Medicinrådet

Bilag til Medicinrådets vurdering af amivantamab i kombination med lazertinib til førstelinjebehandling af patienter med fremskreden EGFR-muteret ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. amivantamab i kombination med lazertinib
2. Forhandlingsnotat fra Amgros vedr. amivantamab i kombination med lazertinib
3. Ansøgers endelige ansøgning vedr. amivantamab i kombination med lazertinib

Johnson&Johnson

Janssen-Cilag A/S
jnj.com

23. januar 2026

Til Medicinrådet

Vedr. tilbagemelding på Medicinrådets udkast til vurdering af amivantamab (Rybrevant) i komb. med lazertinib (Lazcluze) som førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungecancer (NSCLC) med EGFR exon 19-deletioner eller exon 21 L858R-substitutionsmutationer.

Johnson & Johnson takker for udkast til vurderingen af amivantamab (Rybrevant) i komb. med lazertinib (Lazcluze) som førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungecancer (NSCLC). Vurderingen tager udgangspunkt i MARIPOSA studiet, som er et H2H studie, med 37.8 måneders opfølgningstid og en patientpopulation som Medicinrådet også vurderer som repræsentativ for en dansk patient population. Vurderingen viser samlet set, at ami-laz medfører forbedringer i både PFS og OS sammenlignet med nuværende standardbehandling, i overensstemmelse med det indsendte evidensgrundlag.

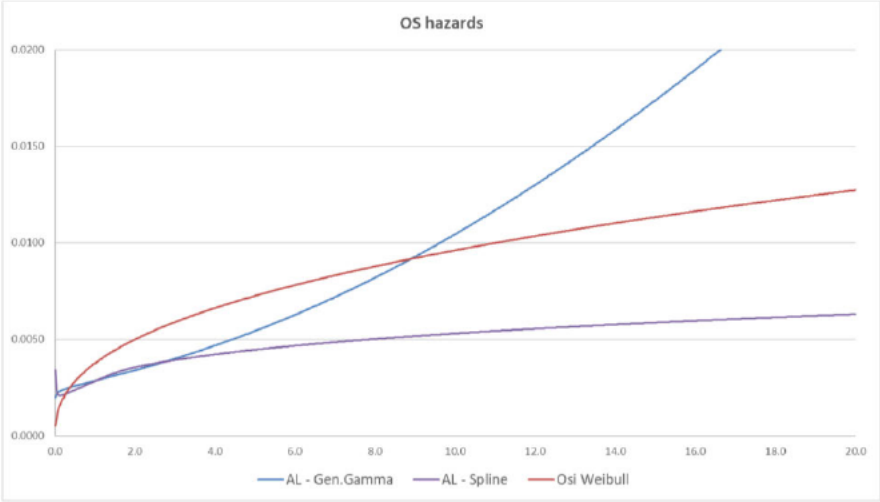
Med udgangspunkt i vurderingsrapporten vil vi gerne bidrage med følgende perspektiver:
Selv om der i vurderingen anerkendes de kliniske fordele ved behandling med ami-laz, **fremstår flere af de sundhedsøkonomiske antagelser som meget konservative, særligt valget af OS-kurve, hvilket resulterer i en fordobling af ICER sammenlignet med vores indsendte base case. Tilgangen afviger desuden fra vurderinger i andre europæiske lande.** NOMA (Norge) estimerer en dobbelt så høj QALY- og livstidsgevinst baseret på samme datagrundlag og komparator. NOMA anvender de samme overlevelseskurver som i vores base case. **Tilsvarende bygger NICE's vurdering af omkostningseffektivitet vs. osimertinib med kemoterapi på kurver i tråd med vores base case og er ligeledes også informeret af klinisk ekspertvurdering**. **De faglige begrundelser for de valgte antagelser i Medicinrådets rapport (sundhedsøkonomisk metode, statistiske overvejelser og overførbarhed) fremgår ikke tilstrækkeligt tydeligt**. Vi har derfor søgt afklaring gennem dialog med Medicinrådet, men har endnu ikke fået svar på, om antagelserne forventes justeret eller yderligere fagligt uddybet i den endelige vurdering.
Det undrer vi os over, og vi er bekymret om at der er sket en fejl, da det udover at være fagligt svært at gennemskue også er meget langt fra den dialog som vi har haft med danske lungeonkologer og HTA-myndigheder i andre europæiske lande.
J&Js primære faglige undren og bekymring i Medicinrådets-valg af OS kurve:

- Medicinrådet har kun ændret OS kurven for ami-laz men ikke for komparator og har valgt en kurve med et dårligere statistisk fit
- **I valget af kurve (gen. gamma) antyder Medicinrådet at risikoen for at dø stiger kraftigt over tid for ami-laz men at den flader ud og er lavere for standard behandling. Det mangler både faglige argumenter og klinisk plausibilitet at en behandling med så meget bedre overlevelse skulle have en stigende mortalitets hazard vs. standardbehandling. NOMA nævner også dette i deres rapport som årsag til at denne kurve ikke er klinisk plausibel, og skriver følgende: "*Tilsvarende anses ekstrapolasjoner med generalisert gamma som for pessimistiske, og DMP finner det ikke plausibelt at dødshasarden er***

høyere i intervensjonsarmen enn i komparatorarmen over tid *(link til fuld rapport nederst)*."

- Medicinrådets valg af kurve halverer forskellen i QALY og leveår og har derfor stor betydning for resultatet.

Se graf af Medicinrådets-valg af OZ hazard for de to behandlinger, hvor rød er standardbehandling og blå er ami-laz, (den lilla er Medicinrådets sensitivitetsanalyse hvor ICER er omkring 1 mio lavere). I Johnson & Johnsons indsendte base case valgte vi samme distribution som osimertinib dvs. Weibull.



Vi anerkender at Medicinrådet i nogle tilfælde må indføre større usikkerhed i modellerne, hvilket kan påvirke ICER væsentligt - f.eks. ved små patientpopulationer, indirekte sammenligninger eller kort opfølgningstid. I den foreliggende ansøgning foreligger imidlertid et head-to-head studie, med lang opfølgning og overførbarhed til dansk klinisk praksis. Derudover har vi at gøre med en behandling som forlænger patienternes gennemsnitlige overlevelse med minimum 8 måneder (i Medicinrådets egen analyse, i vores og NOMAs er den ca. 1 år).
Kombinationsbehandlinger påvirker sikkerhedsprofilen, men den vurderes som håndterbar og forbedret på baggrund af gennemførte sikkerhedsstudier med et veletableret profylaktisk regime.
NICE vurderer - på trods af usikkerhed ved indirekte sammenligning -, at ami-laz som en kombinationsbehandling muligvis har en bedre sikkerhedsprofil end osimertinib i kombination med kemoterapi, og har anbefalet ami-laz til den fulde population, som en omkostnings-effektiv behandling (komparator: osimertinib + kemoterapi).

Vi henleder Rådets opmærksomhed på vigtigheden af at lægge ovenstående til grund for at sikre et balanceret og fagligt robust beslutningsgrundlag, til grund for beslutning om anbefaling og understøttelse af et bredere behandlingsudbud. [redacted]

Andre vurderingsrapporter som vi referer til:
Norge:
https://www.nyemetoder.no/48f3c8/contentassets/aac1225ce06c47b5bc928472324d64ce/id2025_006_amivantamab-lazertinib_rybrevant-lazcluze_ikke-smacellet-lungekreft-nsclc---metodevurdering---offentlig-versjon.pdf
UK: https://www.nice.org.uk/guidance/gid-ta11279/documents/674

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03.02.2026

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.02.2026
Leverandør	Johnson & Johnson
Lægemiddel	Rybrevant (amivantamab) i kombination med Lazcluze (lazertinib)
Ansøgt indikation	Amivantamab i kombination med lazertinib til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft med EGFR exon 19-deletioner eller exon 21 L858R-substitutionsmutationer.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende priser på Rybrevant (amivantamab) og Lazcluze (lazertinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Lazcluze	80 mg (56 stk.), tabl.	36.012,98	[redacted]	[redacted]	[redacted]	[redacted]
Lazcluze	240 mg (28 stk.), tabl.	36.012,98	[redacted]	[redacted]	[redacted]	[redacted]
Rybrevant	350 mg (1 stk.), i.v	9.184,59	[redacted]	[redacted]	[redacted]	[redacted]
Rybrevant	1.600 mg (1 stk.), s.c.	28.144,80	[redacted]	[redacted]	[redacted]	[redacted]

Rybrevant	2.240 mg (1 stk.), s.c.	39.402,72	[redacted]	[redacted]	[redacted]	[redacted]

Prisen på Rybrevant er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Rybrevant, indkøbes Rybrevant 350 mg (1 stk.) i.v. til nuværende SAIP og Rybrevant 1.600 mg (1 stk.) s.c. og 2.240 mg (1 stk.) s.c til AIP.

Prisen på Lazcluze er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Lazcluze, indkøbes lægemidlet til AIP.

Aftaleforhold

[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Tagrisso (osimertinib) monoterapi er i dag førstevalg til patientpopulationen.

[redacted]

Tabel 2 viser de samlede lægemiddeludgifter til et behandlingsforløb for hhv. Tagrisso monoterapi, Tagrisso i kombination med pemetrexed + kemoterapi og Rybrevant i kombination med Lazcluze. Bemærk at behandlingslængderne er forskellige mellem de tre behandlingsalternativer. Behandling med både Tagrisso og Lazcluze kan fortsætte efter regression, en del af behandlingen vil derfor foregå som monoterapi, dvs. uden hhv. pemetrexed + kemoterapi og Rybrevant, jf. Medicinrådets vurdering af hhv. *osimertinib i kombination med pemetrexed og platin-baseret kemoterapi til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft* og *amivantamab i kombination med lazertinib til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft*.

Behandlingsvarighederne er oplyst af Medicinrådet, og forbundet med usikkerhed.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for et behandlingsforløb

Behandling	Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Tagrisso monoterapi	Tagrisso	80 mg (30 stk.)	80 mg dagligt, oralt Behandlingsvarighed: [redacted]	[redacted]	[redacted]
Tagrisso kombinationsbehandling	Tagrisso	80 mg (30 stk.)	80 mg dagligt, oral Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Pemetrexed "Ever Pharma"	25 mg (20 ml)	500 mg/m^2* hver 3. uge, i.v. Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Carboplatin "Fresenius Kabi"	10 mg/ml (45 ml)	400 mg/m^2*, hver 3. uge i 4 serier, i.v. Behandlingsvarighed: [redacted].	[redacted]	[redacted]
	Tagrisso i kombination med pemetrexed og carboplatin				[redacted]
Rybrevant + Lazcluze	Lazcluze	240 mg (28 stk.)	240 mg dagligt, oral Behandlingsvarighed: [redacted]	[redacted]	[redacted]
	Rybrevant	350 mg (1 stk.)**	*Under 80 kg:* Uge 1-4: 1.050 mg ugentlig, i.v. Derefter: 1.050 mg hver 2. uge, i.v. *80 kg eller over:* Uge 1-4: 1.400 mg ugentlig, i.v. Derefter: 1.400 mg hver 2. uge, i.v. Behandlingsvarighed: [redacted]	[redacted]	[redacted] [redacted]
	Rybrevant i kombination med Lazcluze *Under 80 kg:* *80 kg eller over:*				[redacted] [redacted] [redacted]

*BSA =1,84, jf. Medicinrådets vurdering af osimertinib i kombination med pemetrexed og platin-baseret kemoterapi til førstelinjebehandling af voksne patienter med fremskreden ikke-småcellet lungekræft

**Der er en lille prisforskel mellem i.v. og s.c. formulering på Rybrevant, men det ligger i samme prisleje.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
England	Anbefalet	Link til vurdering
Sverige	Ikke vurderet	

Opsummering

[redacted]

[redacted]

Application for the assessment of Rybrevant® in combination with Lazcluze® for first-line treatment of adult patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations

Colour scheme for text highlighting	
Colour of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of colour-coded]

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Tables and Figures

Tables

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criterion
ARR	Administration-related reaction
BIC	Bayesian information criterion
BICR	Blinded independent central review
CEM	Cost-effectiveness model
CI	Confidence interval
CT	Computed tomography
DKK	Danish Krone
DMC	Danish Medicines Council / Medicinrådet
DRG	Diagnosis-related group
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire
ErbB2	Erythroblastic oncogene B

EQ-VAS	EuroQol Visual Analogue Scale
EQ-5D-3L/5L	EuroQol five-dimensional questionnaire, either three level or five level version
ESMO	European Society for Medical Oncology
ESCAT	ESMO Scale for Clinical Actionability of molecular Targets
EU	European Union
ex19del	Exon 19 deletions
Fc	Fragment crystallisable
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IO	Immuno-oncology drug
IRR	Infusion-related reaction
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
IV	Intravenous
L	Line (of treatment)
L858R	Exon 21 leucine-858 to arginine
MET	Mesenchymal-epidermal transition
MMRM	Mixed model for repeated measures
NE	Not estimable
NICE	National Institute for Health and Care Excellence
NGS	Next generation sequencing
NSCLC	Non-small cell lung cancer

NSCLC-SAQ	Non-Small Cell Lung Cancer Symptom Assessment Questionnaire
ORR	Overall response rate
OS	Overall survival
OWSA	One-way sensitivity analysis
PRO	Patient-reported outcome
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
Q2W	Every two weeks
Q4W	Every four weeks
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised control trial
RDI	Relative dose intensity
RECIST	Response evaluation criteria in solid tumours
SC	Subcutaneous
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
TEAE	Treatment emergent adverse event
TTDD	Time to treatment discontinuation or death
TKI	Tyrosine kinase inhibitors
T790M	Secondary point mutation in the EGFR tyrosine kinase domain that substitutes methionine for threonine at amino acid position 790
UK	United Kingdom

VBA	Visual Basic for Applications
VEGFi	Vascular endothelial growth factor inhibitor
VTE	Venous thromboembolism

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Rybrevant /Lazcluze
Generic name	Amivantamab / Lazertinib
Therapeutic indication as defined by EMA	Amivantamab in combination with lazertinib for 1L treatment of adult patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.
Marketing authorization holder in Denmark	Janssen-Cilag A/S
ATC code	L01FX18 + L01EB09
Combination therapy and/or co-medication	Yes, combination of Rybrevant and Lazertinib
(Expected) Date of EC approval	30 December 2024 + amivantamab SC Q4W Q1 2026
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	In addition to the treatment combination in scope, amivantamab is also indicated: • In combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR ex19del or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI.

Overview of the medicine	
	• In combination with carboplatin and pemetrexed for the 1L 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. Lazertinib has no previous approved indications.
Other indications that have been evaluated by the DMC (yes/no)	Yes (amivantamab, patients with EGFR exon 20ins-positive NSCLC after failure of platinum-based chemotherapy as well as 1L treatment of patients with EGFR exon 20ins-positive NSCLC in combination with chemotherapy) No (lazertinib)
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes Is the product suitable for a joint Nordic assessment? No If no, why not? Combination products are treated differently across the Nordics, e.g. lazertinib will be applied for through the prescription pathway through TLV in Sweden, whereas the combination (amivantamab) is in the clinic drug pathway. In addition, separate agreements are already in discussion in each of the markets for the combination drug.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Lazertinib: 80 mg and 240 mg film-coated tablets. Units per pack is 60 and 30 respectively. Amivantamab: 1 vial of 350 mg per pack

2. Summary table

Summary	
Indication relevant for the assessment	1L treatment of adult patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.
Dosage regiment and administration	Lazertinib is administrated orally as tablet once a day, 240 mg. Amivantamab is administrated intravenously (IV) and based on body weight: 1050 milligram (mg) for body weight less than (<) 80 kilogram (kg) and 1400 mg for body weight greater than or equal to (>=) 80 kg in 28-day cycles: once weekly in Cycle 1 (with a split dose on Days 1-2), and then every 2 weeks in subsequent cycles. The IV administration form of amivantamab comprises the base case of this application. Amivantamab is also available as a subcutaneous (SC) administration for dosing every two weeks

Summary	
	(Q2W) and every four weeks (Q4W) is expected in Q1 2026. A scenario analysis of amivantamab SC Q4W is included.
Choice of comparator	Osimertinib, administered orally as tablet, once daily (80 mg) until progression or intolerable side effects.
Prognosis with current treatment (comparator)	Patients with locally advanced or metastatic NSCLC with common EGFR mutations eventually progress on available 1L therapies. Median survival among patients with locally advanced or metastatic NSCLC treated with today's standard of care (osimertinib) at Rigshospitalet generally progress on 1L treatment within [redacted] In a real-world EU study of patients with EGFR-mutated NSCLC who received 1L osimertinib, one in four patients receiving 1L osimertinib died before receiving 2L treatment. The median OS in the Danish patients at Rigshospitalet is only [redacted]. Hence highlighting the need to use the best treatment upfront to prolong life expectancy. In addition to decreased life expectancy advanced NSCLC with common EGFR-mutations is associated with decreased health related quality of life across all EQ-5D domains. Progression of disease has also been found to be associated with worsening HRQoL in patients with EGFR-mutated NSCLC further supporting the need to prevent this clinical outcome.
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	Progression-free survival: In the phase 3 MARIPOSA trial, the primary endpoint was met at the 11 August 2023 data cut-off after a median follow-up on 22.0 months. Amivantamab + lazertinib demonstrated a longer median PFS by BICR of 23.7 months (95% CI: 19.1 to 27.7) compared with 16.6 months (95% CI: 14.8 to 18.5) with osimertinib (HR 0.70; 95% CI: 0.58 to 0.85; p<0.001) Overall survival: The final OS analysis (data cut-off 04 December 2024) from MARIPOSA, after a median study follow-up of 37.8 months, indicated a 25% reduction of the risk of death with amivantamab + lazertinib vs. osimertinib (HR: 0.75; 95% CI: 0.61 to 0.92; p-value <0.005)
Most important serious adverse events for the intervention and comparator	In the phase 3 MARIPOSA trial, for the amivantamab + lazertinib arm, the most common TEAEs (of any Grade) were paronychia (68%), IRRs (63%), rash (62%) and hypoalbuminemia (48%), with rash being the most common Grade ≥3 TEAE (15%). In the osimertinib arm, the most common TEAEs (of any Grade) were diarrhoea (44%) and rash (31%), with VTE and dyspnoea being the most common Grade ≥3 TEAEs (4% each).

Summary	
	Pulmonary embolism was the only serious AE with a frequency of ≥5% in either the amivantamab + lazertinib (n=26, 6.2%) or osimertinib (n=10, 2.3%) treatment arm.
Impact on health-related quality of life	Disease-specific instruments: Patients treated with amivantamab + lazertinib reported stable functioning compared to baseline up to cycle 29, with no meaningful change from baseline in EORTC-QLQ-C30 global health status and all individual subscales. Similarly, lung cancer-associated symptoms remained stable, as measured by the NSCLC-SAQ total scores and individual symptom scores for dyspnoea, pain and cough. EQ-5D-5L VAS/index: At baseline, the mean EQ-5D-5L index score was [redacted] in the amivantamab + lazertinib arm and [redacted] in the osimertinib arm (difference [redacted], 95% CI: [redacted]). Health economic model: Better than comparator
Type of economic analysis that is submitted	Type of analysis: Cost-utility Type of model: Partitioned survival model
Data sources used to model the clinical effects	MARIPOSA
Data sources used to model the health-related quality of life	MARIPOSA
Life years gained	1.17
QALYs gained	1.00
Incremental costs	1,481,597
ICER (DKK/QALY)	1,487,377
Uncertainty associated with the ICER estimate	The ICER was robust in the scenarios tested. In the OWSA, the most impactful parameters were the scale and shape of OS for both amivantamab + lazertinib and osimertinib as well as the parameters of the generalised gamma parametric function for the extrapolation of TTDD for amivantamab, see 12.2.1.
Number of eligible patients in Denmark	198 new patients per year are eligible for amivantamab + lazertinib.
Budget impact (in year 5)	156,920,415

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

This application is for the reimbursement of the combination treatment of amivantamab, a bispecific antibody directed against epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition (MET) receptors, and lazertinib, a third generation EGFR- tyrosine kinase inhibitor (TKI), for advanced non-small cell lung cancer (NSCLC) with common EGFR mutations (exon 19 deletion [ex19del] or exon 21 L858R substitution [Exon 21 leucine-858 to arginine]) in adult patients at the first line (1L) setting (EMA 2025c, EMA 2025b). Advanced refers to locally advanced or metastatic. Amivantamab is available in intravenous (IV) and subcutaneous (SC) formulations, with both formulations included in this application.

There is a high unmet clinical need for new targeted treatments that can improve efficacy without sacrificing tolerability or quality of life (QoL) of people with advanced EGFR-mutated NSCLC. Patients receiving the current standard of care (SoC) osimertinib still experience disease progression within two years (median of 17 to 19 months) (Soria et al. 2018, Johnson & Johnson 2023b) and one in four patients die before receiving 2L therapy (Girard et al. 2023, Pérol et al. 2024). Resistance to third-generation EGFR-TKIs eventually develops in nearly all patients (Hendriks et al. 2023). The mechanisms of resistance are diverse and polyclonal. The most common measurable resistance mechanisms are secondary EGFR pathways alterations and MET pathway activations (Cho et al. 2024). The combination treatment of amivantamab + lazertinib targeting both the TKI and MET pathways offers an opportunity to improve these outcomes.

3.1 The medical condition

Lung cancer has remained the most common malignancy worldwide for the last three decades, with an estimated global incidence of >2.2 million new cases in 2020 (11.4% of all new cancer diagnoses)(Globocan 2020). Lungs are one of the three most common cancer sites among men and women in the Nordic countries (Lundberg et al. 2020), with around 5,000 patients per year are diagnosed with lung cancer in Denmark (Dansk Lunge Cancer Gruppe/Register 2024). Of these, a high proportion (43.5%) are in the most advanced stage at diagnosis (Stage IVB) (Dansk Lunge Cancer Gruppe/Register 2024).

Lung cancer is often aggressive and takes more lives than any other form of cancer (Vyse and Huang 2019, Wood and Taylor-Stokes 2019), constituting 18% of total cancer deaths (Globocan 2020). Lung cancer has a 5-year survival rate of 13% in Europe (van Meerbeeck and Franck 2021). While the population living with lung cancer today is greater than it was 20 years ago owing to improvements in treatments, there remains a substantial unmet need for effective treatments to further improve survival.

Pathophysiology

Figure 1 visualises the flow from all lung cancer to advanced NSCLC with the common EGFR mutations, ex19del and L858R point mutations in exon 21.

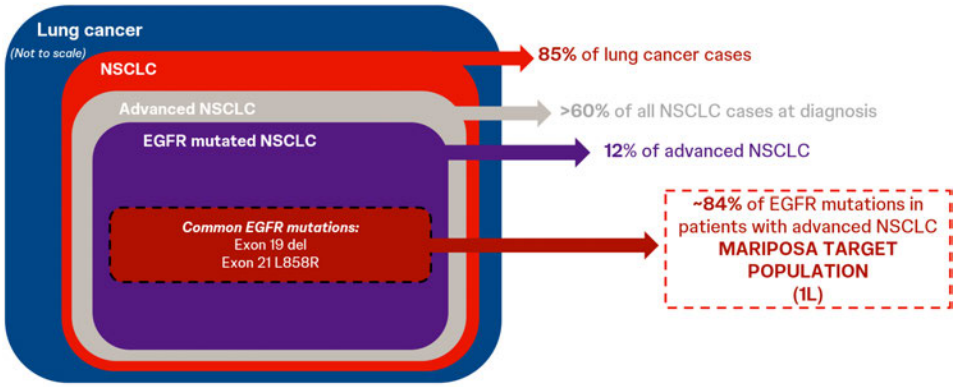


Figure 1: Overview of EGFR-mutated advanced NSCLC

Abbreviations: 1L: First line; del: Deletion; EGFR: Epidermal growth factor receptor; ins: Insertion; NSCLC: Non-small cell lung cancer. Source: Johnson & Johnson, data on file. Figure based on: (Melosky et al. 2022, Zhang et al. 2016, Vyse and Huang 2019, Zappa and Mousa 2016, Castellanos et al. 2017, Ganti et al. 2021).

Clinical presentation

Lung cancer often causes subtle, nonspecific symptoms early in the disease course. Later the symptoms depend on the local, regional, metastatic, or systemic effects of the disease. The symptoms of NSCLC are common to all lung cancers and include:

- Coughing up blood
- Chest pain or discomfort
- Trouble breathing
- Wheezing
- Hoarseness
- Loss of appetite
- Weight loss for no reason
- Fatigue
- Trouble swallowing
- Swelling in the face and/or veins in the neck
- A cough that doesn't go away or gets worse over time

Prognosis

The prognosis for lung cancer is generally poor. Overall 1- and 5-year survival for all Danish lung cancer patients in 2022 was 57% and 24%, respectively (Dansk Lunge Cancer Gruppe/Register 2024). It is even worse for NSCLC, with 5-year survival observed to be only 18.2% in Danish patients, irrespective of mutation and stage (Gouliaev et al. 2024).

Even with today's SoC, people with advanced NSCLC typically experience disease progression after 1.5 years (approximately 17 to 19 months) (Soria et al. 2018) and still experience poor overall survival (OS) outcomes, with at least a quarter not reaching 2L treatment (Girard et al. 2023, Pérol et al. 2024). Similarly, real world data of [redacted] Danish patients with advanced NSCLC shows that patients with today's SoC osimertinib at Rigshospitalet have a median progression-free survival (PFS) of only [redacted] (95% confidence interval [CI]: [redacted]), and OS of [redacted] (95% CI: [redacted]) (Johnson & Johnson 2024g). In addition, with a median follow-up of [redacted], around [redacted] of Danish patients treated with osimertinib 1L died without a subsequent treatment and only [redacted] were alive and initiated 2L (Johnson & Johnson 2024g).

In addition to the primary mutations, other mutations often arise during treatment, leading to acquired resistance to current treatments (Castellanos et al. 2017, Koulouris et al. 2022, Chmielecki et al. 2023). Hence, today's SoC is inadequate in meeting treatment goals of prolonging life. It would be beneficial to patients to have an efficacious targeted treatment in 1L with multiple mechanisms of action to delay resistance and preserve treatment lines.

The impact on the patients' functioning and HRQoL

Patients with NSCLC experience reduced health-related quality of life (HRQoL) compared to the general population (especially in terms of emotional and physical functioning), with greater impairments observed in patients receiving later therapy lines, and in patients with advanced disease (Enstone et al. 2015). Progression of EGFR-mutated NSCLC has also been found to be associated with worsening HRQoL (Sari et al. 2020).The HRQoL impairment experienced by patients with advanced NSCLC in general has been assessed with the EuroQoL five-dimensional questionnaire three level version (EQ-5D-3L) and the European Organisation for Research and Treatment of Cancer Core Questionnaire (EORTC-QLQ-C30) (Wood et al. 2019, Koch et al. 2020, Sari et al. 2020). Advanced NSCLC affects all the domains in EQ-5D-3L (Wood et al. 2019). The most common and severe symptoms assessed by the EORTC-QLQ-C30 were fatigue (46.3), dyspnoea (38.8), appetite loss (36.5), and insomnia (36.4) (Wood et al. 2019). Using the lung cancer module (EORTC QLQ-LC13), an international study found that fatigue was the most pronounced symptom, more so than respiratory symptoms (Koch et al. 2020). In addition, an interview study found that the majority of patients with advanced NSCLC with EGFR ex19del or EGFR L858R mutation and an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, reported a negative impact on daily living activities (77%) and emotional functioning (82%) (Horn et al. 2023). Pain in areas other than the chest (69%), cough (67%), and fatigue (64%) were the most common symptoms and the general impact of NSCLC included feelings of anxiety, isolation and fear.

3.2 Patient population

Epidemiology in Denmark

In Northern Europe, the age-standardised incidence of lung cancer is estimated to be 29.7 per 100,000 with a mortality rate of 20.1 per 100,000 (Globocan 2020). Denmark has historically a high incidence of lung cancer and mortality, with a 1-year net survival from NSCLC of 34% (all stages) (Walters et al. 2013). In 2023 there were 5123 new cases of lung cancer registered in the Danish Lung Cancer Register (Dansk Lunge Cancer Gruppe/Register 2024). Of those diagnosed, the majority (81.7%), were NSCLC (n=4187) (Dansk Lunge Cancer Gruppe/Register 2024). This is in line with international estimates of 85% (Zappa and Mousa 2016, Vyse and Huang 2019). Around half (55.0%) of patients with NSCLC are diagnosed with metastatic disease in Denmark (Walters et al. 2013).

Table 1 contains estimates of the incidence of lung cancer and NSCLC specifically and two estimates of the prevalence of lung cancer, in acknowledgment of the variation.

Table 1: Incidence and prevalence of lung cancer in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence of lung cancer in Denmark	4945	5136	5121	5123	5123
Incidence of NSCLC in Denmark	4061	4207	4164	4187	4187
Prevalence of lung cancer in Denmark (Alt 1)	6105	6168	6199	6232	6232
Prevalence of lung cancer in Denmark (Alt 2)	14 537	15 420	16 060	16 060	16 060

Note: Assume the same incidence in 2024 as in 2023 and assume same prevalence in 2023 and 2024 as in 2022.
Source: Incidence from the DLCR (Dansk Lunge Cancer Gruppe/Register 2024); Two sources for prevalence: Alternative 1: prevalence rate 1 10.394 per 10,000 (Jakobsen et al. 2021) and population data (Statistics Denmark 2025b); Alternative 2: prevalence data from NORDCAN (NORDCAN 2024).

Advanced NSCLC with ex19del or exon 21 L858R substitution mutations

The relevant patient population for this application is previously treatment naïve adult patients with advanced (locally advanced or metastatic) NSCLC with common EGFR mutations (EGFR ex19del and EGFR L858R). Table 2 presents the estimated number of patients eligible for treatment. There were [redacted] patients with advanced NSCLC that were treated with 1L SoC osimertinib at Rigshospitalet during 2024, of which [redacted] had ex19del mutation and [redacted] had exon 21 L858R mutations (Johnson & Johnson 2024g). Considering all of Denmark, the Danish Medicines Council (DMC) has estimated that there are approximately 220 patients per year with EGFR mutations (Medicinrådet 2024a). Given that around 10% of EGFR mutations are rare (Castellanos et al. 2017), this results in approximately 198 patients with the common mutations (ex19del or exon 21 L858R). The market share in year 1 is assumed to be 30% and is expected to increase to 80% by year 5 owing to clinical experience with this combination treatment with unique mechanisms of action.

Table 2: Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	59	79	119	139	158

3.3 Current treatment options

Treatment objectives for patients with advanced NSCLC not amenable to curative therapy include prolongation of PFS and OS while maintaining/improving HRQoL. Targeted systemic anti-cancer therapy is the cornerstone for advanced NSCLC patients with common EGFR mutations. Treatment with an EGFR-TKI (monotherapy) has been the preferred approach for many years in the treatment guidelines in Europe (Hendriks et al. 2025) and Denmark (Medicinrådet 2024a, Danske Multidisciplinære Cancer Grupper 2024). Reimbursement of amivantamab + lazertinib would expand the available targeted treatments, preserve later treatment lines, and align Denmark with the recently updated European Society for Medical Oncology (ESMO) guidelines (Hendriks et al. 2025).

European treatment guidelines

The ESMO treatment guidelines have been recently updated to include combination treatments at 1L, including amivantamab + lazertinib as 1L for patients with stage IV advanced NSCLC EGFR-positive mutations (Hendriks et al. 2025). The combination regimen achieved the highest rating (ESCAT I,A) "ready for routine use" with the clinical implication: "access to the treatment should be considered standard of care". Osimertinib monotherapy was previously the preferred 1L monotherapy for patients with a classical activating EGFR mutation, over the older generation TKIs (Hendriks et al. 2023). However, owing to the limitations of TKI monotherapy, including the inevitable resistance, combination treatments are now recommended at 1L (Hendriks et al. 2025).

Danish treatment guidelines

Investigations leading to a diagnosis and treatment decision often take time owing to few symptoms in the early stages. Upon diagnosis, all NSCLC patients are screened with a targeted next generation sequencing (NGS) panel (Danske Multidisciplinære Cancer Grupper 2024). Targeted therapy is then based on the mutations present (Figure 2) according to guidelines by Danske Multidisciplinære Cancer Grupper (Danske Multidisciplinære Cancer Grupper 2024). The DMC also have treatment guidelines for advanced NSCLC (Figure 3) (Medicinrådet 2024a).

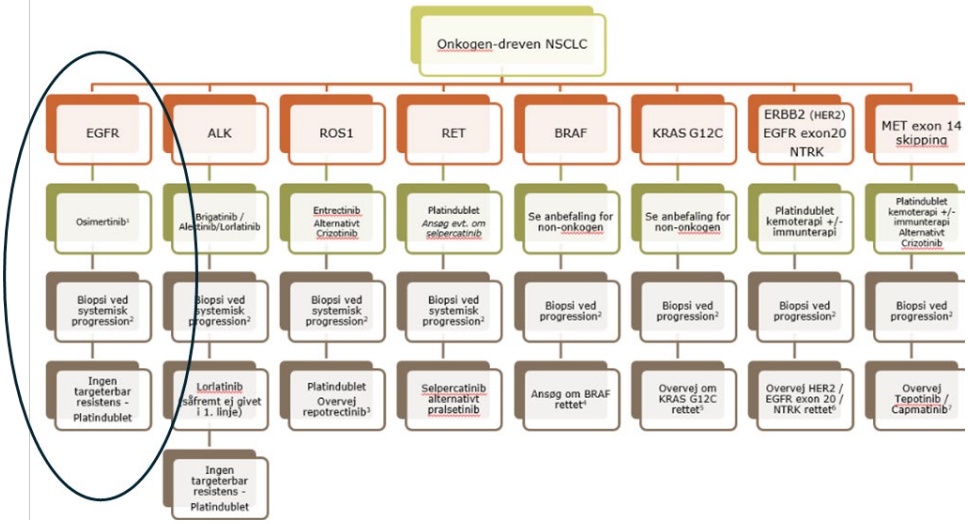


Figure 2: Treatment flowchart for NSCLC by Danske Multidisciplinære Cancer Grupper

Source: Modified from (Danske Multidisciplinære Cancer Grupper 2024).

For patients with an activating EGFR mutation and a performance status score 0-3, the 1L treatment is with osimertinib, until progression or intolerable side effects. For the few patients not treated with osimertinib (around 5%), afatinib, dacomitinib, erlotinib, and gefitinib are all considered equivalent options (Medicinrådet 2024a, Medicinrådet 2024b). Yet, around 1/4 of NSCLC patients do not receive active medical therapy within a year of diagnosis (Dansk Lunge Cancer Gruppe/Register 2024).

At symptomatic progression, rebiopsy can be performed. For later line targeted treatment of EGFR mutations, either erlotinib or gefitinib can be used. Alternatively, patients with systemic progression may have 2L treatment with platinum-based chemotherapy or targeted therapy based on any newly detected mutations.

Anbefaling	Lægemiddel inklusive administration og dosis	Behandlingslængde
Anvend til minimum 95 % af populationen*	Tagrisso (osimertinib), oral, 80 mg × 1 dgl.	Til progression eller intolerable bivirkninger
2. valg (overvej)	Erlotinib "Stada", oral, 150 mg × 1 dgl.	Til progression eller intolerable bivirkninger
3. valg (overvej)	Gefitinib "Stada", oral, 250 mg × 1 dgl.	Til progression eller intolerable bivirkninger

Symbolforklaringer
* Procentsatsen angiver, hvor stor en andel af populationen, der forventes behandlet med det lægemiddel, der er førstevalg i lægemiddelrekommandationen.

Figure 3: Danish Medicines Council's treatment guidelines for EGFR-mutation positive NSCLC

Abbreviations: EGFR: Epidermal growth factor receptor; NSCLC: Non-small cell lung cancer. Source: Modified from (Medicinrådet 2024a)

3.4 The intervention

The current intervention is a combination treatment: amivantamab, a bispecific antibody directed against the EGFR and MET receptors, in combination with lazertinib, a third generation EGFR-TKI, for the treatment of adult patients with locally advanced or metastatic NSCLC with common EGFR mutations (ex19del or exon 21 L858R substitution) in the 1L setting. This efficacious targeted treatment at 1L has multiple mechanisms of action to delay resistance and preserve treatment lines. Further, it is a chemotherapy-free alternative with improved clinical efficacy compared with osimertinib.

Amivantamab IV in combination with lazertinib was approved by the European Commission (EC) on the 30 December 2024 and is indicated for the 1L treatment of adult patients with advanced NSCLC with EGFR ex19del or exon 21 L858R substitution mutations (EMA 2025c, EMA 2025b). Amivantamab IV was already approved in the EU (EMA 2025c):

- as monotherapy for treatment of advanced NSCLC with activating EGFR exon 20 insertion mutations, after failure of platinum-based therapy.
- in combination with carboplatin and pemetrexed for the treatment of advanced NSCLC with EGFR ex19del 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 advanced NSCLC with activating EGFR exon 20 insertion mutations.

Amivantamab is also available with a SC formulation, which was approved by the EC for administration every two weeks (Q2W) in combination with lazertinib for the 1L treatment of adult patients with advanced NSCLC with EGFR ex19del or exon 21 L858R substitution mutations in April 2025. Three studies supported this regulatory extension (PALOMA [NCT04606381](ClinicalTrials.gov 2023b), PALOMA-2 [NCT05498428] (ClinicalTrials.gov 2024b, Johnson & Johnson 2022b), and PALOMA-3 [NCT05388669] (ClinicalTrials.gov 2023c, Johnson & Johnson 2022c)). Approval for administration every four weeks (Q4W) is expected for this indication in Q1 2026. The Q4W formulation is expected to be the preferred SC formulation in Danish clinical practice, however all EMA-

approved formulations can be made available for use in Denmark. Appendix A contains details on the SC formulation of amivantamab.

Mechanisms of action

The multiple mechanisms of action with this combination treatment are well suited to a patient group with heterogenous disease development and mutations. Below follows a description of the mechanisms of action, individually and as a combination treatment.

Amivantamab

Amivantamab is a first-in-class EGFR-MET bispecific antibody with immune cell-directing activity that targets multiple oncogenic pathways of tumour growth and resistance and activates immune cells to attack tumour cells (Cho et al. 2024). The three-pronged approach of amivantamab includes (Johnson & Johnson 2022a) (Figure 4):

1. activating antibody-dependent cellular cytotoxicity and trogocytosis (ADDC)
2. causing EGFR and MET receptor degradation
3. inhibiting ligand binding to the receptors for MET and EGFR

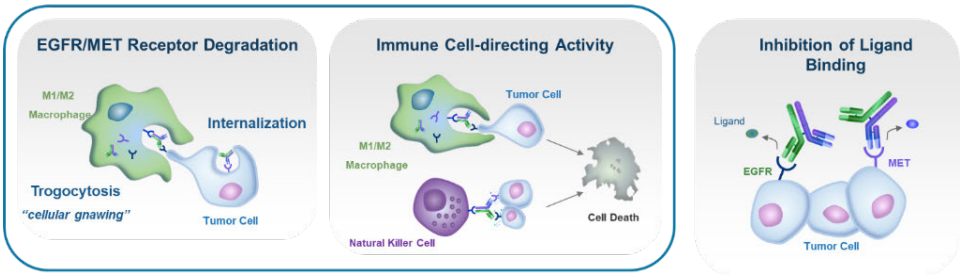


Figure 4: Amivantamab mechanism of action relevant to EGFR-mutated NSCLC

Abbreviations: EGFR: Epidermal growth factor receptor; MET: Mesenchymal-epidermal transition; NSCLC: Non-small cell lung cancer. Source: Data on file (Johnson & Johnson 2022a)

Amivantamab has unique mechanisms of action including ligand blocking, receptor degradation, and engagement of immune effector cells (monocytes, macrophages, and natural killer cells) by means of its optimised Fc domain (Cho et al. 2024). This mechanism enhances the patient's own immune system. By inhibiting EGFR and MET signalling functions, amivantamab also disrupts these signalling pathways, thereby preventing tumour growth and progression. The EGFR and MET pathways are thought to compensate for each other in situations where one is inhibited, leading to the so called 'kinase switch' drug resistance (seen with EGFR TKIs). Thus, simultaneous inhibition of both EGFR and MET has proven to improve overall treatment efficacy by limiting the compensatory pathway activation (Besse et al. 2024).

Lazertinib

Lazertinib is an oral, highly selective third-generation EGFR TKI. It selectively inhibits both primary activating EGFR mutations (ex19del and exon 21 L858R substitution mutations) and the EGFR T790M resistance mutation (EMA 2025b). Lazertinib binds with the novel pyrazole moiety involved in hydrogen bonds and van der Waals interactions that are consistent with drug potency and EGFR-mutant-selectivity (L858R/T790M) (Heppner et al. 2022). The substituted pyrazole of lazertinib is unique among third-generation EGFR

TKIs and may be responsible for the EGFR-mutant-selectivity and improved medicinal chemistry properties observed (Heppner et al. 2022).

Relative to osimertinib, lazertinib has demonstrated a higher selectivity against wildtype EGFR (Yun et al. 2019, Johnson & Johnson 2022a). Lazertinib thereby potently inhibits tumour growth in those with cEGFR mutations (e.g., EGFR ex19del and EGFR exon 21 L858R substitution) and T790M resistance mutations (Yun et al. 2019). HER2 and ErbB2 are not inhibited by lazertinib (contrary to osimertinib), thus reducing the risk of cardiotoxicity (Yun et al. 2019). By targeting both EGFR and T790M mutations yet sparing wildtype EGFR, lazertinib has a wide therapeutic window suitable for use in combination (EMA 2025b, Johnson & Johnson 2022a, Cho et al. 2024). Lazertinib also exhibits high blood-brain barrier penetration, comparable to osimertinib (Johnson & Johnson 2023a).

Amivantamab in combination with lazertinib

The scientific rationale for the combination treatment was to proactively address mechanisms of resistance to osimertinib (Cho et al. 2024, Leonetti et al. 2019) and provide a comprehensive treatment suitable for 1L treatment. The distinct mechanisms of action of amivantamab and lazertinib, which target the extracellular ligand binding domain and the intracellular active site of EGFR, respectively, have the potential to inhibit the EGFR pathway more potently than either agent alone (EMA 2025a). The combination treatment leads to improved treatment outcomes through the following mechanisms (ClinicalTrials.gov 2023a):

1. Inhibition of primary EGFR-activating mutations
2. Prevention of EGFR- or MET-based resistance mutation acquisition
3. Possession of recruitment mechanism of Fc-bearing immune cells in the anti-tumour response, via the Fc domain of amivantamab that has been designed to maximise affinity with immune cell Fc receptors

Treatment with amivantamab + lazertinib for advanced NSCLC with common EGFR mutations in Denmark, will offer a new treatment option with a statistically significant and clinically meaningful OS benefit versus current SoC. The intervention has an innovative mechanism of action with extracellular inhibition targeting both EGFR and MET and preserves subsequent treatment options. Simultaneously targeting EGFR and MET could improve clinical outcomes by concomitantly inhibiting both pathways and reducing occurrence of MET and/or EGFR-driven resistance leading to progression. In addition, the patient's own immune system is enhanced. Accordingly, the combination treatment is efficacious with multiple mechanisms of action to delay resistance and preserve treatment lines.

Posology

The posology is summarised below. This combination is both administered within the patients' home in tablet form orally (lazertinib) as well as within healthcare in the form of an IV infusion or SC injection for amivantamab (EMA 2025b, EMA 2025c, EMA 2025d). There are co-administered treatments especially at treatment initiation, which are detailed in the SmPCs (EMA 2025b, EMA 2025c, EMA 2025d).

Amivantamab

Amivantamab is available in IV and SC formulations, with specific dosing options. The base-case of this application is of amivantamab IV Q2W. The recommended dosages of which, when used in combination with lazertinib, are provided in Table 3 (EMA 2025c). The IV infusion should be administered after dilution at the infusion rates contained in the SmPC (EMA 2025c). Amivantamab should be administered by a healthcare professional with access to appropriate medical support to manage infusion-related reactions (IRRs), if they occur. For details on the SC posology, we refer to Appendix A.1.

Table 3: Recommended dosage of IV amivantamab every 2 weeks

Body weight at baseline[a]	Amivantamab dose	Schedule	No. vials 350 mg/7 mL
<80 kg	1,050 mg	Weekly (total of 4 doses) from Weeks 1 to 4 Week 1 - split infusion on Day 1 and Day 2 Weeks 2 to 4 - infusion on Day 1 Every 2 weeks starting at Week 5 onwards	3
≥80 kg	1,400 mg	Weekly (total of 4 doses) for Weeks 1 to 4 Week 1 - split infusion on Day 1 and Day 2 Weeks 2 to 4 - infusion on Day 1 Every 2 weeks starting at Week 5 onwards	4

a Dose adjustment is not required for subsequent body weight changes. Abbreviations: IV: Intravenous; kg: Kilogram; mg: Milligram; mL: Millilitre; No: Number. Source: Rybrevant SmPC: (EMA 2025c).

Lazertinib

The recommended dose is 240 mg once daily in combination with amivantamab (EMA 2025b). It is recommended to administer lazertinib orally any time prior to amivantamab when given on the same day.

Combination treatment

As per the SmPCs, it is recommended that patients are treated with the combination treatment until disease progression or unacceptable toxicity (EMA 2025b, EMA 2025c, EMA 2025d). There is flexibility with possibilities for dose reductions to manage potential grade 3 or 4 AEs, as well as continue with mono-treatment with lazertinib following such events (EMA 2025b). In case of dose reductions, the prepared dose would be lower than the standard dose based on the weight category. Such intermittent pauses and dose adjustments have not been seen to affect efficacy (See Appendix F). Table 4 presents the RDI for amivantamab IV and lazertinib respectively. Furthermore, symptomatic progression is more important than radiological in treatment decisions in clinical practice. Use post progression is likely in Danish clinical practice as seen in the Rigshospitalet dataset with a median PFS of [redacted] on 1L treatment with osimertinib, but [redacted] until time to next treatment (Johnson & Johnson 2024g).

Summary of the intervention

Amivantamab in combination with lazertinib for the treatment of locally advanced or metastatic NSCLC with common EGFR mutations (ex19del or exon 21 L858R substitution) in adult patients is an efficacious chemotherapy-free targeted treatment at 1L with multiple mechanisms of action to delay resistance and preserve treatment lines. It is supported by a robust clinical trial programme (Cho et al. 2024). A summary overview of the intervention is contained in Table 4. The IV form of amivantamab constitutes the base case of this application, although reimbursement is also sought for SC formulation.

Table 4: Overview of amivantamab in combination with lazertinib

Overview of intervention	
Indication relevant for the assessment	Combination of amivantamab (ATC: L01FX18) + lazertinib (ATC: L01EB09) for the 1L treatment of adult patients with advanced (metastatic or locally advanced) NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. This use is in line with the marketing authorisation.
ATMP	Not applicable
Method of administration	Amivantamab IV: Intravenous infusion Amivantamab IV is for intravenous use. It is administered as an IV infusion following dilution with sterile 5% glucose solution or sodium chloride 9 mg/mL (0.9%) solution for injection and administered with in-line filtration. For infusion rates we refer to the SmPC. Amivantamab IV should be administered by a healthcare professional with access to appropriate medical support to manage IRRs if they occur. Amivantamab SC: Subcutaneous injection Amivantamab SC is for subcutaneous use and is provided as a ready-to-use solution with a single simple preparation step that does not require dilution. Amivantamab SC should be administered by a healthcare professional with access to appropriate medical support to manage ARRs if they occur. The SC formulation improves the treatment process by offering simple and fast preparation and administration, reducing the treatment burden for patients, caregivers, and healthcare providers. Lazertinib: Oral
Dosing	Amivantamab IV: The recommended dosage of amivantamab IV is based on baseline body weight. Dosing is Q2W initially with weekly dosing for the first four weeks and then administered Q2W from Week 5 and onwards. The recommended dose for patients with body weight <80 kg at baseline is 1,050 mg and for patients ≥80 kg 1,400 mg Amivantamab SC: The recommended dosage of amivantamab SC is based on baseline body weight. For Q4W dosing, dosing is weekly initially and then administered Q4W from Week 5 and onwards. The recommended dose for patients with body weight <80 kg at baseline is 3,520 mg and for patients ≥80 kg 4,640 mg. Dosing is also approved for Q2W.

