Amivantamab (Rybrevant®) in combination with carboplatin and pemetrexed for the treatment of advanced non-small cell lung cancer (NSCLC)

General information

Drug description [1]

Amivantamab (Rybrevant®) is an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity.

Indication [2]

Amivantamab (Rybrevant®) is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after the failure of prior therapy, including an EGFR tyrosine kinase inhibitor (TKI).

Incidence

In Austria, in 2022, a total of 5,203 patients were newly diagnosed with cancer of the trachea, bronchia and lung. The age-standardised incidence rate was 68.0/100,000 in men and 48.8/100,000 in women [3].
Exon 19 deletions represent the most common activating EGFR aberration; L858R mutation in exon 21 is the second most common activating EGFR aberration [4].

Current treatment [4]

For the treatment of stage IV B NSCLC with Exon 19 deletion (del19), Onkopedia recommends the following:

- Patients with del19 have the longest remission duration and survival.
- Afatinib significantly prolonged survival compared with platinum-containing chemotherapy in the pivotal trial (HR 0.55; median 12 months). In the subgroup analysis of a randomised phase II trial comparing afatinib vs. gefitinib, PFS was significantly prolonged (HR 0.73; median 0.1 months). OS and rates of treatment discontinuation were not significantly different.
- In the randomised FLAURA trial, osimertinib significantly prolonged PFS (HR 0.46; 18.9 vs 10.2 months) and OS (38.6 vs 31.8 months; HR 0.80; p = 0.046) in first-line therapy compared with erlotinib or gefitinib. The survival benefit for patients with del19 was particularly pronounced with HR 0.68. Also, the benefit was higher in the Caucasian population than in the Asian population. Follow-up of patients in the control arm of the study was similar to European standards in terms of T790M testing rates and availability of osimertinib in the presence of T790M.
- In the ARCHER 1050 randomised trial in patients with del19 or L858R, first-line dacomitinib vs. gefitinib resulted in prolonged PFS (HR 0.59; median 5.5 months) and OS (HR 0.76, median 7.3 months). Patients with brain metastases were excluded. The difference in survival in the subgroup of patients with del 19 was not significant (HR 0.847; p = 0.3021). Data comparing dacomitinib vs. osimertinib or afatinib are not available.
- In cases of progression on TKIs and suspected resistance, the mechanism of resistance should be comprehensively investigated by tissue rebiopsy or liquid biopsy (e.g., panel diagnostics), particularly with the question of an EGFR T790M resistance mutation or other targetable alteration after treatment with a first- or second-generation TKI. Tissue rebiopsy should be performed on a progressive manifestation.
- One of the most common resistance mutations under osimertinib is c-MET amplification; therefore, the addition of a MET inhibitor might be of benefit to the perspective.

For the treatment of stage IV B NSCLC with L858R mutation, Onkopedia recommends the following:

- L858R mutation in exon 21 is the second most common activating EGFR aberration. In patients with mutation L858R, TKIs result in remission rates of 40-70% and significant prolongation of PFS compared to platinum-containing chemotherapy. Afatinib did not prolong OS compared with chemotherapy in this subgroup of the pivotal trial.
- In the randomised FLAURA trial, osimertinib vs. erlotinib or gefitinib resulted in a significant prolongation of PFS (HR 0.51; median 4.9 months) and a lower rate of CNS progression (6 vs. 15%), see the currently applicable regulatory information. OS was also prolonged in the overall group, but the difference was not detectable in the L858R subgroup (HR 1.00). Follow-up therapies in the control arm of the study were similar to European standards in terms of T790M testing rates and availability of osimertinib in the presence of T790M.
- In the ARCHER 1050 randomised trial in patients with del19 or L858R, first-line dacomitinib vs. gefitinib resulted in prolonged PFS (HR 0.59; median 5.5 months) and OS (HR 0.76, median 7.3 months). Patients with brain metastases were excluded. The difference in survival in the subgroup of patients with L858R mutation was statistically significant (HR 0.665; p = 0.0203). Data for direct comparison vs. osimertinib or afatinib are not available.
- In cases of progression on TKIs and suspected resistance, the mechanism of resistance should be comprehensively investigated by tissue rebiopsy or liquid biopsy (e.g., panel diagnostics), especially with the question of EGFR T790M resistance mutation after treatment with a first- or second-generation TKI. Tissue rebiopsy should be performed on a progressive manifestation.

