Polatuzumab vedotin-piiq (POLIVY)
National Drug Monograph
September 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	A CD79b-directed antibody and microtubule inhibitor conjugate
Indication Under Review[1]	1. in combination with a rituximab product, cyclophosphamide, doxorubicin and prednisone (R-CHP) for the treatment of previously untreated patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma (HGBL) and an International Prognostic Index score ≥ 2 2. In combination with bendamustine and a rituximab product for the treatment of relapsed or refractory DLBCL after at least 2 prior lines of therapy (LOT)
Dosage Regimen	Polatuzumab (Pola) 1.8 mg/kg every 21 days for 6 cycles
Dosage Forms Under Review	30 mg or 140 mg polatuzumab vedotin as lyophilized powder in a SDV

EFFICACY CONSIDERATIONS

Trial	**POLARIX (NCT03274492)**	**Study GO29365 (NCT02257567)**
Design	Randomized, double-blind, placebo-controlled	Open-label, single-arm, phase Ib/II
Population	N= 879; Untreated DLBCL with IPI score 2-5; ECOG performance status 0-2 Excluded: transformed lymphoma, primary mediastinal large B-cell lymphoma, known CNS lymphoma or peripheral neuropathy (grade ≥ 2)	N=80; transplant ineligible, relapsed/refractory DLBCL after ≥ 1 LOT
Demographic	mAge 65 yrs (19-80); 54% male; 54% white; 19% Asian, 1.8% Black, 6% Hispanic 38% IPI score 2; 62% IPI score 3-5; 89% stage 3 or 4 disease; 44% bulky disease; 84% DLBCL; 11% HGBL	mAge 69 yrs (30-86); 66% male; 71% white; 98% DLBCL; Ineligible for HSCT due to: age 40%, insufficient response to salvage therapy 26%; prior HSCT failure 20% Median # prior therapies: 2 (1-7)
Intervention	Polatuzumab (Pola) + Rituximab-CHP Pola 1.8mg/kg IV, Rituximab (R) 375 mg/m2 IV, cyclophosphamide 750mg/m2 IV, doxorubicin 50 mg/m2 IV on Day 1; Prednisone 100mg PO once daily Days 1-5; Repeat every 21 days for 6 cycles; R 375 mg/m2 IV on Day 1, cycles 7 and 8	Pola-Bendamustine + Rituximab (BR) R 375 mg/m2 IV on Day 1, Cycles 1-6; Pola 1.8 mg/kg IV on Day 2, Cycle 1; Bendamustine 90mg/m2 IV on Days 2 and 3, Cycle 1 and Days 1 and 2, Cycles 2-6; Repeat every 21 days for 6 cycles
Comparator	R-CHOP R 375 mg/m2 IV, cyclophosphamide 750mg/m2 IV, doxorubicin 50mg/m2 IV, vincristine 1.4 mg/m2 IV on Day 1; Prednisone 100mg PO once daily, Days 1-5; Repeat every 21 days for 6 cycles; R 375 mg/m2 IV on Day 1, cycles 7 and 8	BR R 375 mg/m2 IV on Day 1, Cycles 1-6; Bendamustine 90mg/m2 IV on Days 2 and 3, Cycle 1 and Days 1 and 2, Cycles 2-6; Repeat every 21 days for 6 cycles
Results	**Pola-R-CHP vs. R-CHOP @ 28.2 months** **Primary endpoint: PFS 77 vs. 70%** [HR 0.73 (95% CI 0.57-0.95) p=0.02] Prespecified descriptive analysis: DLBCL PFS [HR 0.75 (95% CI 0.57-0.99)] HGBL PFS [HR 0.48 (95% CI 0.21-1.08)] **OS @ 2 yrs: 88.7 vs. 88.6%** [HR 0.94 (95% CI 0.65-1.37) p=0.75] Exploratory analysis of subgroups showed the following did not show clear benefit with pola-R-CHP:	**Pola-BR vs. BR @ median 22.3 months** **Primary endpoint: CR rate 40 vs. 17.5%; p=0.026** mPFS 9.5 vs. 3.7 months [HR 0.42 (95% CI: 0.21-0.63); p<0.001] mOS 12.4 vs. 4.7 months [HR 0.42 (95% CI 0.24-0.75) p=0.002] Of those achieving CR, 64% DoR ≥ 6 months; 48% DoR ≥ 12 months

