14 November 2024
EMA/580043/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rybrevant

International non-proprietary name: Amivantamab

Procedure No. EMEA/H/C/005454/II/0013

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutical classification system
BICR	blinded independent central review
BLRM	bayesian logistic regression model
BW	body weight
CCO	clinical cutoff
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed serum concentration
CNS	central nervous system
COVID-19	coronavirus disease 2019
CoxPH	Cox proportional hazard
CR	complete response
CSR	Clinical Study Report
CTCAE	common terminology criteria for adverse events
DDI	drug-drug interaction(s)
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate

EGFR	epidermal growth factor receptor
EGFRm NSCLC	locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations
EMA	European Medicines Agency
E-R	exposure-response
EU	European Union
exon 19del	exon 19 deletion
exon 20ins	exon 20 insertion
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GMR	geometric mean ratio
HR	hazard ratio
IB	investigator's brochure
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
iDOR	intracranial duration of response
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
iORR	intracranial objective response rate
IRR	infusion related reaction
iPFS	intracranial progression-free survival
IV	intravenous(ly)
L858R	exon 21 L858R substitution
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MET	mesenchymal-epithelial transition
MRI	magnetic resonance imaging
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival

PD	progressive disease
PFS	progression-free survival
PFS2	progression-free survival after first subsequent therapy
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QT	uncorrected QT interval
QTc	corrected QT
QTCF	QT corrected according to Fridericia's formula
QW	every week
Q2W	every 2 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	risk management plan
RP2CD	recommended Phase 2 combination dose
RP2ChD	recommended Phase 2 dose with combination therapy with platinum doublet chemotherapy
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTE	transthoracic echocardiogram
T_{max}	time to maximum observed serum concentration
TTSP	time to symptomatic progression
ULN	upper limit of normal
US	United States
USM	urgent safety measure
VTE	venous thromboembolic (events)

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 8 February 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations (EGFRm NSCLC), based on results from study 73841937NSC3003 (MARIPOSA). This is a randomized, open-label, Phase 3 study that compares the efficacy and safety of the combination of amivantamab and lazertinib (Arm A) versus osimertinib monotherapy (Arm B) and lazertinib monotherapy (Arm C) in participants with EGFRm NSCLC. The primary objective of the MARIPOSA study was to assess the efficacy of the combination of amivantamab and lazertinib (Arm A), compared with osimertinib (Arm B), as measured by PFS assessed by BICR in adult participants with EGFRm NSCLC.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.6 and 9 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.3 of the EU RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0289/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. The request was withdrawn by the MAH during the procedure as the one year market protection was already granted with procedure EMA/005454/II/10.

Scientific advice

The MAH received Scientific Advice from the CHMP on 28 May 2020 (EMEA/H/SA/4457/1/2020/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	8 February 2024
Start of procedure:	2 March 2024
CHMP Rapporteur Assessment Report	26 April 2024
PRAC Rapporteur Assessment Report	3 May 2024
PRAC members comments	7 May 2024
Updated PRAC Rapporteur Assessment Report	8 May 2024
PRAC Outcome	16 May 2024
CHMP members comments	21 May 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 May 2024
Request for supplementary information (RSI)	30 May 2024
CHMP Rapporteur Assessment Report	20 August 2024
PRAC Rapporteur Assessment Report	20 August 2024
PRAC Outcome	5 September 2024
CHMP members comments	09 September 2024
Updated CHMP Rapporteur Assessment Report	12 September 2024
Request for supplementary information (RSI)	19 September 2024
CHMP Rapporteur Assessment Report	30 October 2024
CHMP members comments	04 November 2024
Updated CHMP Rapporteur Assessment Report	07 November 2024
CHMP Opinion	14 November 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

State the claimed the therapeutic indication

The following new indication is proposed to be added in the product information:

Rybrevant is indicated in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.

Epidemiology

Lung cancer is one of the most common types of cancer and is the most common cause of death from cancer worldwide (Globocan 2020). Lung cancer is a major global health concern, with approximately 238,340 new diagnoses annually in the US (SEER 2023), 318,327 in the EU (ECIS 2021), and more than 1.3 million in Asia (Globocan 2020) with 127,070 deaths annually. NSCLC accounts for approximately 85% of lung cancers (Schabath 2019), with 5-year survival rates dependent, in part, upon the stage at diagnosis and ranging from 63% for localized cancer to 8% for cancer that has spread to distant locations (SEER 2023).

Biologic features

Among patients with NSCLC of adenocarcinoma histology, the most prevalent actionable driver mutations are those that result in the activation of EGFR, which are identified in approximately 15% of Western patients (Pao 2011) and up to 50% of Asian patients (Jänne 2006). The most frequently identified EGFR mutations, exon 19 deletions and exon 21 L858R substitution mutations, are seen in approximately 85% of patients with NSCLC harboring activating EGFR mutations (Gazdar 2009; Harrison 2020).

Management

The current standard of care for the first-line treatment of EGFRm NSCLC is a third-generation EGFR TKI, most commonly osimertinib. Compared with first- and second-generation EGFR TKIs, third-generation EGFR TKIs provide activity against the T790M resistance mutation and may penetrate the blood-brain barrier better (Reungwetwattana 2018). This may delay the incidence of brain metastases, which are reported in up to one-third of patients with EGFRm NSCLC, a higher rate than reported for patients with EGFR wild-type NSCLC (Li 2017; Gillespie 2023).

The FLAURA study compared the third-generation EGFR TKI osimertinib versus a first-generation EGFR TKI (gefitinib or erlotinib) as first-line therapy for patients with EGFRm NSCLC (Soria 2018). FLAURA demonstrated a statistically significant improvement in PFS and OS for participants randomized to osimertinib versus a first-generation EGFR TKI. Median PFS was 18.9 months versus 10.2 months, respectively, with a HR of 0.46 when assessed by investigator (17.7 months versus 9.7 months [HR of 0.45] when assessed by BICR) and median OS was 38.6 months versus 31.8 months, respectively, with a HR of 0.80 (Ramalingam 2020; Soria 2018).

Despite the improved initial disease control, almost all patients treated with first-line osimertinib will develop resistance.

While osimertinib represents a significant advance over earlier EGFR TKIs, there is a need to improve first-line treatment prior to the development of resistance in order to extend PFS beyond what is seen with osimertinib monotherapy.

The most common mechanisms of resistance to osimertinib are due to alterations in the EGFR (eg, C797S mutation, EGFR amplification) and MET (eg, MET amplification, MET exon 14 skipping) pathways (Remon 2016). Given this, an agent with activity in tumors with activated EGFR and MET pathways may be of particular interest in EGFR-mutated NSCLC; as described above, targeting resistance mechanisms proactively may have been central to the improved outcomes seen with osimertinib in FLAURA.

Treatment options for patients with EGFRm NSCLC are limited after treatment with a third-generation EGFR TKI, and there is a high unmet need for additional therapeutics that further control tumor growth.

2.1.2. About the product

Amivantamab is a bispecific antibody targeting EGFR and MET, approved as monotherapy in previously treated advanced NSCLC, now studied in combination with the third-generation EGFR TKI lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC.

Amivantamab (JNJ-61186372) has demonstrated clinical activity against tumors with primary activating EGFR mutations (exon 19del and exon 21 L858R substitution), EGFR exon 20ins mutations, EGFR resistance mutations (eg, T790M and C797S), and activation of the MET pathway (IB Amivantamab 2023). Through its ability to bind to the extracellular domain of EGFR, amivantamab may be able to bypass resistance mechanisms that affect the intracellular binding affinity of TKIs.

Lazertinib (JNJ-73841937; YH-25448), like osimertinib, is an oral, highly potent, third-generation, EGFR TKI. It selectively inhibits both primary activating EGFR mutations and the EGFR T790M resistance mutation, while having less activity against wild-type EGFR. Lazertinib is expected to have activity in central nervous system (CNS) metastasis due to penetration of the blood-brain barrier. Lazertinib is currently approved as monotherapy in South Korea, under the tradename LECLAZA™ (Yuhan Corporation [Yuhan]), for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutations and for patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC who have progressed on or after EGFR TKI therapy.

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.

Combining amivantamab with lazertinib is hypothesized to improve clinical outcomes at least partially by broadening the coverage against the development of resistance pathways in EGFRm NSCLC. Combining these agents in the first-line treatment of patients with EGFRm NSCLC may lead to improved treatment outcomes through synergistic anti-EGFR activity, prevention of EGFR- or MET-based resistance to a third-generation EGFR TKI, and potential recruitment of Fc-bearing immune cells in the anti-tumor response.

When given in combination with lazertinib, it is recommended to administer amivantamab any time after lazertinib when given on the same day.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The Applicant's clinical development program for amivantamab (IV or SC) in NSCLC includes multiple studies in which amivantamab is administered as monotherapy and in combination therapy (see Figure 1). Amivantamab was the first approved targeted therapy for the treatment of EGFR exon 20ins NSCLC, for use after prior therapy with first-line, platinum-based chemotherapy. Based on data from the FIH Study 61186372EDI1001 (hereafter referred to as CHRYSALIS), amivantamab was granted accelerated approval as a monotherapy by the FDA on 21 May 2021 and conditional approval by EMA on 9 December 2021 for patients with EGFR exon 20ins mutations whose disease has progressed on or after platinum-based chemotherapy.

Amivantamab has been approved in Europe for the following indications:

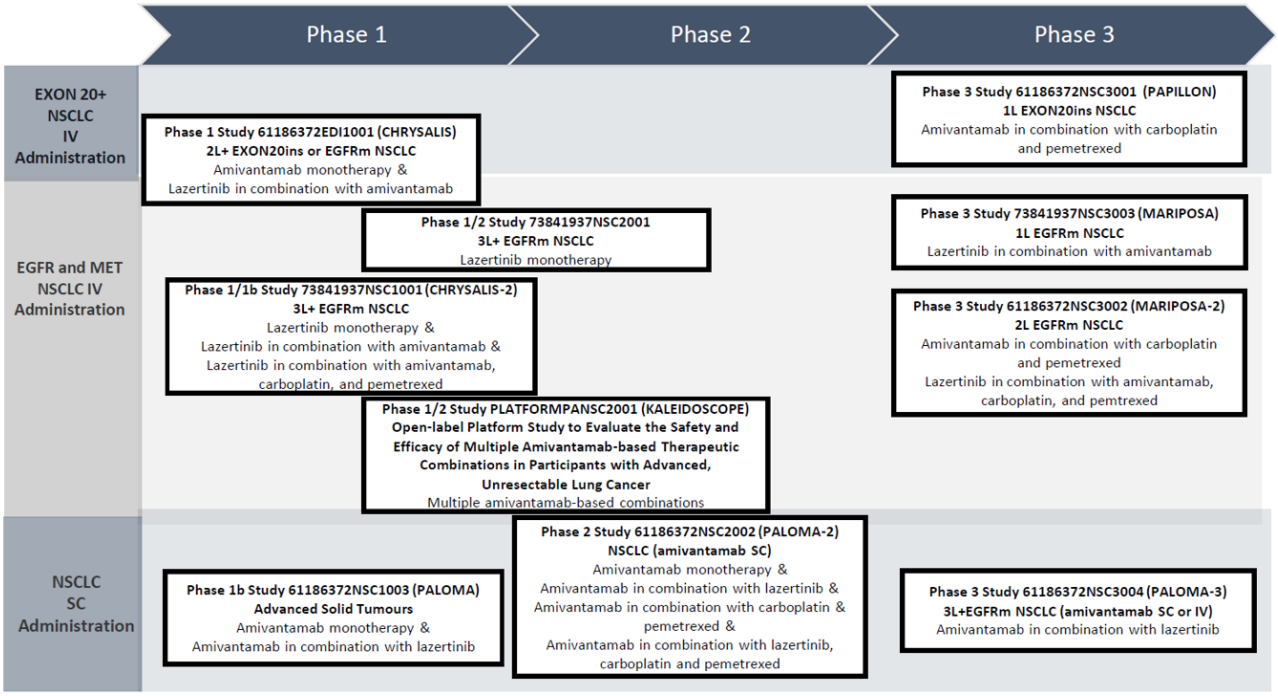
- in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

Lazertinib is developed under a license and collaboration agreement between Yuhan Corporation and Janssen.

Key efficacy and safety data to support this submission are derived from the Phase 3 MARIPOSA study. Further supportive data is derived from Phase 1 Study CHRYSALIS and Phase 1/1b Study 73841937NSC1001 (hereafter referred to as CHRYSALIS-2).

In CHRYSALIS-2, 162 patients with EGFRm NSCLC and disease progression after osimertinib and platinum-based chemotherapy received the combination of amivantamab and lazertinib; a BICR-assessed ORR of 33% and median DOR of 9.6 months were observed (Shu 2022). In a cohort of 45 patients with EGFRm NSCLC who received the combination of amivantamab and lazertinib after disease progression on osimertinib in CHRYSALIS, an overall response rate of 36% and median DOR of 9.6 months were observed. These rates compared favorably to patients receiving amivantamab monotherapy in a series of heterogenous cohorts of patients with previously treated EGFRm NSCLC in CHRYSALIS, described above.

Figure 1: Janssen Clinical Development Program for Amivantamab and Lazertinib in Patients with Locally Advanced or Metastatic NSCLC



Note: All studies are ongoing

The Applicant sought scientific advice from the CHMP on the Phase 3 MARIPOSA study in March 2020, regarding the development the combination of amivantamab and lazertinib for the treatment of first-line EGFRm NSCLC with activating EGFR mutations.

2.1.4. General comments on compliance with GCP

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the respective protocol.

2.2. Non-clinical aspects

2.2.1. Introduction

To support this extension application the applicant has conducted two pharmacology studies in NSCLC xenografts mouse models with the combination therapy of amivantamab and lazertinib, and monotherapies of amivantamab and lazertinib.

No other new non-clinical data have been submitted in this application.

In addition, the applicant provided a summary of the results of toxicology studies, including evaluation of safety pharmacology endpoints, with amivantamab and lazertinib, respectively. No significant overlapping safety issues or toxicities were identified based on their individual non-clinical safety profiles. However, concerns about the potential risks of amivantamab and/or lazertinib to the foetus during pregnancy were identified and have been included in the SmPC.

2.2.2. Pharmacology

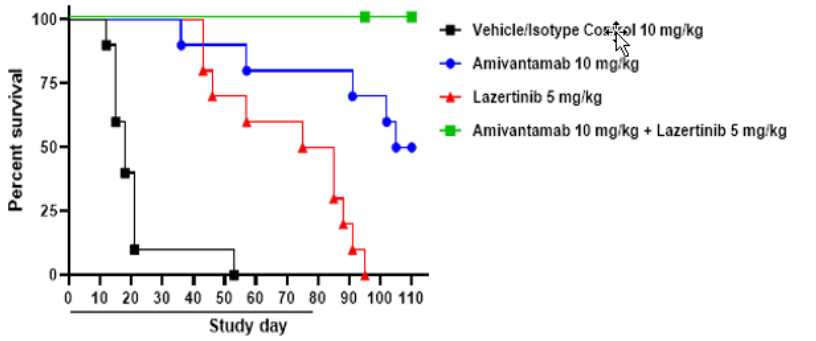
Primary pharmacodynamic studies

The applicant has conducted two in vivo pharmacology studies using NSCLC xenografts mouse model sensitive to EGFR TKIs (H1975) and a model with overexpression of HGF to induce EGFR TKI resistance by MET signalling pathway (H1975/HGF). The combination therapy of amivantamab and lazertinib compared to either amivantamab or lazertinib monotherapy was tested. Amivantamab is a bispecific antibody that binds to the extracellular portion of both EGFR and MET to inhibit ligand-dependent signalling. Lazertinib is an orally administered, highly potent, mutant-selective, irreversible 3rd generation EGFR TKI that targets both exon 19del and exon 21 L858R activating mutations, as well as the T790M resistance mutation.

Study	Test system	Objective and Results
DD18058 **Charles River** **Non-GLP**	Athymic nude mice (NU(Ncr)-Foxn1nu) with SC implanted human H1975 or H1975/HGF tumour cells n=10 females per group Dose: Amivantamab 10 mg/kg biweekly x 3; 6 doses (IP). Amivantamab/Lazertinib: 10 mg/kg biweekly x 3; 6 doses (IP)/10 mg/kg QD for 21 days(PO). Lazertinib:10 mg/kg QD for 21 days (PO).	**Objective:** To assess the in vivo efficacy the of combination therapy of **amivantamab and lazertinib** combination therapy or either monotherapy in NSCLC xenografts mouse models sensitive **(H1975) or resistant (H1975/HGF) to EGFR TKIs** **Results:** Amivantamab in monotherapy eliciting 70% TGI in model H1975/HGF, as compared to controls at Day 28 (p=0.0059) while the activation of MET signalling resulted in amivantamab activity was consistent in both models (TGI: 70% in H1975/HGF vs. 86% in H1975). The combination of amivantamab and lazertinib resulted in 108% (in H1975/HGF) and 112% (in H1975) TGI as compared to controls at Day 28 of treatment (p<0.0001) and significantly improved TGI as compared to amivantamab monotherapy (p<0.0001).
DD21087 **Charles River** **Non-GLP**	Athymic nude mice (NU(Ncr)-Foxn1nu) with SC implanted H1975/HGF tumour cells n=10 females per group Dose: Amivantamab 10 mg/kg twice a week for 11 weeks (IP). Amivantamab/Lazertinib: 10 mg/kg biweekly x 11; 6 doses (IP)/5 mg/kg QD for 78 days(PO). Lazertinib: 5 mg/kg QD for 78 days (PO).	**Objective:** To assess in vivo efficacy of combination therapy of amivantamab and lazertinib or either monotherapy in NSCLC xenografts mouse models sensitive to EGFR TKIs (H1975/HGF) with continual administration for 11 weeks **Results:** When overexpression of HGF and activation of the MET signalling the pathway amivantamab in monotherapy or in combination with lazertinib resulted in 89% and 121% TGI, respectively. At day 95 and day 110 the survival rate was 70% and 50% for amivantamab group and 100% for the combination group. Fig. 1. Tumour Growth Inhibition, p Values, and Partial and Complete Responses for H1975-HGF-Tumor-Bearing Mice

Group	Treatment	%·TGI	p·Value·of·TGI	#·of·PRs	#·of·CRs
1	Isotype·(10·mg/kg)·+·vehicle·control	NA	NA	0	0
2	Amivantamab·(10·mg/kg)	89	<0.0001	1	4
3	Lazertinib·(5·mg/kg)	76	<0.0001	0	0
4	Amivantamab·(10·mg/kg);·lazertinib·(5·mg/kg)	121	<0.0001	0	10

Isotype·control·and·amivantamab·at·10·mg/kg·were·dosed·IP·twice·a·week·for·11·weeks.·Lazertinib·was·orally·dosed·daily·for·78·days.·Percent·ΔTGI·and·p·values·were·calculated·on·Day·15.·Statistical·significance·was·calculated·using·the·Linear·Mixed-Effects·analysis.·Partial·responses·(PRs)·and·complete·responses·(CRs)·were·determined·over·the·course·of·the·study,·which·lasted·110·days.

		Fig. 2. Survival of mice bearing H1975-HGF tumours when administered amivantamab and lazertinib as monotherapies or in combination  Tumor-bearing mice were assigned to groups and dosing was initiated on Day 1. Isotype control and amivantamab at 10 mg/kg were dosed IP twice a week for 11 weeks. Lazertinib was orally dosed daily for 78 days. The overall dosing period is denoted by the line below the X-axis.

2.2.3. Ecotoxicity/environmental risk assessment

Amivantamab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for amivantamab is required.

2.2.4. Discussion on non-clinical aspects

The applicant has submitted two new pharmacology studies (DD18058, DD21087) to evaluate the efficacy of co administrated amivantamab and lazertinib or as monotherapies in NSCLC xenograft mouse models to support this application. No other new non-clinical data have been submitted in this application which is considered acceptable.

Amivantamab generates an effective tumour suppressing effect which was improved, as well as the survival rate, when given as a combination therapy (with lazertinib) in the NSCLC xenograft mouse models. This supports the mode of action of amivantamab and lazertinib, targeting the extracellular ligand-binding domain and intracellular active site of EGFR, respectively, and indicates that the potential to inhibit this pathway is more potent when the two products are given in combination, than amivantamab alone.

In addition, the applicant provided a summary of the results of toxicology studies, including evaluation of safety pharmacology endpoints, with amivantamab and lazertinib, respectively. No significant overlapping safety issues or toxicities were identified based on their individual non-clinical safety profiles. However, concerns about the potential risks of amivantamab and/or lazertinib to the foetus during pregnancy were identified and have been included in the SmPC.

2.2.5. Conclusion on the non-clinical aspects

The combination of amivantamab and lazertinib revealed a superior tumour suppressing effect compared to amivantamab given alone in NSCLC xenograft mouse models. This supports the mode of action of the combination treatment, targeting the extracellular ligand-binding domain and intracellular active site of EGFR, and the clinical use in patients with advanced NSCLC with EGFR exon 19 deletions

or exon 21 L858R substitution mutations. Furthermore, amivantamab is not expected to pose a risk to the environment. In conclusion, the non-clinical data package is supportive of the new indication.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

The general absorption, distribution, metabolism, and excretion characteristics, dose proportionality and time dependency of amivantamab administered as monotherapy are described in procedure number EMEA/H/C/005454/0000.

The clinical pharmacology data, relevant for the current application, originates from the ongoing Phase 3 Study 73841937NSC3003 (MARIPOSA) evaluating amivantamab in combination with lazertinib as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC. The amivantamab PK analyses were based on available data from the pivotal MARIPOSA and supportive studies 61186372EDI1001 (CHRYSALIS) and 73841937NSC1001 (CHRYSALIS-2), see Table 1. The PK data cut-off date for the MARIPOSA study was 11 April 2023, for CHRYSALIS 15 November 2021, and for CHRYSALIS-2 15 July 2022.

Table 1: Overview of Studies Contributing Information to the Summary of Clinical Pharmacology.

Study number	Phase	Population	Amivantamab dose	Number of participants included in popPK
61186372EDI1001 (CHRYSALIS)	1	Adults with Advanced Non-Small Cell Lung Cancer.	**Part 1 (dose escalations):** Amivantamab monotherapy: 140, 350, 700, 1050, 1400, and 1750 mg IV infusion in 4-week cycles QW: Cycle 1 (Days 1, 2, 8, 15, and 22) Q2W: Cycle 2 and beyond Amivantamab and lazertinib combination therapy: Amivantamab 700, 1050, 1400 mg IV infusion in 4-week cycles QW: Cycle 1 (Days 1, 2, 8, 15, and 22) Q2W: Cycle 2 and beyond Lazertinib 240 mg oral administration QD (4-week cycles) **Part 2 (dose expansion):** Amivantamab monotherapy: 1050 mg amivantamab (1400 mg if ≥ 80 kg) IV infusion in 4-week cycles	Part 1 monotherapy: 80 Part 2 monotherapy: 333 Part 1 combination therapy: 63 Part 2 combination therapy (cohort E): 45
73841937NSC1001 (CHRYSALIS-2)	1b	Adults with Advanced Non-Small Cell Lung Cancer.	**Combination cohort:** 240 or 320 mg lazertinib QD, administered orally in 28-day cycles. 700, 1050, 1400, or 1750 mg of amivantamab, administered intravenously. QW: Cycle 1 Q2W: Cycle 2 and beyond **Expansion cohorts (A–D):** 240 mg lazertinib QD, administered orally. 1050/1400 mg of amivantamab administered intravenously. QW: Cycle 1 Q2W: Cycle 2 and beyond	Combination cohort: 6 Expansion cohorts: 392; 156 in cohort A, 68 in cohort B, 64 in cohort C, 104 in cohort D.
73841937NSC3003 (MARIPOSA)	3	First-Line Treatment in Adults with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer.	**Arm A (open-label combination therapy):** 1050 mg amivantamab (1400 mg if ≥ 80 kg) IV infusion in 28-day cycles. QW: Cycle 1 (Days 1, 2, 8, 15, and 22) Q2W: Cycle 2 and beyond. 240 mg lazertinib QD, administered orally.	408

Bioanalytical methods

A validated ECLIA on the MSD platform was used to determine amivantamab concentrations in human serum samples with a lower limit of quantification of 0.32 µg/mL at a 1/40 dilution.

A validated sensitive, drug and target tolerant ECLIA method on the MSD platform was used to assess ADAs to amivantamab in human serum samples.

Pharmacokinetic data analyses

Methods

The PK data analyses were based on serum amivantamab concentrations of samples obtained from participants treated with either amivantamab monotherapy or amivantamab+lazertinib combination therapy in the studies CHRYSALIS, CHRYSALIS-2, and MARIPOSA.

All PK parameters were calculated using conventional non-compartmental methods using actual times of blood sampling, unless otherwise stated in the CSR.

The population PK analysis was performed using nonlinear mixed effects modelling, using standard methodology and adherence to regulatory guidelines for population PK analyses.

Studies contributing to PK

CHRYSALIS study

The CHRYSALIS study is an ongoing, first-in-human Phase 1, open-label, multicenter study of amivantamab, administered as monotherapy or in combination (eg, the combination of amivantamab and lazertinib) in adult participants with advanced or metastatic NSCLC. With regard to the combination of amivantamab and lazertinib, the study consisted of 2 parts: Part 1 comprised a dose escalation phase to determine the RP2CD regimen for the combination of amivantamab and lazertinib using a standard 3+3 design; Part 2 comprised a dose expansion phase to better characterize the safety, tolerability, and efficacy of the combination of amivantamab and lazertinib at the RP2CD. Treatment was administered until disease progression, unacceptable toxicity, or withdrawal of consent.

The amivantamab doses administered in Part 1 were 700 mg, 1050 mg, and 1400 mg. The recommended RP2CD was determined to be 1050 mg for participants weighing < 80 kg, and 1 400 mg for participants weighing ≥ 80 kg. Lazertinib was administered as an oral tablet at 240 mg (3 × 80 mg). Serial blood samples were collected from all participants. For all participants in Part 1 and a fraction of participants in each Part 2 cohort, serum samples were collected at preinfusion, EOI, 2, 6, 24, and 72 hours post-EOI on Day 2 of Cycle 1; preinfusion, EOI, 2, 6, 24, 72, 168, and 240 hours post-EOI on Day 1 of Cycle 2 and 4; and at preinfusion and EOI on other amivantamab infusion days.

CHRYSALIS-2 study

The CHRYSALIS-2 study is an ongoing, Phase 1/1b open-label, multicenter study in participants with EGFRm NSCLC including a Part 1 dose finding component in Japanese participants (Phase 1 lazertinib monotherapy, and Phase 1b combination of amivantamab and lazertinib), and a Part 2 component in global participants (Phase 1b combination of amivantamab and lazertinib).

In the Phase 1b combination of amivantamab and lazertinib cohort, the dose of amivantamab was 1050 mg (for body weight <80 kg) or 1400 mg (for body weight ≥80 kg) administered IV every 7 days (first dose was split into 2 doses and given on Cycle 1 Day 1 and Cycle 1 Day 2) for the first 28 days and every 2 weeks thereafter; the starting combination dose of lazertinib was 240 mg administered orally once daily. Serum samples were collected at preinfusion and EOI on Day 1, 2, 8, 15, 22 of Cycle 1, and Day 1 of every following cycle.

MARIPOSA study

The MARIPOSA study is an ongoing, randomized, multicenter, Phase 3 study in participants with EGFRm NSCLC to compare the efficacy and safety of the combination of amivantamab and lazertinib vs osimertinib as first-line treatment. Eligible participants were randomly assigned to study treatment in a 2:2:1 ratio (amivantamab+lazertinib arm, osimertinib arm, and lazertinib arm, respectively). Amivantamab was administered as an IV infusion at 1050 mg (body weight < 80 kg) or 1400 mg (body

weight ≥ 80 kg). Lazertinib was administered as an oral tablet at 240 mg (3 × 80 mg). Blood samples for the measurement of serum amivantamab were collected on Day 1 and 2 of Cycle 1 at preinfusion and EOI; Day 1 of Cycles 2, 3, 5, 7, 9, 11 and 13, at predose and EOI; and at end-of-treatment (30 days after last dose).

Comparison of PK results across studies

A summary of PK parameters of amivantamab, when administered as monotherapy and in combination with lazertinib in the CHRYSALIS and MARIPOSA studies, respectively, is presented in Table 2. The amivantamab PK results from the amivantamab+lazertinib combination were consistent with the known PK profile of amivantamab when administered as monotherapy.

Table 2: PK parameters of amivantamab derived through non-compartmental analysis of observed concentrations of amivantamab at Cycle 1 Day 1/2, Cycle 2 Day 1, and at steady state (i.e., Cycle 4 Day 1 in CHRYSALIS and CHRYSALIS-2 and Cycle 5 Day 1 in MARIPOSA) after IV infusion of amivantamab 1 050/ 1400 mg every week in Cycle 1 and every 2 weeks in Cycle 2 and onwards, when administered as monotherapy or in combination with oral administration of 240 mg lazertinib daily, respectively, in the CHRYSALIS and MARIPOSA studies, respectively.

Pharmacokinetics of amivantamab mean (SD), t_{max}: median (min–max)	**CHRYSALIS** **Amivantamab (1 050/1 400 mg) monotherapy**	**CHRYSALIS-2** **Amivantamab (1 050/1 400 mg) and lazertinib (240 mg) combination therapy**	**MARIPOSA** **Amivantamab (1 050/1 400 mg) and lazertinib (240 mg) combination therapy**
Cycle 1 Day 1			
n	33[b]	16	-
$C_{max,}$ µg/mL	374 (86.0)	444 (95.3)	-
$AUC_{0\text{-}168h}$, µg×h/mL	32 350 (8 767)	37 365 (7 631)	-
Cycle 1 Day 2			
n	-	78	335[g]
C_{trough}, µg/mL	-	89.4 (28.3)	101 (41.6)
C_{EOI}, µg/mL	-	-	367 (122)
Cycle 2 Day 1			
n	209[c]	79[e]	285[h]
C_{trough}, µg/mL	333 (112)	294 (88.9)	317 (102)
C_{max} or C_{EOI}, µg/mL	793 (248)	859 (297)	745 (231)[i]
t_{max}, h	4.08 (2.03–25.47)	4.31 (2.37–25.42)	-
$AUC_{0\text{-}168h}$, µg×h/mL	90 582 (32 399)	89 562 (21 534)	-
AUC_{τ}, µg×h/mL[a]	146 397 (55 603)	137 967 (36 267)	-
$AR_{AUC0\text{-}168h(C2D1/C1D1)}$	2.92 (0.71)	2.48 (0.70)	-
Cycle 4 Day 1 (CHRYSALIS /CHRYSALIS -2) Cycle 5 Day 1 (MARIPOSA)			
n	151[d]	62[f]	181[j]
C_{trough}, µg/mL	183 (88.7)	144 (55.5)	156 (73.7)
C_{max} or C_{EOI}, µg/mL	586 (123)	642 (168)	560 (172)[i]
t_{max}, h	4.00 (3.92–8.33)	4.31 (2.32–26.00)	-
$AUC_{0\text{-}168h}$, µg×h/mL	66 385 (15 981)	61 721 (13 886)	-
AUC_{τ}, µg×h/mL[a]	102 954 (27 665)	91 073 (25 912)	-
$AR_{AUC0\text{-}168h(C4D1/C1D1)}$	2.44 (0.54)	1.71 (0.30)	-

AR=accumulation ratio; AUC_{τ}= area under the concentration-time curve during a dosing interval; $AUC_{0\text{-}168h}$=area under the concentration-time curve from 0 to 168 h postdose; C_{max}=maximum observed concentration (i.e., end-

of-infusion); C_{trough}=trough concentration; IV=intravenous; PK=pharmacokinetic(s); SD=standard deviation; t_{max}=time to maximum observed concentration.
[a] Scheduled τ is 336 h
[b] n=32 for Cmax
[c] n=34 for t_{max}, C_{max}; n=33 for AUC_{τ}, $AUC_{0\text{-}168h}$; n=28 for $AR_{AUC0\text{-}168h}$
[d] n=6 for t_{max}, C_{max}, $AR_{AUC0\text{-}168h(C2D1/C1D1)}$, AUC_{τ}, $AUC_{0\text{-}168h}$
[e] n=14 for C_{max}, t_{max}, $AUC_{0\text{-}168h}$; n=13 for AUC_{τ}
[f] n=10 for C_{max}, t_{max}, $AUC_{0\text{-}168h}$, $AR_{AUC0\text{-}168h(C4D1/C1D1)}$; n=9 for AUC_{τ}
[g] n=294 for C_{EOI}
[h] n=212 for C_{EOI}
[i] C_{EOI}estimate reported as only sparse amivantamab PK samples were collected in MARIPOSA Arm A
[j] n=148 for C_{EOI}

Population pharmacokinetic analysis

A popPK analysis was performed using the nonlinear mixed effect modelling software NONMEM (version 7.4.3). The popPK model was used to describe PK data from the MARIPOSA study. The FOCE method with the INTERACTION option was used. This approach was validated through conventional numerical and graphical model diagnostics.

The population PK (popPK) analysis was performed by fitting a previously developed nonlinear mixed effects model (EMEA/H/C/005454/II/0010) to the data from CHRYSALIS, CHRYSALIS-2, and MARIPOSA. The covariates were re-tested for statistical significance.

Outliers were removed from the popPK analysis. Outlier detection primarily involved visually inspecting individual and combined concentration-time profiles. PK observations significantly diverging from nearby observations or with a large absolute conditional weighted residual (|CWRES| > 6) were considered outliers. The outliers were reintroduced in a sensitivity analysis of the final popPK model.

Data

When excluding outliers, the final popPK dataset included 27 053 amivantamab PK observations from 1327 participants. These comprised 413 participants (13 369 PK observations) from amivantamab monotherapy treatment arms, and 914 participants (13 684 PK observations) from amivantamab+lazertinib combination treatment arms. Since the percentage of observations below the limit of quantification (BLQ) was low (< 10%), the BLQ samples were omitted from the analysis.

Model

The popPK model is a two-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination. The model is parameterized in terms of linear CL, V_1, Q, V_2, V_{max}, and K_m. Inter-individual variability (IIV) was estimated for CL, V_1, and V_2. The residual variability was proportional (additive on logarithmic scale). The final popPK model included body weight, sex, age, and albumin as covariates on CL, body weight and sex as covariates on V_1, and body weight as a covariate on V_2 (shared scaling exponent for V_1 and V_2). The population parameter estimates were reassessed in this application. The parameter estimates of the final model are presented in Table 3. A prediction corrected visual predictive check (pcVPC) is presented in *Figure 2*, and summary statistics of individual (secondary) PK parameters, derived based on post-hoc parameter estimates of participants in MARIPOSA, are presented in *Table 4*.

Table 3: Parameter estimates in the final population PK model (run07) on pooled PK data from the CHRYSALIS, CHRYSALIS-2, and MARIPOSA studies. (In the right column, a sensitivity analysis using the reintroduced outliers (run08).

