Epcoritamab-bysp (EPKINLY)
National Drug Monograph
November 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. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION

Description / MOA	Bispecific CD20-directed CD3 T-cell engager	
Indications Under Review[1]	1. Relapsed or refractory diffuse large b-cell lymphoma (DLBCL) including DLBCL arising from indolent lymphoma and high-grade b-cell lymphoma (HGBCL) after > 2 prior lines of therapy (LOT) 2. Relapsed or refractory follicular lymphoma (FL) after > 2 prior LOT	
Dosage Regimens	DLBCL and HGBCL D1: epcoritamab Step-Up (SU)1 0.16mg SQ D8: SU2 0.8mg SQ D15: 48mg SQ, first full dose [in hospital] D22: 48mg SQ C2, 3: D1, 8, 15, 22: 48mg SQ C4 – 9: D1 and 15: 48mg SQ C10 +: D1: 48mg SQ Each cycle = 28 days	FL D1: epcoritamab Step-Up (SU)1 0.16mg SQ D8: SU2 0.8mg SQ D15: SU3 3mg SQ D22: first full 48mg C2, 3: D1, 8, 15, 22: 48mg SQ C4 – 9: D1 and 15: 48mg SQ C10 +: D1: 48mg SQ Each cycle = 28 days
Dosage Forms Under Review	Injection: 4mg/0.8ml in SDV Injection: 48mg/0.8ml in SDV	

EFFICACY CONSIDERATIONS

Trial	**EPCORE NHL-1 (NCT03625037)**
Design	Open-label, multicenter, multi-cohort, single-arm *R/R DLBC cohort*
Population	N=148; R/R DLBCL after ≥ 2 LOT Excluded: CNS lymphoma, allo HSCT or SOT, active infection, impaired T-cell immunity
Demographics	mAge 65 yrs (22-83), male 62%, ECOG PS 0-1 97%, ECOG PS 2 3%; White 61%, Asian 20%, NHOPI 0.7%; DLBCL NOS 86% (27% transformed; 14% high-grade); Median # LOT 3 (2-11); 2 LOT 30%; 3 LOT 30%; ≥4 LOT 40%; ASCT 18%; CAR T-cell therapy 39%
Intervention	D1: epcoritamab SU1 0.16mg SQ D8: SU2 0.8mg SQ D15: 48mg SQ, first full dose D22: 48mg SQ C#2, 3: D1, 8, 15, 22: 48mg SQ C#4 – 9: D1 and 15: 48mg SQ C#10 +: D1: 48mg SQ Each cycle = 28 days; Continued until progressive disease or toxicity
Comparator	n/a
Results	ORR 61% (95% CI 52.5-68.7) [CR 38%; PR 23%] mDoR 15.6 mos (range 9.7 – NR) 9-mos estimate 63%

	Notes	**NCCN guidelines DLBCL v3.2024:** 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy • BiTE (epcoritamab, glofitamab) **VA Oncology Clinical Pathway**: Not included **Alternative options**: Refer to **Appendix A.**	
	Trial	**EPCORE NHL-1 (NCT03625037)**	**EPCORE NHL-1 (NCT03625037)**
	Design	Open-label, multi-cohort, single-arm *FL Pivotal cohort*	Open-label, multi-cohort, single-arm *FL C#1 dose-optimization cohort*
	Population	N=128; CD20+ R/R FL grade 1-3A after ≥ 2 LOT (including anti-CD20 mab and alkylator or lenalidomide), ECOG PS 0-2 Excluded: CNS lymphoma, HIV infection, CV disease, active infection, autoimmune disease	N=86 patients;
	Demographics	mAge 65 yrs (55-72); male 62%; ECOG PS 0-1-2 (55-40-5%); FLIPI 3-5 61%; s/p 2LOT 37%; 3LOT 32%; 4+ LOT 31%; primary refractory 54%; double refractory (to alkylator & anti-CD20 mab) 70%	mAge 64 yrs, 57% male
	Intervention	FL pivotal cohort: D1: SU1 0.16mg SQ D8: SU2 0.8mg SQ D15: first full dose 48mg [in hospital] D22: 48mg SQ C#2, 3: D1, 8, 15, 22: 48mg SQ C#4 – 9: D1 and 15: 48mg SQ C#10 +: D1: 48mg SQ Each cycle = 28 days Continue until progressive disease or toxicity	C#1 dose-optimization: D1: SU1 0.16mg SQ D8: SU2 0.8mg SQ D15: SU3 3mg SQ D22: first full 48mg C#2, 3: same C#4-9: same C#10+ same Each cycle = 28 days Continue until progressive disease or toxicity
	Comparator	n/a	n/a
	Results	FL pivotal cohort dates (6/2020-4/2023) • At median follow-up 17.4 months ORR 82% (95% CI 74.3-88.3) CR 62.5% (95% CI 54-71) • Median 8 cycles received (IQR 4-16) • Benefit noted in all high risk subgroups; reduced ORR in those with 4+ LOT (68%; 95% CI 51-81) • CRS 65% (2% gr 3); ICANS 6% (4% gr 1, 2% gr 2)	C1 optimization cohort dates (10/2022-1/2024) • Key endpoints: rate of CRS (> gr 2) and ORR • At median follow-up 5.7 months ORR 86% (95% CI 76.9-92.6) CR 64% (95% CI, 52.9-74) • CRS rate 49% (40% gr 1 and 9% gr 2); CRS after first full dose in 37%; Median onset 60.7 hours (36.6-84.3) • No ICANS reported
	Notes	**NCCN guidelines FL v3.2024:** 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy (CD19-directed) • BiTE (**epcoritamab**, mosunetuzumab) **VA Oncology Clinical Pathway**: Not included **Alternative options:** Refer to **Appendix A**.	