		Patients: age ≤ 60 years; with germinal-center B-cell-like subtype of DLBCL; with bulky (≥ 7cm) disease; with lower IPI score	
	Notes	• **NCCN guidelines DLBCL 2.2024 includes:** **For stage I-II (excluding stage II with extensive mesenteric disease):** RCHOP and Pola-R-CHP (smIPI > 1) **For stage II (with extensive mesenteric disease) or Stage III-IV, preferred regimens:** RCHOP and Pola-R-CHP (IPI ≥ 2) • **VA Oncology Clinical Pathways: DLBCL:** 1L Limited stage (I, II), non-bulky: R-CHOP 1L Limited stage (I, II), bulky: R-CHOP and radiation 1L Advanced stage (III, IV), IPI 0-1: R-CHOP 1L Advanced stage (III, IV), ECOG 0-2, IPI 2-5, germinal center origin: R-CHOP 1L Advanced stage (III, IV), ECOG 0-2, IPI 2-5, non-germinal center: Pola-R-CHP	• **NCCN guidelines DLBCL 2.2024 includes:** 2L Pola ± bendamustine ± rituximab • **NCCN guidelines DLBCL 2.2024** **Bridging Therapy[#] to CAR T-cell includes 6 options, all category 2A:** Pola ± rituximab ± bendamustine (only after leukapheresis, as it may impact cell collection) • **VA Oncology Clinical Pathways: DLBCL, Multiply Relapsed:** Pola-BR in patients who are not candidates for autologous SCT or CAR T-cell therapy • **Bridging Therapy recommendations are per cellular therapy team.** [#]Bridging Therapy defined as anticancer therapy given to patients during the CAR T-cell manufacture period.

SAFETY CONSIDERATIONS

Boxed Warnings	None
Contraindications	None
Other Warnings	Peripheral neuropathy (PN). In POLARIX, 53% reported new or worsening PN; onset 2.3 months; In Study GO29365, 40% reported new or worsening PN; onset 2.1 months Infusion-related reactions. Administer antihistamine and antipyretic prior to administration; monitor Myelosuppression. In POLARIX, 90% received primary prophylaxis with G-CSF. Prophylactic G-CSF should be used for neutropenia due to Pola-R-CHP; In Study G029365, 42% received primary prophylaxis; consider G-CSF for Pola-BR as well. Serious and opportunistic infections. Administer prophylaxis for *Pneumocystis jiroveci* pneumonia and herpesvirus. Progressive multifocal leukoencephalopathy. Reported after Pola-BR. Monitor for new or worsening neurologic, cognitive symptoms or behavioral changes. Tumor lysis syndrome. Those with high tumor burden may be at increased risk. Monitor closely and provide tumor lysis prophylaxis to those at risk. Hepatotoxicity. Serious cases have been reported. Those with pre-existing liver disease, elevated baseline liver enzymes and concomitant medications may increase risk. Monitor LFTs and bilirubin. Embryo-fetal toxicity. Can cause fetal harm in a pregnant woman. Advise effective contraception.
Top 5 AEs	(≥ 20%) with Pola-R-CHP: PN, nausea, fatigue, diarrhea, constipation, alopecia, mucositis, neutropenia (≥ 20%) with Pola-BR: neutropenia, thrombocytopenia, anemia, PN, fatigue, diarrhea, pyrexia
Drug Interactions	Concomitant use with strong CYP3A4 inhibitors may increase Pola AUC and toxicity Concomitant use with strong CYP3A4 inducers may decrease Pola AUC and efficacy

