remains unclear**~~."	expected that treatment would continue until progression or toxicity; this is in line with the recommendation in the SmPC, as acknowledged by the EAG earlier in the quoted paragraph. As such, optimum duration of therapy is not a relevant consideration for this appraisal and should be removed from this report.	
Section 4.2.3, Page 85, states: "Assumption 3. In the base-case analysis, log-logistic distributions were used for modelling PFS, Weibull distributions were used for OS; and exponential distributions were used for TTD; Parametric survival models were fitted separately to data for each trial arm for each endpoint." Table 19, Section 4.2.4, Page 88, "TTD" row, "amivantamab with lazertinib" column, states:	Please amend this wording as follows: "Assumption 3. In the base-case analysis, log-logistic distributions were used for modelling PFS, Weibull distributions were used for OS; and exponential distributions were used for TTD. Parametric survival models were fitted separately to data for each trial arm **(amivantamab-lazertinib and osimertinib)** for ~~**each endpoint**~~ **PFS and OS, and were fitted separately to data for**	While trial-arm data (i.e., combined amivantamab-lazertinib) were modelled for PFS and OS, TTD was modelled separately for amivantamab, lazertinib and osimertinib. This should be clarified for accuracy.	This change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"Exponential model fitted to TTD data for amivantamab **with** lazertinib **arm** of MARIPOSA (DCO 13th May 2023)"	**amivantamab, lazertinib and osimertinib for TTD.**" "Exponential model fitted to TTD data for amivantamab**,** lazertinib **and osimertinib**, ~~**arm of**~~ **informed by** MARIPOSA (DCO 13th May 2023)		
Section 4.2.3, Page 86, states: "Assumption 15. The proportion of patients receiving best supportive care at subsequent lines was informed by an analysis of the MARIPOSA and MARIPOSA-2 trials respectively."	Please amend this wording as follows: "Assumption 15. The proportion of patients receiving best supportive care at subsequent lines **(2L and 3L+)** was informed by an analysis of the MARIPOSA and MARIPOSA-2 trials respectively."	The specific lines of treatment that are being referred to here, and thus interpretation of which line is informed by which trial (MARIPOSA versus MARIPOSA-2) is currently unclear and should be clarified.	We have edited the text as follows: "The proportion of patients receiving best supportive care at **second-line and later lines** was informed by an analysis of the MARIPOSA and MARIPOSA-2 trials respectively."
Table 19, Section 4.2.4, Page 88, "AE costs" row, states: "Cost for VTE – **cost of 5 months rivaroxaban**"	Please update this wording as follows: "Cost for VTE – **one dose of rivaroxaban plus one ultrasound scan**"	This costing approach was updated at the Clarification Questions stage.	This change has been made as suggested, as it accurately reflects what the company did, but the EAG thought the one dose of rivaroxaban was an error in the Excel model rather than a deliberate choice by the company. Rivaroxaban is recommended for at least 3 months when used to treat VTE (TA287).

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			Therefore the EAG implements a longer duration in its analyses (see Table 62).
Table 19, Section 4.2.4, Page 88, "End-of-life costs" row, states: "Assumptions from atezolizumab submission to NICE (TA520),[57] updated with the 2023/24 National Schedule of NHS Costs[64]"	Please update this wording as follows: "Assumptions from atezolizumab submission to NICE (TA520),[57] updated with the 2023/24 National Schedule of NHS Costs[64] **and PSSRU 2023 costs**"	PSSRU costs (2023) informed the cost of a Macmillan nurse in the home setting. This wording should be updated to reflect this, including addition of a suitable reference.	This change has been made.
Section 4.2.4.2, Page 90, states: "Clinicians' estimates of expected PFS provided by the company are presented in **Table 3**. The mean of clinicians' 8-year PFS estimates is [redacted]. The 8-year prediction from the log-logistic distribution is 11.5% and the 8-year prediction from the gamma distribution is **2.7**%." However, 8-year estimates are not presented in the cross-referenced table.	Please update this wording as follows: "Clinicians' estimates of expected PFS provided by the company are presented in **Table 23**. The mean of clinicians' 8-year PFS estimates is [redacted]. The 8-year prediction from the log-logistic distribution is 11.5% and the 8-year prediction from the gamma distribution is **2.8**%." In addition, please add the 8-year estimates to Table 23.	The current table cross-reference and stated 8-year prediction from the gamma distribution are incorrect; these are minor typographical errors. In addition, the 8-year estimates quoted should be added to Table 23, for reference of the reader; currently, this table presents 4- and 6- year estimates only.	This change has been made.
Section 4.2.4.2, Page 98, states:	Please update this wording as follows:	The statement provided regarding visual fit represents the	This change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The spline models offer a better visual fit than the standard parametric models, and the EAG also considers the one-knot hazard model to be appropriate due to its good statistical fit and closeness to the clinician estimates of 10-year OS."	"The **EAG considers that the** spline models offer a better visual fit than the standard parametric models, and **~~the EAG also considers~~ that** the one-knot hazard model **~~to be~~ is** appropriate due to its good statistical fit and closeness to the clinician estimates of 10-year OS.	judgement of the EAG and should be clearly stated as such.	
Section 4.2.4.2, Page 102, states: "Overall, the EAG considers the use of standard parametric models to be adequate for fitting osimertinib OS. Of all the fitted standard parametric models, both the Weibull and gamma models are appropriate as they provide good statistical fit and reasonable hazard shape. The gamma model represents a scenario with higher predictions than the clinician estimates, and the Weibull model represents a scenario with lower predictions than clinician estimates."	Please consider rewording this, as follows: "Overall, the EAG considers the use of standard parametric models to be adequate for fitting osimertinib OS. Of all the fitted standard parametric models, both the Weibull and gamma models are appropriate as they provide good statistical fit and reasonable hazard shape. The gamma model **is associated ~~represents a scenario~~** with higher predictions than the clinician estimates, and the Weibull model **is associated ~~represents a scenario~~** with lower predictions than clinician estimates.	Use of the word "scenario" in relation to the Weibull curve in this context may be confusing, given the EAG's preferred base case selection remains unchanged (from Weibull). The suggested amendments would clarify this.	This change has been made.
Section 4.2.4.3, Page 118, states:	Please state the p-value which evidences this statistical significance,	Currently, statistical significance is stated within this sentence	The text has been amended to say: "The

