Amivantamab and lazertinib (NSCLC, first line 1)

Addendum to Project A25-08 | A25-11 (dossier assessment)[1]

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ILD	Interstitial lung disease
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non–Small Cell Lung Cancer Symptom Assessment Questionnaire
PFS	progression-free survival
PGIS	Patient Global Impression of Severity
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
VTE	thromboembolic events

1 Background

On 12 June 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-08 and Project A25-11 (Amivantamab and lazertinib – Benefit assessment according to § 35a Social Code Book V) [1].

The order comprises the analysis of the final data cut-off from 4 December 2024 of the MARIPOSA study, taking into account the information subsequently submitted with the written comment [2-7]. After the oral hearing on 10 June 2025, the company also submitted further data on patient-reported outcomes, which are also considered in this addendum.

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) MARIPOSA was included for the benefit assessment of amivantamab in combination with lazertinib (hereafter referred to as "amivantamab + lazertinib") in comparison with the appropriate comparator therapy (ACT) as first-line treatment in 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. A detailed description of the MARIPOSA study can be found in dossier assessment A25-08 I A25-11 [1].

In its dossier [6,7], the pharmaceutical company (hereinafter referred to as the "company") submitted the data cut-off from 13 May 2024 for the MARIPOSA study requested by the European Medicines Agency (EMA) as part of the approval procedure. According to the company, the results of the pre-specified final data cut-off of 4 December 2024 were not yet available at the time of dossier submission. Therefore, the results of the data cut-off from 13 May 2024 were used for the benefit assessment. With its comments, the company presented the results of the final data cut-off [2-5,8,9]. The final data cut-off is used for the present assessment.

In its dossier, the company presented comparisons of event proportions on confirmed worsening for the patient-reported outcomes on morbidity and health-related quality of life [6,7]. In dossier assessment A25-08 | A25-11 it was described that a meaningful conclusion on this operationalization requires analyses for the time to confirmed worsening [1]. With its comments, the company has now presented corresponding analyses that were used for the present assessment (see Section 2.2.1) [3,5]. In addition, following the hearing, the company presented the pre-specified analyses for the patient-reported outcomes for the period up to the 1st worsening [8]. In its comments, the company also provides supplementary information on the operationalization of individual outcomes. These relate to the outcomes of symptomatic progression, venous thromboembolic events (VTE) and infusion related reactions. The information provided is taken into account for the subsequent assessment (see Section 2.2.1).

2.1 Study characteristics

The detailed characteristics of the MARIPOSA study, including information on study design, intervention and study population can be found in dossier assessment A25-08 | A25-11 [1]. In the following, only aspects are described for which this addendum shows relevant changes compared to dossier assessment A25-08 | A25-11.

Patient characteristics

According to the company, a total of 260 (62%) patients in the amivantamab + lazertinib arm and 310 (72%) patients in the osimertinib arm discontinued treatment at the final data cut-off on 4 December 2024. The company provides no information on the number of patients who discontinued the study as of 4 December 2024 [1].

Information on the course of the study

Table 1 shows patients' median treatment duration and the median observation period for individual outcomes.

Table 1: Information on the course of the study – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

Study **duration of the study phase** **outcome category/outcome**	**Amivantamab + lazertinib** **N = 429**	**Osimertinib** **N = 429**
MARIPOSA (data cut-off from 4 December 2024)		
Treatment duration [months]		
Median [min; max]	27.0 [0.2; 47.2]	22.4 [0.2; 48.5]
Mean (SD)	24.2 (14.4)	22.8 (13.2)
Observation period [months]		
Overall survival[a]		
Median [min; max]	38.1 [0.0; 48.1]	37.8 [0.3; 47.8]
Mean (SD)	29.8 (12.7)	28.8 (12.0)
Morbidity (EORTC QLQ-C30, NSCLC-SAQ, EQ-5D VAS)		
Median [min; max]	29.5 [ND]	26.0 [ND]
Mean (SD)	ND	ND
Morbidity (PGIS)		
Median [min; max]	23.9 [ND]	22.1 [ND]
Mean (SD)	ND	ND
Health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	29.5 [ND]	26.0 [ND]
Mean (SD)	ND	ND
Side effects	N = 421	N = 428
Median [min; max]	27.9 [ND]	23.4 [ND]
Mean (SD)	ND	ND

a. The observation period was calculated on the basis of the inverse Kaplan-Meier method.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; min: minimum; N: number of analysed patients; ND: no data; NSCLC-SAQ: Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration differed between the study arms (27 months vs. approx. 22 months). The median observation periods between the study arms are sufficiently comparable for all outcomes.

Subsequent therapies

Table 2 shows the subsequent therapies patients received after discontinuing the study medication.

Table 2: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

Study **treatment regimen** **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	amivantamab + lazertinib **N = 429**	**osimertinib** **N = 429**
MARIPOSA (data cut-off from 4 December 2024)		
Further treatment with the study medication ≥ 28 days after progression (% of patients with progression)	ND	ND
Proportion of randomized patients with at least one subsequent therapy[a]	154 (35.9)	209 (48.7)
Chemotherapy- / immunotherapy- based regimens	97 (63.0)	159 (76.1)
Chemotherapy alone	76 (49.4)	119 (56.9)
Carboplatin + pemetrexed	49 (31.8)	70 (33.5)
Docetaxel	9 (5.8)	16 (7.7)
Carboplatin + paclitaxel	10 (6.5)	18 (8.6)
Cisplatin + pemetrexed	4 (2.6)	19 (9.1)
Pemetrexed	8 (5.2)	4 (1.9)
Gemcitabine	1 (0.6)	5 (2.4)
Paclitaxel	0 (0.0)	6 (2.9)
Vinorelbine	1 (0.6)	6 (2.9)
Gimeracil/oteracil/tegafur	0 (0.0)	5 (2.4)
Chemotherapy + VEGF inhibitors	13 (8.4)	27 (12.9)
Bevacizumab + carboplatin + pemetrexed	6 (3.9)	7 (3.3)
Bevacizumab + carboplatin + paclitaxel	4 (2.6)	5 (2.4)
Chemotherapy + VEGFR tyrosine kinase inhibitors + immunotherapy	13 (8.4)	21 (10.0)
Atezolizumab + bevacizumab + carboplatin + paclitaxel	5 (3.2)	10 (4.8)
Bevacizumab + carboplatin + pemetrexed + sintilimab	1 (0.6)	5 (2.4)
Chemotherapy + immunotherapy	8 (5.2)	12 (5.7)
Carboplatin + pembrolizumab + pemetrexed	3 (1.9)	5 (2.4)
Immunotherapy alone	7 (4.5)	7 (3.3)
Atezolizumab	6 (3.9)	2 (1.0)

Table 2: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

Study treatment regimen **drug class** **drug**	**Patients with subsequent therapy, n (%)**	
	amivantamab + lazertinib N = 429	**osimertinib N = 429**
monoclonal anti-EGFR antibodies / TKI or TKI-based regimens	89 (57.8)	98 (46.9)
TKI	78 (50.6)	82 (39.2)
Osimertinib	46 (29.9)	44 (21.1)[b]
Afatinib	8 (5.2)	10 (4.8)
Gefitinib	8 (5.2)	10 (4.8)
Aumolertinib	7 (4.5)	6 (2.9)
Erlotinib	1 (0.6)	12 (5.7)
Furmonertinib	7 (4.5)	3 (1.4)
TKI-based regimens	16 (10.4)	24 (11.5)
Other	7 (4.5)	12 (5.7)

a. All percentages provided below: Institute's calculation, based on the number of patients with subsequent therapy.
b. Osimertinib administered as part of a subsequent therapy.

EGFR: epidermal growth factor receptor; n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VEGFR: vascular endothelial growth factor receptor

At the final data cut-off of the MARIPOSA study on 4 December 2024, approx. 36% vs. 49% of all randomized patients had received at least 1 subsequent therapy. Of these, 44 patients in the comparator arm (21% of patients with at least 1 subsequent therapy) continued to receive treatment with osimertinib as part of a subsequent therapy. The company does not provide any information on how many patients had disease progression at the final data cut-off of the study and how many of them continued to receive the existing study medication (continuation of first-line treatment). Accordingly, the proportion of patients with disease progression who have not received any subsequent therapy remains unclear. At the previous data cut-off, around 30% of patients with disease progression in both study arms had not received any subsequent therapy [1].

For the present data cut-off of 4 December 2024, there is no relevant difference in the subsequent therapies between the study arms. There are no essential changes to the previous data cut-off regarding the frequency of individual treatment regimens [1]. For patients in the control arm who received further treatment with osimertinib after progression as part of a subsequent therapy, the current data provide no information on the proportion who subsequently received subsequent therapy with other drugs. Similarly, there is still no

information on the reasons why patients in the MARIPOSA study did not receive follow-up therapy. It is therefore still unclear to what extent the proportions of patients without subsequent therapy are transferable to the treatment situation in the health care context and whether patients without subsequent therapy after progression might have benefited from subsequent therapy.

Risk of bias across outcomes (study level)

Table 3 shows the risk of bias across outcomes (risk of bias at study level).

Table 3: Risk of bias across outcomes (study level) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
MARIPOSA	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for the MARIPOSA study. Limitations resulting from the open-label study design are described in Section 2.2.2 under the outcome-specific risk of bias.

2.2 Results

2.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - symptomatic progression
  - symptoms measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) symptom scales
  - symptoms, measured using the Non–Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)
  - symptoms, measured using the Patient Global Impression of Severity (PGIS)

- health status, measured with the EQ-5D VAS

- Health-related quality of life
  - measured with the EORTC QLQ-C30 functional scales
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - infusion related reactions
  - VTE (severe AEs)
  - pneumonitis/interstitial lung disease (ILD) (SAEs)
  - skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs)
  - other specific AEs, if any

Table 4 shows for which outcomes data were available in the included study.

Table 4: Matrix of outcomes – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

Study	Outcomes														
	Overall survival	Symptomatic progression[a]	Symptoms (EORTC QLQ-C30)	Symptoms (NSCLC-SAQ)	Symptoms (PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Infusion related reactions[d]	Venous thromboembolic events[e] (severe AEs[b])	Pneumonitis/ILD[f] (PT, SAEs)	Skin and subcutaneous tissue disorders (SOC, AEs)	Further specific AEs[g]
MARIPOSA	Yes	No[h]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[h]	Yes	Yes	Yes	Yes

a. For operationalization, see Section I 4.1 of dossier assessment A25-08 | A25-11 and the following text section on the outcome below this table.
b. Severe AEs are operationalized as CTCAE grade ≥ 3 events.
c. Discontinuation of at least one drug component.
d. Pre-defined as AE of special interest (AESI) according to the study protocol; see also Section I 4.1 of dossier assessment A25-08 | A25-11 and the subsequent text section on the outcome below this table.
e. Predefined as AESI according to the study protocol; operationalized via the SMQ "embolic and thrombotic events"; the complete operationalization is described in Section I 4.1 of dossier assessment A25-08 | A25-11.
f. Pre-defined as AESI according to the study protocol; PT collection of the company "acute interstitial pneumonitis", "interstitial lung disease" and "pneumonitis".
g. The following events are considered (MedDRA coding): "conjunctivitis" (PT, AEs), "constipation" (PT, AEs), "vomiting" (PT, AEs), "oedema peripheral" (PT, AEs), "mucosal inflammation" (PT, AEs), "muscle spasms" (PT, AEs), "pain in extremity" (PT, AEs), "myalgia" (PT, AEs), "paraesthesia" (PT, AEs), "eye disorders" (SOC, AEs), “reproductive system and breast disorders” (SOC, AE), "injury, poisoning and procedural complications" (SOC, SAEs), "paronychia" (PT, severe AEs), "dyspnoea" (PT, severe AEs), "examinations" (SOC, severe AEs), "metabolism and nutrition disorders" (SOC, severe AEs), "gastrointestinal disorders" (SOC, severe AEs), "general disorders and administration site conditions" (SOC, severe AEs) and "vascular disorders" (SOC, severe AEs).
h. No suitable data available; for justification see Section I 4.1 of dossier assessment A25-08 | A25-11 and the following text section on the outcome below this table.

AE: adverse event; AESI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; NSCLC-SAQ: Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; PGI-S: Patient's Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Notes on individual outcomes

Outcome of symptomatic progression

The outcome symptomatic progression is a composite outcome. It was defined as the time from randomization to the first documentation of one of the following events by the investigator:

- Occurrence of new lung cancer-related symptoms or a worsening of symptoms that require an adjustment of systemic cancer therapy, or
- Occurrence of new lung cancer-related symptoms or worsening of symptoms that require clinical intervention to control the symptoms.

As described in the dossier assessment [1], although the outcome is basically relevant to patients, it is not suitable for the benefit assessment in the operationalization presented. The decisive factor here was that it remained unclear on the basis of which events symptomatic progression was determined. In addition, the symptoms that were to be included as events in the analysis were not predefined. Moreover, it was unclear whether all included events are necessarily patient-relevant, whether they actually represent a lung cancer-related progression and to what extent events of varying severity were included in the analysis.

With the comments [2-5], the company presented a list of events that were included in the outcome [3,5]. However, no information is available on the number of events or the distribution between the two treatment arms. The company also does not provide information on the type of recording of the events (e.g. Preferred Terms [PTs]) and on the severity of the events. The list presented by the company also contains events for which it is not clear whether they actually represent a progression of the disease. These include non-specific symptoms such as back pain, abdominal pain, migraine or nausea. In addition, the list does not necessarily include patient-relevant events such as thrombocytopenia, increased aspartate aminotransferase, and increased blood alkaline phosphatase.

The analyses of the company show that the results of the composite outcome of symptomatic progression are largely determined by events in the individual component of symptoms that require clinical intervention to control the symptoms (approx. 90% of events). However, it remains unclear which clinical intervention is involved and whether it is aimed at treating the progression of the underlying disease. The information provided by the company only shows that these were interventions or procedures, radiotherapy or medications not specified in detail. Thus, there is still insufficient information for the benefit assessment regarding the relevance of the single component of symptom worsening requiring clinical intervention to control the symptoms.

Overall, there are still relevant uncertainties for the outcome definition presented by the company. The outcome "symptomatic progression" was therefore excluded from the present benefit assessment.

Analyses on patient-reported outcomes of the categories of morbidity and health-related quality of life

In the MARIPOSA study, the company assessed symptoms, health status and health-related quality of life using the EORTC QLQ-C30, NSCLC-SAQ, PGIS and EQ-5D VAS instruments. The pre-specified operationalization according to the study protocol included responder analyses for the EORTC QLQ-C30 and NSCLC-SAQ for the time to first clinically relevant worsening. In its dossier [6,7] for the benefit assessment, the company only presented analyses on proportions of events for a confirmed worsening (at least 2 surveys and for any subsequent surveys until the end of the observation) instead of time-to-event analyses. Analyses on the pre-specified operationalizations were not available.

As described in dossier assessment A25-08 | A25-11, in a data situation with approximately the same duration of observation of the patient-reported outcomes in both study arms and comparable response rates, the assessment of a definitive deterioration is possible and meaningful in terms of content. For a meaningful conclusion about the achievement of the treatment goal (extension of the time to worsening), however, analyses are necessary for the time to confirmed worsening. With its comments, the company subsequently submitted time-to-event analyses on the confirmed worsening for all patient-reported outcomes for the final data cut-off of 4 December 2024. These analyses were used for this benefit assessment.

In addition, the company presented the pre-specified analyses on the time to first deterioration. These are presented as supplementary information in Appendix B. Compared to the analysis on the time to definitive deterioration, 3 additional relevant (i.e. more than minor) effects to the disadvantage of amivantamab + lazertinib were shown. These relate to the outcomes of constipation, social functioning and physical functioning of the EORTC QLQ-C30.

Infusion related reactions

The analyses on the outcome of infusion related reactions presented by the company for dossier assessment A25-08 | A25-11 were not suitable for the benefit assessment [1]. The key reasons for this were the recording of the outcome in only one study arm (regular IV administration only in the intervention arm without placebo infusion in the control arm), the lack of an aggregated analysis of all symptomatic AEs potentially relevant for the infusion related reactions and the lack of a predefinition of symptoms that reflect the infusion-related reactions.

An aggregated analysis of all symptomatic adverse events (AEs) potentially relevant for the infusion related reactions is also missing in the company's statement. The company only presented a list of symptoms according to SOC/PT for the final data cut-off that were included in the outcome of infusion related reactions for the intervention arm, but without any categorization into severity grades [3,5]. The results for the outcome of infusion related reactions can therefore not be used for the benefit assessment, even after receipt of the company's comments, as they do not allow a comparison between the intervention and the comparator arm.

Irrespective of the aggregated analysis, it is necessary that the individual symptomatic AEs underlying the infusion related reactions are included in the general analysis of AEs. Even with the company's comments, there is no complete analysis of the AEs including the symptomatic AEs underlying the infusion related reactions, although this would have been possible in principle. The disregard of these events further complicates the interpretability of the results for all PTs/SOCs (as well as the overall rate of serious AEs, see below), especially for PTs/SOCs that frequently occurred due to infusion (e.g. skin and subcutaneous tissue disorders, nervous system disorders, eye disorders). It is therefore unclear whether the effect estimate for the individual PTs would change when all events that occurred during the course of the study (regardless of whether they were infusion related or not) at the PT and SOC level had been considered. Reliable conclusions on potential effects at PT/SOC level are therefore still remains impossible for the SOCs/PTs concerned. However, as described in dossier assessment A25-08 | A25-11, the specific AEs included in this assessment already show disadvantages for the intervention [1]. This is still the case for the data cut-off from 4 December 2024.

The information provided by the company in the comments also shows that the categorization into severity grades for the PT was not based on the specific CTCAE criteria for the individual symptoms, but on the (unspecific) CTCAE criteria for the PT of infusion related reaction. The number of patients with severe AEs in the superordinate outcome of severe AEs is therefore potentially underestimated in the amivantamab + lazertinib arm. However, this potential incompleteness does not exist for serious adverse events (SAEs). It can be assumed that the classification of the PT of infusion related reaction as an SAE was based on the specific criteria for SAEs regardless of the underlying symptom.

VTE

In its comments, the company stated that the outcome of VTE used in the benefit assessment was operationalized via the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) "embolic and thrombotic events". All events recorded since the start of the study were included in the analysis.

The SMQ "embolic and thrombotic events also includes events that do not correspond to a VTE, e.g. arterial embolism and thrombosis events. As described in dossier assessment A25-08 | A25-11, the outcome is essentially determined by events of the PTs "deep vein thrombosis", "venous thrombosis of an extremity" and "pulmonary embolism" [1]. As not every venous thrombosis is necessarily a patient-relevant event, the severe CTCAE grade ≥ 3 events are used, as in the dossier assessment, as this means that all patient-relevant events for this outcome are mapped.

2.2.2 Risk of bias

Table 5 describes the risk of bias for the results of the relevant outcomes.