Regulatory status

EMA [2]	FDA
Approval status for this indication: On 25 July 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 as follows: ❖ Rybrevant® is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy, including an EGFR TKI. **Other indications**: 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. ❖ as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations after failure of platinum-based therapy. ✓ **Additional monitoring**	**Approval status for this indication**: not approved In June 2024, the manufacturer announced the submission of a Biologics License Application to the FDA for a fixed combination of amivantamab and recombinant human hyaluronidase for subcutaneous administration for all currently approved or submitted indications of intravenous Rybrevant® in certain patients with NSCLC [5]. **Other indications**: Rybrevant® is indicated: ❖ in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test. ❖ in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test. ❖ 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 [6].

Manufacturer

Rybrevant® is manufactured by Janssen-Cilag International N.V.

Costs [7]

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

Posology

- ❖ Treatment with Rybrevant® should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.
- ❖ Rybrevant® should be administered by a healthcare professional 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 in tumour tissue or plasma specimens must be established using a validated test method.
- ❖ Premedications should be administered to reduce the risk of IRRs with Rybrevant®.
- ❖ Recommended concomitant medicinal products:
  - 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.
  - Glucocorticoids should also be re-initiated after prolonged dose interruptions.
  - Antiemetics should be administered as needed.

Warnings and precautions [8]

- ❖ 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.
- ❖ Infusion-related reactions (IRRs)
  - IRRs commonly occur in patients treated with amivantamab.
  - Prior to the initial infusion (Week1), 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 Week1, Day1 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.

❖ 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 a 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 (TEN)
- TEN has been reported. Treatment with this medicinal product should be discontinued if TEN 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.

❖ 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 [1, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
PALOMA-3 NCT05388669	418 (1:1)	subcutaneous amivantamab[1] + lazertinib (orally, 240 mg daily)	intravenous amivantamab[2] + lazertinib (orally, 240 mg daily)	Co-primary pharmacokinetic noninferiority endpoints: (C_{trough}; on cycle-2-day-1 or cycle-4-day-1) and cycle-2 area under the curve (AUC D1-D15)	7.0 months	**ongoing**[3], phase 3, international, randomised trial	-	Janssen Research & Development, LLC	PALOMA-3 trial [1]

Inclusion criteria[4]	Exclusion criteria	Patient characteristics at baseline (I vs. C, n=206 vs. n=212)
❖ Histologically or cytologically confirmed, advanced or metastatic NSCLC, characterised	❖ Participants have received cytotoxic, investigational, or targeted therapies beyond one regimen of platinum-	❖ Median age (range): 61 (35-82) years vs. 62 (29-81) years ❖ <65 years: 65% vs. 57% ❖ ≥65 to <75 years: 27% vs. 33%

[1] Subcutaneous amivantamab (concentration, 160 mg/mL), co-formulated with hyaluronidase (rHuPH20), was administered by manual injection at a dose of 1600 mg (2240 mg for ≥80 kg weight) weekly for the first 4 weeks and every 2 weeks thereafter.
[2] Intravenous amivantamab (concentration, 50 mg/mL) was administered at the approved dose of 1050 mg (1400 mg for ≥80 kg weight) on the same interval, with the first infusion split over 2 days (350 mg on cycle-1-day-1, the remainder on cycle-1-day-2).
[3] The PALOMA-3 trial is currently ongoing; the estimated study completion date is 01/2025.
[4] For detailed in-and exclusion criteria, please see trial protocol.