	Excluding Outliers (Run07)		All Data (Run08)	
Parameters, unit	Estimate (RSE%)	Shrinkage (%)	Estimate (RSE%)	Shrinkage (%
Fixed effect				
CL (L/h)	0.00981 (1.1)	-	0.00968 (1.9)	-
Weight on CL[a]	0.508 (7.9)	-	0.523 (8.3)	-
Albumin on CL[a]	-0.456 (14.6)	-	-0.440 (13.2)	-
Age on CL[a]	-0.234 (13.7)	-	-0.202 (21.0)	-
Sex=Male on CL[a]	0.227 (9.7)	-	0.229 (13.2)	-
V_1 (L)	2.69 (1.0)	-	2.72 (1.1)	-
Weight on V_1 and V_2[b,c]	0.500 (6.7)	-	0.500 (7.4)	-
Sex=Male on V1[b]	0.131 (14.3)	-	0.134 (15.6)	-
V_2 (L)	2.13 (2.2)	-	2.07 (2.2)	-
Q (L/h)	0.0531 (4.7)	-	0.0652 (4.2)	-
V_{max} (mg/h)	0.600 (1.6)	-	0.677 (0.2)	-
K_m (µg/mL)	1.86 (10.8)	-	7.37 (0.2)	-
Interindividual variability (CV%)[d]				
CL	26.0 (2.4)	10.7	26.0 (2.6)	13.8
V_1	23.4 (2.7)	13.6	24.8 (3.1)	17.4
V_2	49.2 (4.3)	34.7	55.7 (4.0)	38.0
Residual variability[d]				
Proportional error (CV%)	28.6 (0.5)	5.0	36.3 (0.5)	4.5

Parameter estimate RSE (%)=(standard error/estimate)×100%; IIV RSE and residual error RSE (%)=(standard error/variance estimate)/2×100%.

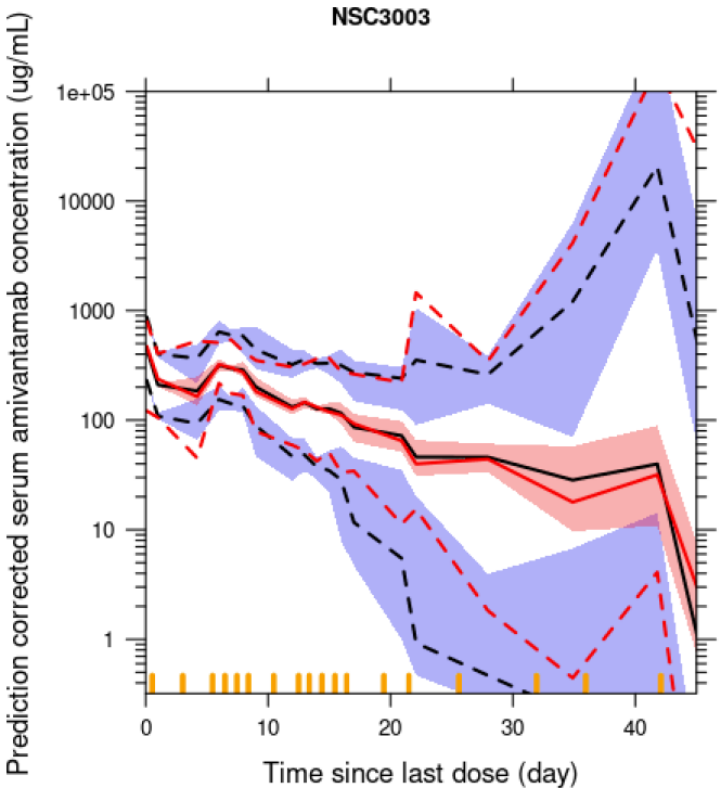
[a] Weight, albumin, age and sex effects on the typical value of CL were modeled as follows: $TVCL=\theta_{CL}\times(WT/60)^{\theta_{wt,CL}}\times(ALB/40)^{\theta_{alb,CL}}\times(AGE/63)^{\theta_{age,CL}}\times(1+\theta_{sex,CL}\times sex)$, where TV stands for "typical value," θ_{CL} is the clearance value in a typical female participant with weight (WT) equal to 60 kg, baseline albumin level (ALB) equal to 40 g/L, age of 63 years, $\theta_{wt,CL}$ is the weight coefficient for clearance, $\theta_{alb,CL}$ is the albumin coefficient for clearance, $\theta_{age,CL}$ is the age coefficient for clearance, *sex* is an indicator variable for female (*sex*=0; reference category) or male (*sex*=1) participants, and $\theta_{sex,CL}$ is the multiplicative term for male s effect on TVCL.

[b] Weight and sex effects on the typical value of V_1 was modeled as follows: $TVV1=\theta_{V1}\times(WT/60)^{\theta_{wt,V}}\times(1+\theta_{sex,V1}\times sex)$, where TV stands for "typical value," θ_{V1} is the central volume of distribution value in a typical female participant with weight (WT) equal to 60 kg, and $\theta_{wt,V}$ is the weight coefficient for the central or peripheral volume of distribution, *sex* is an indicator variable for female (*sex*=0; reference category) or male (*sex*=1) participants, and $\theta_{sex,V1}$ is the multiplicative term for male sex effect on TVV1.

[c] Weight effect on the typical value of V_2 was modeled as follows: $TVV2=\theta_{V2}\times(WT/60)^{\theta_{wt,V}}$, where TV stands f "typical value," θ_{V2} is the peripheral volume of distribution value in a typical participant with weight (WT) eq to 60 kg, and $\theta_{wt,V}$ is the weight coefficient for the central or peripheral volume of distribution.

[d] Estimates in relative percentage scale for IIV and residual error, calculated as $(\exp^{var}-1)^{1/2}\times100\%$, where var represents the variance estimate for log-normally distributed random effects and residual error as returned by NONMEM.

Figure 2: Prediction corrected visual predictive check (pcVPC) for the MARIPOSA predictions from the population PK model.



Solid red line is median, dashed red lines are the 2.5th and 97.5th percentiles of the observations. Solid black line is median, dashed black lines are the 2.5th and 97.5th percentiles predicted by the model. The shaded red area represents the 95% CI of the median and shaded blue areas represent the 95% CI of the 2.5th and 97.5th percentiles predicted by the model. NSC3003 = MARIPOSA

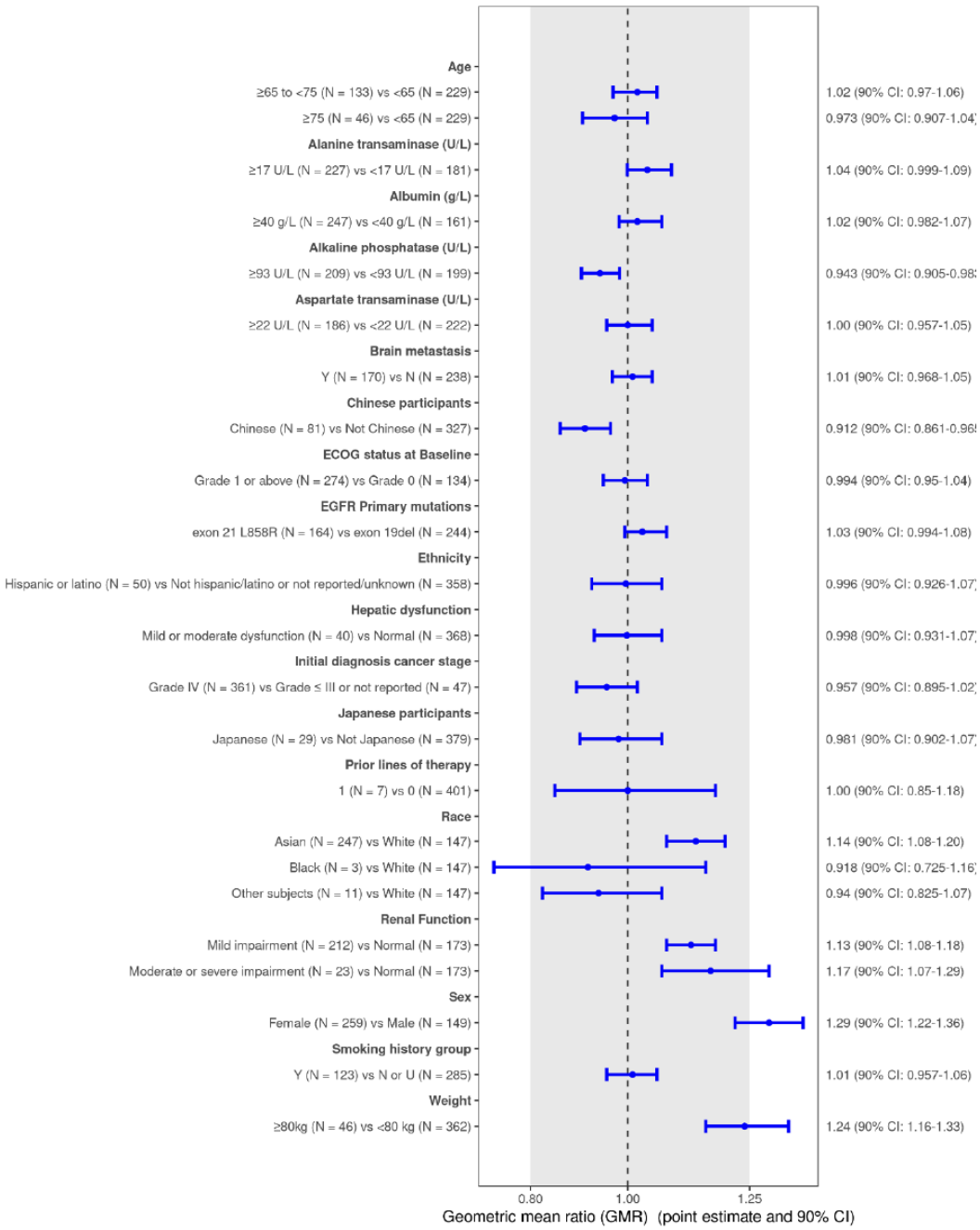
Table 4: Summary of Half-life for Linear Elimination Pathway and Total Volume of Distribution for the final popPK model (run07), derived based on post hoc parameter estimates of participants in MARIPOSA.

Parameter	Number of Participants	Geometric Mean	Geometric CV	Min	5th%	Median	95th%	Max
Total volume of distribution (L)	408	5.04	23.71	1.944	3.53	4.987	7.346	15.44
Linear clearance (mL/day)	408	261.7	30.35	106.6	155.4	265.5	420.5	833.0
Terminal half-life (days)	408	13.93	32.56	4.307	8.478	13.67	23.27	59.99

A comparison of amivantamab steady-state exposures ($AUC_{0\text{-}14\ days,\ ss}$ and $C_{eoi,\ ss}$) was conducted in specific subgroups using forest plots, i.e., by presenting the estimated GMR and its 90% CI for a given covariate stratum relative to the reference stratum. The prediction was done using the individual post hoc PK parameters for the PK population of the MARIPOSA study, assuming all participants received the scheduled doses according to the recommended dose regimen. Subgroups were considered to have comparable exposure if the estimated GMR and 90% CI limits were not entirely outside the 80%–125% range. The trend for $C_{eoi,\ ss}$ was similar to that of $AUC_{0\text{-}14\ days,\ ss}$.

Figure 3 shows that females had an approximately 30% higher exposure than males, consistent with previous findings of amivantamab PK. Additionally, *Figure 4* indicates that lazertinib had a slight yet clinically irrelevant effect on the exposure of amivantamab.

Figure 3: Forest Plot of Subgroup Analyses of AUC0-14 days, ss. Based on the MARIPOSA population in the popPK dataset (run07).

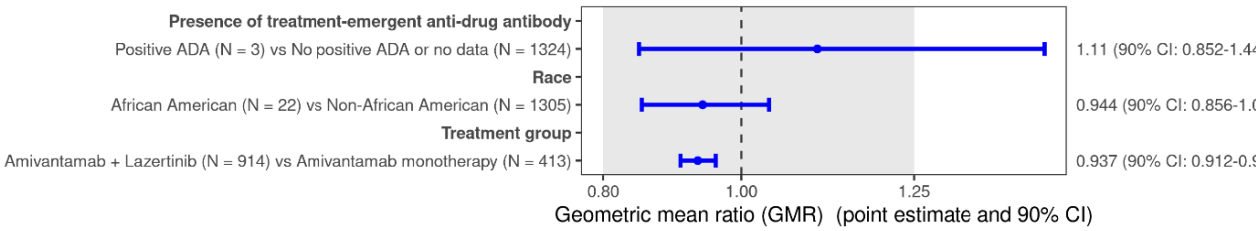


Solid blue circle represents GMR and error bar represents 90% CI. The associated values are shown on the right column. Vertical, dashed line represents reference value of 1. The shaded area refers to 0.8–1.25.

Note: Analyses assumed that all participants included in the popPK analysis dataset received 1 050 mg for participants < 80 kg body weight (at baseline) or 1 400 mg for participants ≥ 80 kg body weight (at baseline), administered as an IV infusion QW for 4 weeks, then every 2 weeks thereafter. Renal function is classified based on eGFR (mL/min) = EGFR (mL/min/1.73 m^2) × BSA(m^2)/1.73, where eGFR is calculated using chronic kidney disease-Epidemiology Collaboration (CKD-EPI) formula. eGFR in the range of ≥ 90, 60–89, 15–59 is defined as normal, mild

impairment, moderate or severe impairment, respectively. Hepatic dysfunction is defined based on NCI Organ Dysfunction Working group criteria.

Figure 4: Forest Plot of Subgroup Analyses of AUC0–14 days, ss. Based on all Participants in popPK Dataset (run07).



Solid blue circle represents GMR and error bar represents 90% CI. The associated values are shown on the right column. Vertical, dashed line represents reference value of 1. The shaded area refers to 0.8–1.25.
Note: Analyses assumed that all participants included in the popPK analysis dataset received 1 050 mg for participants < 80 kg body weight (at baseline) or 1 400 mg for participants ≥ 80 kg body weight (at baseline), administered as an IV infusion QW for 4 weeks, then every 2 weeks thereafter.

Special populations

The current application included one patient with severe renal impairment (15 ≤ CrCl < 29 mL/min) and one patient with moderate hepatic impairment (1.5×ULN < total bilirubin ≤ 3×ULN and any AST). Although these data are very limited, there is currently no evidence to suggest that dose adjustments are required in these patients.

Immunogenicity data analysis

Method

The possible generation of treatment-emergent anti-amivantamab antibodies was assessed in participants treated with combination of amivantamab and lazertinib therapy in the CHRYSALIS, CHRYSALIS-2, and MARIPOSA studies. The assessment of immunogenicity for amivantamab in these studies utilized a tiered assay approach, comprising screening, specificity (confirmatory), and titer assays to detect binding antibodies to amivantamab.

Participants with at least 1 positive sample at any timepoint after exposure to amivantamab were classified as positive for ADA. If a participant had detectable ADA in a baseline (predose) sample, the participant was considered ADA positive only if the peak titer of the posttreatment samples was ≥ 2-fold higher than the titer of the baseline sample.

Participants were designated as negative when there was no positive sample at any timepoint evaluated after exposure to amivantamab. If a participant had detectable ADA in a baseline (predose) sample, the participant was considered ADA negative if no posttreatment samples represented a ≥ 2-fold increase in the titer relative to the baseline sample.

Due to the low risk for immunogenicity and the low incidence of samples positive for antibodies to amivantamab, neutralizing antibodies were not evaluated.

Results

The immunogenicity analysis population consisted of 864 participants who had appropriate samples. All subjects tested negative for treatment-emergent antibodies to amivantamab (Table 5).

Table 5: Summary of the incidence of immunogenicity to amivantamab. AMI=amivantamab, LAZ=lazertinib, C2D1=Cycle 2 Day 1; C2=Cycle 2; IV=intravenous; QW=once weekly; Q2W=every 2 weeks

Study	Cohort	Amivantamab doses tested	Participants with appropriate samples[a]	Participants *positive* for treatment-emergent antibodies to amivantamab[b]	Participants *negative* for treatment-emergent antibodies to amivantamab[c]
61186372EDI1001 (CHRYSALIS)	AMI+LAZ cohort	700/1050 mg (< 80 kg) or 1050/1 400 mg (≥ 80 kg) IV infusion QW up to C2D1, from C2 onwards Q2W	100	0 (0.0%)	100 (100.0%)
7384193NSC1001 (CHRYSALIS-2)	AMI+LAZ, escalation cohort (Japanese)	1050 mg (< 80 kg) or 1400 mg (≥ 80 kg) IV infusion QW up to C2D1, from C2 onwards Q2W	6	0 (0.0%)	6 (100.0%)
	AMI+LAZ, expansion cohorts A, B, C, and D		362[c]	0 (0.0%)	362 (100.0%)
7384193NSC3003 (MARIPOSA)	AMI+LAZ, Arm A		396[d]	0 (0.0%)	396 (100.0%)

[a] Participants who had 1 or more evaluable samples obtained after their first amivantamab administration.
[b] Denominator is number of participants with appropriate samples for antibodies to amivantamab.
[c] In 3 participants, all post-baseline ADA samples contained drug concentrations greater than the assay drug tolerance limit (> 400 µg/mL). These participants were excluded from the ADA descriptive statistics.
[d] In 2 participants, all ADA samples contained drug concentrations greater than the assay drug tolerance limit (> 400 µg/mL) and were excluded.

Pharmacokinetic interaction studies

No formal clinical drug-drug interaction studies were performed, and no interactions with concomitant medications are expected.

Coadministration with lazertinib had no clinically relevant impact on amivantamab exposure, neither based comparison of non-compartmental analyses across studies nor based on the popPK analysis (*Figure 4*).

2.3.3. Pharmacodynamics

Please refer to procedure number EMEA/H/C/005454/0000 for details on the pharmacodynamics (PD) of amivantamab monotherapy. No new clinical PD data are available.

2.3.4. Exposure - response modelling

The analyses for the exposure-response (E-R) relationship for efficacy and safety endpoints were based on available data from Arm A of the pivotal study MARIPOSA. The E-R population included 408 participants who received at least 1 dose of amivantamab and lazertinib and had evaluable efficacy/safety results and individual exposures, derived using each participant's actual dose records, covariates, and post hoc PK parameters (from the population PK analysis).

The E-R analysis for efficacy focused on the primary endpoint PFS evaluated by BICR. The E-R analysis for safety included selected AEs of clinical interest. E-R analyses were performed with R version 3.6.2.

Efficacy

The E-R relationships for PFS by BICR (time-to-event endpoint) were evaluated with Kaplan-Meier plots stratified by amivantamab exposure tertiles using the log-rank test. To account for any imbalance in baseline covariates, Cox-PH regression modelling was conducted. No significant effect of amivantamab exposures on PFS was detected after adjusting for covariate effects.

Safety

The E-R relationship for safety was explored for selected AEs of clinical interest including IRR, rash, VTE, pneumonitis/(ILD), paronychia, hypoalbuminemia, diarrhea, stomatitis, and paresthesia. The occurrence rate of AEs was stratified by the appropriate exposure metrics using bar plots to evaluate whether there was a relationship between the AEs and exposure levels of amivantamab.

Participants with higher $C_{eoi,1st}$ appeared to have lower rate of IRR (any grade). This could be explained by dose interruptions in participants with IRR leading to lower concentrations at the EOI.

The E-R relationship for paronychia and stomatitis suggest a nominal increase in rate of occurrence with increasing exposure ($C_{eoi,\ max}$ and $C_{avg,\ 1st\ cycle}$). These trends were likely related to the mechanism of action of EGFR inhibition.

There were no apparent E-R relationships for the safety endpoints including rash (any Grade and Grade ≥ 3), VTE (any Grade and Grade ≥ 3), pneumonitis/ILD, hypoalbuminemia (any Grade derived from ADAE), hypoalbuminemia (baseline worsening Grade ≥ 3 derived from ADLB), diarrhea, and paresthesia with increasing exposure ($C_{eoi,\ max}$ and $C_{avg,\ 1st\ cycle}$).

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology data, relevant for the current application, originates from the phase 1 CHRYSALIS, phase 1/1b CHRYSALIS-2, and phase 3 MARIPOSA studies. These explore the use of amivantamab as both monotherapy and in combination with lazertinib. It evaluates the pharmacokinetics (PK) of amivantamab, with 1327 participants involved across these studies.

Previous procedures (EMEA/H/C/005454/0000 and EMEA/H/C/005454/0010) described the PK of amivantamab, including assessment of bioanalytical methods and a previously approved popPK model. Relevant pharmacokinetic changes due to the combination with lazertinib are not anticipated and a side-by-side comparison of PK data from CHRYSALIS and MARIPOSA shows that the PK of amivantamab was comparable when administered as monotherapy or in combination with lazertinib.

Regarding the popPK model, parameter estimates were overall comparable to those received in earlier procedures for amivantamab (EMEA/H/C/005454/0000 and EMEA/H/C/005454/0010). For the final model, outliers were reintroduced in a sensitivity analysis. Parameter estimates when reintroducing outliers were generally in agreement to the parameter estimates from the final dataset (i.e., excluding

outliers). The parameter K_m had a higher estimate when including outliers, even higher than in EMEA/H/C/005454/0010. However, given the apparent sensitivity of only one parameter (K_m), and the adequate robustness of the other model parameters, this is not further pursued.

The pcVPC showed an adequate model fit to the observations from the pivotal MARIPOSA study.

The primary objective of the popPK modelling was to understand if and how lazertinib affects amivantamab's exposure. Although no formal covariate testing was performed, a comparison of amivantamab exposure, with and without coadministration of lazertinib, based on post-hoc estimates was presented. Only minor, clinically irrelevant, differences were observed. Similarly, differences in exposure based on gender and body weight were deemed clinically insignificant. The current application included one patient with severe renal impairment (15 ≤ CrCl < 29 mL/min) and one patient with moderate hepatic impairment (1.5×ULN < total bilirubin ≤ 3×ULN and any AST). Although these data are very limited, there is currently no evidence to suggest that dose adjustments are required in these patients.

All subjects tested negative for treatment-emergent antibodies to amivantamab. Therefore, no conclusions can be drawn regarding the impact of antibodies on the PK, efficacy, and safety of amivantamab.

The exposure-response relationship for efficacy (PFS by BICR) showed no variation across a narrow exposure range in MARIPOSA. The exposure-safety profile for amivantamab in combination with lazertinib was slightly different than for amivantamab monotherapy. A small increase in toxicity with increasing exposure was observed for paronychia and stomatitis. This is explained by the MoA of EGFR inhibition which seems reasonable due to the synergistic behaviour of the combination treatment.

2.3.6. Conclusions on clinical pharmacology

Relevant PK changes due to the combination with lazertinib are not anticipated, and both descriptive PK and population PK modelling supports that the PK of amivantamab is comparable when administered as monotherapy or in combination with lazertinib in subjects with advanced non-small cell lung cancer with exon 19del or exon 21sub mutations. Overall, the clinical pharmacology data submitted support this extension of indication.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

The tolerability and efficacy of the combination of amivantamab and lazertinib was first evaluated in the CHRYSALIS study and was further evaluated in CHRYSALIS-2 study. The safety and efficacy data from participants with NSCLC treated with combination of amivantamab and lazertinib demonstrated that the combination therapy at the dose of 1050 mg (body weight <80 kg) or 1400 mg (body weight ≥80 kg) of amivantamab and 240 mg once daily lazertinib is tolerable, effective, and generally consistent with the safety profiles of the individual drug when administered as monotherapy. No DLTs were observed with the proposed combination therapy dose and regimen.

Thus, based on totality of PK, safety, and efficacy data the recommended dose for combination of amivantamab and lazertinib therapy, selected for the MARIPOSA study was 1050 mg (body weight <80 kg) or 1400 mg (body weight ≥80 kg) of amivantamab QW for first 4 weeks (Week 1 dose administered as a split dose on Day 1 and Day 2) and then Q2W thereafter with 240 mg lazertinib once daily.

2.4.2. Main study(ies)

The Phase 3 MARIPOSA study (73841937NSC3003) is pivotal to this application.

Table 6: Overview of the clinical studies

Study Number/Name Status SCE Data Cutoff	Study Design	Treatment Regimen	Study Population/Sample Size (Actual)
MARIPOSA 73841937NSC3003 Ongoing **11 August 2023**	A Phase 3, randomized study of amivantamab+lazertinib combination therapy versus osimertinib, versus lazertinib as first-line treatment in patients with EGFRm NSCLC. The SCE focuses on 3 arms:[a] amivantamab+lazertinib. osimertinib. lazertinib.	**amivantamab+lazertinib arm**: Amivantamab (1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg IV), once weekly for the first 4 weeks (split dose on Cycle 1 Days 1-2) and then once every 2 weeks) and lazertinib (240 mg orally, once daily). **osimertinib arm:** Double-blind treatment with single-agent osimertinib (80 mg orally, once daily). **lazertinib arm**: Double-blind treatment with single-agent lazertinib (240 mg orally, once daily).	**Study Population:** Treatment-naïve participants with EGFRm NSCLC. Randomization was stratified by: - mutation type (exon 19del vs exon 21 L858R) - race (Asian vs non-Asian) - history of brain metastasis (present vs absent) **Sample Size:** amivantamab+lazertinib arm: N=429 osimertinib arm: N=429 lazertinib arm: N=216
CHRYSALIS 61186372EDI1001[b] Ongoing **15 November 2022**	A Phase 1, first-in-human, open-label, dose escalation study in participants with advanced NSCLC. **Part 1 Dose Escalation – First-line Cohort:** Participants with EGFRm NSCLC receiving amivantamab+lazertinib at the RP2CD in a subset of Part 1, as first-line treatment.	**First-line Cohort (subset of Part 1):** Amivantamab: 1050 mg if <80 kg and 1400 mg if >80 kg IV (once weekly for the first 4 weeks [split dose on Cycle 1 Days 1-2] and then once every 2 weeks) and lazertinib (240 mg orally, once daily).	**First-line Cohort (subset of Part 1, n=20):** Treatment-naïve participants with EGFRm NSCLC receiving amivantamab+lazertinib.
YH25448-201 73841937NSC2001 (Part C: Yuhan sponsored) Completed. **8 January 2021**	A Phase 1/2, open-label, multicenter study to evaluate the safety, tolerability, pharmacokinetics and anti-tumor activity of lazertinib given orally to participants with EGFRm NSCLC. **Part C**: lazertinib - Dose extension phase.	**Part C First-line Cohort**: 240 mg lazertinib[c,d]	**Part C: First-line Cohort:** Treatment-naïve participants with EGFRm NSCLC. **Sample Size** Part C First-line lazertinib monotherapy: N=43
YH25448-301 (Yuhan sponsored) Ongoing. **29 July 2022**	A Phase 3, randomized, double-blind, multinational study to assess the efficacy and safety of lazertinib versus gefitinib as first-line treatment in patients with EGFRm NSCLC.	Lazertinib 240 mg orally once daily[e,f] or Gefitinib 250 mg orally once daily.	Treatment-naïve participants with EGFRm NSCLC. **Sample Size:** Lazertinib: N=196; Gefitinib: N=197

EGFR=epidermal growth factor receptor; EGFRm NSCLC=EGFR-mutated locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations; exon 19del=exon 19 deletion; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitors.

[a] Further details of the study design are presented in Section 1.6.1 and the CSR (Mod5.3.5.1/73841937NSC3003/Sec3.1).

[b] CHRYSALIS study consists of different cohorts in which participants either receive amivantamab+lazertinib combination therapy, or amivantamab and carboplatin/pemetrexed combination therapy. Only information regarding the First-line Cohort with treatment-naïve EGFRm NSCLC is included in this table and SCE. See CSR for details (1LE20/Mod5.3.5.2/61186372EDI1001-IA-15Nov2022/Sec3.1).

[c] YH25448-201 consists of different Parts in which participants received lazertinib monotherapy in a dose escalation, expansion or extension phase, or in Part D where participants outside Korea were evaluated. Only information regarding Part C (participants with EGFRm NSCLC receiving lazertinib as first-line treatment) is included in this table and SCE (see Section 1.6.3).

2.4.3. MARIPOSA Pivotal Study

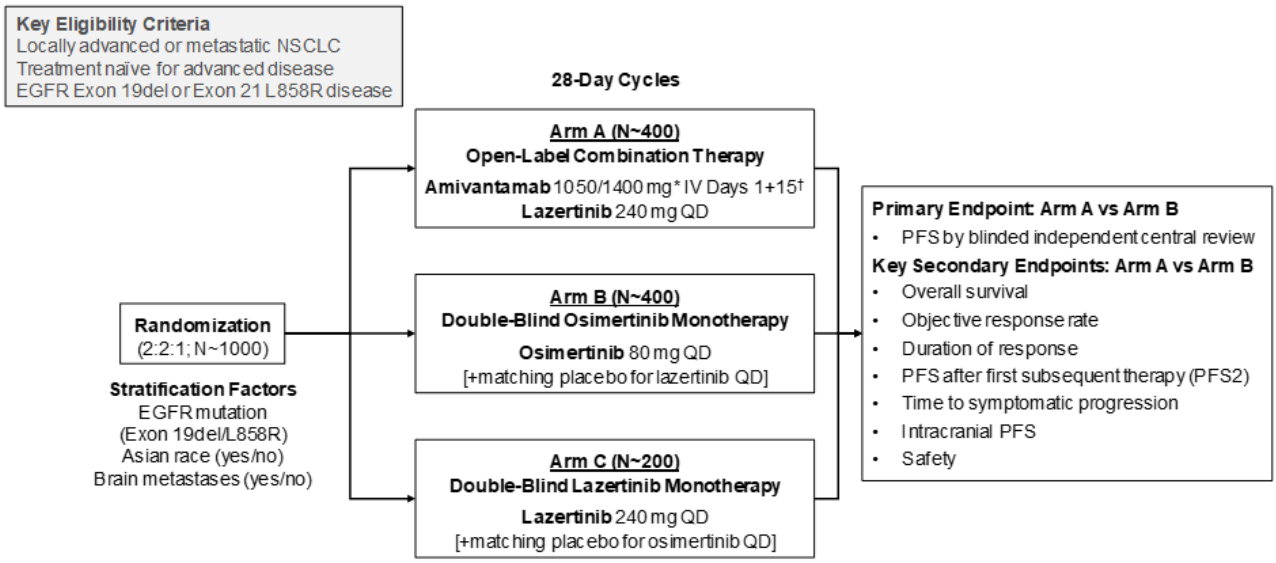
The pivotal study for the current application is the ongoing, multicentre, randomized three arms Phase 3 study multicentre to compare the efficacy and safety of amivantamab + lazertinib (Arm A) versus osimertinib monotherapy (Arm B) as first-line treatment in participants with EGFRm NSCLC.

The contribution of amivantamab to the activity of the combination is also being assessed by comparing the efficacy observed in the amivantamab + lazertinib arm (Arm A) with that in the lazertinib monotherapy arm (Arm C).

The CCO for the results presented occurred on 11 August 2023. An updated analysis based on CCO of 13 May 2024 was provided during the procedure.

2.4.3.1. Overall study design

Figure 5: MARIPOSA: Schematic Overview of the Study Design



EGFR=epidermal growth factor receptor; IV=intravenous; NSCLC=non-small cell lung cancer; PFS=progression-free survival; QD=once daily
Arm A=amivantamab+lazertinib arm; Arm B=osimertinib arm; Arm C=lazertinib arm
*Weight-based dosing: <80 kg/≥80 kg
†Cycle 1: Days 1-2 (split dose), 8, 15, 22; Cycles 2+: Days 1, 15

Methods

Study participants

Number of Participants (planned and analyzed): Approximately 1,000 eligible participants were to be randomly assigned to study treatment in a 2:2:1 ratio (amivantamab + lazertinib arm, osimertinib arm, and lazertinib arm, respectively).

Main Criteria for Inclusion and Exclusion

-Inclusion criteria

- be ≥18 years of age
- have newly diagnosed, histologically or cytologically confirmed, locally advanced or metastatic NSCLC that was treatment naïve and not amenable to curative therapy including surgical resection or chemoradiation
- have a tumour which harboured EGFR exon 19del or exon 21 L858R substitution, as detected by a United States (US) Food and Drug Administration (FDA)-approved or other validated test in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US) in accordance with site standard of care
- have at least 1 measurable lesion, according to RECIST v1.1 that had not been previously irradiated
- have adequate organ and bone marrow function and
- have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

Exclusion Criteria

Participants who had received any prior systemic treatment at any time for locally advanced Stage III or metastatic Stage IV disease, had symptomatic brain metastases, had a history of deep vein thrombosis or pulmonary embolism within 1 month prior to randomization or any of the following within 6 months prior to randomization: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, any acute coronary syndrome, congestive heart failure or had received any prior treatment with an EGFR TKI were excluded from participation in the study.

Treatments

Study Treatments:

Arm A: amivantamab + lazertinib arm (open-label combination therapy): amivantamab 1050 mg (1400 mg if body weight ≥80 kg) IV infusion in 28-day cycles, once weekly for the first 4 weeks (with a split dose on Days 1-2] and then once every 2 weeks, and 3 80-mg lazertinib tablets once daily.

Arm B: osimertinib arm (double-blind osimertinib monotherapy): 1 80-mg osimertinib capsule and 3 placebo tablets (for lazertinib) once daily.

Arm C: lazertinib arm (double-blind lazertinib monotherapy): 1 placebo capsule (for osimertinib) and 3 80-mg lazertinib tablets once daily.

Objectives and endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of the amivantamab and lazertinib combination, compared with osimertinib, in participants with EGFR mutation (Exon 19del or Exon 21 L858R substitution) positive, locally advanced or metastatic NSCLC	• PFS according to RECIST v1.1 by blinded independent central review
Secondary	
To further assess the clinical benefit achieved using the amivantamab and lazertinib combination compared with osimertinib in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• Overall survival • Objective response rate • Duration of response • PFS after first subsequent therapy • Time to symptomatic progression • Intracranial PFS
To evaluate the safety and tolerability of the amivantamab and lazertinib combination compared with osimertinib	• Incidence of severity of adverse events and clinical laboratory abnormalities, assessment of vital signs, and physical examination abnormalities
To evaluate pharmacokinetics or immunogenicity for amivantamab and pharmacokinetics for lazertinib and assess their relationship to selected endpoints (including but not limited to efficacy, safety, and/or patient-reported outcomes)	• Serum amivantamab and plasma lazertinib concentrations, and serum anti-amivantamab antibodies
To assess health-related quality of life and disease-related symptoms in participants treated with the amivantamab and lazertinib combination compared with osimertinib	• NSCLC-SAQ • EORTC-QLQ-C30
To assess the efficacy of the amivantamab and lazertinib combination, compared with lazertinib monotherapy, in participants with EGFR mutation positive, locally advanced or metastatic NSCLC	• PFS • Overall survival

EGFR=epidermal growth factor receptor; EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; NSCLC=non-small cell lung cancer; NSCLC-SAQ=Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours

The primary efficacy endpoint is PFS, defined as the time from randomization until the date of objective disease progression or death, whichever came first, based on blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.

The key secondary endpoint of overall survival (OS) was analysed hierarchically if the comparison for PFS showed statistical significance. Primary and secondary endpoints were type 1 error controlled for the comparison between the combination of amivantamab and lazertinib versus osimertinib for PFS and OS. The comparison of the combination of amivantamab and Lazertinib versus Lazertinib was aimed only to demonstrate the contribution of amivantamab to the activity of combination and was not hypothesis tested.

Sample size

The sample size calculation was based on the assumption that the combination therapy will result in a 27% reduction in the risk of either disease progression or death over the single agent osimertinib therapy (an HR of 0.73, prolongs the median PFS from 19 months to 26 months (Soria 2018). A total of 450 PFS events in Arm A and Arm B combined would provide approximately 90% power to detect a statistically significant difference between the 2 treatment arms with the stratified log-rank test (2-sided alpha=0.05).

When approximately 390 deaths (Arms A and B combined) have been observed from long-term survival follow-up, final analysis of OS would occur. This would provide approximately 80% power to detect a 25% reduction in the risk of death (an HR of 0.75, prolongs the median OS from 39 months to 52 months (Ramalingam 2020)) with a log-rank test at a 2-sided alpha of 0.05.

Randomisation

All participants were centrally randomized to study treatment (using an IWRS) in a 2:2:1 ratio (Arm A, B, and C respectively). The randomization was balanced using randomly permuted blocks and was stratified by mutation type (Exon 19del vs Exon 21 L858R), race (Asian vs non-Asian), and history of brain metastasis (present vs absent).

