Up Close with Epcoritamab

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

Indications

Dosing & Administration

Cytokine Release Syndrome (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

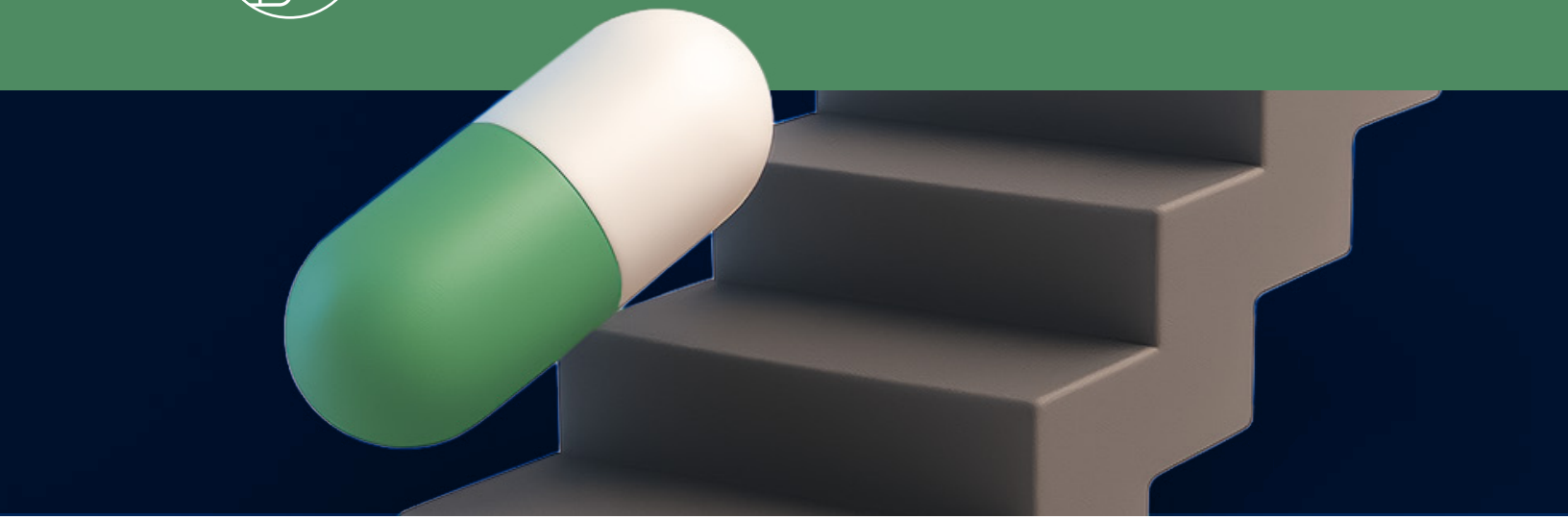
- Relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from indolent lymphoma and high-grade B-cell lymphoma after 2 or more lines of systemic therapy.

This indication is approved under accelerated approval based on response rate and durability of response. Continued approval may depend on verification and description of clinical benefit in a confirmatory trial.

2. Follicular Lymphoma (FL)

- Relapsed or refractory FL after 2 or more lines of systemic therapy.
- Relapsed or refractory FL in combination with lenalidomide and rituximab (R^2).

Dosing & Administration



Epcoritamab is administered **subcutaneously in 28-day cycles**.

- 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

Diffuse Large B-cell Lymphoma or High-grade B-cell Lymphoma

Epcoritamab 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	
	Cycles 2 and 3	1, 8, 15, and 22	48 mg	
	Cycles 4 through 9	1 and 15	48 mg	
	Cycles 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 the 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.		

