RxAdvance

NEW DRUG APPROVAL

Brand Name	Rybrevant™
Generic Name	amivantamab-vmjw
Drug Manufacturer	Janssen Biotech, Inc.

New Drug Approval

FDA Approval Date: May 21, 2021

Review Designation: Priority, Accelerated Approval, Breakthrough Therapy

Type of Review: N/A; Biologic License Application (BLA): 761210

Dispensing Restrictions: Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

NSCLC is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, but there are several other types that occur less frequently, and all types can occur in unusual histologic variants. Although NSCLCs are associated with cigarette smoke, adenocarcinomas may be found in patients who have never smoked.

As a class, NSCLCs are usually less sensitive to chemotherapy and radiation therapy compared with SCLC. Patients with resectable disease may be cured by surgery or surgery followed by chemotherapy. Local control can be achieved with radiation therapy in a large number of patients with unresectable disease, but cure is seen only in a small number of patients. Patients with locally advanced unresectable disease may achieve long-term survival with radiation therapy combined with chemotherapy. Patients with advanced metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy, targeted agents, and other supportive measures.

Estimated new cases is 235,760 and deaths is 131,880 from lung cancer (NSCLC and SCLC combined) in the United States in 2021. Lung cancer is the leading cause of cancer-related mortality in the United States. The 5-year relative survival rate from 2010 to 2016 for patients with lung cancer was 21%. The 5-year relative survival rate varies markedly for patients diagnosed at local stage (59%), regional stage (32%), or distant stage (6%).

Efficacy

The efficacy of Rybrevant™ was evaluated in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in a multicenter, open-label, multi-cohort clinical trial (CHRYSALIS, NCT02609776).

Table 1. CHRYSALIS (NCT02609776): Study Design Summary	
Study Population	• 81 adult male and female patients with metastatic or unresectable NSCLC and *EGFR* exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy were assessed for efficacy: ○ Median age: 62 years (range, 42–84 years) ○ 59% female ○ 49% Asian, 37% White, 2.5% Black ○ 74% had baseline body weight <80 kg ○ 95% had adenocarcinoma ○ 46% had received prior immunotherapy ○ Median number of prior therapies: 2 (range, 1–7) ○ 67% had ECOG performance status of 1 at baseline ○ 53% never smoked ○ All patients had metastatic disease ○ 22% had previously treated brain metastases • **Key exclusion criteria:** Patients with untreated brain metastases and patients with a history of ILD requiring treatment with prolonged steroids or other immunosuppressive agents within the past 2 years were not eligible for the study.
Interventions	Patients received amivantamab via IV infusion once weekly for Cycle 1 and every 2 weeks thereafter at one of two doses, based on weight: • 1050 mg (for patients weighing <80 kg), or • 1400 mg (for patients weighing ≥80 kg)
Endpoints	• **Primary endpoint:** ORR • **Key secondary endpoints:** CBR, DOR, PFS, and OS
Safety Results	• The safety profile was consistent with the known profiles of agents inhibiting the EGFR and MET pathways. • The most common (≥20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting, and pruritus. • The most common grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased phosphate, decreased albumin, increased glucose, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, and increased alkaline phosphatase. • TRAEs occurred in almost all patients; 16% of patients experienced TRAEs of grade 3 or greater severity, serious TRAEs were seen in 9% of patients, and 4% of patients had TRAEs that led to discontinuation.

Abbreviations: CBR, clinical benefit rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; IV, intravenous; MET, mesenchymal epithelial transition; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse effect.

Table 2. CHRYSALIS Efficacy Results	
Endpoint	**Treated With Prior Platinum-Based Chemotherapy (n = 81)**
Overall Response Rate (95% CI)	40% (29%, 51%)
Complete response (CR)	3.7%
Partial response (PR)	36%
Duration of Response (DOR)	
Median, months (95% CI), months	11.1 (6.9, NE)
Patients with DOR ≥6 months	63%

Abbreviations: CI, confidence interval; DOR, duration of response; NE, not estimable.

Safety

ADVERSE EVENTS

- The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting.
- The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyl transferase, and decreased sodium.

WARNINGS & PRECAUTIONS

- **Infusion-Related Reactions (IRR):** Can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. 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**: Can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Promptly refer patients with worsening eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue Rybrevant™ based on severity.
- **Embryo-Fetal Toxicity**: Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Amivantamab-vmjw is a bispecific antibody that binds to the extracellular domains of EGFR and MET. In in vitro and in vivo studies, amivantamab-vmjw was able to disrupt EGFR and MET signaling functions through blocking ligand binding and, in exon 20 insertion mutation models, degradation of EGFR and MET. 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.

Dose & Administration

ADULTS

- Recommended dosage is based on baseline body weight (BW) and administered as an IV infusion after dilution:
  - If BW < 80 kg – 1050mg (3 vials)
  - If BW ≥ 80 kg – 1400 kg (4 vials)
- Administer premedications as recommended.
- Administer via a peripheral line on Week 1 and Week 2.
- Administer weekly for 4 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 2 weeks thereafter.

PEDIATRICS

Safety and efficacy have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed. The pharmacokinetics of amivantamab have not been studied in patients with severe renal impairment (CrCl 15 to 29 mL/min).

HEPATIC IMPAIRMENT

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed. The pharmacokinetics of amivantamab have not been studied in patients with moderate (total bilirubin 1.5 to 3 times the upper limit of normal [ULN]) to severe (total bilirubin greater than 3 times ULN) hepatic impairment.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 350 mg/7 mL (50 mg/mL) colorless to pale yellow solution in a single-dose vial.