Blinding (masking)

The study treatment in arm A (combination of amivantamab and lazertinib) was open label due to the need for infusion.

The study treatments in arm B (osimertinib) and C (lazertinib) were double-blind.

Both amivantamab and lazertinib are new investigational products. Although the lazertinib treatment was masked in arm C, the study arm A (combination of amivantamab and lazertinib) was open label. Therefore, the inferential aspect of the study is considered as open label.

Statistical methods

The hypothesis testing of primary efficacy endpoint and key secondary efficacy endpoint was performed for the comparison between the combination of amivantamab and lazertinib therapy (Arm A) and single agent osimertinib (Arm B). The hypotheses were to be tested at an overall 2-sided significant level of 0.05.

The exact significance level for superiority was to be determined based on the actually observed number of events at the interim and final PFS and OS analyses, respectively, using the group sequential design with the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method (separately for PFS and for OS).

The comparison of the Arm A with the lazertinib monotherapy arm (Arm C) was performed to demonstrate the contribution of amivantamab to the activity of the combination using summary statistics of primary endpoint and secondary endpoints (PFS and OS) along with nominal p-values; there was no hypothesis testing for this comparison.

Analysis sets

Analysis set	Description
Full Analysis Set	All randomized participants, classified according to their assigned treatment arm regardless of the actual treatment received.
Safety	Randomized participants who receive at least 1 dose of any study treatment
Pharmacokinetics	Randomized participants who receive at least 1 dose of any study treatment and have at least 1 evaluable postbaseline concentration measurement.[a]
Biomarkers	Randomized participants who receive at least 1 dose of study treatment and have at least 1 biomarker measurement.

a. Participants may be removed from the estimation of certain pharmacokinetic parameters on an individual basis due to, for example, missing pharmacokinetic samples such that the pharmacokinetic parameters cannot be appropriately derived. These participants were identified at the time of the analyses along with their reason for removal.

Primary endpoint

The primary efficacy endpoint is PFS, defined as the time from randomization until the date of objective disease progression or death, whichever came first, based on blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Participants who have not progressed or have not died at the time of analysis will be censored at their last evaluable RECIST v1.1 assessment date. If the participant progresses or dies after 2 or more missed disease assessments, the participant will be censored at the time of the last evaluable RECIST v1.1 assessment. If the participant has no evaluable visits or does not have baseline data, the participant will be censored at Day 1 (randomization) unless the participant dies within 2 visits of baseline.

Key censoring rules for PFS are summarized below.

Situation	Date of Censoring for PFS
No evaluable baseline or postbaseline disease assessment	Censored at the date of randomization
Lost to follow-up or withdraw from study	Censored at the date of last evaluable disease assessment
No documented disease progression or death	Censored at the date of last evaluable disease assessment
Documented disease progression or death after 2 or more consecutive missed/unevaluable disease assessments*	Censored at the date of last evaluable disease assessment before the missed/unevaluable visits

*If no evaluable disease assessment before the consecutive missed/unevaluable visits, participants will be censored at the date of randomization

Primary analysis

The PFS was analyzed using a log-rank test stratified by mutation type, race, and history of brain metastasis, based on the Full Analysis Set. Hazard ratio and its 95% confidence interval were estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable.

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Study treatment discontinuation due to any reason	Treatment Policy strategy: use time to disease progression or death, regardless of whether or not study treatment discontinuation had occurred
Study treatment switching to other anticancer therapy	Treatment Policy strategy: use time to disease progression or death, regardless of whether or not started subsequent anticancer therapies
Death	Composite Variable strategy: death being a component of the variable

For assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis on pre-specified subgroups was conducted.

Sensitivity analyses conducted to evaluate the robustness of the primary analysis of PFS included analysis using unstratified log-rank test. The proportional hazards assumption was examined by plotting log(-log[estimated survival distribution function]) against log(survival time). In addition, a treatment by
logarithm-transformed time interaction term was added into the primary Cox model and tested. A p -value>0.05 for the interaction term was interpreted as no statistical evidence against the proportional hazard assumption.

Supplementary analyses were performed using progression or death prior to the start of the subsequent anticancer therapy as events. Participants who have not progressed or have not died before the initiation of subsequent therapy were censored at the date of the last evaluable disease assessment prior to the start of subsequent therapy. Additional supplementary analysis was performed using all progression or death, whichever occur first, as event regardless missed/unevaluable disease assessment for 2 or more consecutive visits.

Secondary analyses

Overall Survival (OS)

OS was defined as the time from the date of randomization until the date of death due to 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. Treatment Policy strategy was used for time to death, regardless of switching to other anticancer therapy.

The OS analysis was carried out using the similar methodology and model as for the primary analysis of PFS in the Full Analysis Set. A subgroup analysis on the pre-specified subgroups was conducted. Sensitivity analysis using unstratified log-rank test was performed.

Supplementary analysis was performed using Inverse Probability of Censoring Weighting (IPCW) to adjust for confounding from treatment crossover. The weights to reduce the bias were estimated from baseline covariates and time-dependent covariates predictive of treatment crossover such as baseline disease burden, occurrence of serious adverse event before crossover, based on a logistic regression model. Hazard ratio and its 95% confidence interval were estimated based on a Cox regression analysis with IPCW.

Objective Response Rate (ORR)

ORR was defined as the proportion of participants who achieve either a complete response (CR) or partial response (PR), as defined by BICR using RECIST v1.1. Data obtained up until progression or last evaluable disease assessment in the absence of progression would have been included in the assessment of ORR. However, any CR or PR, which occurred after a further anticancer therapy was received, would have not been included in the numerator for the ORR calculation. Participants who do not have a tumor response assessment for any reason would have been considered non-responders and will be included in the denominator when calculating the response rate.

Duration of Response (DoR)

DoR was defined as the time from the date of first documented response (PR or CR) until the date of documented progression or death, whichever comes first. The end of response should have coincided with the date of progression or death from any cause used for the PFS endpoint. If a participant did not progress following a response, then his/her duration of response would use the PFS censoring time. A Kaplan-Meier plot for duration of response and median duration of response with 95% confidence interval was presented by treatment group.

Progression-free Survival After the First Subsequent Therapy (PFS2)

The PFS2 was defined as the time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first. Any deaths were considered as PFS2 events. Participants alive and for whom a second disease progression has not been observed were censored at the last time known to be alive and without a second disease progression (i.e., last disease assessment).

Situation	**Date of Censoring for PFS2**
No postbaseline disease assessment	Randomization
Disease progression on study treatment and no subsequent therapy	The date of last disease assessment
Two or more subsequent therapies without a progression	The last date of disease assessment prior to the start of 2nd line of subsequent therapy
Treated beyond progression	The last date of disease assessment

Time to Symptomatic Progression (TTSP)

TTSP was defined as the time from randomization to documentation in the eCRF of any of the following (whichever occurs earlier): onset of new symptoms or symptom worsening that was considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms, or death, whichever comes first. The TTSP for a participant who did not experience any of these events would have been censored on the date on which the

participant was last known to be event-free. TTSP was analyzed using the similar method as the primary analysis of PFS.

Intracranial PFS was defined as the time from randomization until the date of objective intracranial disease progression or death, whichever comes first, based on BICR using RECIST v1.1 in participants who had a history of brain metastasis at screening in the Full analysis set. Participants who have not progressed intracranially or 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. Intracranial PFS was analyzed using the similar method as the primary analysis of PFS.

Interim analyses

Planned

Two interim analyses for PFS were planned for this study. An Independent Data Monitoring Committee (IDMC) was commissioned for the study.

The first interim analysis with the main purpose of futility assessment was to be conducted when approximately 120 PFS events from Arms A and B combined have occurred (27% of the planned events). A nominal 2-sided alpha of 0.00001 was allocated. If the hazard ratio from a stratified Cox proportional-hazard model for the combination therapy versus osimertinib was ≥1.0, the study could be stopped for futility.

The second interim analysis of PFS was to be performed to assess the superiority of the combination therapy versus osimertinib, when approximately 280 PFS events from Arms A and B combined (approximately 350 PFS events overall, i.e., in all treatments arms combined) have occurred. The significance level for superiority was determined based on the observed number of PFS events at the interim analysis, using the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method. Assuming 280 PFS events observed at the interim, the 2-sided alpha to be spent at the interim and final PFS analyses were 0.0090, and 0.0472, respectively.

One interim analysis for OS was planned at the time of the final analysis for PFS, when approximately 270 deaths from Arms A and B combined were anticipated (69% of the 390 events planned). The superiority for OS was to be tested with a total 2-sided alpha of 0.05 only if statistical significance for PFS is achieved. Assuming 270 deaths observed at the interim from Arms A and B combined, based on the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method, the 2-sided alpha to be spent at the interim and final OS analyses were 0.0140 and 0.0457, respectively.

Performed

One futility (non-binding) analysis was performed. The IDMC had recommended that the study continue without change after the futility analysis.

At the time of the interim PFS analysis (CCO of 15 January 2023), there were 321 PFS events by BICR observed from the amivantamab + lazertinib and osimertinib arms combined. After reviewing the data on 31 March 2023, the IDMC notified the Sponsor Committee that the efficacy stopping criteria had been met for PFS (HR=0.75 [95% CI: 0.60, 0.93], p=0.0097 [less than the 2-sided significance level criterion of 0.0159 based on the O'Brien-Fleming stopping boundary]), in favor of the combination of amivantamab and lazertinib. Given that the study continued to the final analysis after the efficacy boundary was crossed at an earlier interim analysis, the statistical significance for the primary endpoint (PFS) can be established if the final p-value is smaller than the nominal level (2-sided 0.05) without any alpha penalty for the interim look (Hampson 2013).

Multiplicity

To strongly control Type I error rate at 0.05 for the study, a hierarchical testing approach for the primary endpoint (PFS) and key secondary endpoint (OS) was used. The comparison between the amivantamab and lazertinib combination versus osimertinib for OS was to be conducted only if the comparison for PFS showed statistical significance.

The significance level for superiority at the interim and final analysis of PFS and OS, respectively, was to be determined based on the observed number of events using the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method.

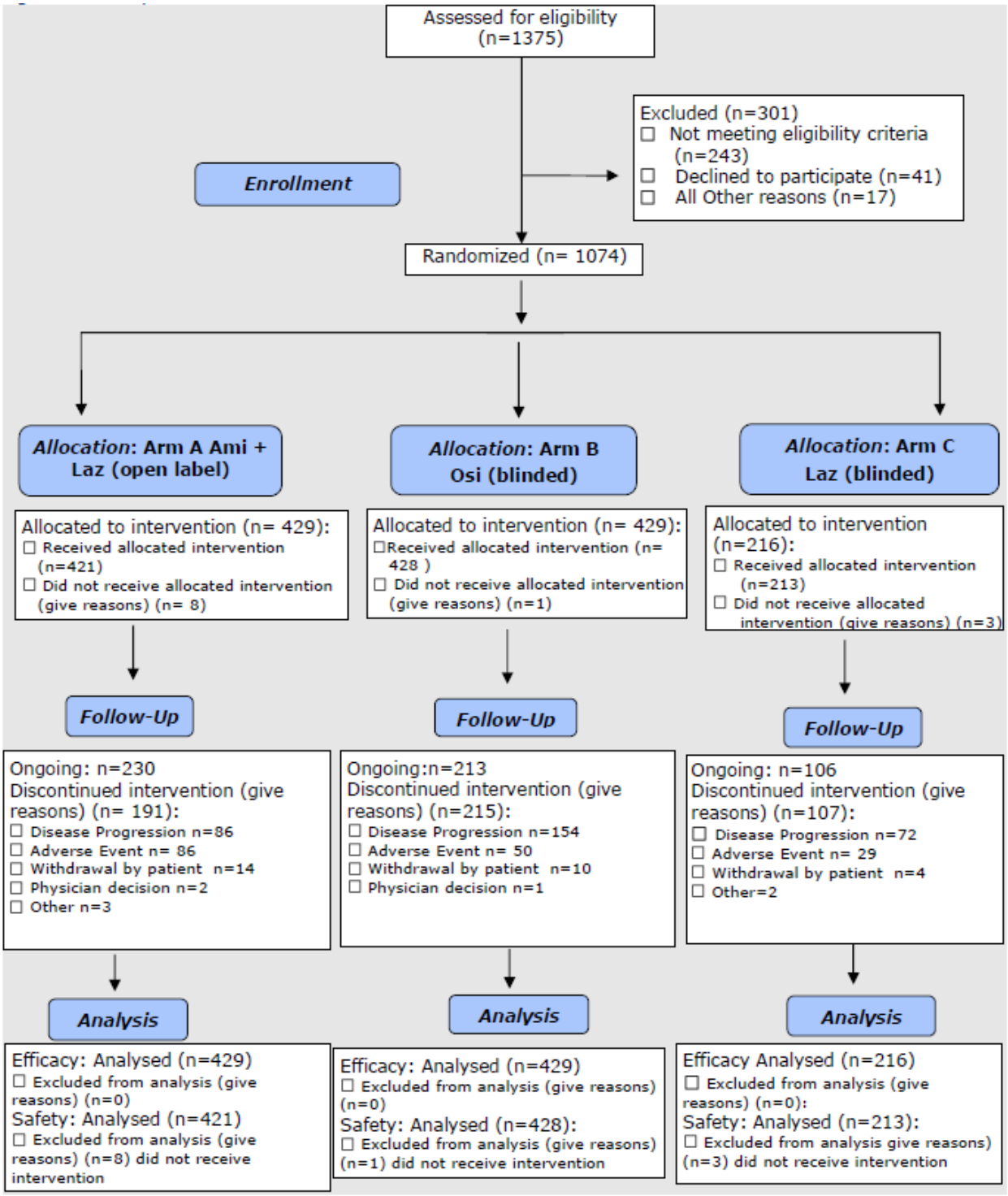
Only comparison between the amivantamab and lazertinib combination versus osimertinib was controlled for multiplicity. The comparison of the combination of amivantamab and lazertinib versus lazertinib was not included in the hierarchical testing procedure.

Changes in the SAP

The statistical analysis plan (SAP) was dated February 11th 2021. The primary PFS analysis was reported in 2023. The SAP has two addenda from 2023 that clarified definition of TTSP and the analysis set of intracranial PFS. Also, additional details on PRO analyses were provided.

Results

Participant flow



Recruitment

Conduct of the study

Study period: The study was initiated on 02 December 2020 (ie, the date that the first participant was screened) and is currently ongoing. This clinical study report describes data through a clinical cut-off date (CCO) of 03 May 2023 (ie, the date of the last observation recorded as part of the database for the final
analysis of the primary endpoint).

Study initiation date: 16 October 2020 (date first participant was screened)

Data cut-off date, primary analysis, final for PFS: 11 August 2023

Study centres: This study was conducted at 262 centers, of which 219 centers enrolled participants in Argentina, Australia, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, Poland, Portugal, Russian Federation, South Korea, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, and the United States (including Puerto Rico)

Disposition of Participants

Of the 1074 participants who entered the study, 429 were randomized to the amivantamab + lazertinib arm, 429 to the osimertinib arm, and 216 to the lazertinib arm. A total of 12 participants (1.1%) who were randomized did not receive any dose of study treatment (8 participants [1.9%] in the amivantamab + lazertinib arm, 1 participant [0.2%] in the osimertinib arm, and 3 participants [1.4%] in the lazertinib arm). 1062 participants (98.9%) (421 [98.1%] in the amivantamab + lazertinib arm, 428 [99.8%] in the osimertinib arm, and 213 [98.6%] in the lazertinib arm) received at least 1 dose of study treatment.

A summary of study disposition is provided below:

Table 7: Study Disposition; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Subjects randomized but not treated	8 (1.9%)	1 (0.2%)	3 (1.4%)	12 (1.1%)
Subjects treated	421 (98.1%)	428 (99.8%)	213 (98.6%)	1062 (98.9%)
Subjects still on the study	313 (73.0%)	297 (69.2%)	149 (69.0%)	759 (70.7%)
Completed study participation [a]	94 (21.9%)	113 (26.3%)	54 (25.0%)	261 (24.3%)
Subjects discontinued the study	22 (5.1%)	19 (4.4%)	13 (6.0%)	54 (5.0%)
Reason for termination				
Withdrawal by subject	19 (4.4%)	18 (4.2%)	13 (6.0%)	50 (4.7%)
Lost to follow-up	3 (0.7%)	1 (0.2%)	0	4 (0.4%)

[a] Completed: if a subject had died before the end of study

At the time of the CCO, 513 participants (48.3%) had discontinued all study treatment:

Table 8: Treatment Disposition; Safety Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Safety	421	428	213	1062
Subjects ongoing any study agent	230 (54.6%)	213 (49.8%)	106 (49.8%)	549 (51.7%)
Discontinued all study agents	191 (45.4%)	215 (50.2%)	107 (50.2%)	513 (48.3%)
Reason for discontinuation of last study agent				
Progressive disease	86 (20.4%)	154 (36.0%)	72 (33.8%)	312 (29.4%)
Adverse event	86 (20.4%)	50 (11.7%)	29 (13.6%)	165 (15.5%)
Adverse event – COVID-19 related	2 (0.5%)	3 (0.7%)	0	5 (0.5%)
Subject refused further study treatment	14 (3.3%)	10 (2.3%)	4 (1.9%)	28 (2.6%)
Physician decision	2 (0.5%)	1 (0.2%)	0	3 (0.3%)
Non-compliance with study drug	1 (0.2%)	0	1 (0.5%)	2 (0.2%)
Lost to follow-up	1 (0.2%)	0	0	1 (0.1%)
Other	1 (0.2%)	0	1 (0.5%)	2 (0.2%)

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

Protocol amendments

Prior to the CCO of 11 August 2023, there were 3 global amendments to the original protocol dated 05 June 2020, as well as several country/territory-specific amendments to address health authority requests.

Key changes implemented with global protocol amendments:

Amendment Number (Date)	Key Changes
Amendment 1 (22 Apr 2021)	• The pregnancy testing requirements were clarified to ensure pregnant women would not receive study treatment. • Clarifications were made to the timing of study procedures to ensure compliance. • Inclusion and exclusion criteria were clarified to ensure only the intended target population was enrolled. • Guidance for the use of concomitant medications that induce, inhibit, or are substrates of CYP3A4/5 was revised based on emerging data regarding the interaction between study treatment and potential concomitant medications. • Several clarifications were made to facilitate study conduct including but not limited to guidance on retreatment at a reduced dose and treatment discontinuation, and clarification of the requirements for collection of tissue samples. • The sponsor's commitment to provide participants with continued access to investigational drug after study closure was added. • The standalone COVID-19 appendix was updated to specify that participants will not be excluded from the study for having received non-live vaccines that are either approved or authorized for emergency use (eg, COVID-19) by local health authorities.

Amendment Number (Date)	Key Changes
Amendment 2 (23 Sep 2021)	• Clarifications were made to tumor imaging and brain imaging assessments. • Additional information was provided on the amivantamab infusion and on IRRs to provide guidance in case of infusion interruption. • Information for paresthesia and pneumonitis management was added based on emerging data. • Information was added on CT and MRI assessment requirements.
Amendment 3 (22 August 2022)	• Information regarding the AESI of VTE events, as well as associated measures for monitoring and prophylaxis of these events, were added. • Clarifications were made in the schedule of assessments and visits and timing of PK sampling. • Clarifications were made to the reporting of symptomatic progression during the follow up period.

AESI=adverse event of special interest; CT=computed tomography; IRR=infusion-related reaction; MRI=magnetic resonance imaging; PK=pharmacokinetic(s); VTE=venous thromboembolic (events)

Amendment 3 (22 August 2022)

Overall Rationale for the Amendment: To implement the adverse event of special interest of venous thromboembolic (VTE) events, as well as associated measures for monitoring and prophylaxis of these events, and to align the protocol with the information provided in Investigator's Brochure for the safety of the participants. This amendment also serves to provide clarity on the schedule of assessments and visits, timing of pharmacokinetic (PK) sampling, the reporting of symptomatic progression during the follow up period, and the documentation of ophthalmology examination results and how to report overdose in the electronic case report form (eCRF).

Major protocol deviations

An overview of the major protocol deviations is provided in Table 9.

Table 9: Summary of Subjects with Major Protocol Deviations; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Subjects with major protocol deviations	23 (5.4%)	26 (6.1%)	14 (6.5%)	63 (5.9%)
Developed withdrawal criteria but not withdrawn	2 (0.5%)	0	1 (0.5%)	3 (0.3%)
Entered but did not satisfy criteria	9 (2.1%)	15 (3.5%)	12 (5.6%)	36 (3.4%)
Received a disallowed concomitant treatment	3 (0.7%)	2 (0.5%)	1 (0.5%)	6 (0.6%)
Received wrong treatment or incorrect dose	6 (1.4%)	1 (0.2%)	0	7 (0.7%)
Other	8 (1.9%)	9 (2.1%)	0	17 (1.6%)
Other - Regional crisis	0	0	0	0
Other - COVID-19	1 (0.2%)	2 (0.5%)	0	3 (0.3%)

Note: Subjects may appear in more than one category.

[tsidev01.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsidev01.sas] 25SEP2023, 19:20

Baseline data

Numbers analysed

The number of participants included in each analysis set is provided in Table 10. All 1074 participants randomized in the study were included in the Full Analysis Set, which was used for the demographics,

baseline disease characteristics, and efficacy analyses. A total of 1062 participants received at least 1 dose of study treatment and were therefore included in the Safety Analyses Set. For the amivantamab + lazertinib arm, the PK Analysis Set included 420 participants and the Immunogenicity Analysis Set included 398 participants.

Table 10: Number of Subjects in Each Analysis Set; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Safety analysis set	421 (98.1%)	428 (99.8%)	213 (98.6%)	1062 (98.9%)

[tsidem03.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsidem03.sas] 25SEP2023, 19:20

Demographic and Other Baseline Characteristics

Stratification factors included mutation type (exon 19del versus L858R), race (Asian versus non-Asian), and history of brain metastasis (present versus absent).

Table 11: Summary of Demographics and Baseline Characteristics; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Age, years				
N	429	429	216	1074
Mean (SD)	62.7 (10.63)	61.9 (11.52)	61.3 (10.69)	62.1 (11.01)
Median	64.0	63.0	63.0	63.0
Range	(25; 88)	(28; 88)	(31; 87)	(25; 88)
18-25	1 (0.2%)	0	0	1 (0.1%)
26-50	52 (12.1%)	71 (16.6%)	42 (19.4%)	165 (15.4%)
51-64	182 (42.4%)	166 (38.7%)	77 (35.6%)	425 (39.6%)
65-74	143 (33.3%)	139 (32.4%)	79 (36.6%)	361 (33.6%)
>=75	51 (11.9%)	53 (12.4%)	18 (8.3%)	122 (11.4%)
Age Group 1, years				
N	429	429	216	1074
<65	235 (54.8%)	237 (55.2%)	119 (55.1%)	591 (55.0%)
>=65	194 (45.2%)	192 (44.8%)	97 (44.9%)	483 (45.0%)
Age Group 2, years				
N	429	429	216	1074
<75	378 (88.1%)	376 (87.6%)	198 (91.7%)	952 (88.6%)
>=75	51 (11.9%)	53 (12.4%)	18 (8.3%)	122 (11.4%)
Sex				
N	429	429	216	1074
Female	275 (64.1%)	251 (58.5%)	136 (63.0%)	662 (61.6%)
Male	154 (35.9%)	178 (41.5%)	80 (37.0%)	412 (38.4%)
Race [a]				
N	429	429	216	1074
American Indian or Alaska Native	7 (1.6%)	7 (1.6%)	4 (1.9%)	18 (1.7%)
Asian	250 (58.3%)	251 (58.5%)	128 (59.3%)	629 (58.6%)
Black or African American	4 (0.9%)	3 (0.7%)	4 (1.9%)	11 (1.0%)
Native Hawaiian or other Pacific Islander	1 (0.2%)	1 (0.2%)	0	2 (0.2%)
White	164 (38.2%)	165 (38.5%)	79 (36.6%)	408 (38.0%)
Multiple	1 (0.2%)	1 (0.2%)	0	2 (0.2%)
Unknown	2 (0.5%)	1 (0.2%)	1 (0.5%)	4 (0.4%)
Ethnicity				
N	429	429	216	1074
Hispanic or Latino	56 (13.1%)	45 (10.5%)	24 (11.1%)	125 (11.6%)
Not Hispanic or Latino	371 (86.5%)	382 (89.0%)	190 (88.0%)	943 (87.8%)
Unknown	0	1 (0.2%)	1 (0.5%)	2 (0.2%)
Not Reported	2 (0.5%)	1 (0.2%)	1 (0.5%)	4 (0.4%)
Weight, kg				
N	429	429	216	1074
Mean (SD)	64.4 (13.43)	63.8 (13.44)	63.1 (13.22)	63.9 (13.39)
Median	62.5	62.4	60.5	62.1
Range	(32; 118)	(35; 109)	(41; 118)	(32; 118)
<80 kg	376 (87.6%)	368 (85.8%)	197 (91.2%)	941 (87.6%)
>=80 kg	53 (12.4%)	61 (14.2%)	19 (8.8%)	133 (12.4%)
Height, cm				
N	429	429	216	1074
Mean (SD)	161.3 (8.73)	162.1 (8.98)	163.1 (9.48)	162.0 (9.00)
Median	160.0	162.0	162.0	161.5
Range	(140; 189)	(141; 192)	(138; 191)	(138; 192)
Body mass index, kg/m^2				
N	429	429	216	1074
Mean (SD)	24.65 (4.265)	24.15 (4.047)	23.67 (3.982)	24.26 (4.135)
Median	24.09	23.66	23.03	23.69
Range	(14.2; 39.6)	(15.6; 42.9)	(16.2; 36.4)	(14.2; 42.9)
Baseline ECOG score				
N	429	429	216	1074
0	141 (32.9%)	149 (34.7%)	76 (35.2%)	366 (34.1%)
1	288 (67.1%)	280 (65.3%)	140 (64.8%)	708 (65.9%)
History of smoking				
N	429	429	216	1074
Yes	130 (30.3%)	134 (31.2%)	73 (33.8%)	337 (31.4%)
Current	13 (3.0%)	13 (3.0%)	6 (2.8%)	32 (3.0%)
Former	117 (27.3%)	121 (28.2%)	67 (31.0%)	305 (28.4%)
No	299 (69.7%)	295 (68.8%)	143 (66.2%)	737 (68.6%)

Key: ECOG = Eastern Cooperative Oncology Group
[a] Based on investigator reported data recorded on eCRF page.
Note: N's for each parameter reflect non-missing values.

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
History of brain metastasis [a]				
N	429	429	216	1074
Present	178 (41.5%)	172 (40.1%)	86 (39.8%)	436 (40.6%)
Absent	251 (58.5%)	257 (59.9%)	130 (60.2%)	638 (59.4%)
Mutation Type [a]				
N	429	429	216	1074
Exon 19del	258 (60.1%)	257 (59.9%)	131 (60.6%)	646 (60.1%)
Exon 21 L858R	172 (40.1%)	172 (40.1%)	85 (39.4%)	429 (39.9%)
Initial diagnosis NSCLC subtype				
N	429	429	216	1074
Adenocarcinoma	417 (97.2%)	415 (96.7%)	212 (98.1%)	1044 (97.2%)
Large cell carcinoma	3 (0.7%)	0	0	3 (0.3%)
Squamous cell carcinoma	6 (1.4%)	5 (1.2%)	2 (0.9%)	13 (1.2%)
Other	2 (0.5%)	9 (2.1%)	2 (0.9%)	13 (1.2%)
Not Reported	1 (0.2%)	0	0	1 (0.1%)
Histology grade at initial diagnosis				
N	429	429	216	1074
Poorly differentiated	61 (14.2%)	61 (14.2%)	32 (14.8%)	154 (14.3%)
Moderately differentiated	90 (21.0%)	108 (25.2%)	42 (19.4%)	240 (22.3%)
Well differentiated	46 (10.7%)	50 (11.7%)	19 (8.8%)	115 (10.7%)
Other	14 (3.3%)	11 (2.6%)	11 (5.1%)	36 (3.4%)
Not Reported	218 (50.8%)	199 (46.4%)	112 (51.9%)	529 (49.3%)
Cancer stage at initial diagnosis				
N	429	429	216	1074
IA	10 (2.3%)	9 (2.1%)	5 (2.3%)	24 (2.2%)
IB	12 (2.8%)	8 (1.9%)	2 (0.9%)	22 (2.0%)
IIA	2 (0.5%)	2 (0.5%)	2 (0.9%)	6 (0.6%)
IIB	5 (1.2%)	3 (0.7%)	0	8 (0.7%)
IIIA	3 (0.7%)	6 (1.4%)	0	9 (0.8%)
IIIB	14 (3.3%)	10 (2.3%)	3 (1.4%)	27 (2.5%)
IIIC	4 (0.9%)	5 (1.2%)	2 (0.9%)	11 (1.0%)
IVA	146 (34.0%)	150 (35.0%)	81 (37.5%)	377 (35.1%)
IVB	233 (54.3%)	236 (55.0%)	121 (56.0%)	590 (54.9%)
Location of metastasis at screening [b]				
N	421	424	216	1061
Bone	206 (48.9%)	180 (42.5%)	90 (41.7%)	476 (44.9%)
Liver	64 (15.2%)	72 (17.0%)	32 (14.8%)	168 (15.8%)
Brain	178 (42.3%)	172 (40.6%)	86 (39.8%)	436 (41.1%)
Lymph Node	282 (67.0%)	289 (68.2%)	144 (66.7%)	715 (67.4%)
Adrenal Gland	41 (9.7%)	45 (10.6%)	19 (8.8%)	105 (9.9%)
Lung	257 (61.0%)	280 (66.0%)	135 (62.5%)	672 (63.3%)
Other	14 (3.3%)	16 (3.8%)	8 (3.7%)	38 (3.6%)
Histology grade at screening				
N	429	429	216	1074
Poorly differentiated	59 (13.8%)	66 (15.4%)	36 (16.7%)	161 (15.0%)
Moderately differentiated	86 (20.0%)	111 (25.9%)	40 (18.5%)	237 (22.1%)
Well differentiated	46 (10.7%)	49 (11.4%)	19 (8.8%)	114 (10.6%)
Other	18 (4.2%)	11 (2.6%)	13 (6.0%)	42 (3.9%)
Not Reported	220 (51.3%)	192 (44.8%)	108 (50.0%)	520 (48.4%)
Cancer stage at screening				
N	429	429	216	1074
IIIA	1 (0.2%)	3 (0.7%)	0	4 (0.4%)
IIIB	11 (2.6%)	5 (1.2%)	2 (0.9%)	18 (1.7%)
IIIC	3 (0.7%)	3 (0.7%)	2 (0.9%)	8 (0.7%)
IVA	131 (30.5%)	119 (27.7%)	66 (30.6%)	316 (29.4%)
IVB	283 (66.0%)	299 (69.7%)	146 (67.6%)	728 (67.8%)
Time since initial lung cancer diagnosis (months) [c]				
N	429	429	216	1074
Mean (SD)	4.785 (14.8980)	4.614 (15.2386)	5.024 (22.1585)	4.765 (16.7202)
Median	1.511	1.413	1.347	1.413
Range	(0.16; 207.87)	(0.26; 162.79)	(0.23; 197.26)	(0.16; 207.87)
Time since metastatic disease diagnosis (months) [c]				
N	421	424	216	1061
Mean (SD)	1.669 (1.8189)	1.491 (1.1084)	1.443 (1.1156)	1.552 (1.4363)
Median	1.314	1.248	1.166	1.248
Range	(0.16; 24.08)	(0.13; 11.66)	(0.20; 9.17)	(0.13; 24.08)

Key: NSCLC = non-small cell lung cancer
[a] Based on investigator reported data recorded on eCRF page.
[b] Subjects can be counted in more than one category.
[c] Relative to the date of randomization.

Prior Therapies

A summary of prior therapies for lung cancer is presented in *Table 12*. The most common prior systemic therapies, all administered in the adjuvant/neo-adjuvant setting, were platinum doublets cisplatin + vinorelbine (8 participants [0.7%]), carboplatin + paclitaxel (3 participants [0.3%]), and cisplatin + pemetrexed (3 participants [0.3%]).

Table 12: Prior Therapies for Lung Cancer; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Total number of subjects with any prior therapies for lung cancer	112 (26.1%)	104 (24.2%)	41 (19.0%)	257 (23.9%)
Prior systemic therapy	8 (1.9%)	10 (2.3%)	3 (1.4%)	21 (2.0%)
Prior radiotherapy	73 (17.0%)	65 (15.2%)	30 (13.9%)	168 (15.6%)
Prior cancer-related surgery	53 (12.4%)	49 (11.4%)	16 (7.4%)	118 (11.0%)
Number of prior lines of systemic therapy				
0	421 (98.1%)	419 (97.7%)	213 (98.6%)	1053 (98.0%)
1	8 (1.9%)	10 (2.3%)	3 (1.4%)	21 (2.0%)

Biomarker analyses

According to the inclusion criterion, the selected patients must have NSCLC tumors that harbors EGFR exon 19del or exon 21 L858R substitution, as detected by an FDA-approved or other validated test in a CLIA certified laboratory (sites in the US) or an accredited local laboratory (sites outside of the US) in accordance with site standard of care.

Table 13: List of Local CE-marked Tests Used in the MARIPOSA Study

	Test Name
	AmoyDX® Pan Lung Cancer PCR Panel
	Biocartis Idaylla™
	Roche cobas® EGFR Mutation Test V2
	Diatech EasyPGX
	Qiagen *therascreen* EGFR RGQ PCR KIT
	EntroGene® EGFR Mutation Analysis Kit
	FoundationOne® CDx
	Guardant360® CDx
	Illumina TruSight™ Comprehensive (EU)
	ThermoFisher Ion Torrent Oncomine Dx Target Test
	OncoDEEP
	Roche Real-time PCR Instrument LC480

Concordance between local laboratory and central testing of EGFR exon 19 deletions or exon 21 L858R substitution mutations and central testing:

Of the 871 participants enrolled to MARIPOSA at sites outside of China, 849 participants had a valid central test result (676 via tissue testing and 173 via plasma testing in place of a missing tissue result). Central cobas tissue testing (using the cobas® EGFR Mutation Test v2) was concordant with

local testing in 96.3% of the samples with a valid cobas tissue test result. Central testing was concordant with local testing in 74.0% of the samples with a valid central Guardant plasma test (using Guardant 360® CDx) when no valid central tissue test was available.

Exposure

The median duration of treatment in the amivantamab + lazertinib arm was 18.50 months (15.24 months [range: 0.0 to 31.3] for amivantamab and 18.50 months [range: 0.2 to 31.4] for lazertinib). The median duration of treatment was 18.00 months (range: 0.2 to 32.7) in the osimertinib arm and 17.05 months (range: 0.4 to 32.1) in the lazertinib arm. Participants in the amivantamab + lazertinib arm received a median of 16.0 cycles of amivantamab, with 2 participants receiving 35 cycles (the largest number of cycles administered at the time of CCO).

The median relative dose intensity, which is a ratio of actual versus prescribed doses (prescribed dose includes planned interruptions), in the amivantamab + lazertinib arm was 100.00% (range: 2.0 to 100.0) for amivantamab and 96.0% (range: 32.7 to 100.8) for lazertinib. In the osimertinib arm, median relative dose intensity was 99.87% (range: 66.7 to 100.3) and in the lazertinib arm was 99.79% (range: 74.5 to 100.8).

