Up Close with Epcoritamab

This section provides an overview of epcoritamab-bysp (EPKINLY®).

- 🏷️ Indications
- 💊 Dosing and Administration
- ⚠️ CRS
- 🧠 Neurotoxicity (including ICANS)
- 🚨 Other Toxicities

🏷️ Indications

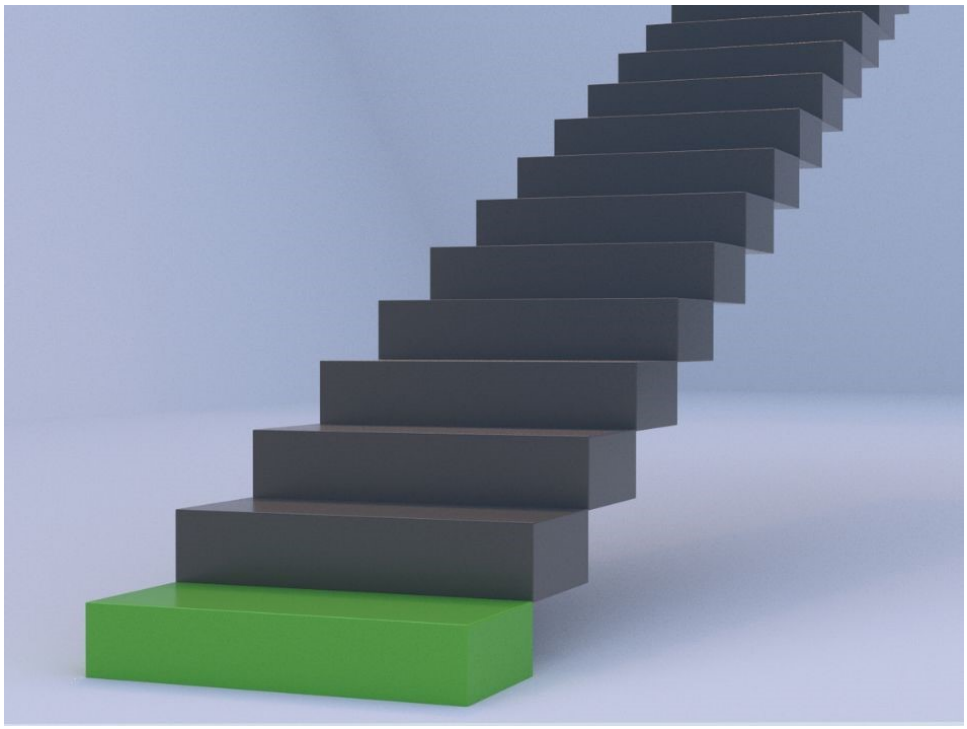
Epcoritamab is a **bispecific CD20-directed CD3 T-cell engager** indicated for the treatment of adults with:

1. **Diffuse large B-cell lymphoma (DLBCL)** or **High-grade B-cell Lymphoma**
   - Relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma and high-grade B-cell lymphoma after 2 or more lines of systemic therapy.

2. **Follicular Lymphoma (FL)**
   - Relapsed or refractory FL after 2 or more lines of systemic therapy.

Note: These indications are approved under accelerated approval based on response rate and durability of response. Continued approval may be contingent upon verification of clinical benefit in confirmatory trials.

💊 Dosing and Administration



Epcoritamab is administered **subcutaneously in 28-day cycles** until disease progression or unacceptable toxicity.

- Cycle 1 is given as a **step-up dosage schedule** to reduce the incidence and severity of cytokine release syndrome (CRS). The step-up dosage schedule varies by indication, where:
    - DLBCL or High-grade B-cell Lymphoma has 2 step-up doses
    - FL has 3 step-up doses

Epcoritamab 2-step up Dosage Schedule for Patients with DLBCL or High-grade B-cell Lymphoma

Indication	Cycle of Treatment	Day of Treatment	Dose of Epcoritamab	
DLBCL or High-grade B-cell Lymphoma	Cycle 1	1	Step-up dose 1	0.16 mg
		8	Step-up dose 2	0.8 mg
		15	First full dose	48 mg
		22	48 mg	
	Cycle 2 and 3	1, 8, 15, and 22	48 mg	
	Cycle 4 to 9	1 and 15	48 mg	
	Cycle 10 and beyond	1	48 mg	

Recommendations for Restarting Therapy with Epcoritamab After Dosage Delay for Patients with DLBCL or High-grade B-cell Lymphoma		
Last Dose Administered	**Time Since Last Dose Administered**	**Action for Next Dose(s)**
0.16 mg (e.g., on Cycle 1 Day 1)	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
0.8 mg (e.g., on Cycle 1 Day 8)	14 days or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 14 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
48 mg (e.g., on Cycle 1 Day 15 onwards)	6 weeks or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 6 weeks	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
*Administer pretreatment medication prior to epcoritamab dose and monitor patients accordingly.		

