For the use of a registered medical practitioner or a hospital or laboratory

Amivantamab Liquid Concentrate for Infusion 350mg

RYBREVANT®

DOSAGE FORMS AND STRENGTHS

Amivantamab is a fully-human immunoglobulin G1(IgG1)-based bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal-epidermal transition (MET) receptors, produced by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology (see *Pharmacodynamic Properties - Mechanism of action*).

RYBREVANT is available as a colorless to pale yellow preservative-free liquid concentrate for intravenous infusion after dilution.

Each single-use vial contains 350 mg of amivantamab per 7 mL vial (or 50 mg of amivantamab per mL).

For excipients, see *List of Excipients*.

CLINICAL INFORMATION

Indications

- RYBREVANT is indicated in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations
- RYBREVANT is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) exon 20 insertion mutations.
- RYBREVANT is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.
- Rybrevant is indicated in combination with carboplatin and pemetrexed for the treatment of patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib.

Dosage and Administration

RYBREVANT should be administered by a healthcare professional with appropriate medical support to manage infusion-related reactions (IRRs) if they occur (see *Warnings and Precautions*). Administer pre-infusion medications (see *Dosage and Administration – Pre-infusion medications*).

Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 4 and 5, with the initial dose as a split infusion on Week 1 on Day 1 and Day 2.
When considering the use of RYBREVANT, EGFR exon 19 deletion, exon 21 L858R substitution, or exon 20 insertion mutation presence should be established using a validated test (see *Pharmacodynamic Effects - Clinical studies*).

Dosage – adults (≥18 years)

Every 3 Weeks

The recommended dosage of RYBREVANT, when used in combination with carboplatin and pemetrexed, is provided in Table 1 (see Infusion Rates – Table 4).

Table 1: Recommended Dose and 3-week Dosing Schedule for RYBREVANT

Body weight at Baseline[a]	RYBREVANT Dose	Schedule	Number of 350 mg/7 mL RYBREVANT Vials
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	4
	1750 mg	Every 3 weeks starting at Week 7 onwards	5
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) for Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	5
	2100 mg	Every 3 weeks starting at Week 7 onwards	6

[a] Dose adjustments not required for subsequent body weight changes.

When used in combination with carboplatin and pemetrexed, RYBREVANT should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then RYBREVANT. See ***Pharmacodynamic Effects - Clinical studies*** and the manufacturer's prescribing information for dosing instructions for carboplatin and pemetrexed.

Every 2 Weeks

The recommended dosage of RYBREVANT monotherapy or in combination with lazertinib is provided in Table 2 (see *Infusion Rates – Table 5*).

Table 2: Recommended Dose and 2-week Dosing Schedule for RYBREVANT

Body weight at Baseline[a]	Recommended Dose	Dosing Schedule	Number of 350 mg/7 mL RYBREVANT Vials
Less than 80 kg	1050 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	3
		Every 2 weeks starting at Week 5 onwards	
Greater than or equal to 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	4
		Every 2 weeks starting at Week 5 onwards	

[a] Dose adjustments not required for subsequent body weight changes.

When used in combination with lazertinib, RYBREVANT should be administered anytime after lazertinib when given on the same day. See *Pharmacodynamic Effects - Clinical studies* and the manufacturer's prescribing information for dosing instructions for lazertinib.

Duration of treatment

It is recommended that patients are treated with RYBREVANT until unacceptable toxicity or lack of clinical benefit.

Pre-infusion medications

Two days before the first infusion:
Oral dexamethasone
During the two days prior to the initial RYBREVANT infusion, patients should receive 8 mg dexamethasone orally, twice daily. On the day of the initial infusion (Week 1, Day 1), patients should receive 8 mg dexamethasone orally, one hour prior to infusion in addition to intravenous dexamethasone to further reduce the risk of IRR.

Day of infusion:
Prior to initial infusion of RYBREVANT (Week 1, Days 1 and 2), administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer antiemetics as needed.

Table 3: Pre-Medications

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT Administration
Antihistamine*		IV	15 to 30 minutes

Table 3: Pre-Medications

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT Administration
	Diphenhydramine (25 to 50 mg) or equivalent	Oral	30 to 60 minutes
Antipyretic	Paracetamol/Acetaminophen (650 to 1,000 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (20 mg) or equivalent	IV	60 to 120 minutes
Glucocorticoid+	Dexamethasone (10 mg) or equivalent	IV	45 to 60 minutes

* Required at all doses.

‡ Required at initial dose (Week 1, Day 1)

+ Required at second dose (Week 1, Day 2); optional for subsequent doses.

Infusion Rates

Administer RYBREVANT infusion every 3 weeks intravenously according to the infusion rates in Table 4, and administer RYBREVANT infusion every 2 weeks intravenously according to the infusion rates in Table 5.

Due to the frequency of IRRs at the first dose, infusion via a peripheral vein at Week 1 and Week 2 should be considered to minimize drug exposure in the event of an IRR; infusion via central line may be administered for subsequent weeks. It is recommended for the first dose to be diluted as close to administration as possible to allow for maximal flexibility in IRR management.

Table 4: Infusion Rates for RYBREVANT Every 3 Weeks

Body Weight Less than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate**†
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1050 mg	33 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Week 4	1400 mg	125 mL/hr	
Subsequent weeks*	1750 mg	125 mL/hr	
Body Weight Greater Than or Equal to 80 kg			

Week	Dose (per 250 mL bag)	Initial Infusion Rate	Subsequent Infusion Rate
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1400 mg	25 mL/hr	50 mL/hr
Week 2	1750 mg	65 mL/hr	
Week 3	1750 mg	85 mL/hr	
Week 4	1750 mg	125 mL/hr	
Subsequent weeks*	2100 mg	125 mL/hr	

* Starting at Week 7, patients are dosed every 3 weeks.

† Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.

Table 5: Infusion Rates for RYBREVANT Every 2 Weeks

Body Weight Less Than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	700 mg	50 mL/hr	75 mL/hr
Week 2	1050 mg	85 mL/hr	
Subsequent weeks*	1050 mg	125 mL/hr	
Body Weight Greater Than or Equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate**	**Subsequent Infusion Rate**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1050 mg	35 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Subsequent weeks*	1400 mg	125 mL/hr	

* After Week 5, patients are dosed every 2 weeks.

† Increase the initial infustion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.

Missed dose(s)

If a planned dose of RYBREVANT is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

The recommended dose reductions for adverse reactions (see Table 7) are listed in Table 6.

Table 6: RYBREVANT Dose Reductions for Adverse Reactions

Dose at which the adverse reaction occurred	1st Dose Reduction	2nd Dose Reduction	3rd Dose Modification
1050 mg	700 mg	350 mg	Discontinue RYBREVANT
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

The recommended dosage modifications for adverse reactions are provided in Table 7.

Table 7: RYBREVANT Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dose Modification
Infusion-Related Reactions (IRR) (see *Warnings and Precautions*)	Grade 1 to 3	• Interrupt infusion at the first sign of IRRs. • Additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated. • Upon resolution of symptoms, resume infusion at 50% of the previous rate. • If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Tables 4 and 5). • Pre-medications should be administered prior to the next dose.

	Recurrent Grade 3 or Grade 4	Permanently discontinue
Interstitial Lung Disease / Pneumonitis (see *Warnings and Precautions*)	Suspected ILD/ pneumonitis	Withhold
	Confirmed ILD/ pneumonitis	Permanently discontinue
Venous Thromboembolic (VTE) Events *(Applies to the combination with lazertinib, see Warnings and Precautions)*	Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withhold RYBREVANT and lazertinib until the patient is clinically stable. Thereafter, both drugs can be resumed at the same dose, at the discretion of the treating physician.
	Recurrent VTE despite therapeutic level anticoagulation	Permanently discontinue RYBREVANT or lazertinib. Treatment can continue with either RYBREVANT or lazertinib, but not both, at the discretion of the treating physician.
Skin and Nail Reactions (see *Warnings and Precautions*)	Grade 1	• Supportive care should be initiated. • Reassess after 2 weeks.
	Grade 2	• Supportive care should be initiated. • If there is no improvement after 2 weeks, consider reducing the dose (see Table 6).
	Grade 3	• Supportive care should be initiated. • Withhold until the adverse reaction improves to ≤ Grade 2 • Resume at reduced dose (see Table 6).
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions)	Permanently discontinue
Other Adverse Reactions (see *Adverse Reactions*)	Grade 3	• Withhold until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at same dose if recovery occurs within 1 week. • Resume at reduced dose (see Table 6) if recovery occurs after 1 week. • Consider permanently discontinuing if recovery does not occur within 4 weeks.
	Grade 4	• Withhold until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at reduced dose (see Table 6) if recovery occurs within 4 weeks. • Consider permanently discontinuing if recovery does not occur within 4 weeks.

Special populations

Pediatrics (17 years of age and younger)

The safety and efficacy of RYBREVANT have not been established in pediatric patients.

Elderly (65 years of age and older)

Of the 661 patients treated with RYBREVANT in EDI1001, NSC3001 and NSC3002, 40% were 65 years of age or older, and 10% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. No dosage adjustment is necessary (see *Pharmacokinetic Properties*).

Renal impairment

No formal studies of amivantamab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment (see *Pharmacokinetic Properties*).

Hepatic impairment

No formal studies of amivantamab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustment is necessary for patients with mild hepatic impairment. No data are available in patients with moderate or severe hepatic impairment (see *Pharmacokinetic Properties*).

Administration

Preparation for administration

RYBREVANT solution must be diluted and prepared for intravenous infusion by a healthcare professional using aseptic technique.

1. Determine the dose required and number of RYBREVANT vials needed based on patient's baseline weight (see *Dosage*). Each vial of RYBREVANT contains 350 mg of amivantamab.
2. Check that the RYBREVANT solution is colorless to pale yellow. Do not use if discoloration or visible particles are present.
3. Withdraw and then discard a volume of either 5% dextrose [glucose] solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
4. Withdraw 7 mL of RYBREVANT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a 0.5 mL overfill to ensure sufficient extractable volume. Discard any unused portion left in the vial.

5. Gently invert the bag to mix the solution. Do not shake.
6. Visually inspect the diluted solution before administration. Do not use if discoloration or visible particles are observed.
7. Diluted solutions should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

Administration

1. Prior to administration, prime the infusion set with the diluent (either 5% dextrose solution or 0.9% sodium chloride solution).
2. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
3. Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.
4. This medicinal product is for single use only. Any unused medicinal product should be disposed of in accordance with local requirements.

Contraindications

None.

Warnings and Precautions

The data described in the WARNINGS AND PRECAUTIONS reflects the safety profile of patients with locally advanced or metastatic NSCLC, including 380 patients who received RYBREVANT monotherapy in Study EDI1001, 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed in Study NSC3001, 130 patients who received RYBREVANT in combination with carboplatin and pemetrexed in Study NSC3002 and 421 patients who received RYBREVANT in combination with lazertinib in Study NSC3003.

Infusion-related reactions

Infusion-related reactions may occur in patients treated with RYBREVANT. The most frequent signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, and vomiting.

Infusion-related reactions occurred in 61% of patients treated with RYBREVANT. Ninety-three percent of IRRs were Grade 1-2. A majority of IRRs occurred at the first infusion with a median time to onset of 60 minutes. The most frequent signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, and vomiting.