Consistent with prior studies in this study population, treatment beyond disease progression was common, indicating that there is a benefit to targeted therapy beyond RECIST PD (Le 2018; Mu 2019). The median duration of study treatment greater than 28 days beyond disease progression as assessed by investigator was 3.94 months (range: 1.0 to 19.9) in the amivantamab + lazertinib arm (78 participants of 147 with PD [53.1%]), 3.09 months (range: 1.0 to 24.7) in the osimertinib arm (103 participants of 203 with PD [50.7%]), and 3.94 months (range: 1.0 to 19.2) in the lazertinib arm (51 participants of 104 with PD [49.0%]).

Outcomes and estimation

Primary Endpoint: Progression Free Survival by BICR

As of the CCO of 11 August 2023, a total of 565 BICR-assessed PFS events had been observed from all 3 arms combined), which met the requirement for the primary analysis of PFS as pre-specified in the SAP.

At a median follow-up of 22.01 months, 192 participants (44.8%) in the amivantamab + lazertinib arm and 252 participants (58.7%) in the osimertinib arm had BICR assessed disease progression or had died.

Table 14: Summary of Progression-Free Survival – Primary Analysis – Stratified Analysis – BICR; Full Analysis Set (Study 73841937NSC3003)

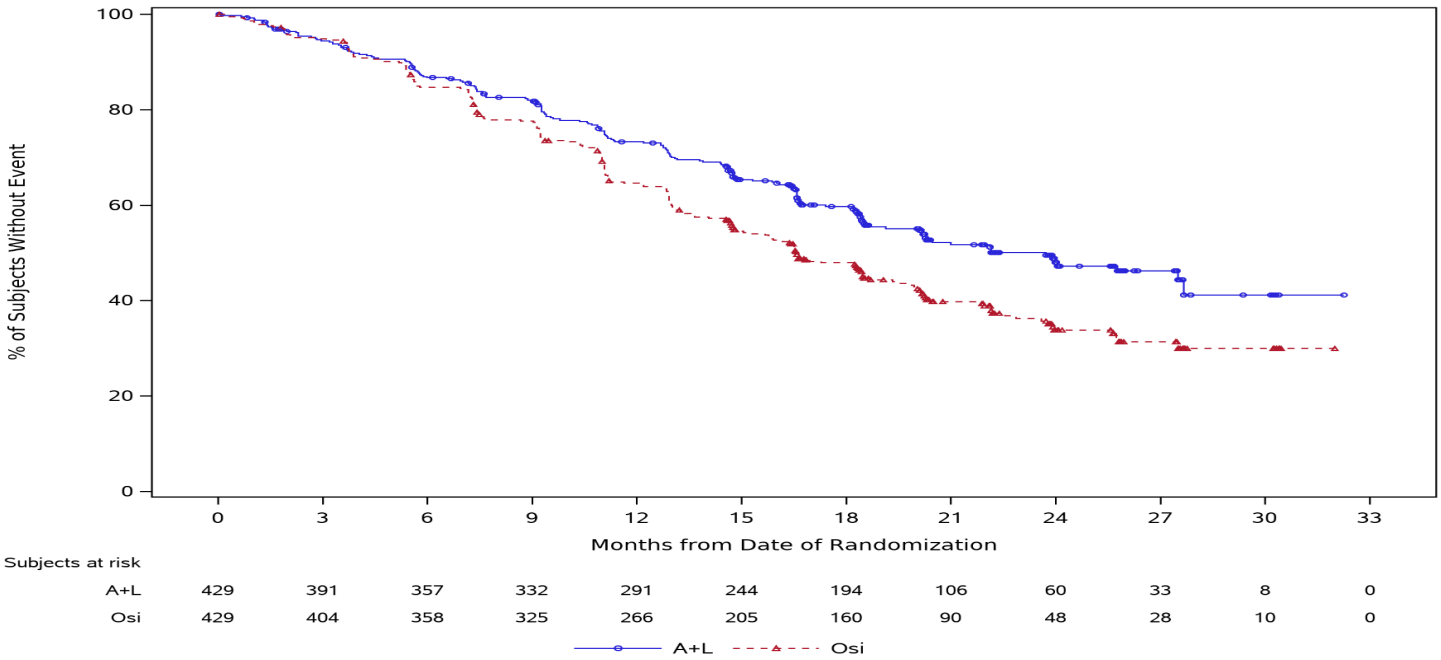
	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	192 (44.8%)	252 (58.7%)	121 (56.0%)
Censored	237 (55.2%)	177 (41.3%)	95 (44.0%)
Time to event (months)			
25th percentile (95% CI)	11.07 (9.36, 12.91)	9.23 (7.49, 10.94)	9.23 (7.43, 11.10)
Median (95% CI)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)	18.46 (14.75, 20.11)
75th percentile (95% CI)	NE (NE, NE)	NE (27.50, NE)	NE (24.05, NE)
Range	(0.0+, 32.3+)	(0.0+, 32.0+)	(0.0+, 30.3+)
6-month event-free rate (95% CI)	0.87 (0.83, 0.90)	0.85 (0.81, 0.88)	0.85 (0.79, 0.89)
12-month event-free rate (95% CI)	0.73 (0.69, 0.77)	0.65 (0.60, 0.69)	0.67 (0.60, 0.73)
18-month event-free rate (95% CI)	0.60 (0.55, 0.64)	0.48 (0.43, 0.53)	0.52 (0.44, 0.58)
24-month event-free rate (95% CI)	0.48 (0.42, 0.54)	0.34 (0.28, 0.39)	0.35 (0.27, 0.42)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.0002		
Hazard ratio (95% CI)[a,b]	0.70 (0.58, 0.85)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.0046		
Hazard ratio (95% CI)[a,b]	0.72 (0.57, 0.90)		

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

Table 15: Summary of Progression-Free Survival Events and Reasons for Censoring – BICR; Full Analysis Set (Study 73841937NSC3003)

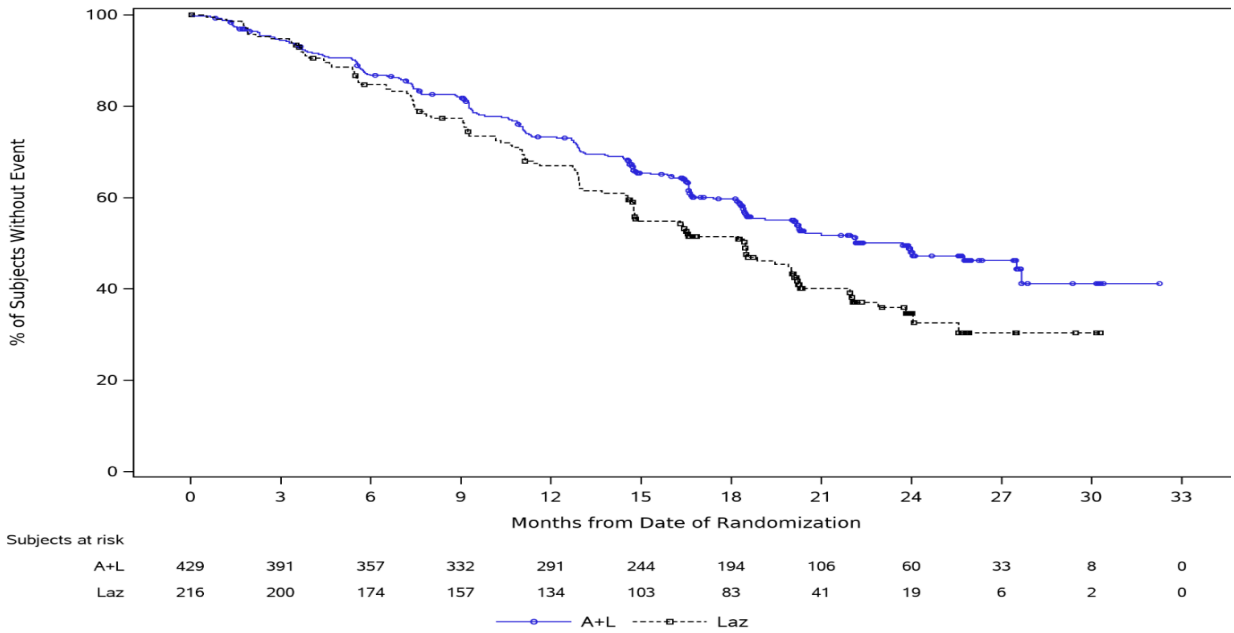
	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Subjects with event	192 (44.8%)	252 (58.7%)	121 (56.0%)
Progressive disease	148 (34.5%)	228 (53.1%)	111 (51.4%)
Death without progressive disease	44 (10.3%)	24 (5.6%)	10 (4.6%)
Subjects censored	237 (55.2%)	177 (41.3%)	95 (44.0%)
Reason for censoring			
Study cut-off	210 (49.0%)	161 (37.5%)	81 (37.5%)
Withdrawal of consent to study participation	15 (3.5%)	8 (1.9%)	8 (3.7%)
No PD or death prior to >= 2 consecutively missing or unevaluable assessments	11 (2.6%)	8 (1.9%)	6 (2.8%)
Lost to follow-up	1 (0.2%)	0	0

Figure 6: Kaplan-Meier Plot of Progression-free Survival for Amivantamab + Lazertinib vs Osimertinib - BICR; Full Analysis Set (Study 73841937NSC3003)



Key: A + L = Amivantamb + Lazertinib; Osi = Osimertinib

Figure 7: Kaplan-Meier Plot of Progression-free Survival for Amivantamab + Lazertinib vs Lazertinib - BICR; Full Analysis Set (Study 73841937NSC3003)



Key: A + L = Amivantamab + Lazertinib; Laz = Lazertinib

Secondary Endpoints

Overall Survival interim analysis

An interim analysis of OS was conducted at the time of the PFS analysis. With 214 deaths observed from the amivantamab + lazertinib and osimertinib arms combined at the CCO, the interim analysis of OS was evaluated at a 2-sided significance level of 0.0050 (O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method). At the time of the CCO date of 11 August 2023, after a median follow-up of 22.01 months, 97 participants (22.6%) in the amivantamab + lazertinib arm and 117 participants (27.3%) in the osimertinib arm had died.

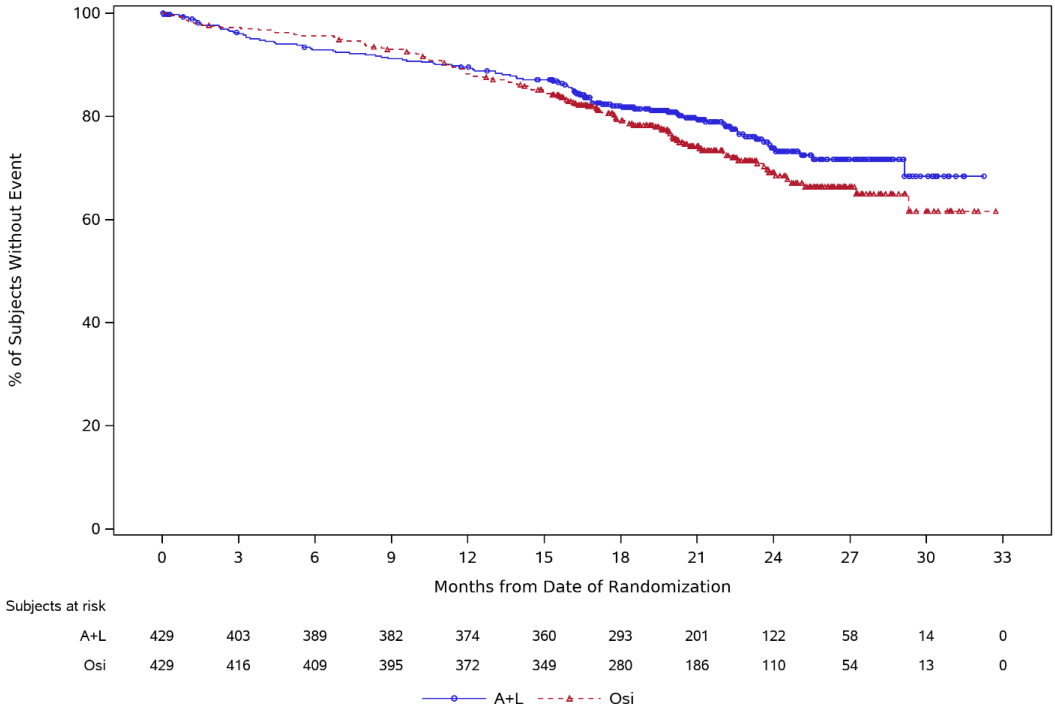
Table 16: Summary of Overall Survival – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003) (DCO: 11 August 2023)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	97 (22.6%)	117 (27.3%)	56 (25.9%)
Censored	332 (77.4%)	312 (72.7%)	160 (74.1%)
Time to event (months)			
25th percentile (95% CI)	23.62 (21.03, NE)	20.30 (18.00, 23.59)	20.30 (14.92, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 32.3+)	(0.3, 32.7+)	(0.0+, 32.1+)
6-month event-free rate (95% CI)	0.93 (0.90, 0.95)	0.96 (0.93, 0.97)	0.95 (0.91, 0.97)
12-month event-free rate (95% CI)	0.90 (0.86, 0.92)	0.88 (0.85, 0.91)	0.86 (0.81, 0.90)
18-month event-free rate (95% CI)	0.82 (0.78, 0.85)	0.79 (0.75, 0.83)	0.78 (0.71, 0.83)
24-month event-free rate (95% CI)	0.74 (0.69, 0.78)	0.69 (0.64, 0.74)	0.71 (0.64, 0.78)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.1099		
Hazard ratio (95% CI)[a,b]	0.80 (0.61, 1.05)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2343		
Hazard ratio (95% CI)[a,b]	0.82 (0.59, 1.14)		

	Amivantamab + Lazertinib	Osimertinib	Lazertinib

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

Figure 8: Kaplan-Meier Plot of Overall Survival for Amivantamab + Lazertinib vs Osimertinib; Full Analysis Set (Study 73841937NSC3003)



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib

Updated OS Analysis - CCO 13 May 2024

To support the EMA request, an updated OS analysis has been conducted based on data available as of 13 May 2024, with median follow-up of 31.3 months, with a nominal 2-sided alpha of 0.00001 spent for this analysis.

Table 17: Summary of Overall Survival – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003), DCO: 13 May 2024

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	142 (33.1%)	177 (41.3%)	80 (37.0%)
Censored	287 (66.9%)	252 (58.7%)	136 (63.0%)
Time to event (months)			
25th percentile (95% CI)	24.05 (21.03, 26.78)	20.21 (18.00, 23.36)	19.45 (14.85, 26.35)
Median (95% CI)	NE (NE, NE)	37.32 (32.53, NE)	NE (32.99, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 41.2+)	(0.3, 41.4+)	(0.0+, 41.1+)
6-month event-free rate (95% CI)	0.93 (0.90, 0.95)	0.96 (0.93, 0.97)	0.94 (0.90, 0.97)
12-month event-free rate (95% CI)	0.90 (0.86, 0.92)	0.88 (0.84, 0.91)	0.85 (0.80, 0.89)
18-month event-free rate (95% CI)	0.82 (0.78, 0.86)	0.79 (0.75, 0.83)	0.77 (0.71, 0.82)

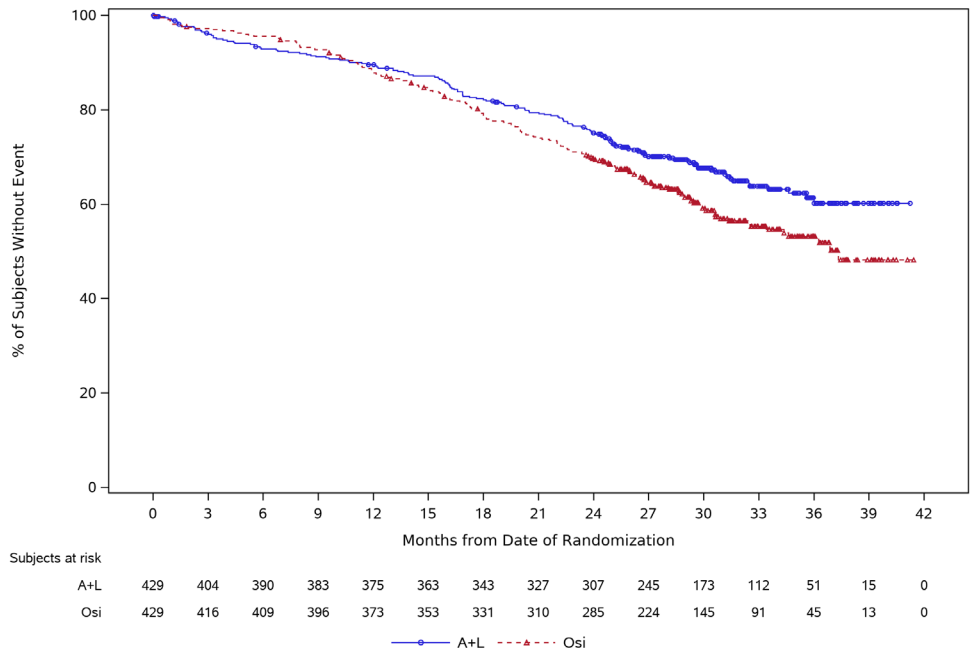
	Amivantamab + Lazertinib	Osimertinib	Lazertinib
24-month event-free rate (95% CI)	0.75 (0.71, 0.79)	0.70 (0.65, 0.74)	0.71 (0.65, 0.77)
30-month event-free rate (95% CI)	0.68 (0.63, 0.72)	0.59 (0.54, 0.64)	0.61 (0.54, 0.68)
36-month event-free rate (95% CI)	0.61 (0.56, 0.67)	0.53 (0.47, 0.59)	0.57 (0.49, 0.64)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.0185		
Hazard ratio (95% CI)[a,b]	0.77 (0.61, 0.96)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2048		
Hazard ratio (95% CI)[a,b]	0.84 (0.64, 1.10)		

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

Table 18: Summary of Overall Survival Events and Reasons for Censoring; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Subjects with event	142 (33.1%)	177 (41.3%)	80 (37.0%)
Subjects censored	287 (66.9%)	252 (58.7%)	136 (63.0%)
Reason for censoring			
Study cut-off	268 (62.5%)	241 (56.2%)	127 (58.8%)
Withdrawal of consent to study participation	16 (3.7%)	10 (2.3%)	9 (4.2%)
Lost to follow-up	3 (0.7%)	1 (0.2%)	0

Figure 9: Kaplan-Meier Plot of Overall Survival for Amivantamab + Lazertinib vs. Osimertinib; Full Analysis Set (Study 73841937NSC3003). DCO: 13 May 2024



Objective Response Rate

As pre-specified in the SAP, ORR was assessed in participants with measurable disease at baseline and responders were defined as participants achieving either CR or PR, as assessed by BICR per RECIST v1.1 criteria.

Table 19: Summary of Objective Response Rate Based on RECIST v1.1 Criteria in Subjects With Measurable Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003) CCO of 11 August 2023

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with measurable disease at baseline	421	414	214
Objective response rate (CR + PR)	363 (86.2%)	350 (84.5%)	177 (82.7%)
95% CI	(82.6%, 89.4%)	(80.7%, 87.9%)	(77.0%, 87.5%)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.4714		
Odds ratio (95% CI)[a,b]	1.15 (0.78, 1.70)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2409		
Odds ratio (95% CI)[a,b]	1.31 (0.83, 2.06)		
Best Overall Response			
Complete Response (CR)	29 (6.9%)	15 (3.6%)	9 (4.2%)
Partial Response (PR)	334 (79.3%)	335 (80.9%)	168 (78.5%)
Stable Disease (SD)	30 (7.1%)	42 (10.1%)	23 (10.7%)
Progressive Disease (PD)	7 (1.7%)	11 (2.7%)	9 (4.2%)
Not Evaluable (NE)	21 (5.0%)	11 (2.7%)	5 (2.3%)

Key: CI = confidence interval
[a] p-value and odds ratio are from logistic regression model stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or non-Asian), and history of brain metastasis (present or absent).
[b] Odds ratio >1 favors Amivantamab + Lazertinib.
Note: Percentages are based on the number of subjects with measurable disease at baseline.
Note: CR and PR do not have to be confirmed.

Duration of Response

Table 20: Summary of Duration of Response in Confirmed Responders With Measurable Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with measurable disease at baseline	421	414	214
Confirmed Responders (Confirmed CR + Confirmed PR)	336	314	160
Event	127 (37.8%)	163 (51.9%)	83 (51.9%)
Censored	209 (62.2%)	151 (48.1%)	77 (48.1%)
Time to event (months)[a]			

Table 20: Summary of Duration of Response in Confirmed Responders With Measurable Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
25th percentile (95% CI)	12.68 (11.04, 13.73)	9.26 (9.13, 10.25)	9.23 (7.39, 11.10)
Median (95% CI)	25.76 (20.14, NE)	16.76 (14.75, 18.53)	16.56 (14.75, 20.21)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (21.95, NE)
Range	(1.4, 28.5+)	(1.9+, 28.7+)	(1.9+, 28.6+)
Duration of response >=6 months	290 (86.3%)	267 (85.0%)	132 (82.5%)
Duration of response >=12 months	228 (67.9%)	181 (57.6%)	94 (58.8%)
Duration of response >=18 months	115 (34.2%)	86 (27.4%)	40 (25.0%)
Duration of response >=24 months	34 (10.1%)	21 (6.7%)	5 (3.1%)

Key: CI = confidence interval; + = censored observation; NE = not estimable
[a] Quartiles and 95% CIs are estimated with Kaplan-Meier method.
Note: Percentages are based on the number of subjects who achieved Confirmed CR or Confirmed PR.

Updated outputs for ORR and DoR in confirmed responders with measurable disease at baseline based on the CCO of 13 May 2024 were provided during the procedure with a median follow-up of 31.3 months. The ORR % (95% CI) was 80% (76%, 84%) in the A+L arm and 77% (72%, 81%) in the O arm, respectively. The median Duration of response (DOR) (95% CI) in responders was 25.8 (20.3, 33.9) months and 18.1 (14.8, 20.1) months, respectively.

Progression-free Survival After the First Subsequent Therapy

Table 21: Summary of Progression-free Survival 2 – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	101 (23.5%)	130 (30.3%)	58 (26.9%)
Censored	328 (76.5%)	299 (69.7%)	158 (73.1%)
Time to event (months)			
25th percentile (95% CI)	22.60 (18.00, 29.14)	18.40 (15.93, 20.50)	19.58 (14.62, 24.80)
Median (95% CI)	30.42 (30.42, NE)	NE (29.31, NE)	28.94 (28.94, NE)
75th percentile (95% CI)	NE (30.42, NE)	NE (NE, NE)	NE (28.94, NE)
Range	(0.0+, 32.3+)	(0.0+, 32.0+)	(0.0+, 30.3+)
6-month event-free rate (95% CI)	0.93 (0.90, 0.95)	0.95 (0.93, 0.97)	0.95 (0.91, 0.97)
12-month event-free rate (95% CI)	0.88 (0.85, 0.91)	0.87 (0.83, 0.90)	0.85 (0.79, 0.89)
18-month event-free rate (95% CI)	0.79 (0.75, 0.83)	0.76 (0.71, 0.80)	0.77 (0.71, 0.82)
24-month event-free rate (95% CI)	0.72 (0.67, 0.77)	0.64 (0.58, 0.69)	0.68 (0.59, 0.75)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.0314		
Hazard ratio (95% CI)[a,b]	0.75 (0.58, 0.98)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.2025		
Hazard ratio (95% CI)[a,b]	0.81 (0.59, 1.12)		

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

With longer follow-up (CCO: 13 May 2024), these results confirmed the degree of improvement for the combination of amivantamab and lazertinib with a 27% reduction in the risk of progression or death after the first subsequent therapy, ie, PFS2 (HR= 0.73, nominal p= 0.0044) and a 29% reduction in the risk of symptomatic progression or death, ie, TTSP (HR=0.71, nominal p=0.0011.

First Subsequent Systemic Therapy

Table 22: First Subsequent Systemic Therapy*

Therapy — no. of patients (%)	**Amivantamab-lazertinib (n=429)**	**Osimertinib (n=429)**
With investigator-assessed disease progression and discontinued all randomized treatment	116	171
Any first subsequent therapy	78 (67)	124 (73)
EGFR-targeted or TKI-based regimen	37 (32)	39 (23)
EGFR-TKI only	30 (26)	29 (17)
Osimertinib	19 (16)	19 (11)
Gefitinib	4 (3)	2 (1)
Furmonertinib	4 (3)	1 (0.6)

Aumolertinib	2 (2)	2 (1)
Icotinib	1 (1)	1 (0.6)
Catequentinib	1 (1)	0
Afatinib	0	2 (1)
Erlotinib	0	1 (0.6)
Afatinib + osimertinib	0	1 (0.6)
EGFR-targeted or TKI-based combination	7 (6)	10 (6)
Osimertinib + carboplatin + pemetrexed	1 (1)	1 (0.6)
Osimertinib + cisplatin + pemetrexed	1 (1)	1 (0.6)
Afatinib + bevacizumab + carboplatin + pemetrexed	1 (1)	0
Aumolertinib + bevacizumab	1 (1)	0
Erlotinib + carboplatin + pemetrexed	1 (1)	0
Osimertinib + bevacizumab + carboplatin + pemetrexed	1 (1)	0
Aumolertinib + HS-10241	0	2 (1)
Amivantamab + lazertinib	0	1 (0.6)
Aumolertinib + carboplatin + etoposide	0	1 (0.6)
Icotinib + carboplatin + etoposide	0	1 (0.6)
Osimertinib + capmatinib	0	1 (0.6)
Osimertinib + tepotinib	0	1 (0.6)
Chemotherapy or immunotherapy-based regimens	40 (34)	81 (47)
Chemotherapy alone	30 (26)	50 (29)
Carboplatin + pemetrexed	16 (14)	26 (15)
Carboplatin + paclitaxel	6 (5)	10 (6)
Carboplatin + etoposide	2 (2)	0
Cisplatin + etoposide	2 (2)	0
Cisplatin + pemetrexed	1 (1)	9 (5)
Pemetrexed	1 (1)	1 (0.6)
Carboplatin	1 (1)	0
Carboplatin + vinorelbine	1 (1)	0
Carboplatin + cisplatin + gemcitabine + paclitaxel	0	1 (0.6)
Carboplatin + docetaxel	0	1 (0.6)
Cisplatin + docetaxel	0	1 (0.6)
Vinorelbine	0	1 (0.6)
Chemotherapy plus VEGF inhibitors	2 (2)	9 (5)
Carboplatin + pemetrexed + bevacizumab	2 (2)	3 (2)
Cisplatin + pemetrexed + bevacizumab	0	3 (2)
Pemetrexed + bevacizumab	0	2 (1)
Carboplatin + cisplatin + pemetrexed + bevacizumab	0	1 (0.6)
Chemotherapy plus immunotherapy	1 (1)	8 (5)
Cisplatin + paclitaxel + serplulimab	1 (1)	0
Carboplatin + pemetrexed + pembrolizumab	0	4 (2)
Carboplatin + pemetrexed + camrelizumab	0	2 (1)
Carboplatin + paclitaxel + atezolizumab	0	1 (0.6)

Carboplatin + durvalumab + etoposide	0	1 (0.6)
Chemotherapy combined with VEGF inhibitors and immunotherapy	6 (5)	14 (8)
Carboplatin + paclitaxel + bevacizumab + atezolizumab	3 (3)	9 (5)
Carboplatin + pemetrexed + bevacizumab + sintilimab	1 (1)	1 (0.6)
Carboplatin + paclitaxel + bevacizumab	1 (1)	1 (0.6)
Cisplatin + paclitaxel + bevacizumab + atezolizumab	1 (1)	0
Carboplatin + pemetrexed + bevacizumab + atezolizumab	0	1 (0.6)
Cisplatin + pemetrexed + bevacizumab + sintilimab	0	1 (0.6)
Pemetrexed + bevacizumab + atezolizumab	0	1 (0.6)
VEGF inhibitor only		
Bevacizumab	1 (1)	0
Other		
Amivantamab monotherapy	0	1 (0.6)
Antibody drug conjugate	0	1 (0.6)
Herbal	1 (1)	1 (0.6)
Antineoplastic agents	0	2 (1)

Time to Symptomatic Progression

Table 23: Summary of Time to Symptomatic Progression – Stratified Analysis; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Event	125 (29.1%)	167 (38.9%)	70 (32.4%)
Symptomatic PD	69 (16.1%)	118 (27.5%)	46 (21.3%)
Death without Symptomatic PD	56 (13.1%)	49 (11.4%)	24 (11.1%)
Censored	304 (70.9%)	262 (61.1%)	146 (67.6%)
Time to event (months)			
25th percentile (95% CI)	17.58 (14.23, 22.34)	14.06 (11.60, 15.90)	13.83 (10.41, 18.86)
Median (95% CI)	NE (NE, NE)	29.31 (25.33, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 32.3+)	(0.2, 32.7+)	(0.0+, 32.1+)
6-month event-free rate (95% CI)	0.88 (0.85, 0.91)	0.90 (0.87, 0.93)	0.90 (0.85, 0.93)
12-month event-free rate (95% CI)	0.82 (0.77, 0.85)	0.79 (0.74, 0.82)	0.79 (0.72, 0.84)
18-month event-free rate (95% CI)	0.74 (0.70, 0.78)	0.67 (0.63, 0.72)	0.71 (0.64, 0.76)
24-month event-free rate (95% CI)	0.67 (0.62, 0.72)	0.59 (0.53, 0.64)	0.65 (0.58, 0.72)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.0049		
Hazard ratio (95% CI)[a,b]	0.72 (0.57, 0.91)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.3083		
Hazard ratio (95% CI)[a,b]	0.86 (0.64, 1.15)		

	Amivantamab + Lazertinib	Osimertinib	Lazertinib

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.

Intracranial Progression-free Survival

Intracranial PFS (i.e., the time from randomization until the date of objective intracranial disease progression or death, whichever came first, based on BICR using RECIST v1.1) is summarized in Table 24. Brain MRI frequency in the MARIPOSA study varied depending on whether the participant had a history of brain metastases; as a result, this analysis is limited to participants with a history of brain metastases.

Table 24: Summary of Intracranial Progression-free Survival in Subjects With History of Brain Metastasis – Stratified Analysis - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with history of brain metastasis	178	172	86
Event	75 (42.1%)	75 (43.6%)	37 (43.0%)
Censored	103 (57.9%)	97 (56.4%)	49 (57.0%)
Time to event (months)			
25th percentile (95% CI)	9.46 (8.44, 13.08)	12.75 (9.30, 14.09)	11.04 (9.10, 16.39)
Median (95% CI)	NE (18.43, NE)	21.09 (18.40, NE)	20.30 (16.59, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (22.67, NE)
Range	(0.0+, 30.3+)	(0.0+, 30.3+)	(0.0+, 28.6+)
6-month event-free rate (95% CI)	0.87 (0.81, 0.91)	0.88 (0.82, 0.92)	0.89 (0.81, 0.94)
12-month event-free rate (95% CI)	0.71 (0.64, 0.77)	0.75 (0.68, 0.81)	0.72 (0.61, 0.80)
18-month event-free rate (95% CI)	0.59 (0.51, 0.66)	0.58 (0.50, 0.66)	0.60 (0.48, 0.70)
24-month event-free rate (95% CI)	0.51 (0.42, 0.59)	0.46 (0.36, 0.55)	0.40 (0.24, 0.55)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.8168		
Hazard ratio (95% CI)[a,b]	0.96 (0.70, 1.33)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.7615		
Hazard ratio (95% CI)[a,b]	0.94 (0.63, 1.40)		

Key: + = censored observation; NE = not estimable
[a] p-value is from a log-rank test stratified by mutation type (Exon 19del or Exon 21 L858R) and race (Asian or Non-Asian).
[b] Hazard ratio is from a stratified proportional hazards model. Hazard ratio <1 favors Amivantamab + Lazertinib.
Note: History of brain metastasis is based on investigator reported data recorded on eCRF page.

At the updated analysis based on the CCO of 13 May 2024, with a median follow-up of 31.11 months, the improvement of the iPFS was supported with 24.90 months observed in the amivantamab + lazertinib arm versus 22.18 months in the osimertinib arm.

Key Exploratory Efficacy Analyses

Intracranial Objective Response Rate

There were 180 participants in the amivantamab + lazertinib arm, 187 participants in the osimertinib arm, and 93 participants in the lazertinib arm that had intracranial disease at baseline as assessed by BICR and were included in the analysis of intracranial ORR.

Table 25: Summary of Intracranial Objective Response Rate Based on RECIST v1.1 Criteria in Subjects With Intracranial Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with intracranial disease at baseline	180	187	93
Objective response rate (CR+PR)	138 (76.7%)	143 (76.5%)	69 (74.2%)
95% CI	(69.8%, 82.6%)	(69.7%, 82.4%)	(64.1%, 82.7%)
Amivantamab + Lazertinib vs Osimertinib			
p-value[a]	0.9964		
Odds ratio (95% CI)[a,b]	1.00 (0.61, 1.63)		
Amivantamab + Lazertinib vs Lazertinib			
p-value[a]	0.6591		
Odds ratio (95% CI)[a,b]	1.14 (0.64, 2.05)		
Best Overall Response			
Complete Response (CR)	112 (62.2%)	108 (57.8%)	51 (54.8%)
Partial Response (PR)	26 (14.4%)	35 (18.7%)	18 (19.4%)
Stable Disease (SD)[c]	35 (19.4%)	39 (20.9%)	17 (18.3%)
Progressive Disease (PD)	3 (1.7%)	2 (1.1%)	4 (4.3%)
Not Evaluable (NE)	4 (2.2%)	3 (1.6%)	3 (3.2%)

Key: CI = confidence interval
[a] p-value and odds ratio are from logistic regression model stratified by mutation type (Exon 19del or Exon 21 L858R) and race (Asian or non-Asian).
[b] Odds ratio >1 favors Amivantamab + Lazertinib.
[c] Includes non-CR/non-PD in subjects with only non-target lesions at baseline.
Note: CR and PR do not have to be confirmed.

Intracranial Duration of Response

Among the 138 participants in the amivantamab + lazertinib arm with an intracranial response by BICR, 46 participants (33.3%) had intracranial disease progression or died by the time of the CCO. In comparison, among 143 participants in the osimertinib arm with an intracranial response by BICR, 38 participants (26.6%) had intracranial disease progression or died by the time of the CCO. The median intracranial DOR was not reached for either arm.

Table 26: Summary of Intracranial Duration of Response in Responders With Intracranial Disease at Baseline - BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Full	429	429	216
Number of subjects with intracranial disease at baseline	180	187	93
Responders (CR + PR)	138	143	69
Event	46 (33.3%)	38 (26.6%)	20 (29.0%)
Censored	92 (66.7%)	105 (73.4%)	49 (71.0%)
Time to event (months)[a]			
25th percentile (95% CI)	11.10 (7.52, 14.75)	12.91 (9.30, 18.07)	12.88 (7.46, 19.25)
Median (95% CI)	NE (20.24, NE)	NE (NE, NE)	20.27 (17.81, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 28.5+)	(0.0+, 25.9+)	(0.0+, 26.8+)
Duration of response >=6 months	107 (77.5%)	111 (77.6%)	55 (79.7%)
Duration of response >=12 months	80 (58.0%)	77 (53.8%)	36 (52.2%)
Duration of response >=18 months	43 (31.2%)	30 (21.0%)	13 (18.8%)
Duration of response >=24 months	14 (10.1%)	6 (4.2%)	2 (2.9%)

Key: CI = confidence interval; + = censored observation; NE = not estimable
[a] Quartiles and 95% CIs are estimated with Kaplan-Meier method.
Note: Percentages are based on the number of subjects who achieved CR or PR.