Table 5: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

Study		Outcomes														
	Study level	Overall survival	Symptomatic progression[a]	Symptoms (EORTC QLQ-C30)	Symptoms (NSCLC-SAQ)	Symptoms (PGIS)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Infusion related reactions[d]	Venous thromboembolic events[e] (severe AEs[b])	Pneumonitis/ILD[f] (PT, SAEs)	Skin and subcutaneous tissue disorders (SOC, AEs)	Further specific AEs[g]
MARIPOSA	L	L	–[h]	H[i, j]	H[i, j]	H[i, j]	H[i, j]	H[i, j]	H[i]	HH[i, k]	H[H l]	–[h]	HH[i, k]	H[i]	H[i, k, m]	H[i, k, m]

a. For operationalization, see Section I 4.1 of dossier assessment A25-08 | A25-11[1] and Section 2.2.1 of this addendum.
b. Severe AEs are operationalized as CTCAE grade ≥ 3 events.
c. Discontinuation of at least one drug component.
d. Pre-defined as AE of special interest (AESI) according to the study protocol; see also Section I 4.1 of dossier assessment A25-08 | A25-11 and Section 2.2.1 of this addendum.
e. Predefined as AESI according to the study protocol; operationalized via the SMQ "embolic and thrombotic events"; the complete operationalization is described in Section I 4.1 of dossier assessment A25-08 | A25-11 and Section 2.2.1 of this addendum.
f. Pre-defined as AESI according to the study protocol; PT collection of the company "acute interstitial pneumonitis", "interstitial lung disease" and "pneumonitis".
g. The following events are considered (MedDRA coding): "conjunctivitis" (PT, AEs), "constipation" (PT, AEs), "vomiting" (PT, AEs), "oedema peripheral" (PT, AEs), "mucosal inflammation" (PT, AEs), "muscle spasms" (PT, AEs), "pain in extremity" (PT, AEs), "myalgia" (PT, AEs), "paraesthesia" (PT, AEs), "eye disorders" (SOC, AEs), “reproductive system and breast disorders” (SOC, AE), "injury, poisoning and procedural complications" (SOC, SAEs), "paronychia" (PT, severe AEs), "dyspnoea" (PT, severe AEs), "examinations" (SOC, severe AEs), "metabolism and nutrition disorders" (SOC, severe AEs), "gastrointestinal disorders" (SOC, severe AEs), "general disorders and administration site conditions" (SOC, severe AEs) and "vascular disorders" (SOC, severe AEs).
h. No suitable data available; for justification see Section I 4.1 of dossier assessment A25-08 | A25-11 and Section 2.2.1 of this addendum.
i. Shortened observation due to potentially informative reasons.
j. Sharp decline in questionnaire response rate over the course of the study; lack of blinding in subjective recording of outcomes.
k. Incomplete consideration of the symptoms underlying the infusion related reactions in the analyses.
l. Subjective decision to discontinue at unblinded recording of outcomes.
m. Unblinded recording of outcomes for non-severe/non-serious events.

AE: adverse event; AESI: adverse event of special interest; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; H: high; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; NSCLC-SAQ: Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; PGI-S: Patient's Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results on the outcome of overall survival was rated as low.

The risk of bias for the results of the patient-reported outcomes on morbidity and health-related quality of life (EORTC QLQ-C30, NSCLC-SAQ, EQ-5D VAS and PGIS) is rated as high. The reasons for this are the lack of blinding in the subjective recording of outcomes, the sharp decline in the response rate to the questionnaires over the course of the study and the resulting shortened observation period for these outcomes, which is also due to potentially informative censoring.

The risk of bias of the results on the outcomes of SAEs, severe AEs, and other specific AEs is rated as high due to incomplete observations. Numerous treatment discontinuations occurred, which resulted in potentially informative censorings for these outcomes. There are differences in the frequencies for several reasons for treatment discontinuation (disease progression: approx. 33% vs. 55% and AEs: approx. 23% vs. 14%). In addition, the symptoms underlying the infusion related reactions in the intervention arm are not included in the analyses on severe AEs and specific AEs. This can lead to further potential disadvantages in the AEs being overlooked, which contributes to the high risk of bias of the results.

The risk of bias for the results on discontinuation due to AEs is rated as high due to the subjective decision to discontinue in an unblinded study design. In addition, due to the unblinded survey, a high risk of bias is assumed for the results on non-serious/non-severe AEs.

Summary assessment of the certainty of conclusions

The assessment of the certainty of conclusions of the results described in dossier assessment A25-08 | A25-11 (unclear transferability to the German health care context due to the inadequate use of prophylactic concomitant treatment with anticoagulants in the intervention arm to prevent VTEs) also applies to the results of the final data cut-off of 4 December 2024. Thus, the certainty of conclusions remains reduced and, based on the available information, at most hints, e.g. of an added benefit, can be derived for all outcomes, regardless of the outcome-specific risk of bias.

In addition, the symptoms underlying the infusion related reactions in the intervention arm still remain unconsidered in the analyses on AEs. The lack of consideration of these events also affects the observed effects in the overall rates of severe AEs as well as specific AEs (see Section 2.2.1). However, these outcomes already show pronounced effects to the disadvantage of the intervention (see Section 2.2.3), so that the results are considered interpretable despite the uncertainty described.

2.2.3 Results

Table 6 and Table 7 summarize the results of the final data cut-off of the MARIPOSA study on the comparison of amivantamab + lazertinib with osimertinib as first-line treatment in

patients with advanced NSCLC and EGFR exon 19 deletions or exon 21 L858R substitution mutations. Where necessary, the data provided by the company are supplemented with calculations conducted by the Institute.

The Kaplan-Meier curves on the outcomes of overall survival, morbidity and health-related quality of life are shown in Appendix A. Appendix B provides additional data on the time to first deterioration for the outcomes of morbidity and health-related quality of life. The results on common AEs, SAEs and discontinuations due to AEs can be found in Appendix C of the full dossier assessment.

Table 6: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

Study outcome category outcome	Amivantamab + lazertinib		Osimertinib		Amivantamab + lazertinib vs. osimertinib
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
MARIPOSA (data cut-off from 4 December 2024)					
Mortality					
Overall survival	429	NA [42.9; NC] 173 (40.3)	429	36.7 [33.4; 41.0] 217 (50.6)	0.75 [0.61; 0.92]; 0.005[a]
Morbidity					
Symptomatic progression	No suitable data[b]				
Symptoms (EORTC QLQ-C30 - confirmed deterioration[c])					
Fatigue	429	NA [40.5; NC] 117 (27.3)	429	NA [42.4; NC] 115 (26.8)	1.05 [0.81; 1.36]; 0.719
Nausea and vomiting	429	NA 28 (6.5)	429	NA 39 (9.1)	0.67 [0.41; 1.09]; 0.110
Pain	429	NA 78 (18.2)	429	NA 67 (15.6)	1.11 [0.80; 1.55]; 0.516
Dyspnoea	429	NA 55 (12.8)	429	NA 53 (12.4)	0.99 [0.68; 1.44]; 0.942
Insomnia	429	NA 55 (12.8)	429	NA 62 (14.5)	0.83 [0.57; 1.19]; 0.311
Appetite loss	429	NA 46 (10.7)	429	NA 70 (16.3)	0.63 [0.44; 0.92]; 0.017
Constipation	429	NA 58 (13.5)	429	NA 44 (10.3)	1.29 [0.87; 1.92]; 0.203
Diarrhoea	429	NA 26 (6.1)	429	NA 56 (13.1)	0.43 [0.27; 0.69]; < 0.001

Table 6: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

Study outcome category outcome	Amivantamab + lazertinib		Osimertinib		Amivantamab + lazertinib vs. osimertinib
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Symptoms (NSCLC-SAQ -confirmed deterioration[d])					
Total score	429	NA 40 (9.3)	429	NA 53 (12.4)	0.74 [0.49; 1.12]; 0.156
Cough	429	NA 35 (8.2)	429	NA 41 (9.6)	-
Pain	429	NA 53 (12.4)	429	NA 63 (14.7)	-
Dyspnoea	429	NA 79 (18.4)	429	NA 63 (14.7)	-
Fatigue	429	NA 68 (15.9)	429	NA 85 (19.8)	-
Appetite loss	429	NA 67 (15.6)	429	NA 96 (22.4)	-
Symptoms (PGIS - confirmed deterioration[e])	429	NA 53 (12.4)	429	NA [44.1; NC] 65 (15.2)	0.75 [0.52; 1.08]; 0.128
Health status (EQ-5D VAS – first deterioration[f])	429	NA 42 (9.8)	429	NA 52 (12.1)	0.78 [0.52; 1.17]; 0.229
Health-related quality of life					
EORTC QLQ-C30 – first deterioration[g]					
Global health status	429	NA 72 (16.8)	429	NA 83 (19.3)	0.84 [0.61; 1.16]; 0.301
Physical functioning	429	NA 101 (23.5)	429	NA 69 (16.1)	1.55 [1.14; 2.12]; 0.005
Role functioning	429	NA [40.9; NC] 118 (27.5)	429	NA 83 (19.3)	1.50 [1.13; 1.99]; 0.005
Emotional functioning	429	NA 43 (10.0)	429	NA 57 (13.3)	0.74 [0.49; 1.10]; 0.133
Cognitive functioning	429	NA 89 (20.7)	429	NA 98 (22.8)	0.90 [0.67; 1.20]; 0.461
Social functioning	429	NA 93 (21.7)	429	NA 88 (20.5)	1.05 [0.79; 1.41]; 0.723

Table 6: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

Study outcome category outcome	Amivantamab + lazertinib		Osimertinib		Amivantamab + lazertinib vs. osimertinib
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value

a. Hazard ratio (including 95% CI and p-value) calculated using a Cox proportional hazards model; stratified by type of mutation (EGFR exon 19 del or EGFR exon 21 L858R sub), family origin (Asian, non-Asian) and history of brain metastases (yes, no).
b. See Section 2.2.1 for the rationale.
c. An increase by ≥ 10 points from baseline in at least 2 consecutive and all subsequent surveys, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 0 to 100).
d. An increase by ≥ 3 points of the scale range in the total score from baseline, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (value range for the total score: 0 to 20).
e. An increase by ≥ 1 point from baseline, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 1 to 6).
f. A decrease by ≥ 15 points from baseline, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 0 to 100).
g. A decrease by ≥ 10 points from baseline, without subsequent improvement until the end of the observation, is considered a clinically relevant, confirmed deterioration (scale range: 0 to 100).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EGFR: Epidermal Growth Factor Receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; Del19: exon 19 deletion; HR: hazard ratio; ILD: interstitial lung disease; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; NC: not calculable; NSCLC-SAQ: Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Table 7: Results (side effects, dichotomous) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

Study outcome category outcome time point	Amivantamab + lazertinib N	 patients with event n (%)	Osimertinib N	 patients with event n (%)	Amivantamab + lazertinib vs. osimertinib RR [95% CI]; p-value[a]
MARIPOSA (data cut-off from 4 December 2024)					
Side effects					
AEs (supplementary information)	421	421 (100.0)	428	426 (99.5)	–
SAEs	421	233 (55.3)	428	177 (41.4)	1.34 [1.17; 1.54]; < 0.001
Severe AEs[b]	421	337 (80.0)	428	224 (52.3)	1.53 [1.38; 1.70]; < 0.001
Discontinuation due to AEs[c]	421	178 (42.3)	428	70 (16.4)	2.59 [2.03; 3.29]; < 0.001
Infusion related reactions			No suitable data[d]		
Venous thromboembolic events (severe AEs)[b, e]	421	51 (12.1)	428	17 (4.0)	3.06 [1.80; 5.21]; < 0.001
Pneumonitis/ILD (PT, SAE)[f]	421	13 (3.1)	428	13 (3.0)	1.03 [0.48; 2.20]; 0.945
Skin and subcutaneous tissue disorders (SOC, AEs)	421	388 (92.2)	428	279 (65.2)	1.41 [1.31; 1.52]; < 0.001
Conjunctivitis (PT, AEs)	421	48 (11.4)	428	10 (2.3)	4.84 [2.48; 9.44]; < 0.001
Constipation (PT, AEs)	421	130 (30.9)	428	70 (16.4)	1.89 [1.46; 2.44]; < 0.001
Vomiting (PT, AEs)	421	59 (14.0)	428	28 (6.5)	2.14 [1.40; 3.28]; < 0.001
Oedema peripheral (PT, AEs)	421	162 (38.5)	428	29 (6.8)	5.70 [3.93; 8.26]; < 0.001
Mucosal inflammation (PT, AEs)	421	48 (11.4)	428	14 (3.3)	3.52 [1.97; 6.27]; < 0.001
Muscle spasms (PT, AEs)	421	84 (20.0)	428	36 (8.4)	2.38 [1.65; 3.42]; < 0.001
Pain in extremity (PT, AEs)	421	72 (17.1)	428	30 (7.0)	2.45 [1.64; 3.66]; < 0.001
Myalgia (PT, AEs)	421	60 (14.3)	428	24 (5.6)	2.54 [1.61; 4.00]; < 0.001
Paraesthesia (PT, AEs)	421	61 (14.5)	428	27 (6.3)	2.31 [1.50; 3.56]; < 0.001
Eye disorders (SOC, AEs)	421	144 (34.2)	428	76 (17.8)	1.93 [1.51; 2.46]; < 0.001
Reproductive system and breast disorders (SOC, AEs)	421	43 (10.2)	428	20 (4.7)	2.21 [1.32; 3.68]; 0.002

Table 7: Results (side effects, dichotomous) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

Study outcome category outcome time point	Amivantamab + lazertinib		Osimertinib		Amivantamab + lazertinib vs. osimertinib
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Injury, poisoning and procedural complications (SOC, SAEs)	421	32 (7.6)	428	16 (3.7)	2.03 [1.13; 3.65]; 0.018
Paronychia (PT, severe AEs[b])	421	49 (11.6)	428	2 (0.5)	24.71 [6.11; 99.96]; < 0.001
Dyspnoea	No suitable data[d]				
Investigations (SOC, severe AEs[b])	421	65 (15.4)	428	42 (9.8)	1.57 [1.09; 2.26]; 0.015
Metabolism and nutrition disorders (SOC, severe AEs[b])	421	66 (15.7)	428	33 (7.7)	2.03 [1.37; 3.01]; < 0.001
Gastrointestinal disorders (SOC, severe AEs[b])	421	41 (9.7)	428	19 (4.4)	2.21 [1.30; 3.74]; 0.003
General disorders and administration site conditions (SOC, severe AEs[b])	421	40 (9.5)	428	22 (5.1)	1.85 [1.12; 3.05]; 0.017
Vascular disorders (SOC, severe AEs[b])	421	34 (8.1)	428	20 (4.7)	1.73 [1.01; 2.96]; 0.044

a. Cochran-Mantel-Haenszel method; stratified by type of mutation (EGFR exon 19 del or EGFR exon 21 L858R sub), family origin (Asian, non-Asian) and history of brain metastases (yes, no).
b. Operationalized as CTCAE grade ≥ 3.
c. Discontinuation of at least 1 drug component.
d. See Section 2.2.1. and Section I 4.1 of dossier assessment A25-08 | A25-11 for the reasoning.
e. Operationalized via the SMQ “embolic and thrombotic events” with CTCAE grade ≥ 3; results are largely determined by the PTs "deep vein thrombosis", "venous thrombosis of an extremity" and "pulmonary embolism".
f. PT collection of the company, operationalized using the following PTs: "acute interstitial pneumonitis", "interstitial lung disease" and "pneumonitis".

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; ILD: interstitial lung disease; n: number of patients with (at least 1) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.2.2 for reasoning).

Mortality

Overall survival

A statistically significant difference between the treatment groups in favour of amivantamab + lazertinib was shown for the outcome of overall survival. However, there was an effect modification by the characteristic of age (see Section 2.2.4).

For the age group < 65 years, there is a hint of an added benefit of amivantamab + lazertinib compared with osimertinib, whereas for the age group ≥ 65 years, there is no hint of an added benefit of amivantamab + lazertinib compared with osimertinib.

Morbidity

Symptomatic progression

No suitable data are available for the outcome of symptomatic progression (see Section 2.2.1 for reasoning). For the outcome of symptomatic progression, there is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-C30)

Diarrhoea

A statistically significant difference in favour of amivantamab + lazertinib was shown between the treatment groups for the outcome of diarrhoea. There is a hint of an added benefit for amivantamab + lazertinib in comparison with osimertinib.

Appetite loss

A statistically significant difference in favour of amivantamab + lazertinib was shown between the treatment groups for the outcome of appetite loss. However, the difference is no more than marginal for this outcome in the category of non-serious/non-severe symptoms / late complications. There is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

Fatigue, nausea and vomiting, pain, dyspnoea, constipation, and insomnia

No statistically significant difference between the treatment groups was shown for any of the outcomes of dyspnoea, fatigue, insomnia, constipation, pain as well as nausea and vomiting. There is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

Symptoms (NSCLC-SAQ)

There was no statistically significant difference between the treatment groups for the outcome of NSCLC-SAQ. There is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

Symptoms (PGIS)

There was no statistically significant difference between the treatment groups for the outcome of PGIS. There is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

health status (EQ-5D VAS)

No statistically significant difference between the treatment groups was shown for the outcome of health status (recorded using the EQ-5D VAS). There is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Physical functioning and role functioning

A statistically significant difference between the treatment groups to the disadvantage of amivantamab + lazertinib was shown for the outcomes of physical functioning and role functioning. In each case, there is a hint of lesser benefit of amivantamab + lazertinib in comparison with osimertinib.

Global health status, emotional functioning, cognitive functioning, and social functioning

No statistically significant difference between the treatment groups was shown for any of the following outcomes of global health status, emotional functioning, cognitive functioning, and social functioning. There is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of overall survival, a statistically significant difference to the disadvantage of amivantamab + lazertinib was shown between the treatment groups. There is a hint of greater harm from amivantamab + lazertinib in comparison with osimertinib.

Severe AEs (CTCAE grade ≥ 3)

For the outcome of severe AEs, a statistically significant difference to the disadvantage of amivantamab + lazertinib was shown between the treatment groups. There is a hint of greater harm from amivantamab + lazertinib in comparison with osimertinib.

Discontinuation due to AEs (at least 1 drug component)

For the outcome of discontinuation due to AEs, a statistically significant difference to the disadvantage of amivantamab + lazertinib was shown between the treatment groups. There is a hint of greater harm from amivantamab + lazertinib in comparison with osimertinib.

Infusion related reactions

No suitable data are available for the outcome of infusion related reactions. For reasons, see Section 2.2.1 and Section I.4.1 of dossier assessment A25-08 | A25.11 [1]. For the outcome of

infusion related reactions, there is no hint of greater or lesser harm from amivantamab + lazertinib compared to osimertinib; greater or lesser harm is therefore not proven.

VTE (severe AEs)

For the outcome of VTE (severe AEs), a statistically significant difference to the disadvantage of amivantamab + lazertinib was shown between the treatment groups. There is a hint of greater harm from amivantamab + lazertinib in comparison with osimertinib.

Pneumonitis/interstitial lung disease (ILD) (SAEs)

For the outcome of pneumonitis/ILD (SAEs), there is no statistically significant difference between the treatment groups. There is no hint of greater or lesser harm from amivantamab + lazertinib compared with osimertinib; greater or lesser harm is therefore not proven.

Skin and subcutaneous tissue disorders (AEs)

A statistically significant difference between treatment groups to the disadvantage of amivantamab + lazertinib was shown for the outcome of skin and subcutaneous tissue disorders (AEs). There is a hint of greater harm from amivantamab + lazertinib in comparison with osimertinib.

Other specific AEs

For each of the outcomes of conjunctivitis (AEs), constipation (AEs), vomiting (AEs), oedema peripheral (AEs), mucosal inflammation (AEs), muscle spasms (AEs), pain in extremity (AEs), myalgia (AEs), paraesthesia (AEs), eye disorders (AEs), reproductive system and breast disorders (AEs); injury, poisoning and procedural complications (SAEs), paronychia (severe AEs), investigations (severe AEs), metabolism and nutrition disorders (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs) and vascular disorders (severe AEs), there was a statistically significant difference between the treatment groups to the disadvantage of amivantamab + lazertinib. In each case, there is a hint of greater harm from amivantamab + lazertinib in comparison with osimertinib.

For the outcome of paraesthesia (AEs), there is an effect modification by the characteristic of sex (see Section 2.2.4). A statistically significant difference to the disadvantage of amivantamab + lazertinib was shown both for women and for men. Thereby, the extent of the effect differs between the subgroups. There is a hint of greater harm from amivantamab + lazertinib in comparison osimertinib for both women and men.