Overview of intervention	
	Lazertinib: The recommended dosage of lazertinib is 240 mg once daily in combination with amivantamab. It is recommended to administer any time prior to amivantamab when given on the same day.
Dosing in the health economic model (including relative dose intensity)	Amivantamab: IV administration (base case). Dosing based on baseline body weight. <80 kg 1,050 mg and ≥80 kg 1,400 mg. Administration IV is to be weekly (total of 4 doses) from Weeks 1 to 4 and then every 2 weeks starting at Week 5 onwards. RDI related to dose reductions is also based on body weight. Patient weight < 80 kg: [redacted] RDI. Patient weight ≥ 80 kg [redacted] RDI The model also enables assessment of amivantamab SC Q4W, with results presented as a scenario analysis. Lazertinib: 240 mg/day, [redacted] RDI
Should the medicine be administered with other medicines?	This is a combination treatment (amivantamab + lazertinib) Prior to the initial dose of amivantamab (Week 1, Day 1), antihistamines, antipyretics, glucocorticoids, and oral corticosteroids should be administered to reduce the risk of IRRs. Oral corticosteroids should also be administered directly prior to the initial infusion in addition to IV dexamethasone. For subsequent doses, antihistamines and antipyretics are required to be administered. Glucocorticoids should also be re-initiated after prolonged dose interruptions. Antiemetics should be administered as needed. At the initiation of treatment, prophylactic anticoagulants should be administered to prevent VTE-events. Patients should receive prophylactic dosing of either a direct acting oral anticoagulant or a low-molecular weight heparin. Sun exposure should be limited during and for 2 months following the combination treatment as well as an alcohol-free emollient cream recommended for dry areas. A prophylactic approach to rash prevention should be considered.
Treatment duration / criteria for end of treatment	As per the SmPC, it is recommended that patients are treated until disease progression or unacceptable toxicity. However, decisions in clinical practice are often driven by symptomatic rather than radiological progression and the SmPCs allow for dose reduction, treatment pauses or monotherapy upon such events. Real-world data (Johnson & Johnson 2024g), has demonstrated that continuation of 1L TKI treatment following progression occurs in Danish clinical practice.
Necessary monitoring, both during administration and during the treatment period	There is no mandated observation time in the SmPC for amivantamab or lazertinib. Monitoring after administration will depend on clinical practice and experience with the treatment.
Need for diagnostics or other tests (e.g. companion diagnostics). How	Not relevant, all diagnostics are completed as standard practice in diagnosing lung cancer. Before initiation of the combination therapy, EGFR-mutation status in tumour tissue or plasma specimens must be

Overview of intervention	
are these included in the model?	established using a validated test method. This is done at the initial diagnosis and does not need to be repeated for initiation of treatment.
Package size(s)	Amivantamab IV: Available in a 7 mL vial (350 mg amivantamab) with concentrate solution for infusion. Amivantamab SC: Amivantamab SC is available ready to use in several vial sizes to reduce drug wastage and offer simple preparation, with dose based on patient baseline weight and treatment schedule. Vials are available as 10, 14, 15 and 22 mL. Where 1 mL of solution for injection contains 160 mL amivantamab. Lazertinib: Lazertinib will be available as 80 mg and 240 mg film-coated tablets. Pack size of 28 tablets with 240 mg lazertinib.

Abbreviations: ATC: Anatomical Therapeutic Chemical; EGFR: Epidermal growth factor receptor; ex19del: Exon 19 deletions; IRR: Infusion-related reaction; kg: Kilogram; L858R: Exon 21 leucine-858 to arginine; mg: Milligram, mL: Millilitre; NSCLC: Non-small cell lung cancer; Q2W: Every two weeks; Q4W: Dosing every four weeks; RDI: Relative dose intensity; SC: Subcutaneous; SmPC: Summary of Product Characteristics; TKI: Tyrosine kinase inhibitor; VTE: Venous thrombosis. Sources: Rybrevant SmPC: (EMA 2025c); Rybrevant SC update: (EMA 2025d); Lazcluze SmPC: (EMA 2025b); CHMP report (EMA 2024); MARIPOSA data on file (Johnson & Johnson 2024f).

3.4.1 Description of ATMP

Not applicable.

3.4.2 The intervention in relation to Danish clinical practice

The anticipated placement of the combination therapy in the current treatment algorithm in Denmark is illustrated in Figure 5. Introduction of amivantamab in combination with lazertinib would replace or complement osimertinib as the 1L targeted treatment choice for patients with advanced (locally advanced or metastatic) NSCLC with common EGFR-mutations. Treatment with amivantamab + lazertinib will offer a new treatment option with an innovative mechanism of action with extracellular inhibition targeting both EGFR and MET while keeping subsequent treatment options open. Simultaneously targeting EGFR and MET can improve clinical outcomes by concomitantly inhibiting both pathways and reducing occurrence of MET and/or EGFR-driven resistance leading to progression. Patients with brain metastases, liver metastases, detectable ctDNA at baseline and during treatment and TP53 co-mutations are known to have poorer prognosis with quicker progression of disease. In MARIPOSA, 89% had at least one high-risk feature at baseline (Felip et al. 2024, Cho et al. 2024). In dialogue with Danish clinicians, it is our clear impression that they want to have multiple treatment options available, to make sure that they can offer the right treatment and sequence of treatment to the right patient. The intervention provides a chemotherapy-free alternative with improved efficacy compared with today's SoC owing to its unique multi-pronged mechanisms of action.

It is also expected that lazertinib may be used in some cases as monotherapy after treatment with amivantamab, based on real world data on osimertinib (Johnson & Johnson 2024g) and dialogue with Danish clinicians. The intervention enables flexibility

in that amivantamab can be taken off for some time (EMA 2025c, EMA 2025b). Some patients had a pause in treatment with amivantamab in the MARIPOSA trial, without it resulting in a worse outcome (del Rosario Garcia Campelo et al. 2024). Hence, the combination allows for flexibility while maintaining efficacy.

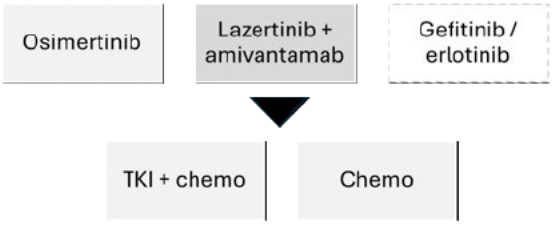


Figure 5: The intervention in relation to Danish clinical practice

3.5 Choice of comparator

As stated in the Danish guidelines in Section 3.3, osimertinib, a third-generation TKI, is the current SoC for 1L treatment of adult patients with advanced NSCLC with common EGFR mutations. Hence osimertinib was selected as the relevant comparator (Table 5).

Table 5: Overview of comparator

Overview of comparator	
Generic name	Osimertinib
ATC code	L01EB04
Mechanism of action	TKI. It is an irreversible inhibitor of EGFRs harbouring sensitising-mutations and TKI-resistance mutation T790M
Method of administration	Oral
Dosing	The recommended dose is 80 mg osimertinib once a day
Dosing in the health economic model (including relative dose intensity)	80 mg orally once a day. RDI: [redacted] (RDI is not included in the cost calculation of the comparator due to equal cost of the 40 and 80 mg tablets)
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	As per the SmPC, treatment is recommended until disease progression or unacceptable toxicity. However, clinical decisions are often driven by symptomatic rather than radiological progression, with real-world data demonstrating continuation of 1L TKI treatment following progression in Danish clinical practice (Johnson & Johnson 2024g).

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Available as 80 mg film-coated tables in packs of 30

Abbreviations: ATC: Anatomical Therapeutic Chemical; EGFR: Epidermal growth factor receptor; L: Line of therapy; mg: Milligram; RDI: Relative dose intensity; SmPC: Summary of product characteristics; TKI: Tyrosine Kinase Inhibitor Source: Osimertinib SmPC (EMA 2025e)

3.6 Cost-effectiveness of the comparator(s)

Osimertinib for 1L treatment of patients with advanced or metastatic EGFR-mutant NSCLC was recommended by the DMC as standard treatment in April 2019. The evaluation was within the previous system, with total incremental costs of 820 000 Danish Krone (DKK) per patient treated with osimertinib (Medicinrådet 2019).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The key efficacy outcomes considered relevant to evaluate the effect of amivantamab + lazertinib compared to osimertinib are based on the MARIPOSA trial with direct comparison of the intervention and comparator (Cho et al. 2024, ClinicalTrials.gov 2023a). PFS and OS are included in this application (Table 6). These measures were considered most appropriate due to their applicability to terminal diseases and their frequent use in efficacy studies of similar treatments and indications. They provide a clear and comparable measure of the impact of amivantamab + lazertinib on outcomes relevant for both practitioners and patients. Other key outcomes in MARIPOSA are objective response rate (ORR), intracranial PFS, time to subsequent therapy, time to symptomatic progression, and HRQoL (See Appendix C). Additional measures and definitions are available on ClinicalTrials.gov (ClinicalTrials.gov 2023a).

Table 6: Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival **MARIPOSA** **NCT04487080**	Median follow-up of 22.0 months at the primary analysis (11	PFS is defined as the time from the date of randomisation to the date of first documented disease progression or death, whichever occurs first. Participants who had not progressed or have	PFS was investigated using RECIST v1.1. guidelines, as assessed by BICR. PFS is analysed only at the primary PFS analysis data cut-off (11 August 2023) owing to mature data already at this time point. The time-to-event data of PFS for the ITT-population (medians and two-

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	August 2023)	not died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST v1.1 assessment	sided 95% CIs) were estimated with the use of the Kaplan-Meier method. HRs and 95% CIs were obtained from a stratified Cox regression model with treatment as the sole explanatory variable in pre-specified analyses.
Overall survival (OS) **MARIPOSA** **NCT04487080**	Median study follow-up of 37.78 months at the final OS analysis (04 December 2024)	OS is defined as the time from date of randomisation to the date of death from any cause. Any participant not known to have died at the time of analysis was censored based on the last recorded date on which the participant was known to be alive.	OS analyses were conducted at 2 timepoints: primary PFS analyses (11 August 2023) and the final OS analyses (04 December 2024) A hierarchical hypothesis-testing approach was used: PFS, and then OS. Same statistical analyses as for PFS. Results of these analyses are reported as point estimates and 95% CIs without adjustment for multiplicity and should not be used to infer definitive treatment effects.

* Time point for data collection used in analysis (follow up time for time-to-event measures). Abbreviations: BICR: Blinded independent central review; CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; OS: Overall survival; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumours.

Validity of outcomes

Treatment objectives for patients with advanced NSCLC include prolongation of PFS and OS while maintaining or even improving HRQoL. The knowledge that a drug is capable of causing a delay in progression or disease stabilisation is of great value to a patient and so PFS and response rates are recognised as patient-relevant endpoints by regulatory guidelines (EMA 2019).

4. Health economic analysis

This application presents the cost-effectiveness of the combination of amivantamab + lazertinib compared to osimertinib alone for 1L treatment of adult patients with locally advanced or metastatic NSCLC with EGFR ex19del or exon 21 L858R substitution mutations in Denmark. Total costs and health outcomes, including quality-adjusted life years (QALYs), over a lifetime perspective are calculated for each treatment strategy. The incremental differences between treatment arms for each measure are also calculated. The cost-utility results are expressed as the incremental cost in DKK per QALY gained.

4.1 Model structure

A de novo cost-effectiveness model (CEM) was designed and developed to conduct a cost-effectiveness analysis for amivantamab + lazertinib to appropriately reflect the clinical trial evidence and patient pathway. The CEM was developed in accordance with

the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Modelling Practices (Weinstein et al. 2003), and in keeping with the requirements of health technology assessment (HTA) bodies such as the UK's National Institute for Health and Care Excellence (NICE) (NICE 2022a).The CEM was fully programmed in Microsoft 365 Excel, with Visual Basic for Applications (VBA) to automate tasks such as conducting of sensitivity analyses and manipulating user interface features.

The CEM uses a partitioned survival model (PSM) approach with three mutually exclusive health states: progression-free, post-progression, and death. This model structure is consistent with most economic evaluations of treatments for metastatic or surgically unresectable common EGFR mutation positive NSCLC. In a PSM, transitions between health states are not modelled directly. Instead, health state membership at any time is determined by OS and PFS, which are modelled independently. The proportion of the cohort in the progression-free state is equal to PFS, the proportion in post-progression state is equal to the difference between OS and PFS, and the proportion dead is calculated as one minus OS (Figure 6). Separately, the proportion of patients remaining on treatment is determined by TTDD. Both PFS and TTDD are capped by the OS.

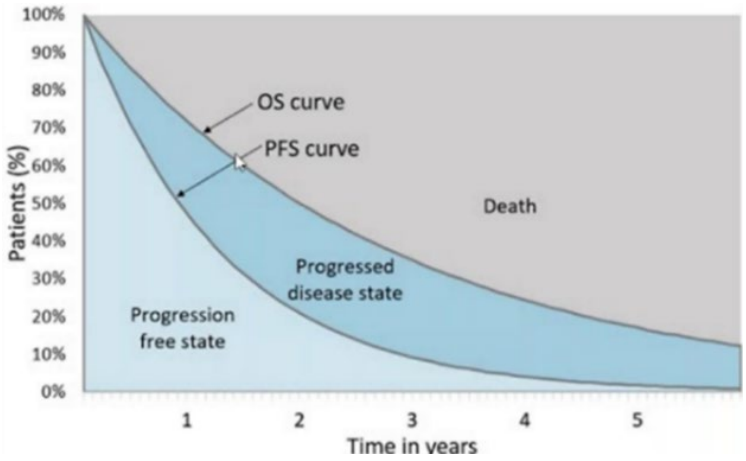


Figure 6: PSM structure

Abbreviations: OS: Overall survival; PFS: Progression-free survival; PSM: Partitioned survival model.

The PSM structure is both simple and flexible enough to extrapolate survival using various methods and can incorporate relative efficacy in numerous ways. It allows for key trial endpoints such as OS and PFS to be modelled directly, and reflects the clinical pathway of disease in that, once progressed, patients cannot return to the progression-free state. The approach is also representative of the clinical pathway for NSCLC in that a patient's treatment course and outcomes will depend largely on whether their disease has progressed or remained progression-free.

Health state-specific utilities are applied to each health state; these are detailed further in 10.2.3. Utility decrements due to adverse events (AEs) are captured as an aggregate QALY loss accrued in the first cycle. As the model progresses cycle by cycle for the duration of the time horizon, cost and utility data are summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between comparators at model completion.

The modelled base case is amivantamab IV + lazertinib vs. osimertinib. The model is based on clinical data from MARIPOSA (amivantamab IV + lazertinib and osimertinib). OS, TTDD, AE incidence and duration, health state utility values, proportion of missed doses, dose reduction proportions, proportion of patients receiving subsequent treatment, and distribution of subsequent treatments are based on the 04 December 2024 data cut, and PFS is from the 11 August 2023 data cut. As described in Table 6, the PFS data was mature at the primary analysis, which explains the different time points.

4.2 Model features

Table 7 presents the features of the economic model.

Table 7: Features of the economic model

Model features	Description	Justification
Patient population	1L treatment of adult patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.	Same patient population as outlined in Section 3.2
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	Based on starting age of the cohort, 30 years is assumed to be sufficient length to capture all differences in costs and outcomes between evaluated treatments, in line with DMC guidelines.
Cycle length	7 days	Allows capturing the varied dosing schedules of comparators
Half-cycle correction	Yes	To account for transitions of patients from one health state to another happening in a continuous process
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Amivantamab IV + lazertinib	The technology being assessed
Comparator(s)	Osimertinib	According to national treatment guidelines, see Section 3.5
Outcomes	OS, PFS assessed by BICR	Relative efficacy (OS and PFS) is based on MARIPOSA trial data

Abbreviations: BICR: Blinded independent central review; EGFR: Epidermal growth factor receptor; IV: Intravenous; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival.

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment and health economic analysis are based on the head-to-head study MARIPOSA, an ongoing, phase III, randomised, multicentre trial in treatment-naïve patients with locally advanced or metastatic NSCLC and common EGFR mutations, which assesses the efficacy and safety of amivantamab IV + lazertinib vs. osimertinib (Cho et al. 2024). As the submission is based on a head-to-head study of the relevant comparison (amivantamab + lazertinib vs. osimertinib as well as amivantamab IV vs. amivantamab SC), a systematic literature review (SLR) was not conducted. Table 8 includes an overview of the relevant literature used in this assessment. In addition, data from PALOMA-3 is utilised if selecting the SC-formulation of amivantamab, to provide relative risks of the AEs SC vs IV.

Table 8: Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Cho, B.C., Lu, S., Felip, E., et al. 2024. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med, 391, 1486-98. (Cho et al. 2024) Yang J.C.H., Kim Y.J., Lee S.H., et al. 2025. Amivantamab Plus Lazertinib vs Osimertinib in First-line EGFR-mutant Advanced NSCLC: Final Overall Survival from the Phase 3 MARIPOSA Study (Oral presentation). European Lung Cancer Congress 2025. (Yang J.C.H. et al. 2025) Gadgeel S.M., Chul C.B., Lu S. et al. 2024. Amivantamab Plus Lazertinib vs Osimertinib in First-line EGFR-mutant Advanced NSCLC: Longer Follow-up of the MARIPOSA Study (Oral presentation). World Conference on Lung Cancer 2024. (Gadgeel SM. 2024) Nguyen, D., Besse, B. & Cho, B.C., et al. 2024. Amivantamab Plus Lazertinib vs Osimertinib in First-line, EGFR-mutant Advanced NSCLC: Patient-relevant Outcomes From MARIPOSA (Presentation). World Conference on Lung Cancer 2024. (Nguyen et al. 2024) del Rosario Garcia Campelo, M., Cho, B.C., Girard, N., et al. 2024. Effect of Amivantamab Dose Interruptions on Efficacy and Safety of First-line Amivantamab Plus Lazertinib in EGFR-mutant Advanced NSCLC: Exploratory Analyses From the MARIPOSA study (Presentation). European Lung Cancer Congress. (del Rosario Garcia Campelo et al. 2024) Spira, A.I., Spigel, D., Nguyen, D., et al. 2023. Amivantamab Plus Lazertinib Versus Osimertinib In First-line EGFR-mutant Advanced NSCLC: A Post-progression and Safety Analysis of MARIPOSA (Presentation). North America Conference on Lung Cancer. (Spira et al. 2023) Cho, B., Felip, E., Spira, AI., et al. 2023. Amivantamab Plus Lazertinib Versus Osimertinib as First-line Treatment in EGFR-mutated Advanced NSCLC - Primary Results from MARIPOSA, a Phase 3, Global, Randomized, Controlled Trial. ESMO Madrid Meeting.(Cho 2023)	MARIPOSA	NCT04487080	Start: 30/09/2020 Completion: 29/06/2029 (estimated) Data cut-off 11/08/2023 (PFS, primary analysis) and 04/12/2024 (OS, pre-specified final analysis) Future data cut-offs: No prespecified data-cuts remaining.	Amivantamab IV + lazertinib vs. osimertinib for the treatment of locally advanced or metastatic NSCLC with common EGFR mutations (Ex19del or Exon 21 L858R substitution) as 1L in adult patients

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Data on file: Johnson & Johnson 2024. Clinical Summary - Final Overall Survival Analysis (Data cut-off 04 December 2024) - A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA). Data on file. (Johnson & Johnson 2024d) Data on file: Johnson & Johnson 2023. Clinical Study Report (Primary Analysis-Final). A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA). Data on file. (Johnson & Johnson 2023b)				
Data on file: Johnson & Johnson 2024. Clinical Study Report (Primary Analysis). Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Administered via Manual Injection Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy (PALOMA-3). (Johnson & Johnson 2024c)	PALOMA-3	NCT05388669	Start: 05/08/2022 Data cut-off 03/01/2024 Completion: 31/12/2025 (estimated)	Amivantamab IV + lazertinib vs. amivantamab SC + lazertinib Used in the scenario analysis for SC formulation of amivantamab

* If there are several publications connected to a trial, include all publications used.
Abbreviations: EGFR: Epidermal growth factor receptor; IV: Intravenous; L: Line (of therapy) NSCLC: Non-small cell lung cancer; SC: Subcutaneous.

5.2 Literature used for the assessment of health-related quality of life

Patients' functioning and overall HRQoL was assessed in the MARIPOSA trial. In the trial, patients completed patient-reported outcome (PRO) measures related to their HRQoL, including the EQ-5D-5L, EuroQoL visual analogue scale (EQ-VAS), EORTC QLQ-C30, and Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire (NSCLC-SAQ). The health economic analysis included health state specific utilities for progression free and progressed disease based on MARIPOSA with EQ-5D-5L utility scores derived using Danish-specific

utility weights. In addition, utility decrements associated with AEs of grade ≥ 3 that had occurred in at least 5% of patients in a treatment arm were estimated from MARIPOSA. The relevant literature for HRQoL data is presented in Table 9.

Table 9: Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Data on file: Johnson & Johnson. A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA) (Data cut-off 04 December 2024) Data on file. (Johnson & Johnson 2024f)	Health states: Progression-free ([redacted]), Progressed disease ([redacted]), and death (0) Disutility: Dermatitis acneiform ([redacted]), Alanine aminotransferase increase ([redacted]), Hypalbuminaemia ([redacted]), Paronychia ([redacted]), Infusion-related reaction ([redacted]), Rash ([redacted]), Pneumonia ([redacted]), Pulmonary embolism ([redacted]), Grade ≤ 2 VTE ([redacted])	Please see Section 10

5.3 Literature used for inputs for the health economic model

Clinical inputs (OS, PFS, and TTDD) were based on the head-to-head trial, MARIPOSA, and extrapolated over time, See Appendix E. Unit cost inputs were based on publicly available literature relevant for Denmark 2025, medicinpriser.dk, the DMC "Catalogue for estimating unit costs" (Katalog for vaerdisaetning af enhedsomkostninger) and AE cost from Sundhedsdatastyrelsen using the relevant Danish Diagnosis-related group (DRG) costs. Resource use was based on a previous HTA report for NSCLC (Medicinrådet 2025). The relevant model inputs and associated literature used in the health economic model are listed in Table 10.

Table 10: Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Cho, B.C., Lu, S., Felip, E., et al. 2024. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med, 391, 1486-98. (Cho et al. 2024) Data on file: Johnson & Johnson 2023. Clinical Study Report (Primary Analysis-Final). A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA). Data on file. (Johnson & Johnson 2023b) Data on file: Johnson & Johnson. A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA) (Data cut-off 04 December 2024) Data on file. (Johnson & Johnson 2024f)	OS, PFS, TTDD	Based on MARIPOSA	See Section 6.1.4
Publicly available literature	Cost inputs	Drug costs were from medicinpriser (Lægemiddelstyrelsen 2025); administration costs, AE costs, and disease management costs from DRG codes (Sundhedsdatastyrelsen 2025), disease management costs were also sourced from the SIRKA database (Kommunernes og Regionernes Løndatakontor 2025). Resource use was informed by a previous HTA report for NSCLC (Medicinrådet 2025).	For further details, see Section 11

Abbreviations: AE: Adverse event; DRG: Diagnosis-related group; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival; TTDD: Time to treatment discontinuation or death

6. Efficacy

6.1 Efficacy of amivantamab + lazertinib compared to osimertinib for adult patients newly diagnosed with locally advanced or metastatic EGFR-mutated NSCLC (EGFR ex19del or EGFR L858R)

Amivantamab in combination with lazertinib is being evaluated in a comprehensive clinical development programme for indications within NSCLC, including 1L treatment of locally advanced or metastatic disease with common EGFR mutations. MARIPOSA, a robust global phase III head-to-head randomised control trial (RCT) in patients with newly-diagnosed locally advanced or metastatic NSCLC and common EGFR mutations, demonstrated that amivantamab + lazertinib has superior efficacy vs. osimertinib (Cho et al. 2024, Gadgeel SM. 2024). Based on MARIPOSA [NCT04487080] (ClinicalTrials.gov 2023a, Cho et al. 2024), an extension of the marketing authorisation for amivantamab (Rybrevant) (IV) in combination with lazertinib (Lazcluze) was granted in the 1L for patients with advanced NSCLC harbouring EGFR ex19del or exon 21 L858R substitution mutations in December 2024 (EMA 2025b, EMA 2025c).

A SC formulation of amivantamab is also being investigated. There are three studies investigating the use of SC formulation in NSCLC populations for which the IV formulation of amivantamab is approved (PALOMA [NCT04606381](ClinicalTrials.gov 2023b), PALOMA-2 [NCT05498428] (ClinicalTrials.gov 2024b, Johnson & Johnson 2022b), and PALOMA-3 [NCT05388669] (ClinicalTrials.gov 2023c, Johnson & Johnson 2022c).

6.1.1 Relevant studies

MARIPOSA provides the efficacy and safety documentation of the intervention for a patient population in line with the indication for amivantamab IV in combination with lazertinib (ClinicalTrials.gov 2023a, Johnson & Johnson 2023a, EMA 2025c, EMA 2025b). In this study, the combination of amivantamab IV + lazertinib was investigated in direct comparison with the relevant comparator (osimertinib). The primary results from 11 August 2023 data cut-off have been published in a peer-reviewed publication (Cho et al. 2024, Felip et al. 2024) and MARIPOSA data has been presented at several conferences (Gadgeel SM. 2024, del Rosario Garcia Campelo et al. 2024, Nguyen et al. 2024, Spira et al. 2023, Cho 2023). This application is further supported with data on file from the final OS analysis data cut-off (04 December 2024)(Johnson & Johnson 2024d) which has been recently presented at the European Lung Cancer Conference (Yang J.C.H. et al. 2025). A summary of this key relevant study is in Table 11.

Table 11: Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
MARIPOSA A Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib in Locally Advanced or Metastatic Non-Small Cell Lung Cancer **NCT04487080** (ClinicalTrials.gov 2023a, Cho et al. 2024)	Randomised, ongoing, open-label, active comparator-control phase III study of amivantamab + lazertinib vs osimertinib vs lazertinib monotherapy	This study is ongoing with an estimated completion date of 29/06/2027. Dosing is in 28-day cycles until end of treatment. Follow-up phase with evaluations ever 12 weeks following last dose of study treatment or disease progression. Median study follow-up of median follow-up of 22.0 months at the primary PFS analysis (data cut-off: 11 August 2023) and 37.8 months at the final OS data-cut off (04 December 2024)	Adult patients newly diagnosed and treatment naïve with locally advanced or metastatic EGFR-mutated NSCLC (EGFR ex19del or EGFR L858R)	240 mg of oral lazertinib once daily as well as 1,050 mg (1,400 mg for patients with body weight ≥80 kg) amivantamab IV once weekly for the first 4 weeks then once every 2 weeks thereafter. This arm was open-label due to the necessity to receive infusions	Osimertinib: 80 mg of oral osimertinib once daily Additional comparator: Lazertinib monotherapy - 240 mg of oral lazertinib once daily Both comparator arms were double-blinded	**Primary outcome**: PFS as per RECIST v1.1 assessed by BICR (Time Frame: Up to approximately 42 months) **Secondary outcomes**: OS [Time Frame: Up to approximately 60 months]; ORR [Time Frame: Up to approximately 42 months]; DOR [Time Frame: Up to approximately 42 months]; PFS2 [Time Frame: Up to approximately 42 months]; TTSP [Time Frame: Up to approximately 42 months]; Intracranial PFS [Time Frame: Up to approximately 42 months]; Incidence and severity of AEs [Time Frame: Up to approximately 60 months]; Number of participants with clinical laboratory abnormalities [Time Frame: Up to approximately 60 months]; Number of participants with vital signs abnormalities [Time Frame: Up to approximately 60 months]; Number of participants with physical examination abnormalities [Time Frame: Up to approximately 60 months]; Serum concentration of amivantamab [Time Frame: Up to approximately 42 months]; Plasma concentration of lazertinib [Time Frame: Up to approximately 42 months]; Number of participants with anti-amivantamab antibodies [Time Frame: Up to approximately 42 months]; Change from baseline in NCSLC-SAQ [Time Frame: Baseline Up to approximately 42 months]; Change from baseline in EORTC-QLQ-C30 [Time Frame: Baseline Up to approximately 42 months]

Abbreviations: AE: Adverse event; BICR: Blinded independent central review; DOR: Duration of Response; EGFR: Epidermal growth factor receptor; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; ex19del: Exon 19 deletions; IV: Intravenous; kg: Kilogram; mg: Milligram; NSCLC-SAQ: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; OS: Overall survival; ORR: Objective response rate; PFS: Progression-free survival; PFS2: PFS after first subsequent therapy; RECIST: Response Evaluation Criteria in Solid Tumours; TTSP: Time to Symptomatic Progression.

MARIPOSA (NCT04487080)

MARIPOSA is an ongoing, randomised, open-label, multicentre, phase III trial designed to compare the efficacy and safety of amivantamab + lazertinib vs. osimertinib for the first-line treatment of patients with locally advanced or metastatic EGFR-mutated NSCLC (EGFR ex19del or EGFR L858R) (Cho et al. 2024). The primary objective of this study was to assess the efficacy and safety of amivantamab + lazertinib as compared with osimertinib monotherapy (Cho et al. 2024). In a third study arm, lazertinib monotherapy was administered to evaluate the contribution of the components in the combination treatment. Hence, patients were randomised in a 2:2:1 treatment ratio to arms A (amivantamab + lazertinib IV), B (osimertinib), and C (lazertinib monotherapy), stratified by mutation type (ex19del vs. exon 21 L858R), race (Asian vs. non-Asian), and history of brain metastasis (present vs absent) (Cho et al. 2024). Overall, 1074 patients were randomised, 429 to amivantamab + lazertinib, 429 to osimertinib, and 216 to lazertinib (Cho et al. 2024). Further details of the study are available in Appendix B, including Figure 36 summarising the study design.

6.1.2 Comparability of studies

Not relevant as MARISPOSA is a head-to-head study of the relevant intervention (amivantamab IV + lazertinib) and comparator (osimertinib).

6.1.2.1 Comparability of patients across studies

Adult patients were eligible to participate in MARIPOSA if they were newly diagnosed with histologically or cytologically confirmed, locally advanced or metastatic NSCLC, with a tumour positive for EGFR ex19del or EGFR L858R (Cho et al. 2024). Patients with brain metastases were eligible if they were asymptomatic. Additional key eligibility criteria are in Table 64 in Appendix B.

Baseline characteristics of the patients included in MARIPOSA are presented in Table 12, and were well balanced across study arms (Cho et al. 2024). The median age of patients in the amivantamab + lazertinib and osimertinib arms was 64 and 63 years, respectively (Cho et al. 2024). Most patients in the amivantamab + lazertinib and osimertinib arms were female (64% and 59%, respectively), Asian (58% and 59%, respectively) and had an ECOG performance status of 1 (67% and 65%, respectively) (Cho et al. 2024). The most prevalent histologic type was adenocarcinoma (97%) and the proportion of patients with a history of brain metastases was similar between arms (41% and 40%) (Cho et al. 2024).

Table 12: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (MARIPOSA)

	MARIPOSA	
	amivantamab + lazertinib (n=429)	osimertinib (n=429)
Age		
Median age, years (range)	64 (25 to 88)	63 (28 to 88)

	MARIPOSA	
	amivantamab + lazertinib (n=429)	osimertinib (n=429)
Distribution, n (%)		
<65 years	235 (55)	237 (55)
≥65 years to <75 years	143 (33)	139 (32)
≥75 years	51 (12)	53 (12)
Sex, n (%)		
Female	275 (64)	251 (59)
Race or ethnic group, n (%)		
American Indian or Alaska Native	7 (2)	7 (2)
Asian	250 (58)	251 (59)
Black	4 (1)	3 (1)
Native Hawaiian or Pacific Islander	1 (<1)	1 (<1)
White	164 (38)	165 (38)
Multiple	1 (<1)	1 (<1)
Unknown	2 (<1)	1 (<1)
Body weight		
Median (range) kg	62.5 (32 to 118)	62.4 (35 to 109)
Distribution, n (%)		
<80 kg	376 (88)	368 (86)
≥80 kg	53 (12)	61 (14)
ECOG performance status, n (%)		
0	141 (33)	149 (35)
1	288 (67)	280 (65)
Time from initial lung cancer diagnosis to randomisation		

	MARIPOSA	
	amivantamab + lazertinib (n=429)	osimertinib (n=429)
Median months (range)	1.5 (0.2 to 207.9)	1.4 (0.3 to 162.8)
Time from metastatic diagnosis to randomisation		
n	421	424
Median months (range)	1.3 (0.2 to 24.1)	1.2 (0.1 to 11.7)
Histologic type at initial diagnosis, n (%)		
Adenocarcinoma	417 (97)	415 (97)
Large cell carcinoma	3 (1)	0
Squamous cell carcinoma	6 (1)	5 (1)
Other	2 (<1)	9 (2)
Not reported	1 (<1)	0
History of metastasis, n (%)		
Brain	178 (42)	172 (40)
Liver	64 (15)	72 (17)
History of smoking, n (%)		
Yes	130 (30)	134 (31)
Type of EGFR mutation, n (%)		
EGFR ex19del	258 (60)	257 (60)
EGFR L858R	172 (40)	172 (40)
EGFR-TP53 co-mutation, n (%)[a]		
Yes	149 (35)	144 (34)
ctDNA analysis, n (%)		
NGS detected ctDNA	320 (75)	316 (74)
ddPCR detected ctDNA	231 (54)	240 (56)

[a] Among patients with detectable baseline pathogenic alterations by NGS (amivantamab + lazertinib n=266, osimertinib n=274). Abbreviations: ctDNA: Circulating tumour deoxyribose nucleic acid; ddPCR: Droplet digital

polymerase chain reaction; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; ex19del: exon 19 deletion; NGS: Next generation sequencing; TP53: Tumour protein p53.
Source: ITT-population MARIPOSA (Cho et al. 2024, Felip et al. 2024).

6.1.3 Comparability of the study population with Danish patients eligible for treatment

The model inputs used include patient age, percentage of patient population who are females, and body weight. The modelled population aligns with the MARIPOSA trial, comprising adult patients with locally advanced or metastatic NSCLC with common EGFR mutations, who are treatment naïve and not amenable to curative therapy. In the head-to-head study, MARIPOSA, the amivantamab + lazertinib arm represents the intervention and the osimertinib arm represents the relevant comparator in Danish clinical practice. The patient population of MARIPOSA is broadly representative of the Danish patient population. There are possible differences in the trial population with regards to the proportion of patients with Asian race. To better reflect the weight of the Danish population, the body weight in the health economic model was based on the non-Asian patient population in MARIPOSA. The mean weight of the non-Asian patient population was [redacted] Previously, the DMC has assumed similar patient characteristics across all EGFR mutations (Medicinrådet 2025), and has also previously accepted a start age of 62 and a proportion of 80.7% <80 kg (Medicinrådet 2023) among patients with EGFR-mutated (exon 20) NSCLC (Medicinrådet 2023). The patient characteristics in the Danish population and in the health economic model are summarised in Table 13.

Table 13: Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	62 (Medicinrådet 2023)	Mean age 62.3 (SD 11.1) (MARIPOSA)
Sex	Higher proportion female, range 70.4% (Ehrenstein et al. 2023) to [redacted] female (Johnson & Johnson 2024g)	61.3% female (MARIPOSA)
Body weight	80.7% <80 kg (Medicinrådet 2023)	[redacted] kg mean [redacted] < 80 kg (MARIPOSA)

Abbreviations: SD: Standard deviation

6.1.4 Efficacy – results per MARIPOSA

The primary hypothesis of MARIPOSA was that the combination of amivantamab and lazertinib would reduce the risk of disease progression or death compared with osimertinib (Johnson & Johnson 2023b). The secondary hypothesis was that the combination of amivantamab and lazertinib would prolong OS compared with osimertinib. A hierarchical testing approach for the primary endpoint (PFS) and key secondary endpoint (OS) was used with a two-sided alpha of 0.05. For the time-to-event data, the HR and 95% CIs were estimated with the use of a stratified Cox regression model, with treatment as the sole explanatory variable in pre-specified analyses. The

time-to-event data of PFS for the intention-to-treat (ITT) population (medians and two-sided 95% CIs) were estimated with the use of the Kaplan-Meier method. A summary of the PFS and OS results from MARIPOSA which are utilised in the health economic model are presented below. Data checks in relation to the proportional hazard assumptions for the Kaplan-Meier data are in Appendix E.

Analyses of additional endpoints, including subgroup analyses are reported as point estimates and 95% CIs without adjustment for multiplicity. Results of key secondary outcomes from MARIPOSA not included in the health economic model are available in Appendix C, highlighting the wider value of this combination treatment.

Progression-free survival (PFS)

The primary efficacy endpoint of MARIPOSA was PFS (the interval between the date of randomisation and the date of documented disease progression or death) as measured by blinded independent central review (BICR) (Cho et al. 2024). Results are reported for the 1,074 patients who were randomised to amivantamab + lazertinib or osimertinib with a median follow-up of 22.0 months (primary analysis data cut-off: 11 August 2023) (Cho et al. 2024). PFS was fully mature at this time and not evaluated in later analyses.

The primary endpoint was met with amivantamab + lazertinib demonstrating a longer median PFS by BICR of 23.7 months (95% CI: 19.1 to 27.7) compared with 16.6 months (95% CI: 14.8 to 18.5) with osimertinib (Cho et al. 2024). Amivantamab + lazertinib significantly reduced the risk of disease progression or death by 30% vs. osimertinib (HR 0.70; 95% CI: 0.58 to 0.85; p<0.001) (Figure 7) (Cho et al. 2024). The event-free rates in the amivantamab + lazertinib and osimertinib arms were 73% and 65%, respectively, at 12 months, 60% and 48% at 18 months, and 48% and 34% at 24 months (Cho et al. 2024). The Kaplan-Meier plot of PFS in Figure 7 shows a distinct early and maintained separation between the treatment arms favouring amivantamab + lazertinib beginning at around 6 months after randomisation (Cho et al. 2024).

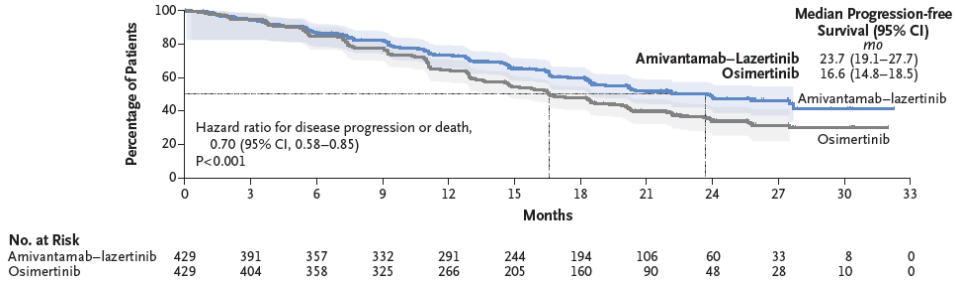


Figure 7: PFS by BICR for amivantamab + lazertinib vs. osimertinib (MARIPOSA primary PFS analysis: 11 August 2023 data cut-off)

Abbreviations: BICR: Blinded independent central review; CI: Confidence interval; mo: Months; PFS: Progression-free survival. Source: (Cho et al. 2024).

Amivantamab + lazertinib also demonstrated consistent PFS benefit across most predefined clinically relevant subgroups (Figure 8), including history of brain metastases, EGFR mutation type, and ECOG performance status (Cho et al. 2024). While no significant treatment benefit with amivantamab + lazertinib vs. osimertinib was seen in patients in the ≥65 years age group, improved PFS was observed in patients aged <65

years, <75 years but also ≥75 years, suggesting that age itself does not preclude benefit with amivantamab + lazertinib (Cho et al. 2024).

A secondary analysis from MARIPOSA also showed consistent PFS benefit vs. osimertinib across different subgroups of patients with and without high-risk features (Felip et al. 2024). Confirming that the PFS benefit vs. osimertinib are seen in patients with and without high-risk features including brain metastasis, liver metastases, TP53 co-mutation and detectable ctDNA status at baseline and during treatment (Felip et al. 2024).

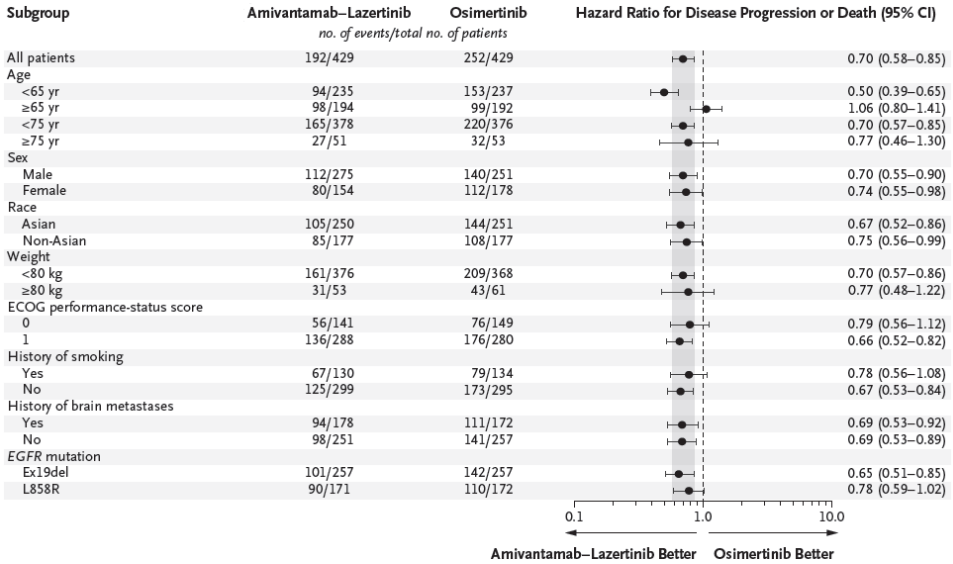


Figure 8: PFS by BICR across predefined clinically relevant subgroups (MARIPOSA, primary PFS analysis: 11 August 2023 data cut-off)

Note: Grey box indicates 95% CI of HR for all randomised patients. Abbreviations: BICR: Blinded independent central review; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; Ex19del: Exon 19 deletions; PFS: Progression-free survival. Source: (Cho et al. 2024).

Overall survival (OS)

At the protocol-specified final OS analysis (data cut-off 04 December 2024), after a median study follow-up of 37.8 months, 390 deaths were observed from arms A (amivantamab + lazertinib , n=173 deaths) and B (osimertinib, n=217 deaths) combined (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d). Figure 9 contains the Kaplan-Meier plot of OS.

Overall, a 25% reduction of the risk of death vs. osimertinib was seen (HR: 0.75; 95% CI: 0.61 to 0.92, p-value 0.0048) (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d). The event-free rates in the amivantamab + lazertinib and osimertinib arms were 75% and 70%, respectively, at 24 months, 60% and 51% at 36 months and 56% and 44% at 42 months (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d). The median OS was not estimable in the amivantamab + lazertinib arm (95% CI: 42.9, NE) and 36.7 months (95% CI: 33.4, 41.0) in the osimertinib arm. Please note that the MARIPOSA study was powered to assess PFS, hence the OS data had not reached maturity at the first data cut-off with a median of 22.0 months. A clinical advisory board assessing the preliminary OS data at August 2023 did not deem the early crossing of the OS curves a major issue, as early overlap of curves with later separation have been observed in other trials in oncology (Johnson & Johnson 2024a).

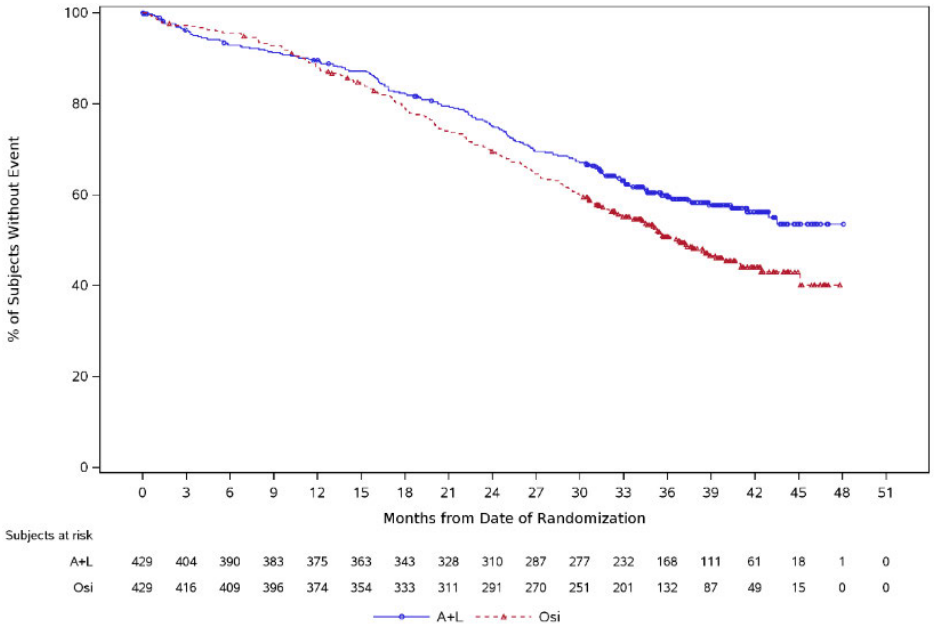
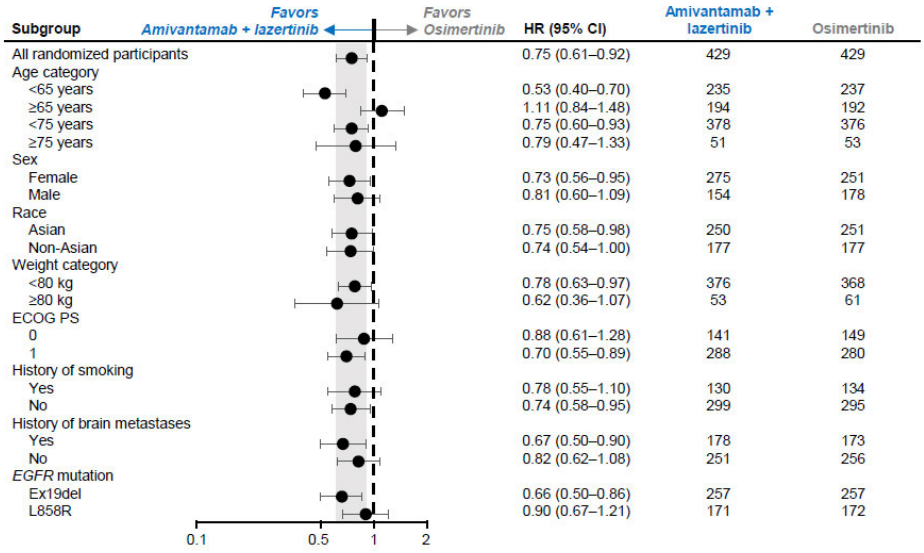


Figure 9: OS analysis for amivantamab + lazertinib vs. osimertinib (MARIPOSA, full analysis set, final OS analysis: 04 December 2024 data cut-off)

Abbreviations: A+L: Amivantamab + lazertinib; OS: Overall survival; Osi: Osimertinib. Source: (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d)

A generally consistent OS benefit for amivantamab + lazertinib over osimertinib was observed across predefined subgroups (Figure 10) (Yang J.C.H. et al. 2025)



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

Figure 10: OS across predefined clinically relevant subgroups (MARIPOSA, final OS analysis: 04 December 2024 data cut-off)

Note: Grey box indicates 95% CI of HR for all randomised patients. Subgroup analyses were not part of the hypothesis testing of the trial and should not be used to infer definitive treatment effects. Abbreviations: CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; HR: Hazard ratio; kg: Kilogram; PS: Performance status. Source: (Yang J.C.H. et al. 2025)

7. Comparative analyses of efficacy

MARIPOSA was a RCT directly comparing the intervention (amivantamab + lazertinib) with the comparator (osimertinib). Hence, some sections in Chapter 7 have been omitted. Results from the comparative analysis are presented in Table 14 below.

7.1.1 Differences in definitions of outcomes between studies

Not relevant.

7.1.2 Method of synthesis

Not relevant.

