Amivantamab (Rybrevant®) with carboplatin and pemetrexed for the first-line treatment of advanced non-small cell lung cancer (NSCLC) with activating EGFR Exon 20 insertion mutations

General information

Drug description [1]

Amivantamab (Rybrevant®) is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumours with activating EGFR Exon 20 insertion mutations.
Amivantamab binds to the extracellular domains of EGFR and MET. Amivantamab disrupts EGFR and MET signalling functions by blocking ligand binding and enhancing the degradation of EGFR and MET, thereby preventing tumour growth and progression. The presence of EGFR and MET on the surface of tumour cells also allows for targeting these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity and trogocytosis mechanisms, respectively.

Indication [2]

Amivantamab (Rybrevant®) is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.

Incidence [3]

In Austria, in 2022, a total of 5,203 persons were newly diagnosed with cancer of the lung, bronchus and trachea. The age-standardised[1] incidence rate was 68.0/100,000 men and 45.8/100,000 women.

Current treatment [4]

Treatment recommendations (Onkopedia) for patients with stage IV NSCLC with Exon 20 insertions:

- Exon 20 insertions are found in up to 12% of all patients with EGFR mutations. The collective is heterogeneous, with over 60 mutations detected to date, some of which are internal duplications.
- Response rates to first- and second-generation TKIs are less than 15% in the overall group, and median PFS is 2-3 months.
- One exception is the EGFR-A763_Y764insFQEA mutation, among others. It occurs at a 5-6% frequency of exon 20 insertion mutations and shows a comparable clinical response to the classic TKI-sensitive mutations.
- In patients with exon 20 insertions other than specific EGFR TKI-sensitive mutations of the UC I group, initial administration of classical EGFR TKIs is not indicated.
- A newly approved drug for patients with evidence of an EGFR exon 20 insertion mutation is the bispecific antibody amivantamab. Amivantamab inhibits the EGF and MET receptors and activates the immune system. After the failure of platinum-containing chemotherapy, amivantamab induced remission in 38.8% of patients in the non-randomised CHRYSALIS trial. The median PFS was 6.7 months, and the median OS was 22.8 months. Indirect comparison with German registry data more than doubled OS, also confirmed by international real-world data. In August 2022, the pharmaceutical company withdrew amivantamab from the German market for commercial reasons. The start of a new treatment with amivantamab is now an off-label use. If further study inclusion is not possible after the failure of amivantamab, systemic therapy as in wild-type patients, is recommended.
- Exon20 insertion-specific EGFR TKIs are currently in clinical development. These include mobocertinib. This oral kinase inhibitor has already been approved in the USA and Switzerland for platinum-containing chemotherapy failure. Approval was based on data from a non-randomised phase I/II trial in 114 patients after platinum-containing prior therapy. The remission rate was 28%, median PFS was 7.3 months, and median OS was 24.5 months.

Regulatory status

EMA [2]	FDA [5, 6]
Approval status for this indication: On 25 April 2024, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Rybrevant®. The CHMP adopted a new indication:	**Approval status for this indication**: On 1 March 2024, the FDA approved amivantamab-vmjw (Rybrevant®) with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic NSCLC with (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test.

[1] European Standard Population 2013.

- ❖ Rybrevant® is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.

Other indications:

- ❖ Rybrevant® is indicated as monotherapy for the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based therapy.

✓ **Medicine under additional monitoring**
✓ **Medicine received a conditional marketing authorisation[2]**

- ✓ Priority Review

Other indications:

- ❖ Rybrevant is indicated as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

Manufacturer

- ❖ Rybrevant® is manufactured by Janssen-Cilag.

Costs [7]

7 ml Rybrevant® concentrate for solution for infusion 350 mg/7ml = 1,406.00 (ex-factory price)

Posology [1]

- ❖ Treatment with Rybrevant® should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.
- ❖ A healthcare professional should administer Rybrevant® with access to appropriate medical support to manage infusion-related reactions (IRRs) if they occur.
- ❖ Before initiation of Rybrevant® therapy, EGFR Exon 20 insertion mutation-positive status must be established using a validated test method.
- ❖ **Premedications** should be administered to reduce the risk of IRRs with Rybrevant. Prior to infusion (Week 1, Days 1 and 2), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs. For subsequent doses, antihistamines and antipyretics are required to be administered. Antiemetics should be administered as needed.
  - Dosing schedule of premedications:
    - o Antihistamine (required at all doses): Diphenhydramine (25 to 50 mg) or equivalent; Recommended dosing window prior to Rybrevant® administration: IV 15 to 30 minutes, oral 30 to 60 minutes.
    - o Antipyretic (required at all doses): Paracetamol/Acetaminophen (650 to 1,000 mg); Recommended dosing window prior to Rybrevant® administration: IV 15 to 30 minutes, oral 30 to 60 minutes.
    - o Glucocorticoid (required at initial dose: Week 1, Days 1 and 2; optional for subsequent doses): Dexamethasone (10 mg) or Methylprednisolone (40 mg) or equivalent: 45 to 60 minutes.