2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the present benefit assessment:

- Sex (male versus female)

- Age (< 65 years versus ≥ 65 years)
- Presence of brain metastases at baseline (yes versus no)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

Table 8 and Table 9 summarize the subgroup results of the comparison of amivantamab + lazertinib with osimertinib as first-line treatment in patients with advanced NSCLC and EGFR exon 19 deletions or exon 21 L858R substitution mutations. The Kaplan-Meier curves on the outcome of overall survival are presented in Appendix A of the full dossier assessment.

Table 8: Subgroups (mortality) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

Study outcome characteristic subgroup	Amivantamab + lazertinib N	Amivantamab + lazertinib median time to event in months [95% CI] patients with event n (%)	Osimertinib N	Osimertinib median time to event in months [95% CI] patients with event n (%)	Amivantamab + lazertinib vs. osimertinib HR [95% CI][a]	 p-value[a]
MARIPOSA						
Overall survival						
Age						
< 65	235	NA 76 (32.3)	237	35.61 [31.05; 42.42] 123 (51.9)	0.53 [0.40; 0.70]	< 0.001
≥ 65	194	35.61 [30.42; NC] 97 (50.0)	192	37.72 [34.23; NC] 94 (49.0)	1.11 [0.84; 1.48]	0.467
Total					Interaction:	< 0.001

a. Unstratified Cox proportional hazard model with the treatment arm as the only explanatory variable.

CI: confidence interval; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial

Table 9: Subgroups (side effects) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

Study outcome characteristic subgroup	Amivantamab + lazertinib		Osimertinib		Amivantamab + lazertinib vs. osimertinib	
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI][a]	p-value[a]
MARIPOSA						
Paraesthesia (PT, AE)						
Sex						
Female	268	39 (14.6)	250	22 (8.8)	1.65 [1.01; 2.71]	0.046
Male	153	22 (14.4)	178	5 (2.8)	5.12 [1.99; 13.19]	< 0.001
Total					Interaction:	0.040

a. Based on Cochran-Mantel-Haenszel method.

AE: adverse event; CI: confidence interval; n: number of patients with event; N: number of analysed patients; PT: Preferred term; RCT: randomized controlled trial; RR: relative risk

Mortality

overall survival

For the outcome of overall survival, there was an effect modification by the characteristic of age.

A statistically significant difference in favour of amivantamab + lazertinib was shown between treatment groups for patients < 65 years of age. There is a hint of added benefit of amivantamab + lazertinib in comparison with osimertinib.

There was no statistically significant difference between the treatment groups for patients aged ≥ 65 years. There is no hint of an added benefit of amivantamab + lazertinib in comparison with osimertinib; an added benefit is therefore not proven.

Side effects

Paraesthesia (PT, AE)

There is an effect modification by the characteristic of sex for the outcome of paraesthesia (PT, AE). For both women and men, a statistically significant difference to the disadvantage of amivantamab + lazertinib was shown between the treatment groups. In women, however, the extent of the effect was no more than marginal. For women, there is no hint of greater or lesser harm from amivantamab + lazertinib compared with osimertinib; greater or lesser harm is therefore not proven. For men, there is a hint of added benefit of amivantamab + lazertinib in comparison with osimertinib.

2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [10].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section 2.2.3 (see Table 10).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier or the company's comments whether the symptom outcomes are serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

For the symptoms outcomes (appetite loss and diarrhoea recorded using the EORTC QLQ-C30), insufficient severity data are available which would allow a classification as serious/severe. The symptom outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 10: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Amivantamab + lazertinib vs. osimertinib** **quantile of time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival Age < 65 years	Median: NA vs. 35.61 HR: 0.53 [0.40; 0.70]; p < 0.001 probability: hint	Outcome category: mortality CI_u < 0.85 added benefit, extent: “major”
≥ 65 years	Median: 35.61 vs. 37.72 HR: 1.11 [0.84; 1.48]; p = 0.467	Lesser/added benefit not proven
Morbidity		
Symptomatic progression	No suitable data	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
EORTC QLQ-C30 symptom scales		
Fatigue	Median: NA vs. NA HR: 1.05 [0.81; 1.36]; p = 0.719	Lesser/added benefit not proven
Nausea and vomiting	Median: NA vs. NA HR: 0.67 [0.41; 1.09]; p = 0.110	Lesser/added benefit not proven
Pain	Median: NA vs. NA HR: 1.11 [0.80; 1.55]; p = 0.516	Lesser/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 0.99 [0.68; 1.44]; p = 0.942	Lesser/added benefit not proven
Insomnia	Median: NA vs. NA HR: 0.83 [0.57; 1.19]; p = 0.311	Lesser/added benefit not proven
Appetite loss	Median: NA vs. NA HR: 0.63 [0.44; 0.92]; p = 0.017	Outcome category: non-serious/non-severe symptoms/late complications 0.90 ≤ CI_u < 1.00 lesser/added benefit not proven[c]

Table 10: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Amivantamab + lazertinib vs. osimertinib** **quantile of time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Constipation	Median: NA vs. NA HR: 1.29 [0.87; 1.92]; p = 0.203	Lesser/added benefit not proven
diarrhoea	Median: NA vs. NA HR: 0.43 [0.27; 0.69]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: “considerable”
NSCLC-SAQ	Median: NA vs. NA HR: 0.74 [0.49; 1.12]; p = 0.156	Lesser/added benefit not proven
PGIS	Median: NA vs. NA HR: 0.75 [0.52; 1.08]; p = 0.128	Lesser/added benefit not proven
EQ-5D VAS	Median: NA vs. NA HR: 0.78 [0.52; 1.17]; p = 0.229	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 (functional scales)		
Global health status	Median: NA vs. NA HR: 0.84 [0.61; 1.16]; p = 0.301	Lesser/added benefit not proven
Physical functioning	Median: NA vs. NA HR: 1.55 [1.14; 2.12]; HR: 0.65 [0.47; 0.88][d]; p = 0.005 probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ lesser benefit, extent: “considerable”
Role functioning	Median: NA vs. NA HR: 1.50 [1.13; 1.99]; HR: 0.67 [0.50; 0.88][d]; p = 0.005 probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ lesser benefit, extent: “considerable”
Emotional functioning	Median: NA vs. NA HR: 0.74 [0.49; 1.10]; p = 0.133	Lesser/added benefit not proven

Table 10: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Amivantamab + lazertinib vs. osimertinib** **quantile of time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Cognitive functioning	Median: NA vs. NA HR: 0.90 [0.67; 1.20]; p = 0.461	Lesser/added benefit not proven
Social functioning	Median: NA vs. NA HR: 1.05 [0.79; 1.41]; p = 0.723	Lesser/added benefit not proven
Side effects		
SAEs	55.3% vs. 41.4% RR: 1.34 [1.17; 1.54]; RR: 0.75 [0.65; 0.85][d]; p < 0.001 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Severe AEs	80.0% vs. 52.3% RR: 1.53 [1.38; 1.70]; RR: 0.65 [0.59; 0.72][d]; p < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5 % Greater harm, extent: “major”
Discontinuation due to AEs	42.3% vs. 16.4% RR: 2.59 [2.03; 3.29]; RR: 0.39 [0.30; 0.49][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”
Infusion related reactions	No suitable data	Greater/lesser harm not proven
Venous thromboembolic events (severe AEs)	12.1% vs. 4.0% RR: 3.06 [1.80; 5.21]; RR: 0.33 [0.19; 0.56][d]; p < 0.001 Probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5 % greater harm, extent: “major”
Pneumonitis/interstitial lung disease (ILD) (SAEs)	3.1% vs. 3.0% RR: 1.03 [0.48; 2.20]; p = 0.945	Greater/lesser harm not proven
Skin and subcutaneous tissue disorders (AEs)	92.2% vs. 65.2% RR: 1.41 [1.31; 1.52]; RR: 0.71 [0.66; 0.76][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: “considerable”

Table 10: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Amivantamab + lazertinib vs. osimertinib** **quantile of time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Conjunctivitis (AEs)	11.4% vs. 2.3% RR: 4.84 [2.48; 9.44]; RR: 0.21 [0.11; 0.40][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Constipation (AEs)	30.9% vs. 16.4% RR: 1.89 [1.46; 2.44]; RR: 0.53 [0.41; 0.68][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Vomiting (AEs)	14.0% vs. 6.5% RR: 2.14 [1.40; 3.28]; RR: 0.47 [0.30; 0.71][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
oedema peripheral (AEs)	38.5% vs. 6.8% RR: 5.70 [3.93; 8.26]; RR: 0.18 [0.12; 0.25][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: “considerable”
Mucosal inflammation (AEs)	11.4% vs. 3.3% RR: 3.52 [1.97; 6.27]; RR: 0.28 [0.16; 0.51][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: “considerable”
Muscle spasms (AEs)	20.0% vs. 8.4% RR: 2.38 [1.65; 3.42]; RR: 0.42 [0.29; 0.61][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: “considerable”
Pain in extremity (AEs)	17.1% vs. 7.0% RR: 2.45 [1.64; 3.66]; RR: 0.41 [0.27; 0.61][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: “considerable”

Table 10: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Amivantamab + lazertinib vs. osimertinib** **quantile of time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Myalgia (PT, AEs)	14.3% vs. 5.6% RR: 2.54 [1.61; 4.00]; RR: 0.39 [0.25; 0.62][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Paraesthesia (AEs)		
Sex		
Female	14.6% vs. 8.8% RR: 1.65 [1.01; 2.71]; RR: 0.61 [0.37; 0.99][d]; p = 0.046	Outcome category: non-serious/non-severe side effects 0.90 ≤ CI_u < 1.00 greater/lesser harm not proven[c]
Male	14.4% vs. 2.8% RR: 5.12 [1.99; 13.19]; RR: 0.20 [0.08; 0.50][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Eye disorders (AEs)	34.2% vs. 17.8% RR: 1.93 [1.51; 2.46]; RR: 0.52 [0.41; 0.66][d]; p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Reproductive system and breast disorders (AEs)	10.2% vs. 4.7% RR: 2.21 [1.32; 3.68]; RR: 0.45 [0.27; 0.76][d]; p = 0.002 probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: “considerable”
Injury, poisoning and procedural complications (SAEs)	7.6% vs. 3.7% RR: 2.03 [1.13; 3.65]; RR: 0.49 [0.27; 0.88][d]; p = 0.018 probability: hint	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent: “considerable”
Paronychia (severe AEs[c])	11.6% vs. 0.5% RR: 24.71 [6.11; 99.96]; RR: 0.04 [0.01; 0.16][d]; p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75 and risk ≥ 5 % greater harm, extent: “major”

Table 10: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

Observation period **outcome category** **outcome** **effect modifier** **subgroup**	**Amivantamab + lazertinib vs. osimertinib** **quantile of time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Dyspnoea	No suitable data available	Greater/lesser harm not proven
Investigations (severe AEs)	15.4% vs. 9.8% RR: 1.57 [1.09; 2.26]; RR: 0.64 [0.44; 0.92][d]; p = 0.015 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: minor
Metabolism and nutrition disorders (severe AEs)	15.7% vs. 7.7% RR: 2.03 [1.37; 3.01]; RR: 0.49 [0.33; 0.73][d]; p < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5 % greater harm, extent: “major”
Gastrointestinal disorders (severe AEs)	9.7% vs. 4.4% RR: 2.21 [1.30; 3.74]; RR: 0.45 [0.27; 0.77][d]; p = 0.003 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
General disorders and administration site conditions (severe AEs)	9.5% vs. 5.1% RR: 1.85 [1.12; 3.05]; RR: 0.54 [0.33; 0.89][d]; p = 0.017 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Vascular disorders (severe AEs)	8.1% vs. 4.7% RR: 1.73 [1.01; 2.96]; RR: 0.58 [0.34; 0.99][d]; p = 0.044 probability: hint	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: minor

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. Institute’s calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: hazard ratio; ILD: interstitial lung disease; NSCLC-SAQ: Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; PGIS: Patient Global Impression of Severity; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.3.2 Overall conclusion on added benefit

Table 11 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 11: Positive and negative effects from the assessment of amivantamab + lazertinib in comparison with osimertinib

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival ▫ age < 65 years: hint of added benefit – extent: “major”	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms/late complications ▪ diarrhoea: hint of an added benefit – extent: “considerable”	–
–	Health-related quality of life ▪ physical functioning: hint of lesser benefit – extent: "considerable" ▪ role functioning: hint of lesser benefit – extent: "considerable"
–	Serious/severe side effects ▪ severe AEs: hint of greater harm – extent: “major” ▫ venous thromboembolic events (severe AE): hint of greater harm – extent "major" ▫ paronychia (severe AEs): hint of greater harm – extent: “major” ▫ examinations (severe AEs): hint of greater harm – extent: “minor” ▫ metabolism and nutrition disorders (severe AEs): hint of greater harm – extent: “major” ▫ gastrointestinal disorders (severe AEs): hint of greater harm – extent: “considerable” ▫ general disorders and administration site conditions (severe AEs): hint of greater harm – extent: "considerable" ▫ vascular disorders (severe AEs): hint of greater harm – extent: "minor” ▪ SAEs: hint of greater harm – extent: "considerable" ▫ injury, poisoning and procedural complications (SAEs): hint of greater harm - extent: "considerable"
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: “considerable” ▪ skin and subcutaneous tissue disorders, conjunctivitis, constipation, vomiting, oedema peripheral, mucosal inflammation, muscle spasms, pain in extremity, myalgia, eye disorders, reproductive system and breast disorders (AEs): hint of greater harm - extent: “considerable” ▪ paraesthesia ▫ sex: male hint of greater harm – extent “considerable"
No suitable data are available on the outcomes of symptomatic progression and infusion related reactions.	
AE: adverse event; SAE: serious adverse event	

In the overall consideration, both positive and negative effects of amivantamab + lazertinib in comparison with osimertinib were found. Data across the entire observation period are available only for overall survival. All other effects relate exclusively to the shortened observation period (patient-reported outcomes on morbidity and health-related quality of life: up to 1 year after discontinuation of the study medication; AEs: up to the end of treatment [plus 30 days]). The analyses presented on the outcome of symptomatic progression are unsuitable for the benefit assessment.

For the outcome of overall survival, there was an effect modification by the characteristic of age. Below, the balancing of the added benefit is presented separately for patients < 65 years and ≥ 65 years.

Patients < 65 years

The decisive factor for patients < 65 years is whether there is a hint of a positive effect with the extent "major" on the outcome of overall survival. In addition, there was a positive effect of considerable extent for the outcome of diarrhoea (non-serious/non-severe symptoms/late complications). The negative effects in the patient-reported outcomes on health-related quality of life (role functioning and physical functioning) and in the outcome category of serious and severe side effects do not entirely call into question the positive effect in overall survival.

The analyses in the outcome category of side effects are subject to uncertainty due to the lack of consideration of the symptoms underlying the infusion related reactions, and the observed effects are therefore potentially underestimated. In contrast to the dossier, the company presented suitable data on patient-reported outcomes on morbidity and health-related quality of life in its comments, so that a major uncertainty was eliminated. It is therefore possible to quantify the added benefit in the overall consideration. There are numerous negative effects with considerable to major extent in health-related quality of life and in the overall rates of the outcomes in the side effects category. In addition, the absolute number of patients with SAEs (55%) and discontinuations due to AEs (42%) in the amivantamab + lazertinib arm is also high.

Overall, there is a hint of minor added benefit of amivantamab in combination with lazertinib over the ACT for patients < 65 years of age due to the large number of negative effects of considerable to major extent and the high number of affected patients.

Patients ≥ 65 years

For patients ≥ 65 years, there are mostly negative effects, particularly in the outcome category of serious and severe side effects. In contrast, there is only a positive effect of considerable extent for the outcome diarrhoea (non-serious/non-severe symptoms/late complications).

Overall, there is a hint of lesser benefit of amivantamab in combination with lazertinib in comparison with the ACT.

2.4 Summary

The data subsequently submitted by the company in the commenting procedure changed the statement on the added benefit of amivantamab + lazertinib from dossier assessment A25-08 | A25-11 for patients with advanced NSCLC and EGFR exon 19 deletions or exon 21 L858R substitution mutations aged < 65 years. For the subgroup of patients ≥ 65 years of age, there is no change from dossier assessment A25-08 | A25-11.

Table 12 summarizes the result of the assessment of added benefit of amivantamab in combination with lazertinib in comparison with the ACT.

Table 12: Amivantamab + lazertinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with advanced NSCLC and EGFR exon 19 deletions or exon 21 L858R substitution mutations[b]; first-line treatment	▪ Afatinib (only for patients with the activating EGFR mutation deletion in exon 19) or ▪ osimertinib	▪ Patients < 65 years: Hint of a minor added benefit[c] ▪ patients ≥ 65 years: hint of lesser benefit

a. Presented is the ACT specified by the G-BA.
b. For the present therapeutic indication, it is assumed as per G-BA that there is neither an indication for definitive radiochemotherapy nor for definitive local therapy. In addition, it is assumed that another molecularly stratified therapy (directed against ALK, BRAF, exon 20, KRAS G12C, METex14, RET, or ROS1) is not an option for the patients at the time of treatment with amivantamab in combination with lazertinib. Since histologically, most EGFR-mutated NSCLC are adenocarcinomas, it is also assumed that treatment options that are explicitly indicated for squamous cell tumour histology are not regularly used in this planned therapeutic indication.
c. Only patients with an ECOG PS of 0 or 1 were included in the MARIPOSA study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group – Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; KRAS: Kirsten rat sarcoma viral oncogene homologue; MET: mesenchymal-epithelial transition factor; METex14: MET gene exon 14; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; ROS1: c-ros oncogene 1

The assessment described above departs from that by the company, which derived an indication of considerable added benefit based on the total population.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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Appendix A Kaplan-Meier curves