SAFETY CONSIDERATIONS		
	Boxed Warnings	Cytokine Release Syndrome (CRS), Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
	Contraindications	None
	Other Warnings	CRS ICANS Infections Cytopenias Embryo-Fetal Toxicity
	Top 5 AEs (≥	DLBCL: CRS, fatigue, MS pain, injection site reactions, pyrexia FL: injection site reactions, CRS, COVID-19, fatigue, Upper RTI, MS pain
	Drug Interactions	

VHA PLACE IN THERAPY			
	Potential Use in VHA	Use in DLBCL 1. DLBCL is the most common subtype of non-Hodgkin lymphoma. Advanced stage disease includes stages III or IV disease. Initial chemoimmunotherapy with an antiCD-20 MAb regimen (i.e. R-CHOP or Pola-R-CHP) results in response in ~60% of patients. For those who do not respond initially (i.e. primary refractory) or have a relapse in disease, prognosis is poor. 2. Second-line options include salvage chemotherapy followed by autologous SCT (ASCT) or CAR T-cell therapy. Limitations exist to both preferred treatment modalities and can include patient age, comorbidities, baseline organ function, inadequate stem cell collections, insufficient response to salvage chemotherapy, access to CAR T-cell therapy along with its manufacturing process, to name a few. 3. EPCORE NHL-1 was a multi-cohort trial; in their R/R DLBCL population of heavily pretreated patients with a median 3 LOT; ~ 40% progressed on prior CAR T-cell therapy; ~ 20% had received prior ASCT, 27% transformed and 14% high-grade disease. The FDA granted accelerated approval to epcoritamab based on ORR 61% and median DoR of 15.6 months. 4. Epcoritamab was not compared to other therapies. Indirect comparison of 3L options in R/R DLBCL lead toward preference for bispecific T-cell engagers instead of monoclonal antibody therapies, yet logistic limitations exist with BiTE therapies. As VA facilities share expertise with establishing BiTE therapy protocols and the patient experience, anticipate utilization will increase. Use in FL 1. Follicular lymphoma is the most common indolent non-Hodgkin lymphoma with no therapy defined as the standard of care in patients with multiple relapses or refractory disease. 2. CAR T-cell therapy is preferred due to high response rates, yet limitations exist, such as patient comorbid conditions, baseline organ function, access to treatment sites and the manufacturing process, to name a few. 3. The bispecific T-cell engagers are thought of as more convenient (i.e. off-the-shelf product) alternative to CAR T-cell therapy, yet they are not without limitations. As VA facilities share expertise with establishing BiTE therapy protocols and the patient experience, anticipate utilization will increase. 4. Epcoritamab and mosunetuzumab are BiTE therapies studied in the R/R FL setting. They have not been compared to other therapies. Indirectly, both appear to be effective with response rates in the 80-82% range with 60-63% achieving CR. They vary by dosing route (SubQ vs. IV), schedule (q21 vs. q28-day cycle), duration of therapy (indefinite vs. fixed-duration), toxicity profile and drug cost.	1.