Updated outputs for the intracranial response point estimates based on the CCO of 13 May 2024 were provided under the procedure.

The intracranial ORR (CR+PR), % (95% CI) was 77% (70%, 83%) in the amivantamab + lazertinib arm and 77% (71%, 83%) in the osimertinib arm and the Complete response (CR) was 63% and 59%, respectively.

The median intracranial DOR was NE in the amivantamab + lazertinib arm and 24.41 months in the osimertinib arm at the updated analysis. The 18 and 24-month intracranial DOR improved with further follow-up, with an intracranial DOR of at least 18 months in 50.4% versus 38.9% for the combination of amivantamab and lazertinib versus osimertinib, respectively, and an intracranial DOR of at least 24 months in 30.9% versus 17.4%, respectively.

PRO data

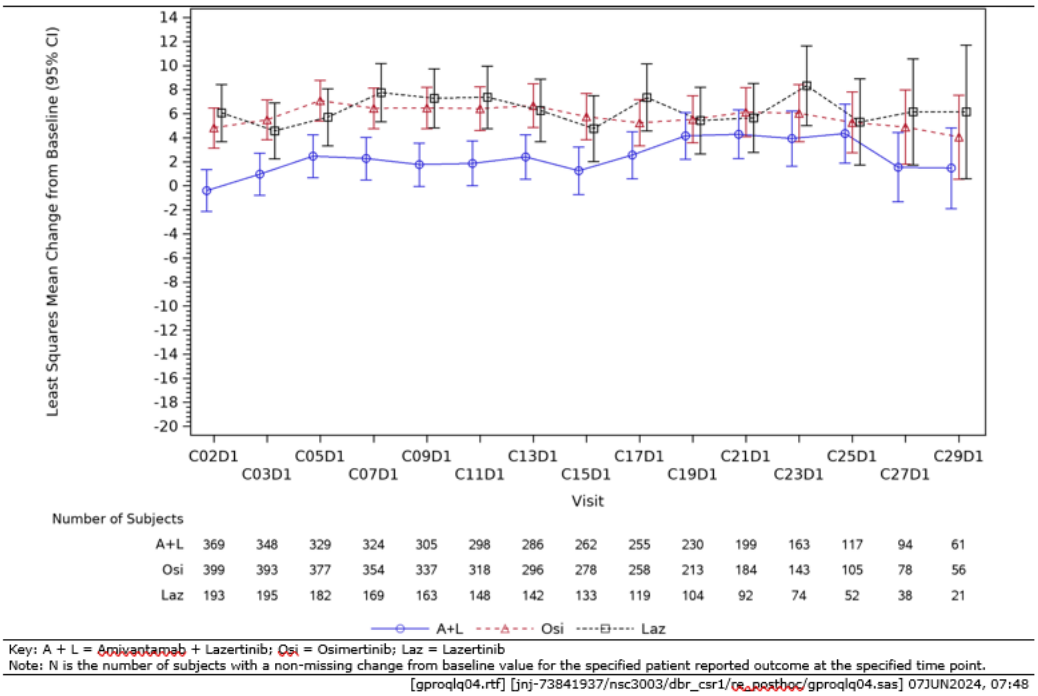
The schedule of assessment was as follows:

Phase		**Treatment (28 Days/Cycle)**									**End of Treatment Visit**[b]	**Follow-Up (Visit or Call)**
Study Period		**Cycle 1**					**Cycle 2**		**Cycles 3+**		**30 Days After Last Dose of Study Treatment**	**Q12 Weeks From the Last Dose of Study Treatment**
Cycle Day	**Screening**	**1**	**2**	**8**	**15**	**22**	**1**	**15**	**1**	**15**		
Visit Window (Days)	**-28 to -1**	-	-	**±1**	**±1**	**±1**	**±1**	**±1**	**±2**	**±2**	+7	**±14**
Arm A: oral lazertinib (open-label)[a]		C1D1 (<15 min pre-infusion), then approximately the same time each day, with or without food										
Arms B/C: oral osimertinib or lazertinib (blinded)		C1D1, then approximately the same time each day, with or without food										
All arms: record oral study treatment compliance							X		X			
Patient-Reported Outcomes (Should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses)												
EQ-5D-5L, EORTC-QLQ-C30, NSCLC-SAQ		X					X		Every 2 cycles starting with C3D1		X	X (Up to 1 year after EOT)
PGIS		X					X		Every 2 cycles starting with C3D1		X	
PGIC							X		Every 2 cycles starting with C3D1		X	

PRO compliance was ≥96% at baseline and ≥85% through Cycle 31 in each treatment arm for the NSCLC-SAQ and EORTC-QLQ-C30

The EORTC QLG Core Questionnaire (EORTC QLQ-C30) is a 30-item instrument designed to measure quality of life in all cancer patients. Results are expressed on a scale from 0-100, with lower scores indicating more severe symptomatology.

Figure 10: Least Squares Mean (95% CI) Change from Baseline for EORTC QLQ-C30: Global Health Status/Quality of Life Score Over Time; Full Analysis Set (Study 73841937NSC3003)

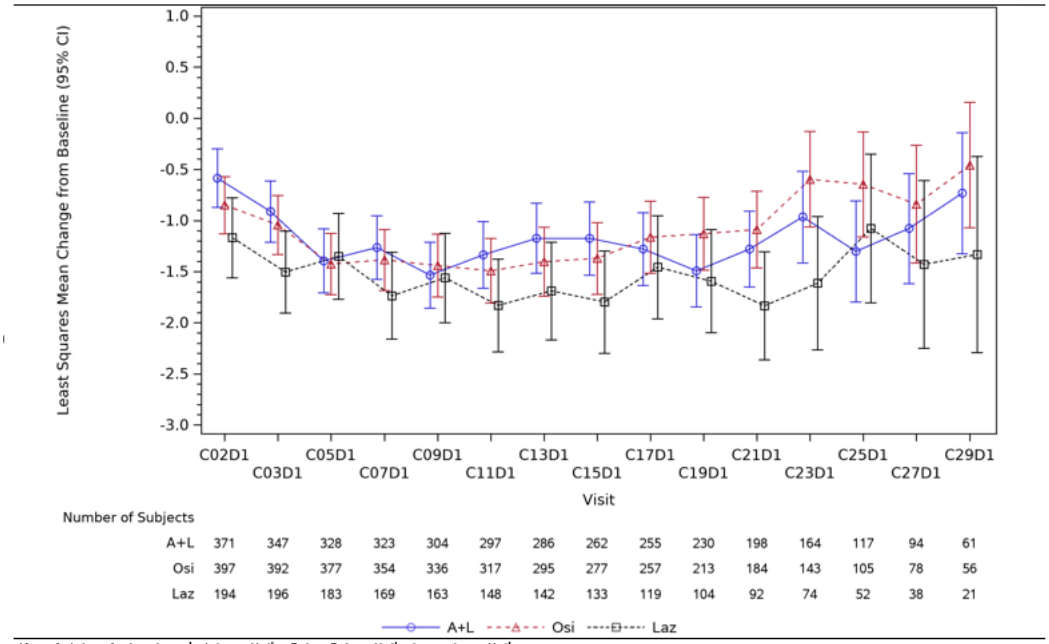


Key: A + L = ~~Amivantamab~~ + Lazertinib; ~~Osi~~ = Osimertinib; Laz = Lazertinib
Note: N is the number of subjects with a non-missing change from baseline value for the specified patient reported outcome at the specified time point.
[gproqlq04.rtf] [jnj-73841937/nsc3003/dbr_csr1/~~re_posthoc~~/gproqlq04.sas] 07JUN2024, 07:48

Referring to EORTC resources, the differences seen between arms are at the lower boundary of what might be considered minimally clinically meaningful.

The NSCLC Symptom Assessment Questionnaire (NSCLC-SAQ) is a 5-domain instrument to assess NSCLC symptom Severity. The NSCLC-SAQ total score is computed as the sum of the 5 domains and ranges between 0 and 20. Higher scores indicate more severe symptomatology.

Figure 11: Least Squares Mean (95% CI) Change from Baseline for NSCLC-SAQ: Total Score Over Time; Full Analysis Set (Study 73841937NSC3003)



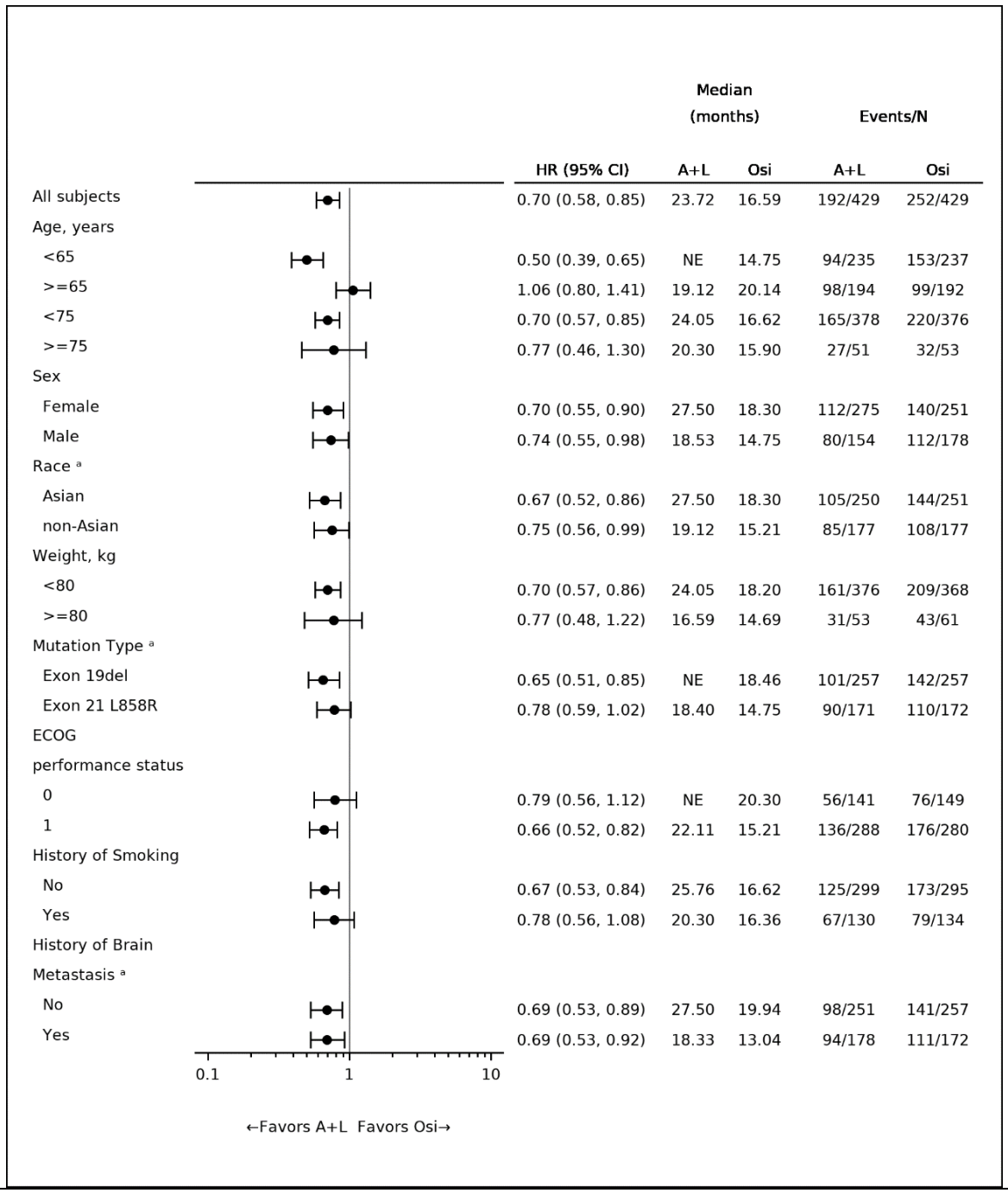
Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; Laz = Lazertinib
Note: N is the number of subjects with a non-missing change from baseline value for the specified patient reported outcome at the specified time point.
[gprosaq04.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_posthoc/gprosaq04.sas] 07JUN2024, 07:50

There are no interpretable differences between scores.

Ancillary analyses

Subgroup Analyses of Progression-free Survival by BICR

Figure 12: Forest Plot of Progression-free Survival for Amivantamab + Lazertinib vs Osimertinib - BICR; Full Analysis Set (Study 73841937NSC3003)



Key: A + L = Amivantamab + Lazertinib; Osi = Osimertinib; ECOG = Eastern Cooperative Oncology Group; NE = not estimable
[a] Based on investigator reported data recorded on eCRF page.
Note: Hazard ratio for the analysis of all subjects is from a proportional hazards model stratified by mutation type (Exon 19del or Exon 21 L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent).
Note: Hazard ratio for the analysis of subgroups is from an unstratified proportional hazards model.

Sensitivity Analyses of PFS

Unstratified Analysis of PFS

The results of the unstratified sensitivity analysis of PFS by BICR showed a treatment benefit for the amivantamab + lazertinib arm relative to both the osimertinib arm (HR=0.71 [95% CI: 0.59, 0.85], nominal p=0.0003) and to the lazertinib arm (HR=0.72 [95% CI: 0.58, 0.91], nominal p=0.0050), similar to observations in the stratified analyses.

Concordance in PFS Assessment Between Investigator and BICR

Analysis was conducted to determine the level of agreement on PFS event status between investigator assessment and assessment by BICR. Agreement on event status (ie, participants had an event by both investigator and BICR and participants were censored by both investigator and BICR) was similar across the treatment arms: amivantamab + lazertinib arm: 86.7%, osimertinib arm: 86.5%, lazertinib arm: 87.5%.

Table 27: Summary of Progression-Free Survival – Concordance Between Investigator and BICR; Full Analysis Set (Study 73841937NSC3003)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Full	429	429	216	1074
Agreement on event status [a]	372 (86.7%)	371 (86.5%)	189 (87.5%)	932 (86.8%)
Event by both BICR and investigator	162 (37.8%)	212 (49.4%)	104 (48.1%)	478 (44.5%)
Complete agreement [b]	91 (21.2%)	92 (21.4%)	40 (18.5%)	223 (20.8%)
Agreement with later date by BICR	23 (5.4%)	28 (6.5%)	23 (10.6%)	74 (6.9%)
Agreement with earlier date by BICR	48 (11.2%)	92 (21.4%)	41 (19.0%)	181 (16.9%)
No event by both BICR and investigator	210 (49.0%)	159 (37.1%)	85 (39.4%)	454 (42.3%)
Disagreement on event status	57 (13.3%)	58 (13.5%)	27 (12.5%)	142 (13.2%)
Event by investigator but not by BICR	27 (6.3%)	18 (4.2%)	10 (4.6%)	55 (5.1%)
Event by BICR but not by investigator	30 (7.0%)	40 (9.3%)	17 (7.9%)	87 (8.1%)

Key: BICR = blinded independent central review
[a] Includes subjects who had event by both investigator and BICR and subjects who were censored by both investigator and BICR.
[b] Includes subjects who had investigator-reported and BICR event that are less than 7 days apart.

Supplementary Analyses of Progression-free Survival by BICR

Censored for Death/PD after Start of Subsequent Anti-cancer Therapy

The results from the analysis of PFS by BICR censored for death/PD after start of subsequent anti-cancer therapy showed a treatment benefit for the amivantamab + lazertinib arm versus the osimertinib arm (HR=0.70 [95% CI: 0.57, 0.84], nominal p=0.0002) and for the amivantamab + lazertinib arm versus the lazertinib arm (HR=0.70 [95% CI: 0.55, 0.88], nominal p=0.0025) similar to that observed in the primary analysis.

Not Censored for Missing More Than One Disease Evaluation

The results from the analysis of PFS by BICR not censored for missing 2 or more consecutive disease evaluations showed a treatment benefit for the amivantamab + lazertinib arm versus the osimertinib arm (HR=0.72 [95% CI: 0.60, 0.86], nominal p=0.0004) and for the amivantamab + lazertinib arm versus the lazertinib arm (HR=0.72 [95% CI: 0.58, 0.90], nominal p=0.0042) similar to that observed in the primary analysis.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the benefit risk assessment (see later sections).

Table 28: Summary of Efficacy for trial MARIPOSA:

Title: MARIPOSA			
Study identifier	146319 EudraCT NUMBER 2020-000743-31		
Design	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		
	Screening phase Treatment phase Follow-up phase		Within 28 days prior to randomization Cycle 1 Day 1 and continued as 28-day cycles until the End of Treatment visit For participants who discontinued study treatment for any reason
Hypothesis	Superiority		
Treatments groups	Arm A: Amivantamab + Lazertinib		N=429
	Arm B: Osimertinib		N=429
	Arm C. Lazertinib		N=216
Endpoints and definitions	Primary endpoint	PFS	
	Secondary endpoint	OS	
	Secondary endpoint	ORR	
Database lock	11 August 2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population. Final PFS analysis, Interim OS analysis		
Descriptive statistics and estimate variability	Treatment group	Amivantamab + Lazertinib	Osimertinib (control)
	Number of subjects	429	429
	Primary endpoint Median PFS (months)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)
	HR PFS (95% CI); p-value	0.70 (0.58, 0.85); p=0.0002	
	Secondary endpoint hypothesis tested: OS (events) Median OS (months)	 22.6% NE	 27.3% NE

HR OS (95% CI); p-value Updated OS (events) Median OS (months) HR OS(95% CI) p-value	HR=0.80 [95% CI: 0.61, 1.05]; p=0.1099. 33.1% NE 0.77 (0.61, 0.96) p=0.0185	 41.3% 37.3
Secondary endpoints: Updated ORR (%) Updated confirmed Median DoR (95%CI) months	 80% 25.8 (20.3, 33.9)	 77% 18.1 (14.8, 20.1)

Clinical studies in special populations

Table 29: Clinical studies in special populations

	Controlled Trials MARIPOSA Amivantamab + Lazertinib (N=421)	**Non-controlled trials CHRYSALIS+CHRYSALIS-2 Amivantamab + Lazertinib (N=526)**
Renal function at baseline		
Normal (eGFR: >= 90 mL/min/1.73m²)	237 (56.3%)	263 (50%)
Mild (eGFR: 60 to < 90 mL/min/1.73 m²)	163 (38.7%)	216 (41.1%)
Moderate (eGFR: 30 to < 60 mL/min/1.73 m²)	20 (4.8%)	47 (8.9%)
Severe (eGFR: < 30 mL/min/1.73 m²)	1 (0.2%)	0
Hepatic function at baseline		
Normal (Total bilirubin <= ULN and AST <= ULN)	381 (90.5%)	457 (86.9%)
Mild ((Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN))	40 (9.5%)	68 (12.9%)
Moderate (1.5 x ULN < Total bilirubin <= 3 x ULN)	0	1 (0.2%)
Severe (Total bilirubin > 3 x ULN)	0	0
Age		
Paediatric patients <18 years	0	0
18-64 years	233 (55.3%)	297 (56.5%)
65-74 years	139 (33.0%)	178 (33.8%)
75-84 years	44 (10.5%)	49 (9.3%)

	Controlled Trials MARIPOSA Amivantamab + Lazertinib (N=421)	Non-controlled trials CHRYSALIS+CHRYSALIS-2 Amivantamab + Lazertinib (N=526)
85+ years	5 (1.2%)	2 (0.4%)

In vitro biomarker test for patient selection for efficacy

Among patients with NSCLC, the most prevalent driver mutations are those that result in the activation of EGFR, which are identified in more than 15% of patients with adenocarcinoma and up to 50% of the corresponding Asian population. Approximately 90% of activating EGFR mutations are exon 19 deletions (exon 19del) or exon 21 L858R substitutions (L858R). There are several authorized assays on the market to detect these common EGFR mutations to support the use of targeted therapy.

Participants enrolled in the MARIPOSA study were enrolled based on a documented local EGFR result using validated PCR or NGS-based assays (a copy of the test report documenting the mutation must have been included in the participant's medical records at the time of randomization). The Applicant received scientific advice (EMA/SA/0000052936) that the use of validated local assays for the detection of EGFR mutations was an acceptable approach.

Table 30: Concordance study summary results - Tissue

tagexinv03-ct: Concordance Study Summary Results - Tissue; cAS+ (Study 73841937NSC3003)				
	Local Lab Test Type			
	PCR (excluding cobas tissue)	NGS	PCR (cobas tissue)	Total
Central cobas Aggregate Call for EGFR L858R or Exon 19 Deletion				
Detected	327	171	153	651
Not Detected	11	9	5	25
Total	338	180	158	676
Concordance (2-sided 95% exact CI)	96.7% (94.3% - 98.4%)	95.0% (90.7% - 97.7%)	96.8% (92.8% - 99.0%)	96.3% (94.6% - 97.6%)

Table 31: Concordance study summary results - Plasma

tagexinv04-ct: Concordance Study Summary Results - Plasma; cAS- and cAS-NT (Study 73841937NSC3003)				
	Local Lab Test Type			
	PCR (excluding cobas tissue)	NGS	PCR (cobas tissue)	Total
Central Guardant Aggregate Call for EGFR L858R or Exon 19 Deletion				
Detected	52	50	26	128
Not Detected	19	11	15	45
Total	71	61	41	173
Concordance (2-sided 95% exact CI)	73.2% (61.4% - 83.1%)	82.0% (70.0% - 90.6%)	63.4% (46.9% - 77.9%)	74.0% (66.8% - 80.4%)

Central tissue testing concordance overall is 96.3% with 651/676 cobas testing results in agreement with the LLTs. Central testing was concordant with local testing in 74.0% of the samples with a valid central Guardant plasma test (using Guardant 360® CDx) when no valid central tissue test was available.

Supportive study(ies)

CHRYSALIS First-line Cohort: Supportive Efficacy Study (Combination of Amivantamab and Lazertinib)

Efficacy information was summarized for the First-line Cohort from Part 1 (N=20) treated with amivantamab + lazertinib based on a CCO of 15 November 2022.

Primary Efficacy Endpoint

Overall Response Rate

Confirmed responses (PR [no CRs were observed]) per RECIST v.1.1 were observed for all 20 participants in the Part 1 First-line Cohort, resulting in an overall response rate of 100.0% (95% CI: 83.2%, 100%).

Secondary Efficacy Endpoint

Duration of Response

The median DOR was not estimable (NE) (95% CI: 20.30, NE), and the longest response was ongoing at 35.6 months as of the CCO. The median duration of treatment was 33.46 months.

2.4.4. Discussion on clinical efficacy

Design and conduct of clinical studies

The MARIPOSA study is an ongoing randomized, three arms, Phase 3 study mainly comparing amivantamab and lazertinib combination (hereafter referred to as AL) with osimertinib (O), in advanced or metastatic NSCLC patients with activating EGFR mutations in the first-line setting. The lazertinib arm (hereafter referred as L) was added to allow evaluation of mono-components contribution to the efficacy of combination, as per CHMP scientific advice (May 2020). The Lazertinib arm was included in the study design before the study initiation with the first patient enrolling 16 October 2020.

Osimertinib is the intended control for the type-1 error tested evaluation of AL efficacy. Osimertinib is approved for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. Moreover, osimertinib is the treatment of choice for the first-line treatment of patients with advanced EGFR-mutated NSCLC. Hence, in the MARIPOSA study, osimertinib is considered an appropriate comparator for the experimental treatment regimen.

Only evaluation of AL combination in comparison with O was type-1 error tested. The comparison of AL with L was not included in the hypothesis testing and was intended only to allow evaluation of mono-components contribution to AL.

The choice of PFS as primary endpoint with OS as key secondary endpoint is acceptable as per *CHMP guideline on the clinical evaluation of anticancer medical products*. and in line with regulatory

precedents. A blinded, independent central review (BICR) assessment of the primary endpoint PFS was planned which is adequate, taking in account the open-label design of AL vs O comparison.

OS analysed following PFS in a hierarchical testing approach is assessed as key secondary endpoint which is in line with the anticancer guideline when PFS is chosen as primary endpoint. Cross-over from osimertinib arm to experimental arm (s) was not allowed in case of confirmed progress.

No other secondary endpoints were included in the testing strategy.

Statistical analysis plan

The analysis methods are conventional for oncology studies and largely acceptable. For the time-to-event endpoints (such as PFS and OS), stratified log-rank test was used for the hypothesis testing, stratified Cox regression model to estimate the treatment effect, and Kaplan-Meier analysis to estimate the survival curves.

Censoring rules for PFS follow EMA rules in not censoring for new anticancer therapy without progression, while censoring in case progression is proceeded by 2 or more missed visits. Sensitivity analyses are deemed adequate to evaluate robustness of the primary analysis of PFS and examine the validity of the proportional hazards' assumption. As anticipated, the OS analysis follows treatment policy.

Supplementary analyses of PFS were performed using progression or death prior to the start of the subsequent anticancer therapy as events. Participants who have not progressed or have not died before the initiation of subsequent therapy were censored at the date of the last evaluable disease assessment prior to the start of subsequent therapy. An additional supplementary analysis was performed using all progression or death, whichever occur first, as event regardless missed/unevaluable disease assessment for 2 or more consecutive visits. The supplementary analyses are helpful to better understand the treatment effect.

Hypothesis testing between the amivantamab and lazertinib combination versus osimertinib was performed for the PFS (primary) and OS (key secondary endpoint) in a hierarchical approach to strongly control the Type I error rate at 5% level 2-sided, which is acceptable. Multiplicity due to the interim analysis of PFS and OS, respectively, is handled conventionally by group sequential design with the O'Brien Fleming alpha spending approach as implemented by the Lan-DeMets method. A small symbolic alpha was allocated to the futility (non-binding) analysis which was performed for PFS.

The interim analysis of PFS was planned to be performed when approximately 280 PFS events from amivantamab + lazertinib and osimertinib arms have occurred, with the accompanying significance/stopping boundary at 0.0090. However, in the interim PFS analysis (data cut-off 15 January 2023), the actual numbers were higher: there were 321 PFS events observed with the accompanying significance/stopping boundary of 0.0159. The attained p-value at the interim analysis (p-value 0.0097) was close to the initially planned stopping boundary which was based on the lower anticipated number of PFS events. It was clarified that the date for the data cut-off was determined through model-based events projection and based on the investigator disease assessment (i.e., not BICR), which contributed to the uncertainty in counting PFS events. To be conservative, target date has been expanded approximately 2 months.

In addition, an analysis of PFS has been requested based on the first observed 280 events in the amivantamab + lazertinib and osimertinib arms combined, in line with the pre-specified PFS interim analysis. This analysis resulted in statistically significant HR in favour of the combination treatment, which reassures that the delay of the interim analysis is acceptable.

At the time of the (final) primary PFS analysis, an interim OS analysis was to be performed, anticipating 270 deaths from amivantamab + lazertinib and osimertinib arm combined.

SAP and protocol amendments

Study MARIPOSA is still ongoing. Until the current cut-off date for the primary analysis, 11 August 2023, three protocol amendments were applied. The original protocol is dated 5 June 2020, four months before study initiation on 16 October 2020 (date first participant was screened).

The last protocol amendment (Amendment 3) was issued on 22 August 2022, roughly 12 months before the data cut-off for final for PFS 11 August 2023. The Protocol Amendment 3 was issued to implement an Urgent Safety Measure intended to minimize the risk for VTE following an identified imbalance in the overall incidence of VTE events associated with the combination of amivantamab and lazertinib compared with osimertinib monotherapy or lazertinib monotherapy.

The statistical analysis plan was authored early during the conduct of the study and is likely not influenced by the study data at hand.

Efficacy data and additional analyses

Patient disposition

Totally, at the time of CCO (11 August 2023), 1074 participants were randomized in the study, 2:2;1, i.e., 429 were randomized to the AL arm, 429 to the O arm, and 216 to the L arm. Those represents the ITT population, hereafter referred as FAS.

The major protocol deviations that occurred were balanced across the three arms. No issues that would suggest impact on the efficacy analysis are observed.

At the time of the inferential PFS analysis, 51.7 of patients remained on the study treatment (54.6% in the AL arm, 49.8%% in the O arm and 49.8% in L arm). Totally 48.3% that discontinued the treatment mostly due to progressive disease.

No important imbalance is seen in discontinuation of treatment due to physician decision or lost to follow up.

Baseline characteristics

Stratification factors including mutation type (exon 19del versus L858R), race (Asian versus non-Asian), and history of brain metastasis (present versus absent) are considered clinically relevant.

Demographics and baseline characteristics were well balanced between the 3 treatment arms. The median age was 63 years (range: 25 to 88) with 45.0% of participants ≥65 years old; 61.6% were female; 58.6% were Asian and 38.0% were White. Baseline ECOG performance status was 0 (34.1%) or 1 (65.9%); 87.6% had weight <80 kg; 68.6% had never smoked.

Among the study participants, 40.6% had a history of brain metastases and 90.0% had Stage IV cancer at the time of initial diagnosis (35.1% with Stage IVa, 54.9% with Stage IVb). The median time from metastatic disease diagnosis of NSCLC to randomization was 1.2 months. A balanced proportion of patients between arms received prior systemic therapy consisting of platinum doublet in neoadjuvant/adjuvant settings.

Overall, all patients randomized in the MARIPOSA study were diagnosed with advanced NSCLC harbouring EGFR activating mutations, i.e., 60.1% had NSCLC harbouring Exon 19 deletions and 39.9% Exon 21 L858R substitution mutations.

Per protocol, the patient samples were required to have one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing. Tumour tissue (94%) and/or plasma (6%) samples for all patients were tested locally to determine EGFR exon 19 deletion and/or exon 21 L858R substitution mutation status using polymerase chain reaction (PCR) in 65% and next generation sequencing (NGS) in 35% of patients.

Various CE-marked tests were used for local testing (LLT). Central testing was performed with either Roche cobas® EGFR Mutation Test v2 (cobas) for tissue samples or Guardant 360® CDx (G360) for plasma samples.

The overall concordance between the three LLTs and central cobas tissue test was 96.3% for the samples with a valid cobas central tissue test result (N=676) and consistent across the used LLTs.

Efficacy results

The median duration of treatment in the amivantamab + lazertinib arm was 18.50 months ([range: 0.2 to 31.4].

The median duration of treatment in the osimertinib arm was 18 months (range: 0.2 to 32.7), and 17.05 months (range: 0.4 to 32.1) in the lazertinib arm.

Primary endpoint: PFS by BICR

At the cutoff date for the final PFS analysis (11 August 2023), with a median follow-up of 22 months, there were totally 565 PFS events in all three arms combined.

The PFS analysis by BICR showed a statistically significant benefit with AL combination versus O with PFS HR 0.70 (95% CI; 0.58, 0.85); p-value 0.0002. The median PFS gain of 7 months (median PFS 23.72 (19.12, 27.66) months in AL arm vs 16.59 (14.78, 18.46) months in O arm) is, based on precedent, deemed clinically relevant.

Although not multiplicity tested the comparison of AL versus L was advantageous for the AL combination, supporting the contribution of the mono-components to their combination. The PFS Hazard ratio was 0.72 (95% CI; 0.57, 0.90) for the AL combination versus L, p-value 0.0046 and a median PFS gain of 5 months (23.72 months in AL arm vs 18.46 months in L arm).

The censoring rules applied combined elements of the FDA and EMA algorithms. The prespecified additional sensitivity PFS analyses to compensate for the censoring rules applied, further support the robustness of the demonstrated PFS benefit. Hence, PFS by BICR censored for death/PD after start of subsequent anti-cancer therapy showed a treatment benefit for the AL versus O (HR=0.70 [95% CI: 0.57, 0.84], nominal p=0.0002) and PFS by BICR not censored for missing 2 or more consecutive disease evaluations showed a treatment benefit for the AL versus O (HR=0.72 [95% CI: 0.60, 0.86], nominal p=0.0004), respectively.

The benefit was observed across all pre-defined clinically relevant subgroups.

Secondary endpoint: OS, type 1 error-controlled

At the interim analysis of OS with a median follow up of 22 months, the event rate was overall lower than estimated (214 deaths in comparison with expected 270 deaths in AL and O arm combined) with 97 (22.6%) events in AL arm and 117 (27.3%) events in O arm. A 2-sided significance level of 0.0050 was allocated to the OS interim analysis following statistically significant final PFS analysis.

A numerical trend towards improved survival in AL arm was observed with HR (95% CI) HR=0.80 (0.61, 1.05), p=0.1099.

An updated OS analysis (CCO 13 May 2024) with additional 9 months FU(totally 31 months median FU) and 129 additional events, continues to show nominally better survival with AL compared with O, with a stronger numerical and statistical trend. HR 0.77 (95% CI; 0.61, 0.96) p 0.0185. Maturity, however, is still limited with 33% events in AL arm compared with 41% events in O arm and 37% events in L arm. The final OS analysis planned per protocol when 490 deaths overall (all treatment arms combined) and 390 deaths from the AL and O arms combined, anticipated in November 2025, is recommended to be submitted (REC). Overall, a detriment in OS can reasonably be excluded.

Secondary endpoints not type-1 error tested.

ORR and DoR

At the primary analysis, the ORR by BICR was similar between the three different treatment regimens, i.e 86.2% for AL, 84.5% for O and 82.7% för L, respectively. The median DoR (95% CI) was 25.76 (20.14, NE) months for AL, 16.76 (14.75, 18.53) months for O and 16.56 (14.75, 20.21) months for L arm respectively.

Updated outputs for ORR and DoR based on the CCO of 13 May 2024 were provided during the procedure. The ORR % (95% CI) was 80% (76%, 84%) in the AL arm and 77% (72%, 81%) in the O arm, respectively. The median Duration of response (DOR) (95% CI) in the confirmed responders was 25.8 (20.3, 33.9) months in AL and 18.1 (14.8, 20.1) months in O arm, respectively.

PFS2

At the latest data update, allocation to the combination of amivantamab and lazertinib was associated with a 27% reduction in the risk of progression or death after the first subsequent therapy, i.e., PFS2 (HR= 0.73, nominal p= 0.0044)

Time to symptomatic progression (TTSP)

The median TTSP was not reached in the AL arm compared with 29.31 months in O arm.

Intracranial response endpoints

A similar intracranial ORR across the three arms, suggest similar intracranial activity for all three regimen, AL, O and L respectively (76.7%, 76.5% and 74.2% respectively). Among participants with an intracranial response by BICR, the median intracranial DOR was not estimable in the AL and O arm and 20.27 (17.81, NE) in L arm. Updated outputs for the intracranial response point estimates based on the CCO of 13 May 2024 showed consistent results with the primary analysis.

The intracranial ORR (CR+PR), % (95% CI) was 77%(70%, 83%) in the amivantamab + lazertinib arm and 77% (71%, 83%) in the osimertinib arm and the Complete response (CR) was 63% and 59%, respectively.

The median intracranial DOR was NE in the amivantamab + lazertinib arm and 24.41 months in the osimertinib arm at the updated analysis.

Although not type-1 error adjusted analyses, inclusion of intracranial ORR +DoR in section 5.1 of the SmPC is agreed, in line with recent CHMP decisions.

Patient reported outcomes

There were no clinically meaningful differences between arms in the NSCLC-SAQ and EORTC-QLQ-C30 (global quality of life) or NSCLC-SAQ (lung cancer symptom) scores. In the light of methodological

limitation in the comparison of the PRO data between arms (i.e. no prespecified handling of missing data, no prespecified type 1 error control, open label study) it is considered that the PRO claims are not warranted for inclusion in section 5.1 of the SmPC.

2.4.5. Conclusions on the clinical efficacy

A statistically significant PFS gain, along with a statistical trend towards increased OS, is shown with the combination of amivantamab with the novel third generation EGFR TKI lazertinib, compared to osimertinib, in first line in patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. Efficacy has been established. The final OS results remain to be submitted as Recommendation (November 2025).

