Glofitamab-gxbm (COLUMNVI)
National Drug Mini-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 (BiTE)
Indication Under Review[1]	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or large B-cell lymphoma (LBCL) arising from follicular lymphoma (FL) after ≥ 2 lines of therapy (LOT)
Dosage Regimen	Day 1 obinutuzumab 1000mg IV x1; Day 8 Step up dose 1: glofitamab 2.5mg IV x1; Day 15 Step up dose 2: glofitamab 10mg IV x1; then Day 1, Cycles #2-12: glofitamab 30mg IV x 1; Repeat every 21 days
Dosage Forms Under Review	Injection 2.5mg/2.5ml and 10mg/10ml in SDVs

EFFICACY CONSIDERATIONS

Trial	**Study NP30179 (NCT03075696)**
Design	Open-label, multicenter, single-arm trial
Population	N=132 patients Relapsed or refractory DLBCL after ≥ 2 LOT; ECOG PS 0-1; ANC ≥ 1500 cells/mcL; platelets ≥ 75,000 cells/mcL; transfusion-independent; SCr ≤ 1.5 x ULN (or CrCl ≥ 50 ml/min), transaminases ≤ 3x ULN Exclusion: active or prior CNS lymphoma, CNS disease, acute infection, recent infection requiring IV antibiotics or prior allogeneic HSCT
Demographics	mAge 67 yrs (21-90), 64% male; 77% White, 4.5%, Asian, 0.8% Black, 5% Hispanic median prior LOT 3 (2-7); 83% refractory to last therapy; 55% primary refractory disease; 30% prior CAR T-cell therapy; 19% s/p auto HSCT
Intervention	Day 1 obinutuzumab 1000mg IV x1; Day 8 Step up dose 1: glofitamab 2.5mg IV x 1; Day 15 Step up dose 2: glofitamab 10mg IV x 1; then Day 1, Cycles #2-12: glofitamab 30mg IV x 1; Repeat every 21 days to 12 cycles
Comparator	none
Results	Objective response rate (ORR) and duration of response (DOR)

Parameter per IRC	Glofitamab n=132
ORR	74 (56%); 95% CI 47-65
CR	57 (43%); 95% CI 35-53
PR	17 (13%); 95% CI 8-20
mDOR	18.4 months (95% CI 11.4-NE)

SAFETY CONSIDERATIONS

Boxed Warnings	Cytokine Release Syndrome (CRS)
Contraindications	None
Other Warnings	Neurologic Toxicity, including ICANS. Monitor for neurologic toxicity, hold or dc based on severity. Serious Infections. Can cause serious/fatal infections. Monitor signs & symptoms and treat appropriately. Tumor Flare. Can cause serious tumor flare. Monitor patients at risk. Embryo-Fetal Toxicity. May cause fetal harm. Advise patients of potential harm and to use effective contraception.
Top 5 AEs	≥ 20%: CRS, MS pain, rash, fatigue
Drug Interactions	CYP substrates may be impacted as the release of cytokines can suppress certain CYP enzymes and thus result in increased exposure to CYP substrates. This increase in exposure is likely to occur after the first dose (C#1, D8) and first 30mg dose (C#2, D1).

	Notes	**NCCN guidelines DLBCL v3.2024:** 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy • BiTE (epcoritamab, glofitamab) **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 **Alternative options:** Refer to **Appendix A.** ***Bispecific T-cell Engagers for R/R DLBCL***

VHA PLACE IN THERAPY	**Potential Use in VHA**	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. NP30179 investigated the response to glofitamab in 132 patients with R/R disease; these patients were heavily pretreated with a median 3 LOT; ~ 30% progressed on prior CAR T-cell therapy; ~ 20% had received prior ASCT and 55% had primary refractory disease. The FDA approved glofitamab based on ORR 56% and median DoR of 18 months. 4. Glofitamab was not compared to other therapies; in this heavily pre-treated population, ORR 56% led to accelerated approval from the FDA; await confirmatory trial to verify and describe clinical benefit. Indirect comparison of 3L options lead toward preference for bispecific T-cell engagers instead of monoclonal antibody therapies. 5. Logistic limitations exist with BiTE therapies. As VA facilities share expertise with establishing BiTE therapy protocols and the patient experience, anticipate utilization will increase.