Prior to initial infusion (Week 1) of RYBREVANT, administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer the initial infusion of RYBREVANT in split doses on Week 1, Days 1 and 2. (see *Dosage and Administration*)

In a Ph2, open-label, multicenter study in patients with NSCLC, patients were administered 8 mg dexamethasone orally, BID on both of the two days prior to the first RYBREVANT infusion and 8 mg orally, 60 minutes prior to infusion on the day of the first infusion (5 doses total) in addition to intravenous dexamethasone. The addition of oral dexamethasone resulted in a reduction of IRR to 22.5% with no grade ≥3 IRRs on the day of the initial infusion (see *Dosage and Administration*).

Treat patients with RYBREVANT in a setting with appropriate medical support necessary to treat IRRs. Interrupt RYBREVANT infusion at the first sign of IRRs and institute post-infusion medication as clinically indicated. Upon resolution of symptoms, resume the infusion at 50% of the previous rate. For recurrent Grade 3 or 4 IRRs, permanently discontinue RYBREVANT (see *Dosage and Administration*).

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.7% of patients treated with RYBREVANT, including 0.1% fatal events. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD have not been studied.

Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). If symptoms develop, interrupt treatment with RYBREVANT pending investigation of these symptoms. Evaluate suspected ILD and initiate appropriate treatment as necessary. Discontinue RYBREVANT in patients with confirmed ILD (see *Dosage and Administration*).

Venous Thromboembolic (VTE) Events with Concomitant Use with Lazertinib

In patients receiving RYBREVANT in combination with lazertinib, venous thromboembolic (VTE) events, including deep venous thrombosis (DVT) and pulmonary embolism (PE) occurred in 36% of patients, predominantly in the first four months of therapy, including 0.5% fatal events. Prophylactic anticoagulants are recommended to be used for the first four months of treatment. Anticoagulants use should align with clinical guidelines, use of Vitamin K antagonists is not recommended.

For VTE events associated with clinical instability, RYBREVANT and lazertinib should be withheld until the patient is clinically stable. Thereafter, both drugs can be resumed at the discretion of the treating physician.

In the event of recurrence despite appropriate anticoagulation, discontinue RYBREVANT or lazertinib. Treatment can resume with either RYBREVANT or lazertinib, but not both (see *Dosage and Administration*).

Skin and nail reactions

Skin and nail reactions may occur in patients treated with RYBREVANT.

Rash (including dermatitis acneiform), pruritus and dry skin occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 15.5% of patients. Rash leading to RYBREVANT discontinuation occurred in 2.9% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3-4 nail toxicity occurring in 6.3% of patients.

Toxic epidermal necrolysis (TEN) has been reported. Permanently discontinue RYBREVANT if TEN is confirmed.

A prophylactic approach to rash prevention should be considered. Instruct patients to limit sun exposure during and for 2 months after RYBREVANT therapy. Protective clothing and use of sunscreen is advisable. Alcohol-free emollient cream is recommended for dry areas with the use of RYBREVANT. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 or poorly-tolerated Grade 2 events, add systemic antibiotics and oral steroids and consider dermatologic consultation. Withhold, dose reduce, or permanently discontinue RYBREVANT based on severity (see *Dosage and Administration*).

Eye disorders

Eye disorders, including keratitis (1.6%), occurred in patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperemia, conjunctival hyperemia, blepharitis and uveitis. Most events were Grade 1-2. Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated.

Interactions

No drug interaction studies have been performed.

Pregnancy, Breast-feeding and Fertility

Pregnancy

There are no human or animal data to assess the risk of RYBREVANT in pregnancy. Administration of other EGFR and MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant woman.

RYBREVANT should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh potential risks to the fetus. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

Breast-feeding

It is not known whether RYBREVANT is excreted in human or animal milk or affects milk production. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from amivantamab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months following the last dose of RYBREVANT.

Contraception

Due to the risk that RYBREVANT can cause fetal harm when administered to pregnant women, advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT. Male patients must use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 months after the last dose of RYBREVANT.

Fertility

No data are available to determine potential effects of RYBREVANT on fertility in males or females.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of amivantamab based on the comprehensive assessment of the available adverse event information. A causal relationship with amivantamab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

First-line Treatment of Non-Small Cell Lung Cancer (NSCLC) with Exon 20 Insertion Mutations

The data described below reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage in 151 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Among patients who received RYBREVANT in combination with carboplatin and pemetrexed the median exposure was 9.7 months (range: 0.0 to 26.9 months).
The median age was 61 years (range: 27 to 86 years); 55.6% were female; 64.4% were Asian, 32.2% were White and 86.1% had baseline body weight <80 kg.

Serious adverse reactions occurred in 37.1% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions in ≥ 2% of patients included rash, interstitial lung disease, vomiting, and hypokalemia. Fatal adverse reactions occurred in 7 patients (4.6%). One death was considered related to RYBREVANT treatment by the investigator.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 5.3% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were rash and ILD.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 64.2% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 37.7% of patients. Adverse reactions requiring dose interruption in ≥ 5% of patients included rash, nail toxicity, and hypokalemia.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 35.8% of patients. Adverse reactions requiring dose reductions in ≥ 5% of patients included rash, and nail toxicity.

The most common adverse reactions (≥ 20%) were rash, nail toxicity, infusion-related reactions, edema, fatigue, stomatitis, constipation, nausea, vomiting, diarrhea, and decreased appetite. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Table 8 summarizes the adverse reactions in Study NSC3001.

Table 8: Adverse Reactions (≥ 10%) in First-line Patients with NSCLC with Exon 20 Insertion Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed – Study NSC3001

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=151)**	**Carboplatin + Pemetrexed (N=155)**

	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Skin and subcutaneous tissue disorders				
Rash*	90.1	19.2	18.7	0
Nail toxicity*	61.6	6.6	3.2	0
Dry skin*	16.6	0	5.8	0
General disorders and administration site conditions				
Edema*	40.4	1.3	18.7	0
Fatigue*	33.8	6.0	37.4	3.9
Pyrexia	15.9	0	5.8	0
Gastrointestinal disorders				
Stomatitis*	43.0	4.0	11.0	0
Constipation	39.7	0	30.3	0.6
Nausea	36.4	0.7	41.9	0
Vomiting	21.2	3.3	18.7	0.6
Diarrhea	20.5	3.3	12.9	1.3
Hemorrhoids	11.9	1.3	1.3	0
Abdominal pain*	10.6	0.7	8.4	0
Injury, poisoning and procedural complications				
Infusion-related reaction	41.7	1.3	1.3	0
Metabolism and nutrition disorders				
Decreased appetite	35.8	2.6	27.7	1.3

* Grouped term

Adverse reactions occurring in < 10% of RYBREVANT-treated patients with NSCLC exon 20 insertion mutations in Study NSC3001 are summarized in Table 9.

Table 9: Adverse Reactions (< 10%) in First-line Patients with NSCLC with Exon 20 Insertion Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed – Study NSC3001

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=151)**		**Carboplatin + Pemetrexed (N=155)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders				
Pruritus	6.6	0	7.7	0
Nervous system disorders				
Dizziness*	9.9	0	11.6	0
Eye disorders				
Other eye disorders*	7.3	0	4.5	0
Visual impairment*	1.3	0	3.9	0
Musculoskeletal and connective tissue disorders				
Myalgia	5.3	1.3	3.2	0.6
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease*	2.6	2.6	0	0

* Grouped term

Table 10 summarizes the laboratory abnormalities in NSC3001.

Table 10: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Firstline Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations in PAPILLON

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed		Carboplatin + Pemetrexed	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased albumin	87	7	34	1
Increased aspartate aminotransferase	60	1	61	1
Increased alanine aminotransferase	57	4	54	1
Decreased sodium	55	7	39	4
Increased alkaline phosphatase	51	1	28	0
Decreased potassium	44	11	17	1
Decreased magnesium	39	2	30	1
Increased gamma-glutamyl transferase	38	4	43	4
Decreased calcium (corrected)	27	1	18	1
Hematology				
Decreased white blood cells	89	17	76	10
Decreased hemoglobin	79	11	85	13
Decreased neutrophils	76	36	61	23
Decreased platelets	70	10	54	12
Decreased lymphocytes	61	11	49	13

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The safety of RYBREVANT in combination with carboplatin and pemetrexed was evaluated in MARIPOSA-2 (NSC3002), which included patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations whose disease has progressed on or after treatment with osimertinib *(*see *Pharmacodynamic Effects - Clinical studies).* Patients received RYBREVANT, 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) by intravenous infusion once weekly for 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. The median treatment duration was 6.3 months (range: 0 to 14.7 months).

The median age was 62 years (range: 36 to 84 years); 62% were female; 48% were Asian, and 46% were White; and 87% had baseline body weight <80 kg.

Adverse reactions described below in Table 11 reflect exposure to RYBREVANT with carboplatin and pemetrexed (N=130) with a median treatment duration of 6.3 months (range: 0 to 14.7) months or exposure to carboplatin and pemetrexed (N=243) with a median treatment duration of 3.7 months (range: 0 to 15.9) months.

The most common adverse reactions ≥ 20% were rash, infusion-related reactions, fatigue, nail toxicity, nausea, constipation, edema, stomatitis, decreased appetite and vomiting. Serious adverse reactions in > 1% of patients were infusion-related reaction, interstitial lung disease and pyrexia.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 60% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 52% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included infusion-related reactions, rash and fatigue. Dose reductions of RYBREVANT due to an adverse reaction occurred in 17% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash.

Fifteen percent of patients permanently discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation in ≥ 1% of patients were infusion-related reactions.

The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Table 11 summarizes the adverse reactions in Study NSC3002.

Table 11: Adverse Reactions (≥ 10%) in Previously Treated Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**		**Carboplatin + Pemetrexed (N=243)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders				
Rash*	72	11	12	0
Nail toxicity*	45	2.3	0.4	0
Pruritus	15	0	7.0	0
Dry skin*	15	0	2.5	0
General disorders and administration site conditions				
Infusion-related reaction	59	5.4	0.4	0
Fatigue*	51	3.8	35	3.7
Edema*	36	1.5	11	0.4
Pyrexia	12	0	10	0
Gastrointestinal disorders				
Nausea	45	0.8	37	0.8
Constipation	39	0.8	30	0
Stomatitis*	35	2.3	11	0
Vomiting	25	0.8	17	0.4
Diarrhea	14	0.8	6.6	0.4
Metabolism and nutrition disorders				
Decreased appetite	31	0	21	1.2

* Grouped term

Adverse reactions occurring in ≤ 10% of RYBREVANT-treated patients with NSCLC exon 20 insertion mutations in Study NSC3002 are summarized in Table 12.

Table 12: Adverse reactions (≤ 10%) in Previously Treated Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**		**Carboplatin + Pemetrexed (N=243)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Nervous system disorders				
Dizziness*	9.2	0	6.6	0
Eye disorders				
Other eye disorders*	7.7	0	1.2	0
Visual impairment*	4.6	0	3.7	0
Keratitis	0.8	0	0.4	0
Trichomegaly (growth of lashes)	0.8	0	0	0
Musculoskeletal and connective tissue disorders				
Myalgia	4.6	0	2.1	0
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease*	1.5	0.8	0	0
Gastrointestinal disorders				
Abdominal pain*	9.2	0	6.6	0
Hemorrhoids	5.4	0	0.4	0

* Grouped term

Table 13 summarizes the laboratory abnormalities in MARIPOSA-2.