by either EGFR Exon 19 deletion (Exon 19del) or Exon 21 leucine 858 to arginine substitution (Exon 21 L858R) mutation by an FDA-approved or other validated test of either circulating tumor deoxyribonucleic acid or tumor tissue in a clinical laboratory improvement amendments certified laboratory. ❖ Progressed on or after osimertinib (or another approved 3rd generation EGFR TKI and platinum-based chemotherapy (irrespective of order). • The 3rd generation EGFR TKI must have been administered as the first EGFR TKI for metastatic disease or as the second TKI after prior treatment with first- or second-generation EGFR TKI in participants with metastatic EGFR T790M mutation positive NSCLC. • Participants who decline or are otherwise ineligible for chemotherapy may be enrolled after discussion with the medical monitor. • Any adjuvant or neoadjuvant treatment, whether with a 3rd generation EGFR TKI or platinum based chemotherapy, would count towards the prior treatment requirement if the participant experienced disease ❖ At least 1 measurable lesion, according to RECIST version 1.1. ❖ ECOG PS of 0 to 1 ❖ Any toxicities from prior anticancer therapy must have resolved to CTCAE Version 5.0 Grade 1 or baseline level.	based chemotherapy and EGFR inhibitors. ❖ Participant has received radiotherapy for palliative purposes less than 7 days prior to randomisation. ❖ Participant has symptomatic or progressive brain metastases. ❖ Participant has leptomeningeal disease, or participant has spinal cord compression not definitively treated with surgery or radiation. ❖ Participant has uncontrolled tumour-related pain. ❖ Participant has a medical history of ILD, including drug-induced ILD or radiation pneumonitis.	❖ ≥75 years: 9% vs. 10% ❖ Female sex: 67% vs. 67% ❖ Race or ethnic group: • Asian: 61% vs. 61% • White: 38% vs. 36% • Black or African American: 0.5% vs. 1% • Multiple: 0 vs. 0.5% • Not reported: 0.5% vs. 0.9% ❖ Body weight: • Median (range): 61.8 (35-130) kg vs. 60.1 (33-150) kg • <80 kg: 89% vs. 87% • ≥80 kg: 11% vs. 13% ❖ Region of enrolment: • North America: 9% vs. 14% • South America: 5% vs. 8% • Europe: 18% vs. 19% • Asia: 61% vs. 57% • Oceania: 6% vs. 2% ❖ ECOG PS • 0: 28% vs. 29% • 1: 72% vs. 71% ❖ History of smoking • No: 68% vs. 68% • Yes: 32% vs. 32% ❖ Median time from initial diagnosis (range): 34.5 (2.8-191.3) months vs. 33.7 (6.1-156.9) months ❖ Median time from metastatic diagnosis (range): 32.7 (0.9-169.0) months vs. 29.7 (0.6-142.6) months ❖ Histologic type: • Adenocarcinoma: 99% vs. 98% • Large cell carcinoma: 0.5% vs. 0.5% • Squamous cell carcinoma: 0.5% vs. 1% • Other: 0 vs. 0.5% ❖ EGFR mutation type at randomisation: • Exon 19 deletion: 66% vs. 65% • L858R: 34% vs. 35% ❖ History of brain metastasis: • Yes: 34% vs. 34% • No: 66% vs. 66% ❖ Last therapy before randomisation: • Osimertinib: 44% vs. 45% • Chemotherapy: 56% vs. 55%
Efficacy (I vs. C)		**Safety** (I vs. C)
<u>Cutoff date 3 January 2024; median follow-up 7.0 months (range, 0.1-14.4)</u>		**Any event**: 99% vs. 99%

Pharmacokinetics

Mean (%CV) C_{trough} at cycle-2-day-1: 365 (33) µg/mL vs. 314 (32) µg/mL

Mean (%CV) C_{trough} at cycle-4-day-1: 224 (39) µg/mL and 162 (42) µg/mL

Geometric mean ratio for C_{trough}: 1.15 (90% CI, 1.04-1.26) at cycle-2-day-1 vs. 1.43 (90% CI, 1.27-1.61) at cycle-4-day-1

Cycle-2 AUCD1-D15 mean (%CV): 142,236 (31) µg•h/mL vs. 135,552 (24) µg•h/mL

Geometric mean ratio for cycle-2 AUCD1-D15: 1.03 (90% CI, 0.98-1.09)

Treatment-emergent anti-amivantamab antibodies detected: 0.6% vs. 0

Treatment-emergent anti-rHuPH20 antibodies in the subcutaneous group: 8%

Efficacy

Objective response (complete or partial): 30% (95% CI, 24-37) vs. 33% (95% CI, 26-39); relative risk 0.92 (95% CI, 0.70-1.23)

Median time to response: 1.5 months (range, 1.2-6.9) vs. 1.5 months (range, 1.2-9.9)

Median DoR among confirmed responders: 11.2 months (95% CI, 6.1-NE) vs. 8.3 months (95% CI, 5.4-NE)

DoR ≥6 months: 29% vs. 14%

Stable disease: 45% vs. 38%

Disease control rate: 75% (95% CI, 69-81) vs. 71% (95% CI, 64-77)