A.1 Mortality: overall survival

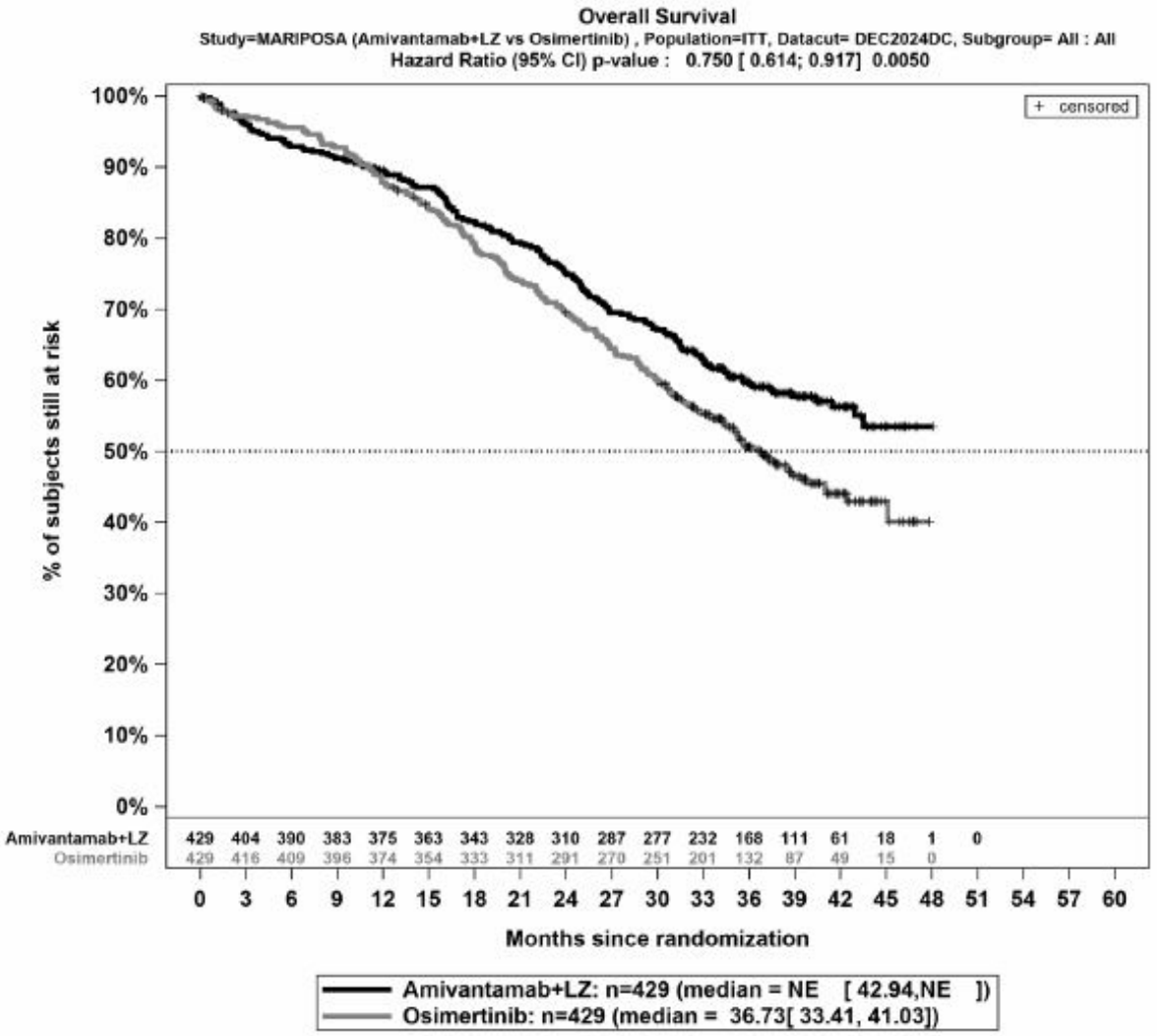

Figure 1: Kaplan-Meier curves for the outcome of overall survival, MARIPOSA study, total population, data cut-off from 4 December 2024

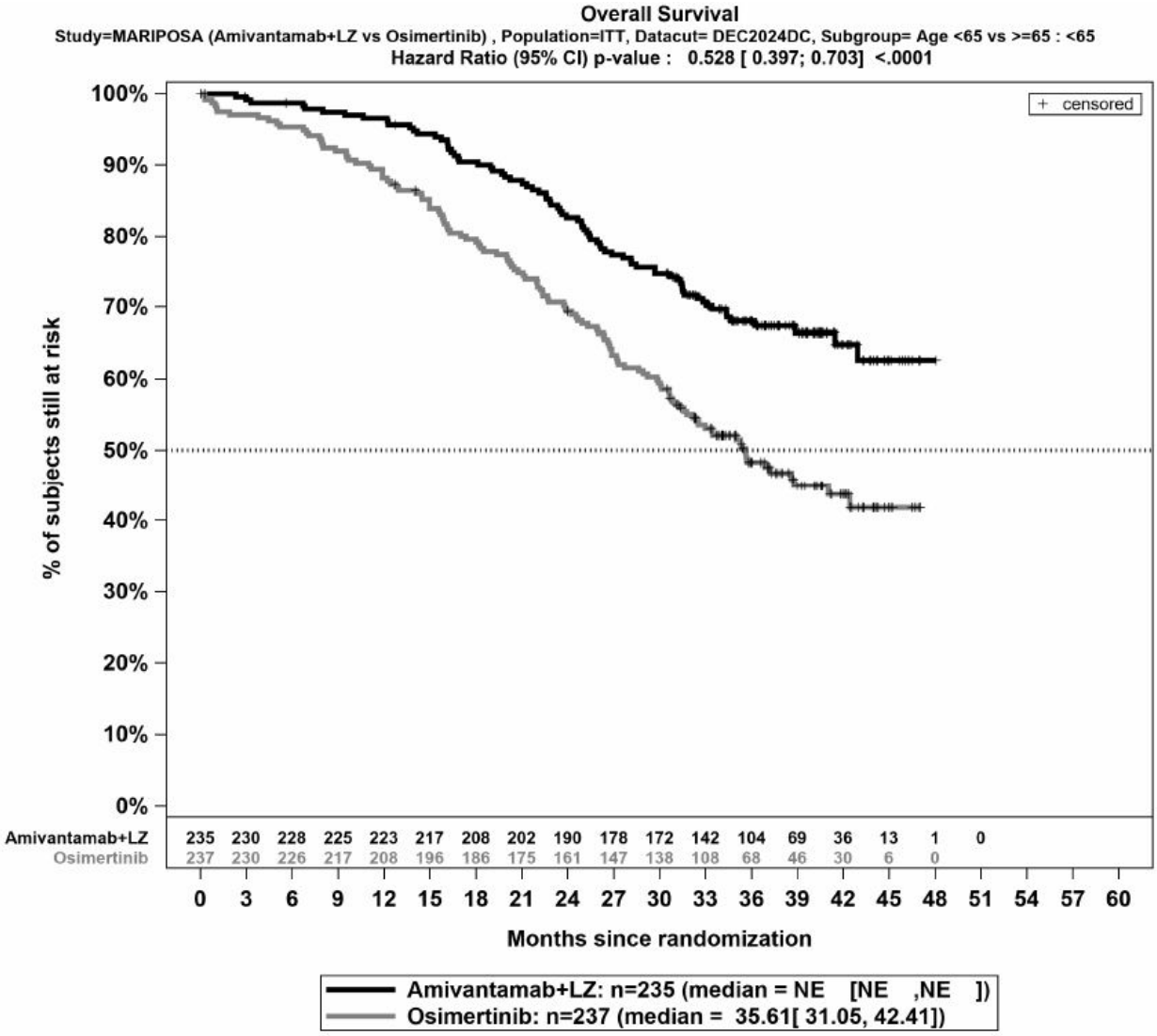

Figure 2: Kaplan-Meier curves for the outcome of overall survival, MARIPOSA study, data cut-off from 4 December 2024; subgroup: age < 65 years

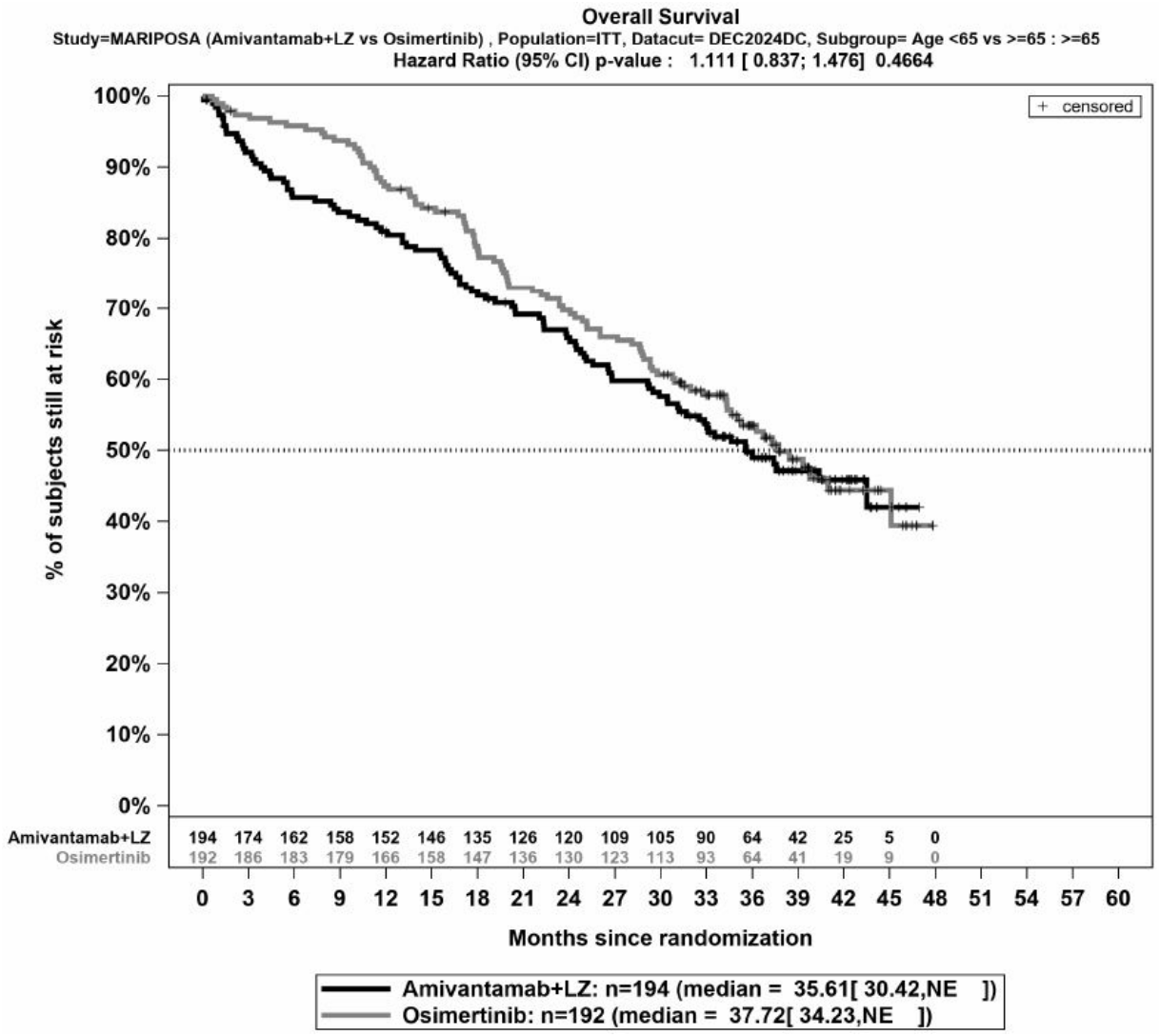

Figure 3: Kaplan-Meier curves for the outcome of overall survival, MARIPOSA study, data cut-off from 4 December 2024; subgroup: age ≥ 65 years

A.2 Morbidity (EORTC QLQ-C30 (symptom scales), NSCLC-SAQ, EQ-5D VAS)

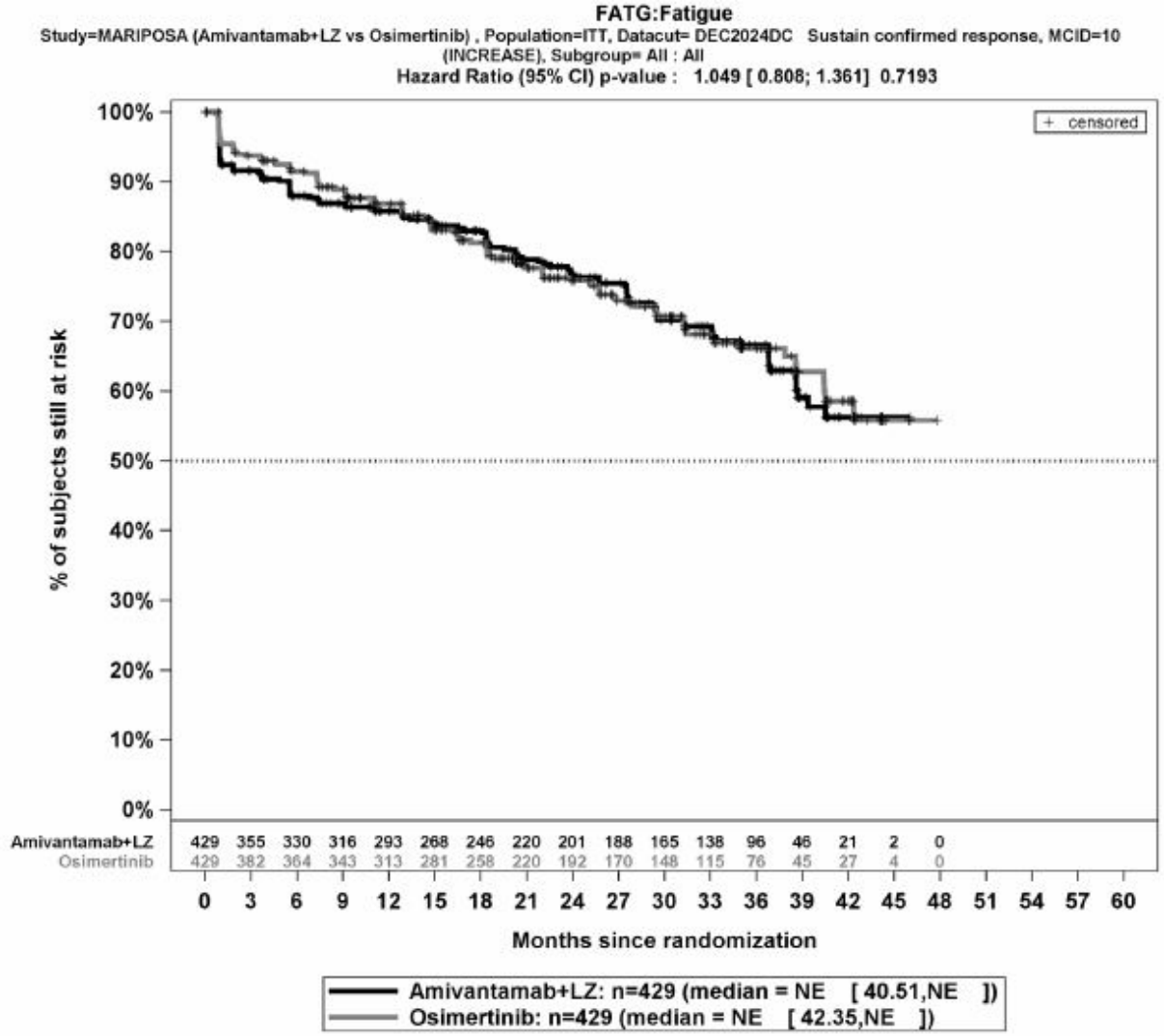

Figure 4: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

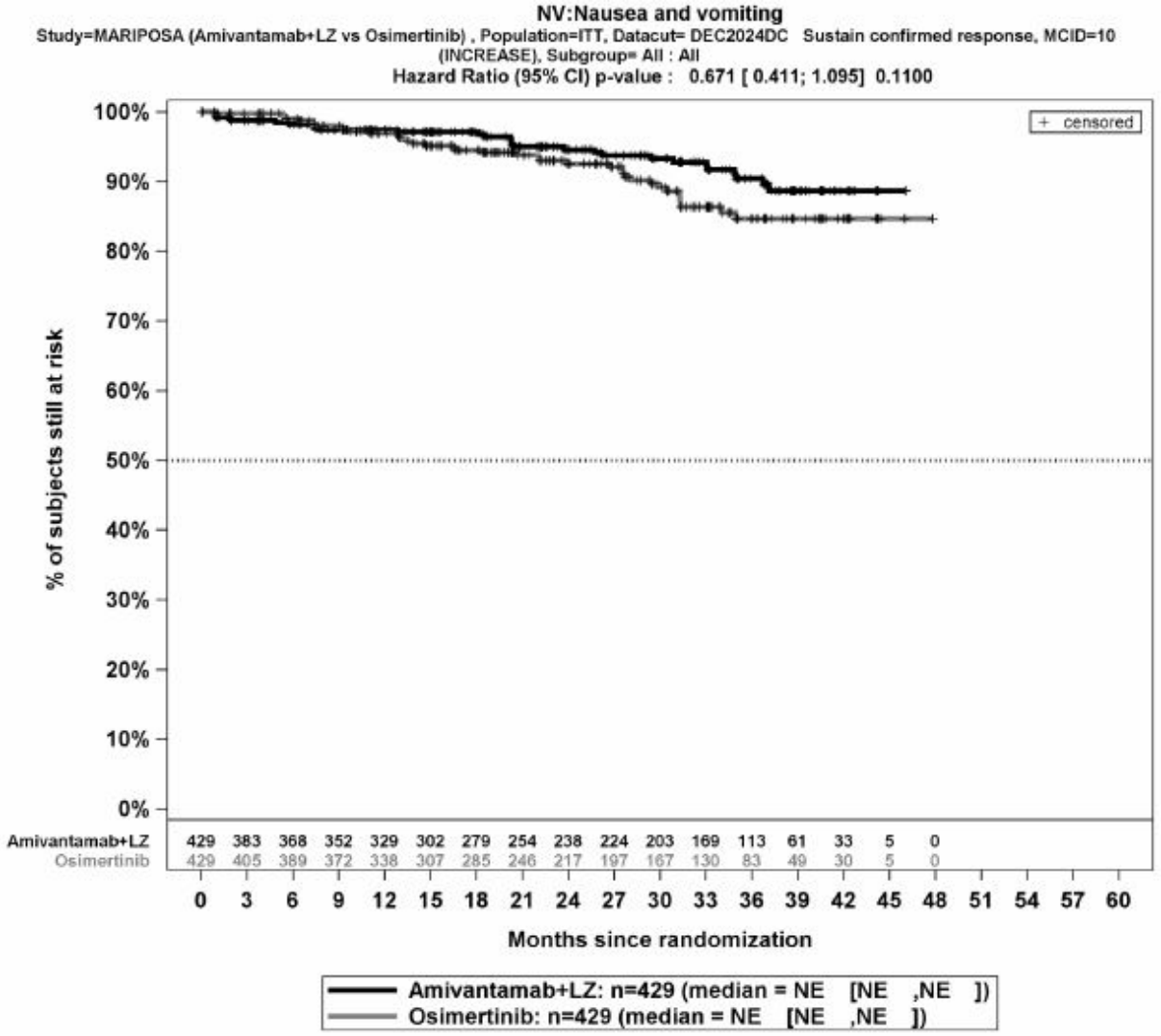

Figure 5: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 4 December 2024)

