Loncastuximab tesirine-lpyl (ZYNLONTA)
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	Loncastuximab is an antibody drug conjugate (ADC) targeting CD19 conjugated to a pyrrolobenzodiazepine (PBD) dimer cytotoxin, SG3199. Once internalized, this payload causes interstrand DNA crosslinks.
Indication Under Review[1]	Treatment of relapsed or refractory large B-cell lymphoma (R/R DLBCL) after ≥ 2 lines of therapy (LOT); includes DLBCL arising from low-grade lymphoma and high-grade B-cell lymphoma Indication expedited through accelerated approval processes based on overall response rate (ORR); continued approval contingent on verification and description of clinical benefit in a confirmatory trial
Dosage Regimen	Loncastuximab IV on day 1 of 21-d cycle: Cycles 1, 2: 0.15mg/kg Cycles 3+: 0.075mg/kg
Dosage Forms Under Review	10mg loncastuximab as lyophilized powder in a SDV for reconstitution and dilution

EFFICACY CONSIDERATIONS

Trial	**LOTIS-2 (NCT03589469)**
Design	Open-label, multicenter, single-arm trial
Population	Open-label, single-arm, phase 2 N=145; R/R DLBCL s/p > 2 LOT; Including MYC and BCL2 and/or BCL6 rearrangements
Demographics	mAge 66 yrs (56-71); 59% male; 88% DLBCL; 8% HGBCL; 20% primary refractory disease; stage III-IV 77%; median 3 LOT (2-4); prior AutoSCT 14%; prior CAR T 9%
Intervention	Loncastuximab IV on day 1 of 21-d cycle: Cycles 1, 2: 0.15mg/kg Cycles 3+: 0.075mg/kg
Comparator	none
Results	Approval based on Overall Response Rate (ORR) @ median follow-up 7.8 months (range, 0.3-42.6) ORR 48.3% (95% CI 39.9-56.7), CR 24.8% (95% CI 17.4-31.9); PR 24%; SD 15%; PD 21% mDOR 10.3 mos; PFS 4.9 mos; OS 9.9 mos Long-term follow up of 35 mos among those with CR (N=36)[3] 44% event-free ≥ 1 year; 31% event-free ≥ 2 years; mOS and mPFS not reached; 24-mos OS rate 68% (59-81); PFS rate 72% (48-86)
Notes	**NCCN guidelines DLBCL v3.2024 includes:** **3L and subsequent therapy** Preferred regimens: • CAR T-cell therapy • BITE (epcoritamab, glofitamab) **Other recommended regimens (cat 2A):** **• Loncastuximab tesirine** • Selinexor **VA Oncology Clinical Pathway: DLBCL, Relapsed, 2L:** Loncastuximab is not included in the current pathways. **Alternative options:** Refer to **Appendix A. *Antibody-Based Therapies for R/R DLBCL***

AFETY CONSIDERATIONS		
	Boxed Warnings	None
	Contraindications	None
	Other Warnings	**Effusion and edema** Gr 3-3% edema; Gr 3-3% pleural effusion **Myelosuppression** Gr 3/4-32% neutropenia; 20% thrombocytopenia; 12% anemia; FN 3% **Infections** ≥ Gr 3-10% sepsis, pneumonia **Cutaneous Reactions** Gr 3-4%, incl photosensitivity **Embryo-Fetal Toxicity**
	Top 5 AEs	(≥ 20%) thrombocytopenia, increased gamma-glutamyltransferase (GGT), neutropenia, anemia, hyperglycemia, liver enzyme abnormalities
	Drug Interactions	

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. LOTIS-2 investigated monotherapy with loncastuximab in a single-arm, phase 2 trial of heavily pretreated patients with DLBCL (≥ 2 LOT) and included high-grade B-cell lymphoma patients with double-hit or triple-hit lymphoma, and disease transforming from low-grade B-cell lymphoma. 4. Loncastuximab was not compared to other therapies; in this heavily pre-treated population, ORR 48% 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, but loncastuximab remains an option if bispecific T-cell engagers are not available.

Prepared September 2024
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References

[1] Loncastuximab tesirine-lpyl (ZYNLONTA) for injection [prescribing information online]. Epalinges, Switzerland: ADC Therapeutics SA. October 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761196s004s005lbl.pdf. Accessed Date: Sept. 3, 2024

[2] Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicenter, open-label, single-arm, phase 2 trial. Lancet Oncol 2021; 22: 790-800

[3] Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma: long-term efficacy and safety from the phase II LOTIS-2 study. Haematologica 2024; 109: 1184-1193

[4] National Comprehensive Cancer Network Guidelines Version 3.2024 Diffuse Large B-Cell Lymphoma. b-cell.pdf (nccn.org) Accessed Aug 26, 2024.

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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**

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Appendix A. Bispecific T-cell Engagers and 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

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