Amivantamab (Rybrevant®) as monotherapy for the treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations

General information

Drug description [1]	Indication [2]
Amivantamab (Rybrevant®, JNJ-61186372) is a fully human EGFR-MET bispecific antibody with immune cell–directing activity designed to engage two distinct driver pathways in NSCLC.	Amivantamab (Rybrevant®) as monotherapy is indicated for the treatment of adult patients with advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

Current treatment [3]

- NICE has recommended the following treatment for NSCLC after progression on chemotherapy:
  - Atezolizumab
  - Nivolumab
  - Pembrolizumab
  - Nintedanib with docetaxel
  - Docetaxel monotherapy.

Regulatory status

EMA

Approval status for this indication: On 14 October 2021, the CHMP adopted a positive opinion, recommending the granting of a conditional marketing authorisation for Rybrevant®.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 09/12/2021

The full indication is:

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

✓ **Medicine received a conditional marketing authorisation**[1]
✓ **Medicine under additional monitoring**

Other indications: none

FDA [5]

Approval status for this indication: On 21 May 2021, the FDA granted accelerated approval to amivantamab-vmjw (Rybrevant™), for 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. The FDA also approved the Guardant360® CDx as a companion diagnostic for amivantamab-vmjw.

- ✓ Indication approved under **accelerated approval** based on ORR and DOR
- ✓ **Breakthrough therapy designation**

Other indications: none

Costs [6]

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

Posology/Premedication [7]

- 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 must be established using a validated test method.
- **Pre-medications** should be administered to reduce the risk of IRRs with Rybrevant®:
  - Recommended concomitant medicinal products:

[1] 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.

- 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.

Warnings and precautions [8]

- **IRRs:**
  - Interrupt infusion at the first sign of IRRs.
  - Reduce infusion rate or permanently discontinue Rybrevant™ based on severity.
- **Interstitial lung disease (ILD)/pneumonitis:**
  - Monitor for new or worsening symptoms indicative of ILD. Immediately withhold Rybrevant™ in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.
- **Dermatologic adverse reactions:**
  - May cause rash including acneiform dermatitis and toxic epidermal necrolysis.
  - Withhold, dose reduce or permanently discontinue Rybrevant™ based on severity.
- **Ocular toxicity:**
  - Promptly refer patients with worsening eye symptoms to an ophthalmologist.
  - Withhold, dose reduce or permanently discontinue Rybrevant™ based on severity.
- **Embryo-foetal toxicity:**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to the foetus and to use effective contraception.

Study characteristics [1, 9-11]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
CHRYSALIS NCT02609776	Efficacy population (n=81) Safety population (n=114)	1,050 mg amivantamab (1,400 mg for patients ≥80 kg)[2] given once weekly for the first 4 weeks and then once every 2 weeks starting at week 5	-	dose-limiting toxicity and ORR	phase I, ongoing[3], open-label, multicenter, dose-escalation, dose-expansion study	EGFR	Janssen R&D	[1]

Efficacy (n=81)	**Safety** (n=114)
ORR (as assessed by BICR): 40% (95% CI, 29-51) **Median DOR** (with 15 responders remaining on treatment at the data cut-off): 11.1 months (95% CI, 6.9-not reached); with 75% of responses observed at the first disease assessment **CBR (**included an additional 28 patients with stable disease ≥11 weeks): 74% (95% CI, 63-83) **Investigator-assessed ORR**: 36% (95% CI, 25-47) **Progression or death**: 58% **Median PFS:** 8.3 months (95% CI, 6.5-10.9) by BICR and investigator	**Grade ≥3 AEs**: n=40/114 (35%) **Treatment-related grade ≥3 AEs**: n=18/114 (16%) **SAEs:** n=34/114 (30%) **Treatment-related SAEs:** n=10/114 (9%) **Treatment-related discontinuation**: n=5/114 (4%) **AEs leading to death:** n=8/114 (7%) **Treatment-related grade 5 AEs**: none

[2] No maximum tolerated dose had been identified through the maximum assessed dose of 1,750 mg; therefore, selection of the RP2D of 1,050 mg (1,400 mg for patients ≥80 kg) was based on safety, pharmacokinetic, and pharmacodynamic data.

[3] The CHRYSALIS trial is currently ongoing; the estimated study completion date is 01/2024.

Median OS: 22.8 months (95% CI, 14.6-not reached); immature endpoint **Efficacy results (investigator assessment, n=114):** **ORR**: 37% (95% CI, 28%-46%) **Complete response**: 0% **Partial response**: 37% **Median duration of response**: 12.5 months (95% CI, 6.5-16.1) **Patients with DOR ≥ 6 months**: 64%	

ESMO-MCBS version 1.1								
The ESMO-MSBS assessment is not applicable, as the present indication does not present an "orphan disease". For the assessment of single-arm studies, these criteria must be fulfilled.								
Risk of bias - study level (case series) [12]								
1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	yes	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	unclear[4]	yes	yes	unclear	yes
Overall risk of bias: low								
First published: 11/2021 **Last updated**: 03/2022								

Abbreviations: AE=adverse event, C=comparator, CBR=clinical benefit rate, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DOR=duration of response, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, FDA=Food and Drug Administration, HR=hazard ratio, I=intervention, ILD=interstitial lung disease, IRR=infusion-related reaction, n=number of patients, NICE=National Institute for Health and Care Excellence, NSCLC=non small cell lung cancer, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, QoL=quality of life, RP2D=recommended phase II dose, SAE=serious adverse event, ST=standard treatment

References:

1. Park K, Haura EB, Leighl NB, Mitchell P, et al. Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol 39:3391-3402. [Available from: https://ascopubs.org/doi/10.1200/JCO.21.00662]
2. European Medicines Agency (EMA). Medicines. Rybrevant. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/rybrevant].

[4] The CHRYSALIS trial is currently ongoing.

3. National Institute for Health and Research (NIHR). Amivantamab for advanced non-small-cell lung cancer. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2021/08/29640-TSID_10440-Amivantamab-for-NSCLC-v1.0-JUL2020-NON-CONF.pdf].
4. European Medicines Agency (EMA). Medicines. EPAR. Rybrevant. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/rybrevant].
5. U.S. Food and Drug Administration (FDA). FDA grants accelerated approval to amivantamab-vmjw for metastatic non-small cell lung cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-amivantamab-vmjw-metastatic-non-small-cell-lung-cancer].
6. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
7. European Medicines Agency (EMA). Rybrevant: EPAR - Product Information. [Available from: https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf].
8. U.S. Food and Drug Administration (FDA). Rybrevant. Label Information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761210s000lbl.pdf].
9. Supplement to: Park K et al.; Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol 39:3391-3402.
10. Appendix to: Park K et al.; Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol 39:3391-3402.
11. U.S. National Library of Medicine, ClinicalTrials.gov. Study of Amivantamab, a Human Bispecific EGFR and cMet Antibody, in Participants With Advanced Non-Small Cell Lung Cancer (CHRYSALIS). [Available from: https://clinicaltrials.gov/ct2/show/NCT02609776].
12. Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist. Edmonton (AB): Institute of Health Economics; 2014. [Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about].