Talquetamab-tgvs (TALVEY) in Multiple Myeloma
National Drug Mini-Monograph
June 2024
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee 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 / MOA**	Bispecific G protein-coupled receptor, family C, group 5, member D (GPRC5D) directed, CD3 T-cell engager
	Indication Under Review[1]	Accelerated approval for adults with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy (LOT) including a proteasome inhibitor, an immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody; continued approval contingent upon clinical benefit verified in a confirmatory trial
	Dosage Regimen	D1: SU1: 0.01mg/kg SQ D4: SU2: 0.06mg/kg SQ D7: 0.4mg/kg, first full dose, then weekly Alternate schedule: D1: SU1: 0.01mg/kg SQ D4: SU2: 0.06mg/kg SQ D7: SU3: 0.4mg/kg SQ D10: 0.8mg/kg SQ, first full dose, every 2 wks
	Dosage Forms Under Review	Injectable for subcutaneous administration

EFFICACY CONSIDERATIONS	**Trial**	**MonumenTAL-1**
	Design	Phase 1/2, single-arm, open-label, multicenter study
	Population	Relapsed or refractory multiple myeloma who received ≥ 3 prior systemic therapies, including a PI, IMiD and anti-CD38 MAb; ECOG PS 0-2; Exclusions: CVA or seizure in prior 6 months, CNS or meningeal involvement, active or history of autoimmune disease (except vitiligo, resolved childhood atopic dermatitis, resolved Graves Disease)
	Demographics	N=187 mAge 67 yrs; male 57%; white 90%; black 5%, Asian 3%, Hispanic 8% Rec'd median 5 LOT (range 4-13); auto HSCT 78% Stage I 44%, Stage II 34%, Stage III 22%; high-risk cytogenetics 29%; extramedullary plasmacytoma 22%
	Intervention	Talquetamab D1: Step Up (SU) dose 1: 0.01mg/kg SQ, D4: SU2: 0.06mg/kg SQ, D7: 0.4mg/kg, first full dose, then weekly (N=100) OR Talquetamab D1: SU1: 0.01mg/kg SQ, D4: SU2: 0.06mg/kg SQ, D7: SU3: 0.4mg/kg SQ, D10: 0.8mg/kg SQ, first full dose, then every 2 wks (N=87)
	Comparator	N/A
	Results	**Weekly regimen.** ORR 73%: sCR 26/CR 9/VGPR 22 /PR 16%; mDOR 9.5 mos mTime To Response (mTTR) 1.2 (range 0.2-10.9) months N=32 rec'd T-cell redirection therapy (81% CAR T-cell; 25% bispecific MAb): At median follow-up 10.4 months, ORR 72% (95% CI 53-86%), 59% responded ≥ 9 months **Biweekly regimen.** ORR 73.6%: sCR 20/CR 13/VGPR 25 /16%; mDOR 13 mos mTTR 1.3 (range 0.2-9.2) months

SAFETY	**Boxed Warnings**	CRS and Neurotoxicity including ICANS **CRS 76%** (gr 3: 1.5%); recurrent CRS 30% **Neurotoxicity 55%** (gr 3-4: 6%), **ICANS 9%**