Table 13: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated With RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

Laboratory Abnormality	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**		**Carboplatin + Pemetrexed (N=243)**	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Chemistry				
Decreased albumin	73	4	26	<1
Decreased sodium	48	11	30	6
Increased aspartate aminotransferase	47	1	52	1
Increased alkaline phosphatase	42	0	29	<1
Increased alanine aminotransferase	39	4	56	6
Decreased magnesium	38	1	17	<1
Decreased potassium	37	11	12	3
Increased gamma glutamyl transferase	30	3	41	1

Decreased calcium (corrected)	25	0	11	1
Hematology				
Decreased white blood cell	90	42	85	19
Decreased neutrophil count	74	49	64	25
Decreased platelet count	74	17	58	9
Decreased hemoglobin	71	12	77	9
Decreased lymphocyte count	69	28	58	18

First-line Treatment of NSCLC with EGFR Exon 19 deletion or Exon 21 L858R Substitution Mutation

The safety data described below reflect exposure to RYBREVANT in combination with lazertinib in 421 treatment-naïve patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletion or exon 21 L858R substitution mutation in MARIPOSA (NSC3003). Patients received lazertinib 240 mg orally once daily and RYBREVANT intravenously at 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Median treatment duration was 18.5 months (range: 0.2 to 31.4 months) for the RYBREVANT in combination with lazertinib arm and the median treatment duration was 18.00 months (range: 0.2 to 32.7 months) for the osimertinib arm. Among the 421 patients who received RYBREVANT in combination with lazertinib, 73% were exposed to RYBREVANT for ≥ 6 months and 60% were exposed to RYBREVANT for > 1 year. For details on the study population, see *Pharmacodynamic Effects - Clinical studies*.

Serious adverse reactions occurred in 17.3% of patients who received RYBREVANT in combination with lazertinib. Serious adverse reactions in ≥ 2% of patients included venous thromboembolism (5.9%), ILD (2.6%), rash (2.4%) and infusion related reactions (2.1%). Fatal adverse reactions occurred in 0.7% of patients who received RYBREVANT in combination with lazertinib due to venous thromboembolism (0.5%) and ILD (0.2%).

Permanent discontinuations of RYBREVANT due to an adverse reaction occurred in 22% of patients. Adverse reactions leading to RYBREVANT discontinuation in ≥1% of patients were rash (5.5%), nail toxicity (3.6%), infusion related reactions (4.5%), ILD (2.9%), venous thromboembolism (2.9%), edema (1.7%), fatigue (1.4%) and hypoalbuminemia (1.4%).

Dose interruptions of RYBREVANT in combination with lazertinib due to an adverse reaction occurred in 81% of patients. Adverse reactions requiring dose interruption in ≥5% of patients were infusion related reactions (54.4%), rash (39.0%), nail toxicity (20.4%), venous thromboembolism (9.0%), alanine aminotransferase increased (5.9%), edema (5.9%), hypoalbuminea (5.5%), fatigue (4.0%), stomatitis (4.5%) and aspartate aminotransferase increased (4.5%).

Dose reductions of RYBREVANT in combination with lazertinib due to an adverse reaction occurred in 42% of patients. Adverse reactions requiring dose reductions in ≥5% of patients were rash (23.5%), and nail toxicity (14.3%).

The most common adverse reactions (≥ 20%) were rash, nail toxicity, infusion-related reaction, edema, stomatitis, venous thromboembolism, fatigue, constipation, diarrhea, dry skin, pruritus, decreased appetite, nausea, and other eye disorders. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased alanine aminotransferase, decreased

sodium, increased aspartate aminotransferase, decreased hemoglobin, and increased gamma glutamyl transferase.

Table 14 summarizes the adverse reactions (≥ 10%) in MARIPOSA.

Table 14: Adverse Reactions (≥ 10%) in Firstline Patients with NSCLC with Exon 19 Insertion or Exon 21 L858R Substitution Mutations in MARIPOSA

System Organ Class Adverse Reaction	**RYBREVANT + lazertinib (N=421)**		**Osimertinib (N=428)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders				
Rash*	89	27	49	0.7
Nail toxicity*	71	11	34	0.7
Dry skin*	26	1.0	20	0.5
Pruritus	24	0.5	17	0.2
General disorders and administration site conditions				
Infusion-related reaction	63	6.4	0	0
Edema*	47	2.9	9	0
Fatigue*	32	3.8	20	1.9
Pyrexia	12	0	9	0
Gastrointestinal disorders				
Stomatitis*	43	2.4	27	0.5
Constipation	29	0	13	0
Diarrhea	29	2.1	44	0.7
Nausea	21	1.2	14	0.2
Vomiting	12	0.5	5.4	0
Abdominal pain*	11	0	10	0
Vascular disorders				
Venous thromboembolism*[a]	36	11	8	3.0
Eye disorders				
Other eye disorders*	21	0.5	7.9	0
Metabolism and nutrition disorders				
Decreased appetite	24	1.0	18	1.4
Nervous system disorders				
Dizziness	13	0	8.9	0
Musculoskeletal and connective tissue disorder				
Myalgia	13	0.7	4.4	0

* Grouped terms

[a] Assessed as ADR for lazertinib and amivantamab combination only

Adverse reactions occurring in ≤ 10% of RYBREVANT-treated patients with NSCLC Exon 20 insertion mutations in Study NSC3003 are summarized in Table 15.

Table 15: Adverse reactions (≤ 10%) in Previously Untreated Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations in MARIPOSA

System Organ Class Adverse Reaction	RYBREVANT + lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Eye disorders				
Visual impairment*	4.5	0	2.3	0
Keratitis	2.6	0.5	0.5	0
Trichomegaly (growth of lashes)	1.9	0	0	0
Respiratory, thoracic and mediastinal disorders				
Interstitial lung disease*	3.1	1.4	3.0	1.4
Gastrointestinal disorders				
Hemorrhoids	9.7	0.2	2.1	0.2
Metabolism and nutrition disorders				
Hypomagnesemia	5.0	0	1.9	0

* Grouped term

Table 16 summarizes the laboratory abnormalities in MARIPOSA.

Table 16: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Firstline Patients with NSCLC with EGFR Exon 19 Insertion or Exon 21 L858R Substitution Mutations in MARIPOSA+

Laboratory Abnormality	RYBREVANT + lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Chemistry				
Decreased albumin	89	8	22	<1
Increased alanine aminotransferase	65	7	29	3
Increased aspartate aminotransferase	52	4	36	2
Decreased calcium (corrected)	41	1	27	1
Increased gamma glutamyl transferase	39	3	24	2
Decreased sodium	38	7	35	5
Increased creatinine	26	1	35	1
Hematology				
Decreased platelet count	52	1	57	1
Decreased hemoglobin	47	4	56	2
Decreased white blood cell	38	1	66	1

+ The denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test.

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

The safety of RYBREVANT was evaluated in Study EDI1001, which included 153 patients with locally advanced or metastatic NSCLC with EGFR exon 20 mutations whose disease has progressed on or after platinum-based chemotherapy. Patients received RYBREVANT 1050 mg

(for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) by intravenous infusion once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The median treatment duration was 5.6 months (range: 0.0 to 23.9 months).

The most common adverse reactions ≥ 20% were rash, IRR, nail toxicity, hypoalbuminemia, fatigue, edema, stomatitis, nausea, constipation, dry skin, and alanine aminotransferase increased. Serious adverse reactions in > 1% of patients included ILD, diarrhea, IRR, and rash. Five percent of patients discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR and ILD.

Table 17: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations in Study EDI1001 Treated with RYBREVANT (N=153)

System Organ Class Adverse Reaction	**Frequency Category**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders			
Rash [a]	Very common	85	4
Nail toxicity [b]	Very common	56	3
Dry skin [c]	Very common	23	0
Pruritus	Very common	16	0
Gastrointestinal disorders			
Stomatitis [d]	Very common	28	0.7
Nausea	Very common	25	0.7
Constipation	Very common	24	0
Diarrhea	Very common	14	3
Vomiting	Very common	14	0.7
Injury, poisoning and procedural complications			
Infusion-related reaction	Very common	63	3
Metabolism and nutrition disorders			
Hypoalbuminemia [e]	Very common	40	3
Decreased appetite	Very common	18	0.7
Hypokalemia	Very common	12	4
Hypomagnesemia	Very common	12	0
Hypocalcemia	Very common	10	0.7
General disorders and administration site conditions			
Fatigue [f]	Very common	33	2
Edema [g]	Very common	29	0.7
Investigations			
Alanine aminotransferase increased	Very common	22	2
Aspartate aminotransferase increased	Very common	16	0.7
Blood alkaline phosphatase increased	Very common	10	0.7
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	12	0
Nervous system disorders			
Dizziness [h]	Very common	12	0.7

[a] Rash: acne, dermatitis, dermatitis acneiform, erythema, folliculitis, palmar-plantar erythrodysesthesia syndrome, perineal rash, pustule, rash, rash erythematous, rash maculo-papular, rash papular, rash pustular, rash vesicular, skin exfoliation, skin lesion
[b] Nail toxicity: nail bed infection, nail cuticle fissure, nail disorder, onychoclasis, onycholysis, paronychia
[c] Dry skin: dry skin, eczema, eczema asteatotic, skin fissures, xeroderma
[d] Stomatitis: aphthous ulcer, cheilitis, glossitis, lip ulceration, mouth ulceration, stomatitis
[e] Hypoalbuminemia: blood albumin decreased, hypoalbuminemia
[f] Fatigue: asthenia, fatigue
[g] Edema: eyelid edema, face edema, generalized edema, edema, edema peripheral, periorbital edema, periorbital swelling, peripheral swelling, swelling face
[h] Dizziness

Adverse reactions occurring in < 10% of RYBREVANT-treated patients with NSCLC exon 20 insertion mutations in Study EDI1001 are summarized in Table 18.

Table 18: Adverse reactions (< 10%) in Patients with NSCLC with Exon 20 Insertion Mutations in Study EDI1001 Treated with RYBREVANT (N=153)

System Organ Class Adverse Reaction	**Frequency Category**	**All Grades (%)**	**Grade 3-4 (%)**
Gastrointestinal disorders			
Abdominal pain [a]	Common	9	0.7
Eye disorders			
Other eye disorders [b]	Common	6	0
Visual impairment [c]	Common	2	0
Growth of eyelashes [d]	Common	1	0
Keratitis	Common	1	0
Uveitis	Uncommon	0.7	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease [e]	Common	4	0.7
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis	Uncommon	0.7	0.7

[a] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort
[b] Other eye disorders: blepharitis, conjunctival hyperemia, corneal irritation, dry eye, episcleritis, eye pruritus, ocular hyperemia
[c] Visual impairment: vision blurred, visual acuity reduced, visual impairment
[d] Growth of eyelashes: growth of eyelashes, trichomegaly
[e] Interstitial lung disease: interstitial lung disease, pneumonitis

Postmarketing Experience

The following adverse reactions associated with the use of RYBREVANT were identified. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Skin ulcer

Overdose

Symptoms and signs

There is no information on overdosage with RYBREVANT.

Treatment

There is no known specific antidote for RYBREVANT overdose. In the event of an overdose, stop RYBREVANT, undertake general supportive measures until clinical toxicity has diminished or resolved.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Monoclonal antibodies and antibody drug conjugates, ATC code: L01FX18.

Mechanism of action

Amivantamab is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET.

