Amivantamab-vmjw (RYBREVANT)
National Drug Monograph
March 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Amivantamab-vmjw is a bispecific human G1 monoclonal antibody that binds to the extracellular domains of both EGFR and MET. While classical EGFR mutations are sensitive to 1st and 2nd generation EGFR tyrosine kinase inhibitors (TKIs), mutations resulting in a exon 20 insertion are associated with de novo resistance to currently available EGFR TKIs.

Indication(s) Under Review in This Document

- Adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

Dosage Form(s) Under Review

- Injection, 350 mg/7mL solution in a single-dose vial

Clinical Evidence Summary

Efficacy Considerations

- Approval was based on the results of the phase 1, open-label, dose-escalation and dose expansion trial that included patient with an EGFR exon 20 insertion mutation and NSCLC.
- The current results are for amivantamab monotherapy following platinum-based chemotherapy for NSCLC in patients with an EGFR exon20 insertion mutation.
- Primary outcomes: safety and objective response by investigator or BICR
- Efficacy data are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Study Design	ECOG PS	Treatment	Results
Park, et al. CHRYSALIS-1[1]	Exclusion • Untreated brain metastases (treated, stable, asymptomatic for 2 weeks and off/low	0-1	Amivantamab <80kg: 1050mg ≥80kg: 1400 mg	N=114 Safety population N=81 Efficacy population (≥3 disease assessments at cut-off) ORR 40% (95%CI 29-51) CR 4%

	dose glucocorticoids allowed) • History of clinically significant cardiovascular disease • Pregnant/breast feeding/planning pregnancy • Positive Hep BSAg, Positive HepC antibody, HIV positive • Clinically active liver disease • Interstitial lung disease Inclusion • Metastatic/unresectable NSCLC • Progression on platinum-based chemotherapy • EGFR exon 20 insertion mutation		weekly x 4 doses then every 2 weeks	PR 36% SD 48% PD 10% PFS 8.3 months (95%CI 6.5-10.9) OS 22.8 months (95%CI 14.6-not reached)

ORR=overall response rate; CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease

- Patients
    - Median age: 62
    - Male: 41%
    - Asian (49%); White (37%); Black (2%)
    - ECOG 0 (31%); ECOG 1 (67%)
    - Non-smoker 53%
    - Brain metastases 22%
- Intervention
    - Mean half-life 11.3 days
    - Recommended phase 2 dose of 1050mg saturated circulating EGFR and MET targets
    - Two-tiered weight-based dosing reduced pharmacokinetic variability and exposure differences
- Outcomes
    - Median Duration of Response (DOR): 11.1 months (95%CI 6.9-not reached)
    - Forest plot showed point estimates for ORR for all subgroups hovered around the median of 40%
- Limits: phase 1/2, nonrandomized, no comparator, immature survival data

Safety Considerations

Safety Results from Clinical Trials:

- AEs associated with EGFR inhibition: rash, paronychia, stomatitis, pruritus, diarrhea
- AEs associated with MET inhibition: peripheral edema, hypoalbuminemia
- Infusion-related reactions were most common during week 1 day 1 and 2 and rarely recurred with subsequent doses

Table 2: Safety results from CHRYSALIS clinical trial

Study	Results
	Any AE: 99% **Grade 3-4:** 35% **TRAEs ≥Grade 3:** 16% **Serious adverse events:** 30% **AEs leading to discontinuation:** 10% **AEs leading to dose interruption/modification:** 48% **Deaths due to AE:** 7%

TRAEs=treatment-related adverse events

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings / precautions**:
    - **Infusion-related reactions**: premedicate with antipyretic, antihistamine, and glucocorticoid. Incidence lessons over time.
    - **Interstitial Lung Disease/Pneumonitis**: 3.3%; Grade 3- 0.7%
    - **Dermatologic Adverse Reactions**: rash/pruritis/dry skin in 74%; Grade 3 rash – 3.3%; recommend avoiding sun exposure for 2 months, protective clothing, UVA/UVB sunscreen daily.
    - **Ocular toxicity**: keratitis (0.7%), uveitis (0.3%), dry eye, conjunctival redness, blurred vision, visual impairment. Primarily Grades 1-2.
    - **Embryo-fetal toxicity**
- **Adverse reactions**
    - **Common:** rash, infusion reactions, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, vomiting.
    - **Serious Adverse events:** 30%: pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, muscular weakness
    - **Deaths:** n=2 (pneumonia); n=1 (sudden death)
    - **Discontinuation:** 11% (pneumonia, infusion reactions, pneumonitis/ILD, dyspnea, pleural effusion, rash

Other Considerations

- **Geriatric Use**: No important differences in efficacy or toxicity between those ≥65 years old and younger patients
- **Dosing**: Under 80kg=1050 mg (3 vials); ≥80kg=1400 mg (4 vials)
    - **Dose Interval**: Weekly x 4 weeks (split Week 1 into 2 doses- Day 1 and 2) then every 2 weeks
- **Infusion schedule**