Follicular Lymphoma

Option 1: Epcoritamab Monotherapy Dosing

Epcoritamab Dosage Schedule for Patients with FL when Given as Monotherapy				
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	Step-up dose 3	3 mg
		22	First full dose	48 mg
	Cycles 2 and 3	1, 8, 15, and 22	48 mg	
	Cycles 4 through 9	1 and 15	48 mg	
	Cycles 10 and beyond	1	48 mg	

Option 2: Epcoritamab + R^2 Combination Dosing

Epcoritamab Dosage Schedule in Combination with Lenalidomide and Rituximab 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	Step-up dose 3	3 mg
		22	First full dose	48 mg
	Cycles 2 and 3	1, 8, 15, and 22	48 mg	
	Cycles 4 through 12	1	48 mg	
*Administer epcoritamab in combination with lenalidomide 20 mg (Days 1 to 21 in Cycles 1 to 12) and rituximab 375 mg/m^2 (Cycles 1 to 5). Refer to the lenalidomide prescribing information and rituximab prescribing information for the respective dosage recommendations, including lenalidomide dosage recommendations for patients with renal insufficiency.				

Note: When epcoritamab is used in combination with R^2, dosing shifts to once per cycle beginning in Cycle 4, with administration only on Day 1 for Cycles 4 through 12.

Recommendations for Restarting Therapy with Epcoritamab After Dosage Delay for Patients with FL		
Last Dose Administered	**Time Since the 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
Cycles 2+	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 3[b] 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.

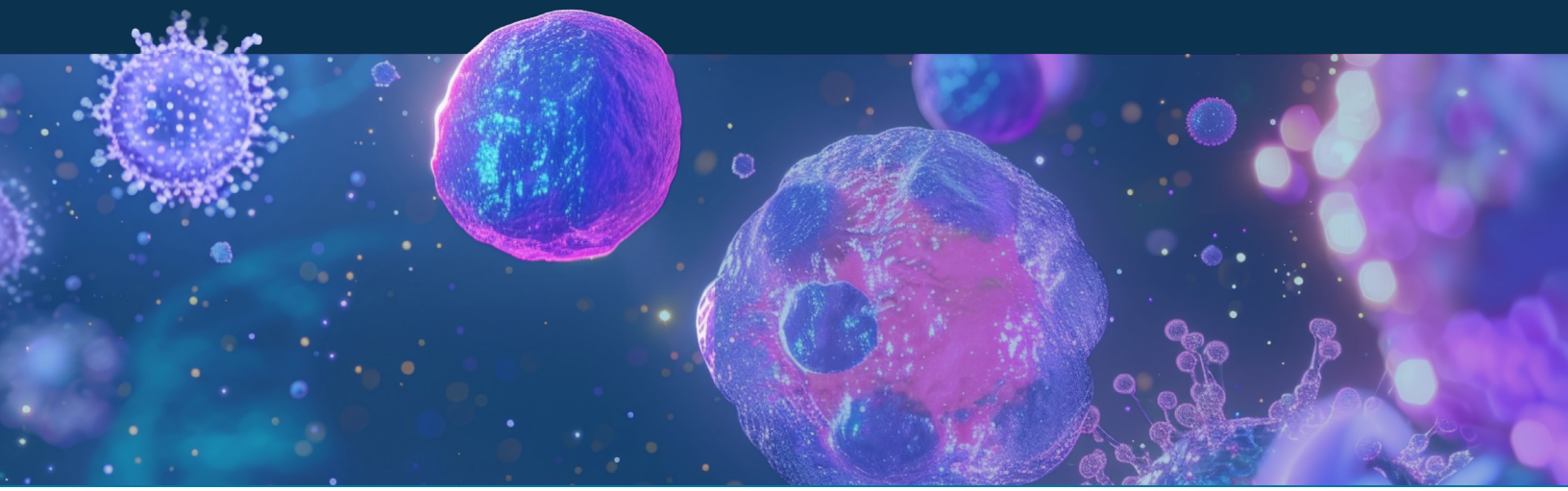
- Based on comorbidities and other situational factors, assess whether hospitalization or outpatient monitoring is appropriate after the first 48-mg dose. Patients monitored as outpatients should remain near a healthcare facility capable of evaluating and managing CRS.

Additional recommendations

- Provide *Pneumocystis jirovecii pneumonia* (PJP) prophylaxis during treatment with epcoritamab.
- Consider herpesvirus prophylaxis during treatment to prevent herpes simplex and herpes zoster.
- Patients should be well hydrated.
- For patients receiving lenalidomide, thromboprophylaxis is recommended. The choice of regimen should be based on an assessment of the patient's underlying risks.