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The results suggest that the coefficients for progression status and treatment arm are statistically significant, after adjusting for the presence of Grade ≥ 3 AEs, and presence of a VTE."	and its source (document and table reference). Please ensure to add confidentiality highlighting to this p-value (and any other numerical results, if presented).	(and wider section) without evidence. Specific reference to the source should be added for reference of the reader.	results **(see Table 3 of the company's later clarification response to B18)** suggest that the coefficients for progression status and treatment arm are statistically significant **(p<0.0001 and p =0.0005 respectively)**, after adjusting for the presence of Grade ≥ 3 AEs, and presence of a VTE. As the interaction term was not statistically significant (p=0.5808), it was not included in the final selected model."
Section 4.2.4.4 (i), Page 121, states: "Administration costs for each treatment are calculated assuming that all drugs are given in an outpatient setting. The unit costs were taken from the National Schedule of NHS Costs 2023/24 (codes SB11Z and SB12Z)."	Please amend this as follows: "Administration costs for each treatment are calculated assuming that all drugs are given in an outpatient setting. The unit costs were taken from the National Schedule of NHS Costs 2023/24 (codes SB11Z, SB12Z **and SB14Z**)."	Reference cost SB14Z (cost per IV administration for combination therapy) was included in the model, as listed in Table 58 of the CS.	This is not a factual inaccuracy. SB14Z is only relevant in the company's base-case for subsequent treatments and as such is mentioned first on page 127 and not here where the EAG is describing administration costs for first-line treatment. However, the section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			header has been amended to make it clearer that only first-line treatments are discussed in this paragraph.
Section 4.2.4.4 (i), Page 121, states: "The company's response to clarification question B28 states that: "the cost of 10 mg dexamethasone has been multiplied by three in the model to account for the full cost of dexamethasone comedication (30 mg total)." This is described as being in accordance with the SmPC recommending 20 mg dexamethasone for the first dose and 10 mg for the second dose. However, the EAG notes that company's model was set to administer a total of 60 mg of dexamethasone, which differs from their explanation provided above." Section 4.4.2, Page 149, states:	Please amend this wording as follows: "The company's response to clarification question B28 states that: "the cost of 10 mg dexamethasone has been multiplied by three in the model to account for the full cost of dexamethasone comedication (30 mg total)." This is described as being in accordance with the SmPC recommending 20 mg dexamethasone for the first dose and 10 mg for the second dose. **~~However,~~ T**he EAG notes that company's model was set to administer a total of 60 mg of dexamethasone **(30 mg per week for two weeks)~~, which differs from their explanation provided above~~**. The wording from Page 149 can therefore be deleted.	The response provided by the company at Clarification Questions is an accurate representation of how dexamethasone costing is modelled *per week* (i.e., per treatment cycle). In total, 60 mg is applied across the full induction period (30 mg per week for two out of four weeks). As such, it is inaccurate to state that the model and Company response conflict. In addition, the model was previously already programmed to account for a dexamethasone dose of 30 mg in the first treatment cycle, so it is inaccurate for the EAG to note this as an amendment made and/or as an error to be corrected. This wording should be deleted, and any associated	The EAG's approach to costing dexamethasone is consistent with Table 5 of the SmPC which states that dexamethasone is required for doses given on Week 1 Day 1 and Week 1 Day 2 (20 mg and 10 mg respectively). It is optional thereafter. The company's induction period is four weeks, and it states that it has assumed 30 mg per week across two out of the four weeks. However, dexamethasone is not required in the SmPC beyond the first week. Therefore, the EAG believes its approach is correct. It also notes that this issue is unlikely to have a significant impact

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
"The dose of dexamethasone was changed from 60 mg to 30 mg during the first treatment cycle."		adjustment to the model removed.	on the cost-effectiveness estimates.
Section 4.2.4.4 (iii), Page 126, states: "Subsequent treatments are categorised into second-line and third-line therapies… The proportion of patients receiving second-line therapy, as opposed to best supportive care, was derived from an analysis of MARIPOSA, while the estimates for patients on the third-line treatment came from MARIPOSA-2 data." Similar wording is presented in Table 51 (Page 127), Table 52 (Page 128), Table 53 (Page 129) and elsewhere in Section 4.2.4.4 (iii).	Please amend this wording as follows: "Subsequent treatments are categorised into second-line and third-line **and beyond** therapies… The proportion of patients receiving second-line therapy, as opposed to best supportive care, was derived from an analysis of MARIPOSA, while the estimates for patients on the third-line **and beyond** treatment came from MARIPOSA-2 data"	Subsequent treatments are defined for patients receiving 2L or 3L**+** treatment. This should be edited for clarity at each usage.	Amended as suggested.
Section 4.2.7, Page 133, states: "The scatter plot (Figure 35) **provided by the company** showed that all PSA iterations resulted in lower costs for	Please amend this wording as follows: "The scatter plot (Figure 35) **generated by the EAG probabilistic analyses** ~~**provided by the company**~~	The presented Figure 35 was generated by the EAG, as noted in the figure footnote.	Amended to say, "… generated by the EAG running the probabilistic analysis for the company's base-case,…."