Median PFS: 6.1 months (95% CI, 4.3-8.1) vs. 4.3 months (95% CI, 4.1-5.7); HR for disease progression or death 0.84 (95% CI, 0.64-1.10); p=0.20

Deaths: n=43 vs. n=62 patients, with 81% vs. 81% caused by progressive disease

Patients alive at 6 and 12 months: 85% (95% CI, 79-89) and 65% (95% CI, 52-74) vs. 75% (95% CI, 68-80) and 51% (95% CI, 37-64)

OS: significantly longer for the subcutaneous compared to the intravenous group (HR for death, 0.62; 95% CI, 0.42-0.92); nominal p=0.02

AE grade ≥3: 52% vs. 56%

Any serious event: 29% vs. 30%

Any event resulting in death: 3% vs. 5%

Any event leading to discontinuation of any study agent: 13% vs. 14%

IRR: 13% vs. 66%

IRR grade 3: 0.5% vs. 4%

VTE: 9% vs. 14%

Death due to AEs: 3% vs. 5%

Patient-reported outcomes

- The subcutaneous injection during cycle-1-day-1 was reported as "very convenient" or "convenient" by 85% of patients, vs. 52% of patients for the intravenous infusion (nominal p<0.001).
- Data at cycle-3-day-1 were consistent with cycle-1-day-1.
- At end of treatment, the subcutaneous injection was reported as "very convenient" or "convenient" by 85% of patients vs. 35% for the intravenous infusion (nominal p<0.001).

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
The ESMO-MCBS was not applicable because the co-primary endpoints "C_{trough}" and "AUC D1-D15" could not be assessed.											

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear[5] unclear risk	-	no high risk	unclear[6] unclear risk	yes[7] high risk	unclear

Ongoing trials [12]

NCT number/trial name	Description	Estimated study completion date

[5] Information not available.

[6] The trial is currently ongoing; to date, only primary analysis results are available.

[7] Industry-funded.

NCT05388669 / PALOMA-3	Please see above.	01/2025
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
NCT04988295 / MARIPOSA-2	A phase 3, open-label, randomised study of amivantamab and lazertinib in combination with platinum-based chemotherapy compared with platinum-based chemotherapy in patients with EGFR-mutated locally advanced or metastatic NSCLC after osimertinib failure.	06/2026

Available assessments

- No assessments were identified via ICER, G-BA, NIHR, NICE and CDA-AMC.

Other aspects and conclusions

- In July 2024, the **CHMP adopted a new indication** for Rybrevant® in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR TKI. This indication is currently **not approved by the FDA**.
- **PALOMA-3 (NCT05388669)** is an **ongoing, phase 3**, international, randomised trial assessing the noninferiority of pharmacokinetics, efficacy, and safety of subcutaneous vs. intravenous amivantamab, both combined with lazertinib, in patients with EGFR-mutated, advanced NSCLC following disease progression on osimertinib and platinum-based chemotherapy. Eligible patients were ≥18 years, had confirmed advanced or metastatic NSCLC harbouring classical EGFR exon 19 deletions (Ex19del) or exon 21 L858R mutations with disease progression on or after osimertinib (or another approved third-generation EGFR-TKI) and platinum-based chemotherapy, irrespective of sequence.
- Primary endpoint outcome
- Analyses of **patient-reported outcomes** showed that at end of treatment, the subcutaneous injection was reported as “very convenient” or “convenient” by 85% of patients vs. 35% for the intravenous infusion.
- The **ESMO-MCBS** was not applicable because the co-primary endpoints “C_{trough}” and “AUC D1-D15” could not be assessed.
- Due to the ongoing status of the trial, the **risk of bias was considered unclear**. However, the risk is increased by the study's open-label design and industry-funded background.
- Beside PALOMA-3, two further phase trials assessing amivantamab in patients with EGFR-mutated locally advanced or metastatic NSCLC were identified via ClinicalsTrials.gov.
- To assess the efficacy and safety of Rybrevant® in adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy, final analysis data from the PALOMA-3 trial and further robust phase 3 data are required.

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Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CTCAE= common terminology criteria for adverse events, DoR=duration of response, 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, ILD=interstitial lung disease, Int.=intention, IRR=infusion-related reaction, MG=median gain, n=number of patients, NE=not estimable, 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, TEN=toxic epidermal necrolysis, TKI=tyrosine kinase inhibitor

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