7.1.3 Results from the comparative analysis

MARIPOSA was a RCT comparing the intervention (amivantamab + lazertinib) with the comparator (osimertinib) directly. Results from the comparative analysis of amivantamab + lazertinib vs. osimertinib for the endpoints included in the health economic analysis are presented in Table 14. The mature trial data shows that treatment with the combination of amivantamab + lazertinib resulted in a statistically significant and clinically meaningful improvement in the primary endpoint PFS assessed by BICR at the primary analysis and the key secondary endpoint OS in the later data cut-off (Cho et al. 2024, Yang J.C.H. et al. 2025). For further details, we refer to Section 6.1.4.

Table 14: Results from the comparative analysis of amivantamab + lazertinib vs. osimertinib for the 1L treatment of adult patients with advanced NSCLC with EGFR ex19del or exon 21 L858R substitution mutations

Outcome measure	Amivantamab + lazertinib (N=429)	Osimertinib (N=429)	Result
PFS Primary PFS analysis (11 August 2023)	192 patients (44.8%) Median: 23.7 months 95% CI: 19.1 to 27.7	252 patients (58.7%) Median: 16.6 months 95% CI: 14.8 to 18.5	HR 0.70 (95% CI: 0.58 to 0.85; p<0.001)
OS Final OS analysis (04 December 2024)	173 patients (40.3%) Median: NE months (95% CI: 42.9, NE)	217 patients (50.6%) Median: 36.7 months (95% CI: 33.4 to 41.0)	HR: 0.75 (95% CI: 0.61 to 0.92; p<0.005)

Abbreviations: CI: Confidence interval; EGFR: Epidermal growth factor receptor; ex19del: Exon 19 deletions; HR: Hazard ratio; NE: Not estimable; NSCLC: Non-small cell lung cancer; OS: Overall survival; PFS: Progression-free survival;. Source: (EMA 2025c); Primary PFS analysis: (Cho et al. 2024, Johnson & Johnson 2023b); and Final OS analysis: (Johnson & Johnson 2024d, Yang J.C.H. et al. 2025).

7.1.4 Efficacy – results

See Section 6.1.4 for efficacy data (intervention vs. comparator) from MARIPOSA.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Clinical data from the MARIPOSA trial were used to model PFS and OS for amivantamab + lazertinib. The results are presented for the 11 August 2023 data cut for PFS and from the 04 December 2024 data cut for OS.

Survival models were fitted to individual subject data from the trial. Standard survival models (exponential, Gompertz, log-logistic, lognormal, gamma, and generalised gamma) were applied for the extrapolation of PFS and OS. The process of selecting a best fitting distribution was in line with NICE 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 (NICE 2011, Latimer 2013).

Crossing of either PFS or TTDD curves with the OS curve is implausible and avoiding it was an additional consideration in selecting appropriate distributions. However, it may be impractical to discard distributions when crossing occurs only at late time points when all curves are at very low values. Therefore, PFS and TTDD extrapolations in the CEM were capped by OS to prevent crossing in such instances. Additionally, to ensure plausible mortality rates predicted at old age, OS, PFS and TTDD rates used in the model were bound by the age- and sex-specific mortality of the general population as a minimum (using Danish life tables (Statistics Denmark 2025a)).

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of PFS

Table 15 presents a summary of the assumptions associated with the extrapolation of PFS assessed by BICR.

Table 15: Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	Clinical data from MARIPOSA [NCT04487080] (ClinicalTrials.gov 2023a) from data-cut 11 August 2023 of PFS as assessed by BICR
Model	Seven standard survival models were fitted to the individual subject data in MARIPOSA. The seven

Method/approach	Description/assumption
	distributions were: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No (See Appendix E.1.3)
Function with best AIC fit	Amivantamab + lazertinib: Gamma Osimertinib: Gamma
Function with best BIC fit	Amivantamab + lazertinib: Gamma Osimertinib: Log-logistic
Function with best visual fit	Amivantamab + lazertinib: Gamma Osimertinib: Gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Amivantamab + lazertinib: Gamma Osimertinib: Gamma
Validation of selected extrapolated curves (external evidence)	Clinical experts
Function with the best fit according to external evidence	Amivantamab + lazertinib: Gamma Osimertinib: Gamma
Selected parametric function in base case analysis	Amivantamab + lazertinib: Gamma Osimertinib: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

PFS as assessed by BICR was the primary endpoint in the MARIPOSA trial. Please see Figure 7 for the PFS KM curves for amivantamab + lazertinib and osimertinib from the 11 August 2023 data cut. Further details on the extrapolations of PFS can be found in Appendix E. The selection of the extrapolation curve in the base case was based on the statistical fit, clinical plausibility and visual fit.

The long-term PFS extrapolations for amivantamab + lazertinib can be found in Figure 11. The gamma model is the best according to Akaike information criterion (AIC) and Bayesian information criterion (BIC) and was selected for the base case. This choice on

statistical fit is also clinically plausible given that clinical experts at the advisory board recommended that the shape of the PFS curve is expected to be similar to the osimertinib curve (Johnson & Johnson 2024a).

The long-term PFS extrapolations for osimertinib are presented in Figure 12. Clinical experts at the advisory board reported an expected PFS of 10 to 15% at 3 years, and close to 0% at 5 years, with the Weibull and Gompertz curves closes to this estimate. However, they saw the Gompertz as too pessimistic as it declines too quickly. Furthermore, 28% of patients in the osimertinib arm of the FLAURA study were still on the trial regimen at 3 years (treatment beyond progression was allowed) (Ramalingam et al. 2020), pointing to plausibility of the Weibull curve (Johnson & Johnson 2024a). Gamma distribution was selected for the base case as providing slightly better fit to the data and to align with the selection for amivantamab + lazertinib, being more optimistic than the Weibull distribution.

Figure 11: Long-term PFS (BICR) projections of amivantamab + lazertinib

Abbreviations: BICR: independent review committee; KM: Kaplan-Meier; PFS: progression-free survival

Figure 12: Long-term PFS (BICR) projections of osimertinib

Abbreviations: BICR: independent review committee; KM: Kaplan-Meier; PFS: progression-free survival

8.1.1.2 Extrapolation of OS

Table 16 presents a summary of assumptions associated with the extrapolation of OS.

Table 16: Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	Clinical data from MARIPOSA [NCT04487080] (ClinicalTrials.gov 2023a) from data cut 04 December 2024
Model	Seven standard survival models were fitted to the individual subject data in MARPOSA. The seven distributions were: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No (See Appendix E.2.3)
Function with best AIC fit	Amivantamab + lazertinib: Gompertz Osimertinib: Gompertz
Function with best BIC fit	Amivantamab + lazertinib: Gompertz Osimertinib: Gompertz
Function with best visual fit	Amivantamab + lazertinib: Weibull Osimertinib: Weibull
Function with best fit according to evaluation of smoothed hazard assumptions	Amivantamab + lazertinib: Weibull Osimertinib: Weibull
Validation of selected extrapolated curves (external evidence)	Clinical experts & RWE
Function with the best fit according to external evidence	Amivantamab + lazertinib: Weibull Osimertinib: Weibull
Selected parametric function in base case analysis	Amivantamab + lazertinib: Weibull Osimertinib: Weibull
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

The extrapolation of OS from MARIPOSA was based on the 04 December 2024 data cut-off. See Figure 9 for OS KM curves for amivantamab + lazertinib and osimertinib. Further

details on the extrapolation can be found in Appendix E. The selection of the extrapolation curve in the base case was based on the statistical fit, clinical plausibility and visual fit.

The long-term OS extrapolations for amivantamab + lazertinib are presented in Figure 13. The Gompertz and exponential curves are the best fitting according to AIC and BIC. Upon review of the standard parametric models for the 11 August 2023 data cut, clinical experts at an advisory board considered any curves above Weibull too optimistic while Gompertz and generalised gamma likely conservative (Johnson & Johnson 2024a). In the 04 December 2024 data cut, Weibull distribution has the second best fit and Weibull survival estimates are in line with clinical input from the advisory board. Weibull was selected as the base case. A scenario analysis is included with gamma distribution, which predicts a more slowly increasing hazard.

The long-term OS extrapolations for osimertinib are presented in Figure 14. The Gompertz was the best fit according to AIC and BIC. Upon review of the standard parametric models, a distribution falling between Weibull (too optimistic) and generalised gamma (too conservative) was seen as the most clinically plausible by clinical experts. Long-term follow-up in the FLAURA study showed that 54% of patients were still alive at 3 years in the osimertinib arm. Clinicians expected that some patients will still be alive at 10 years (Johnson & Johnson 2024a). In the 04 December 2024 data cut, Weibull distribution survival estimates are between the Weibull and generalised gamma from the 11 August 2023 data cut. This selection is also supported by Finnish real-world data presented which indicate that some patients are likely alive at 10-years (Knuuttila et al. 2025) which fits with the projected 10-year OS for osimertinib to be 2.8% using Weibull. Hence, Weibull was selected as it provided the most clinically plausible option.

Extrapolations of OS were reviewed by a Danish clinical expert (REF in here) and the Weibull distribution for OS was considered to provide clinically plausible survival projections for both amivantamab + lazertinib and osimertinib. Furthermore, it can be noted that in the ongoing NICE appraisal of amivantamab + lazertinib, the NICE committee made a similar assessment and concluded that Weibull models for OS were suitable for both treatment arms (National Institute for Health and Care Excellence (NICE) 2025).

Figure 13: Long-term OS projections of amivantamab + lazertinib

Abbreviations: KM: Kaplan-Meier; OS: Overall survival

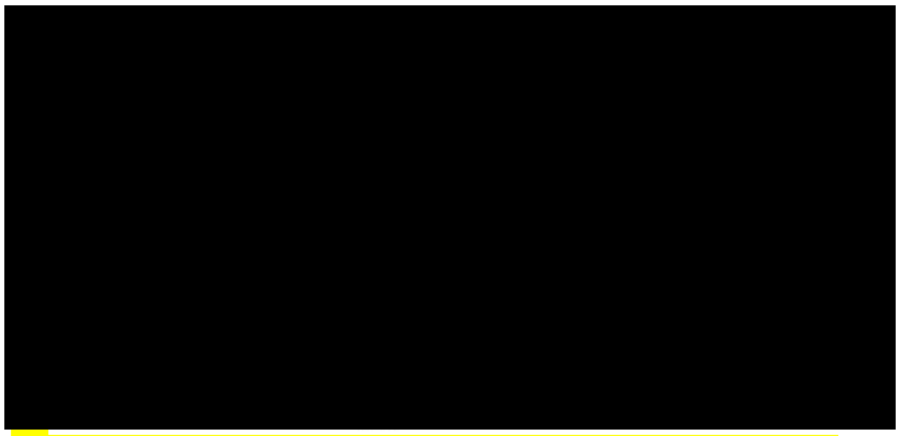


Figure 14: Long-term OS projections of osimertinib

Abbreviations: KM: Kaplan-Meier; OS: Overall survival

8.1.1.3 Extrapolation of TTDD

Table 17 summarises the assumptions associated with the extrapolation of TTDD.

Table 17: Summary of assumptions associated with extrapolation of TTDD

Method/approach	Description/assumption
Data input	Clinical data from MARIPOSA [NCT04487080] (ClinicalTrials.gov 2023a) from data cut 04 December 2024
Model	Seven standard survival models were fitted to the individual subject data in MARPOSA. The seven distributions were: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma or generalised gamma
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Amivantamab: Generalised gamma Lazertinib: Exponential Osimertinib: Gamma
Function with best BIC fit	Amivantamab: Exponential Lazertinib: Exponential Osimertinib: Gamma
Function with best visual fit	Amivantamab: Exponential Lazertinib: Exponential

Method/approach	Description/assumption
	Osimertinib: Gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Amivantamab: Generalised gamma Lazertinib: Exponential Osimertinib: Gamma
Validation of selected extrapolated curves (external evidence)	studies, databases, RWE, clinical experts' opinions on clinical plausibility
Function with the best fit according to external evidence	Amivantamab: Generalised gamma Lazertinib: Exponential Osimertinib: Gamma
Selected parametric function in base case analysis	Amivantamab: Generalised gamma Lazertinib: Exponential Osimertinib: Gamma
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Treatment duration is modelled using TTDD and defined as the time from the date of randomisation to discontinuation of treatment for any reason, and can capture clinical benefit for participants continuing treatment beyond Response evaluation criteria in solid tumours (RECIST) v1.1 defined disease progression (Johnson & Johnson 2023a). TTDD of individuals with ongoing treatment at the data cut-off was censored at the time of the last treatment exposure. TTDD was based on the ITT population and the 04 December 2024 data cut-off, see Figure 15.

TTDD models were fitted separately for amivantamab and lazertinib in the amivantamab + lazertinib arm, as patients may receive one treatment without the other owing to the flexibility of this combination treatment.

Figure 15: MARIPOSA TTDD KM curves for amivantamab + lazertinib and osimertinib

Abbreviations: AMI: amivantamab; KM: Kaplan-Meier; LAZ: lazertinib; TTDD: time to treatment discontinuation or death

The long-term TTDD extrapolations for amivantamab are presented in Figure 16:. Generalised gamma is the best model according to AIC and exponential according to BIC. Generalised gamma predicts the shortest expected treatment duration for amivantamab and was chosen as base case.

Abbreviations: KM: Kaplan-Meier; TTDD: Time to treatment discontinuation or death

Clinical experts recommended that duration of lazertinib treatment should be modelled based on the TTDD curve projections which are expected to be longer than PFS because clinicians would continue treatment with lazertinib post-progression and discontinue amivantamab (Johnson & Johnson 2024a). The exponential curve is the best model according to AIC and BIC, followed by Gompertz. The exponential distribution is selected in the base case, see Figure 17.

Figure 17: Long-term TTDD projections of lazertinib

Abbreviations: KM: Kaplan-Meier; TTDD: Time to treatment discontinuation or death

The long-term TTDD extrapolations for osimertinib are presented in Figure 18. Gamma model is the best fit according to AIC and BIC and was selected for the base case.

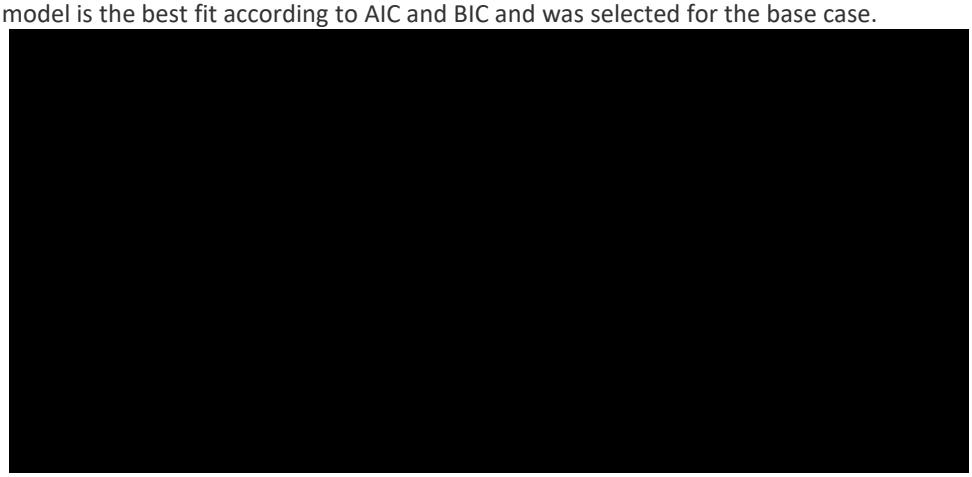


Figure 18: Long-term TTDD projections of osimertinib

Abbreviations: KM: Kaplan-Meier; TTDD: Time to treatment discontinuation or death

8.1.2 Calculation of transition probabilities

Not applicable.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

Table 18 presents the estimates from the CEM and observed median from MARIPOSA.

Table 19 presents the modelled average treatment length and time in model health state, undiscounted and with no half-cycle correction.

Table 19: Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

9. Safety

The safety profile of lazertinib is well defined and tolerable, largely consistent with that seen with other third-generation EGFR-TKIs. Of note, there were no cardiotoxicity-related AEs observed with lazertinib (Lee. SH. 2024). The safety profile of amivantamab is also well defined and tolerable, consistent with its on-target activity against the EGFR and MET pathways.

9.1 Safety data from the clinical documentation

The safety of amivantamab IV + lazertinib is primarily documented in the pivotal trial MARIPOSA. The overall safety profile of amivantamab SC is consistent with that of amivantamab IV while also offering lower rates of administration-related reactions (ARRs) and venous thromboembolism events (VTEs). Details on the SC formulation are in Appendix A. Below is a summary of the clinical documentation of the combination treatment amivantamab IV + lazertinib from MARIPOSA. AEs that occurred during treatment with a study drug (TEAE, treatment-emergent adverse events) were as expected and indicate a favourable safety profile. Treatment-related TEAEs (or "adverse reactions") are also reported. Unless otherwise specified, the data relates to the primary PFS analysis data cut-off (11 August 2023). Mature safety data after an additional 16 months was consistent with the primary analysis that the combination amivantamab + lazertinib was well tolerated (Johnson & Johnson 2024d, Yang J.C.H. et al. 2025).

Johnson & Johnson has invested in additional complimentary clinical studies to address any tolerability concerns. The incidence of selected AEs with therapy management and SC administration of amivantamab was lower in the PALOMA-3 and COCOON trials than MARIPOSA. For PALOMA-3 results, see Appendix A.3.2.

Safety population data

The safety population was defined as all patients who received at least one dose of any study drug (Cho et al. 2024). Safety results presented in this section are reported for safety population (n=1,062; 421 patients in the amivantamab + lazertinib arm, 428 in the osimertinib arm, and 213 in the lazertinib arm).

Treatment exposure

At the primary PFS analysis, there was a median treatment duration of 18.5 months in the amivantamab + lazertinib arm (for both agents) and 18 months in the osimertinib arm (Cho et al. 2024). Details on patient disposition are available in Figure 37 in Appendix B. Below in Table 20, the dose modifications owing to TEAEs are presented. Data on the intervention's efficacy with dose interruptions are available in Appendix F.

Table 20: Dose modifications (MARIPOSA, safety population*, primary analysis data cut August 11, 2023)

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)

TEAE leading to dose reduction †	249 (59)	23 (5)
TEAE leading to dose interruption	350 (83)	165 (39)
TEAE leading to study treatment discontinuation	147 (35)	58 (14)
TEAE leading to death	34 (8)	31 (7)

*The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. †Protocol recommended dose modifications of amivantamab for grade ≥2 related toxicities first; by agent: 328 (78%), 193 (46%), and 145 (34%) interrupted, reduced, and discontinued amivantamab, respectively, and 299 (71%), 176 (42%), and 85 (20%) interrupted, reduced, and discontinued lazertinib, respectively. Abbreviations: TEAE: Treatment-emergent adverse event. Source: Adapted from Table 3 and Table S10 (Cho et al. 2024)

Relative dose intensity

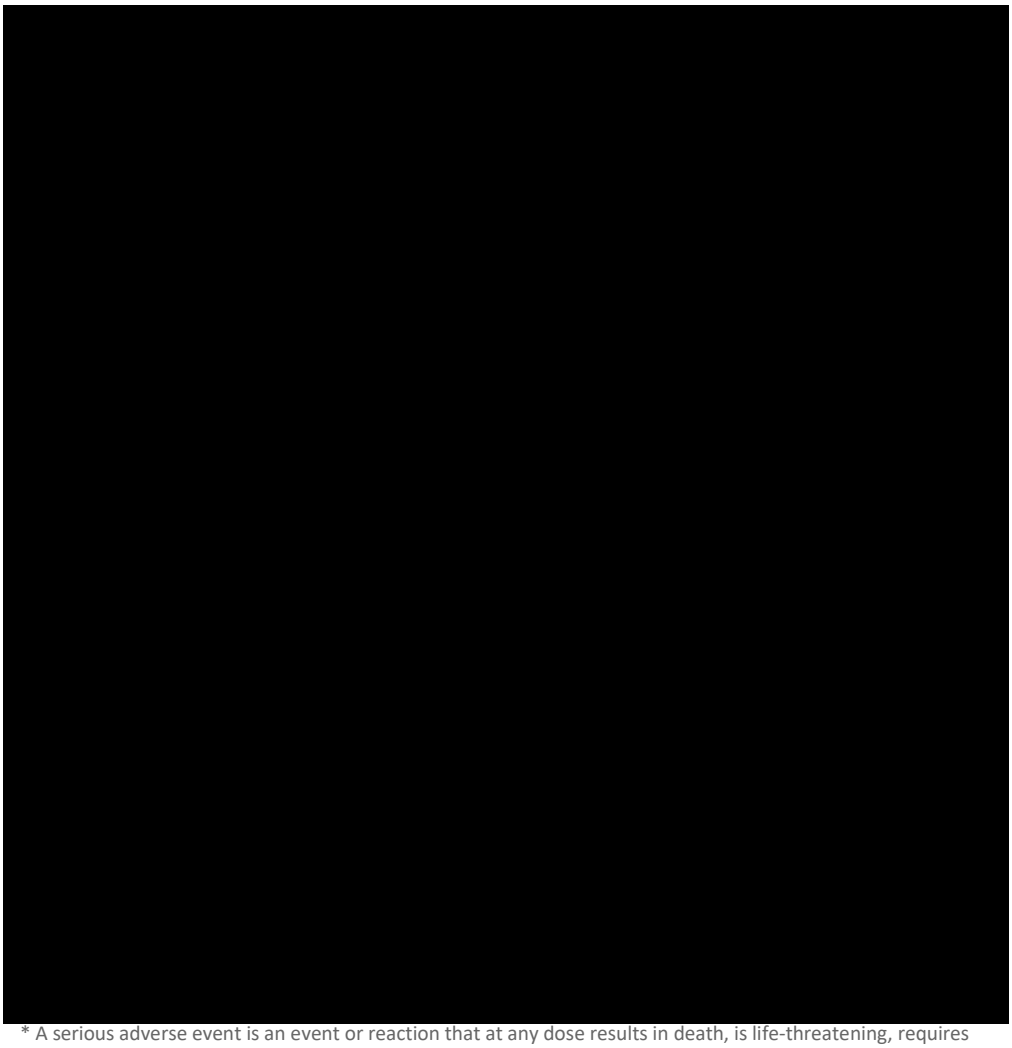
Table 21 presents the proportion of doses missed and relative dose intensity (RDI) as the proportion of planned dose received.

Table 21: Dosing details (MARIPOSA)

Overview of safety events

Table 22 contains an overview of safety events related to TEAEs. Most patients in the trial had at least one TEAE (Cho et al. 2024). Although, most TEAEs observed in the amivantamab + lazertinib arm were Grade 1 or 2.

Table 22: Overview of safety events (MARIPOSA, safety population [a], final OS analysis: 04 December 2024 data cut-off)



* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
§ CTCAE v. 5.0 must be used if available. †Protocol recommended dose modifications of amivantamab for grade ≥2 related toxicities first; by agent: [redacted] interrupted, reduced, and discontinued amivantamab, respectively, and [redacted] interrupted, reduced, and discontinued lazertinib, respectively. a The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment. b Refers to discontinuation of all study agents for individuals in study arm with combination treatment. Abbreviations: CI: Confidence interval; CTCAE: Common terminology criteria for adverse events; n: number; NA: Not available. Source: Data on file from MARIPOSA (Johnson & Johnson 2024f)

Treatment-emergent adverse events

The first onset of key TEAEs for amivantamab + lazertinib (including rash, paronychia, dermatitis acneiform, stomatitis, VTE, peripheral oedema, pruritus and fatigue) occurred within four months of treatment initiation, with late onset uncommon (Spira et al. 2023).

TEAEs ≥ Grade 3 were reported in 75% of the patients treated with amivantamab + lazertinib and in 43% of those treated with osimertinib, with paronychia and rash being the most common events (Cho et al. 2024). In the amivantamab + lazertinib arm, the most common TEAEs (of any Grade) were paronychia (68%), IRRs (63%), rash (62%), and hypoalbuminemia (48%), with rash being the most common Grade ≥3 TEAE (15%) (Cho et al. 2024). In the osimertinib arm, the most common TEAEs (of any Grade) were diarrhoea

(44%) and rash (31%), with VTE and dyspnoea being the most common Grade ≥3 TEAEs (4% each) (Cho et al. 2024).

Serious AEs were reported in 49% of the patients treated with amivantamab + lazertinib and in 33% of those treated with osimertinib (Cho et al. 2024). The three most common serious AEs in the amivantamab + lazertinib arm were pulmonary embolism (n=26, 6%), pneumonia (n=17, 4%), and deep vein thrombosis (n=12, 3%) (Cho et al. 2024). The corresponding numbers and percentages from the osimertinib arm for these events are n=10 (2%), n=21 (5%) and n=2 (<1%), respectively. The three most common serious AEs in the osimertinib arm were pneumonia, pleural effusion and dyspnoea (Cho et al. 2024). Table 23 presents the serious AEs with frequency of ≥ 5% in any treatment arm and all serious AEs are included in Appendix G.

Table 23: Serious adverse events with frequency of ≥ 5% in any treatment arm (MARIPOSA, final OS analysis: 04 December 2024 data cut-off)

Adverse events, n (%)	Intervention Amivantamab + lazertinib (N=421)		Comparator Osimertinib (N=428)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Patients with ≥1 serious AEs	233 (55.3%)	[redacted]	177 (41.4%)	[redacted]
Pneumonia	26 (6.2%)	28	24 (5.6%)	29
Pulmonary embolism	27 (6.4%)	27	11 (2.6%)	11

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). Abbreviations: AE: Adverse event; PFS: Progression-free survival. Source: Data on file from MARIPOSA (Johnson & Johnson 2024f)

Safety of lazertinib monotherapy vs osimertinib

Treatment with osimertinib is associated with a high incidence of cardiotoxicity in patients with EGFR-mutated NSCLC due to the inhibition of HER2 and/or ErbB2 (Yun et al. 2019, Wang et al. 2024). Hence, an exploratory analysis of data from the primary PFS analysis of the MARIPOSA trial was conducted to evaluate cardiotoxicity-related AEs of lazertinib monotherapy vs. osimertinib (both third-generation TKIs) (Lee. SH. 2024).

No clinically meaningful cardiotoxicity-related AEs were observed in the lazertinib arm (Lee. SH. 2024), likely because lazertinib does not inhibit HER2 or ErbB2 (Yun et al. 2019, Wang et al. 2024). Furthermore, lazertinib demonstrated a reduced risk of cardiomyopathy and significantly lower rates of QT interval prolongation compared to osimertinib (Figure 19) (Lee. SH. 2024).

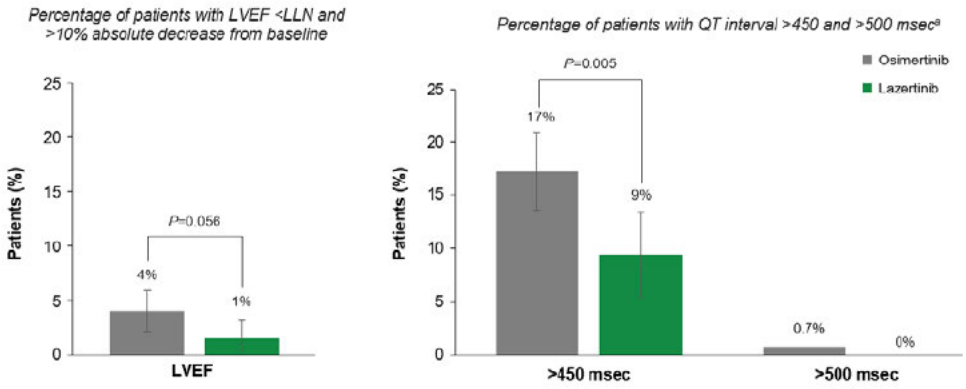


Figure 19: Cardiotoxicity-related AEs for lazertinib vs. osimertinib in MARIPOSA (Primary PFS analysis: 11 August 2023 data cut-off)

Note: Arm C (lazertinib monotherapy) was included in the MARIPOSA trial to assess the contribution of the individual components of amivantamab + lazertinib. a Maximum post-baseline values. Abbreviations: AE: Adverse event; LLN: Lower limit of normal; LVEF: Left ventricular ejection fraction. Source: (Lee. SH. 2024).

Use of safety data in the health economic model

In the CEM, AEs are accounted for in both the costs and HRQoL of patients receiving treatment. Table 24 presents the incidence of AEs used as model inputs for both treatment arms. The AEs are sourced from the MARIPOSA trial based on the December 2024 data cut-off. Included AEs were based on TEAEs of Grade ≥ 3 that had occurred ≥5% of patients in a treatment arm included in the health economic model (Johnson & Johnson 2023b). Any Grade ≥ 3 AEs identified for one treatment arm were included for the other arm as well, if data permitted. Additionally, Grade ≤ 2 VTE is included, based on feedback from the advisory board of the NICE submission.

Table 24: Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Dermatitis acneiform	8.80%	0.00%	Analysis of MARIPOSA trial data (Johnson & Johnson 2024f)	Included AEs were selected owing to being a treatment-emergent AE of grade ≥ 3 that had occurred in at least 5% of patients in a
Alanine aminotransferase increased	6.70%	1.90%		
Hypoalbuminemia	6.41%	0.00%		
Paronychia	11.60%	0.50%		
Infusion-related reaction	6.41%*	0.00%		
Rash	17.30%	0.70%		
Pneumonia	5.20%	5.10%		

Pulmonary embolism	8.60%	2.80%	treatment arm
Grade ≤ 2 VTE*	27.80%	6.80%	

* Incidence of grade ≤ 2 VTE in MARIPOSA includes patients with maximum grade of VTE events of 1 or 2 (i.e., patients who experienced both grade ≤ 2 and grade ≥ 3 VTE were not counted) to avoid double-counting.
Abbreviations: AE: Adverse event; IV: Intravenous; VTE: Venous thromboembolism.

The overall safety profile of amivantamab SC is consistent with that of amivantamab IV while also offering lower rates of ARRs and VTEs (Appendix A.3.2). Hence, in the scenario analysis for SC administration of amivantamab, a relative risk ratio was applied to the incidence of AEs sourced from MARIPOSA for IV administered amivantamab + lazertinib. The relative risks were based on PALOMA-3 (Johnson & Johnson 2024c) which compared amivantamab SC vs amivantamab IV (Table 25).

Table 25: Relative risk of adverse events: amivantamab (SC) + lazertinib vs amivantamab (IV) + lazertinib

Adverse Event	Relative risk
Dermatitis acneiform	1.53
Alanine aminotransferase increased	0.76
Hypoalbuminemia	1.15
Paronychia	2.72
Infusion-related reaction	0.13
Rash	1.02
Pneumonia	0.44
Pulmonary embolism	0.15
Grade ≤ 2 VTE	0.75

Abbreviations: SC: Subcutaneous; IV: Intravenous; VTE: Venous thromboembolism. Source: (Johnson & Johnson 2024c, Johnson & Johnson 2024f)

The impact of AEs on HRQoL was only included for the 1L treatments, given that utility decrements for AEs are not expected to be a key model driver. However, the costs for treating grade ≥ 3 AEs were included for subsequent therapies, see Section 0. AE unit costs are presented in Table 39 in Section 11, and Table 26 below displays the AE incidence rates.

Table 26: Incidence rates (%) of grade ≥ 3 AEs by subsequent therapy

Adverse Event	Platinum-based chemotherapy (%)	EGFR MoA/TKI or TKI based regimen (%)	Non-platinum-based chemotherapy (%)	IO ± chemotherapy ± VEGFi (%)

Anaemia	11.8%	0.0	3.8	6.1
Diarrhoea	11.	69.9	24.4	2.8
Fatigue	0.7	1.3	3.5	3.1
Febrile neutropenia	0.0	0.0	9.4	8.4
Neutropenia	11.8	0.0	14.6	13.7
Decreased neutrophil count	0.0	0.0	11.1	8.7
Rash	0.0	5.9	0.0	1.3
Thrombocytopenia	7.4	0.0	0.0	4.1
Hypertension	0.0	0.0	0.0	6.4
Decreased platelet count	0.0	0.0	0.0	5.1
Source for AE incidence	NICE TA850 (CHRYSALIS trial) (NICE 2022b)	NICE TA850 (CHRYSALIS trial)(NICE 2022b)	NICE TA850 (CHRYSALIS trial)(NICE 2022b)	IMpower150 (Socinski et al. 2018)

Abbreviations: AE: Adverse event; EGFR: Epidermal growth factor receptor; IO: Immuno-oncology drug; MoA; Monoclonal antibody; NICE: National Institute for Health and Care Excellence; TA: Technology appraisal; TKI: Tyrosine kinase inhibitor; VEGFi: Vascular endothelial growth factor receptor inhibitor

9.2 Safety data from external literature applied in the health economic model

Not applicable.

Table 27: Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	NA							

10. Documentation of health-related quality of life (HRQoL)

HRQoL was measured in the MARIPOSA clinical trial using three PROs: EQ-5D-5L, EORTC QLQ-C30, and NSCLC-SAQ (Table 28). The results of the EQ-5D-5L index score were used to derive the utilities for the CEM. The other PROs in MARIPOSA were not included in the CEM, for a summary of findings and patterns of missing data and collection, please see Appendix H. The result from the PROs is based on the 04 December 2024 data-cut which had a median follow-up time of 37.8 months.

Table 28: Overview of included HRQoL instruments

Measuring instrument	Source	Utilisation
EQ-5D-5L	MARIPOSA	Assessed global HRQoL. Consists of two items: EQ-5D descriptive system (measures mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and the EQ-VAS (measures the patient's self-rated health on a vertical visual analogue scale)(EuroQol 2023). The five-domain descriptive system was used to calculate the utility score with Danish weights for this submission (Jensen et al. 2021).
EORTC QLQ-C30	MARIPOSA	Assessed disease-related symptoms. Cancer-specific QoL questionnaire designed to measure cancer patients' physical, psychological, and social functions (EORTC 2023).
NSCLC-SAQ	MARIPOSA	Assessed disease-related symptoms. NSCLC-specific QoL questionnaire designed to measure cough, pain, dyspnoea, fatigue, and poor appetite (McCarrier et al. 2016)

Abbreviations: EORTC QLQ-C30: European Organization of Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L: EuroQol Questionnaire, Five Dimensions, Five Levels; HRQoL: Health related quality of life; NSCLC: Non-small cell lung cancer; NSCLC-SAQ: Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire; QoL: Quality of life; VAS: Visual analogue scale.

10.1 Presentation of the health-related quality of life

Below follows the HRQoL data from MARIPOSA using the EQ-5D-5L instrument that was included in the CEM of this application.

10.1.1 Study design and measuring instrument

MARIPOSA was the source of data for both the clinical outcome data and HRQoL. For details on the study design, see Section 6.1.1. The EQ-5D-5L was included as an exploratory endpoint to further assess HRQoL in participants. Given the generic nature of the EQ-5D instrument, MARIPOSA also included disease-specific instruments to capture specific domains that are particularly relevant for patients with cancer (See Appendix H). The a priori expectations were to maintain or even improve HRQoL with treatment with amivantamab + lazertinib.

The EQ-5D-5L is a validated tool to measure health status and health utility, including mobility, self-care, usual activities, pain, discomfort, and anxiety/depression (EuroQol 2023). It is commonly used in clinical studies to provide a measure of patient utility for clinical and economic appraisals as it is a generic instrument used across various disease areas. The EQ-5D-5L is a revision to the original EQ-5D-3L (with 3 response levels per item versus 5 response levels in EQ-5D-5L) and has been shown to significantly increase reliability and sensitivity (discriminatory power) while maintaining ease of completion.

EQ-5D-5L data were collected in line with the study protocol (Johnson & Johnson 2023a). All patients in the ITT population who had filled out the EQ-5D-5L questionnaire at baseline, as well as at least one other observation on a later date (i.e., the EQ-5D-5L evaluable population) were considered eligible for the utility analyses. Missing observations were excluded from the analysis. Utility values for the progression-free and progressed disease health states were obtained from analysis of MARIPOSA EQ-5D-5L data from the 04 December 2024 data cut-off by data divided by progression status.

10.1.2 Data collection

Data were collected at the following time points (Johnson & Johnson 2023a):

- Cycle 1, Day 1
- Cycle 2, Day 1
- First day of every other following cycle (Cycle 3, 5, 7, etc.) ± 2 days
- 30 days after last dose ± 7 days
- Every 12 weeks ± 14 days during study follow-up (x 4 visits/calls)

The number of subjects who responded to the PRO questionnaire EQ-5D-5L within the progression-free health state, by visit and treatment is presented in Table 29. Overall, there was a high response as indicated by the completion proportions >[redacted]. Further details on responders and non-responders are contained in Appendix I. Pattern of missing data and completion for EORTC QLQ-C30 and NSCLC-SAQ is presented in Table 76 and Table 77.

Table 29: Pattern of missing data and completion

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	A+L	O	A+L	O	A+L	O	A+L	O
Baseline	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 02	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cycle 03	429	429	[redacted]					
Cycle 05	429	429	[redacted]					
Cycle 07	429	429	[redacted]					
Cycle 09	429	429	[redacted]					
Cycle 11	429	429	[redacted]					
Cycle 13	429	429	[redacted]					
Cycle 15	429	429	[redacted]					
Cycle 17	429	429	[redacted]					
Cycle 19	429	429	[redacted]					
Cycle 21	429	429	[redacted]					
Cycle 23	429	429	[redacted]					
Cycle 25	429	429	[redacted]					
Cycle 27	429	429	[redacted]					
Cycle 29	429	429	[redacted]					
Cycle 31	429	429	[redacted]					
Cycle 33	429	429	[redacted]					

EQ-5D-5L utility scores were derived using Danish 5L utility tariffs (Jensen et al. 2021), in alignment with DMC guidelines.

Descriptive statistics were conducted for the ITT population for the 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 was analysed using mixed models for repeated measures (MMRMs) among randomised participants who received at least 1 dose of study treatment and have at least 1 evaluable post-baseline measurement.

10.1.3 HRQoL results

Below follows HRQoL results from MARIPOSA among progression-free patients (Johnson & Johnson 2024e).

EQ-VAS

Figure 20 show that the HRQoL in terms of EQ-VAS score was largely maintained overtime across both treatment arms. Higher levels of variation are observed at later cycles owing to few patients. Figure 21 indicates that for the majority of cycles, that there was a positive improvement from baseline.

Figure 20: Mean EQ-VAS score over time among patients with progression-free disease (MARIPOSA)

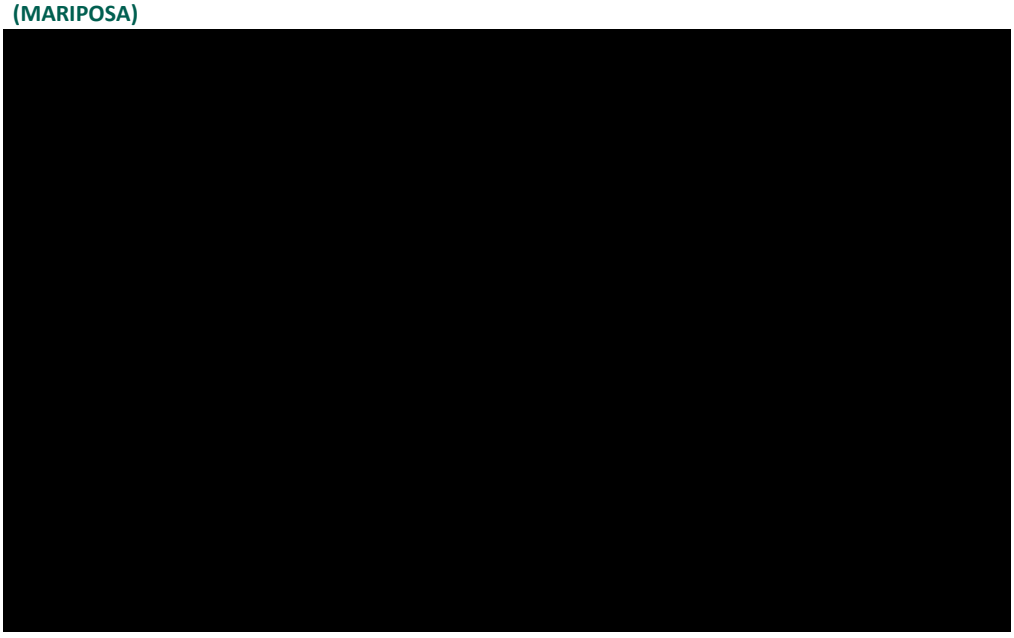


Figure 21 Mean change from baseline in EQ-VAS score

Similarly, the mean index score was maintained overtime in both treatment arms (Figure 22 and Figure 23). Furthermore, Figure 23 suggests a positive change from baseline value for both treatment arms in early cycles. Mean change from baseline including observations post-progression is shown in Appendix I (Figure 74).

Figure 22: Mean EQ-5D-5L index score over time among patients with progression-free disease (MARIPOSA, Danish utility weights)

Figure 23: Mean change from baseline in EQ-5D-5L index value among patients with progression-free disease (MARIPOSA, Danish utility weights)

The summary statistics for the EQ-5D-5L index score are presented in Table 30 by visit (Johnson & Johnson 2024e).

Table 30: HRQoL EQ-5D-5L summary statistics

	Intervention	Comparator	Intervention vs. comparator
	Amivantamab + lazertinib	Osimertinib	

	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 02 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 03 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 05 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 07 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 09 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted])
Cycle 11 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 27 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 31 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 33 Day 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10.2 Health state utility values (HSUVs) used in the health economic model

Data from MARIPOSA (04 December 2024 data cut-off) used to inform utility values for the progression-free and progressed disease health states.

10.2.1 HSUV calculation

State-dependent mean utility values estimated by MMRMs were derived from the MARIPOSA data for the CEM. The pooled cohort was used to estimate health state

specific mean utility values with the Danish utility values (Jensen et al. 2021). No imputation of missing values was conducted owing to the high response frequency overall. For further details on the calculation of the utility values for the two health states respectively, we refer to Appendix I.1.

10.2.1.1 Mapping

Not relevant as EQ-5D-5L was utilised in the MARIPOSA trial.

10.2.2 Disutility calculation

QALY decrements due to AEs are applied once-off upon the start of treatment. UK tariffs are used for disuitilities. However, disutilities have little impact on the model results.

The model includes the detrimental impact of grade ≥ 3 TEAEs on HRQoL. An AE utility decrement of [redacted] was estimated from a repeated-measures linear mixed model in progression-free participants in MARIPOSA. This decrement is multiplied by mean cumulative AE duration in years for each event type from grade ≥ 3 TEAEs in MARIPOSA (pooled across treatment arms) to obtain QALY loss associated with the AE (Table 31). Total QALY loss for each intervention is then calculated by multiplying AE-specific QALY loss by the probability of experiencing that AE. This aggregate QALY loss is then applied once to each intervention arm at the start of the PSM.

Table 31: AE durations and QALY loss

AE	Mean Cumulative Duration (Days)	AE QALYs
Dermatitis acneiform	[redacted]	[redacted]
Alanine aminotransferase increase	[redacted]	[redacted]
Hypalbuminaemia	[redacted]	[redacted]
Paronychia	[redacted]	[redacted]
Infusion-related reaction	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]
Grade ≤ 2 VTE	[redacted]	[redacted]

Abbreviations: AE: Adverse events; QALY: Quality-adjusted life year; VTE: Venous thromboembolism * No duration data available, assumed equal to neutropenia. ** Assumed equal to duration of any AE in body/organ class "Infections and infestations". † Assumed equal to duration of grade 2 AE, as no events of grade ≥ 3 were recorded in MARIPOSA. ‡ Assumed the same as thrombocytopenia.

10.2.3 HSUV results

A single health state-specific utility value is assigned to all patients in the progression-free or progressed disease health states. The results of the compound symmetry MMRM based on the MARIPOSA data for the health state utility values and the AE disutilities are presented in Table 32.

Table 32: Overview of health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression free	[redacted]	EQ-5D-5L	DK	MARIPOSA. MMRM with compound symmetry correlation structure with a time component. Number of questionnaires: 7,391
Progressed disease	[redacted]	EQ-5D-5L	DK	MARIPOSA. MMRM with compound symmetry correlation structure with a time component. Numbers of questionnaires: 1,240
Disutilities				
Grade ≥3 AE	[redacted]	EQ-5D-5L	UK	MARIPOSA. Repeated-measures linear mixed model in progression-free participants in MARIPOSA. This decrement is multiplied by mean cumulative AE duration in years for each event type from grade ≥ 3 TEAEs in MARIPOSA (pooled across treatment arms) to obtain QALY loss associated with the specific AE
Grade ≤2 VTE	[redacted]	EQ-5D-5L	UK	MARIPOSA. Repeated-measures linear mixed model in progression-free participants in MARIPOSA

Abbreviations: AE: Adverse event; CI: Confidence interval; DK: Denmark; EQ-5D-5L: EuroQol five-dimensional questionnaire, five level version; MMRM: Mixed model for repeated measures; VTE: Venous thromboembolism

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not relevant. MARIPOSA is the only source of utility data in the CEM.

10.3.1 Study design

Not relevant.

10.3.2 Data collection

Not relevant.

10.3.3 HRQoL Results

Not relevant.

10.3.4 HSUV and disutility results

Not relevant, accordingly, Table 33 is left blank.

Table 33: Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs	NA			

11. Resource use and associated costs

Disease- and treatment-related costs were applied for each model health state and event. Cost parameters included in the model were related to drug acquisition, co-medications, drug monitoring, drug administration, subsequent treatment, disease management, AE management, terminal care, and patient travel costs.

11.1 Medicines - intervention and comparator

Table 34 presents the medicines used in the model in the intervention and comparator arms. Acquisition and administration costs of amivantamab, lazertinib, and osimertinib (both as monotherapy and as part of combined regimens) are corrected for the proportion of missed doses estimated from MARIPOSA trial data as a ratio of administered doses to the expected number of doses for each patient based on their duration of treatment, see Sections 3.3 for information on amivantamab + lazertinib and 3.5 for osimertinib.

Table 34: Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Amivantamab (IV)	1 050 mg < 80 kg 1 400 mg ≥ 80 kg	[redacted]	Once weekly for the first 4 weeks and then once every 2 weeks	No
Lazertinib	240 mg	[redacted]	Once daily	N/A
Osimertinib	80 mg	[redacted]	Once daily	N/A

* Not applicable due to equal cost of 40-mg and 80-mg tablets.

A correction for dose reduction was not applied to osimertinib as the costs of 80 mg and 40 mg osimertinib tablets are the same, which means that dose reductions would not affect the cost per dose of osimertinib. Table 35 outlines the medicine acquisition costs.

Table 35: Medicine acquisition costs

Medicine	Strength	Pack size	Price per pack (DKK)
Amivantamab (IV)	350 mg	1	9,381.60
Lazertinib	240 mg	28	36,012.98
Lazertinib	80 mg	56	36,012.98
Osimertinib	80 mg	30	37,775
Osimertinib	40 mg	30	37,775

Source: Medicinpriser (Lægemiddelstyrelsen 2025) supplemented with data on file.

11.2 Medicines– co-administration

The CEM includes the costs of concomitant medications. Concomitant medications are defined as any drugs given in addition to the active treatment regimens, and inputs are consistent with the MARIPOSA trial where co-medications were given with amivantamab (Johnson & Johnson 2023a). In MARPOSA, an increased risk of VTE was observed with IV administration when combined with lazertinib (Cho et al. 2024). Hence, the clinical protocol for PALOMA-3 was updated to include prophylaxis use for the first 16 weeks (Johnson & Johnson 2022c). The use of prophylaxis in clinical practice is further supported by the SmPC (EMA 2025c). In the CEM, the total cost of prophylaxis (Rivaroxaban) over the 16 weeks is applied to at treatment initiation (i.e. the first four weeks only). Total duration was aligned with PALOMA-3. Table 36 lists the acquisition costs for the co-medications included for first-line treatments (amivantamab).

Table 36: Co-medication acquisition costs

Medicine	Units per pack	Unit strength	Price per pack (DKK)
Dexamethasone	2 (vial)	8 mg	197
Paracetamol	300	500 mg	49
Diphenhydramine	1	350 mg	66
Rivaroxaban	100	10 mg	1,589

Source: Medicinpriser (Lægemiddelstyrelsen 2025)

11.3 Administration costs

Table 37 outlines the administration costs used in the model. The base case assumes IV administration of amivantamab throughout the modelled time horizon. A bi-weekly SC formulation of amivantamab has recently been approved and dosing every fourth week is expected in the near future. No administration costs are applied for lazertinib or osimertinib which are oral therapies.

