# Amivantamab and lazertinib (NSCLC, first line)

## Benefit assessment according to §35a SGB V[1]

**EXTRACT**

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

**Patient and family involvement**

No feedback was received in the framework of the present dossier assessment.

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# Part I: Benefit assessment

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

# I 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 |
| 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) |
| MMRM | mixed-effects model repeated measures |
| 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) |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |
| VTE | thromboembolic events |

## I 1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug combination of amivantamab with lazertinib as well as the benefit of the drug combination of lazertinib with amivantamab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 22 January 2025 and on 12 February 2025.

### Research question

The aim of this report is to assess the added benefit 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.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of amivantamab + lazertinib

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| 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)<br>or<br>▪ osimertinib |
| a. Presented are the respective ACTs specified by the G-BA.<br>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.<br>ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; 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 company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit.

**Study pool and study design**

The MARIPOSA study was included in the benefit assessment. This concurs with the company's study pool.

The MARIPOSA study is an ongoing, partially blinded, 3-arm RCT comparing amivantamab + lazertinib, osimertinib and lazertinib in monotherapy. Adult patients with newly diagnosed, locally advanced or metastatic NSCLC with exon 19 deletion or exon L858R substitution in the EGFR gene were included. The prerequisite for inclusion in the study was a good general condition according to Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. Patients were not allowed to have received any systemic treatment for locally advanced or metastatic disease prior to inclusion in the study. Pre-treatment with an EGFR tyrosine kinase inhibitor was also generally excluded. Curative therapy, including resection or chemoradiotherapy, was not allowed to be an option for the patients. Even in the presence of symptomatic brain metastases, inclusion in the study was not permitted.

The study included a total of 1074 patients who were randomly assigned in a 2:2:1 ratio to the 3 study arms. The study arms amivantamab + lazertinib and osimertinib, each including 429 patients, are relevant for the present assessment.

Treatment with amivantamab + lazertinib and osimertinib was largely carried out in accordance with the Summary of Product Characteristics (SPC). Contrary to the recommendation provided in the SPC, continuation of the study treatment with both amivantamab + lazertinib and osimertinib was also possible after disease progression if, at the investigator's discretion, there was still a clinical benefit and no discontinuation criteria were present. According to the current S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer, treatment with tyrosine kinase inhibitors can be continued beyond disease progression in this therapeutic indication. Moreover, thrombosis prophylaxis as is intended for this drug combination according to the SPC was largely omitted in the amivantamab + lazertinib arm. This is explained in more detail below in the section on limitations of the study.

Primary outcome of the MARIPOSA study was progression-free survival (PFS). Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

The present benefit assessment uses the results from the first data cut-off of 13 May 2024.

**Limitation of the MARIPOSA study - insufficient thrombosis prophylaxis**

According to the SPC for amivantamab and lazertinib, prophylactic anticoagulation should be initiated from the time of treatment initiation to prevent venous thromboembolic events. In the MARIPOSA study, thrombosis prophylaxis was recommended in the amivantamab + lazertinib arm with the entry into force of Amendment 3 to the study protocol on 22 August 2022 - approx. 2 years after the start of the study. It can therefore be assumed that no prophylactic anticoagulation in accordance with the SPC was used in the amivantamab + lazertinib arm for around 2 years. Moreover, according to the study protocol, prophylactic administration of anticoagulants should only take place during the first 4 months of treatment with amivantamab + lazertinib. However, the SPC does not limit the duration of anticoagulation. In Module 4 A of the dossier, the company states that the majority of the patients included had not received anticoagulation at the time of a venous thromboembolic event (VTE) (a total of 51 [12%] patients in the amivantamab + lazertinib arm and 17 [4%] patients in the osimertinib arm). This was especially due to the fact that prophylactic anticoagulation had not yet been recommended at the time the study was conducted. At the time Amendment 3 to the study protocol came into force, the recruitment of patients had already been completed, so it can be assumed that a large proportion of the patients had already completed the first 4 months of treatment. Thus, the recommendation of thrombosis prophylaxis with Amendment 3 of the study protocol therefore remained without consequences for most patients. The lack of prophylactic administration of anticoagulants represents a relevant limitation of the MARIPOSA study. Although this uncertainty does not fundamentally call into question the suitability of the MARIPOSA study, it is taken into account in the reliability of the results.

**Risk of bias**

The risk of bias across outcomes is rated as low for the MARIPOSA study.

The risk of bias of the results on the outcome of overall survival was rated as low. The risk of bias of the results on the outcomes of serious adverse events (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 also differences in the frequencies for several reasons for treatment discontinuation. In addition, the symptoms underlying the infusion-related reactions in the intervention arm are not included in the analyses.

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***

Due to the insufficient use of prophylactic concomitant treatment with anticoagulants to prevent VTEs in the intervention arm, it remains unclear whether the results of the MARIPOSA study can be transferred to the German health care context without restriction. Thus, the certainty of conclusions is 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.

Furthermore, taking into account the described serious deficiencies in the recording and analysis of the symptoms underlying an infusion related reaction, it also results that no suitable data are available both for the outcome of infusion related reactions as a whole and for the specific AE of dyspnoea. The lack of consideration of these events also affects the observed effects in the overall rates of SAEs and severe AEs as well as some specific AEs. However, these outcomes already show pronounced effects to the disadvantage of the intervention, so that the results are considered interpretable despite the uncertainty described.

**Results**

***Mortality***

*Overall survival*

A statistically significant difference in favour of amivantamab + lazertinib was shown between the treatment groups for the outcome of overall survival. However, there is an effect modification for 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.

***Morbidity***

No suitable data are available for the morbidity outcomes recorded in the MARIPOSA study. For all morbidity outcomes, there is therefore no hint of an added benefit of amivantamab + lazertinib compared with osimertinib.

***Health-related quality of life***

No suitable data are available for the outcomes on health-related quality of life recorded in the MARIPOSA study. For the outcome of health-related quality of life, there is therefore no hint of an added benefit of amivantamab + lazertinib compared with osimertinib.

***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 (Common Terminology Criteria for Adverse Events [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*

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 and dyspnoea*

No suitable data are available for the outcomes of infusion related reactions and dyspnoea. For the outcome of infusion related reaction, there is therefore no hint of greater or lesser harm from amivantamab + lazertinib compared to osimertinib.

*Pneumonitis/interstitial lung disease (ILD) (SAEs)*

For the outcome of pneumonitis/ILD (SAEs), there was no statistically significant difference between the treatment groups. There is no hint of greater or lesser harm from amivantamab + lazertinib compared with osimertinib.

*Other specific AEs*

For each of the outcomes of VTE (severe AEs), skin and subcutaneous tissue disorders (AEs), 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), 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.

**Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]**

On the basis of the results presented, the probability and extent of added benefit of the drug combination of amivantamab + lazertinib in comparison with the ACT are assessed as follows:

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 refer exclusively to the shortened observation period (until the end of treatment [plus 30 days]). The analyses presented on the outcome categories of morbidity and health-related quality of life are not suitable 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. The negative effects, in particular in the outcome category of serious and severe side effects do not completely call into question the positive effect in overall survival. However, it should be noted that 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 addition to the specific AEs, this is particularly relevant for the outcome of SAEs, where the consideration of the symptoms underlying the infusion-related reactions could result in a different extent of greater harm. Overall, the added benefit cannot be quantified due to the uncertainties in the outcome category of side effects and the unsuitable analyses on the outcome categories of morbidity and health-related quality of life. In overall terms, there is a hint of non-quantifiable added benefit of amivantamab in combination with lazertinib compared with the ACT for patients < 65 years.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

**Patients ≥ 65 years**

For patients ≥ 65 years, there are only negative effects, particularly in the outcome category of serious and severe side effects. The uncertainties described above in the outcome category of side effects and the lack of data on the outcome categories of morbidity and health-related quality of life are therefore not decisive for the overall assessment of patients ≥ 65 years. Overall, there is a hint of lesser benefit of amivantamab in combination with lazertinib in comparison with the ACT.

Table 3 summarizes the result of the assessment of added benefit of amivantamab in combination with lazertinib in comparison with the ACT.

Table 3: 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)<br>or<br>▪ osimertinib | ▪ Patients < 65 years: hint of non-quantifiable added benefit[c]<br>▪ 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 approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## I 2 Research question

The aim of this report is to assess the added benefit of amivantamab in combination with lazertinib (hereafter referred to as “amivantamab + lazertinib”) in comparison with the ACT as first-line treatment in adult patients with advanced  with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of amivantamab + lazertinib

| **Therapeutic indication** | **ACT[a]** |
|---|---|
| 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)<br>or<br>▪ osimertinib |
| a. Presented are the respective ACTs specified by the G-BA.<br>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.<br>ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; 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 company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurs with the company’s inclusion criteria.

## I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study lists on amivantamab + lazertinib (status: 12 December 2024)
- Bibliographical literature search on amivantamab + lazertinib (last search on 04 December 2024)
- Search in trial registries/trial results databases for studies on amivantamab + lazertinib (last search on 06 December 2024)
- Search on the G-BA website for amivantamab + lazertinib (last search on 27 November 2024)

To check the completeness of the study pool:

- Search in trial registries for studies on lazertinib (last search on 11 February 2025); for search strategies, see I Appendix A of the full dossier assessment

The review did not identify any additional relevant studies.