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

Cytokine Release Syndrome



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.

CRS is frequently graded using the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.

Signs and symptoms:

- Chills
- Low tissue oxygen level
- Fever
- Rapid heartbeat
- Low blood pressure
- Trouble breathing

Why it matters:

CRS is a common side effect of epcoritamab. **Most CRS events** occurred during **Cycle 1**, with the **highest incidence following the 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 31% of patients**.
  - **Most events** (92%) occurred during **cycle 1,** with **43%** occurring **after the 48 mg dose on cycle 1, day 15**.
- **FL Monotherapy**: CRS occurred in **49% of patients** (45% grade 1, 9% grade 2) and **recurred in 48% of patients**.
  - **Most events** (88%) occurred during **cycle 1,** with **37%** occurring **after the 48 mg dose on cycle 1, day 22**.
- **FL R² Combination Therapy**: CRS occurred in **24% of patients** (19% grade 1, 5% grade 2) and **recurred in 41% of patients**.
  - **Most events** (88%) occurred during **cycle 1**, with **18%** 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.

Why it matters (continued):

- **FL Monotherapy: 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.
- **FL R² Combination Therapy: Median time to CRS onset** across all doses was **78 hours** (range: 0.2–12 days) after administration.

The median **duration of CRS** was **2 days** (range: <1-27 days).

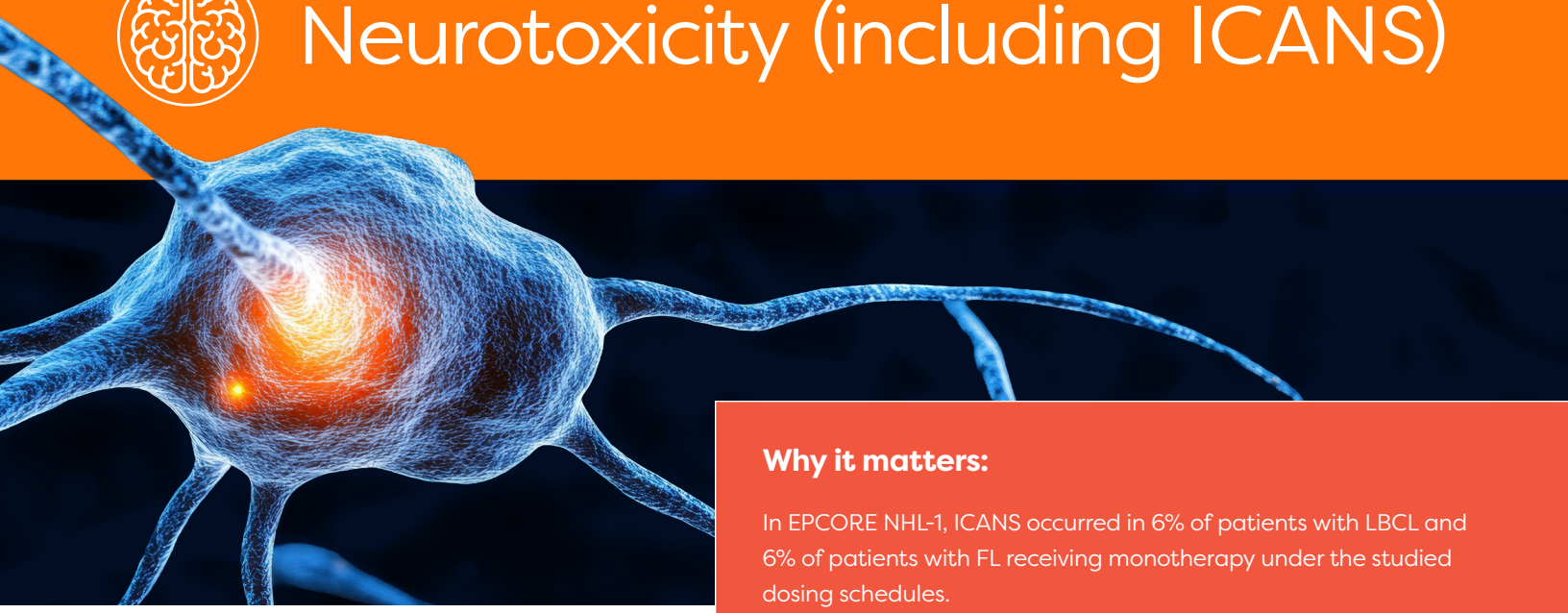
Concurrent neurologic adverse reactions associated with CRS occurred in <5% of patients.