Warnings and precautions [1]

- ❖ **Traceability**
  - In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.
- ❖ **IRRs**
  - IRRs commonly occur in patients treated with amivantamab.
  - Prior to the initial infusion (Week 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs. For subsequent doses, antihistamines and antipyretics should be administered. The initial infusion should be administered in split doses on Week 1, Day 1 and 2.
  - Patients should be treated in a setting with appropriate medical support to treat IRRs. Infusions should be interrupted at the first sign of IRRs of any severity, and post-infusion medicinal products should be administered as clinically indicated. Upon resolution of symptoms, the infusion should be resumed at 50% of the previous rate.
  - For recurrent Grade 3 or Grade 4 IRRs, Rybrevant® should be permanently discontinued.

[2] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- **Interstitial lung disease (ILD)**
  - ILD or ILD-like adverse reactions (e.g., pneumonitis) have been reported in patients treated with amivantamab. Patients should be monitored for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever).
  - If symptoms develop, treatment with Rybrevant® should be interrupted pending investigation of these symptoms. Suspected ILD or ILD-like adverse reactions should be evaluated and appropriate treatment should be initiated as necessary. Rybrevant® should be permanently discontinued in patients with confirmed ILD or ILD-like adverse reactions.
- **Skin and nail reactions**
  - Rash (including dermatitis acneiform), pruritus and dry skin occurred in patients treated with amivantamab. Patients should be instructed to limit sun exposure during and for 2 months after Rybrevant therapy. Protective clothing and the use of broad-spectrum UVA/UVB sunscreen are advisable. Alcohol-free emollient cream is recommended for dry areas.
  - If skin reactions develop, topical corticosteroids and topical and/or oral antibiotics should be administered. For Grade 3 or poorly-tolerated Grade 2 events, systemic antibiotics and oral steroids should also be administered.
  - Patients presenting with severe rash that has an atypical appearance or distribution or lacks improvement within 2 weeks should be referred promptly to a dermatologist. Rybrevant® should be dose reduced, interrupted, or permanently discontinued based on severity.
  - Toxic epidermal necrolysis has been reported. Treatment with this medicinal product should be discontinued if toxic epidermal necrolysis is confirmed.
- **Eye disorders**
  - Eye disorders, including keratitis, occurred in patients treated with amivantamab. Patients presenting with worsening eye symptoms should promptly be referred to an ophthalmologist and should discontinue use of contact lenses until symptoms are evaluated. For dose modifications for Grade 3 or 4 eye disorders, see Product Information.
- **Sodium content**
  - This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say, essentially "sodium-free". This medicinal product may be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet.

Study characteristics [8-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
PAPILLON NCT04538664	308 (1:1)	amivantamab IV[3] + carboplatin-pemetrexed[4]	carboplatin-pemetrexed	PFS according to BICR	14.9 months	**ongoing**[5], open-label, international, randomised phase 3 trial	EGFR exon 20 insertions	Janssen Research and Development	PAPILLON trial [11]

Inclusion criteria[6,7]	Exclusion criteria	Patient characteristics at baseline (n=153 vs. n=155)
❖ Histologically or cytologically confirmed, locally advanced or metastatic, nonsquamous NSCLC with documented	❖ Evidence of synchronous NSCLC disease (as suggested by genetic characterisation or radiographic appearance).	❖ Median age (range): 61 (27–86) vs. 62 (30–92) years ❖ <65 years: 63% vs. 59% ❖ 65 to <75 years: 29% vs. 31% ❖ ≥75 years: 8% vs. 10% ❖ Female sex: 56% vs. 60%

[3] Amivantamab IV at a dose of 1400 mg (1750 mg for a body weight of ≥80 kg) was administered weekly for the first 4 weeks, with the first infusion split over2 days (at a dose of 350 mg on cycle 1, day 1, and the remainder on cycle 1, day 2). Starting at cycle 3 (week 7), the dose of amivantamab was increased to 1750 mg (2100 mg for a body weight of ≥80 kg) administered every 3 weeks until disease progression.

[4] Carboplatin was administered at an area under the concentration-time curve of 5 mg per milliliter per minute (AUC 5) for up to 4 cycles. Pemetrexed was administered at a dose of 500 mg per square meter of body-surface area until disease progression.