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
amivantamab with lazertinib versus osimertinib…"	showed that all PSA iterations resulted in lower costs for amivantamab with lazertinib versus osimertinib…"		
Section 4.3.3.3, Page 142, refers to four formulae, referred to as (1), (2), (3) and (4).	These formulae are not currently presented and should be added to the text.	These formulae have been omitted and their presentation is necessary for understanding of this section. However, as noted above, discussion of the potential underestimation of drug acquisition costs for amivantamab is based on a misunderstanding from the EAG, and thus should be removed from the report.	The EAG's concerns related to calculation of missed and reduced doses has been resolved by the additional explanation provided by the company in Appendix 1 and the additional Excel data sheets. As a result, Section 4.3.3.3 which previously described this issue has been removed, meaning that the text referred to here is no longer in the EAG report. Subsequent sections have been renumbered.
Section 4.3.3, Page 147, states: "The data provided in response to clarification question B21 suggest that approximately 44% of Grade ≤	Please amend the values presented in this sentence and in Table 62 as needed (including updating the average cost for VTE by grade	The Company are unclear how the EAG have derived the value of 44% of Grade ≤2 VTEs and 33% VTEs being PEs; this should	The source for these proportions is the company's response to B21 which states that for Grade ≤2 VTEs," *For*

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
2 VTEs are PEs when estimated across both arms. Therefore, the costs of diagnosis should be based on 66% of patients requiring a leg vein ultrasound (RD40Z) and 44% requiring a CTPA (RD21A)." These data are replicated in Table 62 in Section 4.3.3, Page 149. Table 62 in Section 4.3.3, Page 149, further states that for Grade ≥3 DVT and PE, the distribution is 33% and 77% respectively.	following such amendments), citing the source as relevant.	be specified, with reference to the source provided. In addition, the Company note that 44% and 66% for Grade ≤2 sum to 110%, as do 33% and 77% for Grade ≥3, so request the EAG review and clarify their calculations, as needed.	*amivantamab-lazertinib, [redacted] ([redacted]%) patients had PEs, and [redacted] ([redacted]%) patients had DVT. This breakdown is [redacted] ([redacted]%) and [redacted] ([redacted]%) for the osimertinib arm*." Therefore, the EAG calculated the % of Grade ≤2 VTE that were PE as: 44% = ([redacted]). Having reviewed this calculation, the EAG notes that the actual value should be: 45%=([redacted]). However, correcting this error resulted in an average cost for Grade ≤2 VTE that remained at £875 to the nearest pound, and identical incremental costs to the nearest pound for the EAG base-case analysis. Therefore, the EAG has updated the proportion to 45% in the report but results were not

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			updated due to the minimal impact. For Grade 3+ VTEs, the EAG estimate of 77% being PE was based on the [redacted] Grade 3+ DVTs for amivantamab-lazertinib and [redacted] Grade 3+ DVTs for osimertinib described in the company's response to B21. When combining these with the [redacted] and [redacted] Grade 3+ PEs described in EAG Table 13 this gives the proportion of Grade 3+ VTEs being PE as: 77% = ([redacted]. We hope this clarifies the calculation of this value sufficiently. The EAG acknowledges that not all VTE events are PE or DVT and therefore this calculation is only an approximation based on the ratio of the two most common forms of VTE.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			The EAG has corrected the values of 33% to 23% and 66% to 55% in Table 62 as these were indeed typos, with the cost calculation in Table 62 unaffected as it was driven by the % that are PE.