Table 37: Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV administration for monotherapy	As per respective dosing schedule	1,330	Interactive DRG: 04MA98. Diagnose: DC384: Kraeft i lungehinde+ BWAA62: Medicingivning ved intravenøs infusion.	DRG, takster, (Sundhedsdatastyrelsen 2025)
IV administration for combination therapy	As per respective dosing schedule	1,330	Interactive DRG: 04MA98. Diagnose: DC384: Kraeft i lungehinde+ BWAA62: Medicingivning ved intravenøs infusion.	DRG, takster, (Sundhedsdatastyrelsen 2025)
Oral therapy	N/A	0		Assumption

11.4 Disease management costs

The model captures health-state specific costs for routine monitoring and follow-up. A micro-costing approach is used to determine these costs. Table 38 presents the frequencies and costs of medical resources.

Table 38: Disease management costs used in the model

Activity	Frequency in PF and PD	Unit cost [DKK]	DRG code	Reference
Oncology outpatient visit	Every third month	1,330	04MA98-MDC04 1-dagsgruppe, pat. mindst 7 år.	DRG-takster, (Sundhedsdatastyrelsen 2025)
Disease management	Every third month	1,494	23MA04-Kontrolundersøgelse	DRG-takster, (Sundhedsdatastyrelsen 2025)
CT scan (chest)	Every third month	3,331	30PR05- CT-scanning af hjertet med angiografi.	DRG-takster, (Sundhedsdatastyrelsen 2025)

The types and frequencies of resources by health state were based on previous submission to the DMC for PAPILLON, where the frequencies were based on input from a Danish clinical expert (Medicinrådet 2025), Unit costs were used from relevant sources (Sundhedsdatastyrelsen 2025). In DMC's base case for PAPILLION, monitoring cost amivantamab was added and consisted of: an outpatient visit prior to administration of amivantamab in treatment weeks 1, 2 and 4 and disease management monitoring every three weeks for the first three months of amivantamab treatment (Medicinrådet 2025).

11.5 Costs associated with management of adverse events

Unit costs for AEs are detailed in Table 39. The once-off cost for an AE was calculated from the treatment-specific incidence rate (see Section 9) and the relevant unit cost.

Table 39: Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Dermatitis acneiform	09MA98- MDC09 1-dagsgruppe, pat. mindst 7 år.	1,578
Alanine aminotransferase increased	07MA98- MDC07 1-dagsgruppe, pat. mindst 7 år.	2,072
Hypalbuminaemia	07MA98- MDC07 1-dagsgruppe, pat. mindst 7 år.	2,072
Paronychia	09MA98- MDC09 1-dagsgruppe, pat. mindst 7 år.	1,578
Infusion related reaction	21MA01- Allergiske og allergi lignende reaktioner.	5,163
Rash	09MA98- MDC09 1-dagsgruppe, pat. mindst 7 år.	1,578

	DRG code	Unit cost/DRG tariff
Pulmonary Embolism	04MA04-Lungeemboli.	34,499
Grade ≤ 2 VTE	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år.	2,208
Pneumonia	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år.	2,208

11.6 Subsequent treatment costs

Subsequent treatment inputs directly impact costs but not survival outcomes in the model; the clinical impact of subsequent treatment is already accounted for indirectly within the OS curves. The cost of subsequent treatment is applied as a once-off cost at disease progression and includes drug acquisition, co-medications, monitoring, administration, and AE management. The distributions of subsequent treatments are described in Table 40.

Table 40: Distribution of 2 and 3L+ treatment

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

The distribution of 2L treatment is based on MARIPOSA (Johnson & Johnson 2024f) and proportion of patients receiving 3L+ is based on the chemotherapy arm in MARIPOSA-2 (Johnson & Johnson 2024h) (Table 94 and Table 95 for distribution and duration for 2 and 3L+, respectively). Table 41 outlines the subsequent treatments included in the model. Platinum-based chemotherapy is costed based on carboplatin/cisplatin + pemetrexed, all EGFR TKI-based regimens are costed as osimertinib, non-platinum-based chemotherapy is costed as docetaxel, and immuno-oncology drug (IO) ± chemotherapy ± Vascular endothelial growth factor inhibitor (VEGFi) is costed based on a combination of atezolizumab + bevacizumab + carboplatin + paclitaxel.

Table 41: Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Carboplatin	5 AUC	100%	Every fourth week	No
Cisplatin	75 mg/m^2	100%	Every fourth week	No
Docetaxel	75 mg/m^2	100%	Every fourth week	No
Osimertinib	80 mg	N/A	Once per day	No

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Pemetrexed	500 mg/m^2	100%	Every fourth week	No
Atezolizumab	1 200 mg	100%	Every fourth week	No
Bevacizumab	15 mg/kg	100%	Every fourth week	No
Paclitaxel	200 mg/m^2	100%	Every fourth week	No

Table 42 presents the medicine acquisition costs of subsequent treatment. See Table 96 for dosing details for these subsequent treatments.

Table 42: Medicine acquisition cost subsequent treatment

Medicine	Strength	Pack size	Price per pack (DKK)
Carboplatin	450 mg	1	226
Cisplatin	50 mg	1	100
Docetaxel	20 mg	1	35
Osimertinib	40 mg	30	37,775
Osimertinib	80 mg	30	37,775
Pemetrexed	500 mg	1	552
Atezolizumab	1 200 mg	1	28,345
Bevacizumab	400 mg	1	7,515
Paclitaxel	100 mg	1	1,830

Source: Medicinpriser (Lægemiddelstyrelsen 2025)

11.6.1 Subsequent treatments - concomitant medications

Pemetrexed treatment requires concomitant medication with vitamin B12 (hydroxocobalamin), folic acid, and dexamethasone. Paclitaxel treatment requires concomitant administration esomeprazole, diphenhydramine, and dexamethasone. See Table 43 for acquisition cost and Table 97 for the dosing details of these co-medications.

Table 43: Co-medication acquisition costs

Medicine	Units per pack	Unit strength	Price per pack (DKK)
Vitamin B12	12	1 mg	499
Folic acid	100	5 mg	63

Medicine	Units per pack	Unit strength	Price per pack (DKK)
Dexamethasone	2	8 mg	197
Diphenylamine	1	350 mg	66
Dexamethasone	20	4 mg	78

Source: Medicinpriser (Lægemiddelstyrelsen 2025)

11.6.2 Subsequent treatments - administration cost

The administration costs for subsequent treatments used in the CEM are described in Table 37 in Section 11.3. The total administration cost is calculated from the frequency of subsequent treatments, respectively, see Table 96 in Appendix N.2 for details.

11.6.3 Subsequent treatments - monitoring cost

The unit cost and frequency of monitoring associated with pemetrexed is presented in Table 44. Blood test costs were applied for every dose of pemetrexed (regimen: Platinum-based chemotherapy) in subsequent treatments.

Table 44: Monitoring cost for subsequent treatments

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Lab test - Full blood count	0.33	84	N/A	Taktskort Laboratorieundersøgelser Oct 2024. Cost of Blod, hemablobin and Generel ydelse (Foreningen af Speciallæger 2025)
Lab test - Liver function	0.33	84	N/A	Assumed same as full blood count
Lab test - Renal function	0.33	138	N/A	Taktskort Laboratorieundersøgelser Oct 2024. Cost of urin, creatine and Generel ydelse. (Foreningen af Speciallæger 2025)

Abbreviations: N/A: Not applicable

11.6.4 Subsequent treatments - Adverse events cost

The management of grade ≥3 AEs were included in the costs of subsequent therapy. The total one-off cost of an AE related to subsequent treatment was based on the treatment-specific incidence rate of the AE (see Section 9.2) and the relevant unit cost (Table 45).

Table 45: Cost associated with management of adverse events in subsequent treatments

	DRG code	Unit cost/ DRG tariff
Anaemia	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år	2,208
Diarrhoea	06MA98-MDC06 1-dagsgruppe, pat. mindst 7 år	1,722
Fatigue	23MA03- Symptomer og fund, u. kompl. bidiag.	5,271
Febrile neutropenia	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år	2,208
Neutropenia	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år	2,208
Neutrophil count decreased	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år	2,208
Rash	09MA98- MDC09 1-dagsgruppe, pat. mindst 7 år	1,578
Thrombocytopenia	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år	2,208
Hypertension	05MA11- Hypertension	18,807
Platelet count decrease	16MA98- MDC16 1-dagsgruppe, pat. mindst 7 år	2,208

11.7 Patient costs

The CEM adopts a limited societal perspective and includes non-medical costs for the patients based on the DMC's guidance (Medicinrådet 2024c). Costs for administering amivantamab IV were based on 4.5 hours of administration and a cost for patient time of 188 DKK/hour. In a scenario analysis of amivantamab SC, patient time required at each visit was assumed to be 2 hours based on the substantially shorter time needed for administering amivantamab SC compared to IV (Alexander et al. 2024) The transportation cost to and from treatment was 140 DKK.

Table 46: Patient costs used in the model

Activity	Time spent [minutes, hours, days]	Unit cost (DKK)
Patient cost	4.5 hours	188
Travel cost (round trip)	N/A	140

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

Table 47: Base case overview

Feature	Description
Comparator	Osimertinib
Type of model	Partitioned survival mode approach with three mutually exclusive health states: progression-free, progressed disease and death.
Time horizon	30 years which aligns with the guidelines of a lifetime horizon as the start age of the modelled patient population is 62.3 years old.
Treatment line	1st line. Subsequent treatment lines included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in the MARIPOSA trial (Johnson & Johnson 2023a). Danish population weights were used to estimate health-state utility values for this application (Jensen et al. 2021)
Costs included	Medicine costs, Hospital costs, Costs of adverse events, Patient costs
Dosage of medicine	The dosing schedules for amivantamab + lazertinib and osimertinib are modelled based on the MARIPOSA study
Average time on treatment (mean TTDD), years	Intervention: amivantamab, 2.15 + lazertinib, 3.30 Comparator: osimertinib, 2.47
Parametric function for PFS	Intervention: amivantamab + lazertinib, Gamma Comparator: osimertinib, Gamma
Parametric function for OS	Intervention: amivantamab + lazertinib, Weibull Comparator: osimertinib, Weibull
Inclusion of waste	Yes
Average time in model health state, years	[redacted]

12.1.1 Base case results

The results of the health economic analysis are presented in Table 48 for the base case specified in Table 47. The results indicate that amivantamab + lazertinib was associated with more life years and QALYs than osimertinib. The incremental QALY gain per patient

was 1.00 (3.92 versus 2.92) and 1.17 (4.58 versus 3.41) life years gained. Amivantamab + lazertinib was associated with a total incremental cost per patient of 1,481,597 DKK (2,736,452 versus 1,254,855 DKK). The resulting ICER was 1,487,377 DKK/QALY.

Table 48: Base case results, discounted estimates

	Amivantamab + lazertinib	Osimertinib	Difference
Medicine costs	2 392 887	1 052 403	1 340 484
Administration cost	60 120	0	60 120
Medicine costs – co-administration	3 549	0	3 549
Monitoring costs	8 843	0	8 843
Subsequent treatment cost	108 755	114 137	-5 382
Routine care cost - progression-free	58 275	43 074	15 202
Routine care cost - progressed disease	54 580	40 872	13 708
End-of-life care cost	0	0	0
AE cost	4 872	1 288	3 584
Patient time and transport cost	44 570	3 081	41 489
Total costs	**2,736,452**	**1,254,855**	**1,481,597**
Life years gained (Progression-free)	2.37	1.75	0.62
Life years gained (Progressed disease)	2.22	1.66	0.56
Total life years	**4.58**	**3.41**	**1.17**
QALYs (Progression-free)	2.07	1.53	0.54
QALYs (Progressed disease)	1.86	1.39	0.46
QALYs (adverse reactions)	-0.006	-0.001	-0.01
Total QALYs	**3.92**	**2.92**	**1.00**
Incremental costs per life year gained		**1,261,765**	
Incremental cost per QALY gained (ICER)		**1,487,377**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

In the one-way sensitivity analysis (OWSA), each parameter of interest was changed independently while all others remained at their default values.

OWSA of key input parameters can be used to identify parameters to which the model results are most sensitive (i.e., model drivers) by changing the default value to minimum and maximum plausible values. Where available or possible to calculate, lower and upper bounds of 95% CIs were used as alternative values. In the absence of 95% CIs or information that would allow their calculation, such as standard errors (SEs), upper and lower bounds tested in the OWSA were calculated assuming a SE equal to 10% of the mean value or a sample size of 100 for proportions.

In the case of correlated parameters (namely those of OS, PFS and TTDD distributions), as each of them was tested individually in OWSA by changing its value to the minimum and maximum, the remaining parameters of the joint distribution were set to their conditional mean values, conditioned on the value of the currently tested parameter. See Figure 24 for the tornado diagram and Table 49 for the lower and upper values when applicable.

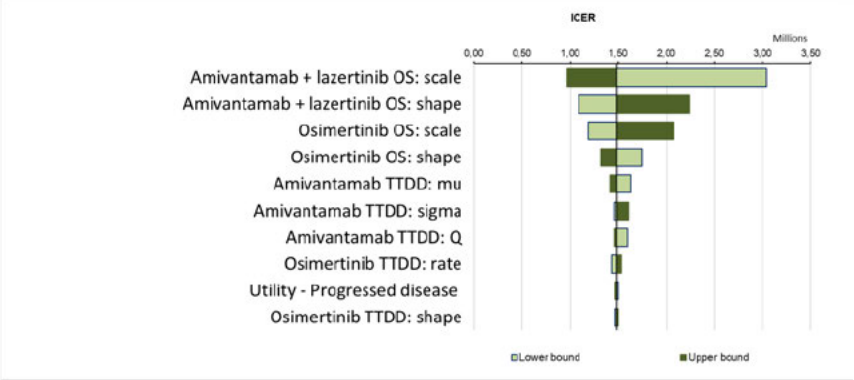


Figure 24: Tornado diagram of the 10 most influential parameters

Table 49: One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY) Lower/Upper
Base case					[redacted]
Amivantamab + lazertinib OS: scale	See section 12.2.1		NR	NR	[redacted]
					[redacted]
	See section 12.2.1		NR	NR	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY) Lower/Upper
Amivantamab + lazertinib OS: shape					[redacted]
Osimertinib OS: scale	See section 12.2.1		NR	NR	[redacted]
					[redacted]
Osimertinib OS: shape	See section 12.2.1		NR	NR	[redacted]
					[redacted]
Amivantamab TTDD: mu	See section 12.2.1		NR	NR	[redacted]
					[redacted]
Amivantamab TTDD: sigma	See section 12.2.1		NR	NR	[redacted]
					[redacted]
Amivantamab TTDD: Q	See section 12.2.1		NR	NR	[redacted]
					[redacted]
Osimertinib TTDD: rate	See section 12.2.1		NR	NR	[redacted]
					[redacted]
Utility - Progressed disease	Lower input: 0.82 Upper input: 0.86		NR	NR	[redacted]
					[redacted]
Osimertinib TTDD: shape	See section 12.2.1		NR	NR	[redacted]
					[redacted]

Abbreviations: DKK: Danish Krone: NR: Not reported; OS: Overall survival; QALY: Quality-adjusted life year; TTDD: Time to treatment discontinuation or death.

12.2.2 Scenario analyses

Assumption for each scenario and rationale is presented in Table 50 with corresponding result shown in Table 52.

Table 50: Settings for scenario analysis

Parameter	Change	Reasoning
PFS definition	INV-assessed	To show endpoint effect on ICER

TTD definition	PFS	If patients are not treated beyond progression
TTDD curve selection amivantamab	Exponential	Generalised gamma is the best model according to AIC and BIC. It predicts the shortest expected treatment duration for amivantamab; the next higher TTTD curve (i.e., exponential) is tested
Amivantamab administration	Amivantamab administrated SC Q4W, 3,520 mg < 80kg, 4,640 mg > 80kg	To show effect of a different preparation
OS curve selection amivantamab + lazertinib	Gamma	OS Gamma distribution has more slowly increasing hazards and is still within the range indicated by KOLs during the advisory board. Note that gamma is not used for OSI OS in a scenario, as gamma is at the upper limit of KOL estimates.
Discounting	0%	Test the discount factors effect on results

Abbreviations; AE: Adverse events; HRQoL: Health-related quality of life; IV: Intravenous; INV: Investigator; OS: Overall survival; PFS: Progression-free survival; Q4W: Dosing every four weeks; SC: Subcutaneous; TTDD: Time to treatment discontinuation or death; TTD: Time to treatment discontinuation; VTE: venous thromboembolism.

For the scenario analysis involving SC treatment administration, the medicine acquisition costs presented in Table 51 were applied. For further details we refer to Appendix A.1.

Table 51: Medicine acquisition costs for the scenario analysis

Medicine	Strength	Pack size	Price per pack (DKK)
Amivantamab (Subcutaneous injection)	1,600 mg	1	[redacted]
	2,240 mg	1	[redacted]
	2,400 mg	1	[redacted]
	3,520 mg	1	[redacted]
	4,640 mg	Administered as 1 x 2,240 mg and 1 x 2,400 mg subcutaneous injection	[redacted]

As shown in Table 53, amivantamab administered SC every four weeks has minimal impact on the ICER. When compared to IV administration, the two treatment methods appear to be very similar in terms of cost-effectiveness from a Danish context.

Table 52: Results from scenario analysis

Scenario analysis	Incremental costs (DKK)	Incremental QALYs	ICER (DKK)
Base case	[redacted]	1.00	[redacted]
PFS definition, INV-assessed	[redacted]	0.99	[redacted]
TTD definition- PFS	[redacted]	1.00	[redacted]
TTDD curve selection amivantamab- exponential	[redacted]	1.00	[redacted]
Ami administration, SC Q4W	[redacted]	1.00	[redacted]
OS curve selection amivantamab + lazertinib- Gamma	[redacted]	1.15	[redacted]
0% discounting	[redacted]	1.30	[redacted]

Abbreviations; AE: Adverse events; HRQoL: Health-related quality of life; IV: Intravenous; INV: Investigator; OS: Overall survival; PFS: Progression-free survival; Q4W: Dosing every four weeks; SC: Subcutaneous; TTDD: Time to treatment discontinuation or death; TTD: Time to treatment discontinuation; VTE: Venous thromboembolism.

12.2.3 Probabilistic sensitivity analyses

To account for the joint uncertainty of the underlying parameter estimates, a probabilistic sensitivity analysis (PSA) was performed. The PSA shows the overall uncertainty of the cost-effectiveness results and provides expected values of model results under parameter uncertainty see Appendix J for full details. Only parameter uncertainty related to sample-based estimation was accounted for in the PSA; parameters such as time horizon and discount rates were not included, as their values constitute structural assumptions.

In the PSA, the average incremental cost was 1,497,125 DKK and QALYs gained with the intervention were 1.01. This results in an ICER of 1,480,982 DKK/QALY. See Figure 25 and Figure 26 for the cost-effectiveness plane and cost-effectiveness acceptability curve.

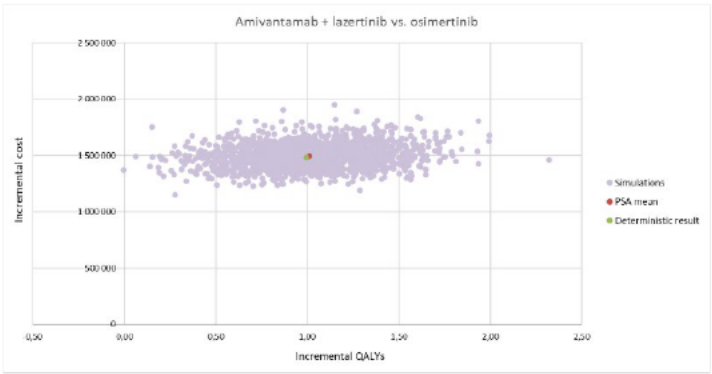


Figure 25: Cost-effectiveness plane

Abbreviations: PSA: probabilistic sensitivity analysis

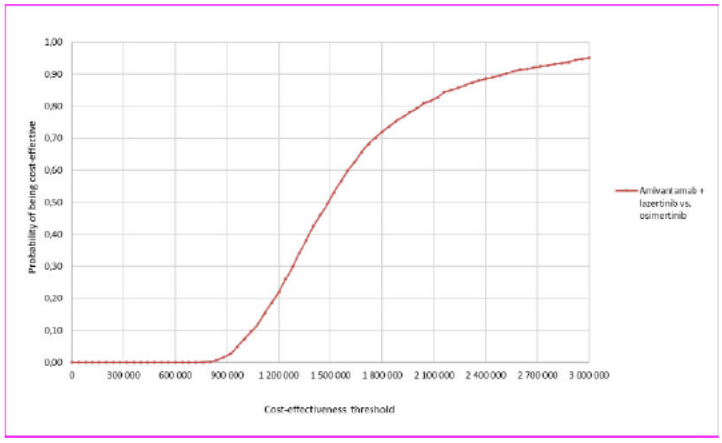


Figure 26: Cost-effectiveness acceptability curve

The stability of the ICER based on the number of PSA simulations conducted is shown in Figure 27. As the number of PSA iterations increases, the mean ICER values begin to stabilise, indicating that the mean ICER is converging to a more stable estimate. After approximately 220 iterations, the curve flattens and beyond this point, increasing the number of simulations has minimal impact on the mean ICER value.

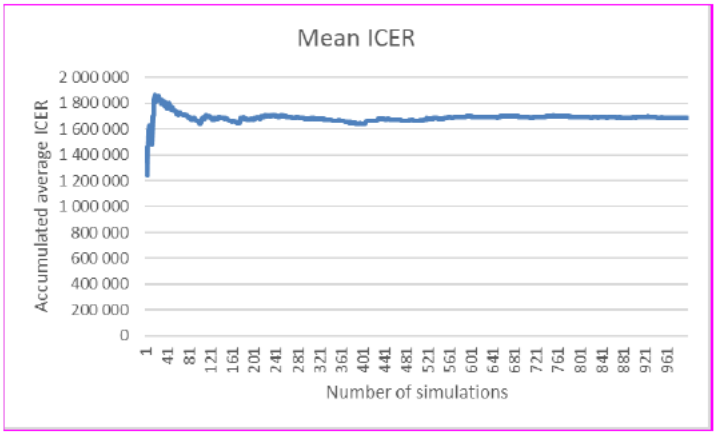


Figure 27: Convergence plot

Abbreviations: ICER: Incremental cost effectiveness ratio

13. Budget impact analysis

The relevant patient population for this application is previously treatment naïve adult patients with advanced (locally advanced or metastatic) NSCLC with common EGFR mutations (EGFR ex19del and EGFR L858R).

13.1 Eligible population calculation

As described in Section 3.2.3, 198 new patients each year are expected to be eligible for treatment with amivantamab + lazertinib. In addition, the market share of amivantamab + lazertinib has been assumed to be 30% year 1, 40% year 2, 60% year 3, 70% year 4, and 80% year 5. Based on this, the number of patients to be treated with amivantamab + lazertinib over the next five years are described in Table 53.

Table 53: Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Amivantamab + lazertinib	59	79	119	139	158
Osimertinib	139	119	79	59	40
			Non-recommendation		
Amivantamab + lazertinib	0	0	0	0	0
Osimertinib	198	198	198	198	198

The base case results from the budget impact analysis are presented in Table 54, displaying the budgetary consequences if amivantamab + lazertinib is recommended. The results are generated using the same settings as in the base case in the health economic model. The budget impact is estimated based on AIP and undiscounted costs. The budget impact in year five is 156,920,415 DKK.

Budget impact

Table 54: Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	120,386,357	209,045,192	286,059,608	345,422,385	394,474,408
The medicine under consideration is NOT recommended	92,762,987	155,636,006	196,215,763	221,736,842	237,553,993
Budget impact of the recommendation	**27,623,370**	**53,409,187**	**89,843,845**	**123,685,543**	**156,920,415**

14. List of experts

[redacted]

15. References

Alexander, M., Cheng, Y., Lee, S. H., et al. 2024. Subcutaneous vs Intravenous Amivantamab: Patient Satisfaction and Resource Utilization Results from the PALOMA-3 Study (Presentation). *World Conference of Lung Cancer,* San Diego, CA USA.

Barroso, A., Estevinho, F., Hespanhol, V., et al. 2024. Management of infusion-related reactions in cancer therapy: strategies and challenges. *ESMO Open,* 9**,** 102922.

Besse, B., Lee, S.-H., Lu, S., et al. 2024. Mechanisms of Acquired Resistance to First-line Amivantamab Plus Lazertinib Versus Osimertinib in Patients With EGFR-mutant Advanced Non-Small Cell Lung Cancer - An Early Analysis from the Phase 3 MARIPOSA study (Oral presentation). *ESMO* Barcelona, Spain.

Castellanos, E., Feld, E. & Horn, L. 2017. Driven by Mutations: The Predictive Value of Mutation Subtype in EGFR-Mutated Non–Small Cell Lung Cancer. *Journal of Thoracic Oncology,* 12**,** 612-623.

Chmielecki, J., Mok, T., Wu, Y. L., et al. 2023. Analysis of acquired resistance mechanisms to osimertinib in patients with EGFR-mutated advanced non-small cell lung cancer from the AURA3 trial. *Nat Commun,* 14**,** 1071.

Cho, B., Felip, E., Spira, AI., et al. 2023. Amivantamab Plus Lazertinib Versus Osimertinib as First-line Treatment in EGFR-mutated Advanced NSCLC - Primary Results from MARIPOSA, a Phase 3, Global, Randomized, Controlled Trial (Presentation). *ESMO,* Madrid, Spain.

Cho, B. C., Lu, S., Felip, E., et al. 2024. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. *N Engl J Med,* 391**,** 1486-1498.

ClinicalTrials.gov. 2023a. *A Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib in Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA)* [Online]. Available: https://classic.clinicaltrials.gov/ct2/show/record/NCT04487080 [Accessed 28/02/2025].

ClinicalTrials.gov. 2023b. *A Study of Amivantamab Subcutaneous (SC) Administration for the Treatment of Advanced Solid Malignancies (PALOMA) (NCT04606381)* [Online]. Available: https://classic.clinicaltrials.gov/ct2/show/NCT04606381 [Accessed 11/03/2025].

ClinicalTrials.gov. 2023c. *A Study of Lazertinib With Subcutaneous Amivantamab Compared With Intravenous Amivantamab in Participants With Epidermal Growth Factor Receptor (EGFR)-Mutated Advanced or Metastatic Non-small Cell Lung Cancer (PALOMA-3)* [Online]. Available: https://classic.clinicaltrials.gov/ct2/show/NCT05388669?term=NCT05388669&draw=2&rank=1 [Accessed 28/02/2025 12/02/2025].

ClinicalTrials.gov. 2024a. *Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib (COCOON) - NCT06120140* [Online]. Available: https://clinicaltrials.gov/study/NCT06120140?term=NCT06120140%20&rank=1 [Accessed 25/02/2025].

ClinicalTrials.gov. 2024b. *A Study of Amivantamab in Participants With Advanced or Metastatic Solid Tumors Including Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small Cell Lung Cancer (PALOMA-2) - NCT05498428* [Online]. Available: https://clinicaltrials.gov/study/NCT05498428?term=NCT05498428&rank=1 [Accessed 28/02/2025].

Dansk Lunge Cancer Gruppe/Register. 2024. *Dansk Lunge Cancer Register - Årsrapport 2023* [Online]. Available: https://www.lungecancer.dk/wp-

content/uploads/2024/12/DLCR-%C3%85rsrapport-2023.pdf [Accessed 02/05/2025].
Danske Multidisciplinære Cancer Grupper. 2024. *Pallierende onkologisk behandling af onkogen-dreven ikke-småcellet lungekræft v1.0* [Online]. Available: https://www.dmcg.dk/kliniske-retningslinjer/kliniske-retningslinjer-opdelt-paa-dmcg/lungecancer/Pallierende-onkologisk-behandling-af-onkogen-dreven-ikke-smaacellet-lungekraeft/ [Accessed 02/05/2025].
del Rosario Garcia Campelo, M., Cho, B. C., Girard, N., et al. 2024. Effect of Amivantamab Dose Interruptions on Efficacy and Safety of First-line Amivantamab Plus Lazertinib in EGFR-mutant Advanced NSCLC: Exploratory Analyses From the MARIPOSA study (Presentation). *European Lung Cancer Congress,* Prague, Czechia.
Ehrenstein, V., Eriksen, K., Taylor, A., et al. 2023. Characteristics and overall survival of patients with early-stage non-small cell lung cancer: A cohort study in Denmark. *Cancer Med,* 12**,** 30-37.
EMA. 2019. *Guideline on the clinical evaluation of anticancer medicinal products* [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf [Accessed 05/01/2019].
EMA. 2024. *Committee for Medicinal Products for Human Use (CHMP): Summary of opinion Lazcluze lazertinib (EMA/CHMP/515529/2024)* [Online]. Available: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-lazcluze_en.pdf [Accessed 03/02/2025].
EMA. 2025a. *Lazcluze : EPAR - Public assessment report* [Online]. Available: https://www.ema.europa.eu/en/medicines/human/EPAR/lazcluze [Accessed 14/04/2025].
EMA. 2025b. *LAZCLUZE, INN-lazertinib SmPC* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/lazcluze-epar-product-information_en.pdf [Accessed 18/03/2025].
EMA. 2025c. *RYBREVANT, INN-amivantamab SmPC* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf [Accessed 11/08/2025].
EMA. 2025d. *RYBREVANT, INN-amivantamab SmPC (Subcutaneous update)* [Online]. Available: https://ec.europa.eu/health/documents/community-register/2025/20250404165577/anx_165577_en.pdf [Accessed 23/05/2025].
EMA. 2025e. *TAGRISSO, INN-osimertinib SmPC* [Online]. Available: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf [Accessed 10/02/2025].
Enstone, A., Panter, C., Manley Daumont, M., et al. 2015. PRM47: Societal burden and impact on health related quality of life (HRQOL) of non-small cell lung cancer (NSCLC) in Europe. *Value in Health,* 18**,** A335-A766.
EORTC. 2023. *Quality of Life* [Online]. Available: https://qol.eortc.org/ [Accessed 7/11/2023].
EuroQol. 2023. *EQ-5D-5L | About* [Online]. Available: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/ [Accessed 07/11/2023].
Felip, E., Cho, B. C., Gutiérrez, V., et al. 2024. Amivantamab plus lazertinib versus osimertinib in first-line EGFR-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. *Annals of Oncology,* 35**,** 805-816.
Foreningen af Speciallæger. 2025. *Takstkort* [Online]. Available: https://laeger.dk/foreninger/faps/takster/takstkort [Accessed 05/02/2025].
Gadgeel SM., C. c. B., Lu S. et al. 2024. Amivantamab Plus Lazertinib vs Osimertinib in First-line EGFR-mutant Advanced NSCLC: Longer Follow-up of the MARIPOSA

Study. (Oral presentation). *World Conference on Lung Cancer* San Diego, CA USA.
Ganti, A. K., Klein, A. B., Cotarla, I., et al. 2021. Update of Incidence, Prevalence, Survival, and Initial Treatment in Patients With Non–Small Cell Lung Cancer in the US. *JAMA Oncology,* 7**,** 1824-1832.
Girard, N., Leighl, N., Ohe, Y., et al. 2023. Mortality Among EGFR-mutated Advanced NSCLC Patients After Starting First-line Osimertinib Treatment: A Real-world, US Attrition Analysis. *European Lung Cancer Congress,* Copenhagen, Denmark.
Globocan, W. H. O. 2020. Lung.
Gouliaev, A., Berg, J., Khalil, A. A., et al. 2024. Factors behind favorable long-term lung cancer survival in Norway compared to Denmark: a retrospective cohort study. *Eur Clin Respir J,* 11**,** 2414485.
Hendriks, L. E., Cortiula, F., Mariamidze, E., et al. 2025. *ESMO Oncogene-Addicted Non-Small Cell Lung Cancer Living Guideline v1.2* [Online]. Available: https://www.esmo.org/living-guidelines/esmo-oncogene-addicted-metastatic-non-small-cell-lung-cancer-living-guideline [Accessed 17/03/2025].
Hendriks, L. E., Kerr, K. M., Menis, J., et al. 2023. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol,* 34**,** 339-357.
Heppner, D. E., Wittlinger, F., Beyett, T. S., et al. 2022. Structural Basis for Inhibition of Mutant EGFR with Lazertinib (YH25448). *ACS Med Chem Lett,* 13**,** 1856-1863.
Horn, M. K., Mathias, S. D., Colwell, H. H., et al. 2023. Qualitative Research to Evaluate Perceptions around Biomarker Testing and Patient-Reported Outcomes (PROs) for Use in Studies of Non-Small Cell Lung Cancer (NSCLC). *European Lung Cancer Congress* Copenhagen, Denmark.
Jakobsen, E., Olsen, K. E., Bliddal, M., et al. 2021. Forecasting lung cancer incidence, mortality, and prevalence to year 2030. *BMC Cancer,* 21**,** 985.
Jensen, C. E., Sørensen, S. S., Gudex, C., et al. 2021. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Appl Health Econ Health Policy,* 19**,** 579-591.
Johnson & Johnson 2022a. Amivantamab - Scientific Communication Platform. *Data on file*.
Johnson & Johnson 2022b. PALOMA-2 (protocol amendment 1) A Phase 2, Open-Label, Parallel Cohort Study of Subcutaneous Amivantamab in Multiple Regimens in Patients with Advanced or Metastatic Solid Tumors including EGFR-mutated Non-Small Cell Lung Cancer. *Data on file*.
Johnson & Johnson 2022c. PALOMA-3 (protocol amendment 2) A Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy. *Data on file*.
Johnson & Johnson. 2023a. *Clinical Protocol: A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA) Protocol 73841937NSC3003, amendment 4* [Online]. clinicaltrials.gov. Available: https://cdn.clinicaltrials.gov/large-docs/80/NCT04487080/Prot_000.pdf [Accessed 10/02/2025].
Johnson & Johnson 2023b. Clinical Study Report (Primary Analysis-Final). A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA). *Data on file*.

Johnson & Johnson 2023c. Primary Endpoint Analysis Clinical Study Report. A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA). *Data on file*.

Johnson & Johnson 2024a. Clinical Advisory Board -Amivantamab in 1st and 2nd line treatment of advanced NSCLC: Global cost-effectiveness modelling and indirect treatment comparison. Final Report March 2024 *Data on file*.

Johnson & Johnson 2024b. Clinical Study Report (Interim Analysis). A Phase 2, Open-Label, Parallel Cohort Study of Subcutaneous Amivantamab in Multiple Regimens in Patients with Advanced or Metastatic Solid Tumors including EGFR-mutated Non-Small Cell Lung Cancer (PALOMA-2 Cohorts 1 and 6). *Data on file*.

Johnson & Johnson 2024c. Clinical Study Report (Primary Analysis). Phase 3, Open-label, Randomized Study of Lazertinib with Subcutaneous Amivantamab Administered via Manual Injection Compared with Intravenous Amivantamab in Patients with EGFR-mutated Advanced or Metastatic Non-small Cell Lung Cancer After Progression on Osimertinib and Chemotherapy (PALOMA-3). *Data on file*.

Johnson & Johnson 2024d. Clinical Summary - Final Overall Survival Analysis (Data cut-off 04 December 2024) - A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA). *Data on file*.

Johnson & Johnson 2024e. Patient reported outcome measures- MARIPOSA (Data cut-off 04 December 2024). *Data on file*.

Johnson & Johnson 2024f. A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer (MARIPOSA) (Data cut-off 04 December 2024) *Data on file*.

Johnson & Johnson 2024g. A Retrospective Database Study to Describe Patient Profiles, Prognostic Factors and Outcomes in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer While on Treatment with Standard of Care Osimertinib: Results using RIGS Hospitalet Data. *Data on file*.

Johnson & Johnson 2024h. A Study of Amivantamab and Lazertinib in Combination With Platinum-Based Chemotherapy Compared With Platinum-Based Chemotherapy in Patients With Epidermal Growth Factor Receptor (EGFR)-Mutated Locally Advanced or Metastatic Non- Small Cell Lung Cancer After Osimertinib Failure (MARIPOSA-2) (NCT04988295). *Data on file*.

Johnson & Johnson 2024i. Time to Symptomatic Progression: A Patient-Relevant Clinical Endpoint in Non-Small Cell Lung Cancer. *Data on file*.

Knuuttila et al. 2025. FIN-EGFRprint: A retrospective observational study to investigate treatments and outcomes in patients with epidermal growth factor receptor-mutated (EGFRm) advanced Non-Small Cell Lung Cancer (aNSCLC) in Finland. *ELCC.* Paris, France.

Koch, M., Hjermstad, M. J., Tomaszewski, K., et al. 2020. Gender effects on quality of life and symptom burden in patients with lung cancer: results from a prospective, cross-cultural, multi-center study. *J Thorac Dis,* 12**,** 4253-4261.

Kommunernes og Regionernes Løndatakontor. 2025. *SIRKA* [Online]. Available: https://www.krl.dk/#/sirka [Accessed 10/02/2025].

Koulouris, A., Tsagkaris, C., Corriero, A. C., et al. 2022. Resistance to TKIs in EGFR-Mutated Non-Small Cell Lung Cancer: From Mechanisms to New Therapeutic Strategies. *Cancers* 14.

Lægemiddelstyrelsen. 2025. *Medicinpriser.dk Søgning* [Online]. Available: https://www.medicinpriser.dk/ [Accessed 30/01/2025].
Latimer, N. R. 2013. Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making,* 33**,** 743-54.
Lee. SH., C., BC., Hayashi, H., et al. 2024. Lazertinib vs Osimertinib in 1L EGFR-mutant Advanced NSCLC: A Randomized, Double-blind, Exploratory Analysis From MARIPOSA (Presentation) *World Conference on Lung Cancer,* San Diego, CA, USA.
Leighl, N. B., Akamatsu, H., Lim, S. M., et al. 2024a. Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study. *Journal of Clinical Oncology,* 42**,** 3593-3605.
Leighl, N. B., Akamatsu, H., Min Lim, S., et al. 2024b. Subcutaneous amivantamab vs intravenous amivantamab, both in combination with lazertinib, in refractory EGFR-mutated, advanced non-small cell lung cancer: Primary results, including overall survival, from the global, phase 3, randomized controlled PALOMA-3 trial. (Presentation). *ASCO* Chicago, IL, USA.
Leonetti, A., Sharma, S., Minari, R., et al. 2019. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer,* 121**,** 725-737.
Lim, S. M., Tan, J.-L., Mourão Dias, J., et al. 2024a. Subcutaneous amivantamab and lazertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Results from the phase 2 PALOMA-2 study. *Journal of Clinical Oncology,* 42**,** LBA8612-LBA8612.
Lim, S. M., Tan, J. L., Dias, J. M., et al. 2024b. Subcutaneous Amivantamab and Lazertinib as First-line Treatment in Patients With EGFR-mutated Advanced Non-small Cell Lung Cancer (NSCLC): Interim Results From the Phase 2 PALOMA-2 Study. *ASCO* Chicago, IL, USA.
Lundberg, F. E., L., A. T. M., Mats, L., et al. 2020. Trends in cancer survival in the Nordic countries 1990–2016: the NORDCAN survival studies. *Acta Oncologica,* 59**,** 1266-1274.
McCarrier, K. P., Atkinson, T. M., DeBusk, K. P., et al. 2016. Qualitative Development and Content Validity of the Non-small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), A Patient-reported Outcome Instrument. *Clin Ther,* 38**,** 794-810.
Medicinrådet. 2019. *Osimertinib (Tagrisso)* [Online]. Available: https://medicinraadet.dk/anbefalinger-og-vejledninger/laegemidler-og-indikationsudvidelser/o/osimertinib-tagrisso-ikke-smacellet-lungekraeft-med-aktiverende-egfr-mutation [Accessed 09/05/2025].
Medicinrådet. 2023. *Medicinrådets anbefaling vedr. amivantamab til behandling af EGFR exon 20ins-positiv ikkesmåcellet lungekræft* [Online]. Available: https://filer.medicinraadet.dk/media/2lhm2lho/medicinr%C3%A5dets-anbefaling-vedr-amivantamab-til-egfr-exon20ins-nsclc-2-linje-vers-1-0x.pdf [Accessed 02/05/2025].
Medicinrådet. 2024a. *Medicinrådets lægemiddelrekommandation vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet v3.2* [Online]. Available: https://filer.medicinraadet.dk/media/po4djred/medicinradets-laegemiddelrekommandation-vedr-laegemidler-til-uhelbredelig-ikke-smacellet-lungekraeft-version-3-2.pdf [Accessed 02/05/2025].
Medicinrådet. 2024b. *Opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til uhelbredelig ikkesmåcellet lungekræft Anbefaling og det kliniske sammenligningsgrundlag* [Online]. Available:

https://filer.medicinraadet.dk/media/z5tbqzlb/opsummering-medicinradets-evidensgennemgang-vedr-laegemidler-til-uhelbredelig-ikke-smacellet-lungekraeft-vers-1-0.pdf [Accessed 06/05/2025].
Medicinrådet. 2024c. *Værdisætning af enhedsomkostninger v1.8* [Online]. Available: https://filer.medicinraadet.dk/media/lemjycrd/vaerdisaetning-af-enhedsomkostninger-vers-1-8.pdf [Accessed 30/01/2025].
Medicinrådet. 2025. *Medicinrådets anbefaling vedr. amivantamab i kombination med kemoterapi til 1. linjebehandling af ikkesmåcellet lungekræft med EGFR exon 20-insertion* [Online]. Available: https://filer.medicinraadet.dk/media/13dlj5gz/medicinradets-anbefaling-vedr-amivantamab-plus-kemo-til-forstelinjebehandling-af-nsclc-vers-1-0-x.pdf [Accessed 06/05/2025].
Melosky, B., Kambartel, K., Häntschel, M., et al. 2022. Worldwide Prevalence of Epidermal Growth Factor Receptor Mutations in Non-Small Cell Lung Cancer: A Meta-Analysis. *Molecular Diagnosis & Therapy,* 26**,** 7-18.
Migliorino, M. R., Santo, A., Romano, G., et al. 2017. Economic burden of patients affected by non-small cell lung cancer (NSCLC): the LIFE study. *J Cancer Res Clin Oncol,* 143**,** 783–791.
National Institute for Health and Care Excellence (NICE). 2025. *Draft guidance consultation: Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-smallcell lung cancer (TA11279)* [Online]. Available: https://www.nice.org.uk/guidance/gid-ta11279/documents/consultation-document [Accessed 11/08/2025].
Nguyen, D., Besse, B. & Cho, B. C., et al. 2024. Amivantamab Plus Lazertinib vs Osimertinib in First-line, EGFR-mutant Advanced NSCLC: Patient-relevant Outcomes From MARIPOSA. *World Conference on Lung Cancer,* San Diego, CA, US.
NICE. 2011. *NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data* [Online]. Available: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf [Accessed 10/09/2023].
NICE. 2022a. *NICE health technology evaluations: the manual* [Online]. Available: https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741 [Accessed 10/09/2023].
NICE. 2022b. *Single Technology Appraisal: Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced nonsmall-cell lung cancer after platinumbased chemotherapy [ID3836]* [Online]. Available: https://www.nice.org.uk/guidance/ta850/documents/committee-papers-2 [Accessed 10/09/2023].
NORDCAN. 2024. *Prevalence - Tables v9.4* [Online]. Available: https://nordcan.iarc.fr/en/dataviz/prevalence_table?years=2023&years_available=1943_2023 [Accessed 06/05/2025].
Odogwu, L., Mathieu, L., Goldberg, K. B., et al. 2018. FDA Benefit-Risk Assessment of Osimertinib for the Treatment of Metastatic Non-Small Cell Lung Cancer Harboring Epidermal Growth Factor Receptor T790M Mutation. *Oncologist,* 23**,** 353-359.
Park, K., Bennouna, J., Boyer, M., et al. 2019. Sequencing of therapy following first-line afatinib in patients with EGFR mutation-positive non-small cell lung cancer. *Lung Cancer,* 132**,** 126-131.
Passaro, A., Wang, J., Wang, Y., et al. 2024. Amivantamab plus chemotherapy with and without lazertinib in EGFR-mutant advanced NSCLC after disease progression on

osimertinib: primary results from the phase III MARIPOSA-2 study. *Ann Oncol,* 35**,** 77-90.
Pérol, M., Chouaid, C., Bjerrum, A., et al. 2024. Prognostic Factors and Outcomes of Patients With Advanced Non–Small Cell Lung Cancer While on Osimertinib Treatment: A Retrospective Database Study. *European Lung Cancer Congress,* Prague, Czechia.
Ramalingam, S. S., Vansteenkiste, J., Planchard, D., et al. 2020. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. *N Engl J Med,* 382**,** 41-50.
Sari, S., Andayani, T., Endarti, D., et al. 2020. Health-Related Quality of Life in Non-Small Cell Lung Cancer (NSCLC) Patients with Mutation of Epidermal Growth Factor Receptor (EGFR) in Indonesia *Research Journal of Pharmacy and Technology*.
Socinski, M. A., Jotte, R. M., Cappuzzo, F., et al. 2018. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med,* 378.
Soria, J. C., Ohe, Y., Vansteenkiste, J., et al. 2018. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. *N Engl J Med,* 378**,** 113-125.
Spira, A. I., Spigel, D., Nguyen, D., et al. 2023. Amivantamab Plus Lazertinib Versus Osimertinib In First-line EGFR-mutant Advanced NSCLC: A Post-progression and Safety Analysis of MARIPOSA (Presentation). *North America Conference on Lung Cancer* Chicago, IL, USA.
Statistics Denmark. 2025a. *HISB8: Life table (2 years tables) by sex, age and life table* [Online]. Available: https://www.statbank.dk/HISB8 [Accessed 09/05/2025].
Statistics Denmark. 2025b. *StatBank Denmark: FOLKL1AM - Population at the first day of the month by region, sex, age and time* [Online]. Available: https://www.statbank.dk/statbank5a/selectvarval/saveselections.asp [Accessed 06/05/2025].
Sundhedsdatastyrelsen. 2025. *DRG-takster - 2025* [Online]. Available: https://sundhedsdatastyrelsen.dk/data-og-registre/sundhedsoekonomi/drg/drg-takster [Accessed 30/01/2025].
Vadagam, P., Lin, I., Musci, R., et al. 2024. Modeled costs of adverse event management in treatment naïve EGFR NSCLC patients with exon 19 deletion or exon 21 L858R mutations treated with amivantamab plus lazertinib, osimertinib plus chemotherapy, or osimertinib alone. *AMCP Nexus,* Las Vegas, NV, USA.
van Meerbeeck, J. P. & Franck, C. 2021. Lung cancer screening in Europe: where are we in 2021? *Translational Lung Cancer Research,* 10**,** 2407-2417.
Vyse, S. & Huang, P. H. 2019. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduction and Targeted Therapy,* 4**,** 5.
Walters, S., Maringe, C., Coleman, M. P., et al. 2013. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. *Thorax,* 68**,** 551-564.
Wang, Y., Deng, X., Qiu, Q., et al. 2024. Risk factors of osimertinib-related cardiotoxicity in non-small cell lung cancer. *Front Oncol,* 14**,** 1431023.
Weinstein, M. C., O'Brien, B., Hornberger, J., et al. 2003. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health,* 6**,** 9-17.
Wood, R. & Taylor-Stokes, G. 2019. Cost burden associated with advanced non-small cell lung cancer in Europe and influence of disease stage. *BMC Cancer,* 19**,** 214.
Wood, R., Taylor-Stokes, G., Smith, F., et al. 2019. The humanistic burden of advanced non-small cell lung cancer (NSCLC) in Europe: a real-world survey linking patient clinical factors to patient and caregiver burden. *Qual Life Res,* 28**,** 1849-1861.
Yang J.C.H., Kim Y.J., Lee S.H., et al. 2025. Amivantamab Plus Lazertinib vs Osimertinib in First-line EGFR-mutant Advanced NSCLC: Final Overall Survival from the Phase 3

MARIPOSA Study (Oral presentation). *European Lung Cancer Congress,* Paris, France.
Yun, J., Hong, M. H., Kim, S. Y., et al. 2019. YH25448, an Irreversible EGFR-TKI with Potent Intracranial Activity in EGFR Mutant Non-Small Cell Lung Cancer. *Clin Cancer Res,* 25**,** 2575-2587.
Zappa, C. & Mousa, S. A. 2016. Non-small cell lung cancer: current treatment and future advances. *Transl Lung Cancer Res,* 5**,** 288-300.
Zhang, Y. L., Yuan, J. Q., Wang, K. F., et al. 2016. The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget,* 7**,** 78985-78993.

