Epcoritamab-bysp

An HCP Tool for AIM with Immunotherapy

Epcoritamab-bysp is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy; adult patients with relapsed or refractory diffuse large B-cell lymphoma; and high-grade B-cell lymphoma after two or more lines of systemic therapy. The indications are under the accelerated approval program of the US FDA.

Clinical trial results

In a phase 2 study with dose escalation in adults with relapsed or refractory diffuse large B-cell lymphoma across four countries, the following was observed:

- The overall response rate in patients was 68% and 45% achieved a complete response at full doses of 12–60 mg
- The overall response rate was 88% (47–100), with 38% achieving a complete response at doses of 48 mg
- The overall response rate was 90% (55–100), among patients with relapsed or refractory follicular lymphoma and 50% achieved a complete response at full doses of 0·76–48 mg

In a dose-expansion cohort of the phase I/II study (NCT03625037), epcoritamab-bysp showed a median duration of response of 12.0 months (among complete responders it was not reached). This suggested potentially durable responses among some patients. At a median follow-up of 10.7 months, the overall response rate was 63.1% (95% CI, 55.0 to 70.6) and the complete response rate was 38.9%.

Pharmacology and FDA Approval

Epcoritamab-bysp (Epkinly) is a bispecific CD20-directed CD3 T-cell engaging antibody administered as subcutaneous injection for use in cancer. This bispecific antibody binds with one arm to the tumor antigen (CD20) and the other arm of the antibody binds to CD3 on the T-cell surface. The simultaneous binding of target cell and T-cell results in activation of the T-cell and cell killing.

It received accelerated approval from the FDA for refractory hematological malignancies, including diffuse large B cell lymphoma and follicular lymphoma. Confirmation of clinical benefit is necessary for continued approval of these indications.

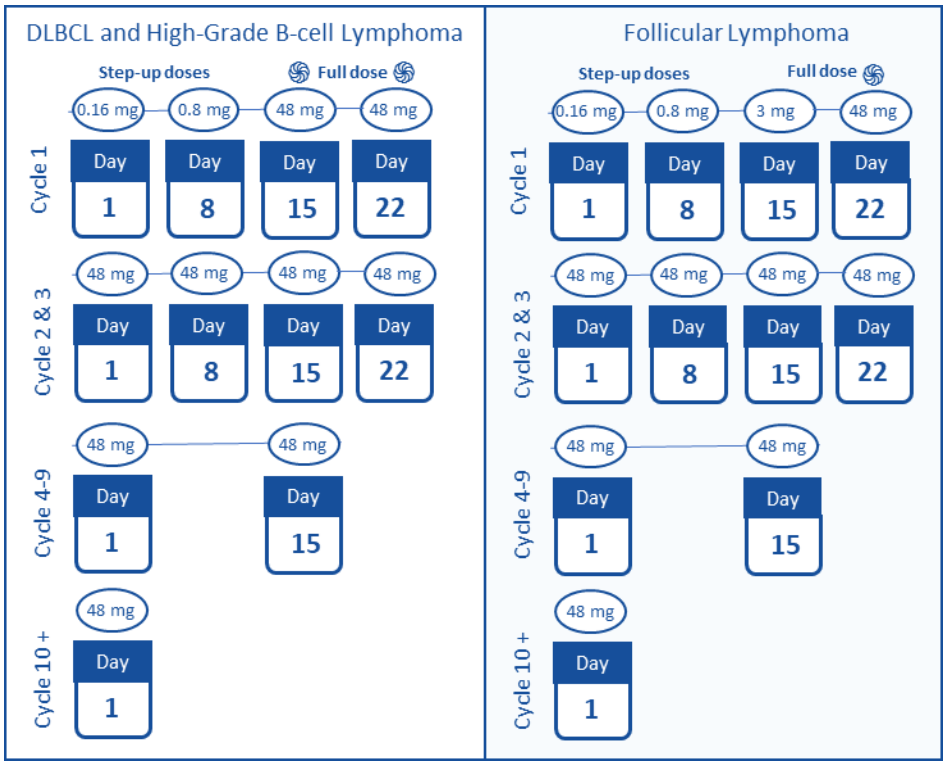
DRUG DOSAGE AND ADMINISTRATION

Epcoritamab-bysp is a subcutaneous injection (i.e. an injection under the skin) usually given to patients in the lower part of the stomach-area (abdomen) or thigh. It comes in a 0.8 mL single-dose vial in two doses: 4 mg and 48 mg. The full dosage after step-up dosing is 48 mg.