Issue 2 Data and Reporting Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1, Page 16, states: "The CS notes that median OS in the NCRAS 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts receiving first-line osimertinib (28.1 months and 26.2 months, respectively) was considerably lower than median OS in the population recruited to the FLAURA RCT (**38.9** months), which was the pivotal trial for first-line osimertinib use."	Please amend this as follows: "The CS notes that median OS in the NCRAS 'MARIPOSA-like' and 'MARIPOSA-expanded' cohorts receiving first-line osimertinib (28.1 months and 26.2 months, respectively) was considerably lower than median OS in the population recruited to the FLAURA RCT (**38.6** months), which was the pivotal trial for first-line osimertinib use."	The currently presented median OS for the FLAURA trial is inaccurate, per Ramalingam *et al.* 2020.	Typo corrected as suggested.
Section 3.2.1.1, Page 46, states: "Over [redacted] of patients had Stage IVA or Stage IVB cancer."	Please update this wording as follows: "**At diagnosis,** over [redacted] of patients **across all three treatment arms** had Stage IVA or Stage IVB cancer."	The Company understand that the EAG are referring to the proportion of patients across all three arms of the MARIPOSA trial who had Stage IVA or Stage IVB cancer at diagnosis. If this is the case, the value currently presented is incorrect (as per Section 4.4.2, Table 9 of the August 2023 DCO CSR) and should be updated. The timepoint (at diagnosis) and arms to which this refers should also be specified.	The EAG was referring to the proportion of patients at screening. The EAG has amended the text for clarity.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2.2, Page 53, states: "BICR-assessed median PFS showed an improvement of **7.1%** in the amivantamab with lazertinib"	This is incorrect; please update to 7.1 **months**.	This data point is incorrect as per Cho et al. NEJM 2024.	This has been amended
Section 3.2.2.2, Page 54, reports the difference in PFS (INV) between amivantamab with lazertinib and osimertinib at 12 months as 7%.	This is incorrect; please update to [redacted]	This data point is incorrect as per the CSR (DCO: 11th August 2023). In addition, confidentiality highlighting is required to ensure confidential information is not shared publicly.	This has been amended
Section 3.2.2.2, Page 60, states: "amivantamab with lazertinib had a median DOR that was [redacted] months longer than patients treated with osimertinib."	This is incorrect; please update to "approximately [redacted] months".	This data point is incorrect as per the CSR (DCO: 13th May 2024).	This information was originally reported in the CS Summary Doc A page 28. As requested this has now been amended.
Section 3.2.2.2, Page 60, states: "**More patients** in the amivantamab with lazertinib arm (**N=27**) received a third-	This is incorrect; please update as follows: "~~**More**~~ **A greater proportion of** patients in the amivantamab with lazertinib arm (~~**N=**~~27**%**) received a third-generation TKI than in the osimertinib arm (~~**N=**~~16**%**) whilst	These data points are incorrect as per Gadgeel *et al.* WCLC 2024. In addition, some wording changes are required.	This has been amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
generation TKI than in the osimertinib arm (**N=16**) whilst more patients in the osimertinib arm **(N=20**) received chemotherapy plus a VEGFi and IO than in the amivantamab with lazertinib arm (**N=12**)."	more patients in the osimertinib arm (~~**N=**~~20**%**) received chemotherapy plus a VEGFi and IO than in the amivantamab with lazertinib arm (~~**N=**~~12**%**)."		
Table 12, Section 3.3, Page 72, reports footnote c as "Data from 13th May 2024 DCO"; however, this is not applicable to row headers 'AEs leading to dose interruption of any study agent' and 'Related AEs to amivantamab'.	Please update the wording for footnote c as follows: "Excludes infusion related reactions" Please then create footnote d for "Data from 13th May 2024 DCO" and replace footnote c in the 'Grade ≥ 3 AEs' row for both treatment arms.	These footnotes have been incorrectly reported.	This has been amended
Table 13, Section 3.3, Page 73 column header '11th August 2023'.	Please amend as follows: "11th August 2023 **DCO; SAS'**	Additional wording is required to make this clear.	Additional text has been added
Table 13, Section 3.3, Page 73 column '11th August 2023'.	Please could NR be added for both treatment arms for the following rows: • Pneumonia • Cardiac disorders • Gastrointestinal disorders • General disorders and administration site conditions	These data were not reported for the August 2023 DCO, as per the CSR (DCO: 11th August 2023).	NR has been added

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	• Nervous system disorders • Vascular disorders Please also define NR as “not reported” in the abbreviations.		
Section 3.8, Page 79, states: “TEAEs resulting in treatment discontinuation were reported in 10% of patients on amivantamab with lazertinib and 3% of patients on osimertinib.”	Please could the source for these data be referenced.	It is unclear where these data are from.	Data are from Cho et al. NEJM 2024. Source reference has been added
Section 4.1.1, Page 81, states: “In addition, relevant conference proceedings (dating back to **2019** in the original SLR, with subsequent years covered in the search updates), HTA websites and other grey literature sources were searched.”	This is incorrect, please update to **2018**.	This date is incorrect as per the economic SLR report.	Amended as suggested.
Section 4.1.2, Page 82, states: “For example, no comment is made regarding the **24** published cost-effectiveness analyses that used a model	This is incorrect, please update to **25**.	This data point is incorrect as per the economic SLR report.	This change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
structure other than a partitioned survival model."			
Table 20, Section 4.2.4.1, Page 89, column 'Base-case value', row 'Body surface area (BSA), m^2'.	Please make it clearer that the number provided within the brackets is the standard deviation.	This should be updated to make the data clearer.	Table edited to add "(SD)" to the body surface area row.
Table 21, Section 4.2.4.2, Page 91, column 'BIC (rank)', row 'Log-normal', states: "[redacted]"	Please update this as follows: "[redacted]"	This data point is incorrect as per the October 2024 advisory board report.	This change has been made.
Table 21, Section 4.2.4.2, Page 91, column 'BIC (rank)', row 'Generalised gamma', states: "[redacted]"	Please update this as follows: "[redacted]"	This data point is incorrect as per the October 2024 advisory board report.	This change has been made.
Figure 9, Section 4.2.4.2, Page 93, caption states: "Hazard plot for amivantamab with lazertinib PFS (BICR) with standard parametric models (reproduced from **clarification response Figure 30**)"	Please update this as follows: "Hazard plot for amivantamab with lazertinib PFS (BICR) with standard parametric models (reproduced from ~~**clarification response**~~ **CS, Figure 25** ~~**30**~~)"	This cross-reference is incorrect.	This is not a factual inaccuracy. The company provided updated hazards plots in the clarification response to C4. It is these plots the EAG has reproduced in its report as the company indicated that these are correct and final and therefore supersede those provided in the CS. The EAG

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			therefore believes these cross references are correct and therefore no amendment has been made. This response also applies for Figures 13, 17, 21, 25, 29 and 33.
Figure 13, Section 4.2.4.2, Page 97, caption states: "Hazard plot for osimertinib PFS (BICR) with standard parametric models (reproduced from **clarification response Figure 31**)"	Please update this as follows: "Hazard plot for osimertinib PFS (BICR) with standard parametric models (reproduced from ~~**clarification response**~~ **CS, Figure 27 ~~31~~**)"	This cross-reference is incorrect.	The EAG believes these cross references are correct and therefore no amendment has been made. See response regarding Figure 9 for more details.
Figure 17, Section 4.2.4.2, Page 101, caption states: "Hazard plot for amivantamab with lazertinib OS with standard parametric models (reproduced from **clarification response, Figure 32**)"	Please update this as follows: "Hazard plot for amivantamab with lazertinib OS with standard parametric models (reproduced from ~~**clarification response**~~ **CS, Figure 30 ~~32~~**)"	This cross-reference is incorrect.	The EAG believes these cross references are correct and therefore no amendment has been made. See response regarding Figure 9 for more details.
Figure 21, Section 4.2.4.2, Page 105, caption states: "Hazard plot for osimertinib OS with standard parametric models (reproduced from	Please update this as follows: "Hazard plot for osimertinib OS with standard parametric models (reproduced from ~~**clarification response**~~ **CS, Figure 32 ~~33~~**)"	This cross-reference is incorrect.	The EAG believes these cross references are correct and therefore no amendment has been made. See response