Preclinical studies show amivantamab is active against tumors with primary EGFR activating mutations such as exon 19 deletions, L858R substitution, and exon 20 insertion mutations; secondary EGFR resistance mutations such as T790M and C797S; and resistance to EGFR inhibition due to activation of the MET pathway. Amivantamab disrupts EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumor growth and progression. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

Pharmacodynamic effects

Albumin

Amivantamab decreased serum albumin concentration, a pharmacodynamic effect of MET inhibition, typically during the first 8 weeks; thereafter, albumin concentration stabilized for the remainder of amivantamab treatment.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical trials of patients with locally advanced or metastatic NSCLC as monotherapy or as part of a combination

therapy, 4 of the 1862 (0.2%) participants who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab antibodies. No evident effect of immunogenicity on efficacy, and safety events (including IRRs) has been observed.

Clinical studies

Previously-untreated NSCLC

Previously-untreated NSCLC Patient with EGFR Exon 20 Insertion Mutations

NSC3001 (PAPILLON) is a randomized, open-label, multicenter phase 3 study comparing treatment with RYBREVANT in combination with carboplatin and pemetrexed to treatment as compared to chemotherapy alone (carboplatin and pemetrexed) in subjects with treatment-naïve, locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as identified by local testing, plasma samples from 209/308 (67.9%) patients were tested retrospectively using Guardant360® CDx, identifying 155/209 (74.2%) samples with an EGFR exon 20 insertion mutation; 50/209 (23.9%) samples did not have an EGFR exon 20 insertion mutation identified. The remaining 4/209 (1.9%) samples generated an invalid test result.

Tumor tissue (92.2%) and/or plasma (7.8%) samples for all 308 patients were tested locally to determine EGFR exon 20 insertion mutation status using next generation sequencing (NGS) in 55.5% of patients and/or polymerase chain reaction (PCR) in 44.5% of patients.

Patients with brain metastases at screening were eligible for participation once they were definitively treated, clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical study.

RYBREVANT was administered intravenously at 1,400 mg (for subjects < 80 kg) or 1,750 mg (for subjects ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1,750 mg (for patients < 80 kg) or 2,100 mg (for subjects ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by ECOG performance status, prior brain metastases, and prior EGFR TKI use. Subjects randomized to the carboplatin and pemetrexed arm who had confirmed disease progression were permitted to cross over to receive RYBREVANT monotherapy.

A total of 308 subjects were randomized (1:1) to RYBREVANT in combination with carboplatin and pemetrexed (N=153) or carboplatin and pemetrexed (N=155). The median age was 62 (range: 27 to 92) years, with 39% of the subjects ≥ 65 years of age; 58% were female; and 61% were Asian and 36% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (35%) or 1 (65%); 58% never smoked; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis.

RYBREVANT in combination with carboplatin and pemetrexed demonstrated a clinically meaningful and statistically significant improvement in progression-free survival (PFS) compared to carboplatin and pemetrexed, with a HR of 0.40 (95% CI: 0.30, 0.53; p<0.0001), demonstrating a 61% reduction in the risk of disease progression or death in the patients. At the time of primary analysis, overall survival showed a strong trend suggestive of a survival benefit in favor of the RYBREVANT-treated arm, where 65 subjects (42%) randomized to receive carboplatin and pemetrexed crossed over to receive RYBREVANT monotherapy (see Figure 3). A greater proportion of patients treated with RYBREVANT in combination with carboplatin and pemetrexed were alive at 12 months and 18 months (74% and 72%, respectively) compared to patients treated with carboplatin and pemetrexed (68% and 54%, respectively). Analyses of post-progression endpoints demonstrated that PFS benefit was preserved through subsequent lines of therapy, with a median follow-up of 14.9 (range: 0.3 to 27.0) months.
Efficacy results for Study 3001 are summarized in Table 19, Figure 1 and Figure 3.

Table 19: Efficacy Results in Study 3001

	RYBREVANT + carboplatin+ pemetrexed (N=151)	**carboplatin+ pemetrexed (N=155)**
Progression-free survival (PFS) [a]		
Number of events (%)	84 (55%)	132 (85%)
Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI); p-value	0.40 (0.30, 0.53); p<0.0001	
Overall response rate[a]		
ORR, % (95% CI)	73% (65%, 80%)	47% (39%, 56%)
Odds ratio (95% CI); p-value	3.0 (1.8, 4.8); p<0.0001	
Complete response	3.9%	0.7%
Partial response	69%	47%
Duration of response (DOR) [a‡]		
Median[b] (95% CI), months	10.1 (8.5, 13.9)	5.6 (4.4, 6.9)
Patients with DOR ≥ 6 months	77%	44%
Patients with DOR ≥ 12 months	45%	11%
Overall survival (OS)[b]		
Number of events	28	42
Median OS, months (95% CI)	NE (NE, NE)	24.3 (22.0, NE)
HR (95% CI); p-value	0.68 (0.42, 1.10); p=0.11	
Time to subsequent therapy (TTST)[c]		
Number of patients who had subsequent therapy (%)	58 (38%)	109 (70%)
Median, months (95% CI)	17.7 (13.7, NE)	9.9 (8.6, 11.1)
HR (95% CI); p-value	0.35 (0.25, 0.49); p<0.0001	
PFS after first subsequent therapy (PFS2)[d]		
Number of patients with second progression	33	61
Median, months (95% CI)	NE (22.8, NE)	17.3 (14.0, 21.5)

HR (95% CI); p-value	0.49 (0.32, 0.76); p=0.001	
Time to symptomatic progression (TTSP)[e]		
Number of events	45 (29%)	64 (41%)
Median, months (95% CI)	NE (18.6, NE)	20.1 (13.1, NE)
HR (95% CI); p-value	0.67 (0.46, 0.98); p=0.039	

CI = confidence interval
NE = not estimable

[a] Blinded Independent Central Review by RECIST v1.1

[b] Based on the results of interim analysis of OS. The OS analysis was not adjusted for the potentially confounding effects of crossover (65 [42%] patients on the carboplatin + pemetrexed arm who received subsequent RYBREVANT monotherapy treatment)

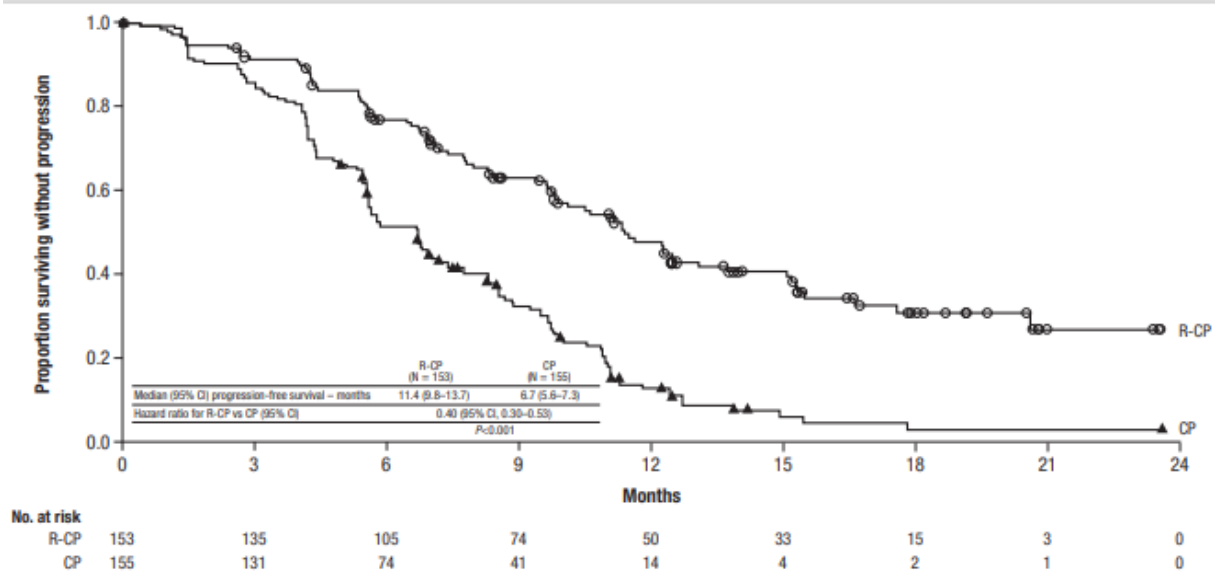
[c] Defined as time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation.

[d] Defined as time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment or death, whichever comes first.

[e] Defined as the time from randomization to onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms, or death, whichever comes first.

[‡] In confirmed responders.

Figure 1: Kaplan-Meier Curve of PFS in Previously Untreated NSCLC Patients by BICR Assessment



The pre-planned sensitivity analysis evaluating PFS as assessed by the treating investigator showed a 62% reduction in the risk of disease progression or death (median 12.9 months) in participants randomized to the RYBREVANT in combination with carboplatin and pemetrexed arm (HR of 0.38 [95% CI: 0.29, 0.52, nominal p<0.001]), consistent with that observed in the BICR assessment of PFS.

Additionally, consistent with the assessment by BICR, results of the DOR and ORR analysis based on the treating investigator's assessment also showed a significant treatment benefit with RYBREVANT in combination with carboplatin and pemetrexed. The median DOR was 15.28 months (95% CI: 10.87, NE) and the ORR analysis showed significantly improved anti-tumor activity with an ORR of 66.0% (95% CI: 57.9, 73.5).

The PFS benefit of RYBREVANT in combination with carboplatin and pemetrexed compared to carboplatin and pemetrexed was consistent across the predefined subgroups of brain metastases at study entry (yes or no), age (<65 or ≥65), sex (male or female), race (Asian or non-Asian), weight (<80 kg or ≥80 kg), ECOG performance status (0 or 1), and smoking history (yes or no). See Figure 2.