### I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: amivantamab + lazertinib compared with placebo

| Study | Study category | | | Available sources | | |
|---|---|---|---|---|---|---|
| | Study for the approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) | CSR (yes/no [citation]) | Registry entries[b] (yes/no [citation]) | Publication (yes/no [citation]) |
| 73841937NSC3003 (MARIPOSA[c]) | Yes | Yes | No | Yes [3,4] | Yes [5-7] | Yes [8] |

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that selected by the company.

## I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6:Characteristics of the study included – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of the study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| MARIPOSA | RCT, partially blinded[b], parallel | Adult patients with newly diagnosed, locally advanced or metastatic NSCLC<br>▪ with EGFR mutation (exon 19 deletion or exon 21 substitution mutation [L858R])[c]<br>▪ without prior systemic treatment[d]<br>▪ ECOG PS 0 or 1 | Study arm A: amivantamab + lazertinib (N = 429)<br><br>study arm B: osimertinib (N = 429)<br><br>study arm C: lazertinib (N = 216)[e] | Screening: up to 28 days<br><br>treatment: until disease progression[f, g], unacceptable toxicity or treatment discontinuation following the physician's decision<br><br>observation[h]: outcome-specific, at most until death or end of the study | 219 centres in Argentina, Australia, Belgium, Brazil, Canada, China, France, Germany, Hungary, India, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, Poland, Portugal, Russian Federation, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United Kingdom and USA<br><br>10/2020–ongoing<br><br>data cut-offs[i]:<br>▪ 11 August 2023[j]<br>▪ 13 May 2024[k]<br>▪ 04 December 2024[l] | Primary: PFS<br>secondary: overall survival, morbidity, health-related quality of life, AEs |

Table 6:Characteristics of the study included – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of the study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Treatment was only blinded in study arms B and C (external appearance and packaging of osimertinib and lazertinib were identical). Study arms B and C were unblinded after the primary analysis on PFS (open-label extension; introduced with Amendment 4 of the study protocol of 14 November 2023).
c. Histologically or cytologically confirmed and with proof of the mutation by an FDA-approved or otherwise validated test in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (study centres in the USA) or an accredited local laboratory (study centres outside the USA) in accordance with the Standard of Care.
d. Only patients for whom curative therapy was not an option (including surgical resection or chemoradiotherapy) were included. Adjuvant or neoadjuvant treatment for early-stage disease was permitted if administered more than 12 months before the onset of locally advanced or metastatic disease.
e. The arm is irrelevant for the assessment and is no longer presented in the tables below.
f. After the final analysis of overall survival, patients who, in the investigator's opinion, continue to benefit from the study treatments also have the option of participating in a long-term extension and continuing treatment with the study medication (introduced with Amendment 4 of the study protocol dated 14 November 2023).
g. If the investigator deemed the patient to continue to benefit from the treatment, further treatment with the study medication according to the local standard was permitted even after disease progression.
h. Outcome-specific information is provided in Table 8.
i. There is another data cut-off from 17 November 2023, which was created as part of the 120-day safety update for the FDA.
j. Primary data cut-off after 444 PFS-events in study arms A and B.
k. Data cut-off requested by the EMA as part of the approval process.
l. Final analysis for PFS and interim analysis for overall survival, planned after 270 deaths in study arms A and B.

AE: adverse event; CLIA: Clinical Laboratory Improvement Amendments; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EMA: European Medicines Agency; FDA: Food and Drug Administration; N: number of randomized patients; NSCLC: non-small cell lung cancer; PFS: progression-free survival; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria in Solid Tumours

Table 7: Characteristics of the intervention – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| MARIPOSA | Amivantamab, IV, in 28-day cycles:<br>▪ Cycle 1:<br>▫ Day 1: 350 mg<br>▫ Day 2: 700 mg (for ≥ 80 kg body weight: 1050 mg);<br>▫ Day 8, 15, 22: 1050 mg (for ≥ 80 kg body weight: 1400 mg)<br>▪ from cycle 2:<br>▫ Days 1, 15: 1050 mg (for ≥ 80 kg body weight: 1400 mg)<br>+<br>lazertinib: 240 mg once daily, orally | Osimertinib 80 mg once daily, orally |
| | Dose interruption[a]:<br>▪ interruption of a component: amivantamab preferred for CTCAE grade 2 events; lazertinib only if there is a strong suspicion of a connection<br>▪ interruption of both components: for CTCAE grade ≥ 3 and VTE events with clinical instability | Dose interruption[a]:<br>▪ for CTCAE grade 2 events: dose interruption or dose reduction possible<br>▪ for CTCAE grade 3 or 4 events: interruption and resumption possibly with a reduced dose |
| | dose adjustment:<br>▪ gradual reduction of amivantamab to 700 mg and 350 mg (for ≥ 80 kg: 1050 mg and 700 mg)<br>▪ gradual reduction of lazertinib to 160 mg; if amivantamab is interrupted, the dose can again be increased to 240 mg<br>▪ subsiding toxicity allows for re-escalation to the original dose (both drugs)[b]<br>▪ in case of a recurrence of an event that has already been responded to with a dose interruption: continuation of therapy with a reduced dose | dose adjustment:<br>▪ reduction to 40 mg<br>▪ re-escalation to initial dose possible[b] |

Table 7: Characteristics of the intervention – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| | **Disallowed pretreatment**<br>▪ systemic treatment for locally advanced or metastatic disease[c]<br>▪ treatment with an EGFR-TKI<br>▪ investigational medication within 12 days before randomization<br><br>**concomitant treatment**<br>▪ required before each amivantamab infusion:<br>▫ glucocorticoids (dexamethasone, methylprednisolone; on Days 1, 2 of Cycle 1), antihistamines (diphenhydramine or equivalent), antipyretics (acetaminophen or equivalent)<br>▪ optionally before each amivantamab infusion:<br>▫ glucocorticoids (from Cycle 1, Day 8), histamine H2 antagonist (ranitidine), anti-emetics (ondansetron or equivalent)<br>▪ optionally after each amivantamab infusion:<br>▫ glucocorticoids, antihistamines, antipyretics, opiates, anti-emetics (as mentioned under premedication)<br>▪ recommended concomitant treatment in the amivantamab + lazertinib arm (introduced with Protocol Amendment 3 of 22 August 2022): prophylactic anticoagulation in accordance with local guidelines during the first 4 months of treatment with amivantamab + lazertinib<br><br><u>further permitted concomitant treatment:</u><br>▪ supportive treatment (antibiotics, analgesics, transfusions, diet, osteoclast inhibitors, etc.) according to local standards<br>▪ localized, short-term radiotherapy for palliative treatment[d]<br>▪ medication for the prevention and treatment of skin side effects: e.g. topical and oral antibiotics, oral and topical steroids, skin care products, antipruritics<br><br>non-permitted concomitant treatment:<br>▪ chemotherapies, systemic cancer therapies, investigational therapies<br>▪ radiotherapy for lesions selected for the assessment of the tumour response<br>▪ all drugs, supplements, e.g. with a CYP3A4/A5-inducing effect | |

a. In case of intolerable toxicity, until the event has subsided to CTCAE grade ≤ 1; in case of skin rash, oral mucositis, paronychia: grade ≤ 2.
b. If in the patient's best interest and after consultation with the clinical monitor.
c. Adjuvant or neoadjuvant treatment for early-stage disease was permitted if administered more than 12 months before the onset of locally advanced or metastatic disease.
d. If possible in the week between amivantamab infusions.

AE: adverse event; CTCAE: Common Technology Criteria for Adverse Events; EGFR: epidermal growth factor receptor; IV: intravenous; RCT: randomized controlled trial; TKI: tyrosine kinase inhibitor; VTE: venous thromboembolic event

## Study design

The MARIPOSA study is an ongoing, partially blinded, 3-arm RCT comparing amivantamab + lazertinib, osimertinib and lazertinib in monotherapy. Adult patients with newly diagnosed,

locally advanced or metastatic NSCLC with exon 19 deletion or exon L858R substitution in the EGFR gene were included. The EGFR mutation was proven by a Food and Drug Administration (FDA)-approved or otherwise validated test in a Clinical Laboratory Improvement Amendments (CLIA)- certified laboratory (for study centres in the USA) or an accredited local laboratory (for study centres outside the USA). The prerequisite for inclusion in the study was a good general condition according to ECOG PS of 0 or 1. Patients were not allowed to have received any systemic treatment for locally advanced or metastatic disease prior to inclusion in the study. Pre-treatment with an EGFR tyrosine kinase inhibitor was also generally excluded. Curative therapy, including resection or chemoradiotherapy, was not allowed to be an option for the patients. Even in the presence of symptomatic brain metastases, inclusion in the study was not permitted.