Due to the risk of cytokine release syndrome (CRS), epcoritamab-bysp is given on a "step-up" schedule once per week, starting at a low dose and increasing to full dose by the third week. In addition, preemptive, or prophylactic, medications are given to reduce the risk for CRS including corticosteroids. The doses for bispecific antibodies are increased or "stepped-up" for safety at pre-defined intervals. Early studies indicate that this strategy helps reduce the risk of severe CRS and also helps to evaluate how well the patient tolerates the regimen. Full strength doses are the end goal with step-up, smaller doses given first. If the dose of epcoritamab-bysp is delayed, the patient may need to repeat the "step-up" dosing schedule.

This type of dosing schedule may also require patients to be hospitalized after each dose to monitor for side effects. For example, patients with DLBCL or high-grade B-cell lymphoma are **hospitalized for 24 hours after administration of the first full strength dose given Cycle 1 Day 15 (48 mg)**. Once a full dose is received without complications, further hospitalization following treatments is not necessary. This guideline is based on results from the phase I and II studies that demonstrated CRS occurred primarily at these time points during "step-up".

The treatment schedule is divided into cycles that are usually 28 days (4 weeks) long. Health care providers determine the number of treatment cycles per patient. The drug is usually given every week for the first three cycles, then every 2 weeks for the cycles 4-9, and every 4 weeks starting with cycle 10. In the studies leading to the accelerated approval, the drug was given until disease progression or intolerance.



Step-up dosing illustration for epcoritamab-bysp

Note: Pre-medications prior to the administration of epcoritamab-bysp are required for all patients.

- Cycle 1: All patients should receive:
  - Dexamethasone (15 mg oral or intravenous) or prednisolone (100 mg oral or intravenous)
  - Diphenhydramine (50 mg oral or intravenous) or equivalent
  - Acetaminophen (650 mg to 1,000 mg oral)
- The pre-administration should take place 30 -120 minutes prior to each weekly administration of epcoritamab-bysp and for three consecutive days following each weekly administration of the drug in the first cycle (i.e. Cycle 1)

- For Cycle 2+: Patients who experienced Grade 2 or Grade 3 CRS with the previous dose
  - Dexamethasone (15 mg oral or intravenous or prednisolone (100 mg oral or intravenous)
- The pre-administration should occur 30 -120 minutes prior to the next administration of epcortimab-bysp after a Grade 2 or Grade 3 CRS event and for three consecutive days following the next administration until the drug is given without subsequent CRS of Grade 2 or higher.

SIDE EFFECTS AND MANAGEMENT

Black boxed drug warnings

There are two black boxed warnings associated with epcortimab-bysp: CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). Both adverse effects are commonly seen with immunotherapies that activate T cells to kill cancer cells, including other bispecific T-cell engaging antibodies and CAR T-cell therapies.

Adverse reactions

Serious adverse reactions can occur in patients receiving epicortimab-bysp. The most common (occurring in ≥ 20% of patients) adverse reactions are CRS, abdominal pain, cough, COVID-19, diarrhea, fatigue, headache, injection site reactions, musculoskeletal pain, nausea, pyrexia, rash, and upper respiratory tract infection. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) are decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Cytokine release syndrome (CRS)

In the phase I/II clinical trial (NCT03625037), CRS was primarily grade 1 or 2 in severity (49.7%; grade 1 or 2: 47.1%). Grade 3 CRS occurred in 2.5% of patients. Once CRS develops, epcortimab-bysp should be withheld until CRS resolves. Depending on severity of CRS, the drug may need to be permanently discontinued.

Signs and symptoms of CRS include chills, confusion, dizziness, fast heartbeat, feeling anxious, fever of 100.4° F or higher, headache, problems with balance and movement, shaking (tremors/rigors) or trouble breathing.

- **Grade 1** = fever of 100.4° F or higher
  - Withhold epcortimab-bysp and manage the patient
  - Ensure CRS symptoms are resolved prior to the next dose

- **Grade 2** = fever of 100.4° F or higher with hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen by nasal cannula or blow-by
  - Withhold epcortimab-bysp and manage the patient
  - Ensure CRS symptoms are resolved prior to the next dose
  - Administer pre-medications prior to the next dose
  - For the next dose, monitor more frequently and consider hospitalization

- **Grade 3** = fever of 100.4° F or higher with hypotension requiring vasopressors and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask
  - Withhold epcortimab-bysp and manage the patient
  - Ensure CRS symptoms are resolved prior to the next dose
  - Administer pre-medications prior to the next dose
  - For the next dose, hospitalization is required
  -
- **Recurrent Grade 3** = permanently discontinue epcoritamab-bysp

- **Grade 4** = fever of 100.4° F or higher with hypotension requiring multiple vasopressors and/or hypoxia requiring oxygen by positive pressure (e.g. CPAP, BiPAP, intubation, and mechanical ventilation)

Immune effector cell–associated neurotoxicity syndrome (ICANS)

Another potentially serious side effect of epicortimab-bysp is neurologic toxicity including ICANS (immune effector cell–associated neurotoxicity syndrome), which includes a host of neurological effects such as severe confusion, attention problems, tremor, and muscle weakness. For ICANS, at the first sign of neurologic toxicity (Grade 1), the drug is withheld until it resolves. The drug may be permanently discontinued based on ICANS severity.