[5] The PAPILLON trial is currently ongoing; the estimated study completion date is 01/2026.

[6] For detailed in- and exclusion criteria, please see trial protocol.

[7] Additional inclusion/exclusion criteria for the crossover arm include: 1) no anticancer or investigational therapy following discontinuation of chemotherapy and 2) all toxicities must have resolved to grade ≤1 severity (except for alopecia, which may be grade 2).

primary EGFR Exon 20ins activating mutation. ❖ Measurable disease according to RECIST v1.1. ❖ ECOG PS 0 or 1 ❖ Participant must agree to genetic characterisation of tumour status through the required pretreatment tumour biopsy (or submission of equivalent archival material), as well as baseline and periodic blood samples for analysis of tumour mutations in the bloodstream. ❖ A female participant of childbearing potential must have a negative serum or urine test at screening and within 72 hours of the first dose of study treatment and must agree to further serum or urine pregnancy tests during the study.	❖ Untreated brain metastases (a participant with definitively, locally treated metastases who is clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomisation is eligible). ❖ History of spinal cord compression that has not been treated definitively with surgery or radiation. ❖ Medical history of ILD, including drug-induced ILD, or radiation pneumonitis. ❖ Participant has a contraindication to the use of carboplatin or pemetrexed (refer to local prescribing information for each agent). ❖ History of hypersensitivity to, or cannot take, vitamin B12 or folic acid.	❖ Race or ethnic group: • Asian: 64% vs. 59% • White: 32% vs. 39% • Black: 1% vs. 0 • American Indian or Alaska Native: 1% vs. 1% • Multiple: 1% vs. 0 • Unknown: 1% vs. 1% ❖ Region of enrolment: • North America: 9% vs. 8% • South America: 4% vs. 3% • Europe: 23% vs. 23% • Asia: 63% vs. 63% • Oceania: 1% vs. 3% ❖ Body weight • Median (range): 61.8 (39–127) vs. 66.5 (37–112) kg • <80 kg: 86% vs. 83% • ≥80 kg: 14% vs. 17% ❖ ECOG PS score: • 0: 35% vs. 35% • 1: 65% vs. 65% ❖ History of smoking • No: 58% vs. 59% • Yes: 42% vs. 41% ❖ Median time from initial diagnosis (range): 1.8 (0.5–80.8) vs. 1.8 (0.6–95.9) months ❖ Median time from metastatic diagnosis (range): 1.5 (0.2–40.0) vs. 1.6 (0.3–30.7) months ❖ Histologic type: • Adenocarcinoma: 99% vs. 99% • Large-cell carcinoma 0 vs.1% • Other: 1% vs. 1% ❖ History of brain metastases: 23% vs. 23%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Primary analysis; data-cutoff date 3 May 2023; median follow-up 14.9 months</u> A total of 65 patients **crossed over** from the chemotherapy group as part of the trial, and 6 additional patients received amivantamab monotherapy as their first subsequent therapy off protocol, representing 66% of patients in the chemotherapy group with disease progression. **Median PFS by BICR**: 11.4 months (95% CI, 9.8-13.7) vs. 6.7 months (95% CI, 5.6-7.3); HR for disease progression or death 0.40 (95% CI, 0.30-0.53; p<0.001) **PFS at 18 months**: 31% vs. 3% **PFS by investigator**: 12.9 months (95% CI, 11.4-16.7) vs. 6.9 months (95% CI, 6.2-8.3); HR for disease progression or death 0.38 (95% CI, 0.29-0.51) **Objective response (CR or PR):** 73% (95% CI, 65 to 80) vs. 47% (95% CI, 39 to 56); rate ratio 1.50 (95% CI, 1.32-1.68; p<0.001) **Mean percent decrease in tumour size**: 53% vs. 34% **Median duration of objective response:** 9.7 months (95% CI, 8.2-13.5) vs. 4.4 months (95% CI, 4.1-5.6)	**Any AE (all grades):** 100% vs. 98% **Any AE grade ≥3:** 75% vs. 54% **Any serious event:** 37% vs. 31% **Any event resulting in death:** 5% vs. 3% **Discontinuation of amivantamab related to amivantamab**: 7% **infusion-related reactions:** 42% vs. 1% **Febrile neutropenia:** 3% vs. 2%

Ongoing treatment at the time of the primary analysis: 49% vs. 17% **Median time until response**: 6.7 weeks (range, 5.1-72.5) vs. 11.4 weeks (range, 5.1 to 60.2) **Interim OS analysis (33% maturity)**: HR for death 0.67 (95% CI, 0.42-1.09; p=0.11)	**Death:** 18% vs. 27%[8] **Death within 30 days after the last dose of a trial medication[9]:** 5% vs. 3%

Patient-reported outcomes

- ❖ According to the trial protocol, analyses of patient-reported outcomes are planned using PROMIS-PF (Physical Function) and EORTC-QLQ-C30.
- ❖ Results are currently not available.