VHA PLACE IN THERAPY		
	Potential Use in VHA	1. R-CHOP has been a standard therapy for DLBCL for many years; it is estimated that ~ 60% of patients will respond to R-CHOP, yet 40% may have refractory disease or relapse post-therapy. 2. The addition of polatuzumab to R-CHOP (minus vincristine due to overlapping neurologic toxicity) was compared to R-CHOP in the untreated DLBCL population. PFS was improved with addition of polatuzumab, yet OS at 2 years was not. Patients possessing certain characteristics (i.e. age < 60 years; with germinal-center B-cell-like subtype of DLBCL; with bulky (> 7cm) disease; with lower IPI score) did not demonstrate benefit with polatuzumab. 3. In the relapsed or refractory DLBCL setting, polatuzumab was studied in combination with bendamustine and rituximab in a single-arm design trial in a population of patients that were ineligible for transplantation. Benefits in CR rate, PFS and OS were noted in this heavily pretreated population (median 2 LOT). 4. Due to the CR benefit, polatuzumab may serve as an effective bridging therapy option for patients planning to undergo CAR T-cell therapy.[4]

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References

1 POLIVY (polatuzumab vedotin) South San Francisco, CA: Genentech. April 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761121s008lbl.pdf

2 Tilly H, Morschhauser F, Sehn L, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med 2022; 386: 351-363.

3 Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020; 38: 155-165.

4 Roddie C, Neill L, Osborne W, et al. Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma. Blood Advances 2023; 7: 2872-2882.

Appendix A. Antibody-Based Therapies for Relapsed/Refractory Diffuse Large B-cell Lymphoma (Sept 2024) page 1

	Tafasitamab-cxix MONJUVI CD19-directed Monoclonal antibody	Polatuzumab-vedotin antiCD79b antibody and microtubule inhibitor conjugate	Loncastuximab CD19-directed antibody drug conjugate
FDA approval	7/31/2020 Accelerated approval based on ORR	6/10/2019	4/23/2021 Accelerated approval based on ORR
Indication	In combination with lenalidomide for treatment of R/R DLBCL who are not eligible for autologous stem cell transplant (ASCT)*	In combination with bendamustine and rituximab for the treatment of R/R DLBCL after at least 2 prior lines of therapy (LOT)	R/R DLBCL after > 2 LOT; including DLBLC from low-grade lymphoma and high-grade B-cell lymphoma
Dosing	Tafasitamab 12 mg/kg IV given on a 28-day cycle: Cycle 1: days 1, 4, 8, 15, 22 Cycles 2, 3: days 1, 8, 15, 22 Cycles 4 +: days 1, 15 Lenalidomide 25 mg PO daily days 1 to 21 to max 12 cycles Repeat cycles every 28-days	Pola-Bendamustine + Rituximab (BR) R 375 mg/m2 IV on Day 1, Cycles 1-6; Pola 1.8 mg/kg IV on Day 2, Cycle 1; Bendamustine 90mg/m2 IV, Days 2, 3; Cycle 1 Days 1, 2; Cycles 2-6; Repeat every 21 days for 6 cycles	Loncastuximab IV on day 1 of 21-d cycle: Cycles 1, 2: 0.15mg/kg Cycles 3+: 0.075mg/kg
Recommended hospitalization?	n/a	n/a	n/a
Boxed warning(s)	none	None	none
REMS	none	None	none
Warnings/precautions	**Infusion-related reactions 6%** 80% during cycles 1 or 2 **Myelosuppression** Neutropenia Gr 3-25%; Gr 4-25% Thrombocytopenia Gr 3-12%; Gr 4-6% Anemia Gr 3-7% **Infections** 73% developed an infection; RTI 24%, UTI 17%, bronchitis 16% PNA Gr 3-7% **Embryo-fetal toxicity**	**Peripheral neuropathy (PN)** **Infusion-related reactions** **Myelosuppression** **Serious and opportunistic infections** **Progressive multifocal leukoencephalopathy (PML)** **Tumor lysis syndrome** **Hepatotoxicity** **Embryo-fetal toxicity**	**Effusion and edema** Gr 3-3% edema; Gr 3-3% Pleural effusion **Myelosuppression** Gr 3/4-32% neutropenia; 20% tcp; 12% anemia; FN 3% **Infections** ≥ Gr 3 – 10% sepsis, pna **Cutaneous Reactions** Gr 3 – 4%, incl photosensitivity **Embryo-Fetal Toxicity**