The assessment of a patient, if arousable, is based on clinical findings along with the patient's ability to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment score. The ICE score is based on the following criteria: Orientation (oriented to year, month, city, hospital = 4 points); Naming (names 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If the patient is unarousable and/or unable to perform the ICE Assessment (Grade 4 ICANS), they receive 0 points.

- **Grade 1** = ICE score 7-9
  - Withhold epcortimab-bysp until ICANS resolves
  - Monitor neurologic symptoms and consider evaluation with neurology or other specialists
- **Grade 2** = ICE score 3-6
  - Withhold epcortimab-bysp until ICANS resolves
  - Administer dexamethasone (10 mg intravenously every 6 hours). Continue dexamethasone use until resolution to Grade 1 or less, then taper.
  - Monitor neurologic symptoms and consider evaluation with neurology or other specialists
- **Grade 3** = ICE score 0-2
  - Withhold epcortimab-bysp until ICANS resolves
  - Administer dexamethasone (10 mg intravenously every 6 hours). Continue dexamethasone use until resolution to Grade 1 or less, then taper.
  - Monitor neurologic symptoms and consider evaluation with neurology or other specialists
  - Provide supportive care, which may include intensive care
- **Recurrent Grade 3**
  - Permanently discontinue epcoritamab-bysp
  - Administer dexamethasone (10 mg intravenously every 6 hours). Continue dexamethasone use until resolution to Grade 1 or less, then taper.
  - Monitor neurologic symptoms and consider evaluation with neurology or other specialists
  - Provide supportive care, which may include intensive care
- **Grade 4** = ICE score 0
  - Permanently discontinue epcoritamab-bysp
  - Administer dexamethasone (10 mg intravenously every 6 hours). Continue dexamethasone use until resolution to Grade 1 or less, then taper.
  - Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days.
  - Monitor neurologic symptoms and consider evaluation with neurology or other specialists
  - Provide supportive care, which may include intensive care

Warnings and drug precautions

Patients should be monitored for signs of infection, including opportunistic infections and testing for latent hepatitis B while taking epcoritamab-bysp. Complete blood cell counts should be monitored during treatment. Females of reproductive potential should use effective contraception since the drug can cause fetal harm. Patients should use effective birth control (contraception) during treatment and for 4 months after the last dose of epcoritamab-bysp.

Recommended treatment interruptions and management

The table below shows management strategies for other side effects associated with epcoritamab-bysp.

Management of other notable side effects of epcoritamab-bysp

Adverse event	Common management guidance
Cytopenias	Neutropenia • Withhold epcoritamab-bysp in patients until the absolute neutrophil count is 0.5 x 10^9 L or higher. Consider neupogen or other similar GCSF support. Thrombocytopenia • Withhold epcoritamab-bysp in patients until the platelet count is 50 x 10^9 L or higher
Infections	All Grades • Withhold epcoritamab-bysp in patients with an active infection until the infection resolves Grade 4 • Consider permanent discontinuation of epcoritamab-bysp
Embryo-Fetal Toxicity	• May cause fetal harm. Females of reproductive potential should use effective contraception during treatment and for 4 months after the last dose.
Other adverse reactions	• Withhold epcoritamab-bysp until the toxicity resolves to Grade 1 or baseline

- Severity is based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.
- Educate patients and caregivers about side effects and the importance of reporting symptoms as soon as possible. Remind patients about the importance of staying on schedule.

QUESTIONS & ANSWERS

Q. **How is epcoritamab given?**

A. The drug is given as an injection under the skin. It is not an infusion, chemotherapy, stem cell therapy or similar therapy. It is injected at a site that is able to administer it, such as an oncology office or an outpatient center.

Q. **How do you modify doses if a patient experiences a severe adverse event like cytokine release syndrome?**

A. Patients who experience severe (Grade 3) reactions will have the drug withheld. If the drug is restarted, step-up dosing applies. Doses are not escalated. Among clinical trial studies, 49-51% of patients experienced cytokine release syndrome. The majority of these were Grades 1 and 2. Cytokine release syndrome resolved in 98-100% of patients and the median duration of the event was 2 days, but this ranged in patients from 1 to 14 days.