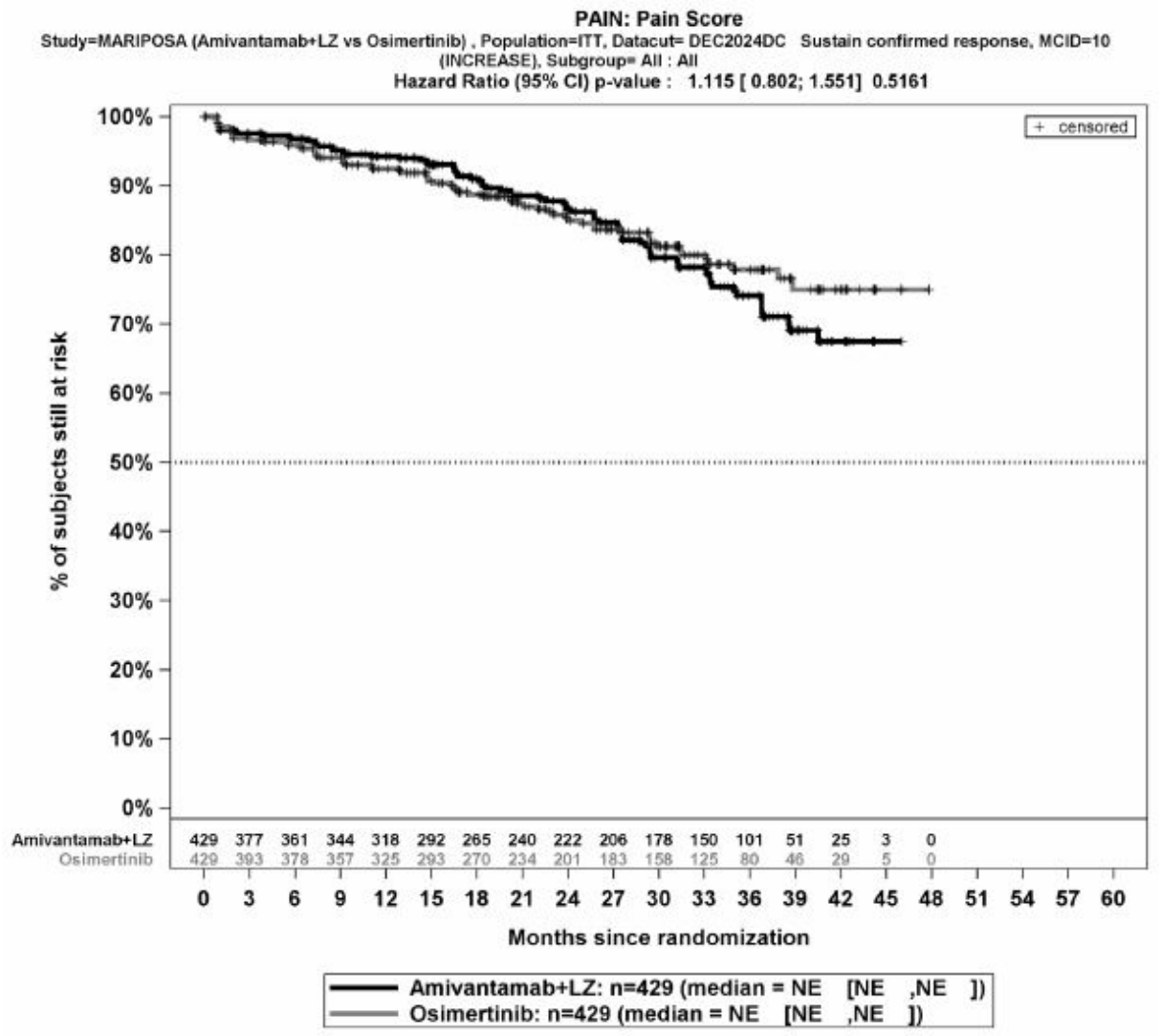

Figure 6: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 4 December 2024

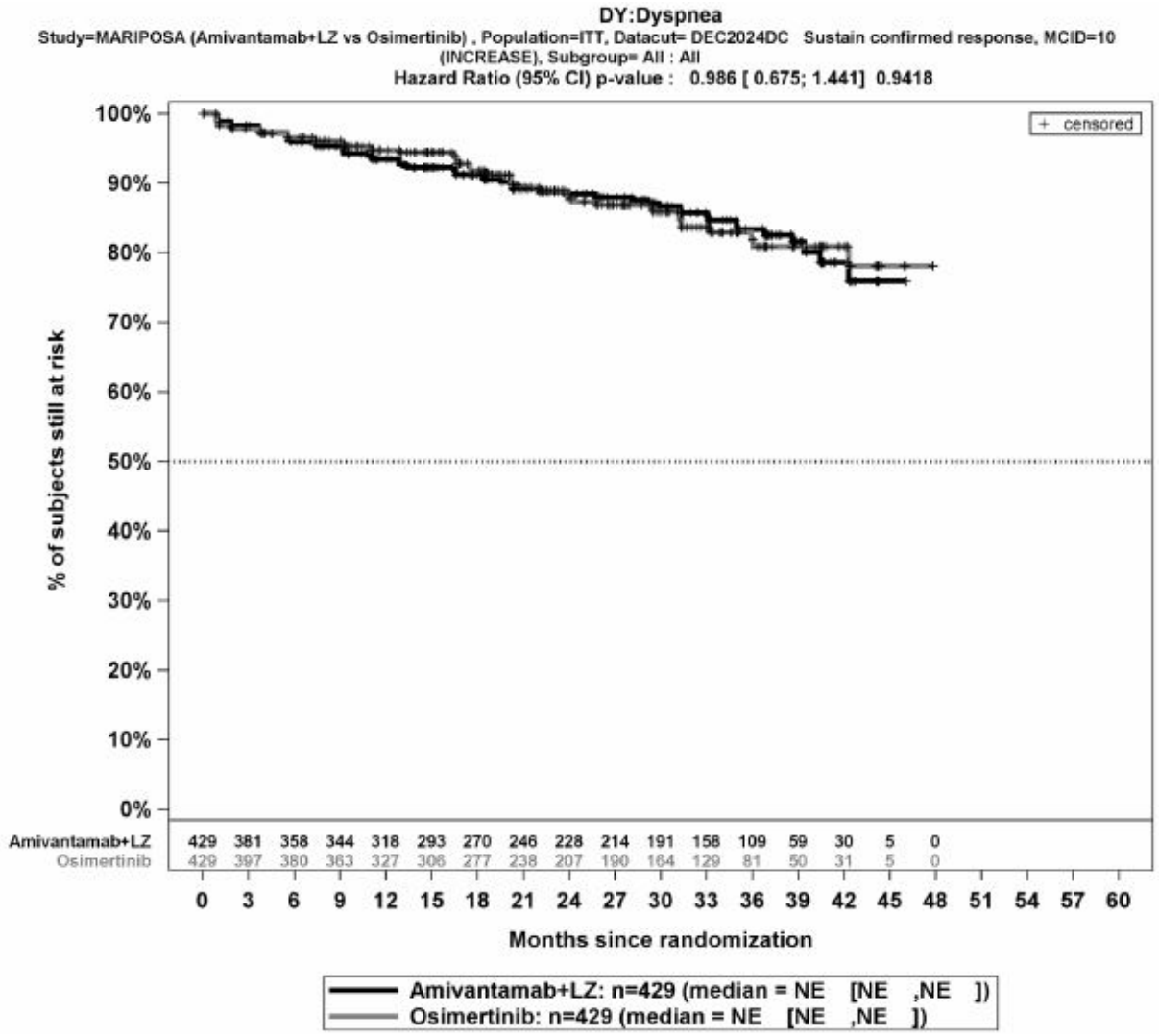

Figure 7: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

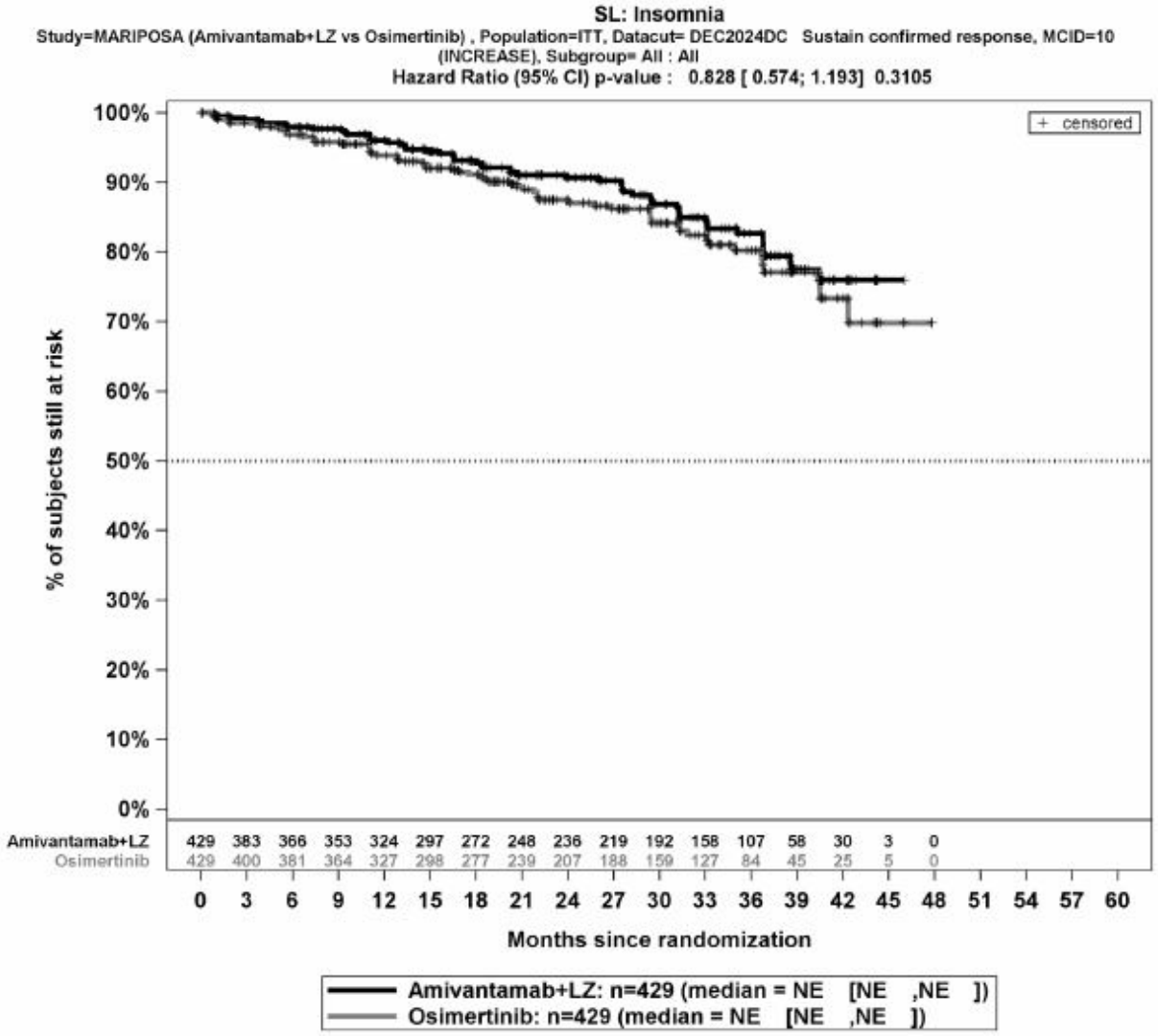

Figure 8: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

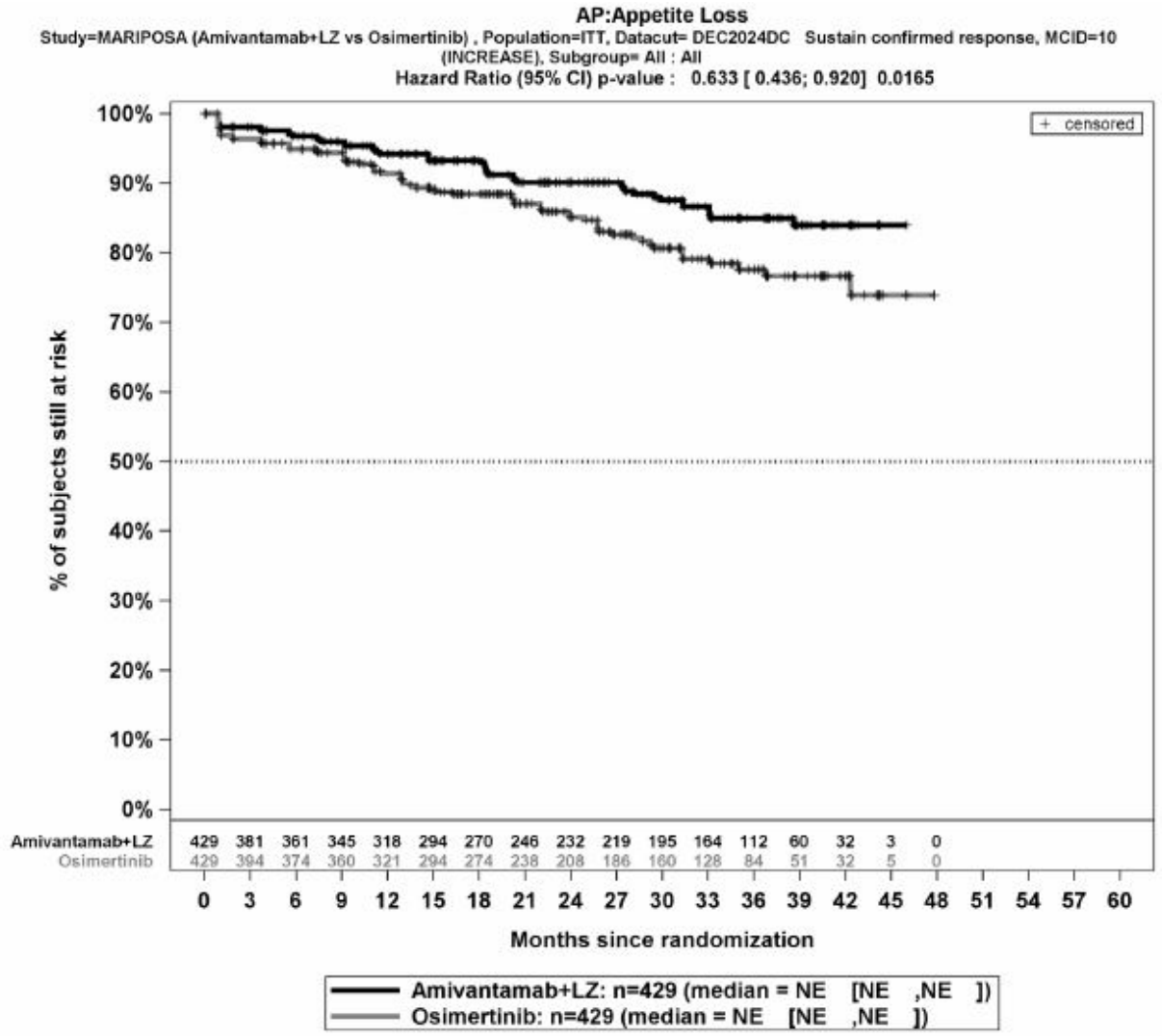

Figure 9: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 4 December 2024

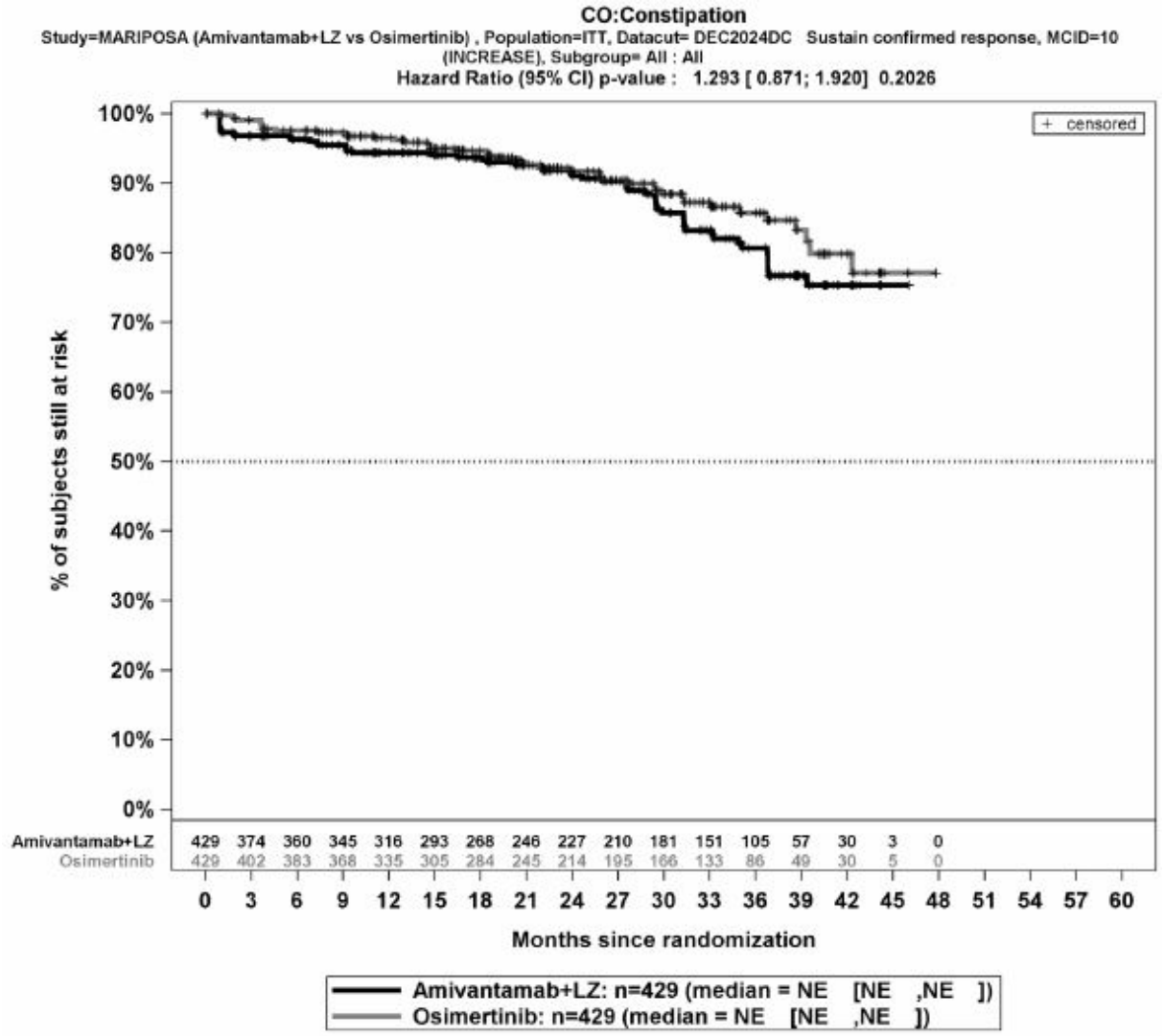

Figure 10: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

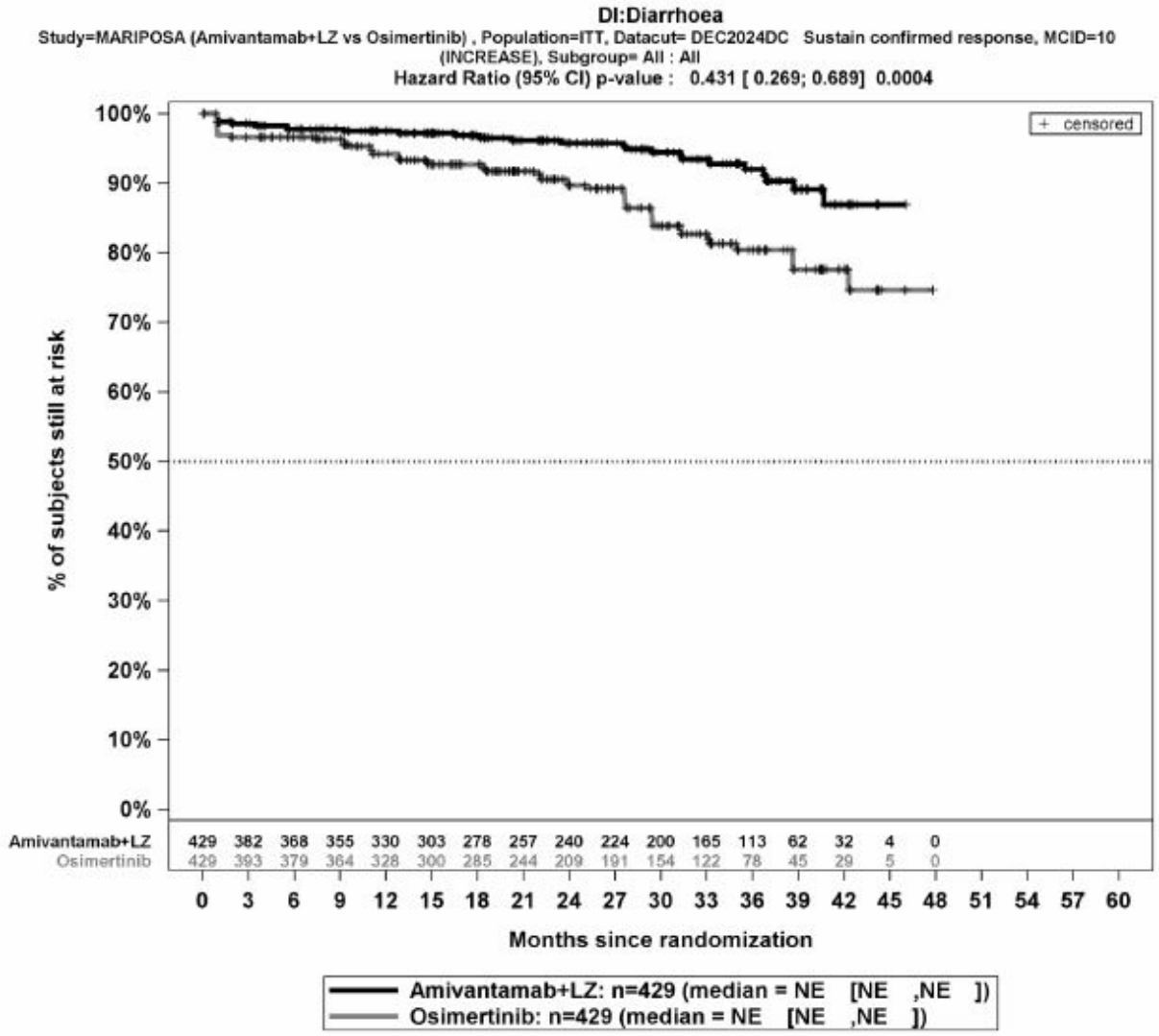

Figure 11: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30 symptom scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