Appendix A. Antibody-Based Therapies for Relapsed/Refractory Diffuse Large B-cell Lymphoma (Sept 2024) page 2

	Tafasitamab-cxix MONJUVI CD19-directed Monoclonal antibody	Polatuzumab-vedotin antiCD79b antibody and microtubule inhibitor conjugate	Loncastuximab CD19-directed antibody drug conjugate
Studies	**L-MIND (NCT02399085)** Open-label, multicenter, single-arm; N=71; R/R DLBCL s/p 1-3 LOT, including anti-CD20 MAb; Not ASCT candidate **Excluded: primary refractory DLBCL (i.e. fail to achieve a CR or relapse within 6 mos), double or triple hit genetics (i.e. MYC, BCL2, and/or BCL6 translocations)** ORR 55% (95% CI, 43-67); CR 37%; PR 18%; DoR 21.7 months (0-24) Final 5-year analysis: ORR 57.5%; CR 41.3% mDoR NR; median F/U 44 mos mPFS 11.6 months (95% CI 5.7-45.7); median F/U 45.6 mos mOS 33.5 months (95% CI: 18.3 – NR); median F/U 65.6 mos	**Study GO29365 (NCT02257567)** Open-label, single-arm, phase 1b/2 N=80; R/R DLBCL s/p > 1 LOT; Not ASCT candidate mAge 69 yrs (30-86); 66% male; 71% white; 98% DLBCL; Ineligible for ASCT due to: age 40%, insufficient response to salvage therapy 26%; prior ASCT failure 20% Median # prior therapies: 2 (1-7) In transplant ineligible patients Pola-BR vs. BR; CR 40 vs. 18% mPFS 10 vs. 4 mos mOS 12 vs. 5 mos	**LOTIS-2 (NCT03589469)** Open-label, single-arm, phase 2 N=145; R/R DLBCL s/p ≥ 2 LOT; **Including *MYC* and *BCL2* and/or *BCL6* rearrangements** **Excluded: bulky disease ≥ 10cm; and active CNS lymphoma** mAge 66 yrs (56-71); 59% male; 88% DLBCL; 8% HGBCL; 20% transformed DLBCL; stage III-IV 77%; median 3 LOT (2-4); prior AutoSCT 14%; prior CAR T 9% ORR 48.3% (95% CI 39.9-56.7), CR 24% (95% CI 17.4-31.9) PR 24%; SD 15%; PD 21% mDOR 10.3 mos; PFS 4.9 mos; OS 9.9 mos
VA Oncology Clinical Pathway Recs	VA Oncology Clinical Pathway: DLBCL, Relapsed, 2L: Tafasitamab + lenalidomide in relapsed in the following 2L setting: Patient is not eligible for ASCT and not a candidate for CAR T-cell therapy	VA Oncology Clinical Pathways: DLBCL, Multiply Relapsed: Pola-BR in patients who are not candidates for ASCT or CAR T-cell therapy	Not on Pathway
NCCN Guidelines Recs	NCCN guidelines DLBCL v3.2024: 2L therapy Preferred regimens (cat 2A) • CAR T-cell therapy (Liso-cel) • Pola ± benda ± rituximab • **Tafasitamab + lenalidomide** •	NCCN guidelines DLBCL 3.2024: 2L therapy Preferred regimens (cat 2A) • CAR T-cell therapy (Liso-cel) • **Pola ± benda ± rituximab** • Tafasitamab + lenalidomide Bridging Therapy to CAR T-cell includes 6 options, all category 2A: Pola ± rituximab ± bendamustine (only after leukapheresis, as it may impact cell collection)	NCCN guidelines DLBCL 3.2024: 3L and subsequent therapy Preferred regimens: • CAR T-cell therapy • BITE (epcoritamab, glofitamab) Other recommended regimens (cat 2A): • **Loncastuximab tesirine** • Selinexor

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