ESMO-MCBS version 1.1 [12]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	>6 months	PFS: +4.7 months	0.40 (0.30-0.53)	HR ≤0.65 AND gain ≥3 months	3	-	NA	+1[10]	4
Adapted	NC	2B	>6 months	PFS: +4.7 months	0.40 (0.30-0.53)	HR ≤0.65 AND gain ≥3 months	3	+21% AE grade ≥3	NA	+1[11]/-1[12]	3

Risk of bias (RCT) [13]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes low risk	-	no[13] high risk	unclear[14] unclear risk	yes[15] high risk	unclear

Ongoing trials [14]

NCT number/trial name	Description	Estimated study completion date
NCT04538664 / PAPILLON	Please see above.	01/2026
NCT04487080 / MARIPOSA	A phase 3, randomised study of amivantamab and lazertinib combination therapy vs. osimertinib vs. lazertinib as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC.	06/2027

Available assessments

- ❖ In March 2022, NIHR published a Health Technology Briefing "Amivantamab with chemotherapy for previously untreated advanced EGFR exon 20 insertion mutations positive non-small cell lung cancer" [15].
- ❖ No assessments were identified via NICE, CDA-AMC, G-BA and ICER.

Other aspects and conclusions: wichtige Informationen **fett**gedruckt**!**

- ❖ In April 2024, the CHMP adopted a new indication for Rybrevant® in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations. In March 2024, the FDA approved Rybrevant® with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic NSCLC with (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test.

[8] 13% in the amivantamab-chemotherapy group and 19% in the chemotherapy-alone group were caused by progressive disease.
[9] Of the 7 deaths in this category in the amivantamab–chemotherapy group, no clear pattern of toxic events was detected, with 1 death considered by investigators to be related to amivantamab.
[10] Upgrade due to >10% improvement in PFS at 1 year.
[11] Upgrade due to >10% improvement in PFS at 1 year.
[12] Toxicity adjustment.
[13] Open-label trial design.
[14] The PAPILLON trial is ongoing, currently only primary analysis data is available.
[15] The trial was designed by representatives of the sponsor, who were responsible for the collection and analysis of the data and for the interpretation of the trial data in collaboration with the authors. Medical writing assistance was funded by the sponsor.

- PAPILLON (NCT04538664) is an ongoing, randomised, open-label phase 3 trial comparing amivantamab + carboplatin-pemetrexed chemotherapy to chemotherapy alone in patients with advanced NSCLC with EGFR exon 20 insertions who had not received previous systemic therapy. Eligible patients were ≥18 years of age and had received no prior treatment for locally advanced or metastatic NSCLC with insertions in EGFR exon 20. Exclusion criteria included evidence of synchronous NSCLC disease, untreated brain metastases and a history of ILD.
- The primary endpoint was PFS according to BICR; primary analysis data showed that PFS was significantly longer in the amivantamab–chemotherapy group than in the chemotherapy group. Median PFS was 11.4 months vs. 6.7 months; HR for disease progression or death 0.40 (95% CI, 0.30-0.53; p<0.001).
- According to the trial protocol, analyses of patient-reported outcomes are planned; results are not available (yet).
- The original and adapted ESMO-MCBS were applied, resulting in a final adjusted magnitude of clinical benefit of 4 and 3, respectively.
- The risk of bias of the PAPILLON trial was considered unclear due to the ongoing status of the study. However, it is increased by the open-label design and the involvement of the sponsor throughout the trial.
- Besides PAPILLON, one further phase 3 trial, evaluating amivantamab and lazertinib combination therapy vs. osimertinib vs. lazertinib as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC, was identified via ClinicalTrials.gov.
- In conclusion, it has to be stated that the present data is based on the primary analysis of the PAPILLON trial. Final analysis data and patient-reported outcome data are lacking. Furthermore, the potentially confounding effect of 65 (of 155) chemotherapy-alone group patients crossing over to amivantamab-chemotherapy group should be considered.

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Abbreviations: AE=adverse event, AJ=adjustment, BICR=blinded independent central review, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, ECOG PS=Eastern Cooperative Oncology Group Performance Status, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, MG=median gain, n=number of patients, NICE=National Institute for Health Care Excellence, NSCLC=non-small cell lung cancer, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment

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