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Positive Quality Intervention: Epcoritamab (epcoritamab-bysp) for Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) and Follicular Lymphoma (FL)

Description: The purpose of this PQI is to discuss the clinical considerations of epcoritamab-bysp (Epcoritamab®) to optimize the outcomes for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).

Background: Epcoritamab-bysp is a subcutaneous bispecific antibody that targets CD20 on B-cells and CD3 on T-cells activating T-cell-mediated destruction of malignant B-cells.[1] It received FDA accelerated approval for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBL), and follicular lymphoma (FL) after two or more lines of systemic therapy. Epcoritamab has an NCCN category 2A recommendation for the treatment of r/r DLBCL, including patients with disease progression after transplantation or CAR T-cell therapy, or r/r classic FL following two prior systemic therapies.[2]

The phase I/II EPCORE NHL-1 trial evaluated its efficacy in 157 patients with r/r DLBCL, including transformed indolent lymphomas and HGBLs, after at least two lines of therapy.[3] The study reported an overall response rate (ORR) of 63%, with a complete response (CR) rate of 39%, while the median progression-free survival (PFS) was 4 months, and the median overall survival (OS) was not reached. In the separate FL cohort of 128 patients, epcoritamab achieved an ORR of 82% and a CR rate of 63%, with notable results across high-risk subgroups, including double-refractory disease (76% ORR).[4-5]

Common treatment-related adverse effects included cytokine release syndrome (CRS), neurotoxicity (ICANS), and injection site reactions (57%-58%).[1,3-5] In patients with DLBCL, any grade CRS was reported in 50% of patients (with grade 3 events at 3%), with a median time to onset of approximately 24 hours (range: 0 to 10 days), while in patients with FL, CRS occurred in 65% of patients (with grade 3 events at 2%), with a median time to onset of approximately 59 hours (range: 0.1 to 7 days). ICANS was reported in 6% of patients in both DLBCL and FL cohorts, with grade 3 events occurring in 3% of patients for both groups, and the median time to onset was approximately 16.5 days (range: 8 to 141 days) for patients with DLBCL and about 21.5 days (range: 14 to 66 days) for patients with FL.

PQI Process: Upon receipt of a new prescription for Epcoritamab in patients with R/R DLBCL or FL:

- Verify required prophylaxis
  - PJP prophylaxis: Sulfamethoxazole/Trimethoprim (800mg/160mg) DS one tablet orally 3 times per week
  - HSV prophylaxis: Valacyclovir 500 mg tablet orally once daily
- Verify required premedication
  - Dexamethasone 15 mg IV or PO (preferred) or prednisolone 100 mg IV or PO or equivalent
    - 30-120 min before each weekly epcoritamab dose AND for 3 consecutive days following each weekly administration of epcoritamab in Cycle 1
  - Diphenhydramine 50 mg oral or IV or equivalent + Acetaminophen 650 mg to 1,000 mg PO
    - 30-120 minutes prior to each weekly administration of epcoritamab

- Patients who experienced Grade 2 or 3 CRS with previous dose:
  - Dexamethasone 15 mg IV or PO or prednisolone 100 mg IV or PO or equivalent 30-120 minutes prior to next administration of epcoritamab after a Grade 2 or 3 CRS event AND for 3 consecutive days following the next administration of epcoritamab until dose is given without ≥ Grade 2 CRS event

Table 1. Epcoritamab Dosing Schedule

DLBCL/HGBCL (3L+*)	Day 1	Day 8	Days 15	Day 22
Cycle 1 (2 step-up doses)	0.16 mg	0.8 mg	48 mg	48 mg
Cycles 2-3	48 mg	48 mg	48 mg	48 mg
Cycles 4-9	48 mg		48 mg	
Cycles 10+	48 mg			
FL (3L+*)	Day 1	Day 8	Days 15	Day 22
Cycle 1 (3 step-up doses)	0.16 mg	0.8 mg	3 mg	48 mg
Cycles 2-3	48 mg	48 mg	48 mg	48 mg
Cycles 4-9	48 mg		48 mg	
Cycles 10+	48 mg			

*3L+; third line plus: epcoritamab is indicated after at least 2 prior therapies to be used until disease progression or unacceptable toxicity

- Hospitalization:
  - Patients with DLBCL or HGBCL should be hospitalized for 24 hours after Cycle 1, Day 15 (first full 48 mg dose)
  - For FL patients, clinical judgment should be used to determine if hospitalization is necessary based on individual patient risk factors and institutional protocols
- Monitor for CRS & ICANS:
  - CRS signs: Pyrexia, hypotension, hypoxia, dyspnea, chills, tachycardia.
  - ICANS signs: Confusion, lethargy, tremor, dysgraphia, aphasia, seizures.
- Monitoring Parameters:
  - CBC: Baseline and prior to each cycle.
  - Vital signs & neurological status: Regular assessments during treatment.
- Restarting therapy after dosage delay:
  - DLBCL or HGBCL:

Previous Dose	
0.16 mg (Cycle 1 Day 1)	> 8 days- restart Cycle Day 1 dosing
0.8 mg (Cycle 1 Day 8)	14 days or less- resume as planned 48 mg
0.8 mg (Cycle 1 Day 8)	>14 days- restart at Cycle 1 Day 1 0.16 mg
48 mg (Cycle 1 Day 15 onwards)	6 weeks or less- continue 48 mg
48 mg (Cycle 1 Day 15 onwards)	>6 weeks- restart Cycle Day 1 dosing

- FL:

Previous Dose	
0.16 mg (Cycle 1 Day 1)	> 8 days- restart Cycle Day 1 dosing
0.8 mg (Cycle 1 Day 8)	> 8 days- restart Cycle Day 1 dosing
3 mg (Cycle 1 Day 15)	14 days or less- resume as planned 48 mg
3 mg (Cycle 1 Day 15)	>14 days- restart at Cycle 1 Day 1 0.16 mg
48 mg (Cycle 1 Day 22 onwards)	6 weeks or less- continue 48 mg
48 mg (Cycle 1 Day 22 onwards)	>6 weeks- restart Cycle Day 1 dosing

- Preparation and Administration:
  - 0.16 mg & 0.8 mg doses require dilution (refer to PI for dilution instructions).
  - 3 mg & 48 mg doses are ready-to-use.
  - Inject subcutaneously into the lower abdomen or thigh.
  - Rotate injection sites and avoid tattoos, scars, or irritated skin.
  - Allow vial to come to room temperature for no more than 1 hour

Patient-Centered Activities:

- Counseling & Education:
  - Educate patients and caregivers/care partners on CRS/ICANS risk and the importance of prompt reporting of symptoms.
  - Explain the step-up dosing schedule and hospitalization requirement for DLBCL patients.
  - Discuss infection risk and ensure patient is receiving PJP and HSV prophylaxis
  - Patients should be well hydrated before each dose of epcoritamab
- Financial Assistance Options:
  - Patients may qualify for co-pay assistance programs through the manufacturer or third-party organizations.

Supplemental Information:

Table 2. Adverse Reaction Management

Adverse Reaction	**Severity**	**Dosage Modification & Management**
Cytokine Release Syndrome (CRS)	Grade 1 (Mild)	Withhold epcoritamab; supportive care (e.g., antipyretics, IV fluids as needed). Monitor closely.
	Grade 2 (Moderate)	Withhold epcoritamab until symptoms resolve to Grade ≤1. Manage per guidelines with IV fluids, oxygen, corticosteroids if needed.
	Grade 3 (Severe)	Withhold epcoritamab until symptoms resolve to Grade ≤1. Administer tocilizumab (IL-6 inhibitor) and/or corticosteroids if indicated. Hospitalize for the next dose.

	Grade 4 (Life-threatening)	Permanently discontinue epcoritamab. Administer tocilizumab and/or corticosteroids as needed. Provide intensive supportive care.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)	Grade 1 (Mild)	Continue epcoritamab; monitor neurological function closely. Supportive care as needed.
	Grade 2 (Moderate)	Withhold epcoritamab until symptoms resolve to Grade ≤1. Consider corticosteroids if necessary.
	Grade 3 (Severe)	Withhold epcoritamab until symptoms resolve to Grade ≤1. Administer IV corticosteroids and provide neurological monitoring.
	Grade 4 (Life-threatening)	Permanently discontinue epcoritamab. Provide intensive supportive care, IV corticosteroids, and neurological evaluation.
Serious Infections	Any Grade	Withhold epcoritamab for active serious infections. Treat infections appropriately before resuming therapy.
Cytopenias (Neutropenia, Anemia, Thrombocytopenia)	Grade 3 or 4	Monitor CBC regularly. Consider dose modification or G-CSF support (for neutropenia) as indicated. Withhold therapy if severe cytopenias occur.
Injection Site Reactions	Mild to Moderate	Continue epcoritamab; manage with topical corticosteroids, oral antihistamines, or analgesics as needed.
Embryo-Fetal Toxicity	Pregnancy Risk	Verify pregnancy status before initiation. Advise contraception during treatment and for 4 months after last dose.

References:

1. Epcoritamab (epcoritamab-bysp). Genmab US, Inc. Plainsboro, NJ. 2024. www.accessdata.fda.gov/drugsatfda_docs/label/2024/761324s003lbl.pdf
2. National Comprehensive Cancer Network (NCCN) Guidelines. B-Cell Lymphomas (Version 3.2024).
3. 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. 2023;41(12):2238-2247. doi:10.1200/JCO.22.01725
4. Linton KM, Vitolo U, Jurczak W, et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. Lancet Haematol. 2024;11(8):e593-e605. doi:10.1016/S2352-3026(24)00166-2
5. Linton K, Jurczak W, Lugtenburg P, et al. Epcoritamab SC monotherapy leads to deep and durable responses in patients with relapsed or refractory follicular lymphoma: First data disclosure from the Epcore NHL-1 follicular lymphoma dose-expansion cohort [abstract]. Blood. 2023;142: Abstract 1655.