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
clarification response Figure 33)"			regarding Figure 9 for more details.
Figure 25, Section 4.2.4.2, Page 109, caption states: "Hazard plot for amivantamab TTD with standard parametric models (reproduced from **clarification response Figure 34**)"	Please update this as follows: "Hazard plot for amivantamab TTD with standard parametric models (reproduced from ~~**clarification response**~~ **CS, Figure 35 ~~34~~**)"	This cross-reference is incorrect.	The EAG believes these cross references are correct and therefore no amendment has been made. See response regarding Figure 9 for more details.
Section 4.2.4.2, Page 110, states: "The 8-year TTD prediction from the company's preferred exponential model is **8.3%**."	Please update this as follows: "The 8-year TTD prediction from the company's preferred exponential model is **8.4**%."	This data point is incorrect as per the October 2024 advisory board report.	Amended as suggested.
Figure 29, Section 4.2.4.2, Page 113, caption states: "Hazard plot for lazertinib TTD with standard parametric models (reproduced from **clarification response Figure 35**)"	Please update this as follows: "Hazard plot for lazertinib TTD with standard parametric models (reproduced from ~~**clarification response**~~ **CS, Figure 37 ~~35~~**)"	This cross-reference is incorrect.	The EAG believes these cross references are correct and therefore no amendment has been made. See response regarding Figure 9 for more details.
Figure 33, Section 4.2.4.2, Page 117, caption states: "Hazard plot for osimertinib TTD with standard parametric models (reproduced from	Please update this as follows: "Hazard plot for osimertinib TTD with standard parametric models (reproduced	This cross-reference is incorrect.	The EAG believes these cross references are correct and therefore no amendment has been made. See response

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
clarification response Figure 36)"	from ~~**clarification response** **CS, Figure 39 36**~~)"		regarding Figure 9 for more details.
Table 46, Section 4.2.4.3, Page 120, caption states: "Disutility for adverse events (adapted from CS, **Table 51**)"	Please update this as follows: "Disutility for adverse events (adapted from CS, **Table 79** ~~**51**~~)"	This cross-reference is incorrect.	This change has been made.
Table 49, Section 4.2.4.4, Page 125, column 'Company's model submitted with the clarification response; PD', row 'ECG', states: "0"	Please update this as follows: "2.00"	This data point is incorrect as per the CEM submitted alongside the clarification questions response.	This change has been made.
Table 53, Section 4.2.4.4, Page 129, column 'Drug acquisition; Strength per unit (mg)', row 'docetaxel', states: "100"	Please update this as follows: "80"	This data point is incorrect as per the CEM submitted.	This change has been made.
Table 53, Section 4.2.4.4, Page 129, column 'Administration; unit cost', row 'osimertinib', states: "297.84"	Please update this as follows: "247.13"	This data point is incorrect as per the CEM submitted.	This change has been made.
Table 54, Section 4.2.4.4, Page 130, column 'First line; Amivantamab with lazertinib',	Please update this as follows: "430.54"	This data point is incorrect as per the CEM submitted.	This change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
row 'One-off costs for managing AEs (£)', states: "430.49"			
Table 54, Section 4.2.4.4, Page 130, column 'First line; Osimertinib', row 'One-off costs for managing AEs (£)', states: "79.05"	Please update this as follows: "79.06"	This data point is incorrect as per the CEM submitted.	This change has been made.
Table 58 in Section 4.2.9 presents incremental life years gained (LYGs) for the Company's deterministic scenario analyses	Please add a footnote to the "LYGs" heading, stating that the values presented are undiscounted.	This should be included for accuracy and clarity.	This change has been made.
Section 4.3.3, Page 145, states: "The company responded that they deemed it inappropriate to use treatment-specific utility because mean progression-free utility value of osimertinib when using this approach [redacted] is higher than…" This value is also presented in Table 44 in Section 4.2.4.3,	Wherever this number is presented, please update it to [redacted].	This data point is incorrect as per the value provided in response to Clarification Question B16.	The value presented on page 145 (now page 141) has been amended as this is the value referred to in the company's clarification response to B16 when making these comparisons. However, the EAG's preferred value for treatment-specific utility ([redacted]) reported in Table 44 (Section 4.2.4.3, page 118) and in Section 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 118, and in Section 5, Page 156.			(page 152) was derived using the coefficients provided in Table 1 of the company's clarification response to B17, and therefore, these values were not amended. This value is now also quoted on page 141 to make it clear which value the EAG prefers. Additional details have also been added to make it clear that the [redacted] value comes from approach 2.
Section 4.3.3, Page 145, states: "The estimated progression-free health-state utility for osimertinib was **0.803**, as presented in the committee papers for TA654."	Please update this as follows: "The estimated progression-free health-state utility for osimertinib was **0.794**, as presented in the committee papers for TA654."	This data point is incorrect as per the committee papers for TA654.	The EAG is referring to the value in Table 48 on page 139 of the CS for TA621/ID1302, which is available as part of historical documents under the committee papers for TA654, which was the review of TA621. The value of 0.803 appears in the row labelled "Progression-free osimertinib" in the Table headed "HSU values from mapped FLAURA values