Contraindications	None
Other Warnings	Oral toxicity and weight loss, infection, cytopenia, skin toxicity, hepatotoxicity, embryo-fetal toxicity **Oral toxicity in 80%** in MonumenTAL-1 (gr 3: 2.1%); median onset 15 days; median time-to-resolution to baseline 43 days (range 1-530); toxicity did not resolve in 65% **Weight loss in 62%,** regardless of oral toxicity; (gr 2: 29%, gr 3: 2.7%); median onset 67 days (range 6-407); median time-to-resolution to baseline 50 days; toxicity did not resolve in 57% **Skin toxicity in 62%** (gr 3: 0.3%); median onset 25 days; median time-to-improvement 33 days **Serious infections in 16%** (gr 3-4: 17%, gr 5: 1.5%) **Cytopenias**. Neutropenia (gr 3-4: 35%); Thrombocytopenia (gr 3-4: 22%) **Hepatotoxicity**. Elevated ALT 33% (gr 3-4: 2.7%), elevated AST 31% (gr 3-4: 3.3%) **Embryo**-Fetal Toxicity. May cause fetal harm. Advise effective contraception during and 3 mos post-dose
Top ARs	**≥ 20%:** pyrexia, CRS, dysgeusia, nail disorder, MS pain, skin disorder, rash, fatigue, decr weight, dry mouth, xerosis, dysphagia, URTI, diarrhea, hypotension, headache **≥ gr 3-4 laboratory abnormalities (≥ 30%):** decreased lymphocyte count, neutrophils, WBCs, hemoglobin **SARs in 47%:** CRS 13%, infection 12.8%, pyrexia 4.7%, ICANS 3.8%, neutropenia 2.1% **Fatal ARs in 3.2%:** COVID, dyspnea, health deterioration, infection, basilar artery occlusion, PE **DC due to AR** in 9% **Dose-interruptions** in 56%, including fever 15%, CRS 12%, infection 25%, neutropenia 6%, rash 6%
Drug Interactions	Talquetamab may increase exposure of CYP substrates (risk C: monitor) Avoid denosumab as immunosuppressive effect may be enhanced (Risk D: modify therapy)

	DRUG	VANF	CFU	FDA	GUIDELINES , ORR, AE Profile
PLACE IN THERAPY	Elranatamab ELREXFIO BCMA-directed, CD3 T-cell engager	TBD		RRMM s/p > 4 LOT	**VA Multiple Myeloma pathway**: n/a **NCCN:** One of the preferred BsAbs s/p > 4 LOT (cat 2A) ORR (no prior BCMA): 61%, (prior BCMA): 33% SubQ dosing; hospitalization recommended x2 Boxed warnings: CRS, Neuro tox including ICANS REMS program CRS 58% (all gr 1-2); recurrent 13% ICANS 3.4% (all gr 1-2) Neurotox 59% (gr 3-4: 7%)
	Teclistamab TECVAYLI BCMA-directed, CD3 T-cell engager	PA-F	Yes	RRMM s/p > 4 LOT	**VA Multiple Myeloma pathway**: RRMM s/p ≥ 4 LOT **NCCN**: A preferred BsAbs s/p > 4 LOT (cat 2A) ORR: 63%, 39% ≥ CR; mDOR 18.4 mos SubQ dosing; hospitalization recommended x3 Boxed warnings: CRS, ICANS REMS program CRS 72% (gr 3-4: 0.6%); recurrent 33% ICANS 6% Neurotox 57% (gr 3-4: 2.4%)
	Talquetamab TALVEY GPRC5D-directed, CD3 T-cell engager	TBD		RRMM s/p > 4 LOT	**VA Multiple Myeloma pathway**: n/a **NCCN**: A preferred BsAbs s/p > 4 LOT (cat 2A) ORR (no prior BCMA): 73%; 35% ≥ CR; mDOR 9-13 mos ORR (N=32, prior BCMA): 72% (95% CI, 53-86%) SubQ dosing; hospitalization recommended x2 Boxed warnings: CRS, ICANS REMS program CRS 76% (gr 3-4: 2%); recurrent 30% ICANS 9% Neurotox 46% (gr 3-4: 6%) Other: oral toxicity 80% (gr 3-4: 6%); wgt loss 62%; skin toxicity 62%

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VHA PLACE IN THERAPY	**Potential Use in VHA**
	• Talquetamab is a first-in-class, off-the-shelf bispecific antibody directed against GPRC5D.
	  • Bispecific antibody therapies provide an option to patients with limited access (due to specialized centers and/or manufacturing issues) to CAR T-cell therapy
	  • Due to their quick time to response, may also be used as bridging therapy to CAR T-cell therapy
	  • Reported responses to anti-B-cell maturation antigen (BCMA) CAR T-cell therapies range from 81-97%[8, 9] yet relapses still occur and treatment options are limited.
	• GPRC5D-targeted therapy provides another mechanism for heavily pretreated patients due to its high expression in myeloma cells, limited expression in normal tissue and activity post-anti-BCMA-directed therapy.
	• Due to the high risk of oral toxicity and weight loss with talquetamab, would caution use in patients with poor nutritional intake and/or those with BMI < 18 (underweight range) and consult with nutrition services.

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Contact person: Berni Heron, Pharm.D., BCOP, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)

References

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