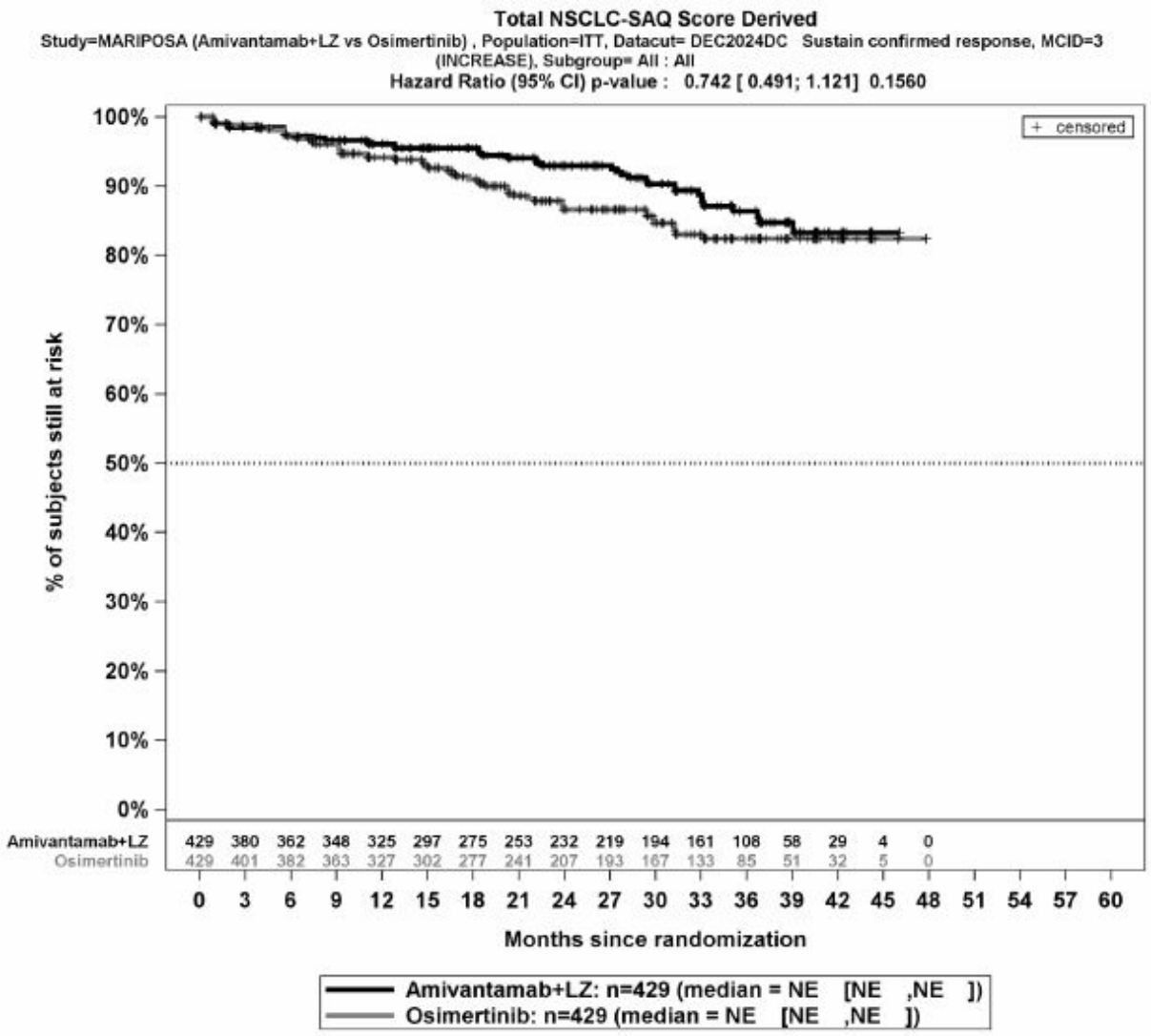

Figure 12: Kaplan-Meier curves for the outcome of NSCLC-SAQ, time to confirmed deterioration, MARIPOSA study, data cut-off from 4 December 2024

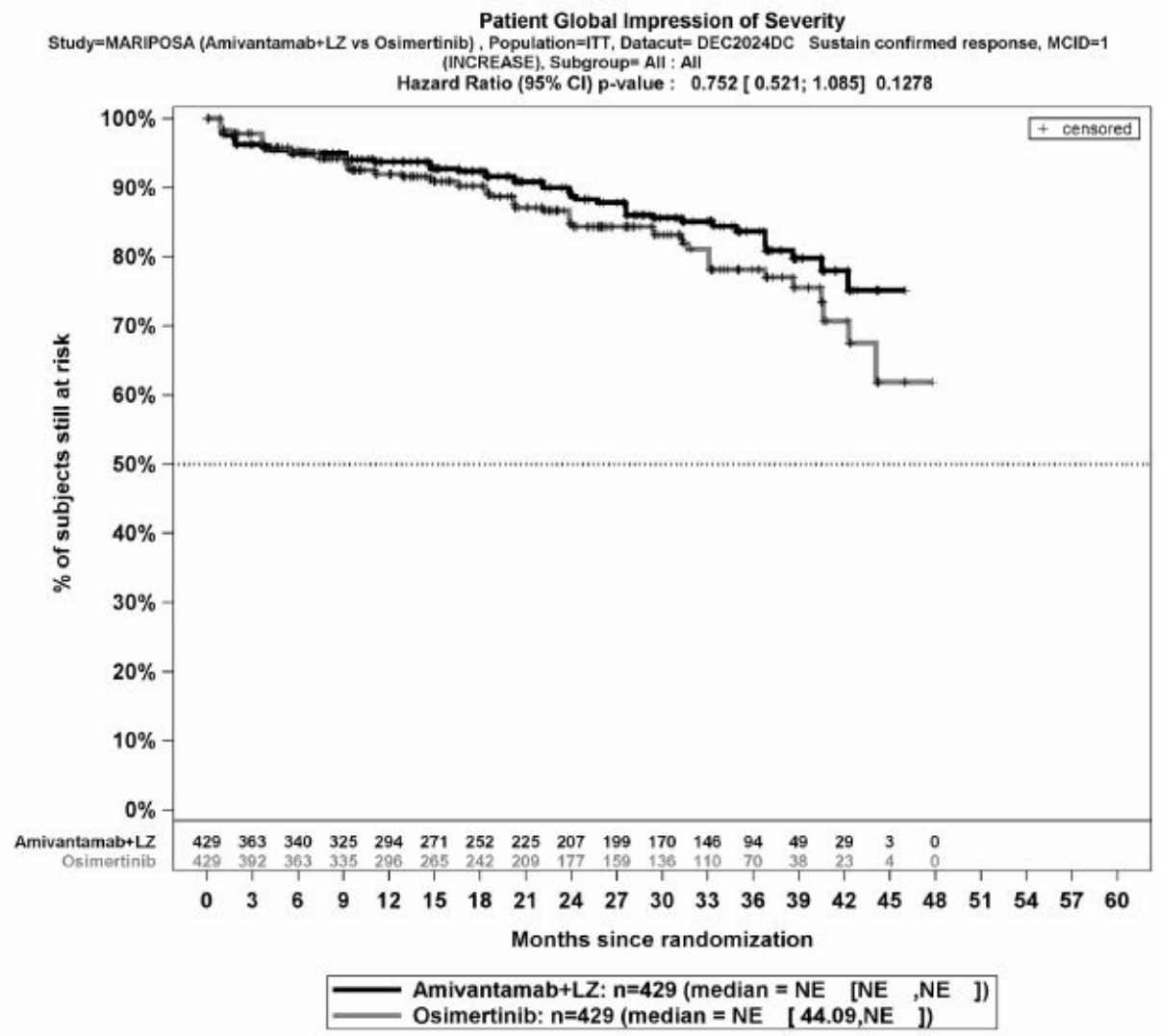

Figure 13: Kaplan-Meier curves for the outcome of PGIS, time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

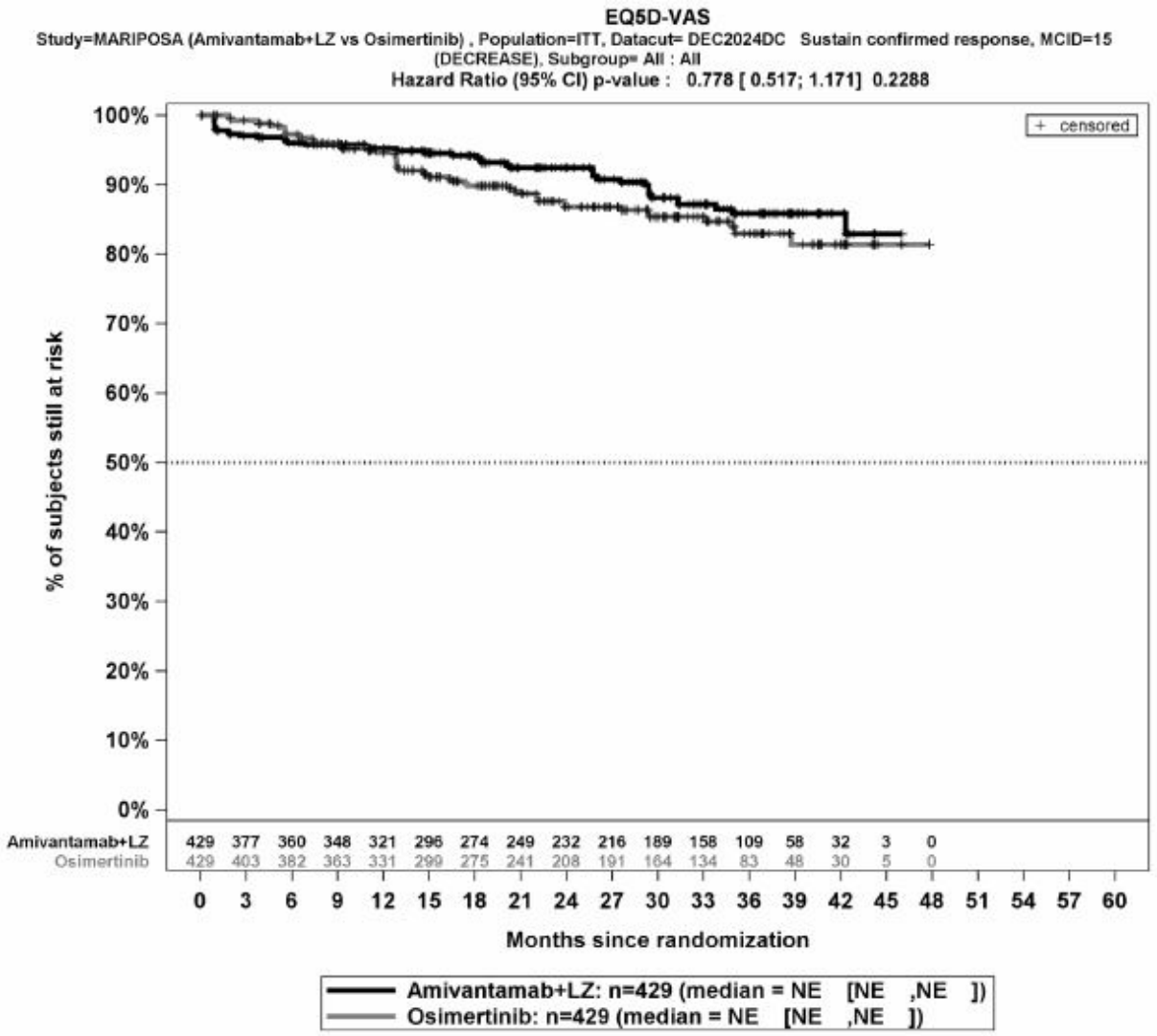

Figure 14: Kaplan-Meier curves for the outcome of EQ-5D VAS; time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

A.3 Health-related quality of life – EORTC QLQ-C30 (functional scales)

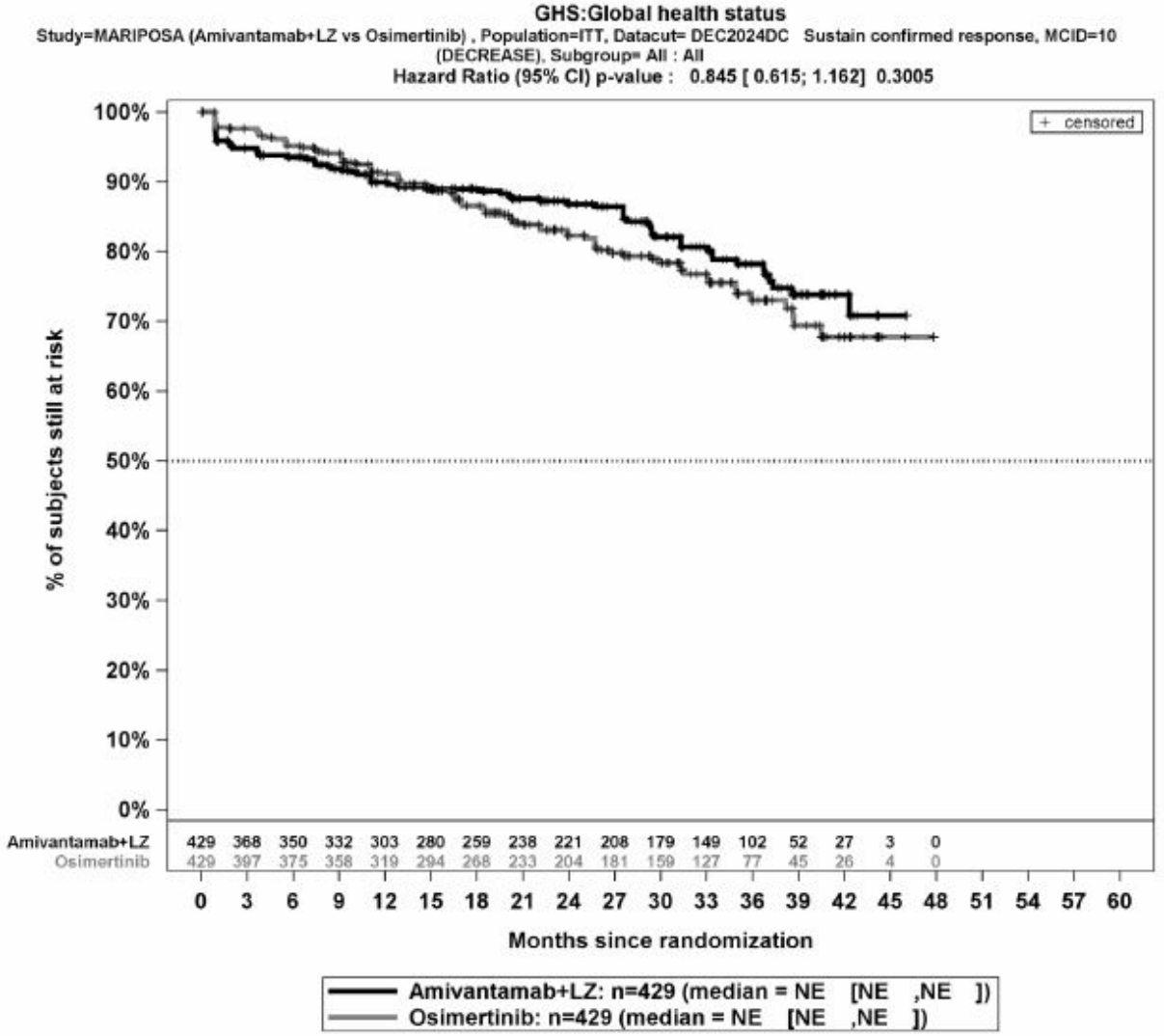

Figure 15: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30 functional scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

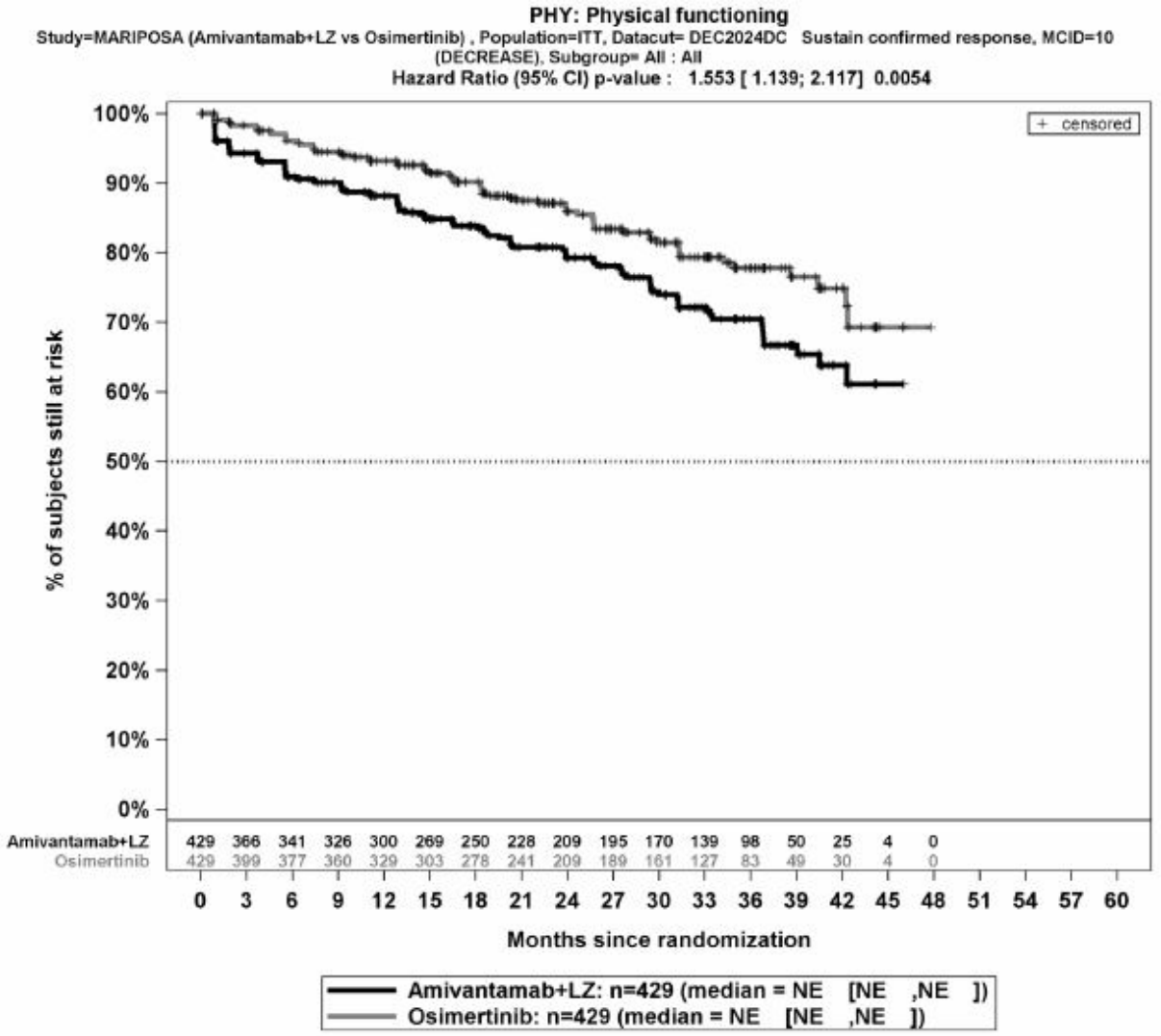

Figure 16: Kaplan-Meier-curves for the outcome of physical functioning (EORTC QLQ-C30 functional scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

