Amivantamab (NSCLC, pre-treated, combination with carboplatin and pemetrexed)

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

EXTRACT

Project: A25-09 Version: 1.0 Status: 28 Apr 2025 DOI: 10.60584/A25-09_en

[1] Translation of Sections I 1 to I 4 of the dossier assessment *Amivantamab (NSCLC, vorbehandelt, Kombination mit Carboplatin und Pemetrexed) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Amivantamab (NSCLC, pre-treated, combination with carboplatin and pemetrexed) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

22 January 2025

Internal Project No.

A25-09

DOI-URL

https://doi.org/10.60584/A25-09_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Amivantamab (NSCLC, pre-treated, combination with carboplatin and pemetrexed); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-09_en.

Keywords

Amivantamab, Carboplatin, Pemetrexed, Carcinoma – Non-Small-Cell Lung, Benefit Assessment

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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 of persons concerned or patient organizations was received within the framework of the present dossier assessment.

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Part I: Benefit assessment

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I List of tables[2]

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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
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NSCLC	non-small cell lung cancer
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
RCT	randomized controlled trial

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 amivantamab (in combination with carboplatin and pemetrexed). 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.

Research question

The aim of this report is to assess the added benefit of amivantamab in combination with carboplatin and pemetrexed in comparison with the appropriate comparator therapy (ACT) 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 after failure of a prior therapy including an EGFR tyrosine kinase inhibitor (TKI).

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of amivantamab + carboplatin + pemetrexed

Research question	Therapeutic indication	ACT[a, b, c]
1	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 0-1	Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel
2	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 2	▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed)[c] or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine (only for patients for whom platinum-based chemotherapy is not suitable)

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, it is assumed that (further) molecularly stratified therapy directed against ALK, BRAF, exon 20, KRAS p.G12C, METex14, NTRK, ROS1 or RET is not an option for the patients at the time of treatment with amivantamab in combination with carboplatin and pemetrexed It is also assumed that the patients are generally eligible for active antineoplastic therapy.
c. Histologically, EGFR-mutated NSCLC is predominantly adenocarcinoma, which is why the G-BA assumes that treatment options that are explicitly indicated for squamous tumour histology are not routinely used in the planned therapeutic indication.

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; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TKI: tyrosine kinase inhibitor

Deviating from the G-BA, the company defined 3 research questions, 2 of which largely reflect the research questions of the G-BA presented in Table 2. The 3rd, additional research question of the company comprises patients with a T790M mutation after failure of a prior therapy including a 1st or 2nd generation EGFR TKI. The company named osimertinib as the ACT for this research question. The present benefit assessment is conducted in comparison with the ACT specified by the G-BA and comprises the two research questions described in Table 2. The company's deviation from the ACT specified by the G-BA will not be further commented below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company nor compared with the ACT specified by the G-BA.

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. This concurs with the company's inclusion criteria.

Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

Results

Consistent with the findings of the company, a review of the completeness of the study pool identified no relevant RCT for the direct comparison of amivantamab in combination with carboplatin and pemetrexed with the ACT for either of the research questions. In the pivotal study MARIPOSA-2, amivantamab in combination with carboplatin and pemetrexed was compared with carboplatin and pemetrexed and thus with the ACT specified by the G-BA for research question 2. However, only patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0–1 were included in the study. In contrast, research question 2 exclusively comprises patients with ECOG PS 2. Concurring with the company's assessment, the MARIPOSA-2 study is not suitable for either of the two research questions to derive conclusions on the added benefit of amivantamab in combination with carboplatin and pemetrexed compared with the ACT. For research question 1, the company therefore conducted an additional information retrieval on RCTs for an indirect comparison. It identified the MARIPOSA-2 study on the intervention side and the ATTLAS study on the comparator side. The company stated in the dossier that it could not conduct an adjusted indirect comparison because it did not have any individual patient data.

Results on added benefit

As no relevant study is available for either research question of the benefit assessment, there is no hint of added benefit of amivantamab in combination with carboplatin and pemetrexed in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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)

Table 3: Amivantamab + carboplatin + pemetrexed – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b, c]	Probability and extent of added benefit
1	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 0-1	Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel	Added benefit not proven
2	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 2	▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) c or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine (only for patients for whom platinum-based chemotherapy is not suitable)	Added benefit not proven

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, it is assumed that (further) molecularly stratified therapy directed against ALK, BRAF, exon 20, KRAS p.G12C, METex14, NTRK, ROS1 or RET is not an option for the patients at the time of treatment with amivantamab in combination with carboplatin and pemetrexed. It is also assumed that the patients are generally eligible for active antineoplastic therapy.
c. Histologically, EGFR-mutated NSCLC is predominantly adenocarcinoma, which is why the G-BA assumes that treatment options that are explicitly indicated for squamous tumour histology are not routinely used in the planned therapeutic indication.

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; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TKI: tyrosine kinase inhibitor

The G-BA decides on the added benefit.

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].

