Product Monograph

INDICATIONS

DLBCL and High-grade B-cell Lymphoma

- EPKINLY is indicated for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma (HGBCL) 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 for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Follicular Lymphoma

- EPKINLY is indicated in combination with lenalidomide and rituximab for the treatment of adults with relapsed or refractory follicular lymphoma (FL).
- EPKINLY is indicated as monotherapy for the treatment of adults with relapsed or refractory FL after 2 or more lines of systemic therapy.

SELECT IMPORTANT SAFETY INFORMATION

BOXED WARNINGS

- **Cytokine release syndrome (CRS), including serious or fatal reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosage schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity.**
- **Immune effector cell–associated neurotoxicity syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity.**

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

Important Safety Information

CRS

- CRS occurred in 51% (80/157) of patients with large B-cell lymphoma (LBCL) receiving EPKINLY at the recommended dosage schedule in EPCORE NHL-1 (37% Grade 1, 17% Grade 2, and 2.5% Grade 3) and recurred in 31% of patients. Most events (92%) occurred during Cycle 1. In Cycle 1, CRS events occurred in 6% of patients after the 0.16 mg dose (Cycle 1, day 1), 12% after the 0.8 mg dose (Cycle 1, day 8), 43% after the first 48 mg dose (Cycle 1, day 15), and 5% after the next 48 mg dose (Cycle 1, day 22). The median time to onset of CRS from the most recent administered dose across all doses was 24 hours (range: 0-10 days). The median time to onset after the first full 48 mg dose was 21 hours (range: 0-7 days).
- CRS occurred in 49% (42/86) of patients with FL receiving EPKINLY monotherapy at the recommended dosage schedule in EPCORE NHL-1 (45% Grade 1, 9% Grade 2) and recurred in 48% of patients. Most events (88%) occurred during Cycle 1. In Cycle 1, CRS events occurred in 12% of patients after the 0.16 mg dose (Cycle 1, day 1), 6% after the 0.8 mg dose (Cycle 1, day 8), 15% after the 3 mg dose (Cycle 1, day 15), and 37% after the first 48 mg dose (Cycle 1, day 22). The median time to onset of CRS from the most recent administered dose across all doses was 59 hours (range: 0.1-7 days). The median time to onset after the first full 48 mg dose was 61 hours (range: 0.1-7 days).
- CRS occurred in 24% (32/131) of patients with FL receiving EPKINLY at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1 (19% Grade 1, 5% Grade 2, and 12% serious adverse reactions due to CRS) and recurred in 41% of patients. Most events (88%) occurred during Cycle 1. In Cycle 1, CRS occurred in 5% of patients after the 0.16 mg dose (Cycle 1, day 1), 3.8% after the 0.8 mg dose (Cycle 1, day 8), 2.3% after the 3 mg dose (Cycle 1, day 15), and 18% after the first 48 mg dose (Cycle 1, day 22). The median time to onset of CRS from the most recent EPKINLY dose was 78 hours (range: 0.2-12 days). The median time to onset after the first 48 mg dose was 41 hours (range: 0.3-12 days).
- For patients with LBCL and FL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose is appropriate based on comorbidities or other situational factors. During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.
- In patients who experienced CRS, the signs and symptoms included pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. CRS resolved in 98% of patients; the median duration of CRS events was 2 days (range: <1-27 days). Concurrent neurological adverse reactions associated with CRS occurred in 2.5% of patients with LBCL, 4.7% of patients with FL receiving EPKINLY monotherapy, and 1.5% of patients receiving EPKINLY in combination with lenalidomide and rituximab (reactions included headache, confusional state, tremors, dizziness, and ataxia).
- Administer pretreatment medications to reduce the risk of CRS.
- Monitor patients for potential CRS. At the first signs or symptoms of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care as appropriate.

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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Important Safety Information

ICANS

- ICANS occurred in 6% (10/157) of patients with LBCL receiving EPKINLY at the recommended dosage schedule in EPCORE NHL-1 (4.5% Grade 1, 1.3% Grade 2, 0.6% fatal). Of the 10 ICANS events, 9 occurred within Cycle 1 of treatment, with a median time to onset of 16.5 days (range: 8-141 days) from the start of treatment. Relative to the most recent administered dose, the median time to onset was 3 days (range: 1-13 days). The median duration of ICANS was 4 days (range: 0-8 days), with ICANS resolving in 90% of patients with supportive care.
- ICANS occurred in 6% (8/127) of patients with FL receiving EPKINLY monotherapy following the 2-step up dosage schedule in EPCORE NHL-1 (3.9% Grade 1, 2.4% Grade 2). The median time to onset was 22 days (range: 14-66 days) from the start of treatment. Relative to the most recent administered dose, the median time to onset of ICANS was 3 days (range: 0.4-7 days). The median duration of ICANS was 2 days (range: 1-7 days), with ICANS resolving in 100% of patients.
- Among patients with FL who received EPKINLY at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1, ICANS occurred in 0.8% (1/131, Grade 1).
- The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Clinical manifestations of ICANS included, but were not limited to, confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus.
- Monitor patients for potential ICANS. At the first signs or symptoms of ICANS, immediately evaluate patient, provide supportive therapy based on severity, and manage per current practice guidelines.