Figure 2: Forest Plot: Subgroup Analysis of PFS – NSC3001

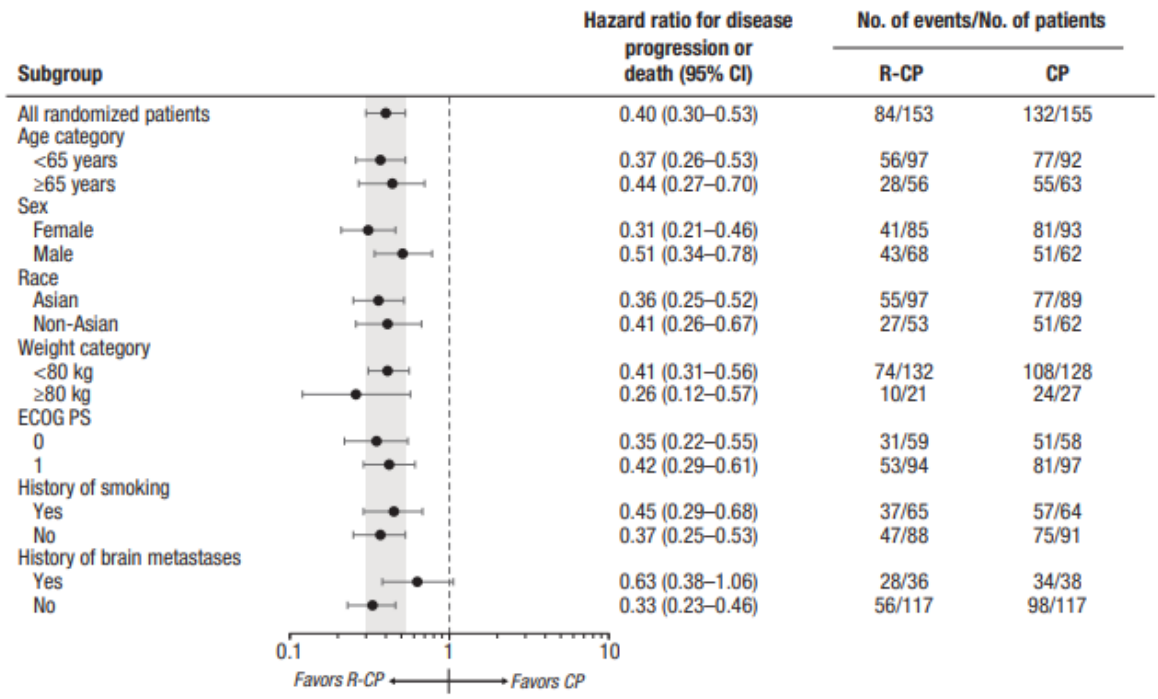
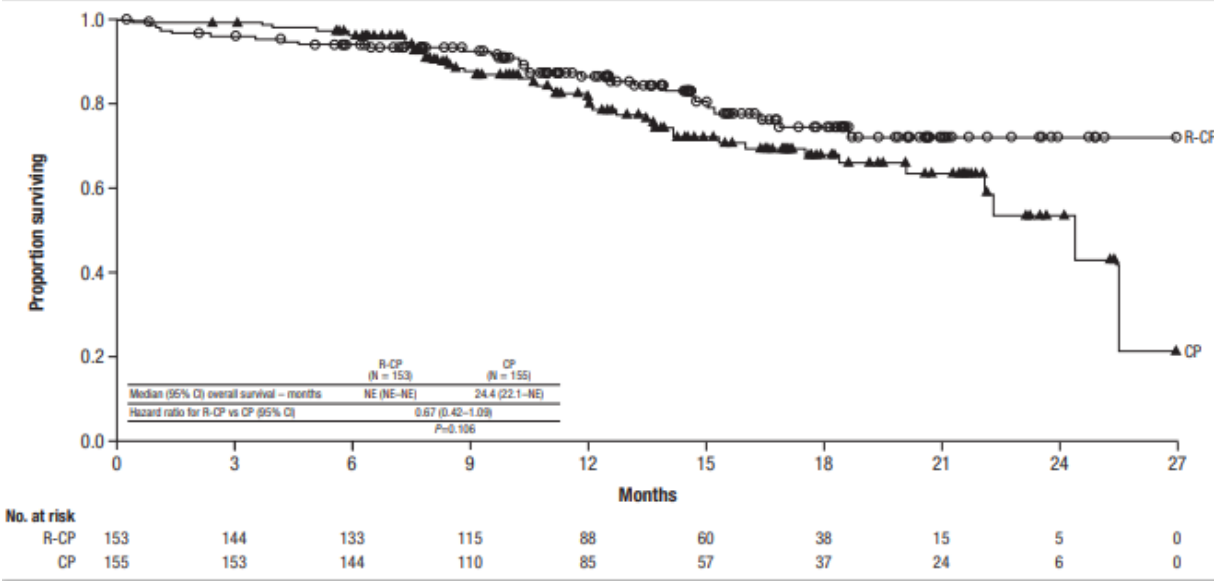


Figure 3: Kaplan-Meier Curve of OS in Previously Untreated NSCLC Patients



Patient Reported Outcomes

Patient-reported symptoms and health-related quality of life (HRQoL) were electronically collected using the EORTC QLQ-C30 and PROMIS-PF. These instruments were administered approximately once every 6 weeks until end of treatment. They were then administered 30 days after last dose of treatment, then once every 12 weeks for one year. Compliance was high at baseline (>97%) and during treatment (>80% through Cycle 31) in both arms. At baseline, patients in both treatment arms reported low symptom burden and high levels of functioning.

The PRO analyses demonstrated that the clinical benefits of receiving RYBREVANT with carboplatin and pemetrexed were achieved without compromising HRQoL. Across all PRO scales, patients' baseline HRQoL was maintained while on treatment in both arms.

Time to deterioration analyses showed that median time to symptom worsening was delayed by 2 to 5 months for RYBREVANT with carboplatin and pemetrexed compared to carboplatin and pemetrexed alone for dyspnea (HR=0.75, 95% CI: 0.55, 1.01), pain (HR=0.74, 95% CI: 0.55, 1.00), insomnia (HR=0.75, 95% CI: 0.54, 1.04), diarrhea (HR=0.67, 95% CI: 0.47, 0.95), and nausea/vomiting (HR=0.74, 95% CI: 0.55, 0.98).

Previously-untreated NSCLC Patients with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

NSC3003 (MARIPOSA) is a randomized, active-controlled, multicenter phase 3 study assessing the efficacy and safety of RYBREVANT in combination with lazertinib as compared to osimertinib monotherapy as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Patient samples were required to have one

of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing.

A total of 1074 patients were randomized (2:2:1) to receive RYBREVANT in combination with lazertinib, osimertinib monotherapy, or lazertinib monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity. RYBREVANT was administered intravenously at 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Lazertinib was administered at 240 mg orally once daily. Osimertinib was administered at a dose of 80 mg orally once daily. Randomization was stratified by EGFR mutation type (exon 19 deletion or exon 21 L858R), race (Asian or non-Asian), and history of brain metastasis (yes or no).

Baseline demographics and disease characteristics were balanced across the treatment arms. The median age was 63 (range: 25–88) years with 45% of patients ≥ 65 years; 62% were female; and 59% were Asian, and 38% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (34%) or 1 (66%); 69% never smoked; 41% had prior brain metastases; and 90% had Stage IV cancer at initial diagnosis. With regard to EGFR mutation status, 60% were exon 19 deletions and 40% were exon 21 L858R substitution mutations.

RYBREVANT in combination with lazertinib demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) by BICR assessment, with a 30% reduction in the risk of progression or death compared with osimertinib (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002). The corresponding median PFS was 23.72 months (95% CI: 19.12, 27.66) for the RYBREVANT in combination with lazertinib arm and 16.59 months (95% CI: 14.78, 18.46) for the osimertinib arm.

The final analysis of OS demonstrated a statistically significant improvement in OS for RYBREVANT in combination with lazertinib compared to osimertinib (see Table 20 and Figure 6). A greater proportion of patients treated with RYBREVANT in combination with lazertinib were alive at 12 months, 18 months, 24 months, 36 months and 42 months (90%, 82%,75%, 60% and 56%, respectively) compared to patients treated with osimertinib (88%, 79%, 70%, 51% and 44%, respectively). RYBREVANT in combination with lazertinib also provided a benefit in the time to second progression or death (PFS2) (HR=0.75 [95% CI: 0.58, 0.98], p=0.0314). While the overall response rate (ORR) was comparable between the arms, the median duration of response (DOR) among confirmed responders was longer with RYBREVANT in combination with lazertinib (25.76 vs 16.76 months). RYBREVANT in combination with lazertinib also provided a benefit in the time to symptomatic progression (TTSP), a measure of the burden of lung cancer

symptoms (HR=0.72 [95% CI: 0.57, 0.91], p=0.0049). Table 20, Figure 4, and Figure 6 summarize efficacy results for RYBREVANT in combination with lazertinib.

Table 20: Efficacy Results in NSC3003 by BICR Assessment

	RYBREVANT + lazertinib (N=429)	**Osimertinib (N=429)**	**Lazertinib (N=216)**
Progression-free survival (PFS)[a]			
Number of events	192	252	121
Median, months (95% CI)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)	18.46 (14.75, 20.11)
HR (95% CI); p-value	---	0.70 (0.58, 0.85); p=0.0002[g]	0.72 (0.57, 0.90); p=0.0046[h]
Overall survival (OS)[b]			
Number of events	173	217	100
Median, months (95% CI)	NE (42.9, NE)	36.7 (33.4, 41.0)	38.5 (36.5, 45.4)
HR (95% CI); p-value	---	0.75 (0.61, 0.92); p=0.0048[g]	0.83 (0.65, 1.06); p=0.1416[h]
Overall response rate (ORR)[a]			
ORR % (95% CI)	86.2% (82.6%, 89.4%)	84.5% (80.7%, 87.9%)	82.7% (77.0%, 87.5%)
Odds ratio (95% CI); p-value[f]	---	1.15 (0.78, 1.70); p=0.4714	1.31 (0.83, 2.06); p=0.2409
Complete response	6.9%	3.6%	4.2%
Partial response	79.3%	80.9%	78.5%
Duration of response (DOR)[c]			
Median (95% CI), months	25.76 (20.14, NE)	16.76 (14.75, 18.53)	16.56 (14.75, 20.21)
Patients with DOR ≥ 6 months	86.3%	85.0%	82.5%
Patients with DOR ≥ 12 months	67.9%	57.6%	58.8%

PFS after first subsequent therapy (PFS2)[d]			
Number of patients with second progression	101	130	58
HR (95% CI); p-value[f]	---	0.75 (0.58, 0.98); p=0.0314 [h]	0.81 (0.59, 1.12); p=0.2025 [h]
Time to symptomatic progression (TTSP)[e]			
Number of events	125	167	70
Median, months (95% CI)	NE (NE, NE)	29.31 (25.33, NE)	NE (NE, NE)
HR (95% CI); p-value	---	0.72 (0.57, 0.91); p=0.0049[g]	0.86 (0.64, 1.15); p=0.3083[h]

BICR = blinded independent central review; CI = confidence interval; NE = not estimable

[a] BICR by RECIST v1.1.

[b] Based on the results of the final analysis of OS **with results from data cut-off 04 Dec 2024 with a median follow-up of 37.8 months**.

[c] BICR by RECIST v1.1 in confirmed responders.

[d] Defined as time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever comes first.

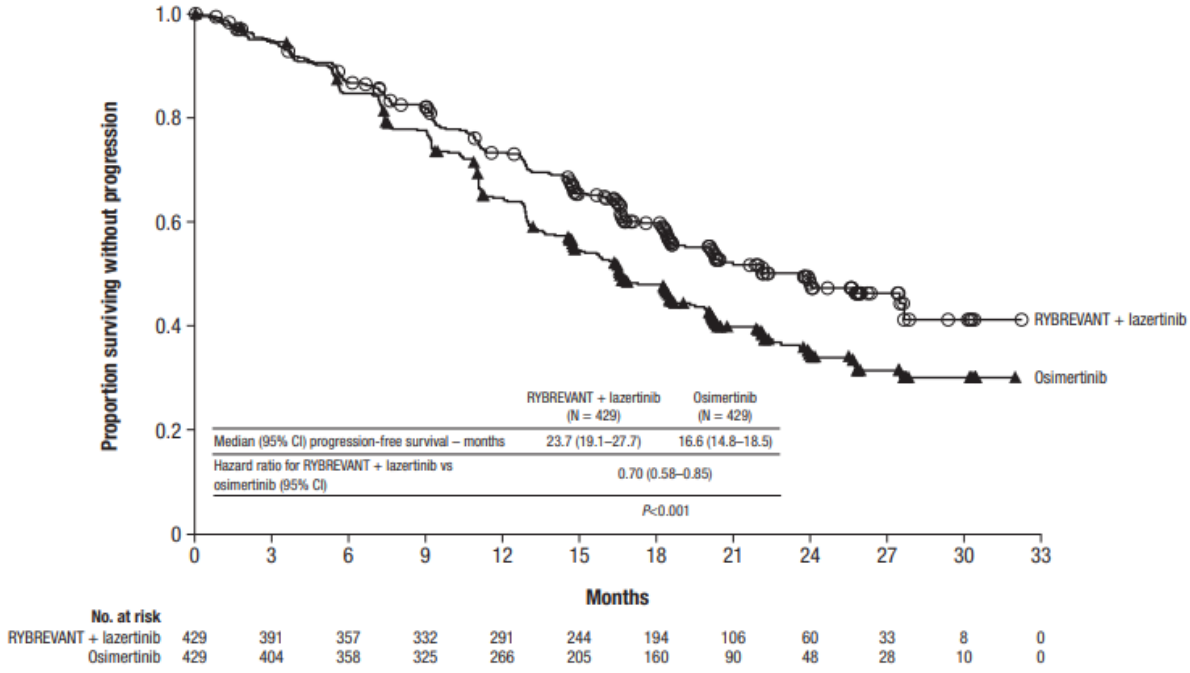
[e] Defined as the time from randomization to onset of new symptoms or symptom worsening that is considered by the investigator to be related to lung cancer and requires either a change in anticancer treatment and/or clinical intervention to manage symptoms, or death, whichever comes first.