2.5. Clinical safety

Introduction

The key safety data are derived from the safety population in pivotal study 73841937NSC3003 (hereafter referred to as MARIPOSA). Data are presented as off clinical cut-off (CCO) 11 Aug 2023.

Supportive safety data are derived from patients that received AL treatment at the recommended phase 2 combination dose (RP2CD) in study 61186372EDI1001 parts 1 and 2 (hereafter referred to as CHRYSALIS, CCO 15 Nov 2022) and study 73841937NSC1001 parts 1 and 2, cohorts A-D (hereafter referred to as CHRYSALIS-2, CCO 15 Nov 2022). Supportive data are also derived from patients who received amivantamab (A) monotherapy at the recommended phase 2 dose (RP2D) in parts 1 and 2 of the CHRYSALIS study (CCO 30 March 2021). Supportive safety data are used for comparison but are not assessed in detail.

The primary comparison of safety data is between the AL arm and O arm in the MARIPOSA study. Supportive safety data on lazertinib monotherapy from other studies than the MARIPOSA study are not assessed in detail but used for comparison when relevant (studies YH25448-201 and YH25448-301).

Furthermore, the primary analysis of the ongoing phase III study JNJ-61186372NSC3004 (hereafter referred to as PALOMA-3) was used as supportive for the introduction of prophylactic anticoagulants.

Table 32: Overview of clinical study data

Study	Study Design	Population	Treatment	Median Total Treatment Duration (months)
MARIPOSA Pivotal	Ongoing, Phase 3, randomized study; open-label for combination therapy; double-blind for osimertinib and lazertinib monotherapies	First-line EGFRm NSCLC	Ami+Laz n=421	18.50
			Osi n=428	18.00
			Laz n=213	17.05
CHRYSALIS Supportive	Ongoing, Phase 1, FIH, dose escalation, dose expansion, multi-cohort, open-label study	**Ami+Laz** Includes pooled data from multiple cohorts of patients with EGFRm NSCLC across different lines of therapy*	Ami+Laz n=97	11.01
		Amivantamab Monotherapy Includes pooled data from multiple cohorts of patients with locally advanced or metastatic NSCLC across different lines of therapy*	Ami n=380	4.14
CHRYSALIS-2 Supportive	Ongoing, Phase 1/1b, dose escalation, dose expansion, multi-cohort, open-label study	**Ami+Laz** Includes pooled data from multiple cohorts of patients with locally advanced or metastatic NSCLC*	Ami+Laz n=429	4.93
		Lazertinib Monotherapy EGFRm NSCLC	Laz n=5	8.11
YH25448-201 Supportive	Ongoing, Phase 1/2, dose escalation, dose expansion, multi-cohort, open-label study	Includes pooled data from multiple cohorts of patients with EGFRm NSCLC across different lines of therapy*	Laz n=136	12.12
YH25448-301 Supportive	Ongoing, Phase 3, randomized, double-blind study	First-line EGFRm NSCLC	Laz n=196	15.06

Patient exposure

Overall extent of exposure

Table 33: Treatment disposition, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib	Total
Analysis set: Safety	421	428	213	1062
Subjects ongoing any study agent	230 (54.6%)	213 (49.8%)	106 (49.8%)	549 (51.7%)
Discontinued all study agents	191 (45.4%)	215 (50.2%)	107 (50.2%)	513 (48.3%)
Reason for discontinuation of last study agent				
Progressive disease	86 (20.4%)	154 (36.0%)	72 (33.8%)	312 (29.4%)
Adverse event	86 (20.4%)	50 (11.7%)	29 (13.6%)	165 (15.5%)
Adverse event – COVID-19 related	2 (0.5%)	3 (0.7%)	0	5 (0.5%)
Subject refused further study treatment	14 (3.3%)	10 (2.3%)	4 (1.9%)	28 (2.6%)
Physician decision	2 (0.5%)	1 (0.2%)	0	3 (0.3%)
Non-compliance with study drug	1 (0.2%)	0	1 (0.5%)	2 (0.2%)
Lost to follow-up	1 (0.2%)	0	0	1 (0.1%)
Other	1 (0.2%)	0	1 (0.5%)	2 (0.2%)

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

[tsids04.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsids04.sas] 25SEP2023, 18:46

Duration of exposure

In MARIPOSA, the median duration of study treatment was comparable between all treatment arms; 18.50 months (range 0.2-31.4) for the AL arm compared to 18.00 months (range 0.2-32.7) for the O arm, and 17.05 months for the L arm (range 0.4-32.1).

Participants in the AL arm received a median of 16.0 cycles of amivantamab, with 215 participants (51.1%) receiving >16 treatment cycles, and two participants receiving 35 cycles (the largest number of cycles administered at the time of CCO). The median relative dose intensity (ratio of actual vs. prescribed doses, where prescribed dose includes planned interruptions) in the AL arm was 100.00% (range 2.0-100.0) for amivantamab and 96.0% (range 32.7-100.8) for lazertinib. In the O arm, the median relative dose intensity was 99.87% (range 66.7-100.3) and in the L arm 99.79% (range 74.5-100.8).

Table 34: Summary of duration of study treatment and dose intensity, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib				
	Total	Amivantamab	Lazertinib	Osimertinib	Lazertinib
Analysis Set: Safety	421			428	213
Duration of study treatment (months)					
N	421	421	421	428	213
Mean (SD)	16.98 (8.417)	14.13 (8.979)	16.97 (8.413)	16.92 (7.872)	16.23 (7.816)
Median	18.50	15.24	18.50	18.00	17.05
Range	(0.2; 31.4)	(0.0; 31.3)	(0.2; 31.4)	(0.2; 32.7)	(0.4; 32.1)
Duration of study treatment (months)					
<3	44 (10.5%)	67 (15.9%)	44 (10.5%)	25 (5.8%)	11 (5.2%)
3-<6	25 (5.9%)	47 (11.2%)	25 (5.9%)	25 (5.8%)	18 (8.5%)
6-<9	16 (3.8%)	30 (7.1%)	16 (3.8%)	33 (7.7%)	20 (9.4%)
9-<12	28 (6.7%)	28 (6.7%)	28 (6.7%)	33 (7.7%)	15 (7%)
12-<15	23 (5.5%)	35 (8.3%)	23 (5.5%)	36 (8.4%)	21 (9.9%)
15-<18	60 (14.3%)	48 (11.4%)	60 (14.3%)	61 (14.3%)	28 (13.1%)
18-<21	76 (18.1%)	52 (12.4%)	76 (18.1%)	76 (17.8%)	31 (14.6%)
21-<24	56 (13.3%)	49 (11.6%)	56 (13.3%)	54 (12.6%)	33 (15.5%)
24-<27	51 (12.1%)	38 (9%)	51 (12.1%)	44 (10.3%)	22 (10.3%)
27-<30	31 (7.4%)	22 (5.2%)	31 (7.4%)	29 (6.8%)	11 (5.2%)
30-<33	11 (2.6%)	5 (1.2%)	11 (2.6%)	12 (2.8%)	3 (1.4%)
Duration of study treatment (months)					
>=3	377 (89.5%)	354 (84.1%)	377 (89.5%)	403 (94.2%)	202 (94.8%)
>=6	352 (83.6%)	307 (72.9%)	352 (83.6%)	378 (88.3%)	184 (86.4%)
>=9	336 (79.8%)	277 (65.8%)	336 (79.8%)	345 (80.6%)	164 (77%)
>=12	308 (73.2%)	249 (59.1%)	308 (73.2%)	312 (72.9%)	149 (70%)
>=15	285 (67.7%)	214 (50.8%)	285 (67.7%)	276 (64.5%)	128 (60.1%)
>=18	225 (53.4%)	166 (39.4%)	225 (53.4%)	215 (50.2%)	100 (46.9%)
>=21	149 (35.4%)	114 (27.1%)	149 (35.4%)	139 (32.5%)	69 (32.4%)
>=24	93 (22.1%)	65 (15.4%)	93 (22.1%)	85 (19.9%)	36 (16.9%)
>=27	42 (10%)	27 (6.4%)	42 (10%)	41 (9.6%)	14 (6.6%)
>=30	11 (2.6%)	5 (1.2%)	11 (2.6%)	12 (2.8%)	3 (1.4%)
Cumulative dose (mg)					
N	-	421	421	428	213
Mean (SD)	-	26001.15 (17616.902)	103556.48 (54834.010)	39824.02 (18896.127)	112585.92 (55832.155)
Median	-	24500.00	110960.00	41900.00	117360.00
Range	-	(7.0; 95200.0)	(1360.0; 224400.0)	(400.0; 77600.0)	(3120.0; 234240.0)
Dose intensity (mg/cycle)[a]					
N	-	421	421	428	213
Mean (SD)	-	1725.51 (750.126)	5552.39 (1135.188)	2136.08 (284.015)	6320.93 (915.291)
Median	-	1704.35	5727.27	2193.98	6535.00
Range	-	(7.0; 5250.0)	(1360.0; 9120.0)	(400.0; 4000.0)	(3120.0; 13680.0)
Number of Amivantamab dose infusions					
N	-	421	-	-	-
Mean (SD)	-	30.1 (18.14)	-	-	-
Median	-	32.0	-	-	-
Range	-	(1; 69)	-	-	-
Total dose days					
N	-	-	421	428	213
Mean (SD)	-	-	485.6 (248.83)	505.8 (237.02)	485.6 (236.15)
Median	-	-	532.0	540.5	514.0
Range	-	-	(6; 935)	(5; 970)	(13; 976)

[a] Dose intensity (mg/cycle) is calculated as the sum of total doses (mg) received divided by the number of treatment cycles. Cycle is derived based on relative dose day assuming 28 days within a cycle.

[tsiex01.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsiex01.sas] 25SEP2023, 18:49

Adverse events

Adverse events overview

TEAEs were defined as any AE that occurred or worsened in severity from the initial administration of study treatment until 30 days after the last dose of study treatment or start of subsequent anti-cancer therapy (whichever was earlier). Serious adverse events (SAEs) considered by the investigator to be related to study treatment were considered treatment-related regardless of time of onset.

Table 35: Overall summary of TEAEs, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more:			
AEs	421 (100.0%)	425 (99.3%)	213 (100.0%)
Related AEs [a]	414 (98.3%)	378 (88.3%)	201 (94.4%)
Related to Amivantamab	413 (98.1%)	-	-
Related to Lazertinib	408 (96.9%)	-	201 (94.4%)
Related to Osimertinib	-	378 (88.3%)	-
Grade >=3 AEs	316 (75.1%)	183 (42.8%)	97 (45.5%)
Related grade >=3 AEs [a]	252 (59.9%)	59 (13.8%)	43 (20.2%)
Related to Amivantamab	245 (58.2%)	-	-
Related to Lazertinib	216 (51.3%)	-	43 (20.2%)
Related to Osimertinib	-	59 (13.8%)	-
Maximum toxicity grade			
Grade 1	2 (0.5%)	50 (11.7%)	18 (8.5%)
Grade 2	103 (24.5%)	192 (44.9%)	98 (46.0%)
Grade 3	259 (61.5%)	136 (31.8%)	78 (36.6%)
Grade 4	23 (5.5%)	16 (3.7%)	7 (3.3%)
Grade 5	34 (8.1%)	31 (7.2%)	12 (5.6%)
AEs leading to death [b]	34 (8.1%)	31 (7.2%)	12 (5.6%)
Serious AEs	205 (48.7%)	143 (33.4%)	75 (35.2%)
Related serious AEs [a]	97 (23.0%)	24 (5.6%)	23 (10.8%)
Related to Amivantamab	91 (21.6%)	-	-
Related to Lazertinib	73 (17.3%)	-	23 (10.8%)
Related to Osimertinib	-	24 (5.6%)	-
AEs leading to discontinuation of any study agent	147 (34.9%)	58 (13.6%)	28 (13.1%)
Discontinuation of Amivantamab	145 (34.4%)	-	-
Related to Amivantamab [a]	100 (23.8%)	-	-
Discontinuation of Lazertinib	85 (20.2%)	-	28 (13.1%)
Related to Lazertinib [a]	38 (9.0%)	-	11 (5.2%)
Discontinuation of Osimertinib	-	58 (13.6%)	-
Related to Osimertinib [a]	-	14 (3.3%)	-
AEs leading to dose reduction of any study agent	249 (59.1%)	23 (5.4%)	27 (12.7%)
Dose reduction of Amivantamab	193 (45.8%)	-	-
Related to Amivantamab [a]	184 (43.7%)	-	-
Dose reduction of Lazertinib	176 (41.8%)	-	27 (12.7%)
Related to Lazertinib [a]	165 (39.2%)	-	24 (11.3%)
Dose reduction of Osimertinib	-	23 (5.4%)	-
Related to Osimertinib [a]	-	16 (3.7%)	-
AEs leading to interruption of any study agent [c]	350 (83.1%)	165 (38.6%)	92 (43.2%)
Interruption of Amivantamab	328 (77.9%)	-	-
Related to Amivantamab [a]	282 (67.0%)	-	-
Interruption of Lazertinib	299 (71.0%)	-	92 (43.2%)
Related to Lazertinib [a]	241 (57.2%)	-	54 (25.4%)
Interruption of Osimertinib	-	165 (38.6%)	-
Related to Osimertinib [a]	-	81 (18.9%)	-
COVID-19 associated AEs [d]	136 (32.3%)	117 (27.3%)	51 (23.9%)
COVID-19 associated serious AEs [d]	13 (3.1%)	11 (2.6%)	3 (1.4%)
COVID-19 associated AEs leading to death [d]	2 (0.5%)	3 (0.7%)	0

Key: AE = adverse event
[a] An AE is assessed by the investigator as related to study agent.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] Excludes infusion related reactions.
[d] COVID-19 associated AEs are based on events that code to a COVID-19 MedDRA term and events that are identified via the COVID-19 Case of AEs form.

[tsfae01.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae01.sas] 25SEP2023, 18:49

Adverse events by system organ class and preferred term

Table 36: Number of subjects with TEAEs with frequency of >10% in any treatment group by system organ class and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more AEs	421 (100.0%)	425 (99.3%)	213 (100.0%)
System organ class Preferred term			
Skin and subcutaneous tissue disorders	383 (91.0%)	273 (63.8%)	163 (76.5%)
Rash	260 (61.8%)	131 (30.6%)	95 (44.6%)
Dermatitis acneiform	122 (29.0%)	55 (12.9%)	45 (21.1%)
Pruritus	99 (23.5%)	73 (17.1%)	36 (16.9%)
Dry skin	67 (15.9%)	60 (14.0%)	38 (17.8%)
Alopecia	15 (3.6%)	20 (4.7%)	27 (12.7%)
Infections and infestations	366 (86.9%)	279 (65.2%)	136 (63.8%)
Paronychia	288 (68.4%)	121 (28.3%)	61 (28.6%)
COVID-19	111 (26.4%)	103 (24.1%)	42 (19.7%)
Conjunctivitis	46 (10.9%)	7 (1.6%)	7 (3.3%)
Upper respiratory tract infection	37 (8.8%)	44 (10.3%)	13 (6.1%)
Gastrointestinal disorders	326 (77.4%)	298 (69.6%)	142 (66.7%)
Constipation	123 (29.2%)	55 (12.9%)	37 (17.4%)
Diarrhoea	123 (29.2%)	190 (44.4%)	68 (31.9%)
Stomatitis	122 (29.0%)	90 (21.0%)	38 (17.8%)
Nausea	90 (21.4%)	58 (13.6%)	38 (17.8%)
Vomiting	52 (12.4%)	23 (5.4%)	24 (11.3%)
General disorders and administration site conditions	307 (72.9%)	185 (43.2%)	100 (46.9%)
Oedema peripheral	150 (35.6%)	24 (5.6%)	24 (11.3%)
Asthenia	78 (18.5%)	46 (10.7%)	31 (14.6%)
Fatigue	70 (16.6%)	42 (9.8%)	23 (10.8%)
Pyrexia	51 (12.1%)	37 (8.6%)	20 (9.4%)
Mucosal inflammation	44 (10.5%)	12 (2.8%)	8 (3.8%)
Metabolism and nutrition disorders	303 (72.0%)	176 (41.1%)	87 (40.8%)
Hypoalbuminaemia	204 (48.5%)	26 (6.1%)	17 (8.0%)
Decreased appetite	103 (24.5%)	76 (17.8%)	31 (14.6%)
Hypocalcaemia	88 (20.9%)	35 (8.2%)	15 (7.0%)
Hypokalaemia	60 (14.3%)	30 (7.0%)	12 (5.6%)
Hyponatraemia	40 (9.5%)	39 (9.1%)	22 (10.3%)
Injury, poisoning and procedural complications	297 (70.5%)	39 (9.1%)	24 (11.3%)
Infusion related reaction	265 (62.9%)	0	0
Investigations	256 (60.8%)	183 (42.8%)	112 (52.6%)
Alanine aminotransferase increased	152 (36.1%)	57 (13.3%)	50 (23.5%)
Aspartate aminotransferase increased	121 (28.7%)	58 (13.6%)	45 (21.1%)
Gamma-glutamyltransferase increased	61 (14.5%)	31 (7.2%)	20 (9.4%)
Blood alkaline phosphatase increased	52 (12.4%)	22 (5.1%)	16 (7.5%)
Blood lactate dehydrogenase increased	49 (11.6%)	24 (5.6%)	21 (9.9%)
Blood creatinine increased	31 (7.4%)	49 (11.4%)	27 (12.7%)
Respiratory, thoracic and mediastinal disorders	239 (56.8%)	215 (50.2%)	100 (46.9%)
Pulmonary embolism	73 (17.3%)	20 (4.7%)	15 (7.0%)
Cough	65 (15.4%)	88 (20.6%)	37 (17.4%)
Dyspnoea	51 (12.1%)	68 (15.9%)	26 (12.2%)
Nervous system disorders	230 (54.6%)	146 (34.1%)	133 (62.4%)
Paraesthesia	58 (13.8%)	25 (5.8%)	33 (15.5%)
Headache	55 (13.1%)	54 (12.6%)	39 (18.3%)
Dizziness	49 (11.6%)	31 (7.2%)	14 (6.6%)
Neuropathy peripheral	41 (9.7%)	3 (0.7%)	23 (10.8%)
Musculoskeletal and connective tissue disorders	223 (53.0%)	180 (42.1%)	101 (47.4%)
Muscle spasms	70 (16.6%)	32 (7.5%)	50 (23.5%)
Pain in extremity	64 (15.2%)	22 (5.1%)	21 (9.9%)
Myalgia	53 (12.6%)	19 (4.4%)	11 (5.2%)
Back pain	48 (11.4%)	45 (10.5%)	22 (10.3%)
Arthralgia	38 (9.0%)	60 (14.0%)	25 (11.7%)
Blood and lymphatic system disorders	164 (39.0%)	181 (42.3%)	65 (30.5%)
Anaemia	96 (22.8%)	91 (21.3%)	43 (20.2%)
Thrombocytopenia	66 (15.7%)	84 (19.6%)	20 (9.4%)
Leukopenia	26 (6.2%)	66 (15.4%)	15 (7.0%)
Neutropenia	20 (4.8%)	56 (13.1%)	7 (3.3%)
Vascular disorders	152 (36.1%)	59 (13.8%)	41 (19.2%)
Deep vein thrombosis	61 (14.5%)	11 (2.6%)	7 (3.3%)
Psychiatric disorders	72 (17.1%)	81 (18.9%)	35 (16.4%)
Insomnia	41 (9.7%)	48 (11.2%)	13 (6.1%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

[tsfae02p10.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae02p10.sas] 25SEP2023, 18:51

Adverse drug reactions

All terms previously identified as adverse drug reactions (ADRs) with amivantamab were retained. In addition, ADRs identified from the PAPILLON and MARIPOSA-2 studies were included.

ADR methodology

Any TEAEs with an absolute incidence of (1) ≥10% in the AL arm and (2) a difference of ≥5% in the AL arm as compared to the O arm were selected for further analysis to determine if they should be classified as ADRs. Additionally, all TEAEs (regardless of frequency) were reviewed for potential plausible biological or pharmacological association with amivantamab. Where possible, similar preferred terms (PTs) were grouped together to assess specific medical concepts.

Furthermore, all SAEs, TEAEs grade ≥3, and laboratory abnormalities (including those with incidence of ≥20% in the AL arm that worsened from baseline and demonstrated a consistent up or down trend of mean values over time) were reviewed.

The frequency of occurrence for each ADR term was calculated for the 421 patients in the MARIPOSA AL arm.

ADRs

Three ADRs that are grouped terms (one new, two existing) had new PTs added to their grouping:

- Venous thromboembolism(new grouped term identified for AL combination treatment had new PTs added))
- Other eye disorders (existing grouped term)
- Nail toxicity (existing grouped term)
- Stomatitis (grouped term)
- Dry skin (grouped term)
- Rash (grouped term)

In the PAPILLON study, pyrexia and haemorrhoids were identified as new ADRs pertaining to amivantamab.

Table 37: Amivantamab adverse reactions in patients receiving amivantamab in combination with lazertinib

System organ class Adverse reaction	Frequency category	Any Grade (%)	Grade 3-4 (%)
Metabolism and nutrition disorders			
Hypoalbuminaemia*	Very common	48	5
Decreased appetite		24	1.0
Hypocalcaemia		21	2.1
Hypokalaemia		14	3.1
Hypomagnesaemia	Common	5.0	0
Nervous system disorders			
Paraesthesia*‡	Very common	34	1.7
Dizziness*		13	0
Vascular disorders			
Venous thromboembolism*	Very common	37	11
Eye disorders			
Other eye disorders*	Very common	21	0.5
Visual impairment*	Common	4.5	0
Keratitis		2.6	0.5
Growth of eyelashes*		1.9	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease/Pneumonitis *	Common	3.1	1.2
Gastrointestinal disorders			
Stomatitis*	Very common	43	2.4
Diarrhoea		29	2.1
Constipation		29	0
Nausea		21	1.2
Vomiting		12	0.5
Abdominal pain*		11	0
Haemorrhoids	Common	10	0.2
Hepatobiliary disorders			
Hepatotoxicity†	Very common	47	9
Skin and subcutaneous tissue disorders			
Rash*	Very common	89	27
Nail toxicity*		71	11
Dry skin*		26	1.0
Pruritus		24	0.5
Palmar-plantar erythrodysaesthesia syndrome	Common	6	0.2
Urticaria		1.2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	Very common	17	0.5
Myalgia		13	0.7
General disorders and administration site conditions			
Oedema*	Very common	47	2.9
Fatigue*		32	3.8
Pyrexia		12	0
Injury, poisoning and procedural complications			
Infusion related reaction	Very common	63	6

* Grouped terms
‡ Assessed as ADR for lazertinib only.
† The most common events included increased ALT (36%), increased AST (29%) and increase blood alkaline phosphatase (12%).

Treatment-related adverse events

Treatment-related TEAEs were reported for 98.3% (414/421) of participants in the AL arm (98.1% related to amivantamab; 96.9% related to lazertinib), 88.3% (378/428) of participants in the O arm, and 94.4% (201/213) of participants in the L arm. The most frequently reported treatment-related

TEAEs were generally consistent with the known safety profiles and on-target activity of amivantamab, osimertinib, and lazertinib against the EGFR pathway (e.g., rash, dermatitis acneiform, paronychia, and stomatitis) or with the on-target activity of amivantamab against the MET pathway (e.g., hypoalbuminemia and peripheral oedema), as well as IRRs in the AL arm.

Treatment-related TEAEs grade ≥3 were reported for 59.9% (252/421), 13.8% (59/428), and 20.2% (43/213) in the AL, O, and L arms, respectively.

Adverse events by severity

Table 38: Number of subjects with toxicity grade >3 TEAEs with frequency >3% in any treatment group by system organ class and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more toxicity grade 3 or higher AEs	316 (75.1%)	183 (42.8%)	97 (45.5%)
System organ class Preferred term			
Skin and subcutaneous tissue disorders	121 (28.7%)	7 (1.6%)	6 (2.8%)
Rash	65 (15.4%)	3 (0.7%)	4 (1.9%)
Dermatitis acneiform	35 (8.3%)	0	0
Infections and infestations	106 (25.2%)	38 (8.9%)	21 (9.9%)
Paronychia	46 (10.9%)	2 (0.5%)	2 (0.9%)
Pneumonia	16 (3.8%)	20 (4.7%)	6 (2.8%)
Respiratory, thoracic and mediastinal disorders	63 (15.0%)	46 (10.7%)	15 (7.0%)
Pulmonary embolism	35 (8.3%)	10 (2.3%)	8 (3.8%)
Dyspnoea	6 (1.4%)	17 (4.0%)	1 (0.5%)
Pleural effusion	6 (1.4%)	15 (3.5%)	2 (0.9%)
Metabolism and nutrition disorders	58 (13.8%)	24 (5.6%)	14 (6.6%)
Hypoalbuminaemia	22 (5.2%)	0	0
Hypokalaemia	13 (3.1%)	3 (0.7%)	5 (2.3%)
Investigations	50 (11.9%)	35 (8.2%)	18 (8.5%)
Alanine aminotransferase increased	21 (5.0%)	8 (1.9%)	6 (2.8%)
Aspartate aminotransferase increased	14 (3.3%)	5 (1.2%)	3 (1.4%)
Injury, poisoning and procedural complications	45 (10.7%)	6 (1.4%)	1 (0.5%)
Infusion related reaction	27 (6.4%)	0	0
Blood and lymphatic system disorders	29 (6.9%)	23 (5.4%)	9 (4.2%)
Anaemia	16 (3.8%)	7 (1.6%)	3 (1.4%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
Note: The event experienced by the subject with the worst toxicity is used.

Adverse events leading to dose adjustments

Dose reduction due to adverse events

Table 39: Number of subjects with TEAEs leading to dose reduction of any study agent with frequency of >1% in any treatment group by system organ class and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib			Osimertinib	Lazertinib
	Reduce Any	Reduce Amivantamab	Reduce Lazertinib	Reduce Osimertinib	Reduce Lazertinib
Analysis set: Safety	421	421	421	428	213
Subjects with 1 or more AEs leading to dose reduction of any study agent	249 (59.1%)	193 (45.8%)	176 (41.8%)	23 (5.4%)	27 (12.7%)
System organ class Preferred term					
Skin and subcutaneous tissue disorders	144 (34.2%)	105 (24.9%)	85 (20.2%)	2 (0.5%)	5 (2.3%)
Rash	84 (20.0%)	62 (14.7%)	42 (10.0%)	2 (0.5%)	3 (1.4%)
Dermatitis acneiform	38 (9.0%)	26 (6.2%)	27 (6.4%)	0	0
Rash maculo-papular	6 (1.4%)	4 (1.0%)	4 (1.0%)	0	0
Skin lesion	5 (1.2%)	5 (1.2%)	1 (0.2%)	0	0
Infections and infestations	90 (21.4%)	66 (15.7%)	53 (12.6%)	2 (0.5%)	0
Paronychia	80 (19.0%)	59 (14.0%)	48 (11.4%)	1 (0.2%)	0
Folliculitis	6 (1.4%)	3 (0.7%)	5 (1.2%)	0	0
Rash pustular	5 (1.2%)	2 (0.5%)	4 (1.0%)	0	0
Gastrointestinal disorders	26 (6.2%)	16 (3.8%)	14 (3.3%)	4 (0.9%)	4 (1.9%)
Stomatitis	5 (1.2%)	3 (0.7%)	3 (0.7%)	0	1 (0.5%)
Nervous system disorders	25 (5.9%)	8 (1.9%)	22 (5.2%)	0	15 (7.0%)
Paraesthesia	8 (1.9%)	2 (0.5%)	7 (1.7%)	0	0
Neuropathy peripheral	5 (1.2%)	3 (0.7%)	4 (1.0%)	0	6 (2.8%)
Peripheral sensory neuropathy	5 (1.2%)	1 (0.2%)	4 (1.0%)	0	4 (1.9%)
General disorders and administration site conditions	20 (4.8%)	17 (4.0%)	6 (1.4%)	1 (0.2%)	2 (0.9%)
Oedema peripheral	7 (1.7%)	5 (1.2%)	3 (0.7%)	0	0
Mucosal inflammation	5 (1.2%)	5 (1.2%)	2 (0.5%)	0	0
Metabolism and nutrition disorders	17 (4.0%)	16 (3.8%)	2 (0.5%)	4 (0.9%)	2 (0.9%)
Hypoalbuminaemia	11 (2.6%)	11 (2.6%)	1 (0.2%)	0	1 (0.5%)
Investigations	12 (2.9%)	8 (1.9%)	7 (1.7%)	6 (1.4%)	2 (0.9%)
Alanine aminotransferase increased	8 (1.9%)	5 (1.2%)	5 (1.2%)	0	1 (0.5%)
Aspartate aminotransferase increased	5 (1.2%)	4 (1.0%)	1 (0.2%)	0	1 (0.5%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

[tsfae02dsrpcut.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae02dsrpcut.sas] 06OCT2023, 10:19

Dose interruption due to adverse events

Table 40: Number of subjects with TEAEs (excluding IRRs) leading to interruption of any study agent with frequency >3% in any treatment group by system organ class and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib			Osimertinib	Lazertinib
	Interrupt Any	Interrupt Amivantamab	Interrupt Lazertinib	Interrupt Osimertinib	Interrupt Lazertinib
Analysis set: Safety	421	421	421	428	213
Subjects with 1 or more AEs leading to interruption of any study agent	350 (83.1%)	328 (77.9%)	299 (71.0%)	165 (38.6%)	92 (43.2%)
System organ class Preferred term					
Infections and infestations	204 (48.5%)	185 (43.9%)	152 (36.1%)	69 (16.1%)	25 (11.7%)
Paronychia	91 (21.6%)	84 (20.0%)	65 (15.4%)	4 (0.9%)	4 (1.9%)
COVID-19	63 (15.0%)	58 (13.8%)	38 (9.0%)	36 (8.4%)	12 (5.6%)
Pneumonia	14 (3.3%)	13 (3.1%)	9 (2.1%)	18 (4.2%)	5 (2.3%)
Skin and subcutaneous tissue disorders	191 (45.4%)	176 (41.8%)	145 (34.4%)	13 (3.0%)	16 (7.5%)
Rash	104 (24.7%)	95 (22.6%)	76 (18.1%)	4 (0.9%)	9 (4.2%)
Dermatitis acneiform	50 (11.9%)	49 (11.6%)	37 (8.8%)	1 (0.2%)	3 (1.4%)
Gastrointestinal disorders	66 (15.7%)	50 (11.9%)	56 (13.3%)	20 (4.7%)	12 (5.6%)
Diarrhoea	19 (4.5%)	15 (3.6%)	15 (3.6%)	6 (1.4%)	5 (2.3%)
Stomatitis	13 (3.1%)	10 (2.4%)	10 (2.4%)	4 (0.9%)	2 (0.9%)
General disorders and administration site conditions	60 (14.3%)	49 (11.6%)	36 (8.6%)	7 (1.6%)	10 (4.7%)
Oedema peripheral	20 (4.8%)	18 (4.3%)	10 (2.4%)	0	0
Asthenia	18 (4.3%)	12 (2.9%)	11 (2.6%)	1 (0.2%)	2 (0.9%)
Investigations	58 (13.8%)	43 (10.2%)	51 (12.1%)	40 (9.3%)	21 (9.9%)
Alanine aminotransferase increased	30 (7.1%)	25 (5.9%)	27 (6.4%)	12 (2.8%)	7 (3.3%)
Aspartate aminotransferase increased	23 (5.5%)	19 (4.5%)	22 (5.2%)	11 (2.6%)	5 (2.3%)
Gamma-glutamyltransferase increased	13 (3.1%)	10 (2.4%)	12 (2.9%)	5 (1.2%)	2 (0.9%)
Respiratory, thoracic and mediastinal disorders	50 (11.9%)	34 (8.1%)	37 (8.8%)	22 (5.1%)	8 (3.8%)
Pulmonary embolism	20 (4.8%)	16 (3.8%)	16 (3.8%)	9 (2.1%)	3 (1.4%)
Metabolism and nutrition disorders	45 (10.7%)	39 (9.3%)	31 (7.4%)	5 (1.2%)	6 (2.8%)
Hypoalbuminaemia	25 (5.9%)	23 (5.5%)	15 (3.6%)	0	0
Vascular disorders	42 (10.0%)	35 (8.3%)	26 (6.2%)	5 (1.2%)	5 (2.3%)
Deep vein thrombosis	19 (4.5%)	15 (3.6%)	13 (3.1%)	2 (0.5%)	1 (0.5%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
[tsfae02intpcut.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae02intpcut.sas] 06OCT2023, 10:19

Adverse events of special interest

Adverse events of special interest (AESIs) of pneumonitis/ILD, IRR, and rash were prospectively identified based upon the identified safety profile of amivantamab. VTE events were later identified as a risk for the combination of amivantamab and lazertinib and was added as an AESI during the study. Apart from IRR, AESIs were evaluated as grouped terms comprising more than one PT.

Table 41: Number of selected TEAEs of special interest by special interest category and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more AEs of special interest	410 (97.4%)	238 (55.6%)	159 (74.6%)
Special interest category Preferred term			
Rash	373 (88.6%)	210 (49.1%)	145 (68.1%)
Rash	260 (61.8%)	131 (30.6%)	95 (44.6%)
Dermatitis acneiform	122 (29.0%)	55 (12.9%)	45 (21.1%)
Folliculitis	27 (6.4%)	7 (1.6%)	9 (4.2%)
Rash maculo-papular	27 (6.4%)	8 (1.9%)	8 (3.8%)
Skin lesion	19 (4.5%)	5 (1.2%)	2 (0.9%)
Acne	18 (4.3%)	7 (1.6%)	3 (1.4%)
Erythema	16 (3.8%)	4 (0.9%)	4 (1.9%)
Rash pustular	16 (3.8%)	4 (0.9%)	2 (0.9%)
Dermatitis	9 (2.1%)	11 (2.6%)	3 (1.4%)
Rash pruritic	9 (2.1%)	4 (0.9%)	6 (2.8%)
Rash papular	7 (1.7%)	2 (0.5%)	0
Rash erythematous	5 (1.2%)	1 (0.2%)	2 (0.9%)
Rash macular	5 (1.2%)	3 (0.7%)	2 (0.9%)
Pustule	4 (1.0%)	2 (0.5%)	0
Dermatitis infected	3 (0.7%)	0	1 (0.5%)
Erythema multiforme	3 (0.7%)	1 (0.2%)	1 (0.5%)
Papule	3 (0.7%)	1 (0.2%)	1 (0.5%)
Drug eruption	2 (0.5%)	2 (0.5%)	3 (1.4%)
Rash follicular	2 (0.5%)	0	0
Rash vesicular	2 (0.5%)	0	0
Skin exfoliation	2 (0.5%)	6 (1.4%)	2 (0.9%)
Epidermolysis	1 (0.2%)	0	1 (0.5%)
Infusion Related Reaction	265 (62.9%)	0	0
Infusion related reaction	265 (62.9%)	0	0
Venous Thromboembolic Event	157 (37.3%)	39 (9.1%)	30 (14.1%)
Pulmonary embolism	73 (17.3%)	20 (4.7%)	15 (7.0%)
Deep vein thrombosis	61 (14.5%)	11 (2.6%)	7 (3.3%)
Venous thrombosis limb	17 (4.0%)	1 (0.2%)	4 (1.9%)
Thrombosis	9 (2.1%)	1 (0.2%)	2 (0.9%)
Venous thrombosis	8 (1.9%)	1 (0.2%)	0
Superficial vein thrombosis	6 (1.4%)	0	2 (0.9%)
Thrombophlebitis	6 (1.4%)	4 (0.9%)	0
Embolism	4 (1.0%)	3 (0.7%)	0
Embolism venous	4 (1.0%)	1 (0.2%)	2 (0.9%)
Jugular vein thrombosis	3 (0.7%)	0	0
Pulmonary infarction	2 (0.5%)	0	0
Axillary vein thrombosis	1 (0.2%)	0	0
Portal vein thrombosis	1 (0.2%)	0	0
Post thrombotic syndrome	1 (0.2%)	0	0
Sigmoid sinus thrombosis	1 (0.2%)	0	0
Superior sagittal sinus thrombosis	1 (0.2%)	0	0
Vena cava thrombosis	1 (0.2%)	0	0
Pelvic venous thrombosis	0	1 (0.2%)	1 (0.5%)
Pulmonary thrombosis	0	1 (0.2%)	0
Superior vena cava syndrome	0	1 (0.2%)	0
Pneumonitis / Interstitial Lung Disease	13 (3.1%)	13 (3.0%)	6 (2.8%)
Pneumonitis	8 (1.9%)	8 (1.9%)	3 (1.4%)
Interstitial lung disease	5 (1.2%)	5 (1.2%)	3 (1.4%)

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

[tsfae04.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae04.sas] 25SEP2023, 19:20

Rash

The median time to onset of rash was 14.0 days (range 1-556) in the AL arm and 29.0 days (range 1-799) in the O arm of the MARIPOSA study. The median time to onset of rash was 28.0 days (range 1-673) in the integrated safety set of all patients receiving fist-line lazertinib monotherapy (pivotal and supportive studies).