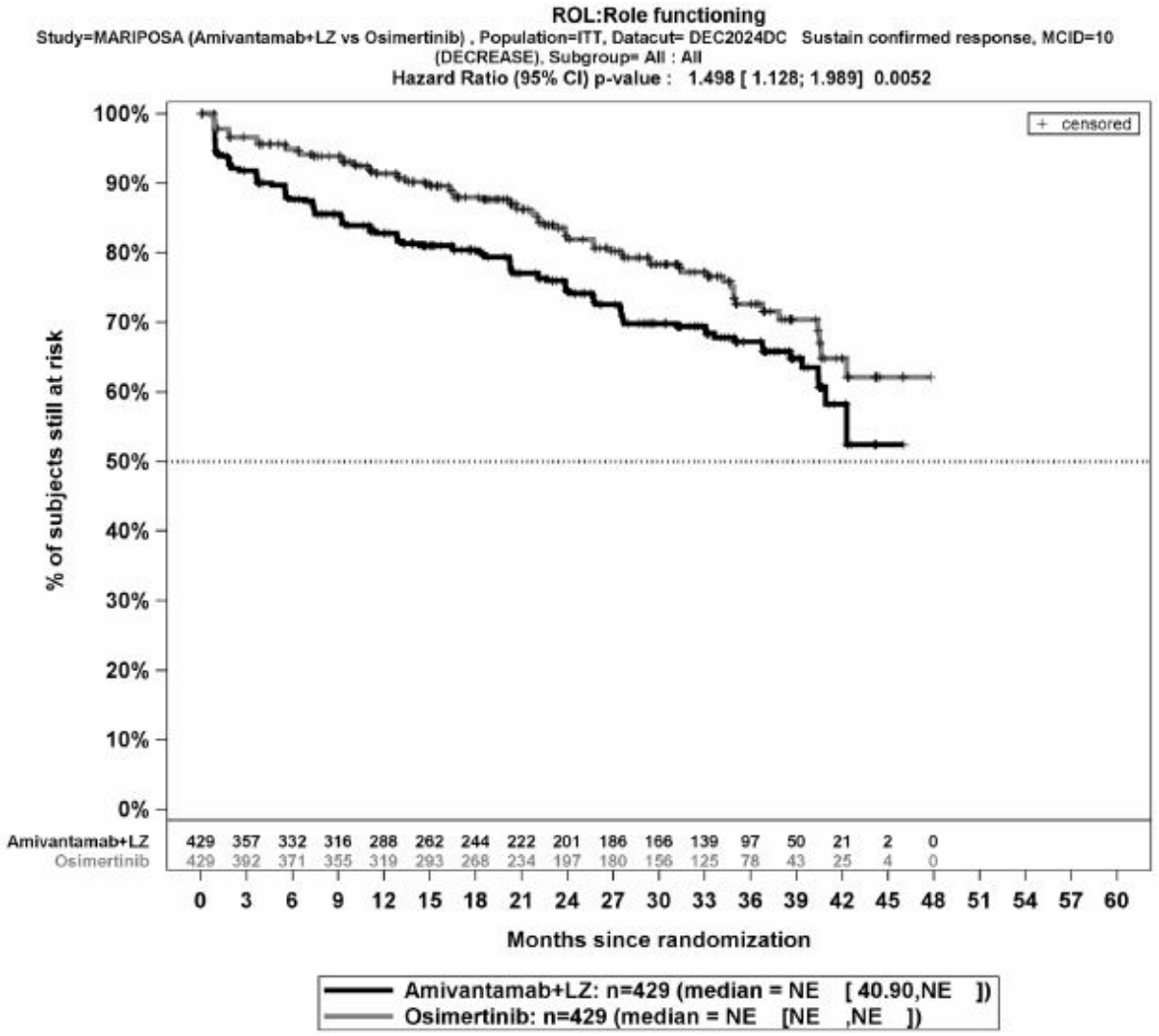

Figure 17: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30 functional scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

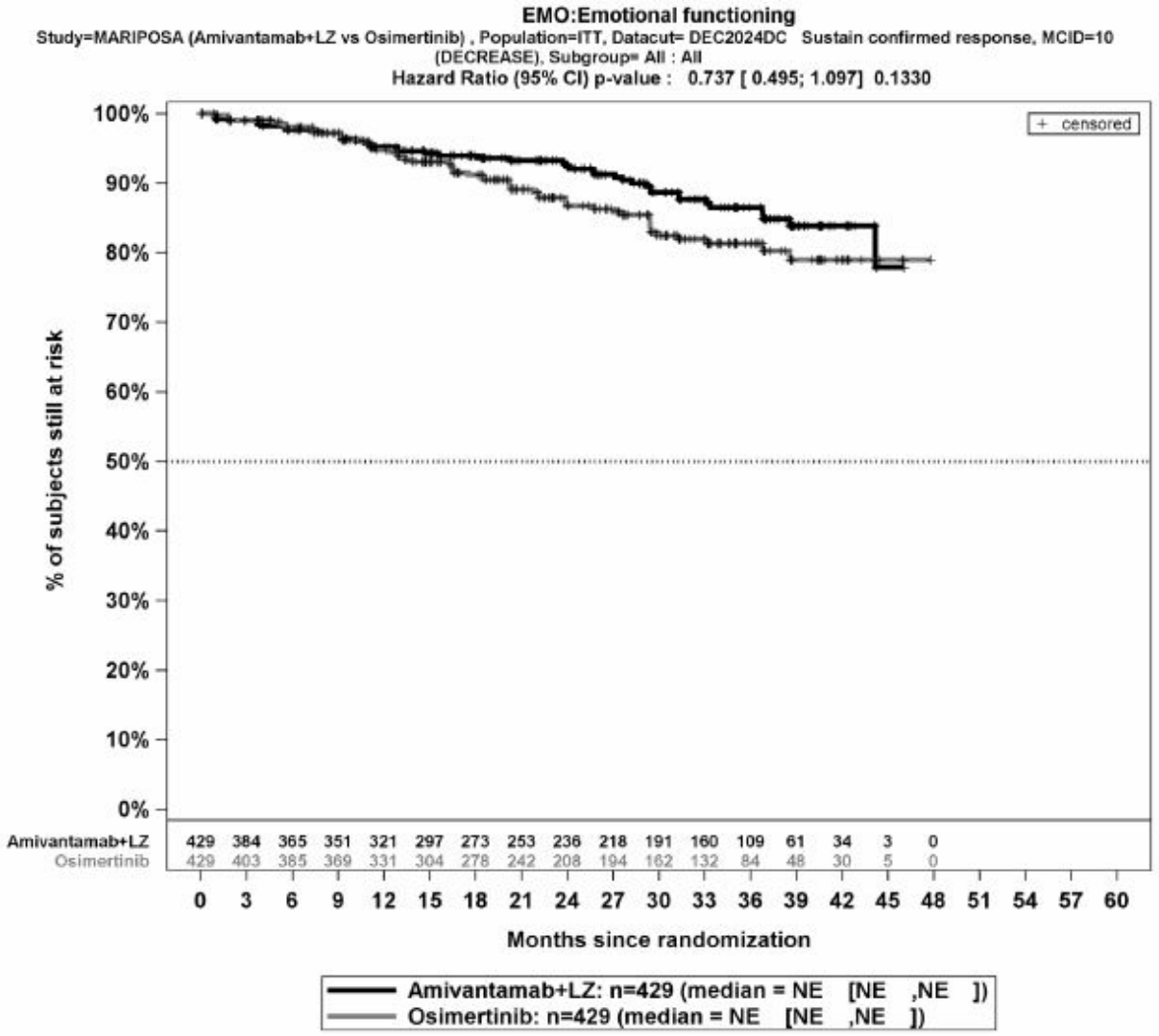

Figure 18: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30 functional scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

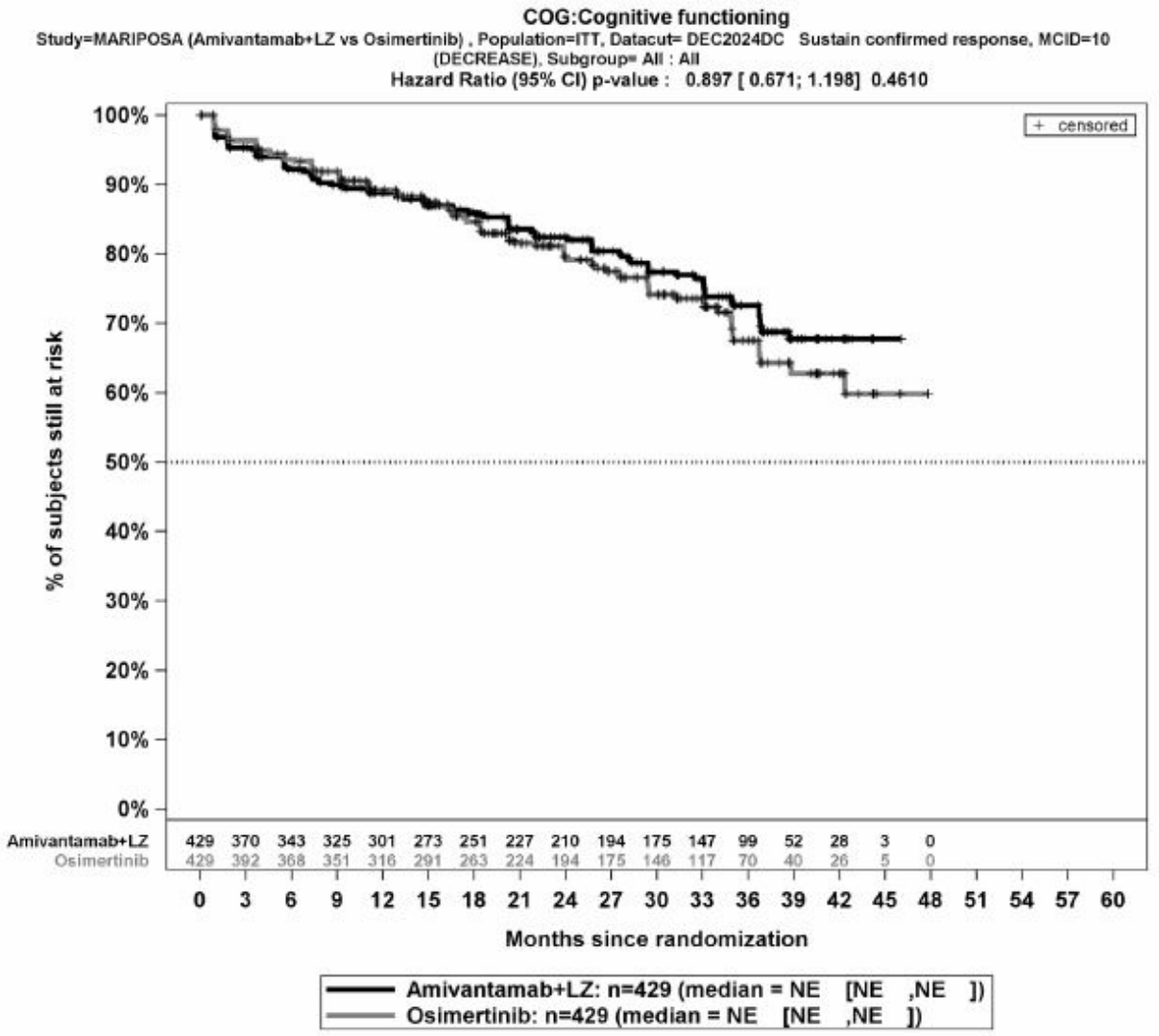

Figure 19: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30 functional scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

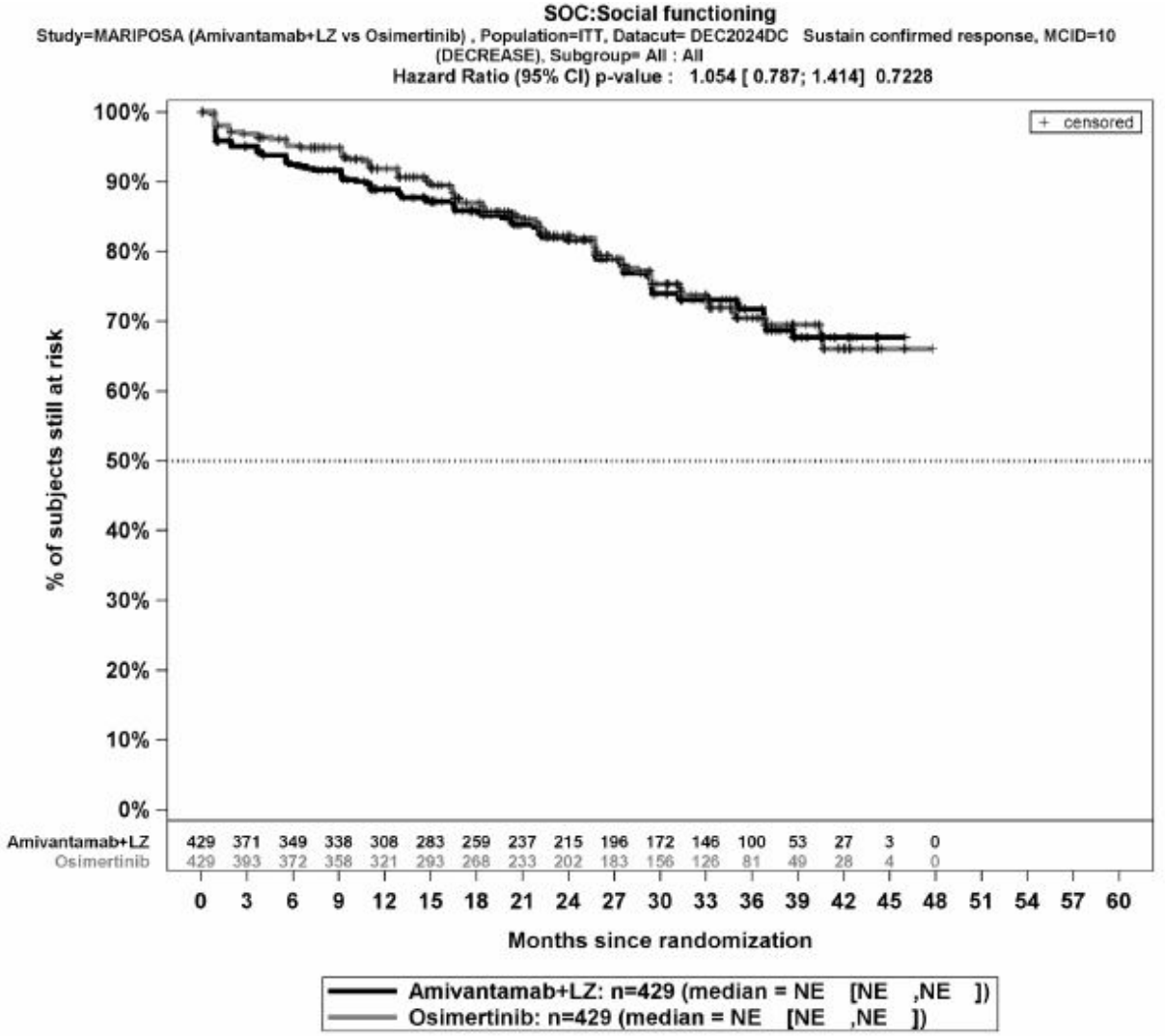

Figure 20: Kaplan-Meier-curves for the outcome of social functioning (EORTC QLQ-C30 functional scales), time to confirmed deterioration, MARIPOSA study, data cut-off from 04 December 2024

Appendix B Supplementary presentation of pre-specified analyses on patient-reported outcomes (time to first deterioration)

Table 13: Results (morbidity, health-related quality of life, time to first deterioration) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

Study outcome category outcome	Amivantamab + lazertinib		Osimertinib		Amivantamab + lazertinib vs. osimertinib
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
MARIPOSA (data cut-off from 4 December 2024)					
Morbidity					
Symptoms (EORTC QLQ-C30 – first deterioration[a]					
Fatigue	429	2.14 [1.91; 3.75] 296 (69.0)	429	7.69 [5.59; 11.17] 289 (67.4)	1.28 [1.08; 1.51]; 0.004
Nausea and vomiting	429	18.50 [13.90; 23.95] 217 (50.6)	429	18.43 [13.01; 22.14] 231 (53.8)	0.96 [0.80; 1.15]; 0.651
Pain	429	9.20 [7.39; 12.95] 264 (61.5)	429	15.05 [12.88; 17.51] 250 (58.3)	1.22 [1.03; 1.46]; 0.023
Dyspnoea	429	14.72 [9.33; 20.34] 225 (52.4)	429	23.98 [17.41; 33.15] 205 (47.8)	1.21 [1.00; 1.47]; 0.047
Insomnia	429	16.59 [12.91; 24.38] 213 (49.7)	429	15.70 [11.11; 20.24] 236 (55.0)	0.93 [0.77; 1.11]; 0.410
Appetite loss	429	9.27 [5.59; 12.98] 244 (56.9)	429	11.11 [7.43; 14.75] 266 (62.0)	1.02 [0.86; 1.21]; 0.835
Constipation	429	9.27 [6.28; 12.88] 248 (57.8)	429	22.21 [16.62; 29.47] 212 (49.4)	1.57 [1.30; 1.88]; < 0.001
Diarrhoea	429	17.05 [12.98; 24.02] 225 (52.4)	429	1.97 [1.91; 3.71] 315 (73.4)	0.50 [0.42; 0.60]; < 0.001
Symptoms (NSCLC-SAQ - first deterioration)[b]					
Total score	429	30.46 [23.95; 38.67] 186 (43.4)	429	25.86 [20.27; 40.58] 194 (45.2)	0.99 [0.81; 1.21]; 0.933
Cough	429	35.06 [27.66; NC] 165 (38.5)	429	18.46 [14.75; 23.95] 224 (52.2)	–
Pain	429	14.72 [11.07; 16.69] 233 (54.3)	429	16.56 [12.91; 20.37] 238 (55.5)	–
Dyspnoea	429	6.05 [5.59; 11.11] 264 (61.5)	429	16.62 [12.88; 20.30] 236 (55.0)	–
Fatigue	429	11.07 [5.59; 14.72] 241 (56.2)	429	16.66 [12.95; 21.98] 236 (55.0)	–
Appetite loss	429	5.62 [3.75; 9.86] 265 (61.8)	429	7.43 [5.59; 11.11] 284 (66.2)	–

Table 13: Results (morbidity, health-related quality of life, time to first deterioration) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

Study outcome category outcome	Amivantamab + lazertinib		Osimertinib		Amivantamab + lazertinib vs. osimertinib
	N	median time to event in months [95% CI] patients with event n (%)	N	median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value
Symptoms (PGIS - first deterioration[c])	429	20.27 [11.20; NC] 193 (45.0)	429	26.51 [22.11; NC] 179 (41.7)	1.16 [0.94; 1.42]; 0.160
Health status (EQ-5D VAS – first deterioration[d])	429	31.24 [22.11; 37.75] 183 (42.7)	429	25.00 [20.07; 30.46] 213 (49.7)	0.91 [0.75; 1.11]; 0.352
Health-related quality of life					
EORTC QLQ-C30 – first deterioration[d])					
Global health status	429	11.11 [7.43; 16.59] 243 (56.6)	429	18.43 [14.75; 22.18] 241 (56.2)	1.18 [0.99; 1.41]; 0.073
Physical functioning	429	7.39 [3.78; 9.27] 278 (64.8)	429	17.41 [14.75; 22.87] 239 (55.7)	1.53 [1.28; 1.82]; < 0.001
Role functioning	429	3.75 [2.04; 5.59] 291 (67.8)	429	12.85 [10.09; 16.59] 259 (60.4)	1.49 [1.26; 1.76]; < 0.001
Emotional functioning	429	22.31 [18.50; 31.24] 200 (46.6)	429	23.92 [18.46; 29.50] 209 (48.7)	1.00 [0.83; 1.22]; 0.979
Cognitive functioning	429	7.72 [5.62; 12.03] 267 (62.2)	429	7.49 [5.65; 11.04] 294 (68.5)	0.89 [0.76; 1.06]; 0.184
Social functioning	429	5.55 [3.75; 7.36] 285 (66.4)	429	12.91 [9.27; 14.78] 263 (61.3)	1.35 [1.14; 1.59]; 0.001

a. A score increase by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range 0 to 100).
b. An increase by ≥ 3 points from baseline was considered a clinically relevant deterioration (scale range for the total score: 0 to 20, for the subscales: 0 to 4).
c. An increase by ≥ 1 point from baseline was considered a clinically relevant deterioration (scale range for the total score: 1 to 6).
d. A decrease by ≥ 15 points from baseline was considered a clinically relevant deterioration (scale range for the total score: 0 to 100).
e. A decrease of the respective score by ≥ 10 points from baseline was considered a clinically relevant deterioration (scale range: 0 to 100).