The study included a total of 1074 patients who were randomly assigned in a 2:2:1 ratio to the 3 study arms. The study arms amivantamab + lazertinib and osimertinib, each including 429 patients, are relevant for the present assessment. In a third study arm, 216 patients were treated with lazertinib in monotherapy. This study arm is not relevant for the assessment and is no longer presented hereinafter. Randomization was stratified by mutation type (EGFR exon 19 deletion vs. EGFR exon 21-L858R substitution), family origin (Asian vs. non-Asian) and presence of brain metastases (yes vs. no). The comparison of amivantamab + lazertinib with osimertinib is unblinded. Whether switching between study names after disease progression was permitted or took place is not clearly stated in the study documents, but it can be assumed that this was not provided for in the study planning.

Treatment with amivantamab + lazertinib and osimertinib was largely in accordance with the SPC [9-11]. Contrary to the recommendation provided in the SPC, continuation of the study treatment with both amivantamab + lazertinib and osimertinib was also possible after disease progression if, at the investigator's discretion, there was still a clinical benefit and no discontinuation criteria were present. According to the current S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer, treatment with tyrosine kinase inhibitors can be continued beyond disease progression in this therapeutic indication (for more information, see the section on subsequent therapies below). Moreover, thrombosis prophylaxis as is intended for this drug combination according to the SPC was largely omitted in the amivantamab + lazertinib arm. This is explained in more detail below in the section on limitations of the study.

Primary outcome of the MARIPOSA study was PFS. Further outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

**Data cut-offs**

According to information provided by the company in Module 4 A, 3 data cut-offs are available for the MARIPOSA study:

- data cut-off from 11 August 2023: pre-specified primary data cut-off after a total of 444 progression events in the study arms with amivantamab + lazertinib and osimertinib
- data cut-off from 13 May 2024: data cut-off requested by the European Medicines Agency (EMA) as part of the approval process
- data cut-off from 04 December 2024: pre-specified final analysis on overall survival

In addition, a data cut-off dated 17 November 2023 is available as part of the 120-day safety update for the FDA. In Module 4 A, the company only presents results for the data cut-off from 13 May 2024, which was requested by the EMA. According to the company, analyses of the final data cut-off could not be presented, as the final data cut-off from 4 December 2024 was still being analysed at the time of dossier preparation. The company's argumentation is comprehensible; the results of the data cut-off from 13 May 2024 are therefore used for the present benefit assessment in analogy to the company's approach.

**Limitation of the MARIPOSA study - insufficient thrombosis prophylaxis**

According to the SPC for amivantamab and lazertinib, prophylactic anticoagulation should be initiated from the time of treatment initiation to prevent venous thromboembolic events. According to clinical guidelines, patients should prophylactically receive a direct oral anticoagulant (DOAC) or a low molecular weight heparin (LMWH). The use of vitamin K antagonists is not recommended [9,10]. In the MARIPOSA study, thrombosis prophylaxis was only recommended in the amivantamab + lazertinib arm with the entry into force of Amendment 3 to the study protocol on 22 August 2022 - approx. 2 years after the start of the study. It can therefore be assumed that no prophylactic anticoagulation in accordance with the SPC was used in the amivantamab + lazertinib arm for around 2 years. Moreover, according to the study protocol, prophylactic administration of anticoagulants should only take place during the first 4 months of treatment with amivantamab + lazertinib. However, the SPC does not limit the duration of anticoagulation. In Module 4 A of the dossier, the company states that the majority of the patients included had not received anticoagulation at the time of a VTE (a total of 163 [39%] patients in the amivantamab + lazertinib arm and 45 [11%] patients in the osimertinib arm). This was especially due to the fact that prophylactic anticoagulation had not yet been recommended at the time the study was conducted. At the time Amendment 3 to the study protocol came into force, the recruitment had already been completed, so it can be assumed that a large proportion of the patients had already completed the first 4 months of treatment. Thus, the recommendation of thrombosis prophylaxis with

Amendment 3 of the study protocol therefore remained without consequences for most patients.

The lack of prophylactic administration of anticoagulants represents a relevant limitation of the MARIPOSA study. Although this uncertainty does not fundamentally call into question the suitability of the MARIPOSA study, it is taken into account in the reliability of the results (see Section I 4.2).

**Planned duration of follow-up observation**

Table 8 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

| **Study**<br>**outcome category**<br>**outcome** | **Planned follow-up observation** |
|---|---|
| **MARIPOSA** | |
| Mortality | |
| Overall survival | Until death or study end |
| Morbidity | |
| Symptomatic progression | Until death or study end |
| Symptoms (EORTC QLQ-C30, NSCLC-SAQ) | Until 1 year after discontinuation of study medication |
| Health status (EQ-5D VAS) | Until 1 year after discontinuation of study medication |
| Symptoms (PGIS) | Until 30 days after receipt of the last dose of the study medication |
| Health-related quality of life | |
| EORTC QLQ-C30 | Until 1 year after discontinuation of study medication |
| Side effects | |
| All outcomes in the side effects category | Until 30 days after the last dose of the study medication[a] |

a. SAEs suspected to be related to the study medication were followed up beyond this period.

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; NSCLC-SAQ: Non–Small Cell Lung Cancer Symptom Assessment Questionnaire; PGIS: Patient Global Impression of Severity; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

With the exception of the Patient Global Impression of Severity (PGIS), a follow-up of up to 1 year after discontinuation of the study medication was planned for the patient-reported outcomes on morbidity and health-related quality of life. For the PGIS, follow-up was planned for 30 days after receipt of the last dose of study medication. Although the observation periods were therefore shortened and did not cover the entire study period, it is positive to

note that the recording was planned to continue beyond the discontinuation of the study medication.

The observation times for the outcomes on morbidity, health-related quality of life and side effects and the morbidity outcome of PGIS are systematically shortened because they were not recorded until the end of the study. As with overall survival, only SAEs deemed to be related to the study treatment should be monitored until the end of the study. Drawing a reliable conclusion on the total study period or the time to patient death would fundamentally require surveying these outcomes for the total period, as was done for survival.

**Patient characteristics**

Table 9 shows the patient characteristics of the included study.

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| Study characteristic category | Amivantamab + lazertinib N = 429 | Osimertinib N = 429 |
|---|---|---|
| **MARIPOSA** | | |
| Age [years], mean (SD) | 63 (11) | 62 (12) |
| Sex [F/M], % | 64/36 | 59/41 |
| Family origin, n (%) | | |
| White | 164 (38) | 165 (39) |
| Black or African American | 4 (< 1) | 3 (< 1) |
| Asian | 250 (58) | 251 (59) |
| Other[a] | 11 (< 1) | 10 (< 1) |
| ECOG status at baseline, n (%) | | |
| 0 | 141 (33) | 149 (35) |
| 1 | 288 (67) | 280 (65) |
| Smoking status, n (%) | | |
| Current smoker | 13 (3) | 13 (3) |
| Former smoker | 117 (27) | 121 (28) |
| Disease stage at screening, n (%) | | |
| IIIA | 1 (< 1) | 3 (< 1) |
| IIIB | 11 (3) | 5 (1) |
| IIIC | 3 (< 1) | 3 (< 1) |
| IVA | 131 (31) | 119 (28) |
| IVB | 283 (66) | 299 (70) |

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| **Study characteristic category** | **Amivantamab + lazertinib N = 429** | **Osimertinib N = 429** |
|---|---|---|
| Histological subtype at initial diagnosis, n (%)[b] | | |
| Adenocarcinoma | 417 (97) | 415 (97) |
| Large-cell carcinoma | 3 (< 1) | 0 (0) |
| Squamous cell carcinoma | 6 (1) | 5 (1) |
| Other | 2 (< 1) | 9 (2) |
| EGFR mutation type, n (%) | | |
| EGFR exon 19 del | 258 (60) | 257 (60) |
| EGFR exon 21 L858R sub | 171[c] (40) | 172 (40) |
| Lymph node involvement and localization of metastases at screening, n (%) | | |
| Bones | 14 (3) | 5 (1) |
| Liver | 1 (< 1) | 1 (< 1) |
| Brain | 11 (3) | 5 (1) |
| Lymph nodes | 11 (3) | 9 (2) |
| Adrenal gland | 0 (0) | 1 (< 1) |
| Lungs | 20 (5) | 22 (5) |
| Other | 14 (3) | 16 (4) |
| Multiple | 350 (83) | 365 (86) |
| Disease duration: time between first diagnosis and randomization [months], median [min; max] | 1.5 [0.2; 207.9] | 1.4 [0.3; 162.8] |
| Type of previous therapies in earlier stages of the disease, n (%) | | |
| Systemic therapy | 8 (2) | 10 (2) |
| Radiotherapy | 73 (17) | 65 (15) |
| Operations or procedures in connection with the cancer | 53 (12) | 49 (11) |
| adjuvant therapy | 8 (2) | 9 (2) |
| neoadjuvant endocrine therapy | 0 (0) | 1 (< 1) |
| Treatment discontinuation, n (%)[d] | 236 (55) | 283 (66) |
| Study discontinuation, n (%)[e] | 24 (6) | 20 (5) |