Use of antibiotic prophylaxis for rash at baseline was reported for 21.4% of the participants in the AL arm and 2.1% of the participants in the O arm.

Table 42: Characteristics of the AESI rash (grouped term, pivotal and supportive studies)

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Incidence (all grades)	373 (88.6%)	813 (85.9%)	210 (49.1%)	334 (60.7%)	291 (76.6%)
Grade 3+	114 (27.1%)	182 (19.2%)	4 (0.9%)	15 (2.7%)	11 (2.9%)
Serious	13 (3.1%)	24 (2.5%)	0	0	3 (0.8%)
Treatment Discontinuation	24 (5.7%)	32 (3.4%)	0	2 (0.4%)	3 (0.8%)
Amivantamab	23 (5.5%)	28 (3.0%)	NA	NA	3 (0.8%)
Lazertinib	6 (1.4%)	13 (1.4%)	NA	2 (0.4%)	NA
Osimertinib	NA	NA	0	NA	NA
Drug Interruption	179 (42.5%)	274 (28.9%)	8 (1.9%)	25 (4.5%)	38 (10.0%)
Amivantamab	163 (38.7%)	243 (25.7%)	NA	NA	38 (10.0%)
Lazertinib	134 (31.8%)	208 (22.0%)	NA	25 (4.5%)	NA
Osimertinib	NA	NA	8 (1.9%)	NA	NA
Dose Reduction	140 (33.3%)	219 (23.1%)	2 (0.5%)	22 (4.0%)	21 (5.5%)
Amivantamab	101 (24.0%)	144 (15.2%)	NA	NA	21 (5.5%)
Lazertinib	84 (20.0%)	144 (15.2%)	NA	22 (4.0%)	NA
Osimertinib	NA	NA	2 (0.5%)	NA	NA

Infusion-related reactions (IRRs)

The median time to onset of IRRs after first administration of amivantamab in the MARIPOSA study was 63.0 minutes (range 0-421).

Of the 265 (62.9%) participants with IRRs, 222 (52.7%) had an IRR associated with their first infusion of amivantamab on cycle 1 day 1.

Furthermore, 118 (28.0%) participants had an IRR associated with a subsequent amivantamab infusion, of which 75 patients had an IRR associated with the cycle 1 day 1 infusion followed by an IRR associated with a subsequent amivantamab infusion and 43 patients experienced their first IRR at later infusion than cycle 1 day 1.

Table 43: Characteristics of the AESI IRR (pivotal and supportive studies)

Adverse Event	Amivantamab + Lazertinib		Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)	
Incidence (all grades)	265 (62.9%)	619 (65.4%)	256 (67.4%)
Grade 3+	27 (6.4%)	56 (5.9%)	8 (2.1%)
Serious	9 (2.1%)	23 (2.4%)	4 (1.1%)
Treatment Discontinuation	19 (4.5%)	32 (3.4%)	4 (1.1%)
Amivantamab	19 (4.5%)	32 (3.4%)	4 (1.1%)
Lazertinib	0	1 (0.1%)	NA
Osimertinib	NA	NA	NA
Drug Interruption	229 (54.4%)	529 (55.9%)	239 (62.9%)
Amivantamab*	229 (54.4%)	528 (55.8%)	239 (62.9%)
Lazertinib	1 (0.2%)	7 (0.7%)	NA
Osimertinib	NA	NA	NA
Dose Reduction	3 (0.7%)	3 (0.3%)	0
Amivantamab	3 (0.7%)	3 (0.3%)	0
Lazertinib	0	0	NA
Osimertinib	NA	NA	NA

ILD

The median time to onset of pneumonitis/ILD was 110.0 days (range 29-443) for the AL arm and 115.0 days (range 9-512) for the O arm in the MARIPOSA study. For patients receiving lazertinib monotherapy first-line (pivotal and supportive studies), the median time to onset was 150.0 days (range 23-253).

Table 44: Characteristics of the AESI pneumonitis/ILD (grouped term, pivotal and supportive studies)

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Incidence (all grades)	13 (3.1%)	36 (3.8%)	13 (3.0%)	13 (2.4%)	10 (2.6%)
Grade 3+	6 (1.4%)	16 (1.7%)	6 (1.4%)	7 (1.3%)	2 (0.5%)
Serious	12 (2.9%)	26 (2.7%)	13 (3.0%)	10 (1.8%)	5 (1.3%)
Treatment Discontinuation	12 (2.9%)	25 (2.6%)	11 (2.6%)	9 (1.6%)	2 (0.5%)
Amivantamab	12 (2.9%)	25 (2.6%)	NA	NA	2 (0.5%)
Lazertinib	12 (2.9%)	25 (2.6%)	NA	9 (1.6%)	NA
Osimertinib	NA	NA	11 (2.6%)	NA	NA
Drug Interruption	1 (0.2%)	9 (1.0%)	3 (0.7%)	1 (0.2%)	7 (1.8%)
Amivantamab	1 (0.2%)	9 (1.0%)	NA	NA	7 (1.8%)
Lazertinib	1 (0.2%)	8 (0.8%)	NA	1 (0.2%)	NA
Osimertinib	NA	NA	3 (0.7%)	NA	NA
Dose Reduction	0	0	0	0	2 (0.5%)
Amivantamab	0	0	NA	NA	2 (0.5%)
Lazertinib	0	0	NA	0	NA
Osimertinib	NA	NA	0	NA	NA

Venous thromboembolism

As stated in the SAP and Protocol amendments section, an Urgent Safety Measure (USM) was issued for the MARIPOSA study after an imbalance in the overall incidence of VTE events associated with the AL combination treatment was identified. At the preferred PT level, pulmonary embolism (PE) (17.3% of participants in the AL arm and 4.7% of participants in the O arm) and deep venous thrombosis (DVT) (14.5% of participants in the AL arm vs. 2.6% of participants in the O arm) were the most frequently reported VTE events in both arms.

Protocol amendment 3 was implemented primarily to address the USM related to VTE. In addition to providing additional guidance for VTE event monitoring and management, the amendment added the recommendation that participants on AL combination treatment should receive prophylactic anticoagulation during the first four months of treatment. At the time of this USM, enrolment in MARIPOSA had completed and only 12 participants were eligible for prophylactic anticoagulation per the recommendation. The risk minimisation strategy with prophylactic anticoagulation therapy is further analysed in study 61186372NSC305 (see section PALOMA-3 interim analysis).

VTE events were graded according to the NCI-CTCAE Version 5.0 for thromboembolic events, where a grade 2 thromboembolic event is considered when medical intervention is indicated, and a grade 3 thromboembolic event is considered when urgent medical intervention indicated (e.g., PE or intracardiac thrombus).

Table 45: Overall summary of TEAEs of VTE event, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more:			
VTEs	157 (37.3%)	39 (9.1%)	30 (14.1%)
Maximum toxicity grade			
Grade 1	5 (1.2%)	0	1 (0.5%)
Grade 2	105 (24.9%)	24 (5.6%)	17 (8.0%)
Grade 3	43 (10.2%)	12 (2.8%)	9 (4.2%)
Grade 4	2 (0.5%)	1 (0.2%)	1 (0.5%)
Grade 5	2 (0.5%)	2 (0.5%)	2 (0.9%)
VTEs leading to death [a]	2 (0.5%)	2 (0.5%)	2 (0.9%)
Serious VTEs	46 (10.9%)	15 (3.5%)	11 (5.2%)
VTEs leading to discontinuation of any study agent	12 (2.9%)	2 (0.5%)	3 (1.4%)
Discontinuation of Amivantamab	12 (2.9%)	-	-
Discontinuation of Lazertinib	7 (1.7%)	-	3 (1.4%)
Discontinuation of Osimertinib	-	2 (0.5%)	-
Worst outcome			
Fatal	2 (0.5%)	2 (0.5%)	2 (0.9%)
Not recovered/not resolved	68 (16.2%)	15 (3.5%)	14 (6.6%)
Recovering/resolving	24 (5.7%)	6 (1.4%)	0
Recovered/resolved with sequelae	0	0	1 (0.5%)
Recovered/resolved	63 (15.0%)	16 (3.7%)	13 (6.1%)

Key: VTE = Venous Thromboembolic Event
[a] VTEs leading to death are based on AE outcome of Fatal.
[tsfae04vteovr.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae04vteovr.sas] 25SEP2023, 18:48

Most of the serious VTE events reported in the AL arm (10.9% of participants) were deemed serious because of the need for hospitalisation for initiation of anticoagulation therapy or as required by local standard of care and not for VTE symptom management.

Table 46: Summary of TEAEs of VTE event – hospitalisation and symptoms, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with any VTE	157	39	30
Subjects with any symptoms of VTE	96 (61.1%)	27 (69.2%)	19 (63.3%)
Required hospitalization or prolongation of hospitalization for VTE	43 (27.4%)	17 (43.6%)	12 (40.0%)
Reason for hospitalization[a]			
Initiation of anti-coagulation treatment	22 (14.0%)	4 (10.3%)	5 (16.7%)
Management of symptoms	13 (8.3%)	10 (25.6%)	7 (23.3%)
Required by local standard of care	9 (5.7%)	1 (2.6%)	0
Other	2 (1.3%)	2 (5.1%)	0

Key: VTE = Venous Thromboembolic Event
[a] Subjects can be counted in more than one category.
[tsfae04vtehosp.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae04vtehosp.sas] 25SEP2023, 18:50

Nearly all first VTE events occurred in participants that were not receiving concomitant anticoagulants and anticoagulation was started for nearly all participants with a first VTE event that occurred while off anticoagulants. Recurrent VTE events while on anticoagulants were uncommon. The most frequently reported VTE TEAEs were PE and DVT.

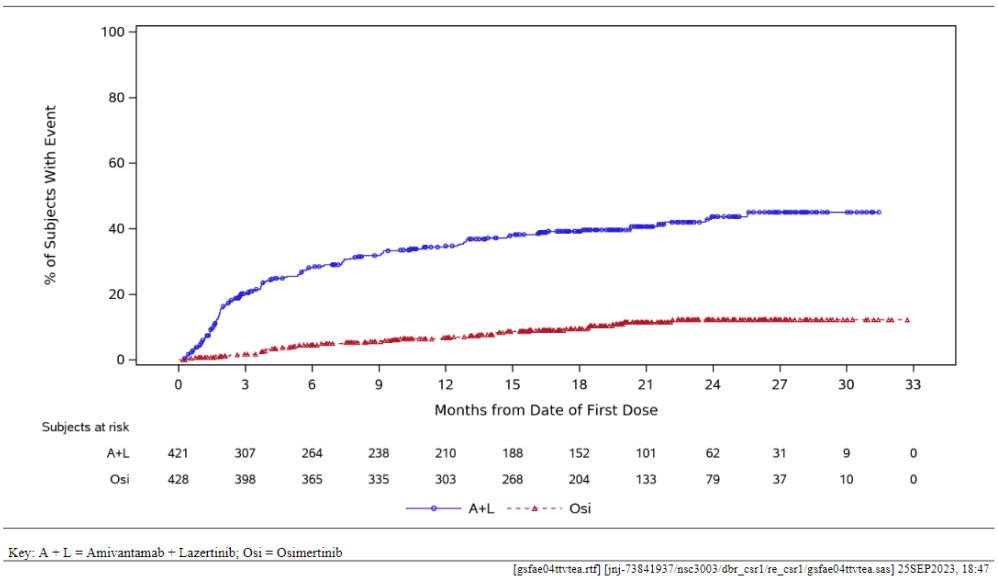
The median time to first onset of VTE event in the MARIPOSA study was 84.0 days (range 6-777) in the AL arm compared to 194.0 days (10-675) in the O arm and 240.5 days (32-774) in the L arm, respectively.

Table 47: Characteristics of the AESI of VTE events (grouped term, pivotal and supportive studies)

Adverse Event	Amivantamab + Lazertinib		Osimertinib (n=428)	Lazertinib (n=550)	Amivantamab (n=380)
	MARIPOSA (n=421)	Total (n=947)			
Incidence (all grades)	157 (37.3%)	278 (29.4%)	39 (9.1%)	69 (12.5%)	38 (10.0%)
Exposure-Adjusted (all grades, per 100 subject-years)	157 (35.2)	278 (36.2)	39 (6.6)	69 (10.1)	38 (18.5)
Incidence (Grade 3 +)	47 (11.2%)	83 (8.8%)	15 (3.5%)	28 (5.1%)	19 (5.0%)
Exposure-Adjusted (Grade 3+, per 100 subject-years)	47 (8.3)	83 (8.8)	15 (2.4)	28 (3.9)	19 (8.8)
Serious	46 (10.9%)	72 (7.6%)	15 (3.5%)	25 (4.5%)	11 (2.9%)
Treatment Discontinuation	12 (2.9%)	14 (1.5%)	2 (0.5%)	6 (1.1%)	1 (0.3%)
Amivantamab	12 (2.9%)	14 (1.5%)	NA	NA	1 (0.3%)
Lazertinib	7 (1.7%)	9 (1.0%)	NA	6 (1.1%)	NA
Osimertinib	NA	NA	2 (0.5%)	NA	NA
Drug Interruption	47 (11.2%)	67 (7.1%)	10 (2.3%)	12 (2.2%)	6 (1.6%)
Amivantamab	39 (9.3%)	56 (5.9%)	NA	NA	6 (1.6%)
Lazertinib	31 (7.4%)	47 (5.0%)	NA	12 (2.2%)	NA
Osimertinib	NA	NA	10 (2.3%)	NA	NA
Dose Reduction	5 (1.2%)	8 (0.8%)	0	2 (0.4%)	0
Amivantamab	4 (1.0%)	4 (0.4%)	NA	NA	0
Lazertinib	2 (0.5%)	5 (0.5%)	NA	2 (0.4%)	NA
Osimertinib	NA	NA	0	NA	NA

Based on the early separation of the Kaplan-Meier curves below and the short median time to first VTE event in the AL arm, prophylactic anticoagulation therapy during the first four months of AL combination treatment was recommended.

Figure 13: Kaplan-Meier plot of time to onset of first TEAEs of VTE event for amivantamab + lazertinib vs. osimertinib, safety analysis set (MARIPOSA)



Although bleeding TEAEs were observed in all three study arms, relatively few bleeding events occurred while participants were receiving anticoagulants (8.1% in the AL arm, 3.3% in the O arm, and 1.4% in the L arm, respectively). The majority of bleeding events were grade 1-2 and none were considered clinically significant. This reported incidence is comparable to other studies of anticoagulation use in similar populations (Carrier 2019). The most common sites of bleeding in the AL arm were epistaxis (1.7%) and haematuria (1.7%).

One participant in the O arm was initially reported to have a grade 5 bleeding event while on anticoagulation but was later found not to have been receiving anticoagulation at the time of the bleeding event.

Table 48: Number of subjects with TEAEs of VTE event compared with the use of anticoagulants, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more VTEs	157 (37.3%)	39 (9.1%)	30 (14.1%)
First VTE started while on anticoagulants	5 (1.2%)	0	0
First VTE started while off anticoagulants	152 (36.1%)	39 (9.1%)	30 (14.1%)
Anticoagulants initiated within 30 days of first VTE	139 (33.0%)	33 (7.7%)	28 (13.1%)
Anticoagulants not initiated within 30 days of first VTE	13 (3.1%)	6 (1.4%)	2 (0.9%)
Recurrent VTE[a] started while on anticoagulants	8 (1.9%)	0	1 (0.5%)
Subjects with 1 or more DVT or PE	116 (27.6%)	27 (6.3%)	22 (10.3%)
First DVT or PE started while on anticoagulants	6 (1.4%)	0	0
First DVT or PE started while off anticoagulants	110 (26.1%)	27 (6.3%)	22 (10.3%)
Anticoagulants initiated within 30 days of first DVT or PE	103 (24.5%)	24 (5.6%)	20 (9.4%)
Anticoagulants not initiated within 30 days of first DVT or PE	7 (1.7%)	3 (0.7%)	2 (0.9%)

Key: VTE = Venous Thromboembolic Event; DVT = Deep Vein Thrombosis; PE = Pulmonary Embolism
[a] Recurrent VTE includes any VTE that started at least 30 days after the start of first VTE.

VTE in PALOMA-3 primary analysis

Study JNJ-61186372NSC3004 (hereafter referred to as PALOMA-3) is an open-label, randomised, phase III, non-inferiority study of lazertinib with subcutaneous (SC) amivantamab compared with intravenous (IV) amivantamab in patients with EGFR-mutated advanced or metastatic NSCLC after progression on osimertinib and chemotherapy.

Due to the increased VTE risk identified in the MARIPOSA study, all patients randomised to AL combination treatment were recommended prophylactic anticoagulants as per local guidelines for the first four months of treatment. At that time-point, no patients had been randomised in the PALOMA-3 study. Hence, all PALOMA-3 patients were recommended prophylactic anticoagulant therapy.

The primary analysis report from PALOMA-3, with CCO of 04 January 2024, was provided as support for the recommendation of prophylactic anticoagulant therapy.

At the time of CCO of the primary analysis, 418 patients were enrolled in the PALOMA-3 study, of which 416 received at least one dose of study treatment and constituted the safety analysis set (SAS). Of these 416 patients, 206 were randomised to receive lazertinib + amivantamab SC and 210 to receive lazertinib + amivantamab IV. The median duration of study treatment was 4.65 and 4.12 months in the SC and IV arms, respectively. The study is still ongoing. The median duration of follow-up was 7.0 months (both arms).

Of the patients in the SAS, 335 (80.5%) received any prophylactic anticoagulant therapy for a median duration of treatment of 5.11 months (range 0.1, 131.1). Of these, 220/335 received continuous prophylactic therapy for at least four months and 115/335 received prophylactic therapy with an interruption. The remaining 81 (19.5%) of the patients in the SAS did not receive any prophylactic anticoagulation therapy. Of all patients receiving prophylactic anticoagulants, 137/335 (40.9%) discontinued anticoagulant therapy after four months.

Prophylactic anticoagulants were recommended for four months in the PALOMA-3 study, but not mandated. The treatment duration as well as administration route of prophylactic anticoagulants was decided by the responsible investigator according to local guidelines. Most of the patients (n=275,

66.1% of the SAS, 82.1% of the patients who received any anticoagulants) on prophylactic anticoagulants received DOACs (direct Factor Xa inhibitors). The remaining patients received other agents, including low molecular weight heparin derivatives and vitamin K antagonists.

Table 49: Overall summary of TEAE VTEs by anticoagulant use, safety analysis set (PALOMA-3)

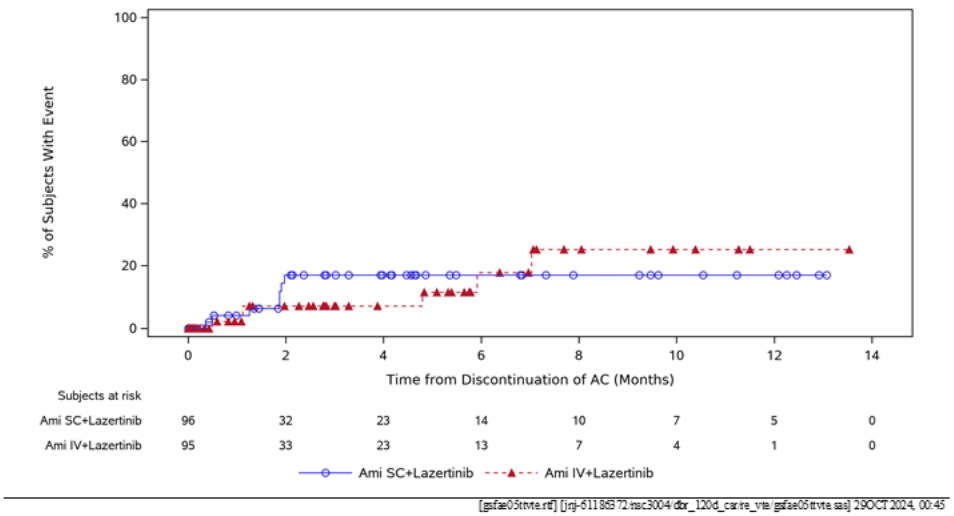
	Total	With Prophylactic Anticoagulation	No Prophylactic Anticoagulation
Analysis set: Safety	416	335	81
% of VTE* events, all grades	49 (11.8%)	32 (9.6%)	17 (21.0%)
Gr3+	9 (2.2%)	4 (1.2%)	5 (6.2%)
Gr5	0	0	0
% of VTE SAE	11 (2.6%)	5 (1.5%)	6 (7.4%)
% of VTE TEAEs leading to discontinuation	2 (0.5%)	0	2 (2.5%)

Key: VTE=Venous Thromboembolic Event; TEAE= Treatment Emergent Adverse Event; SAE=Serious Adverse Event;
Note: *VTEs include all Embolic and thrombotic events, venous (SMQ), Thrombosis and Embolism events.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.

[tsfac01avtca.rtf] [jnj-61186372/nsc3004/dbr_csr/rc_vtc/tsfac01avtca.sas] 18MAR2024, 10:33

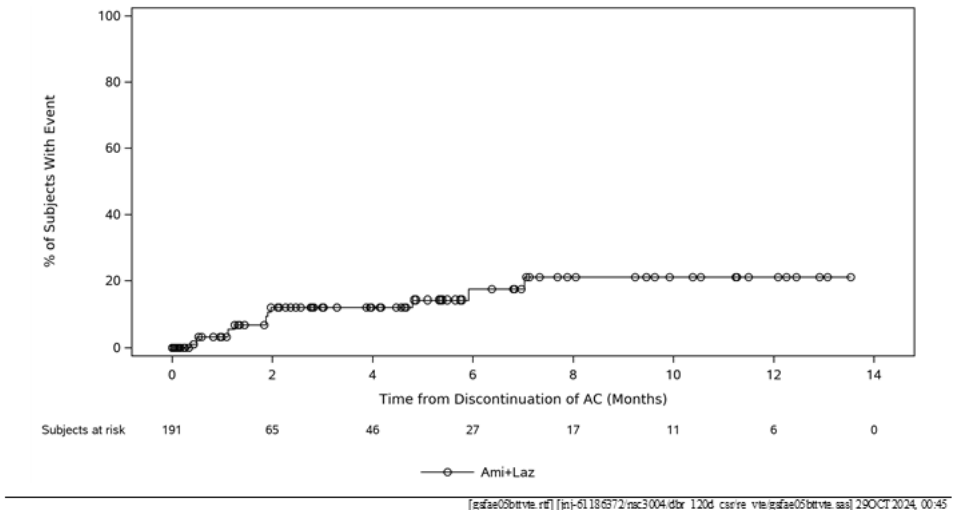
Of all VTE events, 23/49 (46.9%) were symptomatic, and 10 required hospitalisation (seven due to initiation of anticoagulants, as per local routine).The following two K-M curves, depicting time to VTE from time of discontinuing anticoagulation in patients remaining on AL treatment (i.e., censoring patients at the discontinuation of any or both study drugs), were used as support for the notion that four months of prophylactic anticoagulation, as initially recommended, was sufficient.

Figure 14: Kaplan-Meier plot for the time to onset of VTE from discontinuation of anticoagulants by treatment group, safety analysis set (PALOMA-3)



[gsfae05ttvte.rtf] [jnj-61186372/nsc3004/dbr_120d_csr/re_vte/gsfae05ttvte.sas] 29OCT2024, 00:45

Figure 15: Kaplan-Meier plot for the time of VTE from discontinuation of anticoagulants, safety analysis set (PALOMA-3)



The incidence and severity of bleeding reported for those participants who received anticoagulation is comparable to the incidence of major bleeding events in patients with lung cancer on anticoagulation (Chen 2020). Most of the bleeding events only occurred in one participant each and there was no consistent signal of a specific type of bleeding.

Table 50:Overall summary of TEAEs of bleeding, safety analysis set (PALOMA-3)

	Total	With Prophylactic Anticoagulation	No Prophylactic Anticoagulation
Analysis set: Safety	416	335	81
% of Bleeding** events, all grades	102 (24.5%)	92 (27.5%)	10 (12.3%)
Gr3+	5 (1.2%)	4 (1.2%)	1 (1.2%)
Gr5	0	0	0
% of Bleeding SAE	4 (1.0%)	4 (1.2%)	0
% of Bleeding TEAEs leading to discontinuation	1 (0.2%)	1 (0.3%)	0

Key: TEAE= Treatment Emergent Adverse Event; SAE=Serious Adverse Event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.
**based on Bleeding terms (excl laboratory terms) (SMQ)
4 subjects from with prophylactic group had bleeding event prior to the start of prophylactic anticoagulant.
[tsfac01ahcm.rtf] [jnj-61186372/nsc3004/dbr_csr/rc_vtc/tsfac01ahcm.sas] 13MAR2024, 16:47

Amivantamab IV + lazertinib VTE subgroup analysis in PALOMA-3

As the MARIPOSA study only studied use of amivantamab IV, the Applicant also submitted a subgroup analysis of participants treated with amivantamab IV + lazertinib in the PALOMA-3 study.

Table 51: Overall summary of TEAE VTE by anticoagulants use and treatment groups, safety analysis set (PALOMA-3)

	Amivantamab IV + Lazertinib		
	Total	With Prophylactic Anticoagulants	No Prophylactic Anticoagulants
Analysis set: Safety	210	171	39
% of VTE* events, all grades	30 (14.3%)	20 (11.7%)	10 (25.6%)
Gr3+	7 (3.3%)	2 (1.2%)	5 (12.8%)
Gr5	0	0	0
% of VTE SAE	7 (3.3%)	3 (1.8%)	4 (10.3%)
% of VTE TEAEs leading to discontinuation	2 (1.0%)	0	2 (5.1%)

Key: VTE=Venous Thromboembolic Event; IV=Intravenous; SC=Subcutaneous; TEAE= Treatment Emergent Adverse Event; SAE=Serious Adverse Event.
Note: *VTEs include all Embolic and thrombotic events, venous (SMQ), Thrombosis and Embolism events.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 25.1. Toxicity Grade is based on NCI common toxicity criteria, version 5.0.

Of all VTE events in the amivantamab IV subgroup, 19/30 events occurred during the first four cycles of study treatment.

Of the 210 participants in the amivantamab IV + lazertinib subgroup, 112 participants received continuous anticoagulation per protocol for the first four months of treatment and 59 participants received prophylactic anticoagulation with an interruption.

Among the 171 participants who received one or more anticoagulants in the amivantamab IV + lazertinib group, 143 (83.6%) received DOACs (direct Factor Xa inhibitors) and 28 (16.4%) received other anticoagulants including low molecular weight heparin derivatives, other antithrombotic agents, direct thrombin inhibitors, and vitamin K antagonists.

The incidence of bleeding events was 28.1% (n=48) among the 171 participants in the amivantamab IV + lazertinib group who received prophylactic anticoagulants versus and 12.8% (n=5) among the 39 participants who received no prophylactic anticoagulants. Of note, 3 of the 171 participants in the prophylactic anticoagulation group had a bleeding event and experienced the event prior to initiating anticoagulation therapy. The majority of bleeding events were grade 1-2 and non-serious regardless of prophylactic anticoagulation use.

Serious adverse event/deaths/other significant events

Serious adverse events

Table 52: Number of subjects with treatment-emergent serious adverse events with frequency of >1% in any treatment group by system organ class and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more SAEs	205 (48.7%)	143 (33.4%)	75 (35.2%)
System organ class Preferred term			
Respiratory, thoracic and mediastinal disorders	61 (14.5%)	53 (12.4%)	19 (8.9%)
Pulmonary embolism	26 (6.2%)	10 (2.3%)	8 (3.8%)
Pleural effusion	9 (2.1%)	17 (4.0%)	3 (1.4%)
Pneumonitis	7 (1.7%)	8 (1.9%)	3 (1.4%)
Respiratory failure	6 (1.4%)	2 (0.5%)	1 (0.5%)
Interstitial lung disease	5 (1.2%)	5 (1.2%)	3 (1.4%)
Dyspnoea	4 (1.0%)	11 (2.6%)	2 (0.9%)
Infections and infestations	51 (12.1%)	40 (9.3%)	18 (8.5%)
Pneumonia	17 (4.0%)	21 (4.9%)	7 (3.3%)
COVID-19	10 (2.4%)	10 (2.3%)	3 (1.4%)
Injury, poisoning and procedural complications	27 (6.4%)	9 (2.1%)	2 (0.9%)
Infusion related reaction	9 (2.1%)	0	0
Vascular disorders	25 (5.9%)	8 (1.9%)	5 (2.3%)
Deep vein thrombosis	12 (2.9%)	2 (0.5%)	1 (0.5%)
Venous thrombosis limb	4 (1.0%)	0	3 (1.4%)
Metabolism and nutrition disorders	16 (3.8%)	9 (2.1%)	2 (0.9%)
Hypoalbuminaemia	5 (1.2%)	0	0
Hyponatraemia	5 (1.2%)	4 (0.9%)	0
Cardiac disorders	15 (3.6%)	12 (2.8%)	7 (3.3%)
Pericardial effusion	4 (1.0%)	5 (1.2%)	4 (1.9%)
Cardiac failure	1 (0.2%)	5 (1.2%)	1 (0.5%)
Investigations	12 (2.9%)	9 (2.1%)	6 (2.8%)
Alanine aminotransferase increased	8 (1.9%)	6 (1.4%)	4 (1.9%)
Aspartate aminotransferase increased	1 (0.2%)	4 (0.9%)	4 (1.9%)
Skin and subcutaneous tissue disorders	11 (2.6%)	0	0
Rash	7 (1.7%)	0	0

Key: SAE = serious adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.

Deaths

Overall, deaths during study occurred at similar rates in all treatment arms (22.8% in the AL am, 27.1% in the O arm, and 26.3% in the L arm, respectively). The main reason for death during study was progressive disease (11.6%, 18.9%, 16.4%, respectively).

Early death was defined as death within 30 days of first study treatment dose. Early deaths were uncommon in all three treatments arms (1.0% [n=4], 1.9% [n=8], 0.5% [n=7], respectively).

In the AL arm, the death of four patients (1.0%) were registered as early deaths. One person died due to cardiopulmonary failure attributable to progressive disease, two persons died at home from grade 5 unexplained death (no autopsies performed), and one person died of respiratory failure secondary to pneumonia and pleural effusion.

Table 53: Summary of death and cause of death, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Deaths during study	96 (22.8%)	116 (27.1%)	56 (26.3%)
Progressive disease	49 (11.6%)	81 (18.9%)	35 (16.4%)
Adverse event	39 (9.3%)	29 (6.8%)	12 (5.6%)
Other	8 (1.9%)	6 (1.4%)	9 (4.2%)
Deaths within 30 days of first dose	4 (1.0%)	8 (1.9%)	1 (0.5%)
Adverse event	4 (1.0%)	6 (1.4%)	1 (0.5%)
Progressive disease	0	2 (0.5%)	0
Deaths within 90 days of first dose	16 (3.8%)	12 (2.8%)	5 (2.3%)
Adverse event	15 (3.6%)	9 (2.1%)	4 (1.9%)
Progressive disease	1 (0.2%)	3 (0.7%)	1 (0.5%)
Deaths within 30 days of last dose	40 (9.5%)	45 (10.5%)	20 (9.4%)
Adverse event	33 (7.8%)	27 (6.3%)	12 (5.6%)
Progressive disease	6 (1.4%)	18 (4.2%)	7 (3.3%)
Other	1 (0.2%)	0	1 (0.5%)

[tsfdth01.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfdth01.sas] 06OCT2023, 11:14

Note: Deaths attributed to other causes included deaths documented through public records, deaths due to adverse events that were outside the adverse event reporting period, and deaths with indeterminant causality for participants who previously discontinued study treatment.

TEAEs leading to death included TEAEs with an outcome of death, or any grade 5 TEAE that occurred within 30 days after the last dose of treatment or until the start of subsequent anticancer therapy (if earlier), as recorded on the AE page of the eCRF.

Pneumonia and respiratory failure were among the most commonly reported TEAEs leading to death across arms.

Of the 34 cases of TEAEs leading to death in the AL arm, four were considered by the investigator as related to study treatment (two cases of myocardial infarction, one case of sudden death, and one case of pneumonitis).

Table 54: Number of subjects with TEAEs leading to death by system organ class and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib	Osimertinib	Lazertinib
Analysis set: Safety	421	428	213
Subjects with 1 or more AEs leading to death	34 (8.1%)	31 (7.2%)	12 (5.6%)
System organ class Preferred term			
Infections and infestations	11 (2.6%)	11 (2.6%)	3 (1.4%)
Pneumonia	5 (1.2%)	4 (0.9%)	2 (0.9%)
Septic shock	2 (0.5%)	1 (0.2%)	0
Acinetobacter sepsis	1 (0.2%)	0	0
COVID-19	1 (0.2%)	3 (0.7%)	0
COVID-19 pneumonia	1 (0.2%)	0	0
Urosepsis	1 (0.2%)	0	0
Lower respiratory tract infection	0	1 (0.2%)	0
Pneumonia aspiration	0	1 (0.2%)	0
Respiratory tract infection	0	1 (0.2%)	1 (0.5%)
Sepsis	0	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	8 (1.9%)	11 (2.6%)	3 (1.4%)
Respiratory failure	4 (1.0%)	2 (0.5%)	1 (0.5%)
Pulmonary embolism	2 (0.5%)	2 (0.5%)	2 (0.9%)
Acute respiratory distress syndrome	1 (0.2%)	0	0
Pneumonitis	1 (0.2%)	0	0
Dyspnoea	0	3 (0.7%)	0
Haemoptysis	0	1 (0.2%)	0
Interstitial lung disease	0	2 (0.5%)	0
Pleural effusion	0	1 (0.2%)	0
General disorders and administration site conditions	7 (1.7%)	3 (0.7%)	2 (0.9%)
Sudden death	4 (1.0%)	1 (0.2%)	1 (0.5%)
Death	3 (0.7%)	2 (0.5%)	1 (0.5%)
Cardiac disorders	6 (1.4%)	2 (0.5%)	2 (0.9%)
Myocardial infarction	3 (0.7%)	0	0
Arteriosclerosis coronary artery	1 (0.2%)	0	0
Cardiopulmonary failure	1 (0.2%)	0	0
Coronary artery disease	1 (0.2%)	0	0
Myocardial rupture	1 (0.2%)	0	0
Pericardial effusion	1 (0.2%)	1 (0.2%)	0
Cardiac arrest	0	0	2 (0.9%)
Cardiac failure	0	1 (0.2%)	0
Nervous system disorders	2 (0.5%)	2 (0.5%)	2 (0.9%)
Cerebral infarction	1 (0.2%)	0	0
Ischaemic cerebral infarction	1 (0.2%)	0	0
Cerebral haemorrhage	0	1 (0.2%)	0
Cerebrovascular accident	0	1 (0.2%)	1 (0.5%)
Seizure	0	0	1 (0.5%)
Vascular disorders	1 (0.2%)	0	0
Circulatory collapse	1 (0.2%)	0	0
Metabolism and nutrition disorders	0	2 (0.5%)	0
Ketoacidosis	0	1 (0.2%)	0
Metabolic acidosis	0	1 (0.2%)	0

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
Note: AEs leading to death are based on AE outcome of Fatal.