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			(post-baseline)." To make the source clearer, the EAG has amended it to say, "The estimated progression-free health-state utility in the osimertinib arm of the FLAURA trial was 0.803 as presented in TA621 (TA654 was the review of TA621)"
Section 4.3.3, Page 145, states: "The draft SmPC for amivantamab describes an infusion rate of 125 mL/hr from **week 5 onwards** which would require a minimum of 2 hours to administer the 250 mL infusion volume recommended."	Please update this as follows: "The draft SmPC for amivantamab describes an infusion rate of 125 mL/hr from **week 4 onwards** which would require a minimum of 2 hours to administer the 250 mL infusion volume recommended."	This data point is incorrect as per the infusion rates for amivantamab every 2 weeks outlined in the SmPC. Please also remove CIC highlighting as this is not required given this is now publicly available information.	The EAG has amended as suggested and has lifted the CIC marking.
Section 4.3.3.7, Page 147, states: "This would increase the cost of a Grade ≥ 3 PEs from £664 (the EAG's estimate from **Table 58**) to £819."	Please could this be updated as follows: "This would increase the cost of a Grade ≥ 3 PEs from £664 (the EAG's estimate from **Table 60**) to £819."	This cross-reference is incorrect.	Amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 62, Section 4.3.3, Page 149, column 'Resource use category' states: "Short stay admission for PE (see EAG's estimate **Table 24**)"	Please could this be updated as follows: "Short stay admission for PE (see EAG's estimate **Table 60**)"	This cross-reference is incorrect.	This change has been made.
Section 4.4.2, Page 151, states: "The EAG's alternative distributions provide a lower 10-year survival prediction for amivantamab with lazertinib (**12%** one-knot hazard model versus 15% for Weibull) and a higher prediction for osimertinib (**6.3%** for gamma versus 3.1% for Weibull) than the company's preferred Weibull distributions."	Please could this be updated as follows: "The EAG's alternative distributions provide a lower 10-year survival prediction for amivantamab with lazertinib (**11% for** one-knot hazard model versus 15% for Weibull) and a higher prediction for osimertinib (**6.4**% for gamma versus **3.2**% for Weibull) than the company's preferred Weibull distributions."	These data are incorrect as per the CEM submitted.	The EAG has double checked the post-clarification version of the model and only the first value highlighted by the company was incorrect. This single value of 10.4% for the one-knot hazard has been amended.

Issue 3 Minor Typographical and Grammatical Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1, Page 17, states: "Histological classification can also be used to describe **NSCLS** as either squamous-cell carcinoma,	Please amend as follows: "Histological classification can also be used to describe **NSCLC** as either squamous-cell carcinoma,	This is a minor typographical error.	This change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
adenocarcinoma or large-cell carcinoma, with adenocarcinoma being the most common form across all lung cancers."	adenocarcinoma or large-cell carcinoma, with adenocarcinoma being the most common form across all lung cancers."		
Section 3.1.2, Page 36, states: "This is slightly different to the NICE scope, which states that the population for the appraisal relates to people with untreated advanced NSCLC which has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation **and was restricted only to adult patients. The EAG acknowledges that restricting the population to adults is reasonable**."	Please amend as follows: "This is slightly different to the NICE scope, which states that the population for the appraisal relates to people with untreated advanced NSCLC which has an EGFR exon 19 deletion or exon 21 (L858R) substitution mutation. **The CS restricted this to adult patients only, which the EAG acknowledged was reasonable**."	The current wording suggests that the NICE scope restricted the population to adults only, which is incorrect; this restriction was applied by the Company in alignment with the amivantamab-lazertinib licensed indication, and with the MARIPOSA trial.	The text has been amended
Section 3.1.4, Page 38, states: "The company's PRISMA flow diagram (CS, Appendix D, **page 21**, Figure 1) was for the broader global SLR and **was** difficult to follow."	Please amend as follows: "The company's PRISMA flow diagram (CS, Appendix D, **page 48**, Figure 1) was for the broader global SLR and **the EAG found it ~~was~~** difficult to follow."	The PRISMA being difficult to follow represents the opinion of the EAG, so the wording should be updated to reflect this. The minor typographical error in the referenced page number should also be corrected.	This has been changed
