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Positive Quality Intervention: Glofitamab-gxbm (COLUMVI®) for the Treatment of Relapsed or Refractory Large B-cell Lymphoma

Description: The purpose of this PQI is to review clinical considerations around the use of glofitamab-gxbm in the treatment of relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) or large B-cell lymphoma (LBCL) arising from follicular lymphoma.

Background: Glofitamab-gxbm is a bispecific T-cell engaging antibody which combines two CD20 binding sites with an anti-CD3 domain. The dual CD20 binding sites allow for bivalent attachment to CD20 expressing B-cells, while the CD3 domain recruits and activates polyclonal T-cells to release cytokines leading to cell death.[1,2] Glofitamab is indicated for the treatment of adult patients with relapsed or refractory (R/R) DLBCL, NOS or LBCL arising from follicular lymphoma, after two or more lines of systemic therapy.[1] Approval is based on the phase 2 portion of the phase 1-2, open-label, multicenter, single-arm NP30179 trial.[1,2] The efficacy population consisted of 132 patients with DLBCL, NOS (80%) or LBCL arising from follicular lymphoma (20%). Patients received pretreatment with obinutuzumab 1000 mg administered intravenously 7 days before the first dose of glofitamab. Glofitamab was then administered intravenously as step-up doses on day 8 (2.5 mg) and day 15 (10 mg) of cycle 1, followed by a dose of 30 mg on day 1 of cycles 2 through 12 (cycles lasted 21 days).[2] An overall response rate of 56% (n = 74) was seen including complete response in 57 patients (43%; 95% CI, 35-52) and partial response in 17 patients (13%; 95% CI, 8-20).[1] The median duration of objective response was 18.4 months (95% CI, 11.4-NE) with a median time to first complete response of 42 days (range: 31-178 days). The most common adverse event was cytokine release syndrome (CRS) in 63% of patients which was primarily associated with the first three glofitamab doses. CRS events were predominantly low grade (grade 1 [fever] in 47% of the patients and grade 2 in 12%), fully reversible, and led to treatment discontinuation in 1 patient. Neurologic toxicity consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) was rare and generally low grade, occurring in 12 patients (8%) and of grade 3 or higher in 3%. Neutropenia was the most common grade 3 or 4 adverse event and occurred in 27% of patients. Infections were observed in 59 patients (38%) and were grade 3 or higher in 23 patients (15%). The most frequent infections were COVID-19 or COVID-19–related pneumonia. Fatal adverse events (not including progressive disease) occurred in 8 patients (5%; COVID-19 in 5, sepsis in 2, and delirium in 1). No deaths were considered by the investigators to be related to glofitamab therapy.[1,2]

PQI Process:

Upon receiving order for glofitamab-gxbm:

- Confirm indication based on patient chart (R/R LBCL after at least 2 prior therapies)
- Ensure appropriate dose and schedule based on day of treatment, cycle, and any dose delays, especially with the obinutuzumab pre-treatment and glofitamab step-up dosing (SUD) schedule (first two doses), as these schedules aim to reduce the risk of CRS.
    - Glofitamab is administered for a total of 12 cycles (21-day cycles), which is approximately 8.5 months, or until disease progression or unacceptable toxicity
    - The risk of CRS is highest with Cycle 1 Day 8 (SUD1), Cycle 1 Day 15 (SUD2), and Cycle 2 Day 1 (first full dose), in that order, although in rare instances, CRS can occur with Cycles 3+.
    - Glofitamab should be infused through a dedicated line that includes a sterile 0.2 micron in-line filter.
- Ensure appropriate pre-medications are ordered for CRS and infusion reaction prevention (see Table 2)
    - With glofitamab intravenous infusion, premedication with acetaminophen and a corticosteroid may

mask a fever, so for patients with signs/symptoms of CRS without a fever and recent administration of premedications, recommendations for management of CRS should be followed.