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EGFR: Epidermal Growth Factor Receptor; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EGFR: epidermal growth factor receptor; Del19: exon 19 deletion; HR: hazard ratio; ILD: interstitial lung disease; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NSCLC-SAQ: Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Appendix C Results on side effects

For the overall rates of AEs, SAEs and severe AEs (e.g. CTCAE grade ≥ 3) the following tables present events for SOCs and PTs according to the MedDRA, each based on the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rate of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

For the outcome of discontinuation due to AEs, all events which occurred in at least 1% of patients are presented.

Table 14: Common AEsa – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] / **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
MARIPOSA		
Overall AE rate	421 (100.0)	426 (99.5)
Skin and subcutaneous tissue disorders	388 (92.2)	279 (65.2)
Rash	271 (64.4)	136 (31.8)
Dermatitis acneiform	127 (30.2)	55 (12.9)
Pruritus	107 (25.4)	75 (17.5)
Dry skin	72 (17.1)	67 (15.7)
Skin fissures	41 (9.7)	24 (5.6)
Skin ulceration	31 (7.4)	2 (0.5)
Rash maculo-papular	27 (6.4)	9 (2.1)
Palmar-plantar erythrodysaesthesia syndrome	26 (6.2)	16 (3.7)
Skin lesion	21 (5.0)	5 (1.2)
Erythema	20 (4.8)	4 (0.9)
Acne	19 (4.5)	7 (1.6)
Alopecia	18 (4.3)	20 (4.7)
Nail disorder	18 (4.3)	13 (3.0)
Dermatitis	14 (3.3)	10 (2.3)
Hypertrichosis	13 (3.1)	0 (0)
Rash pruritic	12 (2.9)	4 (0.9)
Hirsutism	11 (2.6)	0 (0)
Onycholysis	10 (2.4)	9 (2.1)
Infections and infestations	368 (87.4)	296 (69.2)
Paronychia	291 (69.1)	127 (29.7)
COVID-19	125 (29.7)	112 (26.2)
Upper respiratory tract infection	52 (12.4)	51 (11.9)
Pneumonia	50 (11.9)	46 (10.7)
Conjunctivitis	48 (11.4)	10 (2.3)
Urinary tract infection	37 (8.8)	23 (5.4)
Folliculitis	29 (6.9)	7 (1.6)
Cellulitis	28 (6.7)	6 (1.4)
Nasopharyngitis	21 (5.0)	19 (4.4)
Herpes zoster	20 (4.8)	11 (2.6)
Rash pustular	16 (3.8)	5 (1.2)
Skin infection~	13 (3.1)	3 (0.7)
Influenza	13 (3.1)	6 (1.4)

Table 14: Common AEsa – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	amivantamab + lazertinib N = 421	osimertinib N = 428
Cystitis	11 (2.6)	12 (2.8)
Sinusitis	7 (1.7)	13 (3.0)
Gastrointestinal disorders	336 (79.8)	314 (73.4)
Diarrhoea	133 (31.6)	200 (46.7)
Constipation	130 (30.9)	70 (16.4)
Stomatitis	126 (29.9)	92 (21.5)
Nausea	99 (23.5)	65 (15.2)
Vomiting	59 (14.0)	28 (6.5)
Haemorrhoids	44 (10.5)	10 (2.3)
Abdominal pain upper	36 (8.6)	21 (4.9)
Dyspepsia	33 (7.8)	22 (5.1)
Gastro-oesophageal reflux disease	21 (5.0)	20 (4.7)
Mouth ulceration	21 (5.0)	15 (3.5)
Abdominal pain	21 (5.0)	21 (4.9)
Gingival bleeding	20 (4.8)	2 (0.5)
Anal fissure	19 (4.5)	0 (0)
Gastritis	15 (3.6)	11 (2.6)
Dry mouth	12 (2.9)	10 (2.3)
Toothache	8 (1.9)	10 (2.3)
Abdominal distension	5 (1.2)	11 (2.6)
General disorders and administration site conditions	322 (76.5)	213 (49.8)
Oedema peripheral	162 (38.5)	29 (6.8)
Asthenia	84 (20.0)	54 (12.6)
Fatigue	76 (18.1)	49 (11.4)
Fever	57 (13.5)	48 (11.2)
Mucosal inflammation	48 (11.4)	14 (3.3)
Peripheral swelling	29 (6.9)	6 (1.4)
Malaise	23 (5.5)	16 (3.7)
Oedema	23 (5.5)	2 (0.5)
Chest pain	22 (5.2)	21 (4.9)
Non-cardiac chest pain	18 (4.3)	27 (6.3)
Chest discomfort	12 (2.9)	5 (1.2)
Face oedema	11 (2.6)	4 (0.9)
Pain	6 (1.4)	12 (2.8)

Table 14: Common AEsa – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
Metabolism and nutrition disorders	315 (74.8)	200 (46.7)
Hypoalbuminaemia	216 (51.3)	29 (6.8)
Decreased appetite	114 (27.1)	84 (19.6)
Hypocalcaemia	96 (22.8)	37 (8.6)
Hypokalaemia	63 (15.0)	38 (8.9)
Hyponatraemia	40 (9.5)	46 (10.7)
Hyperglycaemia	30 (7.1)	21 (4.9)
Hypomagnesaemia	25 (5.9)	8 (1.9)
Hypoproteinaemia	22 (5.2)	5 (1.2)
Hyperkalaemia	18 (4.3)	10 (2.3)
Hyperamylasemia	12 (2.9)	4 (0.9)
Hypoglycaemia	10 (2.4)	4 (0.9)
Hypertriglyceridaemia	9 (2.1)	14 (3.3)
Hyperuricaemia	8 (1.9)	19 (4.4)
Injury, poisoning and procedural complications	307 (72.9)	59 (13.8)
Infusion related reaction	275 (65.3)	0 (0)
Fall	20 (4.8)	7 (1.6)
Investigations	275 (65.3)	213 (49.8)
Alanine aminotransferase increased	170 (40.4)	66 (15.4)
Aspartate aminotransferase increased	139 (33.0)	68 (15.9)
Gamma-glutamyltransferase increased	68 (16.2)	36 (8.4)
Blood alkaline phosphatase increased	53 (12.6)	25 (5.8)
Blood lactate dehydrogenase increased	49 (11.6)	25 (5.8)
Weight decreased	41 (9.7)	53 (12.4)
Blood creatinine increased	40 (9.5)	60 (14.0)
Ejection fraction decreased	20 (4.8)	22 (5.1)
SARS-CoV-2 test positive	17 (4.0)	12 (2.8)
Blood creatine phosphokinase increased	17 (4.0)	24 (5.6)
Weight increased	16 (3.8)	16 (3.7)
General condition worsened according to the Eastern Cooperative Oncology Group	16 (3.8)	6 (1.4)
Electrocardiogram QT prolonged	14 (3.3)	8 (1.9)
Fibrin D dimer increased	13 (3.1)	6 (1.4)
Lipase increased	12 (2.9)	3 (0.7)
Blood urea increased	9 (2.1)	11 (2.6)

Table 14: Common AEsa – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
Respiratory, thoracic and mediastinal disorders	259 (61.5)	239 (55.8)
Pulmonary embolism	81 (19.2)	26 (6.1)
Cough	80 (19.0)	105 (24.5)
Dyspnoea	68 (16.2)	77 (18.0)
Epistaxis	41 (9.7)	17 (4.0)
Productive cough	27 (6.4)	25 (5.8)
Pleural effusion	26 (6.2)	31 (7.2)
Rhinorrhoea	16 (3.8)	15 (3.5)
Oropharyngeal pain	16 (3.8)	15 (3.5)
Haemoptysis	15 (3.6)	15 (3.5)
Dysphonia	14 (3.3)	7 (1.6)
Allergic rhinitis	5 (1.2)	10 (2.3)
Musculoskeletal and connective tissue disorders	251 (59.6)	202 (47.2)
Muscle spasms	84 (20.0)	36 (8.4)
Pain in extremity	72 (17.1)	30 (7.0)
Back pain	65 (15.4)	59 (13.8)
Myalgia	60 (14.3)	24 (5.6)
Arthralgia	50 (11.9)	68 (15.9)
Muscular weakness	18 (4.3)	8 (1.9)
Musculoskeletal chest pain	15 (3.6)	14 (3.3)
Neck pain	12 (2.9)	19 (4.4)
Bone pain	10 (2.4)	15 (3.5)
Musculoskeletal pain	10 (2.4)	11 (2.6)
Nervous system disorders	246 (58.4)	169 (39.5)
Headache	67 (15.9)	67 (15.7)
Dizziness	62 (14.7)	38 (8.9)
Paraesthesia	61 (14.5)	27 (6.3)
Peripheral neuropathy	45 (10.7)	5 (1.2)
Hypaesthesia	28 (6.7)	10 (2.3)
Peripheral sensory neuropathy	27 (6.4)	11 (2.6)
Dysgeusia	13 (3.1)	19 (4.4)
Polyneuropathy	10 (2.4)	0 (0)

Table 14: Common AEsa – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
Blood and lymphatic system disorders	178 (42.3)	201 (47.0)
Anaemia	114 (27.1)	112 (26.2)
Thrombocytopenia	74 (17.6)	92 (21.5)
Leukopenia	30 (7.1)	69 (16.1)
Lymphopenia	26 (6.2)	37 (8.6)
Neutropenia	24 (5.7)	64 (15.0)
Leukocytosis	11 (2.6)	9 (2.1)
Vascular disorders	171 (40.6)	67 (15.7)
Deep vein thrombosis	66 (15.7)	13 (3.0)
Hypertension	33 (7.8)	20 (4.7)
Hypotension	33 (7.8)	6 (1.4)
Venous thrombosis of an extremity	18 (4.3)	2 (0.5)
Venous thrombosis	10 (2.4)	1 (0.2)
Eye disorders	144 (34.2)	76 (17.8)
Dry eye	42 (10.0)	21 (4.9)
Cataract	20 (4.8)	16 (3.7)
Blepharitis	18 (4.3)	6 (1.4)
Vision blurred	16 (3.8)	8 (1.9)
Keratitis	14 (3.3)	2 (0.5)
Lacrimation increased	10 (2.4)	0 (0)
Psychiatric disorders	82 (19.5)	95 (22.2)
Insomnia	49 (11.6)	54 (12.6)
Anxiety	16 (3.8)	17 (4.0)
Depression	15 (3.6)	8 (1.9)
Renal and urinary disorders	77 (18.3)	56 (13.1)
Haematuria	21 (5.0)	9 (2.1)
Dysuria	15 (3.6)	6 (1.4)
Renal insufficiency	7 (1.7)	11 (2.6)
Cardiac disorders	66 (15.7)	58 (13.6)
Pericardial effusion	9 (2.1)	10 (2.3)
Hepatobiliary disorders	65 (15.4)	29 (6.8)
Hyperbilirubinaemia	32 (7.6)	16 (3.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44 (10.5)	34 (7.9)
cancer pain	4 (1.0)	13 (3.0)

Table 14: Common AEsa – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
Reproductive system and breast disorders	43 (10.2)	20 (4.7)
Ear and labyrinth disorders	40 (9.5)	29 (6.8)
Tinnitus	13 (3.1)	8 (1.9)
Vertigo	11 (2.6)	9 (2.1)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken unmodified from comments document [3,5]

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus Type 2; SOC: System Organ Class

Table 15: Common SAEsa – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib

Study	**Patients with event n (%)**	
SOC[b] / **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
MARIPOSA		
Overall SAE rate	233 (55.3)	177 (41.4)
Infections and infestations	68 (16.2)	44 (10.3)
Pneumonia	26 (6.2)	24 (5.6)
COVID-19	10 (2.4)	9 (2.1)
Respiratory, thoracic and mediastinal disorders	68 (16.2)	56 (13.1)
Pulmonary embolism	27 (6.4)	11 (2.6)
Pleural effusion	11 (2.6)	17 (4.0)
Dyspnoea	4 (1.0)	12 (2.8)
Injury, poisoning and procedural complications	32 (7.6)	16 (3.7)
Gastrointestinal disorders	27 (6.4)	12 (2.8)
General disorders and administration site conditions	24 (5.7)	10 (2.3)
Vascular disorders	24 (5.7)	9 (2.1)
Deep vein thrombosis	12 (2.9)	2 (0.5)
Metabolism and nutrition disorders	19 (4.5)	14 (3.3)
Nervous system disorders	17 (4.0)	24 (5.6)
Cardiac disorders	16 (3.8)	12 (2.8)
Skin and subcutaneous tissue disorders	15 (3.6)	0 (0)
Investigations	13 (3.1)	9 (2.1)
Musculoskeletal and connective tissue disorders	7 (1.7)	11 (2.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken unmodified from comments document [3,5]

COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Table 16: Common severe AEs (CTCAE grade ≥ 3)a – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] / **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
MARIPOSA		
Overall rate of severe AEs (CTCAE grade ≥ 3)	337 (80.0)	224 (52.3)
Skin and subcutaneous tissue disorders	132 (31.4)	7 (1.6)
Rash	73 (17.3)	3 (0.7)
Dermatitis acneiform	37 (8.8)	0 (0)
Infections and infestations	120 (28.5)	44 (10.3)
Paronychia	49 (11.6)	2 (0.5)
Pneumonia	22 (5.2)	22 (5.1)
Respiratory, thoracic and mediastinal disorders	71 (16.9)	52 (12.1)
Pulmonary embolism	36 (8.6)	12 (2.8)
Dyspnoea	8 (1.9)	19 (4.4)
Pleural effusion	8 (1.9)	15 (3.5)
Metabolism and nutrition disorders	66 (15.7)	33 (7.7)
Hypoalbuminaemia	26 (6.2)	0 (0)
Hypokalaemia	16 (3.8)	3 (0.7)
Hypocalcaemia	11 (2.6)	0 (0)
Hyponatraemia	10 (2.4)	13 (3.0)
Investigations	65 (15.4)	42 (9.8)
Alanine aminotransferase increased	28 (6.7)	8 (1.9)
Gamma-glutamyltransferase increased	16 (3.8)	7 (1.6)
Aspartate aminotransferase increased	15 (3.6)	6 (1.4)
Injury, poisoning and procedural complications	48 (11.4)	13 (3.0)
Infusion related reaction	27 (6.4)	0 (0)
Gastrointestinal disorders	41 (9.7)	19 (4.4)
General disorders and administration site conditions	40 (9.5)	22 (5.1)
Asthenia	13 (3.1)	7 (1.6)
Blood and lymphatic system disorders	34 (8.1)	32 (7.5)
Anaemia	20 (4.8)	10 (2.3)
Lymphopenia	7 (1.7)	12 (2.8)
Vascular disorders	34 (8.1)	20 (4.7)
Hypertension	15 (3.6)	9 (2.1)
Deep vein thrombosis	12 (2.9)	2 (0.5)
Nervous system disorders	30 (7.1)	27 (6.3)

Table 16: Common severe AEs (CTCAE grade ≥ 3)a – RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**amivantamab + lazertinib N = 421**	**osimertinib N = 428**
Cardiac disorders	21 (5.0)	13 (3.0)
Musculoskeletal and connective tissue disorders	19 (4.5)	17 (4.0)
Renal and urinary disorders	12 (2.9)	11 (2.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 25.0; SOC and PT notation taken unmodified from comments document [3,5]

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 17: Common discontinuations (at least one event) due to AEsa - RCT, direct comparison: amivantamab + lazertinib in comparison with osimertinib

Study	Patients with event n (%)	
SOC[b] PT[b]	amivantamab + lazertinib N = 421	osimertinib N = 428
MARIPOSA		
Total rate of discontinuations (of at least one component) due to AEs	178 (42.3)	70 (16.4)
Infections and infestations	40 (9.5)	11 (2.6)
Paronychia	19 (4.5)	0 (0)
Pneumonia	9 (2.1)	3 (0.7)
Skin and subcutaneous tissue disorders	39 (9.3)	0 (0)
Rash	19 (4.5)	0 (0)
Dermatitis acneiform	8 (1.9)	0 (0)
Respiratory, thoracic and mediastinal disorders	34 (8.1)	21 (4.9)
Pneumonitis	8 (1.9)	7 (1.6)
Pulmonary embolism	8 (1.9)	2 (0.5)
Interstitial lung disease	5 (1.2)	4 (0.9)
General disorders and administration site conditions	27 (6.4)	8 (1.9)
Asthenia	7 (1.7)	2 (0.5)
Oedema peripheral	6 (1.4)	0 (0)
Injury, poisoning and procedural complications	26 (6.2)	1 (0.2)
Infusion related reaction	23 (5.5)	0 (0)
Nervous system disorders	14 (3.3)	10 (2.3)
Investigations	9 (2.1)	5 (1.2)
Metabolism and nutrition disorders	9 (2.1)	3 (0.7)
Hypoalbuminaemia	5 (1.2)	0 (0)
Cardiac disorders	8 (1.9)	5 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.7)	2 (0.5)
Gastrointestinal disorders	6 (1.4)	3 (0.7)
Vascular disorders	6 (1.4)	0 (0)
Musculoskeletal and connective tissue disorders	5 (1.2)	3 (0.7)

a. Events which occurred in ≥ 1% of patients in at least 1 study arm.
b. MedDRA version 25.0; SOC and PT notation taken unmodified from comments document [3,5]

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class