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References

1 COLUMVI (glofitamab-gxbm) Injection for Infusion [prescribing information online]. San Francisco, CA: Genentech, Inc. June 2023. Available at: label (fda.gov) . Accessed September 2024.
2 Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-cell Lymphoma. N Engl J Med 2022; 387: 2220.2231.
3 National Comprehensive Cancer Network Guidelines Version 3.2024 Diffuse Large B-Cell Lymphoma b-cell.pdf (nccn.org) Accessed October, 2024.

Appendix A. Bispecific T-cell Engagers for Relapsed/Refractory Diffuse Large B-cell Lymphoma (Sept 2024) page 1

	Epcoritamab EPKINLY CD20-directed CD3 T-cell engager Genmab, Inc.	Glofitamab COLUMVI CD20-directed CD3 T-cell engager Genentech, Inc.
FDA approval	5/19/2023 Accelerated approval based on RR and durability of response	6/15/2023 Accelerated approval based on RR and durability of response
Indication	r/r DLBCL and high-grade B-cell lymphoma, not otherwise specified, including DLBCL s/p ≥ 2 lines prior systemic therapy	r/r DLBCL, not otherwise specified or large B-cell lymphoma arising from follicular lymphoma, after s/p ≥ 2 prior lines of therapy
Dosing	D1: 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 Repeat every 28 days until PD or toxicity	D1: Obinutuzumab IV x 1 D8: SU1 2.5mg IV over 4 hrs D15: SU2 10mg IV over 4 hrs C#2-12: 30mg IV over 4 hrs Repeat every 21 days x12 cycles
Recommended hospitalization?	24 hrs after C#1, day 15 dose	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 ICANS	CRS
REMS	No	No
Warnings/pre-cautions	**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**

Appendix A. Bispecific T-cell Engagers for Relapsed/Refractory Diffuse Large B-cell Lymphoma (Sept 2024) page 2

	Epcoritamab EPKINLY CD20-directed CD3 T-cell engager Genmab, Inc.	Glofitamab COLUMVI CD20-directed CD3 T-cell engager Genentech, Inc.
Clinical Trials	OL, MC single-arm trial ECOG PS 0 - 2 N=148; DLBCL, NOS 86% mAge 65 yrs; male 62%; 97% ECOG 0 or 1; 3% ECOG 2 median prior lines 3 (range 2-11) [30% rec'd 2; 30% - 3; 40% ≥ 4] 39% rec'd prior CAR-T cell therapy 18% prior auto HSCT ORR 61% (95% CI 52.5-68.7) [CR 38%; PR 23%] mDoR 15.6 mos (range 9.7 – NR) 9-mos estimate 63%	OL, MC single-arm trial ECOG PS 0 or 1 N=132; 80% de novo DLBCL 20% LBCL from FL mAge 67 yrs; male 64% median prior lines 3 (range 2-7) 30% rec'd prior CAR-T cell therapy 19% prior auto HSCT ORR 56% (95% CI 47-65) [CR 43%; PR 13%] mDoR 18.4 mos (range 11.4-NE) 9-mos estimate 68.5%
VA Oncology Clinical Pathway Recs	N/A	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 Recs	NCCN guidelines DLBCL v3.2024: 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy • BiTE (**epcoritamab**, glofitamab)	NCCN guidelines DLBCL v3.2024: 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy • BiTE (epcoritamab, **glofitamab**)

Key: SU step up, D day, C cycle, CRS Cytokine Release Syndrome, ICANS Immune Cell-Associated Neurotoxicity Syndrome