[f] Compared to RYBREVANT and lazertinib.

[g] RYBREVANT and lazertinib compared to osimertinib.

[h] RYBREVANT and lazertinib compared to lazertinib.

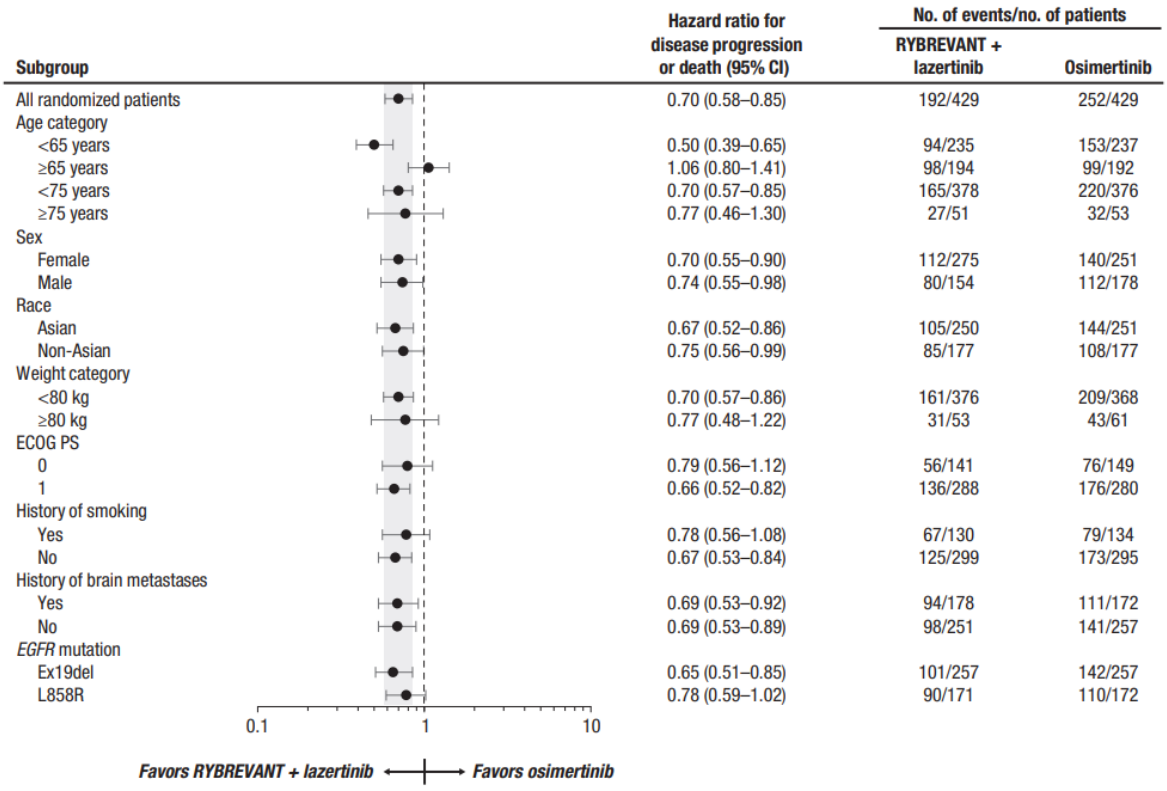
Figure 4: Kaplan-Meier curve of PFS in previously untreated NSCLC patients by BICR assessment



The PFS benefit of RYBREVANT in combination with lazertinib as compared to osimertinib was generally consistent across prespecified, clinically relevant subgroups, including age group, sex,

race, weight, mutation type, ECOG performance status, history of smoking, and history of brain metastasis at study entry (See Figure 5).

Figure 5: Forest plot of PFS in previously untreated NSCLC patients by BICR assessment

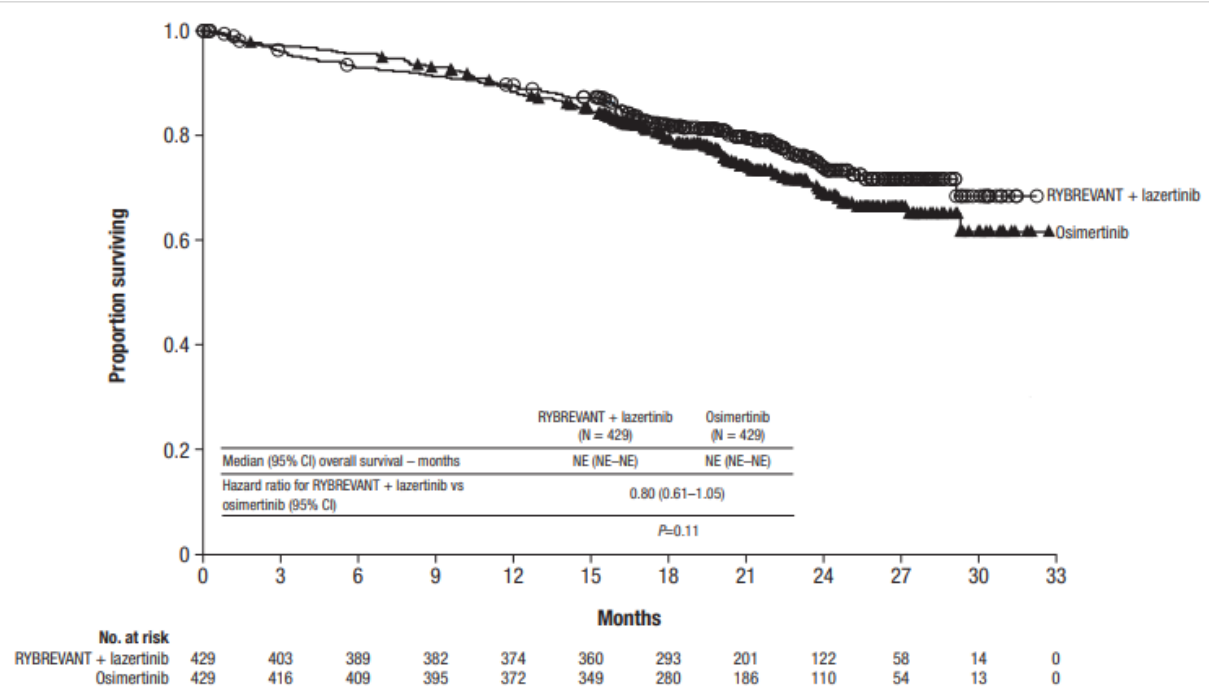


The stratified analysis of investigator-assessed PFS shows that the improved treatment effect of the combination of RYBREVANT and lazertinib relative to osimertinib was also observed when assessed by investigator. Results for the analysis of ORR based on investigator assessment for comparison of the RYBREVANT in combination with lazertinib arm versus the osimertinib arm were consistent with results for ORR based on BICR assessment.

The MARIPOSA study included protocol-mandated brain magnetic resonance imaging (MRIs), which have historically not been used in trials evaluating EGFR-mutated NSCLC. This may have led to earlier detection of recurrences and associated shorter median values for PFS. To account for this, a sensitivity analysis was done whereby patients with brain-only progression as the site of first progression were censored. Extracranial PFS based on BICR assessment was consistent with the treatment benefit observed in the primary analysis. The median extracranial PFS was 27.5

months with RYBREVANT in combination with lazertinib, as compared to 18.37 months with osimertinib (HR=0.68 [95% CI: 0.55, 0.83], nominal p=0.0001).

Figure 6: Kaplan-Meier curve of OS in previously untreated NSCLC patients



Results of pre-specified exploratory analyses of CNS ORR and DOR by BICR, in the subset of patients with measurable intracranial lesions at baseline for the combination of Rybrevant and lazertinib, demonstrated similar intracranial ORR to the control. Per protocol, all **patients in**

MARIPOSA had serial brain MRIs to assess intracranial response and duration. Results are summarized in Table 21.

Table 21: Intracranial ORR and DOR by BICR assessment in subjects with measurable intracranial lesions at baseline - MARIPOSA

	RYBREVANT + lazertinib (N=180)	**Osimertinib (N=186)**	**Lazertinib (N=93)**
Intracranial Tumor Response Assessment			
Intracranial ORR (CR+PR), % (95% CI)	77.8 (71.0, 83.6)	77.4 (70.7, 83.2)	75.0 (64.9, 83.4)
Complete response %	63.9	58.6	54.3
Intracranial DOR			
Number or responders	140	144	69
Median, months (95% CI)	35.0 (20.4, NE)	25.1 (22.1, 31.2)	22.5 (18.8, 31.1)
Response Duration ≥6 months, %	78.6	79.9	81.2
Response Duration ≥12 months, %	63.6	61.1	60.9
Response Duration ≥18 months, %	52.1	41.0	40.6
Response Duration ≥24 months, %	**40.7**	**22.2**	**21.7**
Response Duration ≥30 months, %	27.9	11.1	11.6
Response Duration ≥36 months, %	12.9	4.9	2.9

CI = confidence interval
Intracranial ORR and DOR results are from data cut off 04 Dec 2024 with a median follow up of 37.8 months.

Previously-treated NSCLC

Previously Treated NSCLC Patients with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The efficacy of RYBREVANT was evaluated in patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations (characterized by a validated test at or after the time of locally advanced or metastatic disease diagnosis, as identified by local or central testing) in a randomized (2:2:1), open-label, multicenter phase 3 clinical trial (MARIPOSA-2, NCT04988295). In MARIPOSA-2, patients who have previously received osimertinib received carboplatin and pemetrexed (CP, N=263) or RYBREVANT in combination with carboplatin and pemetrexed (RYBREVANT-CP, N=131). RYBREVANT was administered intravenously at 1,400 mg (for patients < 80 kg) or 1,750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1,750 mg (for patients < 80 kg) or 2,100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity. Additionally, 236 patients received RYBREVANT in combination with lazertinib, carboplatin, and pemetrexed in a separate arm of the study (an unapproved regimen for EGRFm NSCLC).

Patients were stratified by osimertinib line of therapy (first-line or second-line), prior brain metastases (yes or no), and Asian race (yes or no).

Of the 394 patients randomized to the RYBREVANT-CP arm or CP arm, the median age was 62 (range: 31–85) years, with 37.8% of the patients ≥ 65 years of age; 60.4% were female; and 48.2% were Asian and 46.4% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (39.6%) or 1 (60.4%); 65.5% never smoked; 45.2% had history of brain metastasis, and 91.6% had Stage IV cancer at initial diagnosis.