Table 9: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| Study characteristic category | Amivantamab + lazertinib N = 429 | Osimertinib N = 429 |
|---|---|---|
| a. Multiple origin, Hawaiian Natives or Other Pacific Islanders, Native Americans or Native Alaskans or unknown.<br>b. Information on the subtype was lacking for 1 or 0 patients.<br>c. According to the information in the study report, 172 (40%) patients had an EGFR exon 21 L858R submutation.<br>d. Common reasons for treatment discontinuation in the intervention vs. the control arm were (percentages refer to randomized patients): disease progression (28.7% vs. 49.2%) and AEs (21.2% vs. 13.8%); according to the study report, the data include patients who died during treatment with the study medication. The information on reasons for discontinuation provided in Module 4 A of the dossier does not indicate how many patients died during treatment with the study medication. An additional 8 vs. 1 of the randomized patients never started treatment.<br>e. The most common reason for study discontinuation in the intervention vs. the control arm was the following (percentages refer to randomized patients): withdrawal of consent (4.7% compared to 4.2%). Deaths are not included in the data on study discontinuation.<br>AE: adverse event; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; f: female; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation | | |

The characteristics of the patients are largely balanced between the two treatment arms of the MARIPOSA study. The mean age of the patients was 62 years, slightly more than half of them were female and almost exclusively either white (38%) or of Asian family origin (58%). A total of 66% of all patients had an ECOG PS of 1. The frequency of the EGFR exon 19 del and EGFR exon 21 L858R sub mutations was about equal between the treatment groups. Almost all patients had stage IVA or IVB disease (29% and 68% respectively), with over 80% having multiple metastases. A median of 1.4 years had passed since the diagnosis.

In the course of the study, 55% of patients in the intervention arm and 66% of patients in the comparator arm discontinued treatment with the study medication. Overall, approximately 5% of patients discontinued the study.

**Information on the course of the study**

Table 10 shows patients' median treatment duration and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

| **Study**<br>**duration of the study phase**<br>**outcome category/outcome** | **Amivantamab + lazertinib**<br>**N = 429** | **Osimertinib**<br>**N = 429** |
|---|---|---|
| **MARIPOSA** | | |
| Treatment duration [months] | | |
| Median [min; max] | 24.8 [ND] | 22.4 [ND] |
| Mean (SD) | ND | ND |
| Observation period [months] | | |
| Overall survival[a] | | |
| Median [min; max] | 31.3 [ND] | 31.3 [ND] |
| Mean (SD) | ND | ND |
| Morbidity (EORTC QLQ-C30, NSCLC-SAQ, EQ-5D VAS) | | |
| Median [min; max] | 25.7 [ND] | 24.0 [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] | 25.7 [ND] | 24.0 [ND] |
| Mean (SD) | ND | ND |
| Side effects | N = 421 | N = 428 |
| Median [min; max] | 25.8 [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 only slightly between the study arms (approx. 25 months vs. approx. 22 months). The median observation periods between the study arms are also sufficiently comparable for all outcomes. It is noticeable that the median observation periods for the outcomes in the categories of morbidity and health-related quality of life correspond approximately to the median treatment duration, although these outcomes were to be recorded up to 1 year after discontinuation of the study medication (see Table 8). The reasons for this are unclear.

### Subsequent therapies

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 study arm) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| Study treatment regimen<br>drug class<br>drug | Patients with subsequent therapy, n (%) | |
|---|---|---|
| | amivantamab + lazertinib<br>N = 429 | osimertinib<br>N = 429 |
| **MARIPOSA** | | |
| Further treatment with the study medication ≥ 28 days after progression (% of patients with progression[a]) | 104 (55.3) | 135 (51.1) |
| Proportion of randomized patients with at least one subsequent therapy[b] | 133 (31.0) | 186 (43.4) |
| Chemotherapy- / immunotherapy- based regimens | 81 (60.9) | 141 (75.8) |
| Chemotherapy alone | 61 (45.9) | 103 (55.4) |
| Carboplatin + pemetrexed | 39 (29.3) | 62 (33.3) |
| Carboplatin + paclitaxel | 8 (6.0) | 15 (8.1) |
| Cisplatin + pemetrexed | 3 (2.3) | 18 (9.7) |
| Docetaxel | 6 (4.5) | 10 (5.4) |
| Paclitaxel | 0 (0) | 5 (2.7) |
| Tegafur/gimeracil/oteracil | 0 (0) | 5 (2.7) |
| Chemotherapy + VEGF inhibitors | 11 (8.3) | 23 (12.4) |
| Bevacizumab + carboplatin + pemetrexed | 5 (3.8) | 6 (3.2) |
| Bevacizumab + carboplatin + paclitaxel | 3 (2.3) | 5 (2.7) |
| Chemotherapy + VEGFR tyrosine kinase inhibitors + immunotherapy | 12 (9.0) | 19 (10.2) |
| Atezolizumab + bevacizumab + carboplatin + paclitaxel | 5 (3.8) | 8 (4.3) |
| Bevacizumab + carboplatin + pemetrexed + sintilimab | 1 (< 1) | 5 (2.7) |
| Chemotherapy + immunotherapy | 6 (4.5) | 11 (5.9) |
| Carboplatin + pembrolizumab + pemetrexed | 2 (1.5) | 5 (2.7) |
| Immunotherapy alone | 6 (4.5) | 4 (2.2) |
| Atezolizumab | 5 (3.8) | 1 (< 1) |

Table 11: Information on subsequent antineoplastic therapies (≥ 1% of the patients in ≥ 1 study arm) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib (multipage table)

| **Study treatment regimen**<br>**drug class**<br>**drug** | **Patients with subsequent therapy, n (%)** | |
|---|---|---|
| | **amivantamab + lazertinib**<br>**N = 429** | **osimertinib**<br>**N = 429** |
| Monoclonal anti-EGFR antibodies / TKI or TKI-based regimens | 79 (59.4) | 84 (45.2) |
| TKI | 66 (49.6) | 71 (38.2) |
| Osimertinib | 38 (28.6) | 42 (22.6)[c] |
| Gefitinib | 8 (6.0) | 9 (4.8) |
| Afatinib | 8 (6.0) | 8 (4.3) |
| Erlotinib | 1 (< 1) | 10 (5.4) |
| Aumolertinib | 5 (3.8) | 5 (2.7) |
| Furmonertinib | 6 (4.5) | 3 (1.6) |
| TKI-based regimens | 16 (12.0) | 19 (10.2) |
| Other | 2 (1.5) | 8 (4.3) |

a. Based on the safety population, 421 vs. 428 patients.
b. All percentages provided below: Institute's calculation, based on the number of patients with subsequent therapy.
c. Osimertinib administered as part of a subsequent therapy; a further 135 patients (51.1%) in the osimertinib arm received the study medication beyond disease progression.

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

In the MARIPOSA study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. The subsequent therapy was chosen at the investigator's discretion. It is unclear whether a new biopsy was mandatory in the event of progression, as recommended in the S3 guideline on the prevention, diagnosis, treatment and follow-up of lung cancer [12], in order to test the mutation status for possible development of resistance.

After discontinuation of the study medication, 31% vs. 43% of all randomized patients received at least 1 subsequent therapy. Slightly more than half of the patients (55% vs. 51%) with disease progression continued to receive the existing study medication for a period of more than 28 days. This treatment was not documented as a subsequent therapy, but as a continuation of the first-line therapy. In addition, a further 42 patients in the comparator arm (23% of patients with at least 1 subsequent therapy) continued to receive treatment with osimertinib as part of a subsequent therapy. According to the SPC for amivantamab, lazertinib and osimertinib, treatment should be discontinued in the event of disease progression [9-11], however, according to the current S3 guideline on the prevention, diagnosis, treatment and

follow-up of lung cancer [12], further treatment with tyrosine kinase inhibitors can be administered beyond disease progression in the present indication of advanced or metastatic NSCLC with activating EGFR mutations. Overall, the most common subsequent therapies were chemotherapy (46% vs. 55%) and monotherapy with tyrosine kinase inhibitors (50% vs. 38%), including monotherapy with osimertinib (29% vs. 23%). Overall, the subsequent therapies used in the course of the study largely correspond to the current guideline recommendations.

Taking into account the patients in the comparator arm who were further treated with osimertinib as part of a subsequent therapy (which represents a continuation of the existing medication), there was no relevant difference in the subsequent therapies between the study arms. However, based on the information on subsequent therapies provided by the company, it is evident that around 30% (55 in the amivantamab + lazertinib arm vs. 78 in the osimertinib arm) of patients with disease progression subsequent therapy. For patients in the control arm who received further treatment with osimertinib after progression as part of a subsequent therapy, it is unclear what proportion subsequently received subsequent therapy with other drugs. In Module 4 A, the company does not provide any information on the reasons why patients in the MARIPOSA study did not receive any subsequent therapies. Although the proportions of patients without subsequent therapy after progression are comparable between the study arms, it is unclear to what extent these proportions 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 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: 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 I 4.2 under outcome-specific risk of bias.

**Transferability of the study results to the German health care context**

The company describes that the MARIPOSA study was conducted in study centres in the European Union, the USA and Canada, among others, with approximately 38% of the patients included being of White and 58% of Asian family origin. The company referred to the subgroup analyses of the study, which showed that patients of non-Asian family origin benefited to the same extent from treatment with amivantamab in combination with lazertinib as those of Asian family origin.