- Neurologic toxicities, including ICANS, can occur; patients should be monitored for any changes in neurologic status for symptoms such as: headache, peripheral neuropathy, dizziness or vertigo, and mental status changes.
- Review risk of toxicity and any potential interventions (see product label[1] and consensus recommendations[3] on the management of toxicity with CD3 x CD20 bispecific antibody therapy)
- Supportive care considerations with glofitamab:
    - Tumor lysis syndrome (TLS) prophylaxis
        - Prior to treatment, assess for risk of TLS.
            - For patients at risk for TLS (e.g. high tumor burden, circulating disease, poor renal function), initiate appropriate monitoring and prophylactic measures (e.g. anti-hyperuricemics, such as allopurinol; oral and/or intravenous hydration).
    - Anti-viral prophylaxis
        - Prior to treatment, consider initiation of anti-viral prophylaxis to prevent herpes virus (HSV)/varicella-zoster virus (VZV) reactivation with acyclovir or equivalent.
        - Consider monitoring and/or prophylaxis for cytomegalovirus (CMV) infection in patients at increased risk (rare instances of CMV infection have been reported with glofitamab treatment).
    - Pneumocystis jirovecii Pneumonia (PJP) prophylaxis
        - Prior to treatment, consider PJP prophylaxis in patients at increased risk with sulfamethoxazole/trimethoprim or equivalent.
    - Hypogammaglobinemia (IgG ≤400 mg/dL)
        - Consider monitoring immunoglobulin levels, and in cases of hypogammaglobulinemia (e.g. IgG ≤400 mg/dL) and recurrent infections, consider immunoglobulin replacement.
    - Tumor flare monitoring
        - A transient increase in the size of lymphoma lesions may occur with glofitamab treatment, most commonly during Cycle 1, and patients should be monitored expectantly.
    - Growth factor support
        - For patients who are neutropenic during treatment, consider growth factor support and refer to PI for recommendations on withholding glofitamab (see Product Label).
    - Vaccinations
        - Patients should receive standard vaccinations as indicated, including influenza, COVID-19, pneumococcal, herpes zoster (recombinant zoster vaccine), and respiratory syncytial virus (RSV).

Patient-Centered Activities:

- Educate patient on schedule of administration highlighting the following:
    - Obinutuzumab infusion one week prior to glofitamab
    - Weekly step-up dosing with Cycle 1 (SUD1, C1D8; SUD 2, C1D15)
    - Inpatient hospital monitoring recommendations with glofitamab 2.5 mg (SUD1; C1D8)
    - Possibility of subsequent inpatient hospital monitoring if any CRS with glofitamab SUD1
    - Recommended duration of infusion of 4 hours for all glofitamab doses in Cycles 1 and 2, with extended infusion duration of up to 8 hours for patients who experience CRS. Subsequent glofitamab doses can be infused over 2 hours.
- Educate patient on sign/symptoms and monitoring of CRS and neurotoxicity, including ICANS
    - Ensure patient has been provided a glofitamab patient wallet card.

  - Educate patient/care person how to monitor for and instructions in case of signs/symptoms of CRS/neurotoxicity
  - Educate patient against driving or operating machinery if experiencing symptoms of neurologic toxicity
- Educate patient on adequate hydration especially during Cycles 1 and 2.
- Educate patient on risk of infection and to report any symptoms that include, but are not limited to the following: fever, chills/sweats, a new cough, sore throat, nasal congestion, burning or pain with urination, and redness, soreness, or swelling in any area.
- Educate patient on risk of tumor flare, which may include new pleural effusions, and to report any signs/symptoms of pain/swelling at sites of lymphoma lesions and/or shortness of breath.
- Monitor lab values before each cycle and prior to each dose during step-up schedule, including at a minimum neutropenia, thrombocytopenia, electrolyte abnormalities and changes in liver function tests.
  - Consider TLS lab monitoring for patients at risk for TLS during Cycles 1 and 2.
- Recommend female patients of reproductive potential use effective contraception during therapy and for 1 months after last dose.
- Patient Financial Assistance: Columvi Financial Support

References:

1. Glofitamab product label: available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf
2. Dickinson MJ, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2022 Dec 15;387(24):2220-2231. doi: 10.1056/NEJMoa2206913. Epub 2022 Dec 11. PMID: 36507690.
3. Crombie JL, et al. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. Blood. 2024 Apr 18;143(16):1565-1575. doi: 10.1182/blood.2023022432. Epub 2024 Jan 22. PMID: 38252906.
4. Lee DW, et al. ASTCT Consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Blood Marrow Transplant. 2019 Apr;25(4):625-638. doi: 10.1016/j.bbmt.2018.12.758. Epub 2018 Dec 25. PMID: 30592986.

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Supplemental Information:

Table 1: Glofitamab dose and schedule and CRS monitoring recommendations

Treatment Cycle	Day	Glofitamab Dose		Duration of infusion	CRS Monitoring[a]
Cycle 1	Day 1	Obinutuzumab 1000 mg			
	Day 8	Step-up dose 1 (SUD1)	2.5 mg	4 hrs[b]	• For SUD1 (2.5 mg on C1D8), hospitalization for infusion and for 24 hrs after completion of infusion.
	Day 15	Step-up dose 2 (SUD2)	10 mg		• If any Grade CRS with SUD1 (2.5 mg on C1D8), hospitalization for infusion and for 24 hrs after completion of infusion. • If no CRS with C1D8 (2.5 mg on C1D8), outpatient infusion and monitoring (note: CRS can occur with SUD2 in patients who did not experience CRS with SUD1).
Cycle 2	Day 1	30 mg		4 hrs[b]	• If Grade ≥2 CRS with the previous dose, hospitalization for infusion and for 24 hrs after completion of infusion. • If CRS ≤ Grade 1 with the previous dose, outpatient infusion and monitoring.
Cycle 3 to 12	Day 1	30 mg		2 hrs[c]	

[a]In the event of CRS, see COLUMVI prescribing information Table 4: Recommendations for Management of Cytokine Release Syndrome

[b]If the patient experienced CRS with their previous dose of glofitamab, the duration of infusion may be extended up to 8 hours.