1050 mg Dose

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	
Week 3	1050 mg	125 mL/hr	
Week 4	1050 mg	125 mL/hr	
Subsequent weeks*	1050 mg	125 mL/hr	

1400 mg Dose

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	
Week 4	1400 mg	125 mL/hr	
Subsequent weeks*	1400 mg	125 mL/hr	

- **Pre-medications**:
    - **Acetaminophen**: 650 mg or 1000mg prior to each dose
    - **Diphenhydramine**: 25-50mg IV or oral prior to each dose
    - **Dexamethasone 10mg or Methylprednisolone 40mg**: required for initial dose (week 1 days 1 and 2); optional for subsequent doses

Risk-Benefit Assessment (for Oncology NMEs only)

- **Outcome in clinically significant area:** ORR, DOR
- **Effect Size:** ORR 40%;
- **Potential Harms:** Serious AES: 30%
- **Net Clinical Benefit:** Not Available

Other Therapeutic Options

Alternative treatments for EGFR Exon 20 insertion mutation NSCLC are listed in table 3 below

Table 3 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Amivantamab	TBD	• Bispecific EGF receptor and MET receptor monoclonal antibody for advanced NSCLC with EGFR Exon 20 insertion mutation with progression on or after platinum-based chemotherapy	• ORR 40% • Weekly infusion x4 then every 2 weeks • Infusion related reactions with early doses • Weight-based dosing and infusion rate schedule; shortest infusion time 2 hours
Mobocertinib	TBD	• A kinase inhibitor for advanced NSCLC with EGFR Exon 20 insertion mutation with progression on or after platinum-based chemotherapy	• ORR 28% • Boxed Warning: QTc prolongation/Torsade de Pointes • DDIs with CYP3A4 Inhibitors and Inducers • Typical EGFR inhibition adverse events
Docetaxel	F	• Advanced NSCLC after platinum failure	• Second-line use not specific to EGFR Exon 20 insertion mutation • 2 trials with endpoint of overall survival; one trial showed a OS benefit over best supportive care; the other trial did not show a OS benefit over investigator's choice of chemotherapy but did find a 1 year OS benefit

Projected Place in Therapy

- EGFR mutations represent a subset of non-small cell lung cancers. While more common mutations in exon 19 and exon 21 L858R point mutations are sensitive to tyrosine kinase inhibitors (TKIs), the less common EGFR exon 20 insertion mutations are not typically sensitive to inhibition with TKIs. Cancers with exon 20 insertion mutation are more common in never-smokers and Asian ancestry, similar to the more common EGFR mutations. In patients with the exon 20 insertion mutation, overall survival is shorter than with the more common EGFR mutations.[2]
- Some studies have found that an acquired resistance mechanism leading to failure of EGFR TKIs is MET gene amplification. MET gene amplification leads to EGFR-independent phosphorylation of EGFR, necessitating the simultaneous inhibition of EGFR and MET to overcome the MET amplification induced EGFR resistance.[3,4]
- In NCCN and UpToDate, for patients with EGFR exon 20 insertion mutation positive NSCLC who progressed on standard first-line therapy, the 2 choices for 2nd-line therapy are amivantamab or mobocertinib.
- Amivantamab is a choice for the second-line treatment of NSCLC following progression on first-line chemotherapy in patients whose tumor harbors an exon 20 insertion mutation. Considerations for choosing this therapy include the need for premedication for early infusions, the infusion times (especially early in therapy), the frequency of infusion and exposure to the medical center, weight-based dosing which may increase the risk for dose errors, and the need for dose interruption or modification due to adverse events.
- Approval was based on overall response rate and duration of response; overall survival outcomes are still pending. Some of the patient population in the clinical trial were similar to the VA population, but there were more females and individuals of Asian ancestry than is typically seen in the VA.
- In the VA, for patients with NSCLC with an EFGR exon 20 insertion mutation who progress on first-line chemotherapy, amivantamab or mobocertinib should be the choices for second-line therapy. The only other alternative, docetaxel, has not been studied specifically in patients with this mutation and is best utilized following progression on one of these two agents.

References

[1] Park K, Haura EB, Leighl NB, Mitchell P, et al. Amivantamab in EGFR Exon 20 insertion-mutated non-small cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS Phase 1 study. J Clin Oncol 2021; 39:3391-3402.
[2] Oxnard GR, Lo P, Nishino M, Dahlberg S, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. J Thorac Oncol 2013; 8:179-184.
[3] Zhang Z, Yang S, Wang Q. Impact of MET alterations on targeted therapy with EGFR-tyrosine kinase inhibitors for EGFR mutant lung cancer. Biomarker Research 2019; 7: doi.org/10.1186/s40364-019-0179-6.
[4] Neijssen J, Cardoso RMF, Chevalier KM, Wiegman L, et al. Discovery of amivantamab (JNJ-61186372) , a bispecific antibody targeting EGFR and MET. J Biol Chem 2019; 296; 10064.

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Appendix A. Acquisition Prices and Cost Considerations

Refer to VA pricing sources for updated information