Epcoritamab 3-step up Dosage Schedule for Patients with FL				
Indication	**Cycle of Treatment**	**Day of Treatment**	**Dose of Epcoritamab**	
Follicular Lymphoma	Cycle 1	1	Step-up dose 1	0.16 mg
		8	Step-up dose 2	0.8 mg

		15	First full dose	3 m
		22	First full dose	48 mg
	Cycle 2 and 3	1, 8, 15, and 22	48 mg	
	Cycle 4 to 9	1 and 15	48 mg	
	Cycle 10 and beyond	1	48 mg	

Recommendations for Restarting Therapy with Epcoritamab After Dosage Delay for Patients with FL		
Last Dose Administered	**Time Since Last Dose Administered**	**Action for Next Dose(s)***
0.16 mg (e.g., on Cycle 1 Day 1)	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
0.8 mg (e.g., on Cycle 1 Day 8)	More than 8 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
3 mg (e.g., on Cycle 1 Day 15)	14 days or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 14 days	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
48 mg (e.g., on Cycle 1 Day 22 onwards)	6 weeks or less	Administer 48 mg, then resume the planned treatment schedule.
	More than 6 weeks	Repeat Cycle 1 schedule starting at step-up dose 1 (0.16 mg). Following the repeat of Cycle 1 schedule, resume the planned treatment schedule.
*Administer pretreatment medication prior to epcoritamab dose and monitor patients accordingly.		

Recommended Pre- and Post-Administration Medications			
Cycle	**Patients Requiring Medications**	**Medication**	**Administration**
Cycle 1	All patients	• Dexamethasone[a] (15 mg oral or intravenous) or prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to each weekly administration of epcoritamab

			• And for three consecutive days following each weekly administration of epcoritamab in Cycle 1
		• Diphenhydramine (50 mg oral or intravenous) or equivalent • Acetaminophen (650 mg to 1,000 mg oral)	• 30-120 minutes prior to each weekly administration of epcoritamab
Cycle 2 and Beyond	Patients who experienced Grade 2 or 3[b] CRS with previous dose	• Dexamethasone[a] (15 mg oral or intravenous) or prednisolone (100 mg oral or intravenous) or equivalent	• 30-120 minutes prior to next administration of epcoritamab after a Grade 2 or 3b CRS event • And for three consecutive days following the next administration of epcoritamab until epcoritamab is given without subsequent CRS of Grade 2 or higher
[a]Dexamethasone is the preferred corticosteroid when available [b]Patients will be permanently discontinued from epcoritamab after Grade 4 CRS			

Due to the risk of CRS and neurotoxicity, **all patients should be monitored** for signs and symptoms.

- **DLBCL or High-grade B-cell Lymphoma:** Patients **should be hospitalized for 24 hours after administration** of the C**ycle 1, Day 15 dosage of 48 m**g.
    - Real-world application: Some sites administer all doses in the outpatient setting—even the first full dose for patients with DLBCL—by ensuring systems are in place for safe observation.
- **FL:** Patients **do NOT require hospitalization** during any of the step-up doses.

Additional recommendations

- Provide *Pneumocystis jirovecii pneumonia* (PJP) prophylaxis prior to starting treatment with epcoritamab.
- Consider initiating prophylaxis against herpes virus prior to starting epcoritamab to prevent herpes zoster reactivation.
- Patients should be well hydrated.

Go deeper. For more information on dosing and administration, click here.

⚠ CRS

What is it? Cytokine release syndrome (CRS) is a systemic inflammatory response that can occur when the immune system is activated and releases large amounts of cytokines—proteins that help regulate immune responses.

- **Signs and symptoms:** pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia.
- CRS is frequently graded using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.

Why it matters. CRS **occurred in ~50% of patients** in the EPCORE NHL-1. **Most CRS events** occurred during **Cycle 1**, with the **highest events** occurring on the day of t**he first full 48 mg dose**.

- **DLBCL or High-grade B-cell Lymphoma:** CRS occurred in **51% of patients** (37% grade 1, 17% grade 2, and 2.5% grade 3) and **recurred in 16% of patients**.
    - **Most events (92%**) occurred during **cycle 1**, with **61%** occurring **after the 48 mg dose on cycle 1, day 15**.
- **FL:** CRS occurred in **49% of patients** (45% grade 1, 9% grade 2) and r**ecurred in 23% of patients**.
    - **Most events (88%)** occurred during **cycle 1**, with **49%** occurring **after the 48 mg dose on cycle 1, day 22**.

The **time to onset of CRS** varied by indication.

- **DLBCL or High-grade B-cell Lymphoma: Median time to CRS onset** across all doses was **24 hours** (range: 0-10 days) post-administration.
    - **First full 48 mg dose:** 21 hours (range: 0-7 days) post-administration.

- **FL: Median time to CRS onset** across all doses was **59 hours** (range: 0.1-7 days) post-administration.
    - **First full 48 mg dose:** 61 hours (range: 0.1-7 days) post-administration.

The **duration of CRS** was **2 days**.

- **DLBCL or High-grade B-cell Lymphoma:** CRS lasted 2 days (range: 1-27 days).
- **FL:** CRS lasted 2 days (range: 1-14 days).

Concurrent neurological adverse reactions associated with CRS occurred in <5% of patients.