Prepared October 2024.
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References

1 EPKINLY (epcoritamab-bysp) for subcutaneous injection [prescribing information online]. Plainsboro, NJ: Genmab; June 2024. Available at: label (fda.gov). Accessed 9/2024.
2 Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell engaging antibody in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II trial. J Clin Oncol 2022; 41: 2238-2247
3 Linton KM, Vitolo U, Jurczak W, etal. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EP CORE NHL-1): a phase 2 cohort of a single-arm, multicenter study. Lancet Haematol 2024; DOI: 10.1016/S2352-3026(24)00166-2
4 Thieblemont C, Karimi YH, Ghesquieres H, et al. Epcoritamab in relapsed/refractory large B-cell lymphoma: 2-year follow up from the pivotal EPCORE NHL-1 trial. Leukemia 2024; DOI: 10.1038/s41375-024-02410-8

Appendix A. BiTE alternatives for R/R DLBCL and FL

	Mosunetuzumab LUNSUMIO CD20-directed CD3 T-cell engager Genentech, Inc.	Epcoritamab EPKINLY CD20-directed CD3 T-cell engager Genmab, Inc.	Glofitamab COLUMVI CD20-directed CD3 T-cell engager Genentech, Inc.
FDA approval	12/2022 Accelerated approval based on response rate.	• 5/2023 R/R DLBCL • 6/2024 FL Accelerated approval based on RR and durability of response	6/2023 Accelerated approval based on RR and durability of response
Indication	R/R follicular lymphoma (FL) after ≥ 2 prior LOT	r/r DLBCL and high-grade B-cell lymphoma, not otherwise specified, including DLBCL s/p ≥ 2 prior LOT r/r FL after ≥ 2 prior LOT	r/r DLBCL, not otherwise specified or large B-cell lymphoma arising from follicular lymphoma, after s/p ≥ 2 prior LOT
Recommended hospitalization?	None	DLBCL: for 24 hrs after C#1, day 15 dose None for FL	24 hrs after step up #1 and step up #2, if CRS in C#1; if CRS ≥ Gr 2 with infusion, hospitalize during and for 24 hrs after completion of subsequent infusion
Boxed warning(s)	CRS	CRS ICANS	CRS
REMS	No	No	No
Warnings/pre-cautions	**CRS 39%** (Gr 1-28%; Gr 2-15%, Gr 3-2%, Gr 4-0.5%); recurrent CRS 11% **Neurologic toxicity 39%** HA 21%, PN 13%, dizziness 11%, MS changes 6%, ICANS 1% (Gr 1-0.5%, Gr 2-0.5%) **Infections 17%** Upper RTI 14% (Gr 3–2.2%), UTI 10% (Gr 3-1.1%) **Cytopenias** Neutropenia 38% (Gr 4-19%), FN 2%, anemia 19%, tcp 12% (Gr 4-5%) **Tumor Flare 4%** **Embryo-fetal toxicity**	**CRS 51%** (Gr 1-37%; Gr 2-17%; Gr 3-2.5%); CRS in C1- 92%; recurrent CRS 16% **ICANS 6%** (Gr 1-4.5%; Gr 2-1.3%; Gr 5-0.6%) **Infections 15%** (Gr 3/4-14%; Gr 5-1.3%) **Cytopenias** neutropenia (Gr 3/4-32%); FN 2.5% anemia 12%; tcp 12%, **Embryo-fetal toxicity**	**CRS 70%** (Gr 1-52%; Gr 2-14%; Gr 3-2.8%; Gr 4-1.4%) **Neurologic toxicity** HA 10%, PN 8%, dizziness 7%, MS changes 4.8%; ≥ Gr 3-2.1%; ICANS 4.8% **Serious infections 16%** (Gr 3/4- 10%; Gr 5- 4.8%) **Tumor flare 12%** (Gr 2-4.8%; Gr 3- 2.8%) **Embryo-fetal toxicity**
VA Oncology Clinical Pathway	Follicular Lymphoma V1.2024 Multiply relapsed in patients who are not candidates for SCT or CAR T-cell therapy	n/a, either DLBCL or FL	VA Oncology Clinical Pathway: DLBCL, Multiply Relapsed Glofitamab + obinutuzumab recommended if ASCT and CAR T-cell therapies are not an option and having disease progression following rituximab-bendamustine-polatuzumab
NCCN Guidelines	NCCN guidelines FL v3.2024 3L and subsequent therapy Preferred regimens: • BiTE (epcoritamab, **mosunetuzumab**) • CAR T-cell therapy	NCCN guidelines DLBCL v3.2024: 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy • BiTE (**epcoritamab**, glofitamab) NCCN guidelines FL v3.2024 3L and subsequent therapy Preferred regimens: • BiTE (epcoritamab, **mosunetuzumab**) • CAR T-cell therapy	NCCN guidelines DLBCL v3.2024: 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy • BiTE (epcoritamab, **glofitamab**)