Section 3.2.1.1, Page 45, states: "However, Black patients were underrepresented and comprised only **1% of the cohort**."	Please amend as follows: "However, Black patients were underrepresented and comprised only **1% of patients in the amivantamab-**	Black patients represented 2% of the lazertinib monotherapy arm, so the trial arms being referred to here should be	Although not a factual error, the EAG has amended the text for clarity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	lazertinib and osimertinib arms ~~the cohort~~."	clarified to prevent misinterpretation.	
Section 3.2.2.2, Page 60, states: "Median PFS2 was 32.4 months (**95% CI;29.3 months to NE)** in the osimertinib arm and not estimable in the amivantamab with lazertinib arm **(NE 95% CI; 36.0 months to NE)."**	Please amend as follows: "Median PFS2 was 32.4 months (**95% CI: 29.3, ~~months~~ ~~to~~** NE) in the osimertinib arm and not estimable in the amivantamab with lazertinib arm **(~~NE~~ 95% CI: 36.0, ~~to~~ NE)**."	This is a minor typographical error.	This change has been made
Table 9, Section 3.2.2.2, Page 62 has two extra blank rows either side of the "TTST: time to subsequent systemic anti-cancer therapy" row.	Please remove these blank rows.	This is a minor formatting error	Blank rows have been removed
Table 10, Section 3.2.2.2, Page 66, row 'iORR based on RECIST v1.1 criteria in patients with intracranial disease at baseline by **BICR-(13th** May 2024 DCO; FAS)'.	Please amend as follows: "iORR based on RECIST v1.1 criteria in patients with intracranial disease at baseline by **BICR (13th** May 2024 DCO; FAS)"	This is a minor typographical error.	This change has been made.
Section 3.3, Page 72 states: "These included (amivantamab with lazertinib versus osimertinib): rash (16.4% versus 0.7%); paronychia (11.4% versus 0.5%); dermatitis acneiform (9% versus 0%); IRR (6.4% versus 0%);	Please amend as follows: "These included (amivantamab with lazertinib versus osimertinib): rash (16.4% versus 0.7%); paronychia (11.4% versus 0.5%); dermatitis acneiform (9% versus 0%); IRR (6.4% versus 0%); pulmonary embolism	This is a minor typographical error.	This change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
pulmonary embolism (8.6% versus 2.8%) and hypoalbuminemia (5.7% versus **0%)The EAG** notes that as expected, the number of AE slightly increased in both treatment arms at the later DCO."	(8.6% versus 2.8%) and hypoalbuminemia (5.7% versus **0%). The EAG** notes that as expected, the number of AE slightly increased in both treatment arms at the later DCO."		
Section 3.8, Page 79, states: "amivantamab with lazertinib demonstrated a statistically significant improvement in PFS compared to osimertinib (HR 0.70**; CI: 0.58**, 0.85; p<0.001)."	Please amend as follows: "amivantamab with lazertinib demonstrated a statistically significant improvement in PFS compared to osimertinib (HR 0.70**; 95% CI: 0.58**, 0.85; p<0.001)."	This is a minor typographical error.	This change has been made.
Table 19, Section 4.2.4, Page 88, "Health state costs" row, states: "Cost for infusion related reaction – costs in TA651, inflated to 2021/22 **preces** using the NHS Cost Inflation Index…"	Please amend as follows: "Cost for infusion related reaction – costs in TA651, inflated to 2021/22 **prices** using the NHS Cost Inflation Index…"	This is a minor typographical error.	This change has been made.
Section 4.2.4.2, Page 89, states: "Seven standard parametric models were considered including exponential, gamma, Gompertz, log-logistic, log-normal, Weibull, gamma, and generalised gamma distributions."	Please amend as follows: "Seven standard parametric models were considered including exponential, ~~**gamma,**~~ Gompertz, log-logistic, log-normal, Weibull, gamma, and generalised gamma distributions."	Gamma had previously been written twice; this is a minor typographical error.	This change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.3.3.4, Page 143, states: "Therefore, the EAG considers that the differences in utilities showing in Figure 37 are unlikely to be explained by AEs that occur mostly at the start of treatment and resolve **whin** [redacted] days."	Please amend as follows: "Therefore, the EAG considers that the differences in utilities showing in Figure 37 are unlikely to be explained by AEs that occur mostly at the start of treatment and resolve **within** [redacted] days"	This is a minor typographical error.	This change has been made.