Appendix A. Amivantamab subcutaneous administration form

The SC formulation of amivantamab is included in this application as a scenario analysis using dosing every four weeks (Q4W) in combination with lazertinib, as this is the dose regimen that is expected to be most frequently used.

Evidence from the ongoing PALOMA-3 and PALOMA-2 clinical trials demonstrates that amivantamab SC provides comparable efficacy to amivantamab IV while maintaining a consistent safety profile, with reduced administration-related reactions (ARRs) and venous thromboembolism events (VTEs) (Johnson & Johnson 2024b, Johnson & Johnson 2024c). Additionally, amivantamab SC enhances patient convenience and optimises healthcare resources (Johnson & Johnson 2024c, Leighl et al. 2024b, Leighl et al. 2024a, Vadagam et al. 2024). Amivantamab SC Q2W has been approved for the same indications as amivantamab IV in the treatment of advanced EGFR-mutated NSCLC. The same is expected for the Q4W formulation.

Below follows further details on the SC formulation including dosing, a description of the clinical trial programme substantiating the non-inferiority of this administration form as well as results regarding efficacy and safety.

A.1 The intervention

SC formulation of approved IV therapies may offer several potential benefits, including streamlined healthcare delivery, reduced healthcare provider involvement, and improved patient convenience and satisfaction while reducing the risk of administration related reactions (Barroso et al. 2024). Accordingly, amivantamab SC was developed to offer the same high efficacy and pharmacokinetics as amivantamab IV, with low rates of administration related reactions and VTEs.

Amivantamab SC is co-formulated with recombinant human hyaluronidase PH20 (SC-CF), which is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously (EMA 2025d). It is a ready-to-use solution available in several vial size options for SC injection (1,600 mg, 2,240 mg, 2,400 mg, and 3520 mg) (EMA 2025d).

A.1.1 Regulatory approval

Amivantamab SC was approved by the EC for administration every two weeks (Q2W) in combination with lazertinib for the 1L treatment of adult patients with advanced NSCLC with EGFR ex19del or Exon 21 L858R substitution mutations in April 2025. Three studies were behind this regulatory extension (PALOMA [NCT04606381](ClinicalTrials.gov 2023b), PALOMA-2 [NCT05498428] (ClinicalTrials.gov 2024b, Johnson & Johnson 2022b), and PALOMA-3 [NCT05388669] (ClinicalTrials.gov 2023c, Johnson & Johnson 2022c)).

A monthly (Q4W) dosing option for amivantamab SC will introduce patient choice and less frequent treatment regimens may be particularly advantageous for patients with

longer travel distances. The Q4W has been submitted for regulatory approval and is expected to be approved for this indication in Q1 2026.

A.1.2 Posology

The recommended dosages of amivantamab when used in combination with lazertinib, are provided in Table 55 (EMA 2025c, EMA 2025d). Irrespective of formulation, the recommended dosage of amivantamab is based on baseline body weight (above or below 80 kilograms [kg]) (EMA 2025c, EMA 2025d). Amivantamab SC is injected in the SC tissue of the abdomen over approximately five minutes (EMA 2025d).

Based on clinician feedback, it is expected that amivantamab will mainly be administered in SC formulation with a monthly dosing (PALOMA-2, cohort 5, expected EMA approval Q1 2026). PALOMA-3 is supporting the market authorisation of amivantamab SC.

Table 55: Recommended dosage and administration schedules of amivantamab SC when used in combination with lazertinib

	Q2W		Q4W	
	<80 kg	≥80 kg	<80 kg	≥80 kg
Administration	Subcutaneous injection			
Dosing	1,600 mg	2,240 mg	3,520 mg	4,640 mg (2,240 mg + 2,400 mg)
Schedule	Initiation: Weekly (total of 4 doses) 1,600 mg. Starting at Week 5 onwards, patients receive 1,600 mL every two weeks.	Initiation: Weekly (total of 4 doses) 2,240 mg. Starting at Week 5 onwards, patients receive 2,240 mL every two weeks.	Initiation: Weekly (total of 4 doses) 1,600 mg (10 mL vial). Starting at Week 5 onwards, patients receive 3,520 mg once every 4 weeks.	Initiation: Weekly (total of 4 doses) 2,240 mg (14 mL vial). Starting at Week 5 onwards, patients receive 4,640 mg once every 4 weeks.
Vials	10mL vial	14 mL vial	22 mL vial	14 mL + 15mL vial, 29 mL in total
Reference	Rybrevant SC SmPC (EMA 2025d)		PALOMA-2 (ClinicalTrials.gov 2024b)	

Abbreviations: Abbreviations: IV: Intravenous; kg: Kilograms; mg: Milligram; mL: Millilitre; Q2W: Dosing every two weeks; Q4W: Dosing every four weeks; SC: Subcutaneous; SmPC: Summary of Product Characteristics

A.1.3 Summary of the intervention

A summary of the intervention (amivantamab SC + lazertinib) is contained in Table 4.

Table 56: Overview of amivantamab in combination with lazertinib

Overview of intervention	
Indication relevant for the assessment	Combination of amivantamab (ATC: L01FX18) + lazertinib (ATC: L01EB09) for the 1L treatment of adult patients with advanced (metastatic or locally advanced) NSCLC with EGFR ex19del or exon 21 L858R substitution mutations. This use is in line with the marketing authorisation.
ATMP	Not applicable
Method of administration	Amivantamab SC: Subcutaneous injection Amivantamab SC is for subcutaneous use. Amivantamab SC is provided as a ready-to-use solution with a single simple preparation step that does not require dilution. Amivantamab SC should be administered by a healthcare professional with access to appropriate medical support to manage ARRs if they occur. The SC formulation of amivantamab improves the treatment process by offering simple and fast preparation and administration, reducing the treatment burden for patients, caregivers, and healthcare providers. Lazertinib: Oral
Dosing	Amivantamab SC: The recommended dosage of amivantamab SC is based on baseline body weight. For Q4W dosing, dosing is weekly initially for the first four weeks and then administered Q4W from Week 5 and onwards. The recommended dose for patients with body weight < 80 kg at baseline is 3,520 mg and for patients ≥80 kg 4,640 mg. Dosing is also approved for Q2W. Lazertinib: The recommended dosage of lazertinib is 240 mg once daily in combination with amivantamab. It is recommended to administer any time prior to amivantamab when given on the same day.
Dosing in the health economic model (including relative dose intensity)	Amivantamab: SC administration. Dosing based on baseline body weight. <80 kg 3,520 mg and ≥80 kg 4,640 mg. Administration SC is to be weekly (total of 4 doses) from Weeks 1 to 4 and then every 4 weeks starting at Week 5 onwards. RDI related to dose reductions is also based on body weight. Patient weight < 80 kg: [redacted] RDI. Patient weight ≥ 80 kg: [redacted] RDI Lazertinib: 240mg/day, [redacted] RDI
Should the medicine be administered with other medicines?	This is a combination treatment (amivantamab + lazertinib) Premedications should be administered to reduce the risk of ARRs with amivantamab SC. Prior to the initial dose of amivantamab (Week 1, Day 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of ARRs. For subsequent doses, antihistamines and antipyretics are required to be administered. Glucocorticoids should also be re-initiated after prolonged dose

Overview of intervention	
	interruptions. Antiemetics should be administered as needed. At the initiation of treatment, prophylactic anticoagulants should be administered to prevent VTE-events in patients receiving amivantamab in combination with lazertinib. Patients should receive prophylactic dosing of either a direct acting oral anticoagulant or a low-molecular weight heparin. Sun exposure should be limited during and for 2 months following the combination treatment as well as an alcohol-free emollient cream recommended for dry areas. A prophylactic approach to rash prevention should be considered.
Treatment duration / criteria for end of treatment	As per the SmPC, it is recommended that patients are treated until disease progression or unacceptable toxicity. However, decisions in clinical practice are often driven by symptomatic rather than radiological progression.
Necessary monitoring, both during administration and during the treatment period	There is no mandated observation time in the SmPC for amivantamab or lazertinib. Monitoring after administration will depend on clinical practice and experience with the treatment.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Not relevant, all diagnostics are completed as standard practice in diagnosing lung cancer. Before initiation of the combination therapy, EGFR-mutation status in tumour tissue or plasma specimens must be established using a validated test method. This is done at the initial diagnosis and does not need to be repeated for initiation of treatment once EGFR-mutation status has been established
Package size(s)	Amivantamab SC: Amivantamab SC is available in several vial sizes to reduce drug wastage and offer simple preparation, with dose based on patient baseline weight and treatment schedule: • 10 mL • 14 mL • 15 mL • 22 mL Where 1 mL of solution for injection contains 160 mL amivantamab. Lazertinib: Lazertinib will be available as 80 mg and 240 mg film-coated tablets. Pack size of 28 tablets with 240 mg lazertinib.

Abbreviations: ARR: Administration-related reaction; ATC: Anatomical Therapeutic Chemical; EGFR: Epidermal growth factor receptor; ex19del: Exon 19 deletions; kg: Kilogram; L: Line of therapy; L858R: Exon 21 leucine-858 to arginine; mg: Milligram, mL: Millilitre; NSCLC: Non-small cell lung cancer; Q2W: Every two weeks; Q4W: Dosing every four weeks; RDI: Relative dose intensity; SC: Subcutaneous; SmPC: Summary of product characeristics; VTE: Venous thrombosis. Sources: Rybrevant SmPC: (EMA 2025d); Lazcluze SmPC: (EMA 2025b); CHMP report amivantamab + lazertinib combination (EMA 2024); MARIPOSA data on file (Johnson & Johnson 2024f).

A.2 Clinical trial programme

Evidence from the ongoing PALOMA-3 and PALOMA-2 clinical trials demonstrates that amivantamab SC provides comparable efficacy to amivantamab IV while maintaining a consistent safety profile, with reduced ARRs and VTE events (Johnson & Johnson 2024b, Johnson & Johnson 2024c).

The ongoing PALOMA-3 trial is relevant to establish the efficacy of amivantamab with SC administration compared to amivantamab IV administration. The purpose of this study is to simplify amivantamab administration and reduce dose times by assessing a new formulation of amivantamab, amivantamab subcutaneous and co-formulated with recombinant human hyaluronidase (SC-CF), for subcutaneous administration (ClinicalTrials.gov 2023c). In this study, the combination of amivantamab IV + lazertinib is compared against amivantamab SC + lazertinib. Interim findings from PALOMA-3 have been presented at conferences (Leighl et al. 2024b, Alexander et al. 2024) and published in peer-reviewed journal (Leighl et al. 2024a), as well as available as data on file (Johnson & Johnson 2024c). Data from PALOMA-3 is incorporated into the model in sensitivity analyses through relative risks for experiencing an AE if selecting SC administration of amivantamab.

In addition, the ongoing clinical trial PALOMA-2 will provide further supportive information for this submission but is not directly included in the health economic model. PALOMA-2 is designed around the SC formulation of amivantamab being developed to improve patient experience. It is an open-label, parallel cohort, interventional study to evaluate the efficacy, safety, and pharmacokinetics (PK) of amivantamab SC administered via manual injection in various combination treatments and treatment settings for patients with locally advanced or metastatic EGFR-mutated NSCLC previously treated with amivantamab IV (Lim et al. 2024a, Johnson & Johnson 2024b). This study aims to confirm for patients with locally advanced or metastatic EGFR-mutated NSCLC that amivantamab SC has similar anti-cancer activity similar to what is seen in amivantamab as an IV infusion in combination regimens (all cohorts except Cohort 4) as well as to characterise the safety of amivantamab SC (Cohort 4). This trial will provide further data on SC amivantamab in combination with lazertinib for the treatment of advanced EGFR-mutated NSCLC as well as the impact of prophylactic anticoagulants in managing adverse events. Findings from the ongoing PALOMA-2 trial have been presented at conferences (Lim et al. 2024b) and available as data on file (Johnson & Johnson 2024b).

A.2.1 PALOMA-3

The PALOMA-3 trial is the pivotal trial for the documentation of the SC administration of amivantamab. PALOMA-3 is an ongoing phase III RCT assessing non-inferiority of amivantamab SC versus amivantamab IV (both in combination with lazertinib) in patients with locally advanced or metastatic NSCLC and ex19del or exon 21 L858R mutations who progressed on or after treatment with osimertinib and platinum-based chemotherapy (Johnson & Johnson 2024c, Leighl et al. 2024a). A summary of PALOMA-3 is contained in Table 57.

Table 57: Main characteristics of PALOMA-3

PALOMA-3 (NCT05388669)

Study design	A Phase 3, open-label, randomised study of lazertinib with subcutaneous amivantamab compared with intravenous amivantamab in patients with EGFR-mutated advanced or metastatic NSCLC After Progression on Osimertinib and Chemotherapy
Study location(s)	US, Argentina, Australia, Brazil, Canada, China, France, Israel, Italy, Japan, Republic of Korea, Malaysia, Poland, Portugal, Spain, Taiwan, Thailand, Turkey, UK.
Population	**Inclusion Criteria:** Aged 18 years or above Have histologically or cytologically confirmed, advanced or metastatic NSCLC, characterised by either EGFR ex19del or Exon 21 L858R mutation Have progressed on or after osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy (irrespective of order). a) The 3rd generation EGFR TKI must have been administered as the first EGFR TKI for metastatic disease or as the second TKI after prior treatment with first- or second-generation EGFR TKI in participants with metastatic EGFR T790M mutation positive NSCLC. b) Participants who decline or are otherwise ineligible for chemotherapy may be enrolled after discussion with the medical monitor. c) Any adjuvant or neoadjuvant treatment, whether with a 3rd generation EGFR TKI or platinum-based chemotherapy, would count towards the prior treatment requirement if the participant experienced disease Have at least 1 measurable lesion, according to RECIST version 1.1 Have an ECOG performance status of 0 to 1 Any toxicities from prior anticancer therapy must have resolved to CTCAE Version 5.0 Grade 1 or baseline level (except for alopecia [any grade], Grade less than or equal to (<=) 2 peripheral neuropathy, and Grade <=2 hypothyroidism stable on hormone replacement) **Exclusion Criteria:** Participant has received cytotoxic, investigational, or targeted therapies beyond one regimen of platinum-based chemotherapy and EGFR inhibitors Participant has received radiotherapy for palliative purposes less than 7 days prior to randomization Participant has symptomatic or progressive brain metastases Participant has leptomeningeal disease, or participant has spinal cord compression not definitively treated with surgery or radiation Participant has uncontrolled tumour-related pain

	Participant has a medical history of ILD, including drug-induced ILD or radiation pneumonitis Enrolment (actual): 418 (206 patients in the amivantamab SC arm and 212 patients in the amivantamab IV arm)
Intervention	Lazertinib with amivantamab SC-CF. Lazertinib 240 mg will be administered orally once daily. Participants will receive amivantamab subcutaneous and co-formulated with recombinant human hyaluronidase (SC-CF), 1,600 mg/ 2,240 mg depending on the body weight by manual injection.
Comparator	Lazertinib with amivantamab (IV). Lazertinib 240 mg will be administered orally once. Participants will receive amivantamab, 1,050 mg or 1,400 mg depending on the body weight as an IV infusion.
Primary endpoint	Observed Serum Concentration (Ctrough) of amivantamab at Pre-dose of cycle 2 day 1 [time frame: cycle 2 day 1 (28 days cycle)]. Ctrough is the observed serum concentration of amivantamab at pre-dose of cycle 2 day 1 immediately prior to the next drug administration. Area under the concentration time curve from day 1 to day 15 (AUC [day 1-15]) of amivantamab of cycle 2 [time frame: cycle 2 day 1 to cycle 2 day 15 (28 days cycle)]. AUC (day 1-15) defined as area under the concentration time curve from cycle 2 day 1 to day 15.
Important secondary endpoint(s)	Efficacy: ORR, PFS, OS Safety: AEs and laboratory abnormalities, IRRs PRO: TASQ Process: Participant chair time, Duration of treatment administration time, Active healthcare provider time for drug preparation, treatment administration and posttreatment monitoring, Participant time in treatment room
Observation time	At the time of the 3 January 2024 data cut-off, the median follow-up was 7.0 months (range: 0.1, 14.4).
Data cuts	Study start: 2022-08-05 Primary analysis data cut: 2024-01-03 Data cut underlying the application: 2024-01-03 Study completion: 2025-12-31 (estimated)

Abbreviations: AE: Adverse event; AUC: Area under the concentration-time curve; CTCAE: Common Terminology Criteria for Adverse Events; Ctrough; Observed serum concentration of amivantamab at steady state; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; ex19del: exon 19 deletion; ILD: Interstitial lung disease; IRR: Infusion-related reaction; IV: Intravenous; L858R: Exon 21 leucine-858 to arginine; mg: Milligram; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PRO: Patient reported outcome; RECIST: Response Evaluation Criteria in Solid Tumours; SC: Subcutaneous; SC-CF: Subcutaneous and co-formulated with recombinant human hyaluronidase; TASQ: Modified Therapy Administration Satisfaction Questionnaire; TKI: Tyrosine kinase

inhibitor; UK: United Kingdom; US: United States. Sources: PALOMA-3: (ClinicalTrials.gov 2023c) (Leighl et al. 2024a)

A.2.1.1 Study design

PALOMA-3 (NCT05388669) is an ongoing randomised, open-label, multicentre, parallel, international phase III trial designed to optimise the administration of amivantamab in patients with EGFR-mutated locally advanced or metastatic NSCLC who have progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy (Johnson & Johnson 2024c, Leighl et al. 2024b, Leighl et al. 2024a). PALOMA-3 compares the PK, efficacy, and safety of lazertinib + amivantamab SC (Arm A; referred to as the amivantamab SC arm) versus lazertinib + amivantamab IV (Arm B; referred to as the amivantamab IV arm). Patients were randomised to either Arm A or Arm B in a 1:1 ratio (n= 206 in the SC arm and n=212 in the IV arm) (See Figure 28:). Treatment blinding was also not feasible in PALOMA-3, as the two amivantamab formulations used different routes of administration. Given the clear ethical considerations, the use of open-label trials is common in life-threatening diseases like advanced NSCLC. At the time of the January 3, 2024 data cut-off, the median follow-up was 7.0 months (range: 0.1 to 14.4).

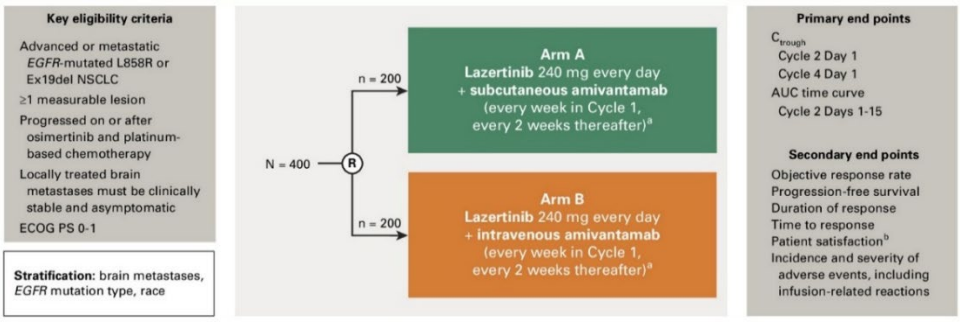


Figure 28: PALOMA-3 study design

[a] Cycle 1 for intravenous amivantamab + lazertinib: Days 1, 2 (Day 2 applies to intravenous split dose only), 8, 15, and 22; Cycle 1 for subcutaneous amivantamab + lazertinib: Days 1, 8, 15, and 22; after Cycle 1 for all: Days 1, 15 (28-day cycles). Subcutaneous amivantamab is co-formulated with recombinant human hyaluronidase. [b] Assessed by using modified TASQ. Abbreviations: AUC: Area under the concentration-time curve; Ctrough; Observed serum concentration of amivantamab at steady state; ECOG PS: Eastern Cooperative Oncology Group performance status score; EGFR: Epidermal growth factor receptor; Ex19del: Exon 19 deletion mutation; NSCLC: Non–small cell lung cancer; R: Random assignment; TASQ: Therapy Administration Satisfaction Questionnaire. Source: Leighl et al. 2024, Figure A1 (Leighl et al. 2024a)

The trial was conducted in three phases (Leighl et al. 2024a):

- The **screening phase** of eligible participants was conducted ≤28 days before randomisation.
- The **treatment phase** began on Day 1, Cycle 1 with 28-day cycles until the end-of-treatment visit. Study treatment continued until clinical and radiographic disease progression or until patient meets another criterion for discontinuation of study treatment. Randomisation was stratified based on the presence or history of brain metastases (yes vs no), EGFR mutation (L858R vs exon19del), race (Asian vs non-Asian), and last therapy (osimertinib [or another approved 3rd generation EGFR TKI] vs chemotherapy) and assigned randomly in a 1:1 ratio into 1 of 2 treatment arms as follows:

- Arm A: Lazertinib 240 mg orally once daily and amivantamab SC by manual injection in 28 days cycles:
  - 1,600 mg (2,240 mg if body weight ≥80 kg) on Cycle 1 Days 1, 8, 15, and 22.
  - 1,600 mg (2,240 mg if body weight ≥80 kg) on Day 1 and 15 of each subsequent 28-day cycle, starting on Cycle 2.
- Arm B: Lazertinib 240 mg orally once daily and Amivantamab by IV infusion in 28-day cycles:
  - 1,050 mg (1,400 mg if body weight ≥80 kg) on Cycle 1 Days 1-2 (split dose), 8, 15, and 22.
  - 1,050 mg (1,400 mg if body weight ≥80 kg) on Days 1 and 15 of each subsequent 28-day cycle, starting on Cycle 2.

- The **follow-up phase** began from end of treatment visit until the end of study, death, lost to follow-up, or withdrawal of consent, which ever came first. For participants who discontinued treatment prior to disease progression, tumour imaging would continue as scheduled until disease progression was documented. Participants who discontinue study treatment for any reason will be followed in the Follow-up Phase after last study treatment until disease progression or death, whichever comes first.

A.2.1.2 Study population

Patients were eligible to participate in PALOMA-3 if they were over 18 years old, had confirmed advanced or metastatic NSCLC, with a tumour positive for EGFR ex19del or exon 21 L858R. Patients have had to progress on or after osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy (irrespective of order). See Table 57 for the key patient eligibility criteria (Leighl et al. 2024b, Leighl et al. 2024a).

A total of 418 patients (amivantamab SC arm: 206, amivantamab IV arm: 212) were randomised between August 5, 2022, and January 3, 2024. Two patients randomised to the amivantamab IV arm did not receive any dose of study treatment due to withdrawal of consent (1 patient) and investigator decision (1 patient). Patients were stratified by the presence of brain metastases at baseline (present vs. absent), EGFR mutation (L858R vs. ex19del), race (Asian vs. Non-Asian), and last therapy (osimertinib [or another approved third-generation EGFR TKI] vs. chemotherapy).

Patient demographics were well balanced between the two treatment arms of PALOMA-3 (see Table 58). In total, 81.6% of patients had Stage IV cancer at the time of diagnosis and the median time from metastatic disease diagnosis of NSCLC to randomisation was 31.24 months. At screening, most patients (411 [98.3%]) were diagnosed with adenocarcinoma and nearly all patients (415 [99.3%]) had Stage IV disease. The mean number of prior lines of therapy were similar across treatment arms (amivantamab SC: 2.3 months [SD 0.71]; amivantamab IV: 2.2 months [SD 0.69]). Regarding EGFR mutation status, 65.3% had ex19del mutations and 34.7% had exon 21 L858R substitution mutations.

Table 58: Summary of demographics and baseline characteristics (PALOMA-3; Full Analysis Set)

	Arm A	Arm B	Total
	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	
Analysis set: Full; N	206	212	418
Age			
N	206	212	418
Median	61.0	62.0	61.0
Range	(35, 82)	(29, 81)	(29, 82)
<50	28 (13.6%)	29 (13.7%)	57 (13.6%)
50-64	105 (51.0%)	91 (42.9%)	196 (46.9%)
65-74	55 (26.7%)	70 (33.0%)	125 (29.9%)
≥75	18 (8.7%)	22 (10.4%)	40 (9.6%)
Sex			
Female	138 (67.0%)	141 (66.5%)	279 (66.7%)
Male	68 (33.0%)	71 (33.5%)	139 (33.3%)
Race			
Asian	126 (61.2%)	129 (60.8%)	255 (61.0%)
Black or African American	1 (0.5%)	3 (1.4%)	4 (1.0%)
White	78 (37.9%)	77 (36.3%)	155 (37.1%)
Multiple	0	1 (0.5%)	1 (0.2%)
Not Reported	1 (0.5%)	2 (0.9%)	3 (0.7%)
Weight, kg			
Median	61.8	60.1	61.0
Range	(35, 130)	(33, 150)	(33, 150)
<80	184 (89.3%)	184 (86.8%)	368 (88.0%)
≥80	22 (10.7%)	28 (13.2%)	50 (12.0%)

Region of enrolment			
North America	19 (9.2%)	30 (14.2%)	49 (11.7%)
South America	11 (5.3%)	17 (8.0%)	28 (6.7%)
Europe	38 (18.4%)	40 (18.9%)	78 (18.7%)
Asia	126 (61.2%)	120 (56.6%)	246 (58.9%)
Oceania	12 (5.8%)	5 (2.4%)	17 (4.1%)
Baseline ECOG score			
0	58 (28.2%)	61 (28.8%)	119 (28.5%)
1	148 (71.8%)	151 (71.2%)	299 (71.5%)
History of smoking			
Yes	65 (31.6%)	67 (31.6%)	132 (31.6%)
No	141 (68.4%)	145 (68.4%)	286 (68.4%)
History of brain metastasis[a]			
Present	70 (34.0%)	72 (34.0%)	142 (34.0%)
Absent	136 (66.0%)	140 (66.0%)	276 (66.0%)
Mutation type at randomisation[a]			
Ex19del	135 (65.5%)	138 (65.1%)	273 (65.3%)
Exon 21 L858R	71 (34.5%)	74 (34.9%)	145 (34.7%)
Initial diagnosis NSCLC subtype			
Adenocarcinoma	204 (99.0%)	207 (97.6%)	411 (98.3%)
Large cell carcinoma	1 (0.5%)	1 (0.5%)	2 (0.5%)
Squamous cell carcinoma	1 (0.5%)	3 (1.4%)	4 (1.0%)
Other	0	1 (0.5%)	1 (0.2%)
Last therapy before randomisation			
Osimertinib	91 (44.2%)	96 (45.3%)	187 (44.7%)
Chemotherapy	115 (55.8%)	116 (54.7%)	231 (55.3%)

Time since initial lung cancer diagnosis (months)			
Median	34.513	33.725	34.316
Range	(2.76, 191.34)	(6.05, 156.85)	(2.76, 191.34)
Time since metastatic disease diagnosis (months)			
Median	32.723	29.700	31.244
Range	(0.85, 168.97)	(0.56, 142.55)	(0.56, 168.97)

[a] Based on investigator reported data recorded on eCRF page. Abbreviations: ECOG: Eastern Cooperative Oncology Group; Ex19del: Exon 19 deletions; IV: Intravenous; NSCLC: Non-small cell lung cancer; SC: Subcutaneous; SD: Standard deviations. Source: (Johnson & Johnson 2024b, Leighl et al. 2024a)

A.2.1.3 Outcome measures

The PALOMA-3 study's primary objective was to assess the noninferiority of PKs of SC versus amivantamab IV in patients with EGFR-mutated advanced NSCLC, in line with regulatory expectations**.** Regulatory agencies and healthcare payers recognize the active ingredient in pharmaceutical products remains consistent with administration routes; thus, demonstrating similar PK parameters (plasma concentrations) between formulations is critical for assessing bioequivalence. Hence, the co-primary endpoints to assess non-inferiority of amivantamab SC versus amivantamab IV were trough concentration (C_{trough}; either at steady state Cycle 4 Day 1 or pre-dose on Cycle 2 Day 1, per regional health authority guidance), and the area under the curve from Day 1 to Day 15 ($AUC_{D1\text{-}D15}$) in Cycle 2 (Leighl et al. 2024b, Leighl et al. 2024a).

The secondary endpoints include efficacy outcomes (e.g., objective response rate [ORR], PFS, duration of response [DOR], time to response [TTR]), safety outcomes (e.g., AEs), PROs (e.g., Modified Therapy Administration Satisfaction Questionnaire [TASQ], change from baseline assessed over time), and time and motion analysis (e.g., chair time, time in treatment room, duration of treatment administration, and health care professional time for drug [preparation, administration, and post-treatment monitoring]). OS was considered a predefined exploratory endpoint.

Disease assessments (computed tomography, magnetic resonance imaging, or other imaging) were performed within 28 days before random assignment, then at 6 weeks (maximum, 7 weeks) after random assignment and subsequently every 6 weeks (within a 1-week window) for the first 18 months and every 12 weeks (within a 1-week window) thereafter until disease progression (Leighl et al. 2024a). All response assessments were performed by the investigator according to RECIST, v1.1. All patients underwent brain imaging at baseline; subsequent imaging was performed every 6 weeks in patients with baseline brain metastases or as clinically indicated.

A.2.1.4 Analysis

The efficacy analysis included all randomly assigned patients (ITT population) (Leighl et al. 2024a). Safety analysis included all patients who received ≥1 dose of any treatment.

A hierarchical testing approach was used for the coprimary pharmacokinetic end points (noninferiority, at a two-sided alpha of .05), followed by the key secondary end points of ORR (noninferiority) and then PFS (superiority). The key secondary end points were tested using a combined two-sided alpha of 0.05. Analyses of additional secondary or other outcomes, including subgroup analyses, were not part of hypothesis testing in the trial, and these results are reported as descriptive statistics without adjustment for multiplicity.

The PK analysis included patients who received all doses without modification and provided the required PK samples through the final required sample relevant to the end point.

All data reported here are based on the data cut-off 03 January 2024.

A.2.2 PALOMA-2

In addition, PALOMA-2 assesses the clinical benefit and safety of amivantamab SC in various treatment combinations (with lazertinib or carboplatin + pemetrexed) (Johnson & Johnson 2024b, Lim et al. 2024b). PALOMA-2 is supporting the market authorisation of amivantamab SC and includes patient populations and treatment combinations in alignment with the pivotal trials for amivantamab IV, including:

- Amivantamab SC Q2W + lazertinib in patients with common EGFR mutations (Cohorts 1 and 6), resembling the MARIPOSA population.
- Amivantamab SC Q4W + lazertinib in patients with common EGFR mutations (Cohort 5), resembling the MARIPOSA population.

The multi-cohort design of PALOMA-2 was implemented to evaluate the efficacy, tolerability, and safety of amivantamab SC in various populations with advanced EGFR-mutated NSCLC and in combination with different treatment regimens, generally aligning with the current indications for amivantamab IV. As of yet, only interim analyses of Cohorts 1 and 6 are available and the study is still recruiting. The analysis from January 2024 does not yet cover Cohort 5, but data will be available in due time. This is because the study protocol was amended to add Cohort 5 in January 2023 and the Q4W dose was adjusted in October 2023.

Table 59: Main characteristics of PALOMA-2

PALOMA-2 (NCT05498428)	
Study design	A phase 2, global, open-label, parallel cohort study of SC amivantamab in multiple regimens in patients with advanced or metastatic solid tumours including EGFR-mutated NSCLC. Allocation is non-randomised.
Study location(s)	US, Brazil, China, France, Germany, Israel, Italy, Japan, Republic of Korea, Malaysia, Spain, UK.
Population	**Inclusion Criteria:**

Participant must have histologically or cytologically confirmed, locally advanced or metastatic, NSCLC that is not amenable to curative therapy including surgical resection or chemoradiation.

Additional Cohort (1,5 or 6) specific disease requirements include:

Cohorts 1, 5, and 6: EGFR ex19del or Exon 21 L858R mutation;

Cohorts 1,5, and 6: Participant should not have received any prior systemic therapy for locally advanced or metastatic NSCLC.

All cohorts except Cohort 4: Participants must have at least 1 measurable lesion, according to RECIST version 1.1. If the only target lesion has been previously irradiated, it must show signs of disease progression since radiation was completed If only 1 non-irradiated measurable lesion exists, which undergoes a biopsy and is acceptable as a target lesion, the baseline tumour assessment scans should be performed at least 14 days after the biopsy

May have a prior or concurrent second malignancy (other than the disease under study) which natural history or treatment is unlikely to interfere with any study endpoints of safety or the efficacy of the study treatment(s)

Have adequate organ (renal, hepatic, haematological, coagulation and cardiac) functions

Participant must have ECOG status of 0 or 1

Cohort 6: Must be eligible for, and agree to comply with, the use of prophylactic anticoagulation with a direct oral anticoagulant or a low molecular weight heparin during the first 4 months of study treatment

A participant must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 6 months after receiving the last dose of study treatment. Female participants should consider preservation of eggs prior to study treatment as anti-cancer treatments may impair fertility

Exclusion Criteria:

Participant has a medical history of ILD, including drug induced ILD or radiation pneumonitis

Participant has a history of hypersensitivity to any excipients of the investigational products to be used in their enrolment cohort

Participant has received a live or live attenuated vaccine within 3 months before Cycle 1 Day 1. The seasonal influenza vaccine and non-live vaccines against Coronavirus disease 19 are not exclusionary

For all cohorts (with regimens potentially including lazertinib): Participant is currently receiving medications or herbal supplements known to be potent Cytochrome (CYP3A4/5) inducers and is unable to stop use for an appropriate washout period prior to Cycle 1 Day 1

Other clinically active liver disease of infectious origin

Participant has a history of clinically significant cardiovascular disease including, but not limited to: a) All cohorts: diagnosis of deep vein thrombosis or pulmonary embolism within 1 month prior to the first

	dose of study treatment(s), or any of the following within 6 months prior to the first dose of study treatment(s): myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated clots, are not exclusionary; b) All cohorts (with regimens potentially including lazertinib): Participant has a significant genetic predisposition to venous thromboembolic events (VTE; such as Factor V Leiden); c) All cohorts (with regimens potentially including lazertinib): Participant has a prior history of VTE and is not on appropriate therapeutic anticoagulation as per NCCN or local guidelines; d) prolonged corrected QT interval by Fridericia (QTcF) interval greater than (>) 480 milliseconds or clinically significant cardiac arrhythmia or electrophysiologic disease (example, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate); e) uncontrolled (persistent) hypertension: systolic blood pressure >160 mmHg(s); diastolic blood pressure >100 mmHg; f) Congestive heart failure defined as NYHA class III-IV or hospitalisation for congestive heart failure (any NYHA class) within 6 months of treatment initiation at Cycle 1/day 1; g) pericarditis/clinically significant pericardial effusion; h) myocarditis; i) baseline left ventricular ejection fraction below the institution's lower limit of normal at screening, as assessed by echocardiogram or multi-gated acquisition scan Participant has 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 Screening are eligible, provided they have been either off corticosteroid treatment or are receiving low-dose corticosteroid treatment (less than or equal to [<=] 10 mg/day prednisone or equivalent) for at least 2 weeks prior to treatment allocation Enrolment (estimated) 390 – recruiting.
Intervention	Cohort 1 (ex19del/Exon21 L858R NSCLC, 1L, Previously Untreated): Amivantamab (Q2W) + Lazertinib Cohort 5 (ex19del/Exon21 L858R NSCLC, 1L, Previously Untreated): Amivantamab (Q4W) + Lazertinib Cohort 6 (ex9del/Exon21L858R, NSCLC1L, Previously Untreated): Amivantamab (Q2W) + Lazertinib + Anticoagulant
Comparator	Not applicable
Primary endpoint	ORR based on investigator assessment.
Key secondary endpoints	Efficacy data: PFS, OS, Duration of response Safety data: Number of AEs including VTEs and abnormalities in clinical laboratory values

	PROs: Patient Global Impression of Change (PGIC) Scale Score and Patient Global Impression of Symptom Severity (PGIS) Scale Score
Observation time	The median follow-up at the data cut-off (January 6, 2024) was 10.0 months for Cohort 1 and 6.1 months for Cohort 6, though it should be noted that the study is still ongoing.
Data cuts	Study start: 2022-11-11 Primary analysis data cut: 2025-10-31 (estimated) Data cut underlying the application: 2024-01-06 Study completion: 2026-08-05 (estimated)

Abbreviations: AE: Adverse event; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; ex19del: exon 19 deletion; ILD: Interstitial lung disease; L: Line of therapy; L858R: Exon 21 leucine-858 to arginine; mg: Milligram; mmHg: Millimetre of mercury; NCCN: National Comprehensive Cancer Network; NSCLC: Non-small cell lung cancer; NYHA: New York Heart Association; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PRO: Patient reported outcome; Q2W: Dosing every second week; Q4W: Dosing every four weeks; QTcF: QT corrected for heart rate by Fridericia's cube root formula; RECIST: Response Evaluation Criteria in Solid Tumours; SC: Subcutaneous; UK: United Kingdom; US: United States; VTE: Venous thromboembolism. Sources: PALOMA-2: (ClinicalTrials.gov 2024b) (Lim et al. 2024b)

A.2.2.1 Study design

PALOMA-2 is an ongoing phase II, open-label, parallel cohort, interventional study to evaluate the efficacy, safety, and PK of amivantamab SC administered via manual injection in various combination treatments and treatment settings for patients with locally advanced or metastatic EGFR-mutated NSCLC previously treated with amivantamab IV (Johnson & Johnson 2024b, Lim et al. 2024a). This study is still recruiting. An overview of the study design is presented in Figure 29:.

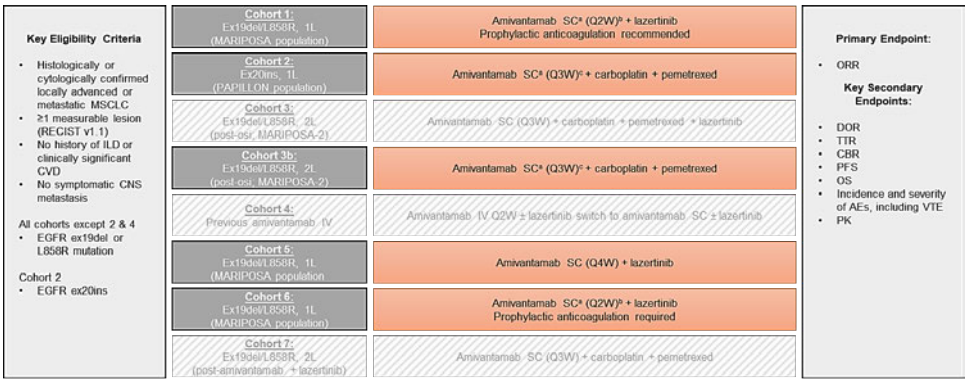


Figure 29: PALOMA-2 study design

[a] Amivantamab SC was administered via manual injection in the abdomen.
[b] Amivantamab SC Q2W dose: 1,600 mg (2,240 mg if ≥80 kg).
[c] Amivantamab SC Q3W dose: 2,400 mg (3,360 mg if ≥80 kg).
Abbreviations: 1L: First line; 2L: Second line; C#: Cycle #; CBR: Clinical benefit rate; DOR: Duration of response; EGFRm: Mutated epidermal growth factor receptor; INV: Investigator assessment; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; PK: Pharmacokinetic; PFS: Progression free survival; QD: once daily; Q2W: Every 2 weeks; Q3W: Every 3 weeks; SC: Subcutaneously; TTR: Time to response; VTE: Venous thromboembolism. Source: (Johnson & Johnson 2024b, Lim et al. 2024a).

A.2.2.2 Study population

Data from Cohorts 1 and 6 at the data cut-off of January 6, 2024 are presented herein (see Figure 29:) (Lim et al. 2024a). Data from Cohort 5 is delayed due to protocol amendments (inclusion into study protocol in January 2023 and Q4W dose was adjusted in an amendment in October 2023).

- **Cohort 1 and 6:** Patients were treatment-naïve with locally advanced or metastatic NSCLC harbouring an EGFR ex19del or exon 21 L858R mutation. Amivantamab SC was administered by manual injection at a dose of 1,600 mg (2,240 mg if body weight ≥80 kg) in 28-day cycles. In Cycle 1, doses were administered on Days 1, 8, 15, and 22. Starting at Cycle 2, doses were administered on Days 1 and 15 (i.e., Q2W). All patients received oral lazertinib 240 mg once daily.
- **Cohort 1:** Patients were *recommended* to receive prophylactic anticoagulation with direct oral anticoagulant or a low molecular heparin from Day 1 through 120 of study treatment.
- **Cohort 6:** Patients were *required* to receive prophylactic anticoagulation with direct oral anticoagulant or a low molecular heparin from Day 1 through 120 of study treatment.
- In addition**, Cohort 5** will provide information on the monthly dosing regimen. Participants in this cohort had treatment-naïve locally advanced or metastatic NSCLC harbouring an EGFR ex19del or exon 21 L858R mutation will receive amivantamab SC-CF induction with 1,600 mg (or 2,240 mg if body weight ≥80 kg) on Cycle 1 Days 1, 8, 15, and 22, starting with Cycle 2 on Day 1 of each next 28-day cycle, amivantamab SC-CF (160 mg/mL co-formulated with rHuPH20) by manual injection at 3,520 mg (or 4,640 mg if body weight ≥80 kg); along with lazertinib 240 mg by mouth once daily from Cycle 1 Day 1 (ClinicalTrials.gov 2024b).

Patient demographics and baseline disease characteristics from Cohorts 1 and 6 at the preliminary data cut-off date of January 6, 2024 are summarised in Table 60 (Lim et al. 2024b). As of January 6, 2024, 68 and 58 patients were enrolled in Cohorts 1 and 6 respectively (Lim et al. 2024b). The median follow-up was 10.0 months for Cohort 1 and 6.1 months for Cohort 6, though it should be noted that the study is still ongoing. As of the data cutoff, 75% of patients in Cohort 1 and 93% of patients in Cohort 6 were still undergoing treatment. In Cohort 1 and 6, 95.6% and 98.3% of patients were diagnosed with adenocarcinoma (Johnson & Johnson 2024b). The median time from initial NSCLC diagnosis was 1.45 months (range: 0.6, 80) in Cohort 1 and 1.35 months (range: 0.5, 156.7) for Cohort 6 (Johnson & Johnson 2024b). Regarding EGFR mutation status, 66.2% had NSCLC with ex19del and 35.3% had NSCLC with L858R substitution mutations in Cohort 1; in Cohort 6, 58.6% had NSCLC with ex19del mutations and 41.4% had NSCLC with L858R substitution mutations (Lim et al. 2024b).

Table 60: Summary of demographic and baseline characteristics (PALOMA-2; Cohorts 1 & 6; Full Analysis Set)

	Cohort 1	Cohort 6	Total

	Amivantamab SC + Lazertinib + recommended prophylactic anticoagulation	Amivantamab SC + Lazertinib + required prophylactic anticoagulation	
Analysis set: Full; N	68	58	126
Age			
Median	58.0	61.5	59.0
Range	28, 85	34, 83	28, 85
Sex			
Female	42 (61.8%)	34 (58.6%)	76 (60.3%)
Race			
Asian	45 (66.2%)	40 (69.0%)	85 (67.5%)
White	19 (27.9%)	16 (27.6%)	35 (27.8%)
Other[a]	4 (5.9%)	2 (3.4%)	6 (4.7%)
Baseline ECOG score			
1	48 (70.6%)	43 (74.1%)	91 (72.2%)
History of smoking			
Yes	15 (22.1%)	18 (31.0%)	33 (26.2%)
History of brain metastasis			
Yes	20 (29.4%)	18 (31.0%)	38 (30.2%)
Mutation Type[b]			
Ex19del	45 (66.2%)	34 (58.6%)	79 (62.7%)
Exon 21 L858R	24 (35.3%)	24 (41.4%)	48 (38.1%)
Initial diagnosis NSCLC subtype			
Adenocarcinoma histology	65 (95.6%)	57 (98.3%)	122 (96.8%)

[a] Other includes Black or African American and American Indian or Alaska Native.
[b] Patients can be counted in more than one category.

Abbreviations: ECOG: Eastern Cooperative Oncology Group; Ex19del: Exon 19 deletions; NSCLC: Non-small cell lung cancer; SC: Subcutaneous; SD: standard deviation.
Source: (Lim et al. 2024b)

A.2.2.3 Outcome measures

The primary endpoint is ORR by investigator assessment. The key secondary endpoints include key efficacy endpoints (ORR by independent central review, DOR, clinical benefit rate [CBR], TTR, PFS, and OS), frequency and severity of VTE, amivantamab PK, and incidence and severity of AEs.

A.2.2.4 Analysis

Please note that the PALOMA-2 trial was designed to have sufficient statistical power for the primary endpoint of ORR by investigator assessment, and the secondary endpoints are not powered.

Preliminary efficacy and safety results for relevant Cohorts 1 and 6 are currently available and described below for the data cut-off 6 January 2024. As of yet, only interim analyses of Cohorts 1 and 6 are available and the study is still recruiting. As of yet, only interim analyses of Cohorts 1 and 6 are available and the study is still recruiting. Data from Cohort 5 is delayed due to protocol amendments (inclusion into study protocol in January 2023 and Q4W dose was adjusted in an amendment in October 2023).

A.2.3 Summary of relevant ongoing studies

The ongoing study COCOON (NCT: NCT06120140) has an estimated primary completion in November 2025 (ClinicalTrials.gov 2024a). COCOON has the primary objective to evaluate the incidence of grade ≥2 dermatologic adverse events of interest (DAEIs) with enhanced vs standard dermatologic management in patients with EGFR-mutated locally advanced or metastatic stage IIIB/C to IV NSCLC treated with first-line amivantamab plus lazertinib. DAEIs included rash, dermatitis, paronychia, skin fissures, acne, erythema, skin exfoliation, skin lesion, skin irritation, and eczema. The study will provide further information on the safety of the combination treatment of amivantamab and lazertinib, including the SC administration form. A summary is provided in Table 61.

Table 61: Summary of relevant ongoing studies

COCOON (NCT06120140)	
Study design	Randomised, open-label, multicentre, international, phase II trial designed to evaluate the impact of enhanced versus standard dermatologic management on selected dermatologic adverse events among patients with locally advanced or metastatic EGFR-mutated NSCLC treated first-line with amivantamab + lazertinib. A sub-study will enrol participants from Arms A and B who experience specific new-onset or persistent DAEIs (Grade >=2) during treatment with IV amivantamab and lazertinib. This sub-study aims to assess the reactive use of dermatologic treatment strategies in these participants. Patients were enrolled in 1:1 design.