Infections

- EPKINLY can cause fatal and serious infections. Serious infections, including opportunistic infections, were reported in 15% of patients with LBCL in EPCORE NHL-1 (most common: 4.5% sepsis, 3.2% pneumonia). Fatal infections occurred in 1.3% of patients (1.3% COVID-19).
- Serious infections, including opportunistic infections, were reported in 40% of patients with FL receiving EPKINLY monotherapy following the 2-step up dosage schedule in EPCORE NHL-1 (most common: 20% COVID-19, 13% pneumonia, 3% urinary tract infections). Fatal infections occurred in 6% of patients (5% COVID-19, 0.8% pneumonia, 0.8% sepsis).
- Among 243 patients with FL who received EPKINLY in combination with lenalidomide and rituximab in EPCORE FL-1, serious infections occurred in 28% of patients. The most common serious infections were pneumonia (15%), COVID-19 (7%), opportunistic infections (5%) and upper respiratory infections (3.3%). The most common opportunistic infections of any grade were cytomegalovirus (CMV) infection (7%) and herpesvirus infection (7%).
- Progressive multifocal leukoencephalopathy (PML), including fatal cases, has occurred in patients treated with EPKINLY. Across a broader clinical trial population, PML was reported in 0.4% (11/3,072) of patients, including in the first-line treatment setting. Of the 11 cases of PML, 6 resulted in fatal outcomes and 1 was unresolved at the time of death.
- Monitor patients for signs and symptoms of infection and treat appropriately. Avoid administration in patients with active infections. Withhold or consider permanent discontinuation of EPKINLY based on severity. Provide *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis during treatment with EPKINLY and consider prophylaxis against herpesvirus.
- Consider monitoring immunoglobulin levels during treatment and administration of immunoglobulin treatment as appropriate.

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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Important Safety Information

Cytopenias

- EPKINLY can cause serious or severe cytopenias. In the clinical trial of patients with LBCL, Grade 3 or 4 decreased neutrophils occurred in 32% (Grade 4, 14%), decreased hemoglobin in 12% (Grade 4, 0%), and decreased platelets in 12% (Grade 4, 7%) of patients. Febrile neutropenia occurred in 2.5% (Grade 4, 0.6%).
- In the clinical trial of patients with FL who received EPKINLY monotherapy following the 2-step up dosage schedule, Grade 3 or 4 decreased neutrophils occurred in 30% (Grade 4, 17%), decreased hemoglobin in 10% (Grade 4, 0%), and decreased platelets in 8% (Grade 4, 4%) of patients. Febrile neutropenia occurred in 3.1% (Grade 4, 0%).
- In patients with FL who received EPKINLY in combination with lenalidomide and rituximab, Grade 3 or 4 decreased neutrophils occurred in 67% (Grade 4, 41%), decreased lymphocytes in 62% (Grade 4, 13%), decreased hemoglobin in 7%, and decreased platelets in 10% (Grade 4, 4.1%) of patients. Febrile neutropenia occurred in 6% (Grade 4, 2.1%).
- Monitor complete blood counts throughout treatment. Based on severity of cytopenias, temporarily withhold or permanently discontinue EPKINLY. Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Embryo-Fetal Toxicity

- EPKINLY may cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose. Verify pregnancy status in females of reproductive potential prior to initiating EPKINLY.

Adverse Reactions

- EPKINLY as monotherapy for LBCL or FL: Most common (≥20%) adverse reactions were CRS, injection site reactions, fatigue, musculoskeletal pain, fever, diarrhea, COVID-19, rash, and abdominal pain. Most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, and decreased platelets.
- EPKINLY in combination with lenalidomide and rituximab for FL: Most common (≥20%) adverse reactions were rash, upper respiratory tract infections, fatigue, injection site reactions, constipation, diarrhea, CRS, pneumonia, COVID-19, and fever. The most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased neutrophils, decreased lymphocytes, and decreased platelets.