RYBREVANT in combination with carboplatin and pemetrexed demonstrated a clinically meaningful and statistically significant improvement in progression-free survival (PFS) compared to carboplatin and pemetrexed, with a HR of 0.48 (95% CI: 0.36, 0.64; p<0.0001) demonstrating a 52% reduction in the risk of disease progression or death and a clinically meaningful longer median survival time in patients randomized to RYBREVANT -CP vs CP. Analyses of post-progression endpoints demonstrated that PFS benefit was preserved through subsequent lines of therapy. At the time of primary analysis, overall survival (OS) showed a strong trend suggestive of survival benefit in favor of the RYBREVANT arm. There were 27 deaths occurring in the RYBREVANT-CP arm and 65 deaths occurring in the CP arm and interim overall survival analysis was HR of 0.77 (95% CI: 0.49, 1.21; p=0.2531). See Figure 7 and Figure 9.

Efficacy results are summarized in Table 22.

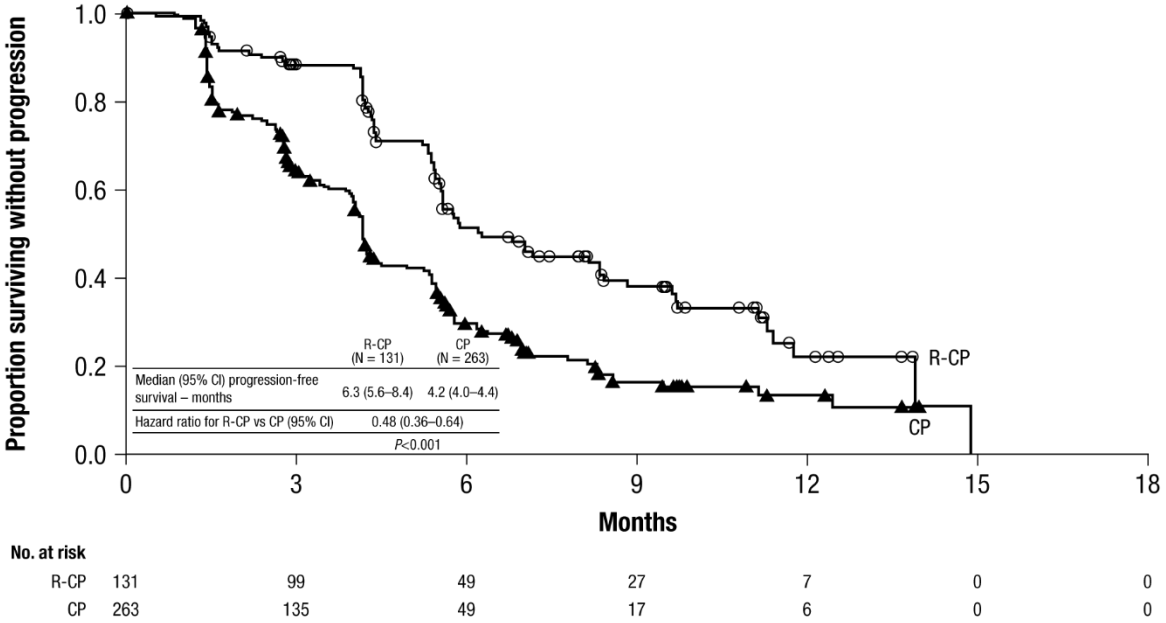
Table 22: Efficacy results in MARIPOSA-2

	RYBREVANT + carboplatin+ pemetrexed (N=131)	**carboplatin+ pemetrexed (N=263)**
Progression-free survival (PFS)[a]		
Number of events (X%)	74 (56.5%)	171 (65.0%)
Median, months (95% CI)	6.28 (5.55, 8.41)	4.17 (4.04, 4.44)
HR (95% CI); p-value	0.48 (0.36, 0.64); p<0.0001	
Overall response rate[a, b]		

ORR, % (95% CI)	63.8% (55.0, 72.1)	36.2% (30.3, 42.3)
Odds ratio (95% CI); p-value	3.10 (2.00, 4.80); p <0.0001	
Complete response	1.5%	0.4%
Partial response	62.3%	35.8%
Duration of response[a] ‡ (DOR)		
Median[b] (95% CI), months	6.90 (5.52, NE)	5.55 (4.17, 9.56)
Patients with DOR ≥ 6 months	31.9%	20.0%
Time to subsequent therapy (TTST)[c]		
Number of events (%)	46 (35.1)	138 (52.5)
Median, months (95% CI)	12.06 (11.04, 14.88)	6.60 (6.24, 8.11)
HR (95% CI); p-value	0.42 (0.30, 0.59); p<0.0001	
PFS after first subsequent therapy (PFS2)[d]		
Number of events (%)	33 (25.2%)	80 (30.4%)
Median, months (95% CI)	13.90 (11.40, NE)	11.27 (9.07, 13.83)
HR (95% CI); p-value	0.60 (0.40, 0.92); p=0.0167	
Intracranial PFS[e]		
Number of events (%)	41 (31.3%)	102 (38.8%)
Median, months (95% CI)	12.45 (10.84, NE)	8.31 (7.29, 11.27)
HR (95% CI); p-value	0.55 (0.38, 0.79); p=0.0011	

CI = confidence interval
NE = not estimatable
[a] Blinded Independent Central Review by RECIST v1.1
[b] Based on Kaplan-Meier estimate.
[c] Defined as time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation.
[d] Defined as time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment or death, whichever comes first.
[e] Defined as time from randomization until the date of objective intracranial disease progression or death, whichever comes first, based on BICR using RECIST v1.1. Specifically, intracranial disease progression is defined as having progression of brain metastasis or occurrence of new brain lesion.
‡ In confirmed responders.

Figure 7: Kaplan-Meier curve of PFS in Previously Treated NSCLC Patients by BICR assessment - MARIPOSA-2



The pre-planned sensitivity analysis evaluating PFS as assessed by the treating investigator showed a 59% reduction in the risk of disease progression or death (median 8.2 months) in participants randomized to the RYBREVANT in combination with carboplatin and pemetrexed arm (HR of 0.41 [95% CI: 0.30, 0.54, nominal p<0.0001]), as compared to a median of 4.2 months in the carboplatin and pemetrexed arm, which is consistent with that observed in the BICR assessment of PFS.

Additionally, consistent with the assessment by BICR, results of the DOR and ORR analysis based on the treating investigator's assessment also showed a significant treatment benefit with RYBREVANT in combination with carboplatin and pemetrexed. The median DOR was 7.13 months (95% CI: 5.55, NE) as compared to 5.45 months (95% CI: 4.27, 6.93) in the carboplatin and pemetrexed arm. The ORR analysis showed significantly improved anti-tumor activity with an ORR of 51.9% (95% CI: 43.0, 60.7) as compared to 27.8% (95% CI: 22.4%, 33.6%) in the carboplatin and pemetrexed arm.

The PFS benefit of RYBREVANT-CP compared to CP was consistent across the predefined subgroups analysed, including ethnicity, age, gender, smoking history, and CNS metastases status at study entry.
Subgroup analysis of PFS are summarized in Figure 8.

Figure 8: Forest Plot: Subgroup analysis of PFS by BICR Assessment– MARIPOSA-2 Study

Subgroup	Hazard ratio for disease progression or death (95% CI)	No. of events/No. of patients	
		R-CP	CP
All randomized patients	0.48 (0.36–0.64)	74/131	171/263
Age category			
<65 years	0.44 (0.31–0.64)	40/79	106/166
≥65 years	0.61 (0.40–0.94)	34/52	65/97
<75 years	0.48 (0.36–0.65)	65/118	160/244
≥75 years	0.70 (0.28–1.75)	9/13	11/19
Sex			
Female	0.48 (0.33–0.68)	45/81	103/157
Male	0.54 (0.35–0.84)	29/50	68/106
Race			
Asian	0.58 (0.39–0.85)	39/63	82/127
Non-Asian	0.47 (0.32–0.71)	34/64	84/129
Weight category			
<80 kg	0.51 (0.38–0.68)	64/113	148/226
≥80 kg	0.51 (0.23–1.11)	10/18	23/37
ECOG PS			
0	0.44 (0.28–0.69)	30/55	65/101
1	0.56 (0.39–0.79)	44/76	106/162
History of smoking			
Yes	0.45 (0.27–0.76)	19/41	61/95
No	0.53 (0.38–0.74)	55/90	110/168
History of brain metastases			
Yes	0.52 (0.35–0.78)	34/58	79/120
No	0.48 (0.33–0.70)	40/73	92/143
Osimertinib line of therapy			
First line	0.47 (0.34–0.66)	54/97	117/181
Second line	0.55 (0.32–0.93)	20/34	54/82
EGFR mutation			
Ex19del	0.60 (0.44–0.83)	58/89	118/183
L858R	0.30 (0.17–0.54)	16/42	53/79

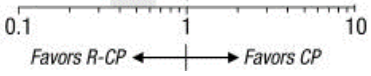
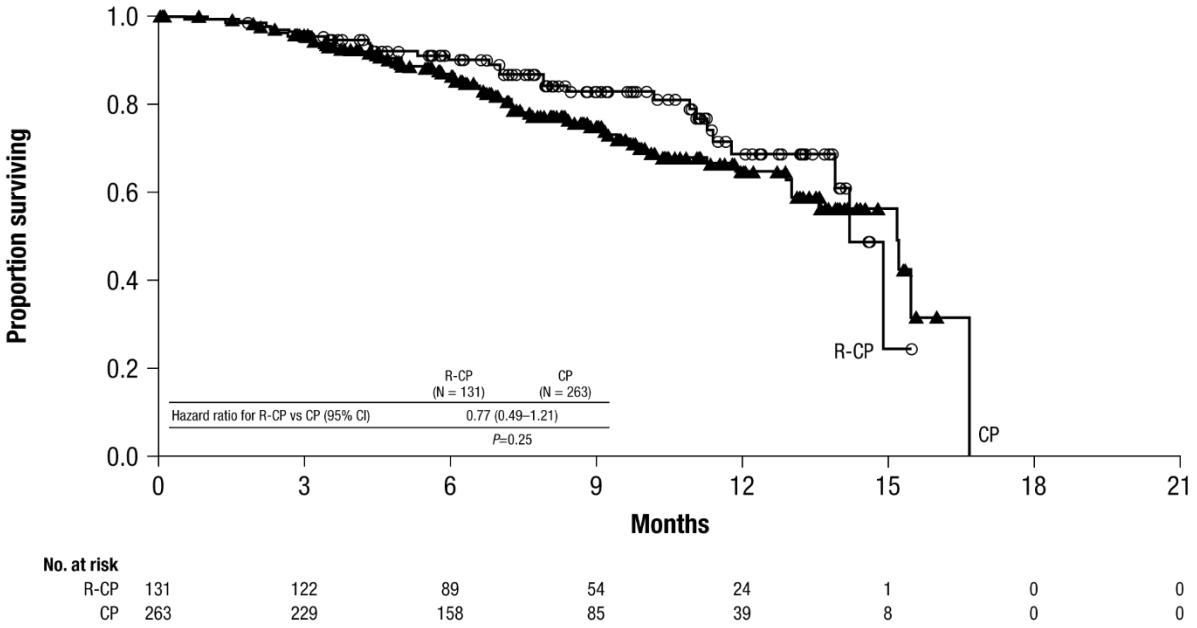