- **DLBCL or High-grade B-cell Lymphoma:** 2.5% of patients.
- **FL:** 4.7% of patients.

The bottom line. CRS was primarily low-grade, predictable, and manageable.

🧠 Neurotoxicity (including ICANS)

What is it? Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) is characterized by various neurologic symptoms resulting from the activation of the immune system and the resultant inflammatory processes.

- **Signs and symptoms:** encephalopathy, headaches, seizures, aphasia, motor deficits, ataxia, and tremor.
- ICANS is frequently graded using the ASTCT consensus criteria.

Why it matters. ICANS occurred in **6%** of patients in the EPCORE NHL-1 trial.

- **DLBCL or High-grade B-cell Lymphoma:** ICANS occurred in **6%** (4.5% grade 1, 1.3% grade 2, 0.6% fatal). Of the 10 ICANS events, 9 occurred in cycle 1 of treatment.
- **FL:** ICANS occurred in **6%** of patients **receiving the 2-step up dosage schedule** in the clinical trial (3.9% grade 1, 2.4% grade 2). **Note:** The approved dosage schedule has 3-step up doses.

The **time to onset of ICANS** varied by indication.

- **DLBCL or High-grade B-cell Lymphoma: Median time to ICANS onset** from the start of treatment was **16.5 days** (range: 8-141 days).
    - **Median time from the most recent administration:** 3 days (range: 0-13 days).
- **FL: Median time to ICANS onset** from the start was **21.5 days** (range: 14-66 days) post-administration.
    - **Median time from the most recent administration:** 3 days (range: 0.4-7 days) post-administration.

ICANS resolved in most cases and lasted a few days.

- **DLBCL or High-grade B-cell Lymphoma:** Resolved in **90% of cases**; duration: **4 days** (range: 0-8 days).
- **FL:** Resolved in 100% of cases; duration: **2 day**s (range: 1-7 days).

The bottom line. ICANS was uncommon and primarily low-grade.

🚨 Other Toxicities

Epcoritamab can cause other adverse reactions such as **infections, cytopenias, and embryo-fetal toxicity**.

Why it matters. In addition to the risks of CRS and neurotoxicity (including ICANS), care teams need to be on the lookout for other **epcoritamab**-associated toxicities.

Infections. Epcoritamab can cause serious and fatal infections.

- **DLBCL or High-grade B-cell Lymphoma: Serious infections** reported in **15%** (most common: 4.5% sepsis, 3.2% pneumonia). **Fatal infections** occurred in **1.3%** (1.3% COVID-19).
- **FL (receiving the 2-step up dosage schedule): Serious infections** reported in **40%** (most common: 20% COVID-19, 13% pneumonia, 3% urinary tract infections). **Fatal infections** occurred in **6%** (5% COVID-19, 0.8% pneumonia, 0.8% sepsis).

The bottom line. Care teams should **monitor patients for signs of infection before and during treatment**; treat appropriately.

- Avoid administration in patients with active infections; withhold or discontinue epcoritamab based on severity.
- Provide PJP prophylaxis and consider herpes virus prophylaxis before starting epcoritamab.

Cytopenias. Epcoritamab can cause serious or severe cytopenias.

- **DLBCL or High-grade B-cell Lymphoma: Grade 3 or 4 events** occurred in **32%** (neutrophils decreased), **12%** (hemoglobin decreased), and **12%** (platelets decreased).
    - Febrile neutropenia occurred in 2.5%.
- **FL** (based on patients receiving the 2-step up dosage schedule, not the FDA-approved 3-step up dosage schedule): **Grade 3 or 4 events** occurred in **30%** (neutrophils decreased), **10%** (hemoglobin decreased), and **8%** (platelets decreased).
    - Febrile neutropenia occurred in 3.1%.

The bottom line. Care teams should **monitor complete blood counts throughout treatment**.

- **Withhold or discontinue epcoritamab based on cytopenia severity**; consider prophylactic granulocyte colony-stimulating factor.

Embryo-Fetal Toxicity. Epcoritamab may cause fetal harm when administered to a pregnant woman.

- Advise **females of reproductive potential** to use effective contraception **during treatment** and **for 4 months after the last dose**.
- Verify pregnancy status before initiating epcoritamab.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed during treatment and for 4 months after the last dose.
- **Geriatric Use:**
    - In EPCORE NHL-1, 52% of patients with relapsed/refractory FL were ≥65 years old, and 13% were ≥75 years old.
    - Higher rate of fatal adverse reactions, mainly infections, including COVID-19, in patients ≥65 years old compared to younger adults.
    - No overall difference in efficacy was observed.
- **Pediatric Use:** At this time, no safety and effectiveness data has been established in pediatric patients.

Updated: 3/25/25

References

1. EPKINLY™ (epcoritamab-bysp) [package insert]. Plainsboro, NJ: Genmab US, Inc.; North Chicago, IL: AbbVie Inc. 2024.
2. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758
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. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. *Lancet*. 2021;398(10306):1157-1169. doi:10.1016/S0140-6736(21)00889-8.