Q. **What should patients avoid while receiving epcoritamab-bysp?**

A. Patients should not drive, operate heavy machinery, or similar activities, especially if they develop dizziness, confusion, tremors, sleepiness, or any other symptoms that impair consciousness until the signs and symptoms go away. These may be signs and symptoms of cytokine release syndrome or neurologic problems. Similarly, Patients who experienced cytokine release syndrome (or other adverse reactions that impair consciousness) should be evaluated and advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Q. **What are possible side effects of epcoritamab-bysp?**

A. Epcoritamab can cause serious side effects, including infection. The signs and symptoms of this include a fever of 100.4°F or above, cough, chest pain, tiredness, shortness of breath, painful rash, sore throat, pain during urination, and feeling weak or generally unwell.

PATIENT RESOURCES

ADDITIONAL INFORMATION RESOURCES

American Cancer Society
Patient programs, services, 24/7 hotline, etc
https://www.cancer.org/

National Cancer Institute
Information about cancer types, treatment, side effects, find a clinical trial, etc
https://www.cancer.gov/

FINANCIAL ASSISTANCE

Cancer Financial Aid Coalition
Facilitates communication, educates and advocates for patients.
www.cancerfac.org

Centers for Medicare and Medicaid Services (CMS)
Apply to determine if you are eligible for government assistance.
www.cms.gov or www.medicare.gov
800-633-4227

Lazarex Foundation
Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.
www.lazarex.org

Needymeds
Database to search for free or low-cost medications, help with medical transportation and other resources.
www.needymeds.org

Patient Advocate Foundation
Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability.
Patient must meet their eligibility for financial assistance.
www.patientadvocate.or
g 800-532-5274

Expect Miracles Foundation
The Sam Fund for Young Adult Survivors of Cancer assists ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.
www.thesamfund.org
info@thesamfund.org

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PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation
Helps with the cost of medication. Availability of funds for patients with specific cancers is subject to availability.
www.cancercarecopay.org
1-866-552-6729

Medicine Assistance Tool
Database to search for patient assistance resources offered by pharmaceutical companies.
www.medicineassistancetool.org/

Patient Advocate Foundation Co-Pay Relief
Provides direct financial support to patients who medically qualify. Funds subject to availability.
https://copays.org
1-866-512-3861

Good Days
Provides assistance with insurance co-pays, and prescription medications. Funds subject to availability.
www.mygooddays.org

Health Well Foundation
For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Funds for patients subject to availability. Patient must also meet eligibility for financial assistance.
www.healthwellfoundation.org or grants@healthwellfoundation.org
1-800-675-8416

The Assistance Fund, Inc
Provides prescription copay and financial assistance, including health insurance premiums. Funds subject to availability.
www.theassistancefund.org
https://tafcares.org
1-855-845-3663

PAN Foundation
Provides financial assistance to cover out-of-pocket treatment costs. Funds subject to availability.
www.panfoundation.org
1-866-316-PANF (7263)

Patient Assistance Program
Comprehensive database of patient assistance programs offering free medications.
www.rxassist.org
info@rxassist.org

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HOUSING

American Cancer Society – Hope Lodge
Provides free housing during treatment appointments. Requires a referral from your social worker.
www.cancer.org/
1-800-227-6333.

American Cancer Society – Extended Stay America
Partnership to offer discounted rooms for patients who have to be away from home for cancer treatment.
https://www.cancer.org/about-us/our-partners/extended-stay-america.html
1-800-227-2345

Healthcare Hospitality Network
Connects patients and their caregivers looking for lodging near their healthcare provider
https://members.hhnetwork.org/locate-a-house
1-800-318-8861

Joe's House
Helping patients with cancer find lodging throughout the U.S.
https://www.joeshouse.org/lodging?state=0
1-877-563-7468

National Council of State Housing Agencies
Emergency rental assistance programs available by state. Federal grants still available in some areas.
https://www.ncsha.org/emergency-housing-assistance/

TRANSPORTATION (AIR AND GROUND)

Air Charity Network
Provides access for people in need who are seeking free air transportation to specialized health care facilities
http://aircharitynetwork.org/
1-877-621-7177

Corporate Angel Network
Nonprofit organization that helps cancer patients by arranging free travel on corporate aircraft
https://www.corpangelnetwork.org/
info@corpangelnetwork.org
1-914-328-1313

Medicaid
Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.
1-877-633-8747

Mercy Medical Angels
Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.
www.mercymedical.org/

Pilots for Patients
Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.
www.pilotsforpatients.org
318-322-5112

ADDITIONAL RESOURCES

EPKINLY (epcoritamab-bysp) injection [prescribing information]. Plainsboro, NJ, and North Chicago, IL, USA: Genmab US, Inc and AbbVie Inc. Available at: https://www.genmab-pi.com/prescribing-information/epkinly-pi.pdf. Updated August 2024. Accessed October 14, 2024.

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.

Middelburg J, Sluijter M, Schaap G et al. T-cell stimulating vaccines empower CD3 bispecific antibody therapy in solid tumors. Nat Commun. 2024;15(1):48. doi: 10.1038/s41467-023-44308-6.

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.