Use in Specific Populations

- **Lactation:** Advise women not to breastfeed during treatment and for 4 months after the last dose of EPKINLY.
- **Geriatric Use:** In patients with relapsed or refractory FL who received EPKINLY in EPCORE NHL-1, 52% were ≥65 years old, and 13% were ≥75 years old. A higher rate of fatal adverse reactions, primarily infections, including COVID-19, was observed in patients ≥65 years old compared to younger adult patients. No overall difference in efficacy was observed.

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  This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Follicular Lymphoma

- EPKINLY is indicated in combination with lenalidomide and rituximab for the treatment of adults with relapsed or refractory follicular lymphoma (FL).
- EPKINLY is indicated as monotherapy for the treatment of adults with relapsed or refractory FL after 2 or more lines of systemic therapy.

SELECT IMPORTANT SAFETY INFORMATION

EPKINLY can cause serious side effects, including **cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS),** Infections, Cytopenias, and Embryo-Fetal Toxicity. **Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.**

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Executive Summary

EPKINLY® (epcoritamab-bysp) is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of:

- **adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma (HGBCL) after two or more lines of systemic therapy.**

This indication is approved under accelerated approval based on response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

DLBCL/HGBCL

The efficacy of EPKINLY was evaluated in EPCORE® NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multicohort, multicenter, single-arm trial in 157 patients with relapsed or refractory LBCL after 2 or more lines of systemic therapy.[1]

- **Efficacy[a]:** EPKINLY provided an ORR[b] of 61% (n=90/148; 95% CI, 53-69), with 38% of patients achieving a CR (n=56/148; 95% CI, 30-46) and 23% achieving a PR (n=34/148; 95% CI, 17-31). Median DOR was 15.6 months (n=90/148; 95% CI, 9.7-NR).[1]

Warnings and Precautions: Monotherapy

For EPKINLY monotherapy, warnings and precautions include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), infections, cytopenias, and embryo-fetal toxicity. The most common adverse reactions (≥20%) are CRS, injection site reactions, fatigue, musculoskeletal pain, fever, diarrhea, COVID-19, rash, and abdominal pain. Most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, and decreased platelets.

CD3=cluster of differentiation 3; CD20=cluster of differentiation 20; CI=confidence interval; CR=complete response; CRS=cytokine release syndrome; DOR=duration of response; IRC=Independent Review Committee; NHL=non-Hodgkin lymphoma; NR=not reached; ORR=overall response rate; PR=partial response.

[a]Determined by Lugano criteria (2014) as assessed by IRC.
[b]Early response assessments were evaluated in the context of potential flare reactions. Of 90 patients who achieved an objective response, 9 patients had early flare reactions identified with objective response demonstrated on subsequent imaging per Lugano criteria.

SELECT IMPORTANT SAFETY INFORMATION

EPKINLY can cause serious side effects, including **cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS),** Infections, Cytopenias, and Embryo-Fetal Toxicity. **Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.**

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Executive Summary

EPKINLY® (epcoritamab-bysp) is a bispecific CD20-directed CD3 T-cell engager indicated for the treatment of:

- **adults with relapsed or refractory follicular lymphoma (FL) in combination with lenalidomide and rituximab.**
- **adults with relapsed or refractory FL after 2 or more lines of systemic therapy as monotherapy.**

FL

The efficacy of EPKINLY in combination with lenalidomide and rituximab R² was evaluated in EPCORE® FL-1 (Study M20-638; NCT05409066), an open-label, randomized, multicenter, global trial in 488 patients with relapsed or refractory FL after at least 1 line of systemic therapy.

- **Efficacy:** EPKINLY + R² demonstrated a 79% reduction in the risk of disease progression or death vs R² (HR=0.21[a]; 95% CI, 0.13-0.33; P<0.0001[b]).[1] EPKINLY provided an ORR of 89% (n=216/243; 95% CI, 84-93), with 74% of patients achieving a CR (n=181/243; 95% CI, 69-80).[1]

The efficacy of EPKINLY was evaluated in EPCORE® NHL-1, an open-label, multicohort, multicenter, single-arm trial in 127 patients with relapsed or refractory FL after at least two lines of systemic therapy.[1]

- **Efficacy[c]:** EPKINLY provided an ORR of 82% (n=104/127; 95% CI, 74-88), with 60% of patients achieving a CR (n=76/127; 95% CI, 51-68) and 22% achieving a PR (n=28/127); 95% CI, 15-30).

Warnings and Precautions: Combination with Lenalidomide + Rituximab

For EPKINLY in combination with lenalidomide and rituximab, warnings and precautions include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), infections, cytopenias, and embryo-fetal toxicity. The most common adverse reactions (≥20%) are CRS, injection site reactions, fatigue, COVID-19, rash, upper respiratory tract infections, infections, constipation, and abdominal pain. The most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocyte count, decreased neutrophil count, decreased hemoglobin, and decreased platelets.