Laboratory findings

Clinical laboratory tests

Laboratory results were classified according to the NCI-CTCAE Version 5.0 and included the haematology and chemistry assessments from the protocol-specified scheduled timepoints.

Haematology

The majority of haematologic laboratory abnormalities that occurred during treatment were grade 1 or 2 in all study arms. The grade 3 or grade 4 haematologic abnormalities occurred in <5% of participants in the respective treatment arms.

Overall, the incidence of haematologic TEAEs was comparable across study arms. The most common haematologic TEAE in all treatment arms was anaemia, reported for 62.3% (grade 1-2) and 3.8% (grade 3-4) in the AL arm, 75.9% (grade 1-2) and 1.9% (grade 3-4) in the O arm, and 70.6% (grade 1-2) and 1.9% (grade 3-4) in the L arm, respectively. The largest differences were noted for neutrophil count decreased grade 1-2 (-18.2% in the AL vs. O arm) and white blood cell count decreased grade 1-2 (-26.4% in the AL vs. O arm).

Chemistry

The majority of chemistry laboratory abnormalities that occurred during treatment were grade 1-2. Overall, the incidence of chemistry laboratory TEAEs was comparable across study arms.

Hypoalbuminaemia and hyponatremia were the only grade 3 abnormalities that occurred in >5% of participants in any treatment arm. There were no grade 4 abnormalities occurring in >1% of participants.

Hypoalbuminaemia grade 1-2 vs. 3-4 was reported for 85.0% and 7.9% respectively of the patients in the AL arm, 33.5% and 0.2% respectively of the patients in the O arm, and 35.1% and 0.5% respectively of the patients in the L arm.

Hyponatremia grade 1-2 vs. 3-4 was reported for 37.5% and 7.4% respectively of the patients in the AL arm, 33.8% and 6.4% respectively of the patients in the O arm, and 29.9% and 9.5% respectively of the patients in the L arm.

Hepatic function

Participants were evaluated for serious drug-induced hepatic toxicity based on eDISH criteria (i.e., ALT or AST ≥3X ULN and total bilirubin ≥2X ULN). All participants were asymptomatic from laboratory abnormalities.

The majority of hepatic function laboratory abnormalities that occurred during treatment were grade 1-2 and, overall, the incidence of hepatic function laboratory TEAEs was comparable across study arms. The only hepatic function TEAE grade 3-4 that occurred in >5% of patients in any study arm was ALT increased (6.7% CTCAE grade 3-4 in the AL arm).

Blood bilirubin increased grade 1-2 vs. grade 3-4 was reported for 15.5% and 0% of the patients respectively in the AL arm, 12.4% and 0.2% respectively in the O arm, and 20.4% and 0.5% respectively in the L arm.

Based on the safety evaluation, no signal for drug-induced serious hepatotoxicity was observed.

Electrocardiogram

Safety data from the initial monotherapy approval showed no signal for QT prolongation with amivantamab. In MARIPOSA, one participant (0.3%) in the AL arm and three participants (0.7%) in the O arm had a maximum post-baseline QTcF value >500 msec.

Safety in special populations

Age

In total, 55.4% (n=588) of the patients in the MARIPOSA study were <65 years and 44.6% (n=474) were ≥65 years. Most of the patients were <75 years; 11.2% were ≥75 years. The age distribution between the treatment arms was identical.

There were no differences in overall incidence of TEAEs, including grade ≥3 TEAEs, related to age in any of the treatment arms.

In the AL arm, there was a higher incidence of SAEs as well as discontinuation of amivantamab or lazertinib in age group ≥65 years compared to age group <65 years.

Sex

In the MARIPOSA study, 38.6% (n=410) of the patients were male and 61.4% (n=652) were female and the distribution was balanced between the treatment arms (36.3% male, 63.4% female in the AL arm, 41.6% male and 58.4% female in the O arm, and 37.1% male and 62.9% female in the L arm).

There were no differences in overall incidence of TEAEs, including grade ≥3 TEAEs and SAEs, or TEAEs leading do dose adjustment (including discontinuation) related to sex in any of the treatment arms.

Race

Of the participants in the MARIPOSA study, 58.8% (n=625) were Asian and 40.8% (n=433) were non-Asian. Race was unknown or not reported for four patients. The distribution was identical between the treatment arms.

There was no difference in overall incidence of TEAEs related to race in any of the treatment arms.

TEAEs grade ≥3, SAEs, and TEAEs leading to dose discontinuation were slightly more common among non-Asian than Asian patients in all study arms. The greatest differences were noted for TEAEs grade ≥3 (80.7% in non-Asian vs. 71.0% in Asian) and TEAEs leading to any dose discontinuation (42.1% non-Asian vs. 29.4% in Asian) in the AL arm.

Hepatic function

Hepatic function was defined as normal (total bilirubin ≤ ULN and AST ≤ ULN), mild (total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin ≤ 1.5 x ULN), moderate (1.5 x ULN < total bilirubin ≤ 3 x ULN), and severe (total bilirubin > 3 x ULN).

In MARIPOSA, there was a similar distribution between the AL and O arms of participants with normal (90.5% and 89.5%), mild (9.5% and 9.8%), moderate (0% and 0.47%), and severe (0% and 0.23%) hepatic impairment. No data on the MARIPOSA L arm were provided.

The sample sizes of the mild, moderate, and severe hepatic impairment groupings were too small to allow for meaningful comparisons of TEAEs.

Based on the population PK analysis for amivantamab and for lazertinib, no dose adjustments for amivantamab or for lazertinib are required for patients with hepatic impairment.

Renal function

Renal function was defined as normal (eGFR ≥90 mL/min/1.73m2), mild impairment (eGFR 60 to <90 mL/min/1.73m2), moderate impairment (eGFR 30 to <60 mL/min/1.73m2), or severe impairment (eGFR <30 mL/min/1.73m2).

In MARIPOSA, there was a similar distribution between the AL and O arms of participants with normal (56.3% and 57.9%), mild (38.7% and 37.6%), moderate (4.8% and 4.5%), and severe (0.24% and 0%) renal impairment. No data on the MARIPOSA L arm were provided.

The sample sizes of the moderate and severe renal impairment groupings were too small to allow for meaningful comparisons of TEAEs.

There was no consistent trend in TEAEs noted between the normal and mild renal impairment groupings in the AL arm except for SAEs. The incidence of SAEs was slightly higher in patients with mild renal impairment (53.4%) compared to patients with normal renal function (45.1%).

Based on the population PK analysis for amivantamab and for lazertinib, no dose adjustments for amivantamab or for lazertinib are required for patients with renal impairment.

Weight

In the MARIPOSA study, 87.7% (n=931) of the patients weighed <80 kg and 12.3% (n=131) weighed ≥80 kg, with a comparable distribution between the treatment arms (87.6% <80 kg and 12.4% ≥80 kg in the AL arm, 85.7% <80 kg and 14.3% ≥80 kg in the O arm, and 91.5% <80 kg and 8.5% ≥80 kg in the L arm).

The size of the subgroup of ≥80 kg was too small to allow for meaningful comparison of TEAEs between weight groups.

Mutation type

In MARIPOSA, the distribution of participants with exon 19del and of participants with exon 21 L858R was identical between all study arms (60% exon 19del, 40% exon 21 L858R, respectively). Mutation status was missing or not reported for one participant in the AL arm.

There were no differences in overall incidence of TEAEs related to mutations status in any of the treatment arms.

History of brain metastasis

In the MARIPOSA study, 40.8% (n=433) of the patients had a history of brain metastasis and 59.2% (n=629) did not. The distribution between the treatment arms was comparable (41.8% with and 58.2% without history in the AL arm, 40.0% with and 60.0% without in the O arm, and 40.4% with and 59.6% without history in the L arm).

There were no differences in overall incidences of TEAEs related to history of brain metastasis in any of the treatment arms. SAEs were slightly more common in the subgroup with history of brain metastasis compared to the subgroup without in all study arms. In the AL arm, SAEs were reported for 58.5% of the patients with a history vs. 41.6% of the patients without a history of brain metastasis.

ECOG performance status

In total, 33.9% (n=360) of the patients had ECOG performance status (ECOG PS) 0 at baseline and 66.1% (n=702) hade ECOG PS 1. The distribution was comparable between the treatment arms (32.7% ECOG 0 and 67.2% ECOG 1 in the AL arm, 34.8% ECOG 0 and 65.2% ECOG 1 in the O arm, and 34.3% ECOG 0 and 65.7% ECOG 1 in the L arm).

There were no differences in overall incidences of TEAEs related to ECOG PS in any of the treatment arms. SAEs were slightly more common in the ECOG 1 compared to ECOG 0 groups in all study arms. In the AL arm, SAEs were reported for 54.4% in the ECOG 1 group vs. 37.0% in the ECOG 0 group.

Smoking

In the MARIPOSA study, a minority of patients had a history of smoking (31.6% [n=336] history of smoking vs. 68.4% [726] no history of smoking). The distribution between the treatment arms was comparable (30.6% with and 69.4% without history of smoking in the AL arm, 31.3% with and 68.7% without history of smoking in the O arm, and 34.3% with and 65.7% without history of smoking in the L arm).

There was no difference in overall incidence of TEAEs related to history of smoking yes/no in any of the treatment arms. SAEs were slightly more common in the subgroup without history of smoking in the AL arm (50.7% without history of smoking vs. 44.2% with history of smoking).

Safety related to drug-drug interactions and other interactions

Amivantamab is a monoclonal antibody. PK DDI’s are not anticipated. All safety findings are additive or synergistic with Lazertinib,

Discontinuation due to adverse events

TEAEs led to discontinuation of any study drug (defined as discontinuation of at least one study agent received) for 34.9% of participants in the AL arm, 13.6% of participants in the O arm, and 13.1% of participants in the L arm. Discontinuation of both amivantamab and lazertinib due to TEAEs occurred for 20.4% of participants in the AL arm.

Table 55: Number of subjects with TEAEs leading to discontinuation of any study agent with frequency of >1% in any treatment group by system organ class and preferred term, safety analysis set (MARIPOSA)

	Amivantamab + Lazertinib			Osimertinib	Lazertinib
	Discontinue Any	Discontinue Amivantamab	Discontinue Lazertinib	Discontinue Osimertinib	Discontinue Lazertinib
Analysis set: Safety	421	421	421	428	213
Subjects with 1 or more AEs leading to discontinuation of any study agent	147 (34.9%)	145 (34.4%)	85 (20.2%)	58 (13.6%)	28 (13.1%)
System organ class Preferred term					
Infections and infestations	33 (7.8%)	31 (7.4%)	17 (4.0%)	10 (2.3%)	4 (1.9%)
Paronychia	14 (3.3%)	14 (3.3%)	2 (0.5%)	0	1 (0.5%)
Pneumonia	8 (1.9%)	8 (1.9%)	8 (1.9%)	3 (0.7%)	2 (0.9%)
Respiratory, thoracic and mediastinal disorders	31 (7.4%)	30 (7.1%)	26 (6.2%)	19 (4.4%)	11 (5.2%)
Pulmonary embolism	8 (1.9%)	8 (1.9%)	6 (1.4%)	2 (0.5%)	3 (1.4%)
Pneumonitis	7 (1.7%)	7 (1.7%)	7 (1.7%)	7 (1.6%)	3 (1.4%)
Interstitial lung disease	5 (1.2%)	5 (1.2%)	5 (1.2%)	4 (0.9%)	3 (1.4%)
Skin and subcutaneous tissue disorders	27 (6.4%)	26 (6.2%)	7 (1.7%)	0	0
Rash	11 (2.6%)	10 (2.4%)	3 (0.7%)	0	0
Dermatitis acneiform	6 (1.4%)	6 (1.4%)	1 (0.2%)	0	0
General disorders and administration site conditions	23 (5.5%)	21 (5.0%)	13 (3.1%)	6 (1.4%)	3 (1.4%)
Asthenia	5 (1.2%)	5 (1.2%)	1 (0.2%)	1 (0.2%)	0
Oedema peripheral	5 (1.2%)	5 (1.2%)	1 (0.2%)	0	0
Injury, poisoning and procedural complications	21 (5.0%)	21 (5.0%)	1 (0.2%)	1 (0.2%)	0
Infusion related reaction	19 (4.5%)	19 (4.5%)	0	0	0
Metabolism and nutrition disorders	9 (2.1%)	9 (2.1%)	3 (0.7%)	3 (0.7%)	0
Hypoalbuminaemia	6 (1.4%)	6 (1.4%)	2 (0.5%)	0	0

Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 25.0.
[tsfae02dscpcut.rtf] [jnj-73841937/nsc3003/dbr_csr1/re_csr1/tsfae02dscpcut.sas] 06OCT2023, 10:19

Post marketing experience

There are currently no post marketing data on the combination of amivantamab and lazertinib.

Post marketing data for amivantamab monotherapy has been accruing since the first marketing approval in 2021. Based on 22,364,767 milligrams distributed worldwide by the company from launch on 21 May 2021 to 31 May 2023, the estimated exposure to amivantamab is 1,825 treatment courses. The post marketing safety profile of amivantamab monotherapy is consistent with the safety information provided in the product information. No new major safety issues have been identified outside clinical trials.

2.5.1. Discussion on clinical safety

The safety assessment is focused on data from the pivotal study MARIPOSA in patients with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R mutations. Data from the phase III, non-inferiority PALOMA -3 study comparing SC. and IV amivantamab as add-on to lazertinib were submitted as support for the recommendation of prophylactic anticoagulant therapy.

In MARIPOSA, 421 patients received treatment with amivantamab + lazertinib (AL), 428 osimertinib (O) monotherapy, and 213 lazertinib (L) monotherapy treatment. The size of the safety database is considered acceptable. The patient exposure appears acceptable and evokes no concern.

The scope of the application is AL vs. O treatment. Data are presented as of clinical cut-off (CCO) 11 Aug 2023. Data on the L arm are used for comparison only.

The median duration of study treatment was comparable between all treatment arms; 18.50 months in the AL arm compared to 18.00 months in the O arm, and 17.05 months in the L arm, respectively.

Almost all patients in the MARIPOSA study experienced TEAEs of any grade (100.0% in the AL and L arms, 99.3% in the O arm).

The incidence of TEAEs related to study treatment was higher in the AL arm (98.3%) than in the O and L arms (88.3% and 94.4%, respectively). Among the most common TEAEs with ≥10% higher incidence in the AL arm compared to any of the comparator arms were rash (+32.2% vs O, +17.2% vs L), dermatitis acneiform (+16.1% vs O, +7.8% vs L), paronychia (+40.3% vs. O, +40.0% vs. L), and ALT and AST increased (+22.8% and +15.% vs. O, +12.6% and +7.6% vs. L), all pertaining to EGFR inhibition and attributable to both amivantamab and lazertinib. Other common TEAEs were hypoalbuminaemia (+42.4% vs. O, +40.5% vs. L) and peripheral oedema (+30.0% vs. O, + 24.3% vs. L), pertaining to MET inhibition and attributable to amivantamab.

Due to the increased risk of skin toxicities with AL treatment, the existing information in the SmPC 4.4 was expanded. The warning in section 4.4 now emphasizes that prophylactic therapy with oral antibiotic (e.g., doxycycline or minocycline, 100 mg twice daily) is to be initiated on Day 1 and to be continued for the first 12 weeks of treatment. After completion of oral antibiotic therapy, topical antibiotic lotion should be used to the scalp (e.g., clindamycin 1%) for the next 9 months of treatment. Non-comedogenic skin moisturiser on the face and whole body (except scalp) is to be considered for the first 12 months of treatment. It also recommended to have prescriptions for topical and/or oral antibiotics and topical corticosteroids available at treatment start to aid active management if rash is observed. IRR is an established ADR of amivantamab and associated with injection therapy. As in previous amivantamab studies the incidence of IRR in the AL arm was high (62.9%).

Overall, the reported TEAE incidences in the AL arm were higher than in the supportive studies on amivantamab and lazertinib monotherapy. AL combination treatment, thus, appears considerably more toxic than the individual treatment components alone.

Most TEAEs in all treatment arms were grade 1-2. The incidence of grade ≥3 treatment-related TEAEs was significantly higher in the AL arm (59.9%) compared to the O and L arms (13.8% and 20.2%, respectively). Of these, the vast majority were grade 3. Grade 4 and 5 TEAEs were reported at low and comparable levels in all three treatment arms (5.5%, 3.7%, and 3.3% grade 4 in the AL, O, and L arms, respectively compared to 8.1%, 7.2%, and 5.6% grade 5, respectively).

The incidence of SAEs was also higher in the AL arm (48.7%) than in the comparator arms of the MARIPOSA study (33.4% in the O arm, 35.2% in the L arm, respectively). The main difference was attributable to the new ADR VTE (see below).

TEAEs leading to dose reductions and dose interruptions of any study agent occurred more frequently in the AL arm (59.1% dose reduction, 83.1% dose interruption) compared with both the O arm (5.4% dose reduction, 38.6% dose interruption) or L arm (12.7% and 43.2%, respectively). These differences were largely driven by a higher proportion of participants in the AL arm with cutaneous toxicities.

Overall, dose reductions and interruptions due to TEAEs were significantly more common in the AL arm of the MARIPOSA study compared to supportive studies of amivantamab and lazertinib monotherapy, further underlining the increased toxicity with AL combination treatment.

In the AL arm, more TEAEs led to discontinuation of amivantamab (34.9%) than of lazertinib (20.2%) and most of the TEAEs leading to treatment discontinuation were known amivantamab related TEAEs, e.g., paronychia, rash and dermatitis acneiform, peripheral oedema, hypoalbuminaemia, and IRR. Although 20.4% discontinued both amivantamab and lazertinib due to TEAEs (vs. 13.6% discontinuation of osimertinib and 13.1% lazertinib), the majority of patients could continue their treatment with the help of dose adjustments and supportive measurements.

There were no differences in overall incidence of TEAEs related to the subgroups of special populations in any of the treatment arms. Although the incidence of overall AEs was similar in both <65 and ⩾65 subpopulations, older patients (≥ 65 years of age) reported more Grade 3 or higher adverse events compared to patients < 65 years of age (81% vs. 70%). While the rates of drug interruptions and dose reductions were similar, the rate of adverse events leading to any treatment discontinuation was higher in patients ≥ 65 years of age compared to patients < 65 years of age (47% vs. 25%).This is reflected in section 4.8 of the SmPC.

Venous thromboembolism

The incidence of VTE events in MARIPOSA, comprising e.g., pulmonary embolism (PE), DVT, and other venous thrombotic events, was significantly higher in the AL arm (37.3%) than in the comparator arms (9.1% O, 14.1% L) and VTE was identified as a new ADR for AL combination treatment.

This prompted an Urgent Safety Measure (USM). Prophylactic anticoagulants were recommended during the first four months of study treatment since, according to the Applicant, the VTE risk was greatest during this time-period.

As support for the prophylactic anticoagulant therapy, the Applicant provided the primary analysis of the ongoing PALOMA-3 study (SC vs. IV amivantamab plus lazertinib). In this study, the majority of patients received prophylactic anticoagulants (335/416 [80.5%] any anticoagulants vs. 81/416 [19.5%] no anticoagulants).

It is noted that none of the MARIPOSA or PALOMA-3 studies were designed to investigate the required duration of anticoagulation. PALMOMA-3 was also performed in a later-line setting where the duration of AL combination treatment was considerably shorter than anticipated in the first line setting.

Furthermore, the duration of prophylactic therapy in PALOMA-3 was at the investigators'/treating physicians' discretion. It was recommended for four months but not mandatory. Interestingly, the median duration of prophylactic therapy was 5.11 months, i.e., longer than the median duration of study treatment (4.65 and 4.12 months for amivantamab SC vs. IV, respectively) and longer than the recommended four months.

Prophylactic anticoagulants significantly decreased the risk of VTE in PALOMA-3 participants (9.6% VTEs in patients with anticoagulants vs. 21.0% in patients without). Only a minority (137/335 [40.9%]), though, discontinued anticoagulants after four months, making it difficult to draw any conclusions on the risk of experiencing a VTE while still on AL treatment but after discontinuing anticoagulants. Data do, thus, not suffice to recommend only four months of prophylactic anticoagulants. The risk may also differ depending on mode of administration.

Prophylactic anticoagulants are both safe and do effectively mitigate the risk of VTE during AL treatment. A warning was implemented in the SmPC 4.4, emphasising that patients treated with AL should receive prophylactic anticoagulants with DOACs or LMWHs. Furthermore, patients should be monitored for signs and symptoms of VTE and treated as clinically indicated in the event of a VTE. For patients who are clinically circulatory unstable, AL treatment should be temporarily withheld and resumed only when the patient is clinically stable. In the event of a recurrent VTE, despite appropriate anticoagulation, amivantamab should be discontinued but lazertinib monotherapy can be continued.

VTE was also added to the RMP as an important identified risk associated with AL combination treatment and prophylactic anticoagulation identified as a measure to minimise this risk.

2.5.2. Conclusions on clinical safety

The safety dataset is sufficiently large to describe the safety profile of amivantamab + lazertinib (AL) combination treatment. The toxicity with AL combination treatment is significantly increased compared to both the well characterised toxicity of amivantamab monotherapy and the toxicity profile of lazertinib monotherapy. This includes pronounced increased incidence of grade $\geq$3 (60% versus 14-20%) and SAE (49% versus 33-35%). Moreover, VTE has been identified as a new adverse reaction for the combination of amivantamab and lazertinib. This risk is mitigated by the use of concomitant anticoagulant therapy throughout treatment.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.2 with the following content:

Safety concerns

Important Identified Risks	Infusion-related reaction
	Venous thromboembolic (VTE) events*
Important Potential Risks	Hepatotoxicity
	Impaired fertility and embryofetal toxicity
Missing Information	None

* Applies only to the combination of amivantamab and lazertinib.

Venous thromboembolic events have been added as an important identified risk for the combination of amivantamab and lazertinib. No other changes in the Summary of Safety Concerns.

Pharmacovigilance plan

The pharmacovigilance plan remains unchanged.

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Infusion-related reaction	**Routine risk minimization measures:** SmPC Section 4.2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 3 PL Section 4 Recommendations to administer RYBREVANT in a setting with appropriate medical support, for administration of pre-infusion medicinal products, for RYBREVANT initial infusion administration in split doses on Week 1 (Days 1 and 2), and for RYBREVANT administration via specific infusion rates are provided in SmPC Sections 4.2 and 4.4, and PL Section 3. Recommendations regarding the management of IRRs (eg, interruption or discontinuation of infusion, administration of supportive medicinal products) are provided in SmPC Sections 4.2 and 4.4, and PL Section 4. Patients with side effects during infusion of RYBREVANT should notify their doctor or nurse immediately, as described in PL Sections 2 and 4. Legal status. **Additional risk minimization measures:** None	None **Additional pharmacovigilance activities:** None
Venous thromboembolic (VTE) events*	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4. An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4 and PL Section 2. Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. Legal status. **Additional risk minimization measures:** None	
Hepatotoxicity	**Routine risk minimization measures:** SmPC Section 4.8 PL Section 4 Legal status. **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Impaired fertility and embryofetal toxicity	**Routine risk minimization measures:** SmPC Section 4.6 SmPC Section 5.3 PL Section 2 The potential harmful effects of EGFR inhibition on embryofetal	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of amivantamab, are provided in SmPC Section 4.6 and PL Section 2. Patients should notify their doctor or nurse immediately about a potential or confirmed pregnancy before and during treatment with RYBREVANT, as described in PL Section 2. Legal status. **Additional risk minimization measures:** None	

* Applies only to the combination of amivantamab and lazertinib.

Routine risk minimisation measures remain sufficient to mitigate the risks of Amivantamab.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated. Particularly, new warnings and recommendations with regard to VTE and skin and nails reactions have been added to the product information. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Germany and Northern Ireland.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There have not been revisions that significantly affect the overall readability and design of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The approved new indication is:

Rybrevant is indicated:

- *in combination with lazertinib for the first line treatment of adult patients with advanced non small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations.*

Among patients with NSCLC of adenocarcinoma histology, the most prevalent of these driver mutations that are actionable are those that result in the activation of EGFR, which are identified in approximately 15% of Western patients (Pao 2011) and up to 50% of Asian patients (Jänne 2006). The most frequently identified EGFR mutations, exon 19 deletions and exon 21 L858R substitution mutations, are seen in approximately 85% of patients with NSCLC harbouring activating EGFR mutations (Gazdar 2009; Harrison 2020).

3.1.2. Available therapies and unmet medical need

The current standard of care for the first-line treatment of EGFRm NSCLC is a third-generation EGFR TKI, most commonly osimertinib. Osimertinib have demonstrated improved PFS and OS in comparison with previous generations of TKIs.

Despite the improved initial disease control, almost all patients treated with first-line osimertinib will develop resistance, and there are no approved targeted therapies for treatment of these patients once resistance has developed. While osimertinib represents a significant advance over earlier EGFR TKIs, there is a need to improve first-line treatment prior to the development of resistance in order to improve treatment outcomes beyond what is seen with available therapies.

3.1.3. Main clinical studies

The pivotal study for this application is MARIPOSA study. This is an ongoing, randomized, multicentre Phase 3 study planned as three arm study to compare the combination of amivantamab and lazertinib (AL in arm A) with osimertinib (O in arm B) and with lazertinib (L in arm C), respectively.

The ITT population consists of 1074 participants randomized 2:2:1(429 to AL, 429 to O, and 216 to L).

Since Osimertinib monotherapy represents the present standard of care, evaluation of AL combination in comparison with O was type 1 error-controlled. Lazertinib shares mechanism of action with Osimertinib. The comparison of AL with L was not included in the hypothesis testing and was intended to allow for the evaluation of mono-components contribution to AL.

All patients in MARIPOSA tested positive for either of the two relevant EGFR mutations: Exon 19 deletions or Exon 21 L858R substitution mutations. The primary endpoint was PFS by BICR and the key secondary endpoint was OS.

3.2. Favourable effects

The inferential PFS analysis by BICR showed a statistically significant benefit with AL combination versus O with PFS HR 0.70 (95% CI; 0.58, 0.85); p-value 0.0002. The median PFS gain was 7 months (median PFS 23.7 months in AL arm vs 16.6 months in O arm).

The PFS benefit was consistent across all pre-defined subgroups.

At the time of the inferential PFS analysis, OS was tested at a maturity rate of approximately 25% and with 270 events in the entire study. A numerical trend towards improved survival with AL versus O was observed with HR (95% CI) HR=0.80 (0.61, 1.05), p=0.1099.

At the updated OS analysis (CCO 13 May 2024) with additionally 9 months FU (totally 31 months median FU) and 129 more events in the entire study, the HR was 0.77 (0.61, 0.96) p 0.0185. Median survival was not reached with AL combination compared with 37.32 (32.53, NE) months with O. Maturity was still limited with 33% events in AL arm compared with 41% events in O arm and 37% events in L arm.

3.3. Uncertainties and limitations about favourable effects

The impact of amivantamab + lazertinib over osimertinib on OS has not been statistically established. The final OS analysis planned per protocol when 490 deaths overall (all treatment arms combined) and 390 deaths from the AL and O arms combined is anticipated in November 2025. The final OS data will be submitted by the MAH as a post authorisation measure **(REC).**

3.4. Unfavourable effects

The safety assessment is based on the MARIPOSA trial with patients randomised to amivantamab + lazertinib (AL, n=421), osimertinib monotherapy (O, n=428), or lazertinib monotherapy (L, n=213). The size of the safety data set is considered acceptable.

The overall median duration of treatment was 18.05 months in the AL arm compared to 18.00 months in the O arm and 17.50 months in the L arm, respectively.

The most frequently occurring TEAEs in the AL arm corresponded to known amivantamab ADRs pertaining to EGFR and MET inhibition.

Among TEAEs by PT with ≥10% incidence in the AL arm were rash and dermatitis acneiform (89%), nail toxicity (mostly paronychia_ 71%), and ALT and AST increased (36% and 29%), all pertaining to EGFR inhibition and attributable to both amivantamab and lazertinib.

Other common TEAEs were hypoalbuminaemia (48%) and peripheral oedema (47%), pertaining to MET inhibition and attributable to amivantamab.

As in previous amivantamab studies the incidence of IRR in the AL arm was high (62.9%).

The incidence of grade ≥3 treatment-related TEAEs was higher in the AL arm (59.9%) compared to the O and L arms (13.8% and 20.2%, respectively). The majority of grade ≥3 TEAEs were related to inhibition of the EGFR pathway. Among the most common grade ≥3 TEAEs were rash and dermatitis acneiform, paronychia, and pulmonary embolism (PE). PE is part of the new ADR VTE.

Grade 4 and 5 TEAEs were reported at low and comparable levels in all three treatment arms (5.5%, 3.7%, and 3.3% grade 4 in the AL, O, and L arms, respectively compared to 8.1%, 7.2%, and 5.6% grade 5, respectively).

The incidence of SAEs was also higher in the AL arm (48.7%) than in the comparator arms of the MARIPOSA study (33.4% in the O arm, 35.2% in the L arm, respectively). The main difference was attributable to the new ADR VTE.

In total 20.4% of the patients in the AL arm discontinued all study treatment due to TEAEs (compared to 13.6% in the O arm and 13.1% in the L arm, respectively).

At CCO, 34 patients (8.1%) in the AL arm died due to TEAEs. Four cases were considered related to the study treatment by the investigator (two cases of myocardial infarction, one case of sudden death, and one case of pneumonitis).

37.3% of patients in the AL arm experienced a VTE event. There were two (0.5%) fatal VTE events in the AL arm. VTE is a new ADR associated with AL treatment. It appears to be a synergistic effect when this is given together with lazertinib.

3.5. Uncertainties and limitations about unfavourable effects

Data from PALOMA-3 indicate that, as anticipated, prophylactic anticoagulation will reduce the VTE risk. Therefore as a risk minimisation measure prophylactic anticoagulation should be given while on treatment as indicated in section 4.2 and 4.4 of the SmPC.

3.6. Effects Table

Table 56: Effects Table for study MARIPOSA

Effect	Short Description	Unit	Treatment Ami+Lazer n=429	Control Osimertinib n=429	Uncertainties/ Strength of evidence	References
Favourable Effects						
Median BICR-PFS	Progression free survival by blinded independent central review	Months	23.7 95% CI 19.1, 27.7 HR 0.70 95% CI 0.58, 0.85	16.6 95% CI 14.8, 18.5	Primary PFS analysis, DCO 11 Aug 2023 Stat. significant for AL vs. O.	CSR
Median OS	Overall survival	Months	NE 95% CI NE, NE HR 0.77 95% CI 0.61, 0.96	37.3 95% CI 32.5, NE	OS updated analysis, DCO 13 May 2024 Not stat. significant for AL vs. O. Immature data.	CSR
Unfavourable Effects						
AEs	Any adverse event	%	100	99		SCS, ISS
≥G3 AEs	Grade 3 or higher AEs	%	75	43		SCS, ISS

Effect	Short Description	Unit	Treatment Ami+Lazer n=429	Control Osimertinib n=429	Uncertainties/ Strength of evidence	References
SAEs	Serious AEs	%	49	33		SCS, ISS
G5 AEs	AEs leading to death	%	8	7		SCS, ISS
AEs discount	AEs leading to discontinuation	%	35	14		SCS, ISS
AEs interrupt	AEs leading to interruption	%	83	39		SCS, ISS
AEs reduction	AEs leading to dose reduction	%	59	5		SCS, ISS
Rash	Rash and dermatitis acneiform	% All % G3-4%	89 27	47 1		SCS, ISS
IRR	Infusion related reactions	% All % G3-4%	63 6	0		SCS, ISS
Nail toxicity	Mostly paronychia	% All % G3-4%	71 11	33 1		SCS, ISS
VTE	Venous thromboembolism	% All % G3-4%	37 11	8 3		SCS, ISS
Hepatotoxicity		% All % G3-4%	47 9	25 4		SCS, ISS

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the primary analysis (final analysis for PFS and interim for OS) MARIPOSA study has demonstrated a statistically significant PFS gain with amivantamab in combination with lazertinib (AL) (HR 0.70 (95% CI; 0.58, 0.85); p-value 0.0002) versus osimertinib, in patients with EGFR mutations positive advanced NSCLC in first line setting. The size of this effect is deemed clinically relevant in accordance with precedent.

At the time of the interim analysis, OS was trending towards a benefit, with an upper bound of the 85% CI at 1.05, indicating that any detrimental effect is unlikely. A data update at approximately 35% maturity shows an OS HR 0.77 (0.61, 0.96) with a nominal p 0.0185. This provides reassurance that there will be no detrimental effect and is indicative that a positive final OS result may be likely. The Applicant will submit final OS data to fulfil the CHMP Recommendation, the final CSR is anticipated by November 2025 (REC).

The safety dataset is sufficiently large to describe the safety profile of AL combination treatment. The toxicity associated with AL treatment is significantly increased compared to both the well characterised toxicity of amivantamab monotherapy and the toxicity profile of lazertinib monotherapy. This includes pronounced increased incidences of grade ≥3 TEAEs (60% versus 14-20%) and SAEs (49% versus 33-35%)

VTE was identified as a new ADR for AL treatment, with an incidence of 37.3% (11.7% grade ≥3, 10.9% SAEs), including two fatal cases (0.5%). VTE is a significant toxicity but should be minimised by the recommendation for prophylactic anticoagulant therapy throughout the whole treatment.

3.7.2. Balance of benefits and risks

Overall, a clinically relevant PFS gain has been shown. A detrimental effect on OS may be ruled out, and a positive final OS result may be considered likely. There is considerable additional toxicity. However, the most common adverse effects are anticipated to be reversible, and PRO outcomes do not seem to indicate a clinically meaningful deterioration. An increased risk of VTE has been shown when amivantamab is combined with lazertinib; however, this has been demonstrated to be manageable with the recommendation for prophylactic anticoagulant therapy throughout the duration of treatment.

Consequently, the beneficial effect of amivantamab in combination with Lazertinib outweighs the risks.

3.8. Conclusions

The overall B/R of amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations is positive. The MAH will submit final OS data by November 2025 (REC).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include amivantamab in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR exon 19 deletions or exon 21 L858R substitution mutations (EGFRm NSCLC), based on results from study 73841937NSC3003 (MARIPOSA). This is a randomized, open-label, Phase 3 study that compares the efficacy and safety of the combination of amivantamab and lazertinib (Arm A) versus osimertinib monotherapy (Arm B) and lazertinib monotherapy (Arm C) in participants with EGFRm NSCLC. The primary objective of the MARIPOSA study was to assess the efficacy of the combination of amivantamab and lazertinib (Arm A), compared with osimertinib (Arm B), as measured by PFS assessed by BICR in adult participants with EGFRm NSCLC.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.2 of the EU RMP has also been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

-At the request of the European Medicines Agency;

-Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.