Study location(s)	US, Argentina, Brazil, China, France, Germany, Republic of Korea, Malaysia, Spain, Taiwan, Turkey.
Population	This study is still recruiting patients. All participants were aged 18 years and older. Inclusion Criteria: Have histologically or cytologically confirmed, locally advanced or metastatic NSCLC; Is treatment naïve and not amenable to curative therapy including surgical resection or (chemo) radiation. Adjuvant or neoadjuvant therapy for Stage I, Stage II or Stage IIIA disease is allowed if last dose administered more than 12 months prior to the development of locally advanced or metastatic disease Have a tumour that harbours an EGFR ex19del or exon 21 L858R substitution, as detected by an FDA-approved or other validated test in a clinical laboratory improvement amendments)-certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US) in accordance with site standard of care A participant with asymptomatic or previously treated and stable brain metastases may participate in this study. Participants with a history of symptomatic brain metastases must have had all lesions treated as clinically indicated (that is, no current indication for further definitive local therapy). Any definitive local therapy to brain metastases must have been completed at least 14 days prior to randomisation, and the participant can be receiving no greater than 10 mg prednisone or equivalent daily for the treatment of intracranial disease Can have prior or concurrent second malignancy (other than the disease under study) which natural history or treatment is unlikely to interfere with any study endpoints, safety, or the efficacy of the study treatment(s) Have an ECOG performance status of 0 to 1 Sub-study inclusions: Participants must have new-onset or persistent (defined as non-responsive to SoC) Grade >=2 specific DAEIs of the scalp, face, or body, as defined by NCI CTCAE Grading v5.0 for DAEIs (excluding paronychia) Exclusion Criteria: History of uncontrolled illness, including but not limited to uncontrolled diabetes; ongoing or active infection (includes infection requiring treatment with antimicrobial therapy [participants will be required to complete antibiotics 1 week prior to starting background anticancer treatment] or diagnosed or suspected viral infection); active bleeding diathesis; impaired oxygenation requiring continuous oxygen supplementation; refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of background anticancer treatment or doxycycline/minocycline; psychiatric illness, social situation, or any other circumstances that would limit compliance with study requirements; any ophthalmologic condition that is

	clinically unstable; pre-existing skin condition that would prevent adequate evaluations of dermatologic toxicity, as determined by the investigator Medical history of interstitial lung disease, including drug-induced or radiation pneumonitis Known allergy, hypersensitivity, or intolerance to the excipients of amivantamab, lazertinib, or to tetracyclines, doxycycline, minocycline, or their excipients or to any component of the enhanced dermatologic management Participant has received any prior systemic treatment at any time for locally advanced stage III B/C or metastatic stage IV disease (adjuvant or neoadjuvant therapy for stage I, II or IIIA disease is allowed if last dose administered more than 12 months prior to the development of locally advanced or metastatic disease) Participant has an active or past medical history of leptomeningeal disease Sub-study exclusions: Participants who have received prior treatment for EGFR-induced DAEIs with JAK inhibitors (for Cohort A) or calcineurin inhibitors (for Cohort B)
Intervention	Experimental: Arm A and Subcutaneous (SC) Expansion Cohort: Enhanced Dermatologic Management Participants will receive enhanced dermatologic management to reduce toxicities in skin and nail with doxycycline tablet or minocycline capsule (100 mg twice daily for 12 weeks), clindamycin 1 % topical lotion, chlorhexidine 4% topical solution, and noncomedogenic skin moisturizer (once daily) during background anticancer treatment of advanced or metastatic EGFR-mutated NSCLC with amivantamab (1,050 mg for body weight less than 80 kg and 1,400 mg for body weight greater than or equal to 80 kg as IV infusion [Arm A], once weekly for the first 4 weeks, then once every 2 weeks) and subcutaneously (expansion cohort) (cycle 1: 1,600 mg or 2,240 mg once weekly based on body weight; cycles 2 onwards: 3,520 mg or 4,640 mg based on body weight on Day 1 of each 28-day cycle) with lazertinib (240 mg, tablet, once daily) until documented disease progression RECIST version 1.1). Sub-study: Experimental: Sub-study: Cohort A: Ruxolitinib Participants enrolled in Arms A and B of the main study who experience new-onset or persistent specific DAEIs (Grade greater than or equal to [>=] 2, as defined by NCI CTCAE v5.0) will be enrolled and receive reactive treatment with ruxolitinib 1.5% cream twice daily for up to 12 weeks in the sub-study. Participants in the sub-study will continue to receive amivantamab and lazertinib.
Comparator	Active Comparator: Arm B: Standard-of-Care Dermatologic Management Participants will receive standard care for dermatologic management according to local practice to reduce dermatologic toxicities in skin and nail during background anticancer treatment of advanced or metastatic EGFR-mutated NSCLC with amivantamab administered as IV infusion plus lazertinib, dose and dosing schedule as same as experimental arm.

	Sub-study: Experimental: Sub-study: Cohort B: Tacrolimus Participants enrolled in Arms A and B of the main study who experience new-onset or persistent specific DAEIs (Grade >= 2, as defined by NCI CTCAE v5.0) will be enrolled and receive reactive treatment with tacrolimus 0.1% ointment twice daily for up to 12 weeks in the sub-study. Participants in the sub-study will continue to receive amivantamab and lazertinib
Primary endpoint	Number of participants with grade greater than or equal to 2 DAEIs within 12 weeks after initiation of anticancer treatment.
Key secondary endpoints	Safety data – Number of AEs including VTEs and abnormalities in clinical laboratory values, based on NCI CTCAE v 5.0 PRO: PGI-S, EORTC-QLQ-C30, EQ-5D Efficacy: PFS, ORR, DoR
Primary data cut	Primary data cut is estimated for 07/11/2025
Estimated completion date	31/03/2026
Relevance of this study for the decision problem	Reduce any potential uncertainty in relation to safety profile of the intervention and provide data on management strategies.

Abbreviations: AE: Adverse event; DAEIs: Dermatologic adverse events of interest; DoR: Duration of Response; ECOG: Eastern cooperative oncology group; EGFR: Epidermal growth factor receptor; EORTC-QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: EuroQol 5 – Dimension; FDA: Food and Drug Administration; IV: Intravenous; JAK: Janus kinase; kg: Kilogram mg: Milligram; NCI CTCAE : National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC: Non-small cell lung cancer; ORR: Overall Response Rate; PFS: Progression-free survival; PGIS: Patient's Global Impression-Severity; PRO: Patient-reported Outcome; RDI: Relative Dose Intensity; SC: Subcutaneous; SoC: Standard of care; US: United States. Source: (ClinicalTrials.gov 2024a)

A.3 Results

A.3.1 Efficacy

Amivantamab SC demonstrated non-inferior PK to amivantamab IV, and amivantamab IV has consistently demonstrated OS benefits in several Phase 3 trials in various patient populations in advanced EGFR-mutated NSCLC. In the Phase 3 PALOMA-3 trial that directly compared amivantamab SC and IV, a prespecified exploratory analysis showed that amivantamab SC was associated with numerically longer OS compared to amivantamab IV. While investigation is ongoing in the PALOMA-2 trial, it is anticipated that amivantamab SC will continue to show OS benefits in additional patient populations that have been previously assessed in MARIPOSA.

A.3.1.1 PALOMA-3

The efficacy of amivantamab SC formulation in patients with EGFR-mutated locally advanced or metastatic NSCLC is based on achieving non-inferior PK exposure to IV amivantamab in the non-inferiority study PALOMA-3. The study demonstrated non-inferior efficacy of subcutaneous to intravenous amivantamab given in combination with lazertinib in patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease has progressed on or after treatment with osimertinib and platinum-based chemotherapy.

Pharmacokinetic outcomes

Amivantamab SC demonstrated non-inferior pharmacokinetics compared to amivantamab IV in patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease progressed on or after treatment with osimertinib (or another approved 3rd generation EGFR TKI) and platinum-based chemotherapy (See Figure 30:)(Johnson & Johnson 2024c, Leighl et al. 2024b, Leighl et al. 2024a).

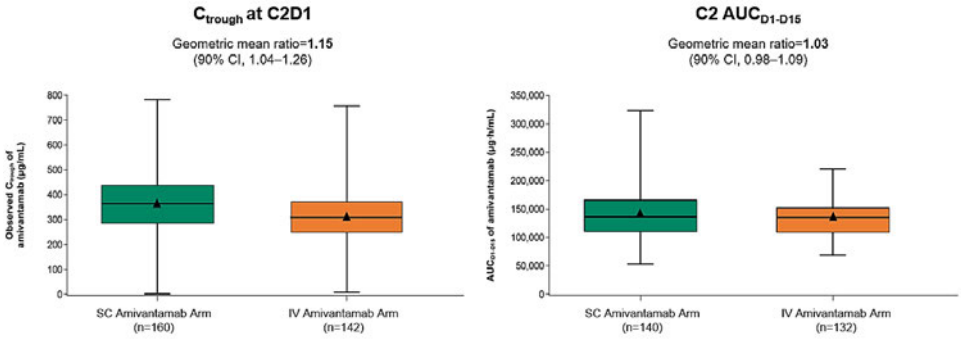


Figure 30: Co-primary pharmacokinetic endpoints amivantamab SC vs amivantamab IV (PALOMA-3, data cut-off 3 January 2024, Full analysis set)

Note: The PK analysis for primary endpoints included all patients who received all doses without dose modification and provided the required PK samples through the final required PK sample relevant to the endpoint. The upper and lower ends of the boxes indicate the 25th and 75th quartiles, the triangles indicate the means, the horizontal lines within the boxes indicate the medians, and the error bars indicate 95% CIs. Abbreviations: AUC: Area under the concentration-time curve; C: Cycle; CI: Confidence interval; Ctrough: Observed serum concentration of amivantamab at steady state; D: Day; IV: Intravenous; PK: Pharmacokinetic; SC: Subcutaneous. Source: (Leighl et al. 2024b)

Clinical efficacy outcomes

The pharmacokinetic outcomes are reinforced by the clinical efficacy outcomes from PALOMA-3.

The ORR, defined as a complete response (CR) or partial response (PR), was non-inferior in the amivantamab SC arm compared to the amivantamab IV arm, at 30.1% (95% CI: 23.9%, 36.9%) and 32.5% (95% CI: 26.3%, 39.3%), respectively. The ORR was non-inferior for amivantamab SC versus amivantamab IV, with a relative risk (RR) of 0.92 (95% CI: 0.70, 1.23) (Leighl et al. 2024b, Leighl et al. 2024a). The lower bound of the 95% CI (0.70) indicated at least 70% retention of ORR with 97.5% confidence, thus meeting the non-inferiority criteria, which was defined at a retention of 60% (Johnson & Johnson 2024c, Leighl et al. 2024a).

A higher proportion of patients exhibited stable disease in the amivantamab SC arm (45.1%) than in the amivantamab IV arm (38.2%), and there was a similar rate of

progressed disease in the amivantamab IV arm (19.8%) than the amivantamab SC arm (18.0%) (Leighl et al. 2024b, Leighl et al. 2024a). The amivantamab SC arm and amivantamab IV arm showed similar rates of CR (0.5% vs. 0.5%, respectively) and PR (29.6% vs. 32.1%). There was also a higher proportion of patients with unknown or non-evaluable response in the amivantamab IV arm (9.4%) than the amivantamab SC arm (6.8%). The ORR was shown to be consistent across all clinically relevant prespecified subgroups in both the treatment arms (Leighl et al. 2024a).

In addition, patients treated with amivantamab SC had numerically prolonged PFS relative to patients treated with amivantamab IV, with a median PFS of 6.11 months (95% CI: 4.30 to 8.11) and 4.30 months (95% CI: 4.14 to 5.72), respectively (HR of 0.84; 95% CI: 0.64 to1.10; nominal p=0.2006) (see Figure 31:) (Leighl et al. 2024a, Leighl et al. 2024b). The 6- and the 12-month event-free rates were also numerically higher in the amivantamab SC arm than the amivantamab IV arm (6-month: 50% vs. 42%; 12-month: 37% vs. 20%) (Leighl et al. 2024b).

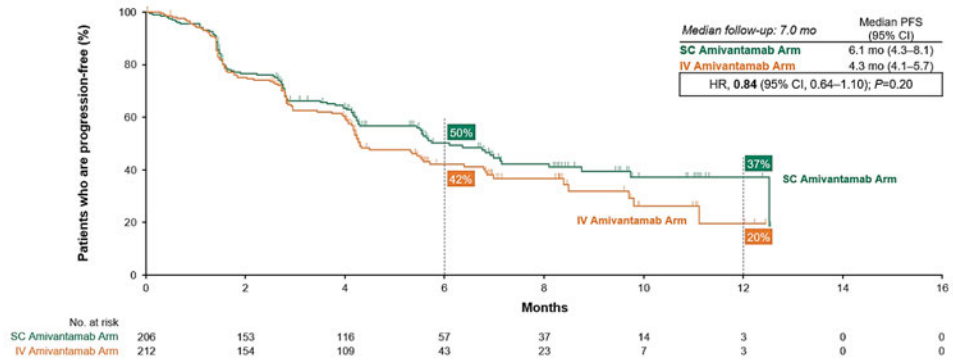


Figure 31: Kaplan-Meier plot for PFS (by investigator assessment) (PALOMA-3, data cut-off 3 January 2024, Full analysis set)

Abbreviations: CI: Confidence interval; HR: Hazard ratio; IV: Intravenous; PFS: Progression-free survival; SC: Subcutaneous. Source: (Leighl et al. 2024b)

Ultimately, OS was nominally longer in the amivantamab SC arm compared to the amivantamab IV arm at a median follow-up of 7.0 months, with a 38% reduction in risk of death (HR=0.62; 95% CI: 0.42 to 0.92; nominal p=0.0169) (Leighl et al. 2024a, Leighl et al. 2024b). The OS rate was greater in the amivantamab SC arm versus the amivantamab IV at all time points assessed, including 6 months (85% vs. 75%), 9 months (77% vs. 62%), and 12 months (65% vs. 51%) (Leighl et al. 2024a). Longer-term follow-up is needed given the high censoring rates at the time of the data cut-off (Johnson & Johnson 2024c). The improved tolerability of amivantamab SC may contribute to the resulting OS benefit.

Patient-reported outcomes on convenience and healthcare resource use

The PALOMA-3 trial also demonstrated a reduction in treatment administration time and higher patient-reported convenience with SC vs. IV administration of amivantamab:

- On Cycle 1 Day 1, median duration of treatment administration was 4.8 minutes with SC amivantamab vs. 5 hours with amivantamab IV. Similarly, on Cycle 3 Day 1, median duration of treatment administration was 4.8 minutes with amivantamab SC vs. 2.3 hours with amivantamab IV (Leighl et al. 2024a).

- On Cycle 1 Day 1, significantly more patients receiving the SC injection of amivantamab rated it as ‘very convenient’ or ‘convenient’ compared to those receiving the IV infusion of amivantamab (85% vs. 52%; p<0.001) (Leighl et al. 2024a).

The PALOMA-3 study also assessed patient satisfaction and the healthcare resource use (HCRU) burden of SC amivantamab as secondary endpoints. Overall, patient satisfaction scores were markedly higher in the amivantamab SC arm than the amivantamab IV arm, as assessed using the 11-item modified TASQ. Higher patient satisfaction scores were observed for most domains assessed (convenience, impact on activities of daily living, psychological impact, and treatment satisfaction).

Patients receiving amivantamab SC were less inconvenienced by injection/infusion, with 85.5% of these patients indicating SC as convenient or very convenient at baseline (vs. 52% of patients for the IV infusion; p<0.001) and by end of treatment (vs. 35% for IV, p<0.001) (See Figure 32:)(Leighl et al. 2024b, Leighl et al. 2024a).

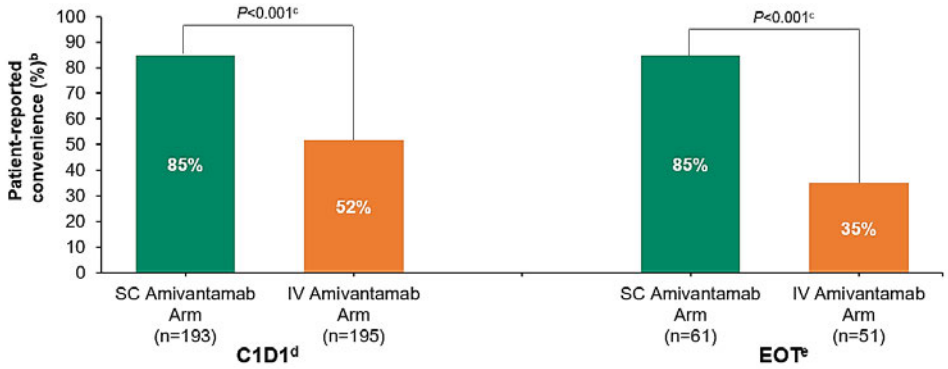


Figure 32: Frequency of patient-reported infusion/injection convenience per Modified TASQ[a] (PALOMA-3, data cut-off 3 January 2024, Full Analysis Set)

Note: Cycles included: Baseline, C3D1 and EOT. Baseline is Cycle 1 Day 1. For Amivantamab IV patients who received split dose, Cycle1 Day 2 will be the baseline if the questionnaires were completed on that visit. [a] Response categories on the modified TASQ convenience question included “Very convenient”, “Convenient”, “Neither convenient nor inconvenient”, “Inconvenient”, and “ Very Inconvenient”. [b] Includes patients whose answer was “Very convenient” or “Convenient.” [c] P-values were nominal and obtained by Pearson’s chi-squared test. [d] C1D2 for patients who received IV amivantamab due to split dosing. [e] Could have been collected after the last dose of treatment. Abbreviations: C: Cycle; D: day; EOT: End of treatment; IV: Intravenous; SC: Subcutaneous; TASQ: Treatment Administration Satisfaction Questionnaire. Source: (Leighl et al. 2024b)

Patient-reported data was favourable to the subcutaneous form (Alexander et al. 2024):

- At Cycle 1 and Cycle 3, the majority of patients that received SC amivantamab were satisfied with SC administration of amivantamab, preferred it to IV infusion and would recommend it to other patients (Figure 33:).
- Patients treated with SC amivantamab also spent less time in a chair while receiving treatment compared to those treated with amivantamab IV.
- Similarly, time spent in the treatment room and active healthcare provider time were lower with SC administration of amivantamab compared to IV infusion.
- After the administration of the first dose, patients in the amivantamab SC arm felt less restricted compared to the amivantamab IV during administration (66% vs. 29%

were “not at all restricted”) and were less bothered by administration time (69% vs. 30% were “not at all” bothered).

- In both treatment arms, the majority of patients experienced mild or no injection/infusion site pain (amivantamab SC: 86%; amivantamab IV: 91.3%).

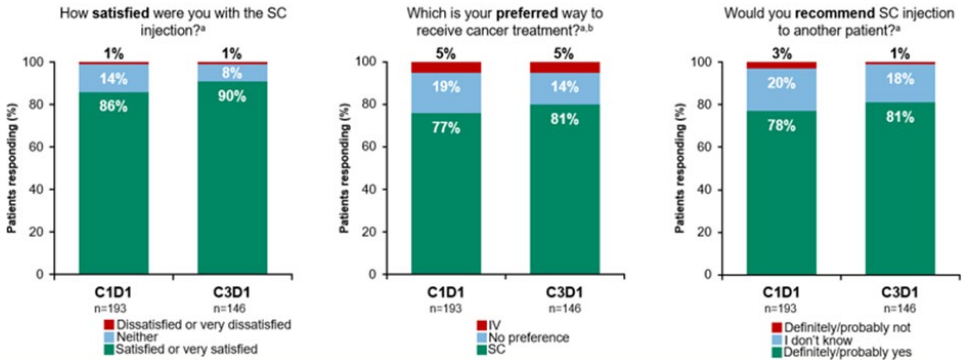


Figure 33: Patient satisfaction, preference and recommendation in the SC arm (PALOMA-3, data cut-off 3 January 2024, Full analysis set)

Notes: [a] Percentages may not add up to 100% due to rounding. [b] Patients in the SC arm compared SC amivantamab to other IV treatments they had received; these patients did not receive amivantamab (IV). Abbreviations: C: Cycle; D: day; SC: Subcutaneous; IV: Intravenous. Source: (Alexander et al. 2024)

In conclusion, PALOMA-3 demonstrated a favourable benefit-risk profile for amivantamab SC compared to amivantamab IV for the third-line treatment of locally advanced or metastatic EGFR-mutated NSCLC. Amivantamab SC showed non-inferiority to amivantamab IV for PK exposure and ORR. The amivantamab SC arm was also associated with an improvement in median PFS and OS, as well as a higher number of patients who remained in response for ≥6 months. In addition, a higher proportion of patients exhibited stable disease when treated with amivantamab SC, demonstrating a potential clinical benefit in disease control. Favourable PROs also substantiate the use of amivantamab SC. Results from PALOMA-3 confirm that patients generally prefer the SC formulation of amivantamab, reporting substantially greater treatment satisfaction and convenience, as well as higher likelihood to recommend to other patients. While caregiver preference was not directly assessed, the improved convenience of SC administration may represent a promising alternative for caregivers (i.e., by reducing the time needed to accompany patients to appointments). The SC formulation reduces healthcare resource use relative to IV administration, offering improved efficiency for HCPs, while still allowing an opportunity to monitor safety and adherence in an outpatient setting.

A.3.1.2 PALOMA-2

Overall, results from PALOMA-2 show that amivantamab SC provides similar efficacy and tolerability as that observed previously with amivantamab IV, with notable reductions in the incidence of ARRs and VTE events. While the data from PALOMA-2 are not yet mature, initial findings at a median follow-up of 8.6 months indicate that amivantamab SC provides high response rates in patients with advanced NSCLC with EGFR mutations. Additional follow-up for the PALOMA-2 trial is underway and is expected to further support long-term benefits of amivantamab SC.

Among all patients (i.e., confirmed and unconfirmed responders across both cohorts), the overall investigator-assessed ORR, PALOMA-2 primary efficacy endpoint, was 77% (95% CI: 68-84) (Lim et al. 2024b). The ORR by investigator assessment was 75% (95% CI: 63-85) for Cohort 1 and 80% (95% CI: 65-90) for Cohort 6 (Lim et al. 2024b). Due to short follow-up, PFS, OS, and duration of response were not estimable.

In Cohorts 1 and 6 in the PALOMA-2 study, the overall safety profile of amivantamab SC plus lazertinib was consistent with that of amivantamab IV plus lazertinib in the MARIPOSA trial, with the notable exception of markedly reduced incidence of ARRs/IRRs and VTE events in PALOMA-2 (15% vs. 63% and 13% vs. 37%, respectively). Although VTE rates should be considered within the context of differing prophylactic anticoagulant usage, SC administration may reduce the relative risk of VTE by minimising damage to the veins during treatment administration.

A.3.2 Safety

Johnson & Johnson has invested in additional complimentary clinical studies to address the tolerability concerns. As a result, the incidence of selected AEs with therapy management and SC administration of amivantamab was lower in the PALOMA-3 (Leighl et al. 2024a) and COCOON trial compared to MARIPOSA. The safety and tolerability profile of amivantamab was improved in the PALOMA-3 study (Leighl et al. 2024a). the overall safety profile of amivantamab SC is consistent with that of amivantamab IV while also offering lower rates of ARRs and VTEs. Below follows details of the safety data from PALOMA-3.

Treatment exposure

At the time of the 3 January 2024 data cut-off, the median follow-up was 7.0 months (range: 0.1, 14.4). with a median duration of study treatment of 4.7 months (range: 0.1, 13.2) for the amivantamab SC arm and 4.1 months (range: 0.0, 13.2) for the amivantamab IV arm (Leighl et al. 2024a). At this time, 114 patients (55.3%) in the amivantamab SC arm and 114 (54.3%) patients in the amivantamab IV arm had discontinued all study treatments (Johnson & Johnson 2024c). In both treatment arms, the most common reason for discontinuation of amivantamab or lazertinib was progressive disease (Johnson & Johnson 2024c). Overall, few participants discontinued amivantamab ([redacted] in amivantamab SC+ lazertinib and [redacted] in amivantamab IV+ lazertinib) or lazertinib [redacted] in amivantamab SC+ lazertinib and [redacted] in amivantamab IV+ lazertinib) due to an AE (Johnson & Johnson 2024c).

TEAEs led to dose reduction of any study treatment in 30.6% of participants in the amivantamab SC + lazertinib arm [redacted] for amivantamab and [redacted] for lazertinib) and for 24.8% in the amivantamab IV + lazertinib arm [redacted]) (Johnson & Johnson 2024c). The incidence of TEAEs, other than IRRs, leading to study treatment interruption was comparable for the two treatment arms (Johnson & Johnson 2024c). Except for dermatitis acneiform, rash, paronychia, and COVID-19, TEAEs leading to any study treatment interruption occurred at a frequency of less than 5% in both treatment arms (Johnson & Johnson 2024c).

The mean RDI, which is a ratio of actual versus prescribed doses (prescribed dose includes planned interruptions), was [redacted] (standard deviation [SD]: [redacted]) for

amivantamab SC and [redacted] (SD [redacted]) for lazertinib in the amivantamab SC + lazertinib arm. In the amivantamab IV + lazertinib arm, the mean RDI was [redacted] for amivantamab IV and [redacted] for lazertinib (Johnson & Johnson 2024c).

Rates of treatment modifications (reductions, interruptions, or discontinuations) were generally comparable across treatment arms in the PALOMA-3 trial, indicating that both the SC and IV formulations of amivantamab are safe and well-tolerated.

Treatment-emergent adverse events (TEAEs)

Most patients in each treatment arm experienced ≥1 TEAE (amivantamab SC: 99.0%; amivantamab IV: 99.5%) (Leighl et al. 2024b, Leighl et al. 2024a). Grade ≥3 TEAEs were reported at a similar rate across treatment arms (amivantamab SC: 51.9%%; amivantamab IV: 56.2%) (Leighl et al. 2024b). The most common Grade ≥3 TEAEs were dermatitis acneiform (amivantamab SC arm: 8.7%; amivantamab IV arm: 5.7%) and lymphopenia (amivantamab SC arm: 0.5%; amivantamab IV arm: 8.1%) (Leighl et al. 2024a) (Table 62). The incidence of serious TEAEs was comparable between the amivantamab SC arm (28.6%) and the amivantamab IV arm (30.5%) (Leighl et al. 2024a, Leighl et al. 2024b, Johnson & Johnson 2024c). The incidence of TEAEs leading to death were 3.4% in the amivantamab SC arm and 4.8% in the amivantamab IV arm (Leighl et al. 2024a).

Table 62: AEs reported in ≥15% of patients in either amivantamab (SC) + lazertinib or amivantamab (IV) + lazertinib

TEAE, n (%)	Amivantamab (SC) + lazertinib (n=206)		Amivantamab (IV) + lazertinib (n=210)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Paronychia	111 (54)	8 (4)	108 (51)	3 (1)
Hypoalbuminemia	96 (47)	9 (4)	77 (37)	8 (4)
Rash	95 (46)	8 (4)	91 (43)	8 (4)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Nausea	60 (29)	1 (0.5)	52 (25)	3 (1)
Stomatitis	57 (28)	1 (0.5)	69 (33)	5 (2)
Peripheral oedema	52 (25)	6 (3)	58 (28)	1 (0.5)
Increased alanine aminotransferase	46 (22)	6 (3)	56 (27)	8 (4)
Decreased appetite	45 (22)	1 (0.5)	52 (25)	3 (1)
Fatigue	44 (21)	3 (1)	43 (20)	5 (2)

Vomiting	44 (21)	2 (1)	41 (20)	1 (0.5)
Diarrhoea	43 (21)	3 (1)	39 (19)	2 (1)
Constipation	42 (20)	0	42 (20)	1 (0.5)
Headache	42 (20)	1 (0.5)	36 (17)	1 (0.5)
Increased aspartate aminotransferase	42 (20)	2 (1)	45 (21)	3 (1)
Anaemia	39 (19)	4 (2)	40 (19)	5 (2)
Pruritus	22 (16)	0	25 (12)	0
Hypokalaemia	33 (16)	0	27 (13)	0
Myalgia	32 (16)	0	13 (6)	0
Asthenia	31 (15)	4 (2)	23 (11)	2 (1)
Thrombocytopenia	29 (14)	4 (2)	22 (16)	2 (1)
IRR	27 (13)	1 (0.5)	138 (66)	8 (4)

Abbreviations: IRR: Infusion-related reaction; IV: Intravenous; TEAE: Treatment-emergent adverse event
Source: (Leighl et al. 2024a)

Administration/Infusion-related reactions

A range of symptoms or systemic reactions that can occur in response to the infusion or administration of amivantamab were recorded as IRRs, such as chills, dyspnoea, chest discomfort, fever, flushing (Johnson & Johnson 2024c). The ARRs reported in the amivantamab SC arm were considered systemic reactions related to SC administration.

In PALOMA-3, there was a five-fold reduction in the rate of ARRs (13.1% with amivantamab SC vs. 65.7% with IRRs with amivantamab IV) and the ARRs experienced tended to be of a lower grade than in the IV arm (Figure 34:) (Leighl et al. 2024a). A single patient (0.5%) reported a Grade 3 ARR in the amivantamab SC arm, while there were 8 patients (3.8%) with grade 3 IRRs in the amivantamab IV arm (Leighl et al. 2024a). This corresponds to an 87.3% reduction in the risk of the incidence of grade 3 or higher IRRs between SC and IV. Overall, most ARRs/IRRs were Grade 1 or 2 in severity, and no Grade 4 or 5 ARR events were reported in either arm. Other infusion-related AEs ranged between 0% to 6% in the SC arm and 2% to 20% in the IV arm (Leighl et al. 2024a). There were no treatment discontinuations due to ARRs in the SC arm, while 2% of patients discontinued treatment due to IRRs in the IV arm (Leighl et al. 2024a).

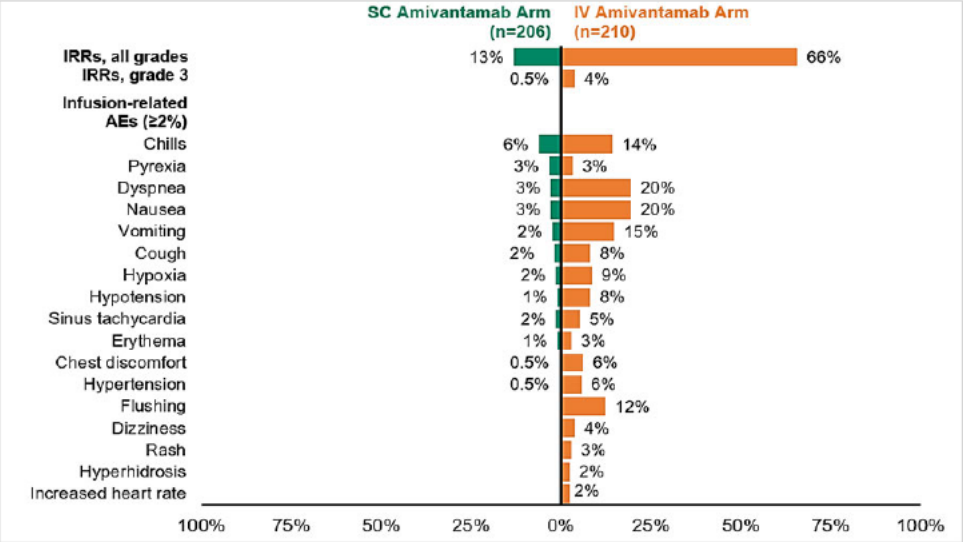


Figure 34: Incidence of ARR/IRR-related AEs in PALOMA-3 SC vs IV (Safety Analysis Set)

Note: Infusion-related reaction reported in the amivantamab subcutaneous arm is considered as a systemic reaction related to subcutaneous administration. Abbreviations: ARR: Administration-related reaction; AE: Adverse event; IRR: Infusion-related reaction; IV: Intravenous; SC: Subcutaneous. Source: (Leighl et al. 2024a)

Venous thromboembolic events

Anticoagulation use was similar between arms (amivantamab SC: 79.6%; amivantamab IV: 81.4%), although the incidence of VTE was lower in the amivantamab SC arm (9.2% vs. 14.3%) (Table 63) (Leighl et al. 2024a, Leighl et al. 2024b). Across both treatment arms, a total of 49 patients (11.8%) experienced a VTE event while receiving prophylactic anticoagulation (Leighl et al. 2024a). The majority of VTE events were grade 1 or grade 2 in severity; 8 patients (1.9% of all patients) experienced a grade 3 event, 6 (2.9%) of which were in the amivantamab IV arm (Leighl et al. 2024a). No grade 4 or 5 VTE events were reported in the amivantamab SC arm, and one patient reported a grade 4 VTE event in the amivantamab IV arm (Leighl et al. 2024a). No deaths related to VTE events were reported. Majority of the VTE events occurred during the first 4 cycles, which was consistent with previous studies. Among those who did not receive prophylactic anticoagulants, the incidence of VTE events was lower in the amivantamab SC arm (16.7%) compared to the amivantamab IV arm (25.6%), and Grade ≥3 VTEs were only reported in the amivantamab IV arm (5 patients [12.8%]; see Figure 35:) (Leighl et al. 2024b).

While prophylactic anticoagulant use is expected to minimize the risk of VTEs, the lower rates of these events observed in the amivantamab SC arm of the PALOMA-3 trial compared with the amivantamab IV arm suggests the SC formulation may contribute to the VTE risk reduction for patients with advanced NSCLC.

Table 63: Overall summary of treatment-emergent VTEs (PALOMA-3; Safety Analysis Set)

	Arm A	Arm B	Total
	Amivantamab SC + Lazertinib	Amivantamab IV + Lazertinib	

Analysis set: Safety; N	206	210	416
Patients with ≥1:			
VTEs [a]	19 (9.2%)	30 (14.3%)	49 (11.8%)
Maximum toxicity grade			
Grade 1	1 (0.5%)	7 (3.3%)	8 (1.9%)
Grade 2	16 (7.8%)	16 (7.6%)	32 (7.7%)
Grade 3	2 (1.0%)	6 (2.9%)	8 (1.9%)
Grade 4	0	1 (0.5%)	1 (0.2%)
Grade 5	0	0	0
VTEs leading to discontinuation of study agent	0	2 (1.0%)	2 (0.5%)
VTEs leading to death [b]	0	0	0

Note: [a] A VTE is assessed by the investigator as related to study agent. [b] VTEs leading to death are based on AE outcome of Fatal. Abbreviations: IV: Intravenous; SC: Subcutaneous; VTE: Venous thromboembolic event. Source: (Leighl et al. 2024b)

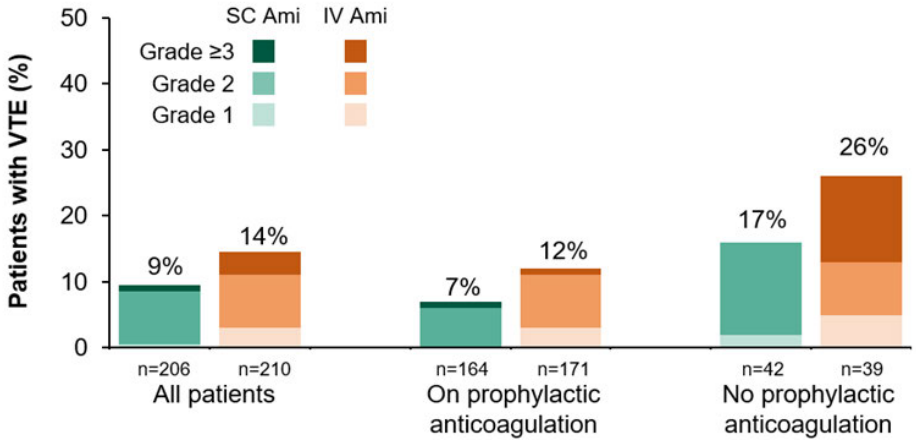


Figure 35: Incidence of VTE by treatment arm and prophylaxis use in PALOMA-3 (Safety Analysis Set)

Note: Grouping includes pulmonary embolism, deep vein thrombosis, venous embolism, venous thrombosis limb, embolism, thrombosis, subclavian vein thrombosis, superficial vein thrombosis, pulmonary infarction, venous thrombosis. VTE prophylaxis with apixaban, rivaroxaban, dalteparin, or enoxaparin was recommended by protocol (per the National Comprehensive Cancer Network guideline Cancer-Associated Venous Thromboembolic Disease v .2022). Abbreviations: Ami: Amivantamab; IV: Intravenous; SC: Subcutaneous; VTE: Venous thromboembolism. Source: (Leighl et al. 2024b)

Appendix B.Main characteristics of studies included

Table 64 contains a summary of the main characteristics of the MARIPOSA trial. Below follows further details on the trial, including Figure 36: summarising the study design and Figure 37: summarising the patient disposition.

Table 64: Main characteristic of studies included

Trial name: MARIPOSA	**NCT number: NCT04487080**
Objective	Assess the efficacy of the amivantamab and lazertinib combination, compared with osimertinib, in participants with epidermal growth factor receptor (EGFR) mutation (Exon 19 deletions [Exon 19del] or Exon 21 L858R substitution) positive, locally advanced or metastatic non-small cell lung cancer (NSCLC).
Publications – title, author, journal, year	MARIPOSA: phase 3 study of first-line amivantamab + lazertinib versus Osimertinib in EGFR-mutant non-small-cell lung cancer. Cho et al. *Future Oncol.* 2022. Amivantamab plus lazertinib vs osimertinib as first-line treatment in patients with EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results from MARIPOSA, a phase III, global, randomized, controlled trial. Cho et al. *Annals of oncology*. 2023 Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. Cho, et al. *N Engl J Med.* 2024 Amivantamab plus lazertinib versus osimertinib in first-line EGFR-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. Felip, E. et al. *Annals of Oncology,* 2024 Amivantamab plus lazertinib versus osimertinib as first-line treatment in EGFR-mutated advanced non-small cell lung cancer: MARIPOSA Asian subset. Cho, et al. *Lung Cancer,* 2025
Study type and design	MARIPOSA is an ongoing phase 3, international, randomized trial. Patients were randomly assigned 2:2:1 to arm A) amivantamab + lazertinib (open label), Arm B) Osimertinib (blinded) and Arm C) lazertinib (blinded). The primary end point was progression-free survival in the amivantamab–lazertinib group as compared with the Osimertinib group, as assessed by blinded independent central review.
Sample size (n)	1074 patients, of which 429 to arm A, 429 to arm B and 216 to arm C.
Main inclusion criteria	Aged 18 years and above. Newly diagnosed, histologically or cytologically confirmed, locally advances or metastatic NSCLC that is treatment-naïve and not amenable to curative therapy including surgical or chemoradiation.

Trial name: MARIPOSA	NCT number: NCT04487080
	Any toxicities from prior anticancer therapy must have resolved to common terminology criteria for AEs Grade 1 or baseline level. The patient must have at least 1 measurable lesion, according to Response Evaluation Criteria in Solid Tumours v1.1 that has not been previously irradiated. ECOG performance status 0 or 1.
Main exclusion criteria	Prior systemic anticancer therapy in the locally advanced or metastatic setting (adjuvant or neoadjuvant therapy for Stage I or II disease is allowed if administered >12 months prior to the development of locally advanced or metastatic disease). Previous treatment with Osimertinib at any time. Active or a history of interstitial lung disease/pneumonitis, including drug-induced or radiation interstitial lung disease/pneumonitis. Symptomatic brain metastases. Uncontrolled tumour-related pain. Any prior treatment with an EGFR TKI.
Intervention	Arm A (n=429): open-label treatment with the combination of amivantamab (1,050 mg for body weight < 80 kg and 1,400 mg for body weight ≥ 80 kg by IV infusion, once weekly for the first 4 weeks and then once every 2 weeks) and lazertinib (240 mg orally, once daily)
Comparator(s)	Arm B (n=429): double-blind treatment with osimertinib monotherapy (80 mg orally, once daily) [Additional comparator in trial] Arm C (n=216): double-blind treatment with lazertinib monotherapy (240 mg orally, once daily)
Follow-up time	At the primary analysis (data cut-off: 11 August 2023) there is a median follow-up of 22.0 months of PFS. At the final OS analysis (data cut-off: 04 December 2024), there is a median study follow-up of 37.78 months of OS.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	PFS, OS, ORR, intracranial PFS, Time-to-subsequent treatment, TTSP, AE, TEAEs, NSCLC-SAQ, EORTC-QLQ-C30, TTDD, EQ-5D-5L. **Endpoints included in this application:** The primary endpoint was progression-free survival, according to RECIST version 1.1. Secondary endpoint included was overall survival.

Trial name: MARIPOSA	NCT number: NCT04487080
	Exploratory endpoints were TTDD and EQ-5D. Safety outcomes were AE and TEAEs. **Other endpoints:** PFS as per investigator assessment, ORR, intracranial PFS, Time-to-subsequent treatment, TTSP, NSCLC-SAQ and EORTC-QLQ-C30 were included in the study but not in the health economic model.
Method of analysis	The efficacy analysis included all randomly assigned patients (ITT population). Safety analysis included all patients who received ≥1 dose of any treatment. The Kaplan-Meier product limit method and a stratified Cox model was used to estimate time-to-event variables and to obtain the HR and confidence interval. Unless otherwise specified, stratified log-rank tests was used to test the treatment effect for time-to-event variables; response rate variables will be evaluated using the chi square statistic or the exact test if the cell counts are small.
Subgroup analyses	Pre-specified subgroup analysis was performed for PFS and included the following groups: • Age (<65, >= 65, <75 and >= 75) • Sex (female, male) • Race (Asian, non-Asian) • Weight (<80 kg, >80 kg) • Performance status (0, 1) • History of smoking (No, yes) • History of brain metastasis (No, Yes)
Other relevant information	None

Study design

MARIPOSA had three phases: a screening phase, treatment phase, and follow-up phase.

- The **screening phase** of eligible participants was conducted ≤28 days before randomisation.
- The **treatment phase** began on Day 1, Cycle 1 with 28-day cycles until the end-of-treatment visit. Arm A was open-label due to the necessity to receive infusions and Arms B and C were double-blinded.
    - Patients in Arm A received 240 mg of oral lazertinib once daily as well as 1,050 mg (1,400 mg for patients with body weight ≥80 kg) amivantamab IV once weekly for the first 4 weeks then once every 2

weeks thereafter. Arm A represents the intervention of this submission.
    - Patients in Arm B received 80 mg of oral osimertinib once daily. Arm B represents the comparator in this submission.
    - Patients in Arm C received 240 mg of oral lazertinib once daily. Arm C was included to assess the contribution of components.
- The **follow-up phase** evaluated patients every 12 weeks (± 14 days) after the last dose of study treatment or disease progression, through to the end of the study, death, loss of follow-up or withdrawal of consent. Data were collected pertaining to survival, subsequent treatment, PROs and disease status.

Patients received their assigned treatment until they experienced unacceptable toxic effects or withdrew consent. Continuation of study treatment after disease progression was allowed in MARIPOSA in accordance with local practice, after consultation with the medical monitor, if the investigator believed the participant was still deriving clinical benefit (Johnson & Johnson 2023a). Participants continuing treatment after progression continued within the treatment phase of the study until the termination of study treatment. The patient disposition (Figure 37) is available in Appendix B.

There were required and optional pre-infusion medications for IRRs (Johnson & Johnson 2023a). Required pre-infusion medications were glucocorticoids, antihistamines, and antipyretics. Optional additional pre-infusion medications were continued glucocorticoids, H2 antagonist, and antiemetic treatments. Optional post-infusion medications could be prescribed and continued for up to 48 hours after the infusion if clinically indicated, at the discretion of the investigator. These included glucocorticoids, antihistamines, antipyretics, opiates, and antiemetics.

Disease assessments (by means of computed tomography [CT] and magnetic resonance imaging [MRI]) were performed within 28 days before randomisation (baseline), then every 8 weeks for the first 30 months, and every 12 weeks thereafter until disease progression (Cho et al. 2024). Survival, subsequent treatment, and disease status were assessed every 12 weeks after the discontinuation of treatment or disease progression (whichever occurred first) until the end of the trial, death, loss to follow-up, or withdrawal of consent.

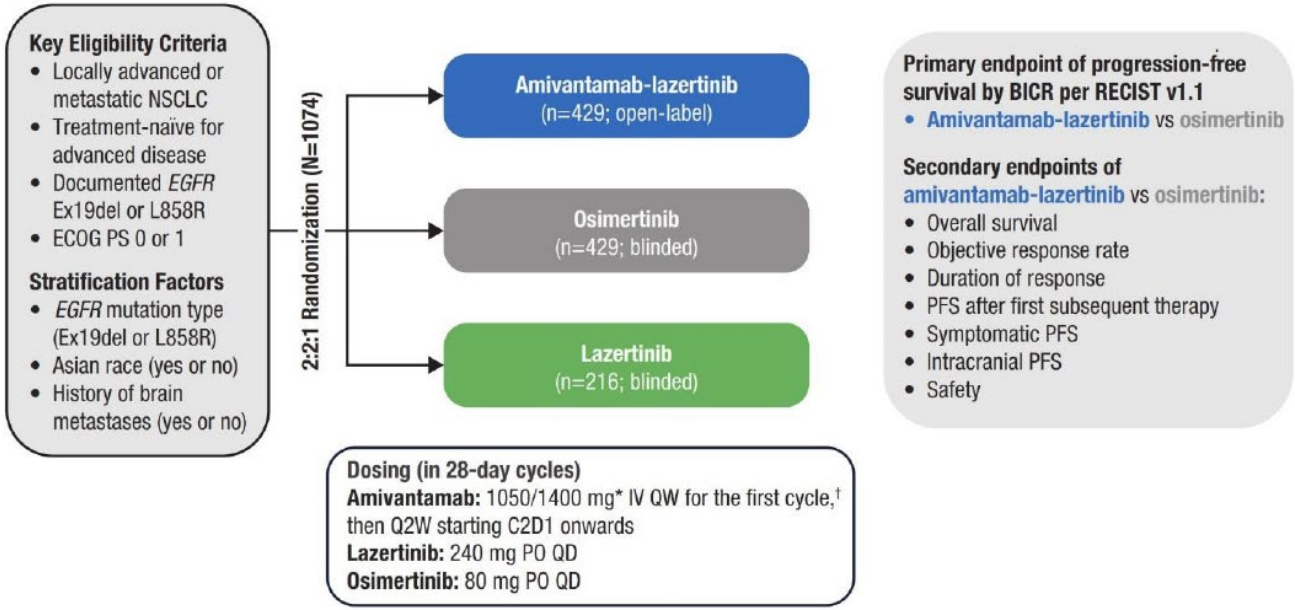


Figure 36: MARIPOSA study design

*Baseline brain MRI was required for all patients and performed ≤28 days prior to randomisation; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. Extracranial tumour assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR.

†Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs. osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.

Abbreviations: BICR: Blinded independent central review; CT: Computed tomography; DoR: Duration of response; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; ex19del: exon 19 deletion; HR: Hazard ratio; MRI: Magnetic resonance imaging; NSCLC: Non-small cell lung cancer; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PS: Performance status; RECIST: Response Evaluation Criteria in Solid Tumours.

