Written By: Syed Zia Khan, PharmD, BCSCP
Institution: The START Center for Cancer Care

Epcoritamab (Epkinly®) for Relapsed/Refractory Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

Description:

- The purpose of this PQI is to discuss clinical considerations of epcoritamab (Epkinly®) treatment for patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL).

Background:

- Epcoritamab is a bispecific antibody that targets CD20 on B-cells and CD3 on T-cells activating T-cell-mediated destruction of malignant B-cells
- FDA approved for the treatment of:
  - R/R DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma (HGBCL) after ≥ 2 lines of systemic therapy
  - R/R FL
    - In combination with lenalidomide and rituximab (R^2) after ≥ 1 line of systemic therapy
    - As monotherapy after ≥ 2 lines of systemic therapy
- Most common (≥ 20%) adverse reactions:
  - Epcoritamab as monotherapy for DLBCL or FL – cytokine release syndrome (CRS), injection site reactions, fatigue, musculoskeletal pain, fever, diarrhea, COVID-19, rash abdominal pain
    - Grade 3/4 lab abnormalities (>10%): decreases in lymphocyte count, neutrophil count, Hgb, and platelets
  - Epcoritamab in combination with R^2 for FL – rash, upper respiratory tract infections, fatigue, injection site reactions, constipation, diarrhea, CRS, pneumonia, COVID-19, fever
    - Grade 3/4 lab abnormalities (>10%): decreased neutrophil count, lymphocyte count, and platelets
- Incidence and timing of CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) (boxed warnings)
  - DLBCL:
    - CRS (any grade – 51%); median time to onset: 24 hours (range: 0-10 days)
    - ICANS (any grade – 6%); median time to onset: 3 days (range: 1-13 days)
  - FL
    - Monotherapy
      - CRS (any grade – 49%); median time to onset: 59 hours (range: 0.1-7 days)
      - ICANS (any grade – 6%); median time to onset: 21.5 days (range: 14-66 days)
    - In combination with R^2
      - CRS (any grade – 24%); median time to onset: 78 hours (range 0.2-12 days)
      - ICANS (any grade – 0.8% [grade 1])

PQI Process:

- Verify required prophylaxis
  - PJP prophylaxis: sulfamethoxazole/trimethoprim (800mg/160mg) DS one tablet orally 3 times per week
  - HSV prophylaxis: valacyclovir 500 mg tablet PO once daily
  - Thromboprophylaxis: refer to lenalidomide prescribing information for recommendations on prophylaxis for venous and arterial thrombotic events
- Verify required premedication:

Table 1. Premedication

Cycle	Patients requiring medication	Medication	Administration
Cycle 1	All patients	Dexamethasone 15 mg PO/IV or prednisolone 100 mg PO/IV 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 PO/IV or equivalent Acetaminophen 650 mg to 1,000 mg PO	30-120 min prior to each weekly dose of epcoritamab
Cycle 2+	Patients who experienced Grade 2 or 3 CRS with previous dose	Dexamethasone 15 mg PO/IV or prednisolone 100 mg PO/IV or equivalent	30-120 minutes prior to next dose of epcoritamab after a Grade 2 or 3 CRS event AND for 3 consecutive days following the next dose of epcoritamab until dose is given without ≥ Grade 2 CRS event

Table 2. Epcoritamab dosing schedule

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

FL (2L+) combo with R^2	Day 1	Day 8	Day 15	Day 22
Cycle 1 (3 step-up doses)	0.16 mg	0.8 mg	3 mg	48 mg
Cycles 2 and 3	48 mg	48 mg	48 mg	48 mg
Cycles 4 to 12	48 mg			

3L+: third line plus; 2L+: second line plus; R^2: lenalidomide 20 mg (Days 1 to 21 in Cycles 1 to 12) and rituximab 375 mg/m2 (Cycles 1 to 5)

