

Amivantamab (Rybrevant) Plus Lazertinib (Lazcluze)

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1. WHO IS THIS DRUG APPROVED FOR?

On August 20, 2024, the FDA approved amivantamab plus lazertinib as a first-line chemotherapy-free treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations.¹ This is a category 1 recommendation for this indication in the National Comprehensive Cancer Network guidelines.²

WHAT EFFICACY DATA BACK IT UP?

This approval was based on the results of the phase 3 MARIPOSA trial (NCT04487080), which showed amivantamab and lazertinib, when compared with osimertinib for first-line treatment of patients with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations, reduced the risk of disease progression by 30% (23.7 months vs 16.6 months; HR 0.70; 95% CI, 0.58-0.85). Data showed a median duration of

response that was 9 months longer than that with osimertinib (25.8 months vs 16.7 months).³

HOW IT WORKS

Amivantamab is a bispecific antibody that blocks *EGFR* and *MET* activity, degrades *EGFR* and *MET*, and activates immune cell responses.⁴

Lazertinib is a highly selective, brain-penetrating third-generation tyrosine kinase inhibitor that specifically targets *EGFR*.⁵

HOW IT'S ADMINISTERED

Amivantamab is administered intravenously. Careful attention must be paid to the rate of infusion, which is gradually increased over the first 4 weeks of treatment and varies based on the dose.⁶

Amivantamab has a high incidence of infusion-related reaction (IRR) during the first infusion and therefore should be given via peripheral line on week 1 and week 2. Central line may be used for administration of all subsequent doses.⁶ We recommend patients be seated near the nurses' station during week 1 and that the

treating nurse be aware of the high likelihood of IRR. In addition, the nurse should have emergency medications ready and have access to the patient's provider in case of reaction.

Premedication with antihistamines and antipyretics is required for all doses. Administer additional premedication with glucocorticoid on day 1 and 2 of week 1. Subsequent premedication with glucocorticoid is optional if there was no IRR during the prior administration.⁶

After prolonged dose interruption, include glucocorticoid premedication upon reinitiation.⁶

Lazertinib is an oral tablet and should not be crushed, split, or chewed. Strong and moderate CYP3A4 inducers should be avoided with this drug.⁶

THE RECOMMENDED DOSE

The dose of amivantamab is based on patient weight:

Less than 80 kg: 1050 mg
More than 80 kg: 1400 mg

- **Week 1:** initial dose of amivantamab split between days 1 and 2
- **Weeks 2 to 5:** 1 infusion weekly
- **Week 6:** no dose
- **Week 7 and beyond:** infusion every 2 weeks until unacceptable toxicity or disease progression²

The recommended dosage of lazertinib is 240 mg by mouth once daily with or without food. It should be administered in combination with amivantamab. Lazertinib should be taken prior to amivantamab when given on the same day.²

HOW TO MANAGE ASSOCIATED ADVERSE EVENTS (AES)

Serious AEs were reported in 49% of patients in the MARIPOSA trial. Proactive supportive care is critical to reduce the risk and severity of some AEs. Close monitoring and accurate Common Terminology Criteria for Adverse Events (CTCAE) grading of symptoms is essential to properly manage AEs. Refer to the package insert for detailed management guidelines.

- **IRR:** Sixty-three percent of patients in the MARIPOSA trial experienced IRR during their first infusion. IRR rarely occurs during subsequent infusions. The median onset to IRR was 1 hour.⁶ Infusion should be interrupted if IRR is suspected. Give supportive medication, resume at reduced infusion rate or discontinue for the day, and/or permanently discontinue based on severity of the reaction. If IRR occurs, corticosteroid premedication should be administered with the next amivantamab administration.⁷ Cardiopulmonary resuscitation medication and equipment should be available during treatment.
- **Venous thrombus embolism (VTE):** Prophylactic anticoagulant is required for the first 4 months of treatment and may be continued per provider discretion. Vitamin K antagonists are not recommended.⁵



■ **Dermatologic**

reactions: Eighty-six percent of patients experienced dermatologic AEs with a median onset of 14 days. Skin and nail AEs occurred most frequently in the first 4 months and declined over the next 4 months.⁸ We have found this to be one of the most challenging AEs for patients and one of the most difficult to manage. Proactive skin care includes twice-daily application of both 1% hydrocortisone cream and alcohol-free emollients, regular use of sunscreen, and gentle skin care. Oral antibiotics (minocycline or doxycycline) are recommended for at least the first 6 weeks of treatment. Prophylactic antibiotics have been shown to reduce the risk of grade 2 to 4 rash by 64% and all grades of rash by 46%.⁷ Patients may benefit from starting the recommended skin care regimen 2 weeks prior to starting therapy.⁹

Dermatologic AE management consists of a combination of supportive care, dose modifications/discontinuation, oral steroids, and dermatology referral depending on severity based on CTCAE grade. Supportive care in the form of topical steroids and topical and/or oral antibiotics should be initiated for any skin reactions.⁷ We advise early intervention and early dermatology referral.

■ **Paronychia:** Prophylactic antibiotics have been shown to reduce the risk of paronychia by 39%.⁷ Patients should avoid irritants to the nails, wear gloves and comfortable shoes, and apply thick emollients or ointments to the nails twice daily.¹⁰ Start antimicrobial topicals and nail soaks for any sign of paronychia. Withhold, reduce the dose, or permanently discontinue amivantamab and/or lazertinib based on severity.¹⁰

■ **Ocular toxicity:**

Monitor for ocular toxicity, including keratitis. Any patient with new eye

Advice for Nurses

This drug combination has a wide range of toxicities requiring careful monitoring. Proactive skin care and minimizing exposure to sun should be emphasized. Providers should pay particular attention to the psychological effects of skin toxicity and provide resources and reassurance as needed.

symptoms should be referred promptly to an ophthalmologist. Withhold, reduce the dose, or permanently discontinue amivantamab based on severity.⁷

■ **Interstitial lung disease (ILD)/pneumonitis:** Withhold both amivantamab and lazertinib if suspected. If confirmed, permanently discontinue both drugs.⁵

WHAT TO INFORM PATIENTS ABOUT TO START TREATMENT

Prophylactic measures are critical to mitigate the incidence and severity of AEs. It is important that patients understand the symptoms of IRR prior to starting therapy and when to report symptoms to their infusion therapy nurse.

Patients should avoid sun exposure and use sunscreen during treatment and for 2 months after discontinuation.

Patients should also be informed about the symptoms of VTE and ILD and be encouraged to promptly report any concerning signs.

Amivantamab and lazertinib can cause fetal harm. Both male and female patients of childbearing age should use effective contraception while receiving treatment and for 3 months after stopping amivantamab, as well as for 3 weeks after the last dose of lazertinib.⁵ ●

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