Source: Cho et al. 2024 Figure S1 (Cho et al. 2024)

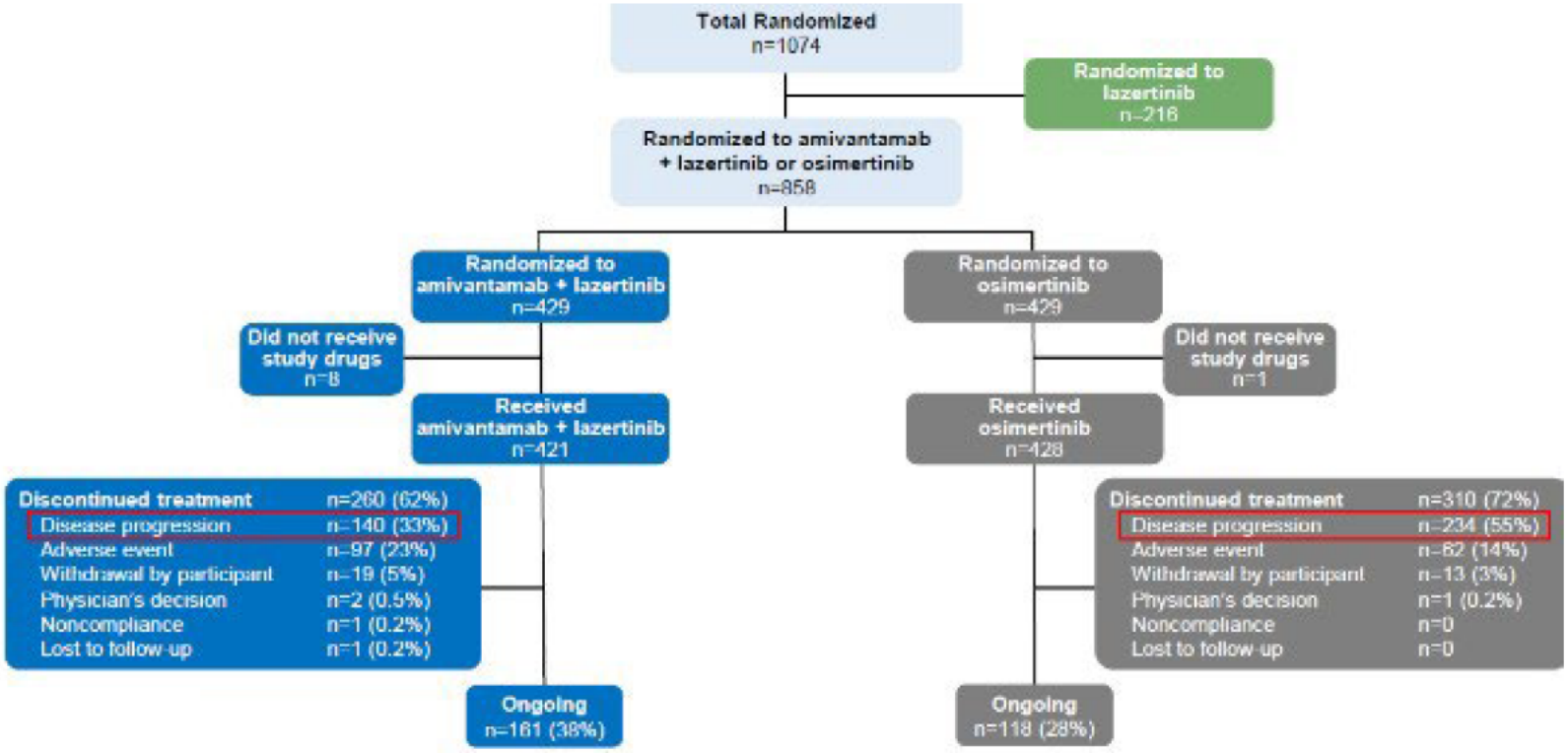


Figure 37: MARIPOSA patient disposition (Data cut-off 04 December 2024)

Source: (Yang J.C.H. et al. 2025)

Appendix C.Efficacy results per study

Table 65 contains a summary of the results of the MARIPOSA trial. The key efficacy outcomes presented in this submission have also been presented in previous assessments and are relevant endpoints to evaluate clinical efficacy in oncology, including NSCLC (Medicinrådet 2023, Medicinrådet 2025). OS and PFS were both used by the DMC in producing the evidence-based guidelines for NSCLC (Medicinrådet 2024b) as they are clinically relevant endpoints to evaluate treatment effect. In combination with time to treatment discontinuation or death (TTDD), the three endpoints are also able to model the disease progression. Lastly, these outcomes were directly measurable in the clinical trial and are patient-relevant (delaying or stopping progression while maintaining good tolerability is the primary treatment goal). Below the table follows further details of the key secondary outcomes not directly included in the health economic model.

Table 65: Results per study

Results of [MARIPOSA (NCT04487080)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median PFS (months) Primary PFS analysis (11 August 2023)	Amivantamab + lazertinib	429	23.7 (19.1, 27.7)	[redacted]	[redacted]	[redacted]	HR: 0.70	0.58, 0.85	0.0002	Number of PFS events: [redacted] amivantamab + lazertinib and [redacted] osimertinib. The median survival is based on the Kaplan-Meier estimator. The 95% CI for the difference in median was constructed assuming normal distribution. The HR is based on a Cox proportional hazards model and the P value comes from a log-rank test. Both the Cox model and the log-rank	MARIPOSA (Cho et al. 2024, Johnson & Johnson 2023c)
	Osimertinib	429	16.6 (14.8, 18.5)								

Results of [MARIPOSA (NCT04487080)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										test were stratified by the trial stratification factors.	
Median OS (months) Final OS analysis (04 December 2024)	Amivantamab + lazertinib	429	NE (42.9, NE)	[redacted]	[redacted]	[redacted]	HR: 0.75	0.61, 0.92	0.0048	Number of events: 173 amivantamab + lazertinib and 217 osimertinib OS was analysed using the same methodology and model as for the analysis of PFS.	MARIPOSA (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d)
	Osimertinib	429	36.7 (33.4, 41.0)								
Median TTDD (months) Final OS analysis (04 December 2024)	Amivantamab + lazertinib	429	27.0 (22.3, 30.6)	4.5	[redacted]	[redacted]	HR: 0.79	0.67, 0.93	0.0052	Number of events: [redacted] amivantamab + lazertinib and [redacted] osimertinib. TTDD was defined as the time interval between randomisation of patients in the study and subsequent discontinuation of treatment for any reason, including disease progression, treatment toxicity or death. Analysis used	MARIPOSA data on file (Johnson & Johnson 2024d)
	Osimertinib	429	22.6 (20.3, 24.5)								

Results of [MARIPOSA (NCT04487080)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										the same methods as the other time-to-event endpoints.	
ORR Primary PFS analysis (11 August 2023)	Amivantamab + lazertinib	421	86.2% (82.6%, 89.4%)	1.7%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Number of events: 363 amivantamab + lazertinib and 350 osimertinib. The risk difference is based on the Mantel-Haenszel estimator. The OR is based on logistic regression. Stratification by the randomisation stratification factors was used in both estimations.	MARIPOSA (Cho et al. 2024) Supplemented with data on file (Johnson & Johnson 2023b).
	Osimertinib	414	84.5 % (80.7%, 87.9%)								
Median Intracranial PFS (months) Final OS analysis (04 December 2024)	Amivantamab + lazertinib	178	25.4 (20.1, 29.5)	3.22	[redacted]	[redacted]	HR: 0.79	0.61,1.02	0.0678	Number of events: [redacted] amivantamab + lazertinib and [redacted] osimertinib. Intracranial PFS was defined as time from randomisation until the date of intracranial disease progression (progression of brain metastasis or occurrence of new brain lesions) or death, based on BICR using RECIST v1.1	MARIPOSA (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d)
	Osimertinib	173	22.2 (18.4, 26.9)								

Results of [MARIPOSA (NCT04487080)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										among participants with a history of brain metastases. The median survival is based on the Kaplan-Meier estimator. The 95% CI for the difference in median was constructed assuming normal distribution. The HR is based on a Cox proportional hazards model and the P value comes from a log-rank test. Both the Cox model and the log-rank test were stratified by the trial stratification factors.	
Median Time to subsequent treatment (months) Final OS analysis (04 December 2024)	Amivantamab + lazertinib	429	30.3 (26.6, 34.4)	6.2	1.9, 10.6	NA	HR: 0.76	0.64, 0.90	0.0018	Number of events: [redacted] amivantamab + lazertinib and [redacted] osimertinib. Time to subsequent therapy is defined as the time from the date of randomisation to the start of the next therapy following study treatment discontinuation or death (whichever came first).	MARIPOSA data on file (Johnson & Johnson 2024d)
	Osimertinib	429	24.0 (22.2, 26.2)								

Results of [MARIPOSA (NCT04487080)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										Analysis used the same methods as the other time-to-event endpoints.	
Median Time to symptomatic progression (months) Final OS analysis (04 December 2024)	Amivantamab + lazertinib	429	43.6 (36.0, NE)	14.3	NE	NA	HR: 0.69	0.57, 0.83	<0.001	Number of events: [redacted] amivantamab + lazertinib and [redacted] osimertinib. Symptomatic progression is a patient-relevant endpoint that measures time from randomisation to the onset of new/worsening lung cancer symptoms requiring a change in therapy, clinical intervention, or death, based on investigator discretion. The median survival is based on the Kaplan-Meier estimator. The 95% CI for the difference in median was constructed assuming normal distribution. The HR is based on a Cox proportional hazards model and the P value comes from a log-rank test. Both the Cox	MARIPOSA (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d)
	Osimertinib	429	29.3 (26.4, 33.4)								

Results of [MARIPOSA (NCT04487080)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										model and the log-rank test were stratified by the trial stratification factors..	

Abbreviations: BICR: Blinded Independent Central Review; CI: Confidence interval; EGFR: Epidermal Growth Factor Receptor; HR: Hazard ratio; NA: Not available; NE: Not estimable; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumors; TTDD: Time to treatment discontinuation or death.

Below follows efficacy data from relevant supportive outcomes that are not directly used in the health economic model.

Objective response rate (ORR)

Overall response was assessed during the primary PFS analysis. The objective response (complete or partial response) was assessed by BICR. Included in the analysis were 421 patients with measurable disease at baseline in the amivantamab + lazertinib group and 414 patients with measurable disease at baseline in the lazertinib group. The odds ratio is from a logistic regression model stratified by EGFR mutation type, Asian race, and history of brain metastasis.

The percentage of patients with an objective response was 86% (95% CI: 83 to 89) in the amivantamab + lazertinib group and 85% (95% CI: 81 to 88) in the osimertinib group (Table 66) (Cho et al. 2024). This corresponded to an odds ratio of 1.15 (95% CI: 0.78 to 1.70, p-value 0.4714) (Johnson & Johnson 2023b).

Table 66: Response efficacy endpoints amivantamab + lazertinib vs. osimertinib (MARIPOSA primary PFS analysis: 11 August 2023 data cut-off)

Endpoint	Amivantamab + lazertinib (n=429*)	Osimertinib (n=429*)
Objective response †		
Patients (95% CI) including all responders %	86 (83–89)	85 (81–88)
Patients (95% CI) including only confirmed responders %	80 (76–84)	76 (71–80)
Best overall response †— no. (%)		
Complete response‡	29 (7)	15 (4)
Partial response‡	334 (79)	335 (81)
Stable disease	30 (7)	42 (10)
Progressive disease	7 (2)	11 (3)
Not evaluable	21 (5)	11 (3)
Response duration†		
Median (95% CI) among all responders — months	24.0 (18.5–NE)	14.9 (12.9–17.5)
Median (95% CI) among confirmed responders — months	25.8 (20.1–NE)	16.8 (14.8–18.5)

Notes: *The efficacy population included all the patients who had undergone randomization.
†The objective response (complete or partial response) and response duration were assessed by blinded independent central review. Included in the analysis were 421 patients with measurable disease at baseline in the amivantamab + lazertinib group and 414 in the osimertinib group. ‡Includes all responders. Abbreviations: CI: Confidence interval; NE: Not estimable. Source: (Cho et al. 2024).

Response was confirmed in 336 patients in the amivantamab + lazertinib group and in 314 in the osimertinib group. Among patients with a confirmed response, the median duration of response

was 25.8 months (95% CI: 20.1 to could not be estimated) in the amivantamab + lazertinib group and 16.8 months (95% CI; 14.8 to 18.5) in the osimertinib group (Figure 38) (Cho et al. 2024).

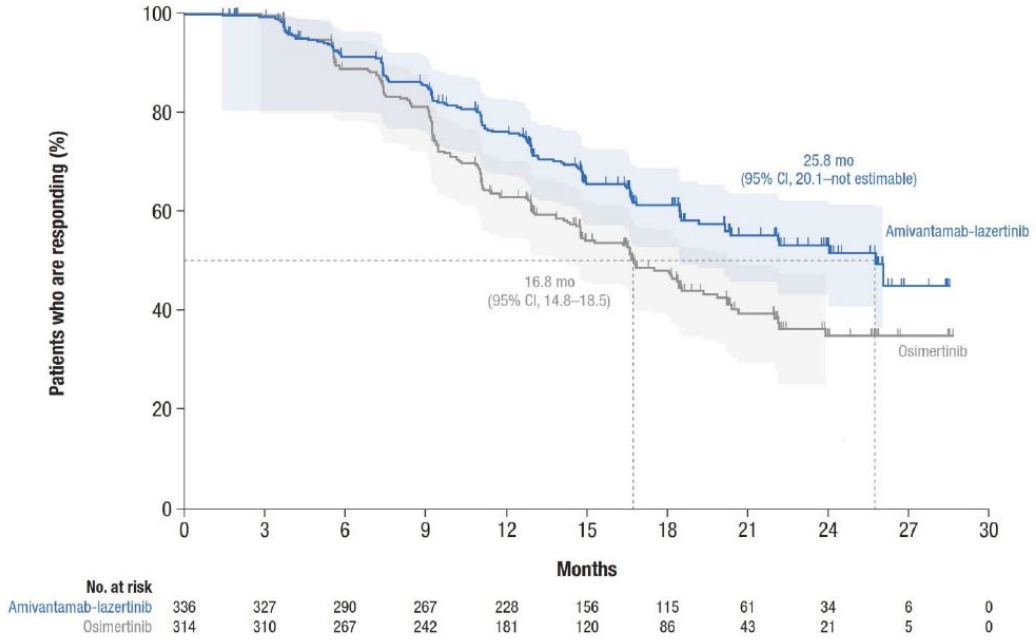


Figure 38: Response duration amivantamab + lazertinib vs. osimertinib (MARIPOSA primary analysis: August 2023 data cut-off)

Notes: Shown is a Kaplan-Meier estimate of response duration among confirmed responders in the efficacy population. The efficacy population included all patients who had undergone randomisation. Included in this analysis were the 336 confirmed responders (out of the 421 patients with measurable disease at baseline by blinded independent central review) in the amivantamab + lazertinib group and the 314 confirmed responders (out of 414 patients) in the osimertinib group. Tick marks indicate censoring of data, and the shaded area indicate 95% confidence bands. Abbreviations: CI: Confidence interval; No: Number; mo: Months. Source: (Cho et al. 2024).

Intracranial PFS

Intracranial PFS was defined as the time from randomisation to BICR-assessed intracranial disease progression (progression of brain metastasis or occurrence of new brain lesions) or death, among patients with a history of brain metastases. The frequency of brain MRIs in the MARIPOSA study was dependent on the presence or absence of the history of brain metastases, with participants with a history of brain metastases having more frequent brain MRIs performed. As a result, intracranial PFS was analysed among participants with history of brain metastasis. Intracranial PFS data were not released for the primary analysis. Data for the final OS analysis is presented below.

Amivantamab + lazertinib demonstrated a clinically meaningful improvement in intracranial PFS with durable responses (Johnson & Johnson 2024d, Yang J.C.H. et al. 2025). The hazard ratio observed for intracranial progression or death for the amivantamab + lazertinib arm versus osimertinib arm was 0.79 (95% CI: 0.61 to 1.02, nominal p=0.07), with median time to intracranial progression or death of 25.4 months (95% CI: 20.1 to 29.5) in the amivantamab + lazertinib arm and 22.2 months (95% CI: 18.4 to 26.9) in the osimertinib arm (Figure 39) (Johnson & Johnson 2024d, Yang J.C.H. et al. 2025). At 36 months, the amivantamab + lazertinib arm demonstrated sustained and durable CNS control, with double the proportion event-free (36%) compared with the osimertinib arm (18%)(Johnson & Johnson 2024d, Yang J.C.H. et al. 2025).

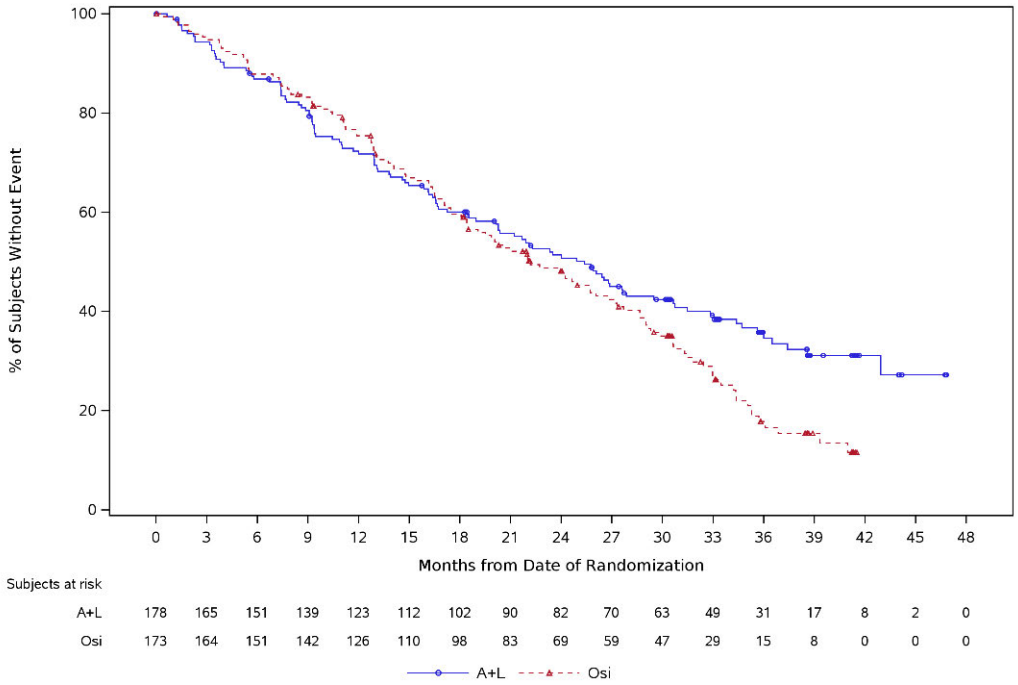


Figure 39: Kaplan-Meier plot of intracranial PFS by BICR among patients with a history of brain metastasis for amivantamab + lazertinib vs. osimertinib (MARIPOSA, full analysis set, final OS analysis: 04 December 2024 data cut-off)

Abbreviations: A+ L: Amivantamab + lazertinib; BICR: Blinded independent central review; PFS: Progression-free survival; Osi: Osimertinib. Source: (Johnson & Johnson 2024d, Yang J.C.H. et al. 2025)

Time to subsequent therapy

MARIPOSA also reports data on subsequent therapy which were based on local treatment practices at the treating physician's discretion (Johnson & Johnson 2023a). At the final OS analysis, 74% (129/175) of participants in the amivantamab + lazertinib arm were willing and able to receive a subsequent therapy and 76% (195/258) of participants in the osimertinib arm were willing and able to receive a subsequent therapy (Yang J.C.H. et al. 2025). Figure 40 summarises the most common first subsequent systemic therapy classes in the amivantamab + lazertinib and osimertinib arm, respectively (Johnson & Johnson 2024d). These represent 2L treatment.

In general, first subsequent therapies were balanced between amivantamab + lazertinib and osimertinib arms (Yang J.C.H. et al. 2025). In the amivantamab + lazertinib arm, 39% and 56% of patients treated with any subsequent treatment received any TKI and any chemotherapy, respectively. In the osimertinib arm, 28% and 67% of patients treated with any subsequent treatment received any TKI and any chemotherapy, respectively.

Time to subsequent therapy is defined as the time from the date of randomisation to the start of the next therapy following study treatment discontinuation or death (whichever came first) (Gadgeel SM. 2024). At the primary analysis, the median time to subsequent therapy was not reached in the amivantamab + lazertinib arm compared with 24.1 months in the osimertinib arm, for a reduction in risk of 18% amivantamab + lazertinib vs. osimertinib (HR 0.82; 95% CI: 0.66 to 1.00; nominal p=0.05) (Spira et al. 2023, Cho et al. 2024). Event-free rates in the amivantamab + lazertinib and osimertinib arms were 78% and 77%, respectively, at 12 months, 67% and 63% at 18 months and 57% and 51% at 24 months (Johnson & Johnson 2023b, Spira et al. 2023).

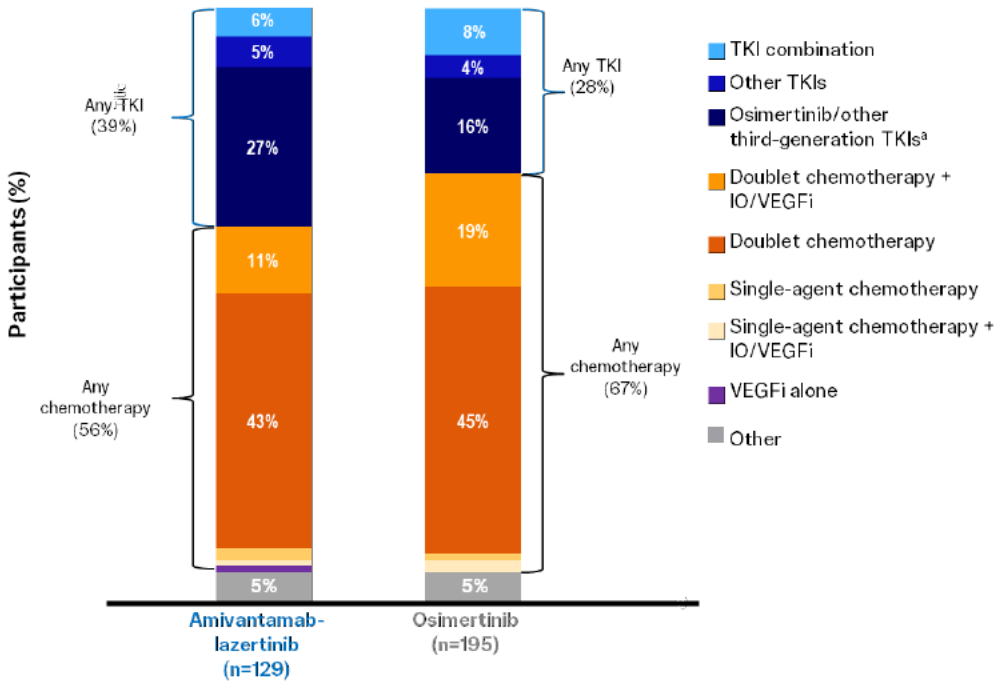


Figure 40: Most common first subsequent therapy (MARIPOSA, full analysis set, final OS analysis: 04 December 2024 data cut-off)

Abbreviations: IO: Immuno-oncology drug; TKI: Tyrosine kinase inhibitor; VEGFi: Vascular Endothelial Growth Factor inhibitors. Source: (Johnson & Johnson 2024d).

At the final OS analysis data cut, the median time to initiate subsequent therapy or death for the amivantamab + lazertinib arm was 30.26 months (95% CI: 26.64 to 34.43), as compared to 24.02 months (95% CI: 22.18 to 26.18) in the osimertinib arm (Figure 41) (Johnson & Johnson 2024d). This corresponds to a 24% reduction in risk (HR: 0.76; 95% CI: 0.64 to 0.90, nominal p=0.0018).The 30-, 36-, and 42-month event-free rates were 50.0%, 44.0% and 39.0%, respectively, in the amivantamab + lazertinib arm and 40.0%, 32.0% and 26.0%, respectively, in the osimertinib arm (Johnson & Johnson 2024d).

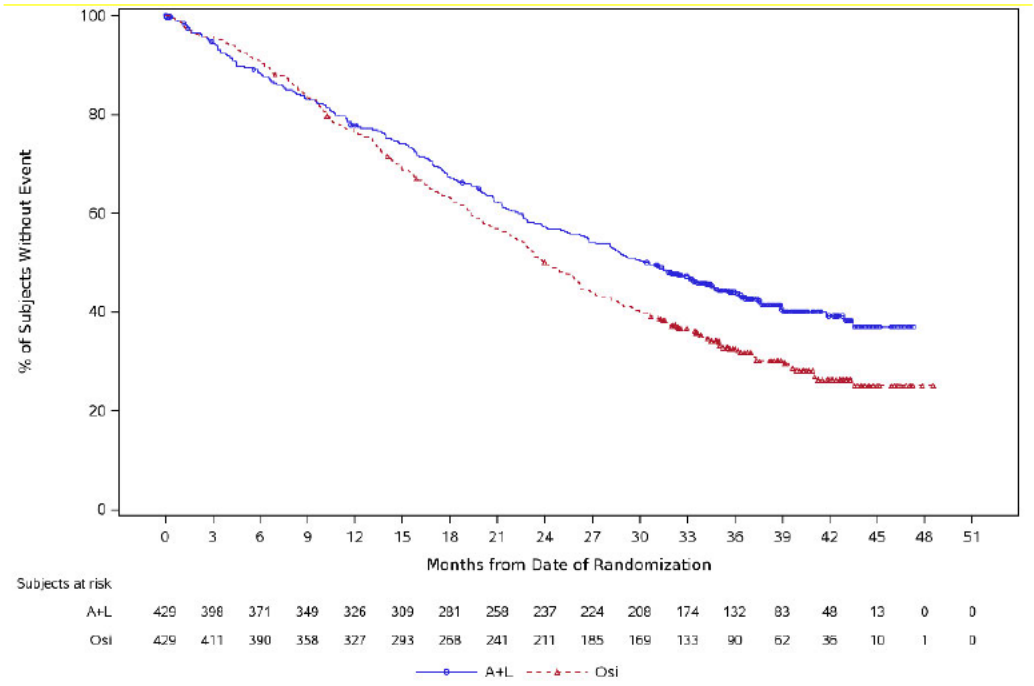


Figure 41: Kaplan-Meier plot of time to subsequent therapy for amivantamab + lazertinib vs osimertinib (MARIPOSA, full analysis set, final analysis: December 2024 data cut-off)

Abbreviations: A+L: Amivantamab + lazertinib; Osi: Osimertinib. Source: (Johnson & Johnson 2024d).

Time to symptomatic progression (TTSP)

Time to symptomatic progression (TTSP) is a time-to-event clinical endpoint that aims to document symptomatic events or death events. Symptomatic events correspond to the onset or worsening of relevant symptoms that are confirmed by a clinician as related to lung cancer, and thus distinguished from symptoms that arise due to other causes, such as drug toxicity (Johnson & Johnson 2024i).

TTSP captures patient experience in two ways; the symptomatic event reported by a clinician is based on information obtained from the patient, and the symptomatic event is of a severity that requires either a change in anticancer treatment (e.g., switching to alternative chemotherapy, immunotherapy, targeted therapy or addition of treatments to the existing regimen) and/or a clinical intervention to manage the corresponding symptom to be implemented (such as local anticancer therapies [e.g., radiotherapy or surgery], palliative/supportive therapies [e.g., systemic pain medication], or other interventions [e.g., therapeutic bronchoscopy, thoracentesis, ascites removal, pericardial fluid removal, or mediastinoscopy]). All death events also count as symptomatic progression events (Johnson & Johnson 2024i). TTSP represents an innovative patient-relevant endpoint that captures disease progression as well as the clinical benefit of a treatment for a patient, while also having the potential to provide results earlier than OS data and possibly PFS data. TTSP could also be complimentary to safety outcomes and PROs in providing a holistic view of the clinical effectiveness and tolerability of a treatment and its impact on a patient's overall well-being (Johnson & Johnson 2024i).

TTSP was assessed during the primary PFS analysis. Amivantamab + lazertinib led to a significant 28% reduction in the risk of symptomatic progression or death vs. osimertinib (HR 0.72; 95% CI: 0.57 to 0.91; nominal p=0.005) (**Figure** 43) (Nguyen et al. 2024). Event-free rates in the amivantamab + lazertinib and osimertinib arms were 82% and 79%, respectively, at 12 months, 74% and 67% at 18 months and 67% and 59% at 24 months (Johnson & Johnson 2023b, Nguyen et al. 2024).

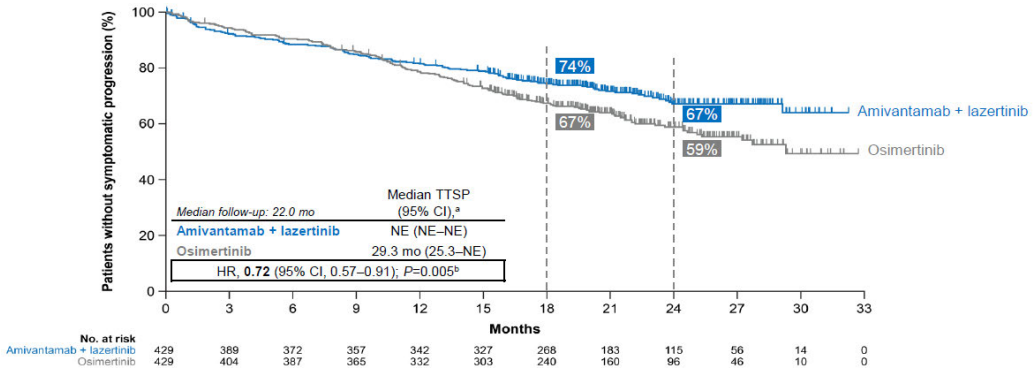


Figure 42: TTSP for amivantamab + lazertinib vs. osimertinib (MARIPOSA, primary PFS analysis: 11 August 2023 data cut-off)

a Median TTSP of the ITT population with 95% CI calculated using the Kaplan-Meier method. b HR with 95% CI calculated using a stratified Cox regression model; nominal p value was calculated using a stratified log-rank test. Abbreviations: CI: Confidence interval; HR: Hazard ratio; ITT: Intention-to-treat; IV: Intravenous; NE: Not evaluable; TTSP: Time to symptomatic progression. Source: (Nguyen et al. 2024)

At the final OS analysis, participants in the amivantamab + lazertinib arm had a 31% reduction in the risk of symptomatic progression or death compared to participants in the osimertinib arm (HR: 0.69; 95% CI: 0.57 to 0.83; nominal p<0.001) (Yang J.C.H. et al. 2025, Johnson & Johnson 2024d). Median TTSP was 43.6 months in the amivantamab + lazertinib arm (95% CI: 36.0 to NE) compared to 29.3 months in the osimertinib arm (95% CI: 26.4 to 33.4) (Johnson & Johnson 2024d, Yang J.C.H. et al. 2025). TTSP results are described in **Figure** 43. The 24-, 36-, and 42-month event-free rates were 66%, 55% and 51%, respectively, in the amivantamab + lazertinib arm and 58%, 42% and 35%, respectively, in the osimertinib arm (Yang J.C.H. et al. 2025).

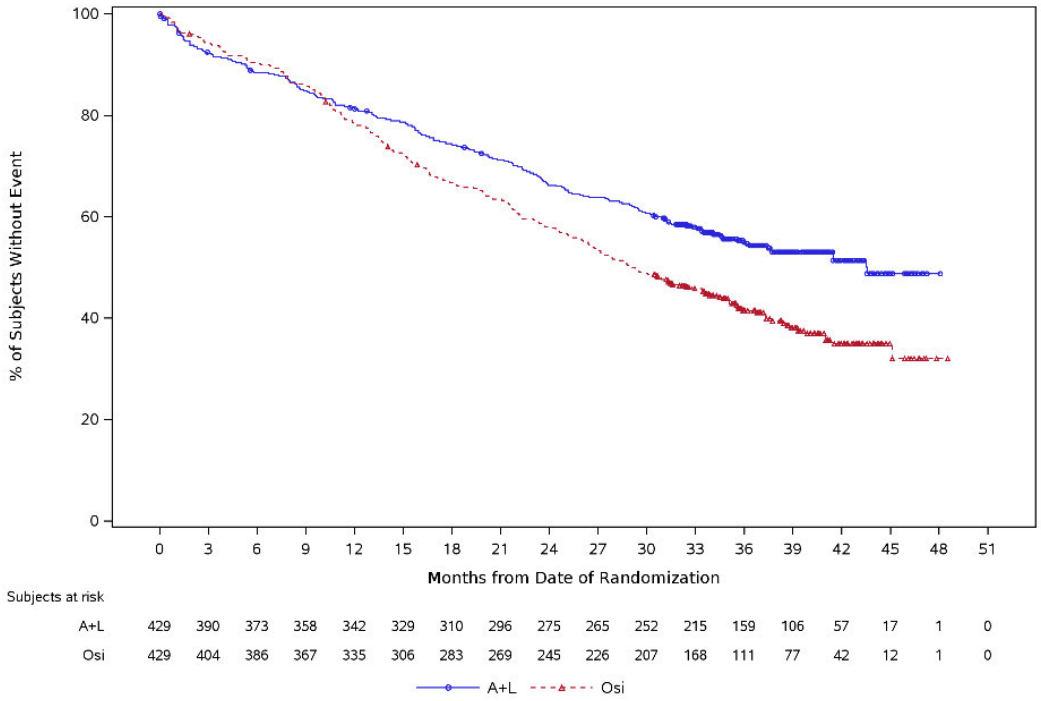


Figure 43: Kaplan-Meier plot of time to symptomatic progression for amivantamab + lazertinib vs. osimertinib (MARIPOSA, full analysis set, final OS analysis: 04 December 2024 data cut-off)

Abbreviations: A+ L: Amivantamab + lazertinib; Osi: Osimertinib. Source: (Johnson & Johnson 2024d, Yang J.C.H. et al. 2025).

Appendix D. Comparative analysis of efficacy

Not applicable owing to the head-to-head randomised clinical trial MARIPOSA providing the efficacy data for the intervention (amivantamab + lazertinib) and relevant comparator (osimertinib).

Appendix E. Extrapolation

E.1 Extrapolation of PFS

E.1.1 Data input

PFS was extrapolated from individual-level data from the MARIPOSA trial.

E.1.2 Model

Standard parametric functions, including exponential, Weibull, lognormal, log-logistic, Gompertz, gamma and generalised gamma were used see Table 67.

Table 67: Parametric Survival Functions in use in the model

Distribution	Equation
Exponential	S(t) = EXP(-1*(t* EXP(rate)))
Weibull	S(t) = EXP(-1*((t/exp(scale))^ EXP(shape)))
Log-normal	S(t) = 1-LOGNORM.DIST(t,meanlog,EXP(sdlog),TRUE)
Log-logistic	S(t) = (1/(1+(t/EXP(scale))^(EXP(shape))))
Gompertz	S(t) =EXP(-(EXP(rate)/shape)*(EXP(shape*t)-1))
Gamma	S(t) = 1-GAMMA.DIST(t,EXP(shape),1/EXP(rate),TRUE)
Generalised gamma	S(t) = GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE) when Q<0 S(t) = 1-GAMMA.DIST(((1/Q)^2)*((t*EXP(-(mu)))^(1/EXP(sigma))^Q),(1/Q)^2,1,TRUE)) when Q≥0

E.1.3 Proportional hazards

The proportional hazard (PH) assumptions for PFS were assessed graphically by the cumulative hazard plot (Figure 44) and the Shoenfeld residuals (Figure 45). For the cumulative hazard plot, non-parallel lines indicate a potential violation of the PH assumption. For the Schoenfeld residuals plot, random scatter around a flat line indicates PH, while systematic patterns indicate a violation of the PH assumption. If either plot shows signs of a violation, it suggests that the hazard ratios are not constant over time. The Shoenfeld plot (and individual test, checking for time-dependence of a treatment covariate) shows violation of the PH assumption, and the log cumulative hazard plot indicates crossing of hazards, i.e. a violation of the PH assumption. Thus, independent survival models were used for the extrapolation of OS.

Figure 44: Log cumulative hazard (log-log) plot for amivantamab + lazertinib and osimertinib (PFS)

Abbreviations: BICR: Blinded independent central review; PFS: Progression-free survival

Figure 45: Shoenfeld plot and test for amivantamab + lazertinib and osimertinib (PFS)

E.1.4 Evaluation of statistical fit (AIC and BIC)

The goodness-of-fit statistics for amivantamab + lazertinib are presented below in Table 68 and Table 69 for osimertinib. The overall best-fitting distribution was chosen for the base case for amivantamab + lazertinib. The overall best-fitting distribution based on AIC

and BIC was the gamma distribution. Clinical experts at the advisory board recommended that the shape of the PFS curve is expected to be similar to the osimertinib curve (Johnson & Johnson 2024a), and therefore gamma is selected for osimertinib as well.

Table 68: PFS (BICR) individual fits for amivantamab + lazertinib

Base-case distribution and lowest (i.e., best) AIC and BIC scores are in boldface. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BICR: independent review committee; N/A: not applicable; PFS: progression-free survival

Table 69: PFS (BICR) individual fits for osimertinib

Base-case distribution and lowest (i.e., best) AIC and BIC scores are in boldface. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; BICR: independent review committee; PFS: progression-free survival

E.1.5 Evaluation of visual fit

Figure 46 and Figure 47 show the observed time-to-event data with all investigated extrapolation functions for amivantamab + lazertinib and osimertinib, respectively.

Figure 46: Long-term PFS projections of amivantamab + lazertinib

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

Figure 47: Long-term PFS projections of osimertinib

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

E.1.6 Evaluation of hazard functions

The smoothed hazards for amivantamab + lazertinib and osimertinib (Figure 48 and Figure 49) are presented below. The smoothed hazard may be used to identify trends in the development of the hazard, such as whether it is increasing, decreasing, or levelling off over time. For example, an increasing hazard implies worsening survival rates over time, which is common in diseases like cancer, where risk increases with time. A decreasing hazard might suggest that survival chances improve after surviving an initial high-risk period (like with some treatments or acute conditions). Constant hazard implies a steady risk, which may be appropriate for chronic conditions. The interpretation of the hazard at later times, when the number of patients still at risk is low, should be made cautiously.

The smoothed hazard for both arms in the trial shows an increase in the risk for progression or death up until approximately 15 months with a spike for amivantamab +

lazertinib later in the model where the patient count is low. The individual plots emphasise this trend.

Figure 48: Smoothed and unsmoothed hazard plot for amivantamab + lazertinib PFS (BICR)

Abbreviations: BICR: Blinded independent central review; PFS: Progression-free survival

Figure 49: Smoothed and unsmoothed hazard plot for osimertinib PFS (BICR)

Abbreviations: BICR: Blinded independent central review; PFS: Progression-free survival

In Figure 50 and Figure 51, the smoothed hazards are overlayed with the fitted survival models. Visual comparison indicates that log-logistic curve for amivantamab + lazertinib is a good fit over the study period. However, as that would imply a lowered risk of mortality over time, it is not clinically plausible. The Gompertz distribution models a too rapid increasing hazard at later time points, that is also considered clinically implausible. Gamma and Weibull distributions are both good fits (also confirmed using AIC and BIC)

up until month 20 after which they have a slow steady increase which deviates from the observed smoothed hazard. However, at month 20 the numbers of patients at risk have decreased and hazards are more uncertain. The Gamma distribution captures the decline in the increase of hazard with time and is a more suitable choice for extrapolation beyond the trial duration. Overall, gamma distribution has the best statistical fit for amivantamab + lazertinib and it models a steady hazard with time that slowly increases and produces results in line with according to expert the expected number of individuals alive at highlighted time points.

The smoothed hazard for osimertinib indicates that log-logistic is visually aligns with the decrease in mortality but as its implications is not clinically plausible the Gamma and Weibull are better fitted to extrapolate PFS. As gamma indicates a decrease of hazard over time compared to Weibull it is argued to be a more suitable choice for extrapolation beyond the trial period.

Figure 50 : Smoothed hazard plot with parametric extrapolations for amivantamab + lazertinib PFS (BICR)

Abbreviations: BICR: Blinded independent central review; PFS: Progression-free survival

Figure 51: Smoothed hazard plot with parametric extrapolations for osimertinib PFS (BICR)

Abbreviations: BICR: Blinded independent central review; PFS: Progression-free survival

E.1.7 Validation and discussion of extrapolated curves

The assessment of the visual and statistical fit of the PFS curves was deemed acceptable to determine the distribution for PFS (gamma) given the maturity of the subject-level data from MARIPOSA and reasonably similar extrapolations across distributions.

E.1.8 Adjustment of background mortality

The general mortality for the Danish population was used. The probability of death per year, as modelled, is shown in Figure 52, from 62 years to 98 years. Crossing of either PFS or TTDD curves with the OS curve is plausible and avoiding it was an additional consideration in selecting appropriate distributions. However, it may be impractical to discard distributions when crossing occurs only at late time points when all curves are at very low values. Therefore, PFS and TTDD extrapolations in the CEM were capped by OS to prevent crossing in such instances. Additionally, to ensure plausible mortality rates predicted at old age, OS, PFS and TTDD rates used in the model were bound by the age- and sex-specific mortality of the general population as a minimum.

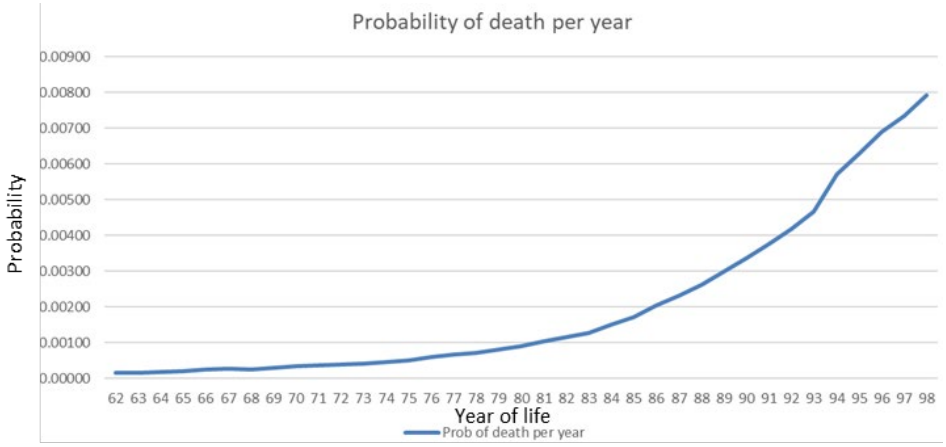


Figure 52: General population risk of death (cycle-length probability)

E.1.9 Adjustment for treatment switching/cross-over

Not applicable.

E.1.10 Waning effect

Not applicable.

E.1.11 Cure-point

Not applicable.

E.2 Extrapolation of OS

E.2.1 Data input

OS was extrapolated from individual-level data from the MARIPOSA trial.

E.2.2 Model

See section E.1.2.

E.2.3 Proportional hazards

The PH assumption for OS was assessed graphically by the cumulative hazard plot (Figure 53) and the Schoenfeld residuals (Figure 54). For a discussion on the interpretation of the plots, see section E.1.3. For PFS, the log cumulative hazard plot indicates crossing hazards, i.e., a violation of the PH assumption. Thus, independent survival models were used for extrapolating OS.

Figure 53: Log cumulative hazard (log-log) plot for amivantamab + lazertinib and osimertinib (OS)

Abbreviations: BICR: Blinded independent central review; OS: Overall survival

Figure 54: Schoenfeld plot and test for amivantamab + lazertinib and osimertinib (OS)

Abbreviations: OS: Overall survival

E.2.4 Evaluation of statistical fit (AIC and BIC)

Statistical or goodness of fit was assessed by AIC and BIC which are presented in Table 70 and Table 71 for amivantamab + lazertinib and osimertinib, respectively.

Table 70: OS Individual Fits for amivantamab + lazertinib

Distribution	AIC	BIC	5-year OS	10-year OS	Median OS (Months)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

To Base-case distribution and lowest (i.e., best) AIC and BIC scores are in boldface. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival

Table 71: OS Individual Fits for osimertinib

Distribution	AIC	BIC	5-year OS	10-year OS	Median OS (Months)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

Base-case distribution and lowest (i.e., best) AIC and BIC scores are in boldface. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival

E.2.5 Evaluation of visual fit

Figure 55 and Figure 56 show the observed time-to-event data with all the investigated extrapolation functions for amivantamab + lazertinib and osimertinib, respectively. Several of the parametric survival models provided an adequate visual fit to the observed Kaplan–Meier curves. Nevertheless, the extrapolated survival estimates varied considerably across models. According to clinical expert opinion, the Weibull model yielded the most clinically plausible projections, whereas the Gompertz model produced

too conservative (i.e., pessimistic) estimates for both treatment arms (Johnson & Johnson 2024a).

Figure 55: Long-term OS projections of amivantamab + lazertinib

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

Figure 56: Long-term OS projections of osimertinib

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

E.2.6 Evaluation of hazard functions

The smoothed hazards for amivantamab + lazertinib and osimertinib are presented below (Figure 57 and Figure 58). The smoothed hazard for both arms in the trial shows an increase in the mortality rate up until approximately 30 months, after that patient count is low and the rate decreases.

Figure 57: Smoothed and unsmoothed hazard plot for amivantamab + lazertinib OS

Abbreviations: OS: Overall survival.

Figure 58: Smoothed and unsmoothed hazard plot for osimertinib OS

Abbreviations: OS: Overall survival.

In Figure 59 and Figure 60 below, the smoothed hazards are overlayed with the fitted survival models. For amivantamab + lazertinib the Weibull and Gamma distributions are both good fits. Gamma and Weibull project a slight increase over time which is line with expected for the patient population. A clinical advisory board based on the August 2023 Ad board argued that any curves projecting above the Weibull to be overly optimistic,

while the Gompertz and Generalised Gamma models were deemed likely to be conservative (Johnson & Johnson 2024a). Weibull for December 2024 data cut is in line with what was deemed clinically plausible for amivantamab + lazertinib. Based on the hazard functions, Weibull is the best fit both visually and generates clinically plausible projections over time.

For osimertinib, Weibull and Gamma are both a good fit where Weibull has slightly better visual fit. Gompertz indicate a rapid increase in hazard over time, which is not clinically plausible which further argued by clinicians as it projects too conservative long-term survival (Johnson & Johnson 2024a). Based on hazard function Weibull is chosen due to best visual fit and clinical plausibility both long term and expected hazard over time.

Figure 59: Smoothed hazard plot with parametric extrapolations for amivantamab + lazertinib - OS

Abbreviations: OS: Overall survival.

Figure 60: Smoothed hazard plot with parametric extrapolations for osimertinib – OS

Abbreviations: OS: Overall survival.

E.2.7 Validation and discussion of extrapolated curves

The assessment of the visual and statistical fit of the OS curves was deemed acceptable to determine the distribution for OS (gamma) given the maturity of the patient-level data from MARIPOSA. The predicted survival based on the gamma distribution was also validated by clinical experts as the most clinically plausible extrapolation (Johnson & Johnson 2024a).

E.2.8 Adjustment of background mortality

See section E.1.8.

E.2.9 Adjustment for treatment switching/cross-over

Not applicable.

E.2.10 Waning effect

Not applicable.

E.2.11 Cure-point

Not applicable.

E.3 Extrapolation of TTDD

E.3.1 Data input

TTDD was extrapolated from individual-level data from the MARIPOSA trial.

E.3.2 Model

See section E.1.2.

E.3.3 Proportional hazards

The PH assumption was not considered as TTDD was modelled with three independent and separately fitted distributions for amivantamab, lazertinib and osimertinib.

E.3.4 Evaluation of statistical fit (AIC and BIC)

The goodness-of-fit statistics for the three treatments in the trial are presented below in Table 72, Table 73, and Table 74. The overall best-fitting distribution was generalised gamma for amivantamab, exponential for lazertinib, and gamma for osimertinib, based on both AIC and BIC.

Table 72: TTDD outcomes individual fits for amivantamab

Distribution	AIC	BIC	5-year TTDD	10-year TTDD	Median TTDD (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 and lowest (i.e., best) AIC and BIC scores are in boldface. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTDD: Time to treatment discontinuation or death

Table 73: TTDD outcomes individual fits for lazertinib

Distribution	AIC	BIC	5-year TTDD	10-year TTDD	Median TTDD (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 and lowest (i.e., best) AIC and BIC scores are in boldface. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTDD: time to treatment discontinuation or death

Table 74: TTDD individual fits for osimertinib

Distribution	AIC	BIC	5-year TTDD	10-year TTDD	Median TTDD (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 and lowest (i.e., best) AIC and BIC scores are in boldface. Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; TTDD: time to treatment discontinuation or death

E.3.5 Evaluation of visual fit

The long-term TTDD extrapolations for amivantamab, lazertinib, and osimertinib are presented in Figure 61, Figure 62, and Figure 63, respectively. Extrapolated survival estimates varied considerably across models and selected distribution is the visually the most positive for both arms.

Figure 61: Long term TTDD projections of amivantamab

Abbreviations: KM: Kaplan-Meier; TTDD: Time to treatment discontinuation or death.

Figure 62: Long term TTDD projections of lazertinib

Abbreviations: KM: Kaplan-Meier; TTDD: Time to treatment discontinuation or death.

Figure 63: Long term TTDD projections of osimertinib

Abbreviations: KM: Kaplan-Meier; TTDD: Time to treatment discontinuation or death.

E.3.6 Evaluation of hazard functions

The smoothed hazards for amivantamab + lazertinib and osimertinib TTDD are presented below (Figure 64, Figure 65, Figure 66, Figure 67, Figure 68, and Figure 69).

Figure 64: Smoothed and unsmoothed hazard plot for amivantamab + lazertinib (amivantamab alone) TTDD

Abbreviations: TTDD: Time to treatment discontinuation or death.

Amivantamab indicated a relatively flat or slight increasing hazard up to month 20 and a decreasing hazard beyond that time point. In PFS, 8 and 10 patients are at risk for amivantamab + lazertinib and osimertinib respectively, at month 30 which indicates the increasing uncertainty in hazards over time. Overall, visually neither extrapolation curves capture the increase and decrease of the hazard over time and overall, the extrapolations curves are somewhat aligned, beside log-logistic and log-normal which have too sharp of a decrease to be clinically plausible. Exponential and generalised gamma is considered both a visually a good fit, but generalised gamma is chosen based on slight increase as it better captures the overall fit of the hazard over the whole time period.