I 2 Research question

The aim of this report is to assess the added benefit of amivantamab in combination with carboplatin and pemetrexed in comparison with the ACT in adult patients with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of a prior therapy including an EGFR TKI.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of amivantamab + carboplatin + pemetrexed

Research question	Therapeutic indication	ACT[a, b, c]
1	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 0-1	Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel
2	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 2	▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) c or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine (only for patients for whom platinum-based chemotherapy is not suitable)

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, it is assumed that (further) molecularly stratified therapy directed against ALK, BRAF, exon 20, KRAS p.G12C, METex14, NTRK, ROS1 or RET is not an option for the patients at the time of treatment with amivantamab in combination with carboplatin and pemetrexed. It is also assumed that the patients are generally eligible for active antineoplastic therapy.
c. Histologically, EGFR-mutated NSCLC is predominantly adenocarcinoma, which is why the G-BA assumes that treatment options that are explicitly indicated for squamous tumour histology are not routinely used in the planned therapeutic indication.

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; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TKI: tyrosine kinase inhibitor

Deviating from the G-BA, the company defined 3 research questions, 2 of which largely reflect the research questions of the G-BA presented in Table 4. The 3rd, additional research question of the company comprises patients with a T790M mutation after failure of a prior therapy

including a 1st or 2nd generation EGFR TKI. The company named osimertinib as the ACT for this research question. This benefit assessment is conducted in comparison with the ACT specified by the G-BA and comprises the two research questions described in Table 4. The company's deviation from the ACT specified by the G-BA will not be further commented on below because the company did not present any suitable data for the benefit assessment – neither compared to a comparator therapy designated by the company nor compared to the ACT specified by the G-BA (see Chapter I 3).

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. Since no suitable data are available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

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 list on amivantamab (status: 27 November 2024)
- Bibliographical literature search on amivantamab (last search on 27 November 2024)
- Search in trial registries/trial results databases for studies on amivantamab (last search on 27 November 2024)
- Search on the G-BA website for amivantamab (last search on 06 December 2024)
- Bibliographical literature search on the ACT (last search on 11 December 2024)
- Search in trial registries/trial results databases for studies on the ACT (last search on 11 December 2024)
- Search on the G-BA website for the ACT (last search on 13 December 2024)

To check the completeness of the study pool:

- Search in trial registries for studies on amivantamab (last search on 10 February 2025); for search strategies, see I Appendix A of the full dossier assessment

Consistent with the findings of the company, a review of the completeness of the study pool identified no relevant RCT for the direct comparison of amivantamab in combination with carboplatin and pemetrexed with the ACT for either of the research questions. In the pivotal study MARIPOSA-2 [3], amivantamab in combination with carboplatin and pemetrexed was compared with carboplatin and pemetrexed and thus with the ACT specified by the G-BA for research question 2. However, only patients with an ECOG PS 0 or 1 were included in the study. In contrast, research question 2 exclusively comprises patients with ECOG PS 2. Concurring with the company's assessment, the MARIPOSA-2 study is not suitable for either of the two research questions to derive conclusions on the added benefit of amivantamab in combination with carboplatin and pemetrexed compared with the ACT.

Since the company did not identify any RCTs for the direct comparison of amivantamab in combination with carboplatin and pemetrexed versus the ACT, it additionally conducted an information retrieval on RCTs for an adjusted indirect comparison via a common comparator for research question 1. For an adjusted indirect comparison with the common comparator carboplatin + pemetrexed, the company identified the MARIPOSA-2 study on the intervention side and the ATTLAS study [4,5] on the comparator side. The company stated in the dossier that it could not conduct an adjusted indirect comparison because it did not have any individual patient data. The completeness of the study pool for the indirect comparison was not checked.

I 4 Results on added benefit

No data are available to assess the added benefit of amivantamab in combination with carboplatin and pemetrexed versus the ACT in adult patients with NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of a previous therapy, including an EGFR TKI. There is no hint of added benefit of amivantamab in combination with carboplatin and pemetrexed in comparison with the ACT for either research question of the benefit assessment; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of amivantamab in combination with carboplatin and pemetrexed in comparison with the ACT.

Table 5: Amivantamab + carboplatin + pemetrexed – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a, b, c]	Probability and extent of added benefit
1	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 0-1	Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel	Added benefit not proven
2	Adults with advanced NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI; ECOG PS 2	▪ Carboplatin in combination with a third-generation cytostatic agent (vinorelbine or gemcitabine or docetaxel or paclitaxel or pemetrexed) c or ▪ carboplatin in combination with nab-paclitaxel or ▪ monotherapy with gemcitabine or vinorelbine (only for patients for whom platinum-based chemotherapy is not suitable)	Added benefit not proven

a. Presented are the respective ACTs specified by the G-BA.
b. According to the G-BA, it is assumed that (further) molecularly stratified therapy directed against ALK, BRAF, exon 20, KRAS p.G12C, METex14, NTRK, ROS1 or RET is not an option for the patients at the time of treatment with amivantamab in combination with carboplatin and pemetrexed. It is also assumed that the patients are generally eligible for active antineoplastic therapy.
c. Histologically, EGFR-mutated NSCLC is predominantly adenocarcinoma, which is why the G-BA assumes that treatment options that are explicitly indicated for squamous tumour histology are not routinely used in the planned therapeutic indication.

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; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; RET: rearranged during transfection; ROS1: c-ros oncogene 1; TKI: tyrosine kinase inhibitor

The assessment described above corresponds to that of the company insofar as the company does not derive an added benefit for any of the 3 research questions defined by it.

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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