[c]If the patient experienced CRS with their previous dose of glofitamab, the duration of infusion should be maintained at 4 hours.

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Table 2: Glofitamab premedication recommendations

Treatment Cycle and Day	Patients requiring premedication	Premedication	Administration
Cycle 1 Day 8 Cycle 1 Day 15 Cycle 2 Day 1 Cycle 3 Day 1	All patients	Dexamethasone 20 mg intravenously[a]	At least 1 hour prior to glofitamab infusion.
		Acetaminophen 500 mg to 1,000 mg orally	At least 30 minutes prior to glofitamab infusion.
		Antihistamine (diphenhydramine 50 mg orally or intravenously or equivalent)	At least 30 minutes prior to glofitamab infusion.
All subsequent infusions	All patients	Acetaminophen 500 mg to 1,000 mg orally	At least 30 minutes prior to glofitamab infusion.
		Antihistamine (diphenhydramine 50 mg orally or intravenously or equivalent)	At least 30 minutes prior to glofitamab infusion.
	Patients with any grade CRS with the previous dose	Dexamethasone 20 mg intravenously[a]	At least 1 hour prior to glofitamab infusion.

[a]Dexamethasone is the preferred corticosteroid premedication as it is associated with a lower incidence and severity of CRS compared with other corticosteroid regimens

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Table 3: Recommendations for restarting glofitamab after dose delay

Last Dose Administered	Time Since Last Dose Administered	Action for Next Dose(s)[a]
Obinutuzumab pretreatment (Cycle 1 Day 1)	≤ 2 weeks	• Administer glofitamab 2.5 mg (Cycle 1 Day 8)[b], then resume the planned treatment schedule
	> 2 weeks	• Repeat obinutuzumab 1,000 mg pretreatment (Cycle 1 Day 1) • Then administer glofitamab 2.5 mg (Cycle 1 Day 8)[b] and resume the planned treatment schedule
Glofitamab 2.5 mg (Cycle 1 Day 8)	≤ 2 weeks	• Administer glofitamab 10 mg (Cycle 1 Day 15)[c], then resume the planned treatment schedule
	> 2 to ≤ 4 weeks	• Repeat glofitamab 2.5 mg (Cycle 1 Day 8)[b] • Then administer glofitamab 10 mg (Cycle 1 Day 15)[c] and resume the planned treatment schedule
	> 4 weeks	• Repeat obinutuzumab 1,000 mg pretreatment (Cycle 1 Day 1) and glofitamab 2.5 mg (Cycle 1 Day 8)[b] • Then administer glofitamab 10 mg (Cycle 1 Day 15)[c] and resume the planned treatment schedule
Glofitamab 10 mg (Cycle 1 Day 15)	≤ 2 weeks	• Administer glofitamab 30 mg (Cycle 2 Day 1), then resume the planned treatment schedule
	> 2 to ≤ 6 weeks	• Repeat glofitamab 10 mg (Cycle 1 Day 15).[c] • Then administer glofitamab 30 mg (Cycle 2 Day 1) and resume the planned treatment schedule
	> 6 weeks	• Repeat obinutuzumab 1,000 mg pretreatment (Cycle 1 Day 1), glofitamab 2.5 mg (Cycle 1 Day 8)[b], and glofitamab 10 mg (Cycle 1 Day 15)[c] • Then administer glofitamab 30 mg (Cycle 2 Day 1) and resume the planned treatment schedule
Glofitamab 30 mg (Cycle 2 onwards)	≤ 6 weeks	• Administer glofitamab 30 mg, then resume the planned treatment schedule
	> 6 weeks	• Repeat the Cycle 1 regimen described in Table 1: obinutuzumab 1,000 mg pretreatment (Day 1), glofitamab 2.5 mg (Day 8)[b], and glofitamab 10 mg (Day 15)[c]

[a] Administer premedication as per glofitamab premedication recommendations table to all patients
[b] Patients should be hospitalized during and for 24 hours after completing infusion of the 2.5 mg dose
[c] Patients should be hospitalized during and for 24 hours after completing infusion of the 10 mg dose if any grade CRS occurred during the most recent 2.5 mg dose