Warnings and Precautions: Monotherapy

For EPKINLY monotherapy, warnings and precautions include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), infections, cytopenias, and embryo-fetal toxicity. The most common adverse reactions (≥20%) are CRS, injection site reactions, fatigue, musculoskeletal pain, fever, diarrhea, COVID-19, rash, and abdominal pain. Most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocytes, decreased neutrophils, decreased hemoglobin, and decreased platelets.

CD3=cluster of differentiation 3; CD20=cluster of differentiation 20; CI=confidence interval; CR=complete response; CRS=cytokine release syndrome; DOR=duration of response; IRC=Independent Review Committee; NHL=non-Hodgkin lymphoma; NR=not reached; ORR=overall response rate; PR=partial response.

[a]Cox proportional hazards hazard ratio stratified by disease history and region.
[b]Log-rank *P*-value (one-sided) stratified by disease history and region.
[c]Determined by Lugano criteria (2014) as assessed by IRC.

SELECT IMPORTANT SAFETY INFORMATION

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Unmet Need

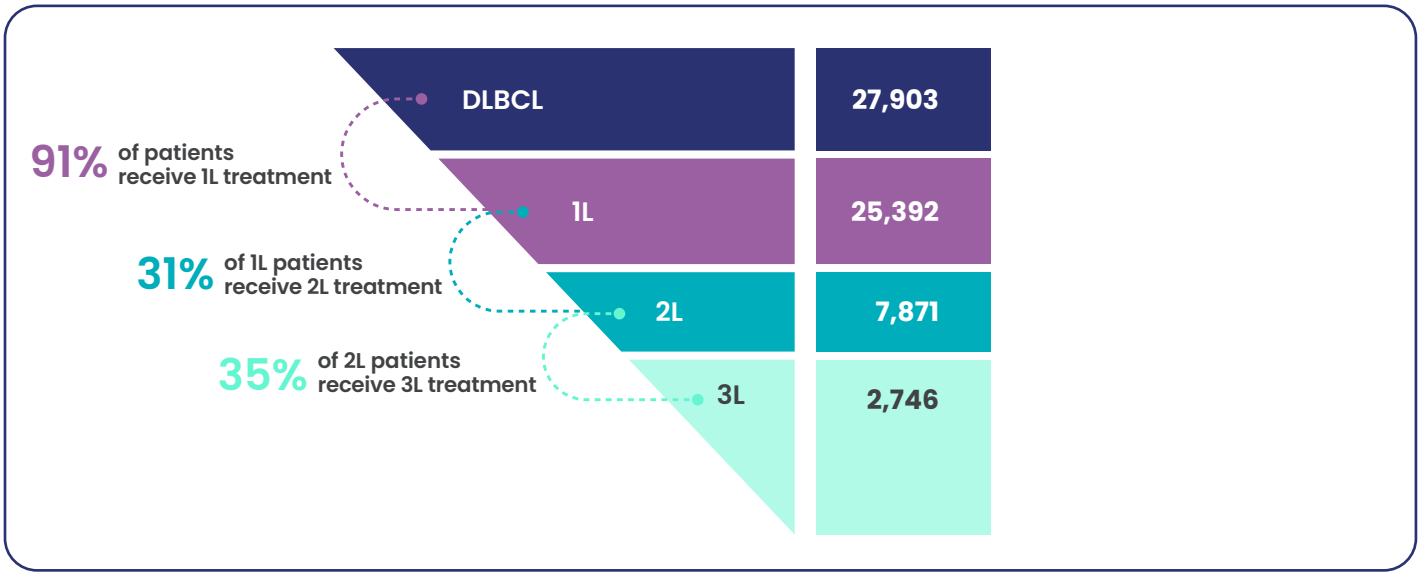
Non-Hodgkin lymphoma (NHL), which includes diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL), is the seventh most common cancer in the United States; an estimated 80,350 new cases of NHL were diagnosed in 2025.[2,3]

Diffuse Large B-Cell Lymphoma

DLBCL is the most common type of NHL, accounting for approximately 30% of all NHL cases, and the projected 10-year prevalence of DLBCL in the United States is expected to increase by 12%.[2,4] The incidence of DLBCL is significantly higher among older patients, with 31.9 cases per 100,000 among Medicare patients (≥65 years of age), compared to 3.9 per 100,000 among commercially insured patients (<65 years of age).[5]