Issue 4 Confidentiality Highlighting Errors

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
• Table 3 in Section 2.3, row "Population", Page 23 • Section 2.3.2, Page 29 • Section 3.1.2, Page 35 • Table 17, Section 4.2, Page 82 • Section 4.2.1, Page 82	The license indication for amivantamab-lazertinib is marked as confidential.	Since the original CS, amivantamab-lazertinib received marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA) on 5th March 2025 for the 1L treatment of advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.[2] As such, all confidentiality highlighting related to the marketing authorisation wording can now be lifted.	Confidential marking removed as requested.
Section 3.2.2.2, Page 51, reports the median duration of follow-up across both treatment arms [redacted] months.	Please can this be reported as: 31.1 months	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.
Section 3.2.2.2, Page 54, reports the difference in PFS (BICR) between amivantamab with lazertinib and osimertinib at 12 months as [redacted]	Please can this be reported as: 8%	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3.2.2.2, Page 54, reports the difference in PFS (BICR) between amivantamab with lazertinib and osimertinib at 24 months as [redacted]	Please can this be reported as: 14%	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.
Section 3.2.2.2, Page 54, reports the difference in PFS (INV) between amivantamab with lazertinib and osimertinib at 24 months.	Please can this be reported as: [redacted]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	This change has been made.
Section 3.2.2.2, Page 56, reports the total number of patients that have died in the osimertinib arm as [redacted]	Please can this be reported as: [redacted]429	Confidentiality highlighting is not required for the total number of patients in the treatment arm as this is publicly available information.	This change has been made.
Section 3.2.2.2, Page 56, reports the HR; 95% CI and p-value as ([redacted]).	Please can this be reported as: (HR: 0.77; 95% CI: 0.61, 0.96; p=0.019)	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.
Section 3.2.2.2, Page 64, provides commentary on the number of patients in the amivantamab with lazertinib arm who had BICR-assessed intracranial disease progression or had died, compared with those in the osimertinib arm.	Please can this be reported as: [redacted]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	This change has been made.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Section 3.2.2.2, Page 65, reports the proportions of patients in the amivantamab-lazertinib and osimertinib arms that achieved an intracranial PR.	Please can this be reported as: [redacted] and [redacted]	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	This change has been made.
Table 10, Section 3.2.2.2, Page 66, column 'Amivantamab with lazertinib (N=429)', row 'Median (95% CI)'.	Please can this be reported as: 24.9 (20.1, 34.7)	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.
Table 10, Section 3.2.2.2, Page 66, column 'Osimertinib (N=429)', row 'Median (95% CI)'.	Please can this be reported as: 22.2 (18.4, 26.1)	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.
Table 10, Section 3.2.2.2, Page 66, column 'Amivantamab with lazertinib (N=429)', row '24-month event-free rate (95% CI)'.	Please can this be reported as: 0.51 [redacted]	Confidentiality highlighting on the event-free rate is not required as this is publicly available information.	This change has been made.
Table 10, Section 3.2.2.2, Page 66, column 'Osimertinib (N=429)', row '24-month event-free rate (95% CI)'.	Please can this be reported as: 0.48 [redacted]	Confidentiality highlighting on the event-free rate is not required as this is publicly available information.	This change has been made.
Table 10, Section 3.2.2.2, Page 66, column 'Amivantamab with lazertinib (N=429)', row '36-month event-free rate (95% CI)'.	Please can this be reported as: 0.38 [redacted]	Confidentiality highlighting on the event-free rate is not required as this is publicly available information.	This change has been made.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 10, Section 3.2.2.2, Page 66, column 'Osimertinib (N=429)', row '36-month event-free rate (95% CI)'.	Please can this be reported as: 0.18 [redacted]	Confidentiality highlighting on the event-free rate is not required as this is publicly available information.	This change has been made.
Table 10, Section 3.2.2.2, Page 66, row 'p-value'.	Please can this be reported as: 0.165	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.
Table 10, Section 3.2.2.2, Page 66, row 'HR (95% CI)'.	Please can this be reported as: 0.82 (0.62, 1.09)	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.
Section 3.2.2.2, Page 68 discusses the difference in scores between three PRO measures	Please can this be reported as: "There was [redacted] in the scores between the three PRO measures and overall scores were [redacted] in the osimertinib arm than the amivantamab with lazertinib arm at start of Q2W dosing schedule and end of treatment."	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	This change has been made.
Table 13, Section 3.3, Page 73, column '11th August 2023', both treatment arms.	Please can the following data be unredacted: • Patients with 1 or more Grade ≥ 3 AEs • Rash • Dermatitis acneiform	Confidentiality highlighting is not required as this is publicly available information.	This change has been made.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	• Paronychia • Pulmonary embolism • Hypoalbuminaemia • Alanine aminotransferase increased • IRR		
Section 3.3, Page 74, discusses the proportion of rash events leading to discontinuations in each of the study treatment arms.	Please can this be reported as: "Rash events leading to discontinuation of any study treatment occurred in [redacted] of participants in the amivantamab with lazertinib arm (amivantamab discontinuation: [redacted] patients; lazertinib discontinuation: [redacted] patients) compared with [redacted] patients in the osimertinib arm."	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	This change has been made.
Section 3.3, Page 74, reports the proportion of VTE AEs in each treatment arm that occurred within the first four months of treatment.	Please can this be reported as: "Among the VTE AEs, [redacted] of events occurred in the first four months of treatment compared with [redacted] in the osimertinib group."	Confidentiality highlighting is required to ensure confidential information is not shared publicly.	This change has been made.
Table 45, Section 4.2.4.3, Page 120, column 'QALY loss; Scenario analysis'.	Please can the QALY losses associated with the following AEs be unredacted *in the scenario analysis column only*: • Hypoalbuminaemia • Pulmonary embolism	Confidentiality highlighting is not required as this is publicly available information.	This change has been made as requested by the company.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
	• Pneumonia • VTE		

Appendix A: Further explanation of missed dose calculations

As outlined in response to Clarification Question B.23 and illustrated in **Figure *1*** provided below (based on the May 2024 DCO), the correction of acquisition and administration costs of amivantamab to account for the proportion of missed doses was based on a ratio of administered doses to the expected number of doses for each patient based on their duration of treatment—that is, the number of doses (infusions) received in the trial was divided by the number of doses (infusions) that theoretically should have been received based on the time on treatment in the trial (time to treatment discontinuation [TTD]). Further explanation of this calculation, including an example calculation, is provided in the reference pack submitted alongside this document.

In addition to, and separate from this adjustment for missed doses, a correction was applied to incorporate dose reductions, which is necessary to account for the fact that dose modifications could occur in the course of treatment. This was calculated as a ratio of the total cumulative amivantamab dose that was prepared for injections to be administered in the trial to the total cumulative amivantamab dose that would have been prepared if there had been no dose modifications; i.e. if a patient had a missed dose, this dose would not be counted in the dose reduction calculation as it was never administered and therefore not included in the total cumulative dose amount for amivantamab. For a patient with baseline weight below 80 kg, the total cumulative dose that would have been prepared if there had been no dose modifications was calculated as 350 mg (cycle 1 day 1) plus 700 mg (cycle 1 day 2, if the patient had received it) plus 1,050 mg times the number of infusions received by that patient from cycle 1 day 8 onwards. For a patient with baseline weight equal to or higher than 80 kg, the same quantity was calculation as 350 mg (cycle 1 day 1) plus 1,050 mg (cycle 1 day 2, if the patient had received it) plus 1,400 mg times the number of infusions received by that patient from cycle 1 day 8 onwards.

Therefore, these calculations adjust for two different ways in which the actual amivantamab dose received by patients differed from what a strict dosing scheduled assumed in the economic model would predict; this does not represent double-counting of any missed doses.

As such, wording relating to this issue should be removed throughout the report. Likewise, adjustment for it in the EAG preferred base case should be removed.

Figure 1: Calculation of missed doses and dose reductions in MARIPOSA

TTTD: time to treatment discontinuation

References

1. Johnson & Johnson Data on File. MARIPOSA Clinical Study Report. DCO: 13 May 2024.
2. Medicines & Healthcare Products Regulatory Agency. Amivantamab Summary of Product Characteristics. Available at: https://mhraproducts4853.blob.core.windows.net/docs/2651997e28fed1931541e4899ce091c8e225362b [Accessed: January 2025].