Furthermore, according to the company, the study population was comparable to the target population in Germany in terms of ECOG PS and the percentage of patients in the investigated disease stages. Moreover, there was no evidence of biodynamic or kinetic differences between the individual population groups and regarding German health care to an extent which would significantly impact study results. Based on this information, the company concludes that the study results are fundamentally transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

## I 4 Results on added benefit

### I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptomatic progression
  - symptoms measured with the EORTC QLQ-C30 symptom scales
  - symptoms, measured using the Non–Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)
  - symptoms, recorded using the 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/ILD (SAEs)
  - skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows for which outcomes data were available in the included study.

Table 13: 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] (PTs, severe AEs[b]) | Pneumonitis/ILD[f] (PT, SAEs) | Skin and subcutaneous tissue disorders (SOC, AEs)[g] | Further specific AEs[h] |
| MARIPOSA | Yes | No[i] | No[i] | No[i] | No[i] | No[i] | No[i] | Yes | Yes | Yes | No[i] | Yes | Yes | Yes | Yes |

a. For the operationalization, see the following text section.
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 the text section on the outcome below this table.
e. Pre-defined as AESI according to the study protocol; the complete operationalization is described in the text section on the outcome below this table.
f. Pre-defined as AESI according to the study protocol; PT collection of the company "acute interstitial pneumonitis", "interstitial lung disease" and "pneumonitis".
h. 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), "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).
i. No suitable data available; for the reasoning, see the 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; SOC: System Organ Class; VAS: visual analogue scale

## Notes on individual outcomes

### *Outcome of symptomatic progression*

The outcome of 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 deterioration of symptoms that require an adjustment of systemic cancer therapy, or
- occurrence of new lung cancer-related symptoms or deterioration of symptoms that require clinical intervention to control the symptoms.

In addition to the results for the composite outcome, the company also presents the results of the two individual components. In the original study planning, deaths were not to be counted as an event, but patients were to be censored in the event of death. In an addendum to the statistical analysis plan dated 14 February 2023, the operationalization of the outcome was adjusted so that deaths were also counted as an event. In Module 4 A, the company presents analyses of the original operationalization (censoring in case of death) as well as sensitivity analyses (death as an event).

Symptomatic progression is generally a patient-relevant outcome. However, based on the information available, it is not possible to assess whether the outcome is suitable for the benefit assessment in the present operationalization. The reasons for this are provided below.

Although the outcome was pre-defined by the company, there is no information on how this composite outcome was recorded and analysed in detail. The electronic case report form (eCRF) shows that the symptoms that were rated as symptomatic progression were linked to AE entries. However, it remains unclear on the basis of which events symptomatic progression was determined. The symptoms relevant to progression should be defined in advance if possible. When recording via AEs, this would be possible, as in other studies, via a pre-defined list of relevant PTs. However, patient-reported questionnaires that explicitly record the specific symptoms and their relevance for the patient are preferable.

For a composite outcome to be eligible for inclusion in a benefit assessment, the individual components of the outcome must be patient-relevant. For the present operationalization of the outcome of symptomatic progression, it remains unclear whether all recorded events are necessarily patient-relevant and represent progression and to what extent events of varying severity were included in the analysis. The assessment requires a precise list of which events are actually included in the composite outcome. In addition, as already described in previous benefit assessments [13,14], linking the symptoms to the adjustment or initiation of a therapy, as was done in the study, is insufficient to record the events of symptomatic progression with sufficient sensitivity. Instead, only the symptomatic event should be recorded directly and not only in connection with the adjustment or initiation of therapy.

Overall, the outcome of symptomatic progression is not suitable for the present benefit assessment without the further information described above.

***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. During the treatment phase, all instruments were recorded at the start of Cycles 1, 2 and 3 (i.e. every 4 weeks) and then at the start of every second cycle (i.e. every 8 weeks). After discontinuation of the study medication, recordings were carried out at 12-week intervals for a further year, regardless of whether a subsequent therapy was initiated or not. The pre-defined operationalization according to the study protocol was the change from baseline using a mixed-effects model repeated measures (MMRM) and responder analyses for the EORTC QLQ-C30 and NSCLC-SAQ for the time to first clinically significant deterioration. For the EORTC QLQ-C30, the proportion of patients with clinically significant improvement should also be reported. However, with an addendum to the statistical analysis plan, the responder analyses for the NSCLC-SAQ and the analysis of the proportion of patients with clinically significant improvement for the EORTC QLQ-C30 were removed. However, the analyses pre-defined in the study protocol for the time until the first clinically significant deterioration (response criterion ≥ 10 points) for the EORTC QLQ-C30 and the planned MMRM analyses are neither provided in Module 4 nor in the study documents, although these are to be submitted in accordance with the module template.

In the analyses in Module 4 A, the company deviates from the procedure pre-defined in the study protocol. Firstly, it does not present time-to-event analyses, but compares the proportions of patients with an event. As justification for this, the company stated that there were sufficiently similar observation periods between the study arms across all survey instruments. On the other hand, it does not use the initial deterioration for its analyses, as pre-specified, but the permanent deterioration. With reference to the G-BA, it justifies this with greater relevance for patients. In Module 4 A, permanent deterioration is defined as a deterioration in which the respective threshold value is exceeded in at least 2 surveys and in any subsequent surveys until the end of the observation. Due to the shortened observation period (see Table 10), the company describes this operationalization as a confirmed deterioration. In each case, a deterioration by ≥ 15 % of the scale span serves as the response threshold. The definition of permanent or confirmed deterioration and the response criterion is adequate.

The consideration of a permanent instead of a single deterioration is generally sensible, as a deterioration that persists over a longer period of time is considered to be more relevant for patients due to its permanence. A progressive course of the disease is to be expected in the present therapeutic indication, which is why the prevention of increasing morbidity and the maintenance of health-related quality of life are key therapeutic goals in addition to prolonged survival. In the present data situation with approximately the same observation period for the

patient-reported outcomes in both study arms and comparable response rates, the permanent deterioration can be considered. However, the operationalization of the proportions of patients with permanent deterioration chosen by the company in Module 4 A is not suitable for the benefit assessment. This is due to the fact that all patients with a permanent deterioration are included in the analysis as equivalent events, regardless of when the deterioration occurred. The mere comparison of event proportions therefore does not reflect the treatment goal of extending the time to (permanent) deterioration in morbidity and health-related quality of life as far as possible. In order to make a meaningful statement about the achievement of this target, it would therefore be necessary to present analyses for the time to permanent deterioration.

Overall, the analyses presented by the company on the outcome categories of morbidity and health-related quality of life are not suitable for the benefit assessment because, on the one hand, the pre-specified analyses were not presented and the available analyses on the proportions of patients with permanent deterioration are not suitable for the benefit assessment.

***Outcomes in the category of side effects***

*Infusion related reactions*

The outcome of infusion related reactions is defined as AE of special interest in the MARIPOSA study. According to the study documents, the outcome was recorded as (Preferred Term) PT "infusion related reaction". The analyses presented by the company are not suitable for the benefit assessment; this is described below.

In principle, due to the open-label study design (without placebo infusion) and regular intravenous administration, events in the PT "infusion related reactions" could only be recorded in the intervention arm under the study medication. In order to be able to obtain meaningful data on the outcome of infusion related reactions for the benefit assessment also in unblinded studies comparing orally and intravenously administered drugs, an aggregated analysis of all symptomatic AEs potentially relevant for the infusion related reactions (e.g. chills, headache, nausea or fever, whether or not in a temporal connection with an infusion) would be required. Specific AEs that represent infusion related reactions should either be predefined or refer to content-based compilations based on publications or compilations of the MedDRA system (e.g. a PT list) and should be recorded in both study arms. Irrespective of the aggregated analysis, it is necessary that the individual symptoms underlying the infusion reaction are included in the general analysis of AEs. For this purpose, the respective symptoms had to be included in the AE analyses via the corresponding PT (e.g. PT dyspnoea) (as, for instance, in the MAIA study, see [15]). It is not clear from the study protocol whether only the diagnosis of an infusion-related reaction or whether the underlying individual symptoms should also be recorded. However, based on the information in the study report on the 1st

data cut-off, it can be seen that the individual symptoms were recorded, but were not included in the general analysis of AEs (events are reported separately in the study report and only for the intervention arm). A list of the symptoms recorded as infusion related reactions is shown in Table 25 of the full dossier assessment. Analyses of all symptomatic AEs that occurred during the course of the study (i.e. all AEs, regardless of whether they were infusion related or not) are therefore currently unavailable. In addition, it must be criticised that no specific criteria were specified in the MARIPOSA study (e.g. a predefined PT list) for the investigators' assessment of whether an AE is to be classified as an infusion related reaction.