- **DLBCL or High-grade B-cell Lymphoma**: 2.5% of patients.
- **FL Monotherapy**: 4.7% of patients.
- **FL R² Combination Therapy**: 1.5% of patients.

THE BOTTOM LINE:

CRS is common and usually Grade 1 or 2, but serious and fatal events can occur. Most events occur during Cycle 1, particularly after the first full 48-mg dose.

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:

- Confusion
- Dizziness
- Headache
- Memory issues
- Motor Deficits
- Shaking
- Trouble finding or words speaking

ICANS is frequently graded using the ASTCT consensus criteria.

THE BOTTOM LINE:

ICANS is uncommon and usually low grade, but life-threatening and fatal events can occur.

Why it matters:

In EPCORE NHL-1, ICANS occurred in 6% of patients with LBCL and 6% of patients with FL receiving monotherapy under the studied dosing schedules.

- **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 Monotherapy:** 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.
- **FL R2 Combination Therapy:** ICANS occurred in 0.8% of patients (0.8% grade 1).

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: 1-13 days).
- **FL Monotherapy: Median time to ICANS onset** from the start after treatment was **22 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 days** (range: 1-7 days).

Note: ICANS is uncommon and primarily low grade with epcoritamab monotherapy. Detailed time-to-onset, duration, and resolution data for ICANS with the R^2 regimen are not provided in the PI.

Other Toxicities

Epcoritamab may 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 look-out 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).
- **FL R^2 Combination Therapy: Serious infections** reported in **28%** (most common: 15% pneumonia, 7% COVID-19, 5% opportunistic infections, 3.3% upper respiratory tract infections). The most common opportunistic infections of any grade were CMV infection (7%) and herpesvirus infection (7%).
- **Progressive multifocal leukoencephalopathy (PML)**, including fatal cases, has occurred. Across a broader clinical-trial population, PML was reported in **0.4%** of patients.

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.
- Provide PJP prophylaxis and consider herpesvirus prophylaxis before starting epcoritamab.
- Consider monitoring immunoglobulin levels and administering immunoglobulin treatment when appropriate.
- Withhold or consider permanently discontinuing epcoritamab based on infection severity.

Cytopenias. Epcoritamab can cause serious or severe cytopenias.

- **DLBCL or High-grade B-cell Lymphoma: Grade 3 or 4** decreased neutrophils occurred in **32%**, decreased hemoglobin in **12%**, and decreased platelets in **12%** of patients.
  - 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** decreased neutrophils occurred in **30%**, decreased hemoglobin in **10%**, and decreased platelets in **8%** of patients.
  - Febrile neutropenia occurred in 3.1%.
- **FL R² Combination Therapy: Grade 3 or 4** decreased neutrophils occurred in **67%**, decreased lymphocytes in **62%**, decreased hemoglobin in 7**%**, and decreased platelets in **10%** of patients.
  - Febrile neutropenia occurred in 6% (Grade 4: 2.1%).

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**
  - **LBCL:** In EPCORE NHL-1, 49% of patients were ≥65 years old and 19% were ≥75 years old. No clinically meaningful differences in safety or efficacy were observed between patients ≥65 years old and younger adults.
  - **FL R² Combination Therapy:** In EPCORE FL-1, 36% of patients were ≥65 years old and 8% were ≥75 years old. No clinically meaningful differences in safety or efficacy were observed between patients ≥65 years old and younger adults.
  - **FL Monotherapy:** In EPCORE NHL-1, 52% of patients were ≥65 years old and 13% were ≥75 years old. Patients >65 years old experienced a higher rate of fatal adverse reactions, primarily infections, including COVID-19, compared with younger adults. No overall difference in efficacy was observed.
- **Pediatric Use:** At this time, no safety and effectiveness data have been established in pediatric patients.

References:

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