Figure 65: Smoothed hazard plot with parametric extrapolations for amivantamab TTDD

Abbreviations: TTDD: Time to treatment discontinuation or death

Figure 66: Smoothed and unsmoothed hazard plot for amivantamab + lazertinib (lazertinib alone) TTDD

Abbreviations: TTDD: Time to treatment discontinuation or death

Figure 67: Smoothed hazard plot with parametric extrapolations lazertinib TTDD

Abbreviations: TTDD: Time to treatment discontinuation or death.

The hazard of lazertinib is relatively flat over time with a decrease around month 25. As previously discussed for PFS, there is fewer patients at risk over time, and it is expected that the TTDD curve to visually be similar to that of PFS. Hence, overall, the exponential curve is the best fit, which is also supported by the AIC and BIC.

Figure 68: Smoothed and unsmoothed hazard plot for osimertinib TTDD

Abbreviations: TTDD: Time to treatment discontinuation or death.

Figure 69: Smoothed hazard plot with parametric extrapolations for osimertinib TTDD

Abbreviations: TTDD: Time to treatment discontinuation or death.

Osimertinib hazard function for TTDD increases over time, flattens out and then decrease around month 30. For the earlier months, Generalised gamma, Weibull and Gamma has the best fit visually. Gompertz has a rapid increase over time and is not

clinically plausible. Overall, Gamma has a slightly better fit and visually similar with the PFS curve. The choice is further supported by the AIC and BIC.

E.3.7 Validation and discussion of extrapolated curves

The assessment of the visual and statistical fit of the TTDD curves was deemed acceptable to determine the distributions for TTDD given the maturity of the patient-level data from MARIPOSA and reasonably similar extrapolations across distributions. For amivantamab generalised gamma is the best model according to AIC and BIC and was selected for the base case. For lazertinib exponential curve is the best model according to AIC and BIC, followed by Gompertz. For osimertinib, gamma model is the best fit according to AIC and BIC and was selected for the base case.

E.3.8 Adjustment of background mortality

See section E.1.8.

E.3.9 Adjustment for treatment switching/cross-over

Not applicable.

E.3.10 Waning effect

Not applicable.

E.3.11 Cure-point

Not applicable.

Appendix F. Dose interruptions and efficacy

The study protocol recommended treatment with amivantamab to be interrupted for patients with Grade ≥2 toxicities (Johnson & Johnson 2023a, del Rosario Garcia Campelo et al. 2024). In the amivantamab + lazertinib arm, TEAEs leading to a dose interruption of any trial agent were reported in 350 patients (83%), leading to any dose reduction in 249 (59%), and leading to any discontinuation of treatment in 147 (35%); the corresponding numbers in the osimertinib arm were 165 (39%), 23 (5%), and 58 (14%) (Cho et al. 2024). A total of 10% of the patients in the amivantamab + lazertinib arm and 3% of those in the osimertinib arm discontinued all trial agents owing TEAEs (Cho et al. 2024).

Almost half of patients treated with at least one dose of amivantamab (49%) had a dose interruption during the first 4 months of treatment, which is when key skin and gastrointestinal AEs occurred most frequently (del Rosario Garcia Campelo et al. 2024). The prevalence of key AEs declined between Months 5 and 8, including rash (~50% decrease), paronychia (~30% decrease) and diarrhoea (~70% decrease)(del Rosario Garcia Campelo et al. 2024).

Among patients with and without amivantamab dose interruptions in the first 4 months, efficacy outcomes were similar, including median PFS (23.9 vs. 23.7 months, respectively) and ORR (87% vs. 89%) (del Rosario Garcia Campelo et al. 2024). Outcomes after the first four months were also evaluated to minimise bias (with patients who discontinued the study, had disease progression or died in the first four months not evaluated)(del Rosario Garcia Campelo et al. 2024). Among patients with and without amivantamab dose interruptions during the initial four months of treatment, median PFS was similar beyond four months (Figure 70); dose interruption was not significantly associated with PFS after adjustment for age, ECOG performance status, EGFR mutation type, Asian race, and history of brain metastases by multivariable analysis (HR 1.06; 95% CI: 0.73, 1.44) (del Rosario Garcia Campelo et al. 2024). Based on this analysis, AEs with this combination treatment can be meaningfully managed with amivantamab dose interruptions, without compromising PFS (del Rosario Garcia Campelo et al. 2024).

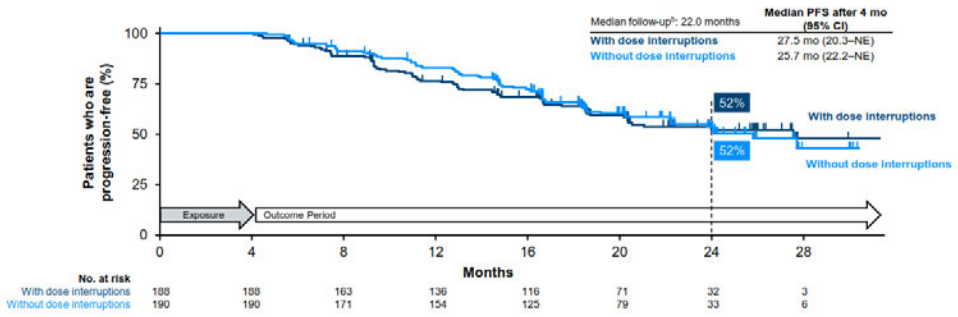


Figure 70: PFS for amivantamab + lazertinib among patients with and without dose interruptions (Primary PFS analysis: 11 August 2023 data cut-off)

Notes: a Dose interruptions of amivantamab occurring during the first four months of treatment. b Median follow-up of the MARIPOSA study, as of the data cut-off of 11 August 2023. Abbreviations: CI: Confidence

interval; IV: Intravenous; NE: Not estimable; PFS: Progression-free survival. Source: (del Rosario Garcia Campelo et al. 2024)

Appendix G. Serious adverse events

Table 75 lists all the treatment-emergent serious AEs as recorded in the MARIPOSA trial in the Safety Analysis Set at the primary PFS data cut-off (11 August 2023) by System Organ Class and Preferred Term.

Table 75: Number of participants with treatment-emergent serious adverse events

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Subjects with 1 or more SAEs	**205 (48.7%)**	**143 (33.4%)**
Respiratory, thoracic and mediastinal disorders	**61 (14.5%)**	**53 (12.4%)**
Pulmonary embolism	26 (6.2%)	10 (2.3%)
Pleural effusion	9 (2.1%)	17 (4.0%)
Pneumonitis	7 (1.7%)	8 (1.9%)
Respiratory failure	6 (1.4%)	2 (0.5%)
Interstitial lung disease	5 (1.2%)	5 (1.2%)
Dyspnoea	4 (1.0%)	11 (2.6%)
Pneumothorax	3 (0.7%)	2 (0.5%)
Acute respiratory distress syndrome	1 (0.2%)	0
Asthma	1 (0.2%)	0
Chronic obstructive pulmonary disease	1 (0.2%)	0
Cough	1 (0.2%)	0
Dyspnoea exertional	1 (0.2%)	1 (0.2%)
Hydrothorax	1 (0.2%)	1 (0.2%)
Hypercapnia	1 (0.2%)	0
Hypersensitivity pneumonitis	1 (0.2%)	0
Pulmonary haemorrhage	1 (0.2%)	0

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Pulmonary oedema	1 (0.2%)	0
Respiratory distress	1 (0.2%)	0
Haemoptysis	0	1 (0.2%)
Hypoxia	0	1 (0.2%)
Infections and infestations	**51 (12.1%)**	**40 (9.3%)**
Pneumonia	17 (4.0%)	21 (4.9%)
COVID-19	10 (2.4%)	10 (2.3%)
Cellulitis	4 (1.0%)	0
Sepsis	3 (0.7%)	1 (0.2%)
Septic shock	3 (0.7%)	1 (0.2%)
Urinary tract infection	3 (0.7%)	1 (0.2%)
Dermatitis infected	2 (0.5%)	0
Achromobacter infection	1 (0.2%)	0
Acinetobacter sepsis	1 (0.2%)	0
Appendicitis	1 (0.2%)	1 (0.2%)
Appendicitis perforated	1 (0.2%)	0
Bacteraemia	1 (0.2%)	0
COVID-19 pneumonia	1 (0.2%)	1 (0.2%)
Cystitis	1 (0.2%)	0
Device related infection	1 (0.2%)	0
Gastrointestinal infection	**1 (0.2%)**	**0**
Pneumonia aspiration	1 (0.2%)	1 (0.2%)
Post procedural infection	1 (0.2%)	0
Pustule	1 (0.2%)	0
Respiratory tract infection	**1 (0.2%)**	**1 (0.2%)**

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Skin infection	1 (0.2%)	0
Staphylococcal sepsis	1 (0.2%)	0
Subcutaneous abscess	1 (0.2%)	0
Tinea cruris	1 (0.2%)	0
Urosepsis	1 (0.2%)	1 (0.2%)
Wound infection	1 (0.2%)	0
Arthritis bacterial	0	1 (0.2%)
Epididymitis	0	1 (0.2%)
Gastroenteritis	0	2 (0.5%)
Herpes virus infection	0	1 (0.2%)
Lower respiratory tract infection	0	1 (0.2%)
Scrub typhus	0	1 (0.2%)
Soft tissue infection	0	1 (0.2%)
Tuberculosis	0	1 (0.2%)
Injury, poisoning and procedural complications	**27 (6.4%)**	**9 (2.1%)**
Infusion related reaction	9 (2.1%)	0
Femoral neck fracture	4 (1.0%)	0
Hip fracture	3 (0.7%)	0
Accidental overdose	1 (0.2%)	1 (0.2%)
Ankle fracture	1 (0.2%)	0
Fall	1 (0.2%)	0
Femur fracture	1 (0.2%)	0
Lower limb fracture	1 (0.2%)	0

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Lumbar vertebral fracture	1 (0.2%)	0
Muscle rupture	1 (0.2%)	0
Radiation injury	1 (0.2%)	0
Recall phenomenon	1 (0.2%)	0
Spinal compression fracture	1 (0.2%)	2 (0.5%)
Tibia fracture	1 (0.2%)	0
Upper limb fracture	1 (0.2%)	0
Head injury	0	2 (0.5%)
Procedural pneumothorax	0	1 (0.2%)
Radiation pneumonitis	0	1 (0.2%)
Subdural haemorrhage	0	1 (0.2%)
Toxicity to various agents	0	1 (0.2%)
Vascular disorders	**25 (5.9%)**	**8 (1.9%)**
Deep vein thrombosis	12 (2.9%)	2 (0.5%)
Venous thrombosis	4 (1.0%)	0
Venous thrombosis limb	4 (1.0%)	0
Jugular vein thrombosis	2 (0.5%)	0
Circulatory collapse	1 (0.2%)	0
Embolism venous	1 (0.2%)	0
Orthostatic hypotension	1 (0.2%)	0
Peripheral artery thrombosis	1 (0.2%)	0
Thrombosis	1 (0.2%)	0
Embolism	0	2 (0.5%)
Haemorrhage	0	1 (0.2%)

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Hypotension	0	1 (0.2%)
Peripheral arterial occlusive disease	0	1 (0.2%)
Superior vena cava syndrome	0	1 (0.2%)
General disorders and administration site conditions	**22 (5.2%)**	**8 (1.9%)**
Sudden death	4 (1.0%)	1 (0.2%)
Asthenia	3 (0.7%)	1 (0.2%)
Death	3 (0.7%)	2 (0.5%)
Fatigue	2 (0.5%)	2 (0.5%)
General physical health deterioration	2 (0.5%)	0
Oedema peripheral	2 (0.5%)	0
Pyrexia	2 (0.5%)	1 (0.2%)
Generalised oedema	1 (0.2%)	0
Malaise	1 (0.2%)	1 (0.2%)
Mucosal inflammation	1 (0.2%)	0
Oedema	1 (0.2%)	0
Peripheral swelling	1 (0.2%)	0
Chest pain	0	1 (0.2%)
Gastrointestinal disorders	**21 (5.0%)**	**7 (1.6%)**
Diarrhoea	4 (1.0%)	2 (0.5%)
Colitis	2 (0.5%)	0
Nausea	2 (0.5%)	0
Constipation	1 (0.2%)	0
Gastric ulcer perforation	1 (0.2%)	0

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Gastritis	1 (0.2%)	0
Haemorrhoidal haemorrhage	1 (0.2%)	0
Haemorrhoids	1 (0.2%)	0
Ileus	1 (0.2%)	0
Ileus paralytic	1 (0.2%)	0
Intestinal haemorrhage	1 (0.2%)	0
Intestinal obstruction	1 (0.2%)	0
Large intestine perforation	1 (0.2%)	0
Mallory-Weiss syndrome	1 (0.2%)	0
Pancreatitis	1 (0.2%)	1 (0.2%)
Pancreatitis acute	1 (0.2%)	0
Peptic ulcer	1 (0.2%)	0
Upper gastrointestinal haemorrhage	1 (0.2%)	0
Vomiting	1 (0.2%)	0
Gastrointestinal haemorrhage	0	2 (0.5%)
Inguinal hernia	0	1 (0.2%)
Intra-abdominal haemorrhage	0	1 (0.2%)
Metabolism and nutrition disorders	**16 (3.8%)**	**9 (2.1%)**
Hypoalbuminaemia	5 (1.2%)	0
Hyponatraemia	5 (1.2%)	4 (0.9%)
Hypocalcaemia	3 (0.7%)	0
Decreased appetite	2 (0.5%)	0
Hypercalcaemia	1 (0.2%)	0

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Hypoglycaemia	1 (0.2%)	0
Hypophagia	1 (0.2%)	0
Dehydration	0	1 (0.2%)
Diabetic ketoacidosis	0	1 (0.2%)
Failure to thrive	0	1 (0.2%)
Ketoacidosis	0	1 (0.2%)
Metabolic acidosis	0	1 (0.2%)
Cardiac disorders	**15 (3.6%)**	**12 (2.8%)**
Myocardial infarction	4 (1.0%)	0
Pericardial effusion	4 (1.0%)	5 (1.2%)
Acute coronary syndrome	1 (0.2%)	0
Arteriosclerosis coronary artery	1 (0.2%)	0
Atrial fibrillation	1 (0.2%)	1 (0.2%)
Atrioventricular block second degree	1 (0.2%)	0
Cardiac failure	1 (0.2%)	5 (1.2%)
Cardiac tamponade	1 (0.2%)	0
Cardiopulmonary failure	1 (0.2%)	0
Cardiovascular insufficiency	1 (0.2%)	0
Coronary artery disease	1 (0.2%)	0
Myocardial rupture	1 (0.2%)	0
Acute myocardial infarction	0	2 (0.5%)
Nervous system disorders	**13 (3.1%)**	**17 (4.0%)**
Cerebral infarction	2 (0.5%)	4 (0.9%)

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Cerebellar ataxia	1 (0.2%)	0
Cerebral haemorrhage	1 (0.2%)	1 (0.2%)
Cerebral thrombosis	1 (0.2%)	0
Cerebrovascular accident	1 (0.2%)	2 (0.5%)
Dizziness	1 (0.2%)	0
Haemorrhagic stroke	1 (0.2%)	0
Headache	1 (0.2%)	1 (0.2%)
Hydrocephalus	1 (0.2%)	0
Ischaemic cerebral infarction	1 (0.2%)	0
Loss of consciousness	1 (0.2%)	0
Seizure	1 (0.2%)	1 (0.2%)
Superior sagittal sinus thrombosis	1 (0.2%)	0
Brain oedema	0	2 (0.5%)
Dysarthria	0	1 (0.2%)
Epilepsy	0	2 (0.5%)
Meningism	0	1 (0.2%)
Paraparesis	0	1 (0.2%)
Spinal cord compression	0	1 (0.2%)
Tremor	0	1 (0.2%)
Investigations	**12 (2.9%)**	**9 (2.1%)**
Alanine aminotransferase increased	8 (1.9%)	6 (1.4%
Eastern Cooperative Oncology Group performance status worsened	2 (0.5%)	0

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Aspartate aminotransferase increased	1 (0.2%)	4 (0.9%)
Troponin I increased	1 (0.2%)	0
Blood bilirubin increased	0	1 (0.2%)
Blood creatine phosphokinase increased	0	1 (0.2%)
Blood lactate dehydrogenase increased	0	1 (0.2%)
Gamma-glutamyltransferase increased	0	1 (0.2%)
Skin and subcutaneous tissue disorders	**11 (2.6%)**	**0**
Rash	7 (1.7%)	0
Decubitus ulcer	1 (0.2%)	0
Dermatitis	1 (0.2%)	0
Dermatitis acneiform	1 (0.2%)	0
Drug eruption	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	**5 (1.2%)**	**7 (1.6%)**
Flank pain	1 (0.2%)	0
Intervertebral disc protrusion	1 (0.2%)	1 (0.2%)
Myalgia	1 (0.2%)	0
Osteoarthritis	1 (0.2%)	1 (0.2%)
Pain in extremity	1 (0.2%)	0
Arthralgia	0	2 (0.5%)
Neck pain	0	1 (0.2%)
Periarthritis	0	1 (0.2%)

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Spinal pain	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**5 (1.2%)**	**1 (0.2%)**
Cancer pain	1 (0.2%)	0
Chronic myeloid leukaemia	1 (0.2%)	0
High-grade B-cell lymphoma	1 (0.2%)	0
Papillary thyroid cancer	1 (0.2%)	0
Prostate cancer	1 (0.2%)	0
Basal cell carcinoma	0	1 (0.2%)
Blood and lymphatic system disorders	**3 (0.7%)**	**2 (0.5%)**
Anaemia	2 (0.5%)	1 (0.2%)
Bone marrow failure	1 (0.2%)	0
Thrombocytopenia	0	1 (0.2%)
Renal and urinary disorders	**3 (0.7%)**	**6 (1.4%)**
Ureterolithiasis	2 (0.5%)	0
Renal impairment	1 (0.2%)	1 (0.2%)
Acute kidney injury	0	2 (0.5%)
Chronic kidney disease	0	1 (0.2%)
Renal failure	0	1 (0.2%)
Urinary retention	0	1 (0.2%)
Urogenital disorder	0	1 (0.2%)
Eye disorders	**2 (0.5%)**	**0**
Giant papillary conjunctivitis	1 (0.2%)	0
Keratitis	1 (0.2%)	0

Category	Amivantamab + lazertinib (n=421)	Osimertinib (n=428)
Papilloedema	1 (0.2%)	0
Hepatobiliary disorders	**2 (0.5%)**	**2 (0.5%)**
Cholecystitis	1 (0.2%)	0
Hepatic function abnormal	1 (0.2%)	1 (0.2%)
Cholelithiasis	0	1 (0.2%)
Product issues	**2 (0.5%)**	**0**
Device dislocation	2 (0.5%)	0
Psychiatric disorders	**2 (0.5%)**	**1 (0.2%)**
Delirium	1 (0.2%)	0
Mental status changes	1 (0.2%)	0
Panic disorder	0	1 (0.2%)
Reproductive system and breast disorders	**2 (0.5%)**	**0**
Genital tract inflammation	1 (0.2%)	0
Pelvic pain	1 (0.2%)	0
Surgical and medical procedures	**1 (0.2%)**	**1 (0.2%)**
Pleurodesis	1 (0.2%)	0
Cholecystectomy	0	1 (0.2%)

Appendix H. Health-related quality of life

MARIPOSA also investigated patient-reported outcomes (PROs). The findings from the PROs add further to the evidence of the value of the combination treatment of amivantamab + lazertinib. In MARIPOSA, patients completed patient-reported outcome measures related to their HRQoL, including the EuroQol Questionnaire, Five Dimensions, Five Levels (EQ-5D-5L), as well as the European Organization of 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).

Below follows a brief summary of the EORTC-QLQ-C30 and NSCLC-SAQ data collection and findings from the primary PFS analysis data cut-off.

H.1 EORTC-QLQ-C30

The EORTC-QLQ-C30 assesses functioning domains and common cancer symptoms with recall in the past week (EORTC 2023).

H.1.1 Data collection

Pattern of missing data based on the December 2024 data-cut is presented in Table 76 for EORTC-QLQ-C30.

Table 76: Pattern of missing data and completion- EORTC-QLQ-C30

Time point	HRQoL population N		Missing N (%)		Expected to complete N		Completion N (%)	
	Number of patients at randomization		Number of patients for whom data is missing (% of patients at randomization)		Number of patients "at risk" at time point X		Number of patients who completed (% of patients expected to complete)	
	A+L	O	A+L	O	A+L	O	A+L	O
Baseline	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 02 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 03 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 05 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cycle 07 Day 1	429	429	[redacted]					
Cycle 09 Day 1	429	429	[redacted]					
Cycle 11 Day 1	429	429	[redacted]					
Cycle 13 Day 1	429	429	[redacted]					
Cycle 15 Day 1	429	429	[redacted]					
Cycle 17 Day 1	429	429	[redacted]					
Cycle 19 Day 1	429	429	[redacted]					
Cycle 21 Day 1	429	429	[redacted]					
Cycle 23 Day 1	429	429	[redacted]					
Cycle 25 Day 1	429	429	[redacted]					
Cycle 27 Day 1	429	429	[redacted]					
Cycle 29 Day 1	429	429	[redacted]					
Cycle 31 Day 1	429	429	[redacted]					
Cycle 33 Day 1	429	429	[redacted]					

H.1.2 EORTC-QLQ-C30 results

The result is based on the primary PFS analysis data cut-off. Across both treatment arms, patients reported stable functioning compared to baseline, with no meaningful change from baseline in EORTC-QLQ-C30 global health status and all individual subscales (Figure 71) (Nguyen et al. 2024). Similarly, lung cancer-associated symptoms remained stable and were comparable across treatment arms, as measured by the NSCLC-SAQ total

scores and individual symptom scores for dyspnoea, pain and cough (Figure 72) (Nguyen et al. 2024).

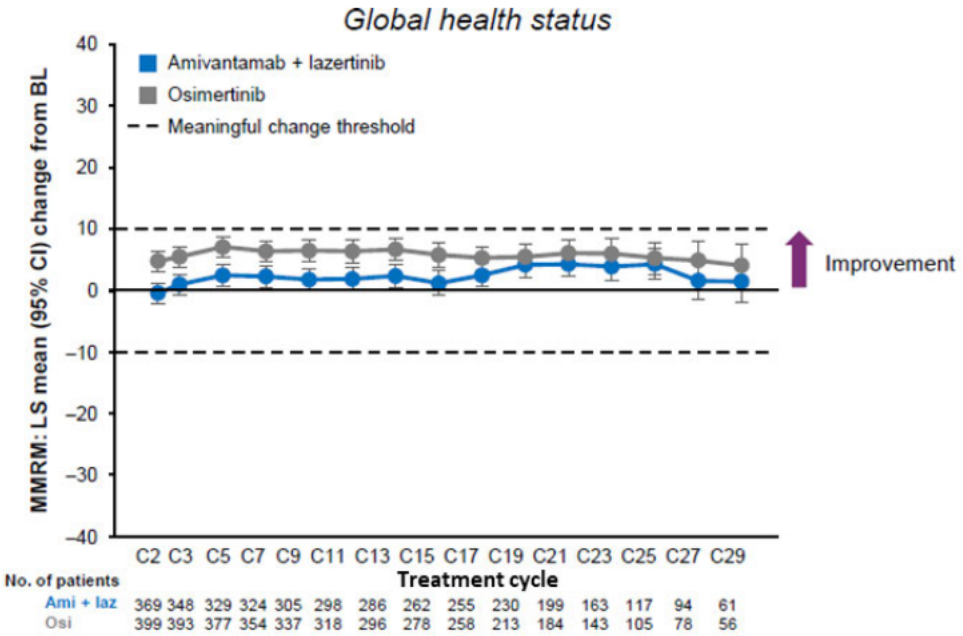


Figure 71: LS mean change from baseline in patient-reported overall functioning, as measured by the EORTC-QLQ-C30 for amivantamab + lazertinib vs. osimertinib (MARIPOSA, primary analysis: August 2023 data cut-off)

Note: Dashed line indicates thresholds for meaningful change (i.e., 10 points). Abbreviations: Ami + laz: Amivantamab + lazertinib; BL: Baseline; C: Cycle; CI: Confidence interval; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; LS: Least squares; MMRM: Mixed model for repeated measures; osi: Osimertinib. Source: (Nguyen et al. 2024)

H.2 NSCLC-SAQ

The NSCLC-SAQ was developed for use in clinical trials of NSCLC (McCarrier et al. 2016). It contains seven items that assess cough, pain, dyspnoea, fatigue, and poor appetite over a 7-day recall period.

H.2.1 Data collection

Pattern of missing data based on the December 2024 data-cut is presented in Table 77 for NSCLC-SAQ.

Table 77: Pattern of missing data and completion- NSCLC-SAQ results

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)

	A+L	O	A+L	O	A+L	O	A+L	O
Baseline	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 02 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 03 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 05 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 07 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 09 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 11 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 13 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 15 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 17 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 19 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 21 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 23 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 25 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 27 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 29 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cycle 31 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cycle 33 Day 1	429	429	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

H.2.2 NSCLC-SAQ results

In summary, amivantamab + lazertinib maintained HRQoL while providing improved efficacy vs. SoC among patients with treatment-naïve EGFR-mutated NSCLC. The expected increase in EGFR/MET-related AEs with amivantamab + lazertinib did not meaningfully impact patients' functioning or HRQoL over time (Nguyen et al. 2024).

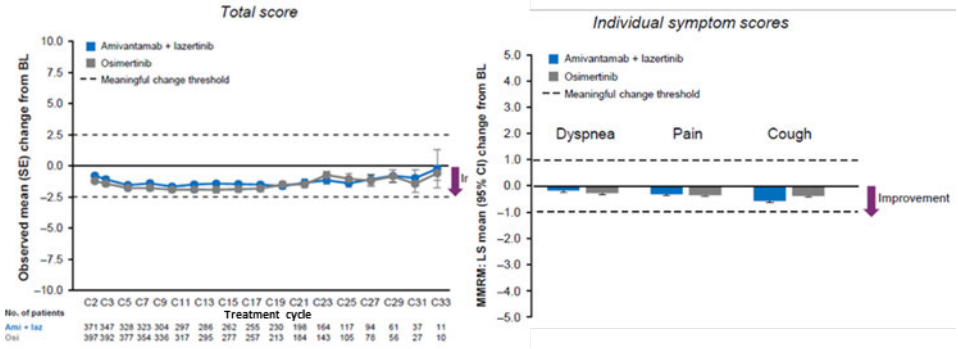


Figure 72: Change from baseline in lung cancer-associated symptoms, as measured by the NSCLC-SAQ for amivantamab + lazertinib vs. osimertinib (MARIPOSA, primary analysis: August 2023 data cut-off)

Note: PROs were measured on Day 1 of each cycle. Dashed lines indicate thresholds for meaningful change (i.e., 1 point for individual symptoms; 2.5 points for total score). Abbreviations: Ami + laz: Amivantamab + lazertinib; BL: Baseline; C: Cycle; CI: Confidence interval; LS: Least squares; MMRM: Mixed model for repeated measures; NSCLC-SAQ: Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; osi: Osimertinib; PRO: Patient-reported outcome; SE: Standard error. Source: (Nguyen et al. 2024)

Appendix I. Utility calculations

I.1 HSUV calculation

Data from MARIPOSA (04 December 2024 data cut-off) used to inform utility values for the progression-free and progressed disease health states.

State-dependent mean utility values estimated by MMRMs were derived from the MARIPOSA data for the CEM. The pooled cohort was used to estimate health state specific mean utility values with the Danish utility values (Jensen et al. 2021). No imputation of missing values was conducted owing to the high response frequency overall.

Mean utilities over time may be estimated using a single MMRM. However, a drawback of this method is that observations from patients who progressed early would still impact pre-progression utility estimates at later time points, because MMRM assumes that observations over time from the same patient are correlated (within-subject correlation). Accordingly, cycle-specific MMRM analyses were conducted so that utility estimates of patients who have progressed before a cycle do not influence the utility estimate for that cycle. This method is more aligned with the CEM, where the composition of the cohort in progression free health state varies over time.

First, for each EQ-5D-5L collection time point, a separate MMRM was fitted using information only from patients who stayed progression-free until that time point, including all their available EQ-5D-5L results up to and including that time point, and using visit as a categorical predictor, to get time-specific utility estimates.

The formula used in the MMRMs to estimate time-specific mean progression free utility is as follows:

$$Y = X\beta + \epsilon$$

Where Y is the 1 by N vector that combines all visit results from all subjects included in that MMRM, so that there are $N = \sum_i^n m_i$ observations in total, where m_i is the number of visits for patient i and n is the number of patients. X is the N by p design matrix: each row of X relates to a patient-visit (y_i) observation and has a 1 for visit i and 0 for other visits, and where p is the number of visits included in that MMRM. β is the 1 by p vector of coefficients for visits, estimated in the MMRM. $\in$ is the 1 by N error matrix that has a mean of 0 and variance Ω, which is an N by N matrix that contains subject specific variance-covariance matrices (Σ_i) in its diagonal entries and has 0 values elsewhere. Each subject specific variance-covariance matrix Σ_i is an m by m matrix that includes the covariance (estimated in the MMRM) between utility values across the visits (the size of each Σ_i depends on how many visits each patient has).

Second, from each of these MMRMs, the marginal (model-based) mean estimate of the last time point was used as the utility estimate for patients still progression free at that time point. These time-specific estimates (each of which was obtained from a different MMRM) are plotted in Table 78 and their latest time point mean estimates are provided in Figure 73. Each of the MMRMs had a compound symmetry correlation structure,

which assumes that variances are homogenous and correlation between time points is constant regardless of their distance. This structure was selected due to having the lowest AIC among correlation structures in an MMRM that included all EQ-5D-5L measurements in progression-free state (AIC column in Table 79).

Table 78: Modelled progression-free utility over time from MARIPOSA data

Cycle	Number at Risk	Estimate (SE)
0	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
5	[redacted]	[redacted]
7	[redacted]	[redacted]
9	[redacted]	[redacted]
11	[redacted]	[redacted]
13	[redacted]	[redacted]
15	[redacted]	[redacted]
17	[redacted]	[redacted]
19	[redacted]	[redacted]
21	[redacted]	[redacted]
23	[redacted]	[redacted]
25	[redacted]	[redacted]
27	[redacted]	[redacted]
29	[redacted]	[redacted]
31	[redacted]	[redacted]
33	[redacted]	[redacted]

Abbreviations: SE: standard error

Figure 73: Modelled Progression-free Utility Over Time in MARIPOSA

The area under the curve of the progression-free estimates was calculated by first linearly interpolating mean values for cycles with a PRO to cycles without a PRO, summing all time-specific means and dividing the sum by the number of cycles. Table 79 includes the area under the curve results with different correlation structures.

Table 79: Health state utility estimates for progression-free

Health state	Correlation structure	Estimate (SE)*	AIC**	Rank
Progression-free	Autoregression(1)[1]	[redacted]	[redacted]	[redacted]
	Compound symmetry[2]	[redacted]	[redacted]	[redacted]
	Variance components[3]	[redacted]	[redacted]	[redacted]

Boldface indicates lowest AIC value. The corresponding estimate and standard error are used in the health economic model.

* Mean and SE estimates are based on area under the curve of time-specific MMRMs.

** AIC values are based on MMRM models that includes PROs while patients are progression free.

[1] Homogenous variance, correlation that declines exponentially with time. [2] Homogenous variance, constant correlation between measurements over time. [3] No correlation between measurements over time.

Abbreviations: AIC: Akaike information criterion; MMRM: Mixed model for repeated measures; PRO: Patient-reported outcome; SE: Standard error

The progressed disease mean utility estimate is based on EQ-5D-5L questionnaires administered after disease progression, including 1,240 assessments from 303 patients. In the CEM, the progressed-disease health state includes patients who have entered the state at different time points and have been in the state for different amounts of time. The progressed disease state utility was therefore estimated without a time component. All assessments administered after progression were used in an MMRM that does not include visits as covariates and considers the correlation between observations from same patients via a correlation matrix (Table 80).

Table 80: Health state utility estimates for progressed disease

Health state	Correlation structure	Estimate (SE)	AIC	Rank
Progressed disease	Autoregression(1)[1]	[redacted]	[redacted]	[redacted]
	Compound symmetry[2]	[redacted]	[redacted]	[redacted]
	Variance components[3]	[redacted]	[redacted]	[redacted]

Boldface indicates lowest AIC value. The corresponding estimate and standard error is used in the health economic model.
[1] Homogenous variance, correlation that declines exponentially with time. [2] Homogenous variance, constant correlation between measurements over time. [3] No correlation between measurements over time.
Abbreviations: AIC: Akaike information criterion; SE: standard error

I.2 Responders and non-responders

The distribution of baseline characteristics among responders and non-responders across the cycles when progression-free is presented in Table 81. Missing was defined those who had at least one cycle had not responded. Owing to the repeated measurements at each cycle, the data is averaged across all cycles. Cross-tabulating the average missingness based on patient demographic and baseline characteristics does not indicate systematic differences between the two groups. Patients of White race more frequently had missing questionnaires and conversely patients of Asian race had lower proportions of missing questionnaires. Furthermore, there was a slight tendency of more missingness among patients of older ages. Otherwise, there are no notable differences.

Table 81: Baseline demographics among EQ-5D responders and non-responders

Baseline category	Responded		Missing		Total sample	
	A+L	O	A+L	O	A+L	O
Age						
<65 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥65 years to <75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥75 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex						
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race or ethnic group						

American Indican or Alaksa Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Body weight						
≥80 kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<80 kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG performance status						
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Histologic type at initial diagnosis						
Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Large cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous cell carcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not reported	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of metastasis						
Brain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
History of smoking						

Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Type of EGFR mutation						
Ex19del	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exon 21 L858R	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EGFR: Epidermal growth factor receptor; Ex19del: Exon 19 deletion
Source: MARIPOSA data on file

I.3 EQ-5D per cycle incl. post-progression observations

Change from baseline in EQ-5D values per cycle including observations post progression is shown in Figure 74 below.

Figure 74. Mean change from baseline in EQ-5D-5L index value (MARIPOSA, Danish utility weights)

Appendix J. Probabilistic sensitivity analyses

Probability distributions were assigned to model parameters to characterise their uncertainty see Table 82. The PSA was conducted using 1,500 simulations.

Table 82: Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Clinical Inputs				
Individual curve fitting for OS				
A+L-Weibull shape	0.1557			Multi-normal (Cholesky decompensation)
A+L-Weibull scale	4.1909			Multi-normal (Cholesky decompensation)
O-Weibull shape	0.3418			Multi-normal (Cholesky decompensation)
O- Weibulll scale	3.8812			Multi-normal (Cholesky decompensation)
Individual fitting for PFS				
A+L- Gamma shape	0.2881			Multi-normal (Cholesky decompensation)
A+L- Gamma rate	-3.1150			Multi-normal (Cholesky decompensation)
O-Gamma shape	0.4431			Multi-normal (Cholesky decompensation)
O-Gamma rate	-2.6354			Multi-normal (Cholesky decompensation)

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Individual fitting for TTD				
A (combo) Generalised gamma shape	3.4328			Multi-normal (Cholesky decompensation)
A (combo) Generalised gamma rate	-0.0906			Multi-normal (Cholesky decompensation)
A (combo) Generalised gamma Q	1.3823			Multi-normal (Cholesky decompensation)
L- Exponential rate	-3.6776			Multi-normal (Cholesky decompensation)
O (mono)- Gamma shape	0.2899			Multi-normal (Cholesky decompensation)
O (mono)- Gamma rate	-3.1010			Multi-normal (Cholesky decompensation)
Adverse event incidence (%) Amivantamab + lazertinib				
Dermatitis acneiform	0.09	0.06	0.12	Beta
Alanine aminotransferase increased	0.07	0.04	0.09	Beta
Hypoalbuminaemia	0.06	0.04	0.09	Beta
Paronychia	0.12	0.09	0.15	Beta
Infusion related reaction	0.06	0.04	0.09	Beta
Rash	0.17	0.14	0.21	Beta
Pulmonary embolism	0.09	0.06	0.11	Beta
Grade ≤ 2 VTE	0.28	0.24	0.32	Beta
Pneumonia	0.05	0.03	0.08	Beta

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Adverse event incidence (%) Osimertinib				
Dermatitis acneiform	0.00	0.00	0.00	Beta
Alanine aminotransferase increased	0.02	0.01	0.03	Beta
Hypoalbuminaemia	0.00	0.00	0.00	Beta
Paronychia	0.00	0.00	0.01	Beta
Infusion related reaction	0.00	0.00	0.00	Beta
Rash	0.01	0.00	0.02	Beta
Pulmonary embolism	0.03	0.01	0.05	Beta
Grade ≤ 2 VTE	0.07	0.05	0.09	Beta
Pneumonia	0.05	0.03	0.07	Beta
Patient Characteristics				
Starting age	62.3	61.557	63.043	Normal
Proportion female	0.61	0.58	0.65	Beta
Body weight	70.4	69.503	71.297	Normal
Body surface area	1.68	1.667	1.693	Normal
Proportion of patients < 80 kg	0.75	0.72	0.78	Beta
HSUV				
Progression-free	0.87	0.87	0.88	Beta
Progressed disease	0.84	0.82	0.86	Beta
AE-related disutilities — AE-pooled				
Dermatitis acneiform	-0.07	-0.09	-0.06	Normal

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Alanine aminotransferase increased	-0.07	-0.09	-0.06	Normal
Hypoalbuminaemia	-0.07	-0.09	-0.06	Normal
Paronychia	-0.07	-0.09	-0.06	Normal
Infusion related reaction	-0.07	-0.09	-0.06	Normal
Rash	-0.07	-0.09	-0.06	Normal
Pulmonary embolism	-0.07	-0.09	-0.06	Normal
Grade ≤ 2 VTE	-0.02	-0.04	0.00	Normal
Pneumonia	-0.07	-0.09	-0.06	Normal
Costs				
Proportion of doses missed				
Amivantamab, < 80 kg	0.19	0.18	0.19	Beta
Amivantamab, ≥ 80 kg	0.17	0.16	0.19	Beta
Lazertinib	0.07	0.07	0.07	Beta
Osimertinib	0.02	0.02	0.02	Beta
Proportion of planned dose administered				
Amivantamab IV, < 80 kg	0.78	0.78	0.79	Beta
Amivantamab IV, ≥ 80 kg	0.77	0.76	0.78	Beta
Distribution of actual doses				
Lazertinib, 80 mg	0.00	-	-	Dirichlet
Lazertinib, 160 mg	0.39	-	-	Dirichlet
Lazertinib, 240 mg	0.61	-	-	Dirichlet

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Lazertinib, 320 mg	0.00	-	-	Dirichlet
Lazertinib, 400 mg	0.00	-	-	Dirichlet
Lazertinib, 480 mg	0.00	-	-	Dirichlet
Osimertinib, 40 mg	0.04	-	-	Dirichlet
Osimertinib, 80 mg	0.96	-	-	Dirichlet
Osimertinib, 160 mg	0.00	-	-	Dirichlet
Osimertinib, 240 mg	0.00	-	-	Dirichlet
Osimertinib, 320 mg	0.00	-	-	Dirichlet
Subsequent treatment lines				
Distribution of 2L treatments by 1L treatments: Amivantamab + lazertinib				
Platinum-based chemotherapy	0.38	-	-	Dirichlet
EGFR MoA/ TKI or TKI-based regimen	0.49	-	-	Dirichlet
Non-platinum-based chemotherapy	0.01	-	-	Dirichlet
IO ± chemotherapy ± VEGFi	0.12	-	-	Dirichlet
Distribution of 2L treatments by 1L treatments: Osimertinib				
Platinum-based chemotherapy	0.45	-	-	Dirichlet
EGFR MoA/ TKI or TKI-based regimen	0.31	-	-	Dirichlet
Non-platinum-based chemotherapy	0.02	-	-	Dirichlet
IO ± chemotherapy ± VEGFi	0.21	-	-	Dirichlet

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Duration of 2L treatments				
Platinum-based chemotherapy	4.20	3.42	5.06	Gamma
EGFR MoA/ TKI or TKI-based regimen	10.10	8.22	12.17	Gamma
Non-platinum-based chemotherapy	4.20	3.42	5.06	Gamma
IO ± chemotherapy ± VEGFi	8.30	6.75	10.00	Gamma
Unit costs				
Administration unit costs				
Other cost related parameters				
Costing approach for the routine care cost by health state				
Resource use calculation PROGRESSION FREE				
Oncology outpatient visit	4.00	3.25	4.82	Gamma
CT scan (chest)	4.00	3.25	4.82	Gamma
Disease management	4.00	3.25	4.82	Gamma
Resource use calculation PROGRESSED DISEASE				
Oncology outpatient visit	4.00	3.25	4.82	Gamma
CT scan (chest)	4.00	3.25	4.82	Gamma
Disease management	4.00	3.25	4.82	Gamma
Disease management costs				
Cost of routine follow-up care cost per week - progression free	471.84	383.91	568.71	Gamma

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Cost of routine follow-up care cost per week - progressed disease	471.84	383.91	568.71	Gamma

Appendix K. Literature searches for the clinical assessment (N/A)

The clinical assessment was informed by the head-to-head study MARIPOSA used in this application. Therefore, this appendix is not applicable, and the template has been left blank.

K.1 Efficacy and safety of the intervention and comparator(s)

Not applicable.

Table 83 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	NA		
Medline			
CENTRAL			

Abbreviations:

Table 84 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	NA		
e.g. EMA website			

Abbreviations:

Table 85 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	NA			

K.1.1 Search strategies

Not applicable.

Table 86 of search strategy table for [name of database]

No.	Query	Results
#1	NA	
#2		
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

K.1.2 Systematic selection of studies

Not applicable.

Table 87 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	NA		
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

Table 88 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	NA					
Study 2						

K.1.3 Excluded fulltext references

Not applicable.

K.1.4 Quality assessment

Not applicable.

K.1.5 Unpublished data

Not applicable.

Appendix L. Literature searches for health-related quality of life (N/A)

The health-related quality of life data was informed by the head-to-head study MARIPOSA used in this application. Therefore, this appendix is not applicable, and the template has been left blank.

L.1 Health-related quality-of-life search

Not applicable.

Table 89 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	NA		
Medline			
Specific health economics databases[1]			

Abbreviations:

Table 90 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	NA		
CEA Registry			

Table 91 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	NA			

L.1.1 Search strategies

Not applicable.

Table 92 Search strategy for [name of database]

No.	Query	Results
#1	NA	
#2		
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

L.1.2 Quality assessment and generalizability of estimates

Not applicable.

L.1.3 Unpublished data

Not applicable.

Appendix M. Literature searches for input to the health economic model (N/A)

Inputs for the health economic model were sourced via targeted search in publicly available sources. Therefore, this appendix is not applicable.

Appendix N. Dose details and model cost

N.1 Medicines- dosing of concomitant

Table 93: Co-medication dosing for amivantamab

Co-medication	Duration of treatment	Dose (mg)	Dosing frequency	Units (vials/caps) per admin
Dexamethasone	2 cycles	10.0	C1D1, C1D2	1.0
Paracetamol	Until progression	825.0	Once per admin	2.0
Diphenhydramine	Until progression	37.5	Once per admin	2.0
Rivaroxaban	4 cycles	10 mg	Once daily	1.0

* After correcting for doses missed
Abbreviations: C: cycle; D: day; mg: Milligram; DKK: Danish krone.
Source: Amivantamab IV SmPC (EMA 2025c).

N.2 Subsequent treatment cost

Table 94: Distribution and duration of 2L subsequent treatments

	Amivantamab + Lazertinib	Osimertinib	Median PFS (Months)	Median PFS Source	Duration in Weeks
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IO ± chemotherapy ± VEGFi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	100.0%	100.0%			

Note: Subsequent therapy distributions are adapted from the subsequent distributions from MARIPOSA (based on the clinical study report (Johnson & Johnson 2023b)), with additional context provided by clinical experts' feedback. Experts in the ad board mentioned that typical clinical practice would consist of EGFR-TKI, platinum-based chemotherapy and others. The proportions from the clinical study report were adjusted, excluding the patients in the "Others" treatment category from MARIPOSA as the treatments in these categories are not a typical part of the clinical practice.
Abbreviations: 1L: first-line; 3L: third-line; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor

Table 95: Distribution and duration of 3L+ subsequent treatments

	Amivantamab + Lazertinib	Osimertinib	Median PFS (Months)	Median PFS Source	Duration in Weeks
Platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EGFR MoA/ TKI or TKI-based regimen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-platinum-based chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IO ± chemotherapy ± VEGFi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]			

* Subsequent therapy distributions are based on the subsequent treatment distribution in MARIPOSA-2 chemotherapy arm (based on the clinical study report) (Johnson & Johnson 2024h) with additional context provided by clinical experts' feedback. Experts in the ad board mentioned that typical clinical practice would consist of mostly non-platinum chemotherapy and EGFR-TKIs. The proportions from the MARIPOSA-2 clinical study report were adjusted, excluding the patients in the "Others" treatment category from MARIPOSA-2 as the treatments in these categories are not a typical part of the clinical practice.
Abbreviations: 1L: first-line; 3L: third-line; EGFR: epidermal growth factor receptor; IO: immuno-oncology drug; MoA: monoclonal antibody; TKI: tyrosine kinase inhibitor; VEGFi: vascular endothelial growth factor inhibitor

Table 96: Dosing details for subsequent therapies

Treatment category	Component	Induction period (weeks)	Dose	Treatment duration	Dosing frequency per week	Average dose per admin
Platinum-based chemotherapy*	Pemetrexed	12	500 mg/m²	Until progression	0.33	855 mg
	Carboplatin	12	AUC 5	4 cycles	0.33	550 mg†
	Cisplatin	12	75 mg/m²	4 cycles	0.33	126 mg
EGFR MoA/ TKI or TKI-based regimen	Osimertinib	1‡	80 mg	Until progression	7.00	80 mg
Non-platinum-based chemotherapy	Docetaxel	12	75 mg/m²	12 weeks	0.33	126 mg
IO ± chemotherapy ± VEGFi	Atezolizumab	12	1,200 mg	Until progression	0.33	1,200 mg
	Bevacizumab	12	15 mg/kg	Until progression	0.33	962 mg
	Carboplatin	12	6 AUC	12 weeks	0.33	660 mg††
	Paclitaxel	12	200 mg/m²	12 weeks	0.33	336 mg

* Treatment regimen is costed based on the assumption that 50% receive carboplatin and 50% cisplatin, both combined with pemetrexed.
† An average dose per administration of 550 mg is assumed for carboplatin.
†† An average dose per administration of 660 mg is assumed for carboplatin.
‡ 1-week induction period included to model different administration costs for the first cycle; there is no induction period with regards to dosing requirements.
Abbreviations: AUC 5: Area under the concentration-time curve 5 mg/mL per minute; EGFR: Epidermal growth factor receptor; IO: Immuno-oncology drug; mg: Milligram; MoA: Monoclonal antibody; TKI: Tyrosine kinase inhibitor; VEGFi: Vascular endothelial growth factor inhibitor.

Table 97: Co-medication dosing for subsequent treatments

Regimen	Component	Co-medication	Duration of treatment	Dose (mg)	Dosing Frequency	Units (vials/caps) per admin
Platinum-based chemotherapy	Pemetrexed	Vitamin B12 (hydroxocobalamin)	Until progression	1.0	Once within 7 days of first cycle, then every 3 cycles afterwards	1.0
		Folic acid	Until progression	0.68	Once daily, week before 1st dose of pemetrexed until 21 days after last dose	1.0
		Dexamethasone	Until progression	4.0	Twice daily day before, day of, and day after each dose of pemetrexed	1.0
IO ± chemotherapy ±VEGFi	Paclitaxel	Diphenhydramine	Until progression	37.5	Once per admin	1.0
		Dexamethasone	Until progression	20	Once per admin	1.0

* After correcting for doses missed

Abbreviations: C: Cycle; D: Day; EGFR: Epidermal growth factor receptor; mg: Milligram; RDI: Relative dose intensity; TKI: Tyrosine kinase inhibitor; VEGF: Vascular endothelial growth factor.

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