The company's approach (symptoms of the infusion reaction are not included in the analyses of outcomes on AEs) makes it difficult to interpret the results on all PTs/SOCs (as well as the superordinate AE outcomes), 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 changes when considering 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. This can be seen in the PT “dyspnoea", which is documented in the study report as an infusion related AE in 23% of patients, but as a non-infusion-related event in only 12% vs. 16% of patients (data from the 1st data cut-off). It is not possible to add up both rates, as a patient may have experienced both an infusion related and a non-infusion related event. This means that individual PTs, which frequently occurred as infusion-related events (e.g. dyspnoea and cough as well as nausea), were not completely recorded. Reliable conclusions on potential effects at PT/SOC level are therefore not possible for the SOCs/PTs concerned. However, the specific AEs included in the present assessment already show disadvantages for the intervention; the same applies to the overall rates of the outcomes on SAes and severe AEs. Suitable data for the benefit assessment are only lacking for the PT “dyspnoea” (severe AEs); here, an advantage was shown for the intervention for which it is questionable whether it continues to exist when taking into account the infusion related reactions and symptomatic AEs.

Due to the high number of infusion related events that were not included in the general analyses of AEs, the interpretability of the effects of all outcomes in the side effects category is limited. This uncertainty is taken into account when determining the risk of bias (see Section I 4.2).

*VTE*

The outcome of VTE is defined as AE of special interest in the MARIPOSA study. A targeted recording of this outcome was only introduced with Amendment 3 to the study protocol of 22 August 2022, after a higher incidence of these events had been observed in the course of the study so far. However, there is no pre-defined list of symptoms that are to be recorded as VTE. It is also unclear whether all events that occurred during the course of the study were

recorded under the outcome, or whether the analysis only included events that occurred after Amendment 3 had come into force.

Consideration of the results of the AEs shows that the outcome is essentially determined by events of the PTs "deep vein thrombosis", "venous thrombosis of an extremity" and "pulmonary embolism" (see information on frequent AEs in Table 21 of the full dossier assessment). Furthermore, the number of events for the PTs "deep vein thrombosis", "venous thrombosis of an extremity" and "pulmonary embolism" suggest that the analysis for this outcome was based on all events that occurred during the course of the study.

Due to the pronounced effects in the present operationalization of the company, the outcome is considered interpretable for the benefit assessment despite the existing uncertainties and is used accordingly. However, not every vein thrombosis is necessarily a patient-relevant event, as thromboses are not necessarily symptomatic or in need of treatment and may, under certain circumstances, only be identified on the basis of diagnostic test results. Therefore, the severe events of CTCAE grade ≥ 3 are used for the present benefit assessment, as all patient-relevant events for this outcome are thus depicted.

### I 4.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

| Study | Study level | Outcomes | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Overall survival | Symptomatic progression[a] | Symptoms (EORTC QLQ-C30) | Symptoms (NSCLC-SAQ) | Symptoms (EQ-5D VAS) | Symptoms (PGIS) | 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] (PTs, severe AEs[b]) | Pneumonitis/ILD[f] (PT, SAEs) | Skin and subcutaneous tissue disorders (SOC, AEs) | Further specific AEs[g] |
| MARIPOSA | L | L | –[h] | –[h] | –[h] | –[h] | –[h] | –[h] | H–[i] | H–[i] | H–[i] | –[h] | H–[i] | H–[i] | H–[i, k] | H–[i, k] |

a. See Section I 4.1 of this dossier assessment for information on the operationalization.
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 this dossier assessment.
e. Pre-defined as AESI according to the study protocol; for full operationalization see Section I 4.1 of this dossier assessment.
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), "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 this dossier assessment.
i. Shortened observation for potentially informative reasons; incomplete consideration of the symptoms underlying the infusion related reactions in the analyses.
j. Subjective decision to discontinue at unblinded recording of outcomes.
k. Unblinded recording of outcomes for non-serious/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; L: low; 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; 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 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 also differences in the frequencies for several reasons for treatment discontinuation. In

addition, the symptoms underlying the infusion-related reactions in the intervention arm are not included in the analyses.

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**

Due to the insufficient use of prophylactic concomitant treatment with anticoagulants to prevent VTEs in the intervention arm, it remains unclear whether the results of the MARIPOSA study can be transferred to the German health care context without restriction (for a detailed explanation, see Section I 3.2). Thus, the certainty of conclusions is 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.

Furthermore, taking into account the described serious deficiencies in the recording and analysis of the symptoms underlying an infusion related reaction (see Section I 4.1), it also results that no suitable data are available both for the outcome of infusion related reactions as a whole and for the specific AE of dyspnoea. The lack of consideration of these events also affects the observed effects in the overall rates of SAEs and severe AEs as well as some specific AEs (see Section I 4.1).. However, these outcomes already show pronounced effects to the disadvantage of the intervention (Section I 4.3), so that the results are considered interpretable despite the uncertainty described.

### I 4.3 Results

Table 15 and Table 16 summarize the 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. Where necessary, IQWiG calculations are provided to supplement the data from the company’s dossier.

The Kaplan-Meier curves on the outcome of overall survival are presented in I Appendix B of the full dossier assessment. The results on common AEs, SAEs and discontinuations due to AEs can be found in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, time to event) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib

| Study<br>outcome category<br>outcome | Amivantamab + lazertinib<br>N | <br>median time to event in months [95% CI]<br>patients with event n (%) | Osimertinib<br>N | <br>median time to event in months [95% CI]<br>patients with event n (%) | Amivantamab + lazertinib vs. osimertinib<br>HR [95% CI]; p-value |
|---|---|---|---|---|---|
| **MARIPOSA** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 429 | NA<br>142 (33.1) | 429 | 37.3 [32.5; NC]<br>177 (41.3) | 0.77 [0.62; 0.96]; 0.019[a] |
| **Morbidity** | | | | | |
| Symptomatic progression | No suitable data[b] | | | | |

a. Cox proportional hazards model and log-rank test; 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 I 4.1 for reasons.

CI: confidence interval; EGFR: epidermal growth factor receptor; exon 19 del: exon 19 deletion mutation; exon 21 L858R sub: exon 21 L858R substitution mutation; 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 16: Results (morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

| Study<br>outcome category<br>outcome<br>time point | Amivantamab + lazertinib<br>N | <br>patients with event n (%) | Osimertinib<br>N | <br>patients with event n (%) | Amivantamab + lazertinib vs. osimertinib<br>RR [95% CI]; p-value[a] |
|---|---|---|---|---|---|
| **MARIPOSA** | | | | | |
| **Morbidity** | | | | | |
| Symptoms (EORTC QLQ-C30 symptom scales) | No suitable data[b] | | | | |
| Symptoms (NSCLC-SAQ) | No suitable data[b] | | | | |
| Symptoms (PGIS) | No suitable data[b] | | | | |
| Health status (EQ-5D VAS) | No suitable data[b] | | | | |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30, functional scales | No suitable data[b] | | | | |

Table 16: Results (morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

| Study<br>outcome category<br>outcome<br>time point | Amivantamab + lazertinib<br>N | <br>patients with event<br>n (%) | Osimertinib<br>N | <br>patients with event<br>n (%) | Amivantamab + lazertinib vs. osimertinib<br>RR [95% CI];<br>p-value[a] |
|---|---|---|---|---|---|
| **Side effects** | | | | | |
| AEs (supplementary information) | 421 | 421 (100.0) | 428 | 425 (99.3) | – |
| SAEs | 421 | 222 (52.7) | 428 | 168 (39.3) | 1.35 [1.16; 1.56]; < 0.001 |
| Severe AEs[c] | 421 | 329 (78.1) | 428 | 210 (49.1) | 1.60 [1.43; 1.78]; < 0.001 |
| Discontinuation due to AEs[d] | 421 | 172 (40.9) | 428 | 67 (15.7) | 2.61 [2.04; 3.35]; < 0.001 |
| Infusion related reactions | | | | No suitable data[b] | |
| Venous thromboembolic events (severe AEs)[b] | 421 | 51 (12.1) | 428 | 17 (4.0) | 3.06 [1.80; 5.21]; < 0.001 |
| Pneumonitis/ILD (SAEs)[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 | 385 (91.4) | 428 | 278 (65.0) | 1.41 [1.30; 1.52]; < 0.001 |
| Conjunctivitis (PT, AEs) | 421 | 49 (11.6) | 428 | 9 (2.1) | 5.47 [2.73; 10.97]; < 0.001 |
| Constipation (PT, AEs) | 421 | 128 (30.4) | 428 | 66 (15.4) | 1.97 [1.51; 2.57]; < 0.001 |
| Vomiting (PT, AEs) | 421 | 54 (12.8) | 428 | 27 (6.3) | 2.03 [1.31; 3.14]; 0.002 |
| Oedema peripheral (PT, AEs) | 421 | 157 (37.3) | 428 | 28 (6.5) | 5.72 [3.92; 8.36]; < 0.001 |
| Mucosal inflammation (PT, AEs) | 421 | 45 (10.7) | 428 | 14 (3.3) | 3.30 [1.84; 5.90]; < 0.001 |
| Muscle spasms (PT, AEs) | 421 | 78 (18.5) | 428 | 36 (8.4) | 2.21 [1.52; 3.19]; < 0.001 |
| Pain in extremity (PT, AEs) | 421 | 69 (16.4) | 428 | 28 (6.5) | 2.52 [1.66; 3.81]; < 0.001 |
| Myalgia (PT, AEs) | 421 | 58 (13.8) | 428 | 23 (5.4) | 2.56 [1.61; 4.08]; < 0.001 |
| Paraesthesia (PT, AEs) | 421 | 60 (14.3) | 428 | 26 (6.1) | 2.36 [1.52; 3.66]; < 0.001 |
| Eye disorders (SOC, AEs) | 421 | 141 (33.5) | 428 | 71 (16.6) | 2.02 [1.57; 2.60]; < 0.001 |
| Injury, poisoning and procedural complications (SOC, SAEs) | 421 | 30 (7.1) | 428 | 11 (2.6) | 2.78 [1.41; 5.48]; 0.003 |
| Paronychia (PT, severe AEs[c]) | 421 | 48 (11.4) | 428 | 2 (0.5) | 24.20 [5.98; 97.96]; < 0.001 |
| Dyspnoea | | | | No suitable data[b] | |
| Examinations (SOC, severe AEs[c]) | 421 | 62 (14.7) | 428 | 39 (9.1) | 1.62 [1.11; 2.36]; 0.012 |
| Metabolism and nutrition disorders (SOC, severe AEs[c]) | 421 | 62 (14.7) | 428 | 31 (7.2) | 2.03 [1.35; 3.04]; < 0.001 |
| Gastrointestinal disorders (SOC, severe AEs[c]) | 421 | 39 (9.3) | 428 | 18 (4.2) | 2.22 [1.29; 3.81]; 0.004 |
| General disorders and administration site conditions (SOC, severe AEs[c]) | 421 | 39 (9.3) | 428 | 21 (4.9) | 1.89 [1.13; 3.15]; 0.016 |
| Vascular disorders (SOC, severe AEs[c]) | 421 | 33 (7.8) | 428 | 19 (4.4) | 1.77 [1.02; 3.06]; 0.042 |