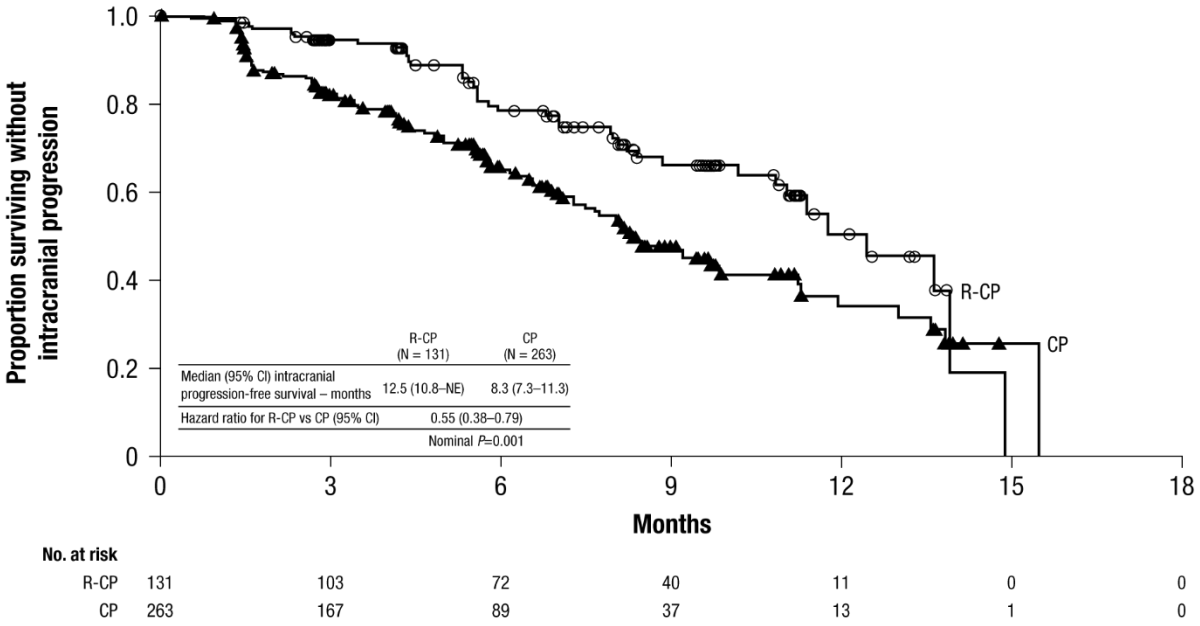
Figure 9: Kaplan-Meier curve of OS in Previously Treated NSCLC Patients - MARIPOSA-2



Intracranial metastases efficacy data

Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to be randomized in MARIPOSA-2. Baseline disease assessment, including brain Magnetic Resonance imaging (MRI) was performed at treatment initiation. All patients underwent serial brain MRI during the trial. Treatment with RYBREVANT -CP was associated with a marked improvement in intracranial PFS (with median intracranial PFS of 12.45 months vs 8.31 months in the RYBREVANT-CP vs CP arm, respectively; HR=0.55; nominal p=0.0011), including in participants that had a history of brain metastases (HR=0.52, nominal p=0.0093), and in participants with a history of brain metastases who had not received prior radiotherapy to the brain (HR=0.36, p=0.0129). In addition, treatment with RYBREVANT-CP showed a numeric increase in intracranial ORR (26.7% for RYBREVANT-CP versus 14.8% for CP, odds ratio of 2.10; nominal p=0.1758]) and intracranial DOR (not estimable in the RYBREVANT-CP arm compared with 3.48 months in the CP arm).

Figure 10: Kaplan-Meier curve of Intracranial PFS by BICR assessment in subjects with CNS metastases at baseline - MARIPOSA-2



Patient Reported Outcomes

Patient-reported symptoms and health-related quality of life (HRQoL) were electronically collected using the NSCLC-SAQ, EORTC-QLQ-C30 and PROMIS-PF. These instruments were administered on the first day of each treatment cycle, at the end of the treatment visit, and once every 12 weeks for one year. Compliance was high at baseline (>94%) and during treatment (>80%) in both arms. At baseline, patients in both treatment arms reported low symptom burden and high levels of functioning.

The PRO analyses demonstrated that the clinical benefits of receiving RYBREVANT with carboplatin and pemetrexed were achieved without compromising HRQoL. Patients' baseline HRQoL was maintained, and was similar between arms, while on treatment.

Previously-treated NSCLC

EDI1001 (CHRYSALIS) is a multicenter, open-label, multi-cohort study conducted to assess the safety and efficacy of RYBREVANT in subjects with locally advanced or metastatic NSCLC. Efficacy was evaluated in 114 subjects with locally advanced or metastatic NSCLC who had EGFR exon 20 insertion mutations as determined by previous local standard of care testing, whose disease had progressed on or after platinum-based chemotherapy, and who had median follow-up of 12.5 months. RYBREVANT was administered intravenously at 1050 mg for subjects < 80 kg or 1400 mg for subjects ≥ 80 kg once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity.

The median age was 62 (range: 36–84) years, with 41% of the patients ≥ 65 years of age; 61% were female; and 52% were Asian and 37% were White. The median number of prior therapies was 2 (range: 1 to 7 therapies). At baseline, 29% had Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 70% had ECOG performance status of 1; 57% never smoked; 100% had Stage IV cancer; and 25% had previous treatment for brain metastases. Insertions in exon 20 were observed at 8 different residues; the most common residues were A767 (22%), S768 (16%), D770 (12%), and N771 (11%).

Efficacy results are summarized in Table 23.

Table 23: Efficacy Results for EDI1001 (CHRYSALIS)

	BICR Assessment (N=114)	**Investigator Assessment (N=114)**
Overall Response Rate[a,b] (95% CI)	43% (34%, 53%)	37% (28%, 46%)
Complete response	3%	0%
Partial response	40%	37%
Clinical Benefit Rate[a,c] (95% CI)	74% (65%, 82%)	75% (67%, 83%)
Duration of Response[a] **(DOR)**		
Median (95% CI), months[d]	10.8 (6.9, 15.0)	12.5 (6.5, 16.1)
Patients with DOR ≥ 6 months	55%	64%
Median Progression-Free Survival[a] (95% CI), months	6.7 (5.5, 9.7)	6.9 (5.6, 8.6)
Median Time to Treatment Failure (95% CI), months	8.1 (6.7, 10.6)	
Median Overall Survival (95% CI), months	22.8 (17.5, NE)	

BICR=Blinded Independent Central Review; NE=Not Estimable

[a] by RECIST v1.1

[b] Confirmed response.

[c] Clinical benefit rate is defined as complete response + partial response + stable disease (duration of at least 11 weeks).

[d] Based on Kaplan-Meier estimate

Anti-tumor activity was observed across studied mutation subtypes.

Pharmacokinetic Properties

Based on RYBREVANT monotherapy data, amivantamab area under the concentration-time curve (AUC_{1week}) increases proportionally over a dose range from 350 to 1750 mg.

Based on the population pharmacokinetics of RYBREVANT, steady-state concentrations of RYBREVANT were reached by week 13 for both the recommended 3-week and 2-week dosing regimen and the systemic accumulation was 1.9-fold.

Distribution

Amivantamab mean (± SD) volume of distribution estimated from population PK parameters was 5.34 ± 1.81 L following administration of the recommended dose of RYBREVANT.

Elimination

The geometric mean (% CV) linear clearance (CL) and terminal half-life associated with linear clearance estimated from population PK parameters were 0.266 L/day (30.4%), and 13.7 days (31.9%), respectively.

Special populations

Pediatrics (17 years of age and younger)

The pharmacokinetics of RYBREVANT in pediatric patients have not been investigated.

Elderly (65 years of age and older)

No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (21-88 years).

Renal impairment

No clinically meaningful effect on the pharmacokinetics of amivantamab was observed in patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min) and moderate (29 ≤ CrCl < 60 mL/min) or severe (15 ≤ CrCl < 29 mL/min) renal impairment. Data in patients with severe renal impairment are limited (n=1), but there is no evidence to suggest that dose adjustment is required in these patients. No data are available in patients with end stage renal disease (CrCl <15 mL/min).

Hepatic impairment

Changes in hepatic function are unlikely to have any effect on the elimination of amivantamab since IgG1-based molecules such as amivantamab are not metabolized through hepatic pathways. No clinically meaningful effect in the pharmacokinetics of amivantamab was observed based on mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN and any AST)] or moderate hepatic impairment (1.5×ULN < total bilirubin ≤3×ULN and any AST). Data in patients with moderate hepatic impairment are limited (n=1), but there is no evidence to suggest that dose adjustment is required in these patients. No data are available in patients with severe hepatic impairment (total bilirubin > 3×ULN and any AST).

Gender

The clearance of amivantamab was 24% higher in males than in females; however, no clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on gender.

Weight

The central volume of distribution and clearance of amivantamab increased with increasing body weight. Similar amivantamab exposures were achieved at the recommended dose of RYBREVANT in patients with a body weight < 80 kg who received 1050 mg and patients with a body weight ≥ 80 kg who received 1400 mg.

NON-CLINICAL INFORMATION

In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 6 weeks or 3 months (~6-8x C_{max} and ~5-7x AUC human exposure for 1050 and 1400 mg intravenous doses). There were no effects on cardiovascular, respiratory, and nervous system function. Clinical pathology demonstrated non-adverse elevations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and globulins, and non-adverse decreases in albumin when compared to the control group. All these values returned to normal ranges in recovery groups. A subcutaneous local tolerance study showed that amivantamab was well tolerated at injection sites in cynomolgus monkeys administered two 125 mg/kg weekly doses.

Carcinogenicity and Mutagenicity

No animal studies have been performed to establish the carcinogenic potential of amivantamab. Routine genotoxicity and carcinogenicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Reproductive Toxicology

No reproductive toxicology studies have been performed to evaluate the potential effects of amivantamab.

PHARMACEUTICAL INFORMATION

List of Excipients

EDTA disodium salt dihydrate
L-Histidine
L-Histidine hydrochloride monohydrate
L-Methionine
Polysorbate 80
Sucrose
Water for Injection

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in *Dosage and Administration*.

Shelf Life
Unopened vials:
36 Months
After dilution:
Since amivantamab solutions do not contain a preservative, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. Administer diluted solutions within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

Storage Conditions
Store in a refrigerator at 2°C to 8°C.
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see Shelf-Life.

Nature and Contents of Container
RYBREVANT is available in cartons containing 1 single-use vial.

Instructions for Use and Handling and Disposal
Keep out of the sight and reach of children.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Patient Councelling Information
Infusion-Related Reactions
Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions *[see Warnings and Precautions]*.

Interstitial Lung Disease/Pneumonitis
Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms *[see Warnings and Precautions]*.

Dermatologic Adverse Reactions
Advise patients of the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure, to use broad spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT *[see Warnings and Precautions]*. Advise patients to apply alcohol free emollient cream to dry skin.

Ocular Toxicity
Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated *[see Warnings and Precautions]*.

Paronychia
Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia *[see Adverse Reactions]*.

Embryo-Fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the final dose, and to inform their healthcare provider of a known or suspected pregnancy. *[see Warnings and Precautions, Pregnancy, Breast-feeding and Fertility]*.

Lactation
Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the final dose *[see Pregnancy, Breast-feeding and Fertility]*.

Manufactured by:
Cilag AG, Hochstrasse 201, Schaffhausen, CH-8200 Switzerland.

Imported and Marketed in India by:
Johnson & Johnson Pvt. Ltd.,
Gala No. 3, BULDG No. B-2, Citylink Warehousing Complex, S.No. 120-121, Mumbai Nashik Highway, Village Vadpe, Taluka – Bhiwandi - 421302, Maharashtra.

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