- Hospitalization:
  - For patients with DLBCL/HGBCL, clinical judgment should be used to determine if hospitalization is necessary after Cycle 1, Day 15 (first full 48 mg dose) based on individual patient risk factors and institutional protocols
  - For patients with FL, clinical judgment should be used to determine if hospitalization is necessary after Cycle 1, Day 22 (first full 48 mg dose) based on individual patient risk factors and institutional protocols
- Monitoring for CRS & ICANS:
  - CRS signs: pyrexia, hypotension, hypoxia, dyspnea, chills, tachycardia
  - ICANS signs: confusion, lethargy, tremor, dysgraphia, aphasia, seizures
- Other monitoring parameters:
  - CBC: a baseline and prior to each cycle
  - Vital signs & neurological status: regular assessments during treatment
- Restarting therapy after dosage delay:
  - DLBCL or HGBCL:

Previous Dose	Action for Next Dose(s)
0.16 mg (Cycle 1 Day 1)	> 8 days- restart at Cycle 1 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 dosing
48 mg (Cycle 1 Day 15 onwards)	6 weeks or less- continue 48 mg
48 mg (Cycle 1 Day 15 onwards)	>6 weeks- restart at Cycle 1 Day 1 dosing

  - FL:

Previous Dose	Action for Next Dose(s)
0.16 mg (Cycle 1 Day 1)	> 8 days- restart at Cycle 1 Day 1 dosing
0.8 mg (Cycle 1 Day 8)	> 8 days- restart at Cycle 1 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 dosing
48 mg (Cycle 1 Day 22 onwards)	6 weeks or less- continue 48 mg
48 mg (Cycle 1 Day 22 onwards)	>6 weeks- restart at Cycle 1 Day 1 dosing

Refer to the lenalidomide prescribing information and rituximab prescribing information for the respective dosage adjustments

- Preparation and administration:
  - 0.16 mg & 0.8 mg doses require dilution (refer to PI for dilution instructions)
    - 3 mg & 48 mg doses do not require dilution
  - 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 prior to administration

Patient-Centered Activities:

- Educate patients and caregivers/care partners on CRS/ICANS risk and the importance of prompt reporting of symptoms.
- Explain the step-up dosing schedule (DLBCL & FL) and hospitalization requirements (DLBCL)
- Discuss infection risk and ensure patients receive PJP and HSV prophylaxis as appropriate
- Inform patients they should be well hydrated before each dose of epcoritamab
- Verify pregnancy status before initiation. Advise contraception during treatment and for 4 months after last dose.
- Financial assistance options:
    - Genmab *MyNavCare Patient Support* offers resources, services, and support

Supplemental Information:

Managing CRS if it occurs (pages 16-17)

Managing ICANS if it occurs (pages 18-20)

Table 3. Adverse Reaction Management

Adverse Reaction	Severity	Dosage Modification & Management
Infections	Any Grade	Withhold epcoritamab for active infections until resolution. For grade 4, consider permanent discontinuation of epcoritamab.
Neutropenia	ANC less than 0.5 x 109/L	Withhold epcoritamab until ANC is 0.5 x 10^9/L or higher. Consider prophylactic G-CSF support as applicable.
Thrombocytopenia	Platelet count less than 50 x 109/L	Withhold epcoritamab until platelet count is 50 x 10^9/L or higher.
Other adverse reactions	≥ Grade 3	Withhold epcoritamab until the toxicity resolves to Grade 1 or baseline.

ANC: absolute neutrophil count

References:

1. EPKINLY [package insert]. Plainsboro, NJ: Genmab US, Inc. and North Chicago, IL: AbbVie Inc. 2024.
2. 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. December 22, 2022. doi:10.1200/JCO.22.01725
3. 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
4. Falchi L, Nijland M, Huang H, et al. Epcoritamab, lenalidomide, and rituximab versus lenalidomide and rituximab for relapsed or refractory follicular lymphoma (EPCORE FL-1): a global, open-label, randomised, phase 3 trial. Lancet. 2026 Jan 10;407(10524):161-173. doi: 10.1016/S0140-6736(25)02360-8. Epub 2025 Dec 7.