Table 16: Results (morbidity, health-related quality of life, side effects, dichotomous) – RCT, direct comparison: amivantamab + lazertinib vs. osimertinib (multipage table)

| Study<br>outcome category<br>outcome<br>time point | Amivantamab + lazertinib<br>N | Amivantamab + lazertinib<br>patients with event<br>n (%) | Osimertinib<br>N | Osimertinib<br>patients with event<br>n (%) | Amivantamab + lazertinib vs. osimertinib<br>RR [95% CI];<br>p-value[a] |
|---|---|---|---|---|---|
| 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).<br>b. See Section I 4.1 for reasons.<br>c. Operationalized as CTCAE grade ≥ 3.<br>d. Discontinuation of at least one drug component.<br>e. For operationalization of the outcome, see Section I 4.1; results largely determined by the PTs "deep vein thrombosis", "venous thrombosis of an extremity" and "pulmonary embolism".<br>f. Operationalized via the following PTs: "acute interstitial pneumonitis", "interstitial lung disease" and "pneumonitis".<br>AE: adverse event; CI: confidence interval; 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; n: number of patients with (at least 1) event; N: number of analysed patients; 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; RR: System Organ Class; VAS: visual analogue scale | | | | | |

Based on the available information, at most hints, e.g. of an added benefit, can be determined for all outcomes (for reasons, see Section I 4.2).

**Mortality**

***Overall survival***

A statistically significant difference in favour of amivantamab + lazertinib was shown between the treatment groups for the outcome of overall survival. However, there was an effect modification by the characteristic of age (see Section I 4.4).

When looking at the Kaplan-Meier curves for this outcome, it is noticeable that a clear separation in favour of the intervention arm only emerges in the later course from around Month 12 (see Figure 1). Between Month 3 and Month 10, in contrast, the Kaplan-Meier curve tends to fall more sharply in the intervention arm than in the control arm. Initially, this suggests that some patients reap less benefit or no benefit at all from the intervention. The Kaplan-Meier curves for the subgroups < 65 years and ≥ 65 years, on the other hand, show no such overlaps, with the subgroup results showing opposite directions of effect (see Figure 2 and Figure 3).

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**

No suitable data are available for the outcomes on morbidity recorded in the MARIPOSA study (see Section I 4.1 for reasons). For all morbidity outcomes, there is therefore no hint of an added benefit of amivantamab + lazertinib compared with osimertinib.

**Health-related quality of life**

No suitable data are available for the outcomes on health-related quality of life recorded in the MARIPOSA study (see Section I 4.1 for reasons). For the outcome of health-related quality of life, there is therefore no hint of an added benefit of amivantamab + lazertinib compared with osimertinib.

**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***

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 and dyspnoea***

No suitable data are available for the outcomes of infusion related reactions and dyspnoea. See Section I 4.1 of the present dossier assessment for the reasoning. For the outcome of infusion related reaction, there is therefore no hint of greater or lesser harm from amivantamab + lazertinib compared to osimertinib.

***Pneumonitis/ ILD (SAEs)***

For the outcome of pneumonitis/ILD (SAEs), there was no statistically significant difference between the treatment groups. There is no hint of greater or lesser harm from amivantamab + lazertinib compared with osimertinib.

***Other specific AEs***

For each of the outcomes of VTE (severe AEs), skin and subcutaneous tissue disorders (AEs), 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), 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.

### I 4.4 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 17 summarizes the subgroup results on the comparison of amivantamab + lazertinib 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 I Appendix B of the full dossier assessment.

Table 17: Subgroups (mortality) – RCT, direct comparison: amivantamab + lazertinib compared with osimertinib

| Study<br>outcome<br>characteristic<br>subgroup | Amivantamab + lazertinib<br>N | Amivantamab + lazertinib<br>median time to event in months [95% CI]<br>patients with event n (%) | Osimertinib<br>N | Osimertinib<br>median time to event in months [95% CI]<br>patients with event n (%) | Amivantamab + lazertinib vs. osimertinib<br>HR [95% CI][a] | <br>p-value[a] |
|---|---|---|---|---|---|---|
| **MARIPOSA** | | | | | | |
| **Overall survival** | | | | | | |
| Age | | | | | | |
| < 65 | 235 | NA<br>59 (25.1) | 237 | 36.86 [30.62; NC]<br>102 (43.0) | 0.51 [0.37; 0.70] | < 0.001 |
| ≥ 65 | 194 | 36.01 [30.42; NC]<br>83 (42.8) | 192 | 37.32 [34.37; NC]<br>75 (39.1) | 1.19 [0.87; 1.63] | 0.270 |
| Total | | | | | Interaction: | < 0.001 |

a. Unstratified Cox proportional hazard model with the study 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

## Mortality

### *Overall survival*

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

## I 5 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 IQWiG *General Methods* [1].

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.

### I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is assessed based on the results presented in Chapter I 4 (see Table 18).

**Determination of the outcome category for the outcome "discontinuation due to AEs"**

For the outcome of discontinuation due to AEs, insufficient severity data are available which would allow them to be classified as serious/severe. The outcome of discontinuation due to AEs was therefore assigned to the outcome category of non-serious/non-severe AEs.

Table 18: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

| **Observation period**<br>**outcome category**<br>**outcome**<br>**effect modifier**<br>**subgroup** | **Amivantamab + lazertinib vs. osimertinib**<br>**quantile of time to event (months) or proportion of events (%)**<br>**effect estimation [95% CI];**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Outcomes with observation over the entire study duration** | | |
| **Mortality** | | |
| Overall survival<br>Age<br>< 65 years | Median: NA vs. 36.86 months<br>HR: 0.51 [0.37; 0.70];<br>p < 0.001<br>probability: hint | Outcome category: mortality<br>$CI_u$ < 0.85<br>added benefit, extent: “major” |
| ≥ 65 years | Median: 36.01 vs. 37.32 months<br>HR: 1.19 [0.87; 1.63];<br>p = 0.270 | Lesser/added benefit not proven |
| **Morbidity** | | |
| Symptomatic progression | No suitable data | Lesser/added benefit not proven |

Table 18: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

| **Observation period**<br>**outcome category**<br>**outcome**<br>**effect modifier**<br>**subgroup** | **Amivantamab + lazertinib vs. osimertinib**<br>**quantile of time to event (months) or proportion of events (%)**<br>**effect estimation [95% CI];**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Outcomes with shortened observation period** | | |
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30 symptom scales) | No suitable data | Lesser/added benefit not proven |
| Symptoms (NSCLC-SAQ) | No suitable data | Lesser/added benefit not proven |
| Symptoms (PGIS) | No suitable data | Lesser/added benefit not proven |
| Health status (EQ-5D VAS) | No suitable data | Lesser/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 (functional scales) | No suitable data | Lesser/added benefit not proven |
| **Side effects** | | |
| SAEs | 52.7% vs. 39.3%<br>RR: 1.35 [1.16; 1.56];<br>RR: 0.74 [0.64; 0.86][c];<br>p < 0.001<br>extent: Reference point | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>Greater harm, extent: "at least considerable"[d] |
| Severe AEs | 78.1% vs. 49.1%<br>RR: 1.60 [1.43; 1.78];<br>RR: 0.63 [0.56; 0.70][c];<br>p < 0.001<br>extent: reference point | Outcome category: serious/severe side effects<br>$CI_u < 0.75$ and risk ≥ 5%<br>greater harm, extent: "major" |
| Discontinuation due to AEs | 40.9% vs. 15.7%<br>RR: 2.61 [2.04; 3.35];<br>RR: 0.38 [0.30; 0.49][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u < 0.80$<br>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%<br>RR: 3.06 [1.80; 5.21];<br>RR: 0.33 [0.19; 0.56][c];<br>p < 0.001<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u < 0.75$ and risk ≥ 5%<br>greater harm, extent: "major" |
| Pneumonitis/interstitial lung disease (ILD) (SAEs) | 3.1% vs. 3.0%<br>RR: 1.03 [0.48; 2.20];<br>p = 0.945 | Greater/lesser harm not proven |

Table 18: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

| **Observation period**<br>**outcome category**<br>**outcome**<br>**effect modifier**<br>**subgroup** | **Amivantamab + lazertinib vs. osimertinib**<br>**quantile of time to event (months) or proportion of events (%)**<br>**effect estimation [95% CI];**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Skin and subcutaneous tissue disorders (AEs) | 91.4% vs. 65.0%<br>RR: 1.41 [1.30; 1.52];<br>RR: 0.71 [0.66; 0.77][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Conjunctivitis (AEs) | 11.6% vs. 2.1%<br>RR: 5.47 [2.73; 10.97];<br>RR: 0.18 [0.09; 0.37][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Constipation (AEs) | 30.4% vs. 15.4%<br>RR: 1.97 [1.51; 2.57];<br>RR: 0.51 [0.39; 0.66][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Vomiting (AEs) | 12.8% vs. 6.3%<br>RR: 2.03 [1.31; 3.14];<br>RR: 0.49 [0.32; 0.76][c];<br>p = 0.002<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Oedema peripheral (AEs) | 37.3% vs. 6.5%<br>RR: 5.72 [3.92; 8.36];<br>RR: 0.17 [0.12; 0.26][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Mucosal inflammation (AEs) | 10.7% vs. 3.3%<br>RR: 3.30 [1.84; 5.90];<br>RR: 0, 30 [0.17; 0.54][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Muscle spasms (AEs) | 18.5% vs. 8.4%<br>RR: 2.21 [1.52; 3.19];<br>RR: 0.45 [0.31; 0.66][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |

Table 18: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

| **Observation period**<br>**outcome category**<br>**outcome**<br>**effect modifier**<br>**subgroup** | **Amivantamab + lazertinib vs. osimertinib**<br>**quantile of time to event (months) or proportion of events (%)**<br>**effect estimation [95% CI];**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Pain in extremity (AEs) | 16.4% vs. 6.5%<br>RR: 2.52 [1.66; 3.81];<br>RR: 0.40 [0.26; 0.60][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Myalgia (AEs) | 13.8% vs. 5.4%<br>RR: 2.56 [1.61; 4.08];<br>RR: 0.39 [0.25; 0.62][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Paraesthesia (AEs) | 14.3% vs. 6.1%<br>RR: 2.36 [1.52; 3.66];<br>RR: 0.42 [0.27; 0.65][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Eye disorders (AEs) | 33.5% vs. 16.6%<br>RR: 2.02 [1.57; 2.60];<br>RR: 0.50 [0.38; 0.64][c];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: “considerable” |
| Injury, poisoning and procedural complications (SAEs) | 7.1% vs. 2.6%<br>RR: 2.78 [1.41; 5.48];<br>RR: 0.36 [0.18; 0.71][c];<br>p = 0.003<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75 and risk ≥ 5 %<br>greater harm, extent: “major” |
| Paronychia (severe AEs[c]) | 11.4% vs. 0.5%<br>RR: 24.20 [5.98; 97.96];<br>RR: 0.04 [0.01; 0.17][c];<br>p < 0.001<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75 and risk ≥ 5 %<br>greater harm, extent: “major” |
| Dyspnoea | No suitable data available | Greater/lesser harm not proven |
| Investigations (severe AEs) | 14.7% vs. 7.2%<br>RR: 1.62 [1.11; 2.36];<br>RR: 0.62 [0.42; 0.901][c];<br>p = 0.012<br>probability: hint | Outcome category: serious/severe side effects<br>0.90 ≤ $CI_u$ < 1.00<br>greater harm, extent: minor |

Table 18: Extent of added benefit at outcome level: amivantamab + lazertinib vs. osimertinib (multipage table)

| **Observation period**<br>**outcome category**<br>**outcome**<br>**effect modifier**<br>**subgroup** | **Amivantamab + lazertinib vs. osimertinib**<br>**quantile of time to event (months) or proportion of events (%)**<br>**effect estimation [95% CI];**<br>**p-value**<br>**probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Metabolism and nutrition disorders (severe AEs) | 14.7% vs. 7.2%<br>RR: 2.03 [1.35; 3.04];<br>RR: 0.49 [0.33; 0.74][c];<br>p < 0.001<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75 and risk ≥ 5%<br>greater harm, extent: “major” |
| Gastrointestinal disorders (severe AEs) | 9.3% vs. 4.2%<br>RR: 2.22 [1.29; 3.81];<br>RR: 0.45 [0.26; 0.78][c];<br>p = 0.004<br>probability: hint | Outcome category: serious/severe side effects<br>0.75 ≤ $CI_u$ < 0.90<br>greater harm, extent: “considerable” |
| General disorders and administration site conditions (severe AEs) | 9.3% vs. 4.9%<br>RR: 1.89 [1.13; 3.15];<br>RR: 0.52 [0.32; 0.88][c];<br>p = 0.016<br>probability: hint | Outcome category: serious/severe side effects<br>0.75 ≤ $CI_u$ < 0.90<br>greater harm, extent: “considerable” |
| Vascular disorders (severe AEs) | 7.8% vs. 4.4%<br>RR: 1.77 [1.02; 3.06];<br>RR: 0.56 [0.33; 0.98][c];<br>p = 0.042<br>probability: hint | Outcome category: serious/severe side effects<br>0.90 ≤ $CI_u$ < 1.00<br>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. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Incomplete consideration of the symptoms underlying the infusion related reactions in the analyses of AEs (see Section I 4.2).

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

## I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 19: 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<br>▪ overall survival<br>▫ age < 65 years: hint of added benefit – extent: “major” | – |
| **Outcomes with shortened observation period** | |
| – | Serious/severe side effects<br>▪ severe AEs: hint of greater harm – extent: “major”<br>▫ venous thromboembolic events (severe AE): hint of greater harm – extent "major"<br>▫ paronychia (severe AEs): hint of greater harm – extent: “major”<br>▫ metabolism and nutrition disorders (severe AEs): hint of greater harm – extent: “major”<br>▫ gastrointestinal disorders (severe AEs): hint of greater harm – extent: “considerable”<br>▫ general disorders and administration site conditions (severe AEs): hint of greater harm – extent: "considerable"<br>▫ examinations (severe AEs): hint of greater harm – extent: “minor”<br>▫ vascular disorders (severe AEs): hint of greater harm – extent: "minor”<br>▪ SAEs: hint of greater harm – extent: "considerable"<br>▫ injury, poisoning and procedural complications (SAEs): hint of greater harm – extent: “major” |
| – | Non-serious/non-severe side effects<br>▪ discontinuation due to AEs: hint of greater harm – extent: “considerable”<br>▪ skin and subcutaneous tissue disorders, conjunctivitis, constipation, vomiting, oedema peripheral, mucosal inflammation, muscle spasms, pain in extremity, myalgia, paraesthesia, eye disorders (AEs): hint of greater harm - extent: “considerable” |
| No suitable data are available on the outcome categories of symptomatic progression, morbidity, health-related quality of life, infusion related reactions and dyspnoea. | |
| 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 refer exclusively to the shortened observation period (until the end of treatment [plus 30 days]). The analyses presented on the

outcome categories of morbidity and health-related quality of life are not suitable 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. The negative effects, in particular in the outcome category of serious and severe side effects do not completely call into question the positive effect in overall survival. However, it should be noted that 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 addition to the specific AEs, this is particularly relevant for the outcome of SAEs, where the consideration of the symptoms underlying the infusion-related reactions could result in a different extent of greater harm. Overall, the added benefit cannot be quantified due to the uncertainties in the outcome category of side effects and the unsuitable analyses on the outcome categories of morbidity and health-related quality of life. In overall terms, there is a hint of non-quantifiable added benefit of amivantamab in combination with lazertinib compared with the ACT for patients < 65 years.

**Patients ≥ 65 years:**

For patients ≥ 65 years, there are only negative effects, particularly in the outcome category of serious and severe side effects. The uncertainties described above in the outcome category of side effects and the lack of data on the outcome categories of morbidity and health-related quality of life are therefore not decisive for the overall assessment of patients ≥ 65 years. Overall, there is a hint of lesser benefit of amivantamab in combination with lazertinib in comparison with the ACT.

Table 20 summarizes the result of the assessment of added benefit of amivantamab in combination with lazertinib in comparison with the ACT.

Table 20: 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)<br>or<br>▪ osimertinib | ▪ Patients < 65 years: hint of non-quantifiable added benefitc<br>▪ 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.

## I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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