Data from the Surveillance, Epidemiology, and End Results (SEER) Program were used to develop an analytic model estimating the number of patients eligible for DLBCL and LBCL treatment in the United States. The model projected 27,903 incident DLBCL cases in 2023 (Figure 1).[6] Projections indicate 91% of patients receive first-line (1L) therapy, 31% of those progress to second-line (2L) therapy, and only 35% of 2L patients advance to third-line (3L) therapy.[6] Of those diagnosed with DLBCL, claims data indicate 62% are covered by Medicare and 31% by commercial insurance.[7]

Figure 1: Estimated Diffuse Large B-Cell Lymphoma Patients by Line of Therapy in the United States (2023)[6]



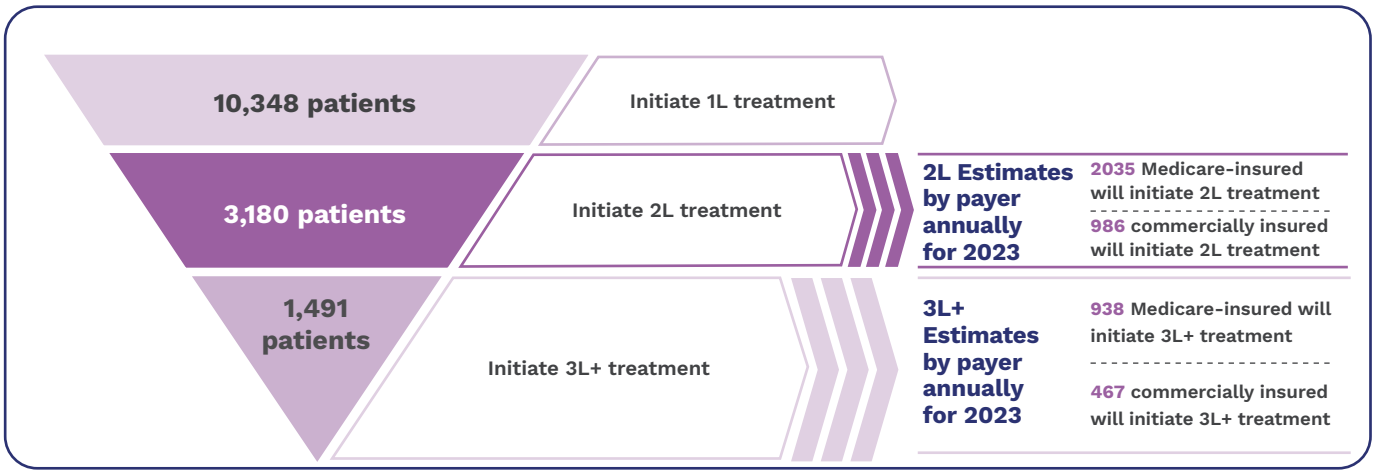
By 3L+, patients have a poor prognosis, facing low response and worsening survival rates with each subsequent line of therapy.[8] Currently, there is no standard of care for 3L+ therapy, and while some 3L+ DLBCL patients may achieve remission, the approved options are not always accessible or effective for all patients due to both clinical and nonclinical factors.[9-15]

Follicular Lymphoma

FL is the second most common type of NHL, representing approximately 22% of NHL cases.[2] An estimated 13,374 cases were diagnosed in 2024, translating to a yearly projected incidence of 4.0 per 100,000.[4,16] Most patients with FL—63%—are covered by Medicare, while 31% are commercially insured.[7]

While the majority of patients receive 1L treatment, fewer than 1 of every 10 receive 3L therapy.[17] Across the United States, 1,491 initiate 3L+ treatment annually, including an estimated 938 Medicare-insured and 467 commercially insured.[17,18] Among 3,180 2L patients, an estimated 2,035 were Medicare-insured and 986 were commercially insured.[17,18]

Figure 2: Estimated Follicular Lymphoma Patients by Line of Therapy in the United States (2024)[17,18]



FL is a slow-growing, indolent condition where patients may relapse or become refractory to multiple lines of therapy and experience declining outcomes. The estimated 5-year overall survival for patients initiating 3L treatment is 35%, compared to 60% for those initiating 1L treatment.[19,20] As patients relapse and experience disease recurrence, outcomes such as overall survival (OS) and progression-free survival (PFS) decline across lines of therapy.[21] Despite the availability of multiple therapies, there is no established standard of care for 3L+ FL treatment, and the presence of prognostic factors, such as double refractory disease, advanced age (>65 years), and high-risk Follicular Lymphoma International Prognostic Index (FLIPI) scores, can further worsen outcomes.[22,23]

About EPKINLY® for DLBCL and FL

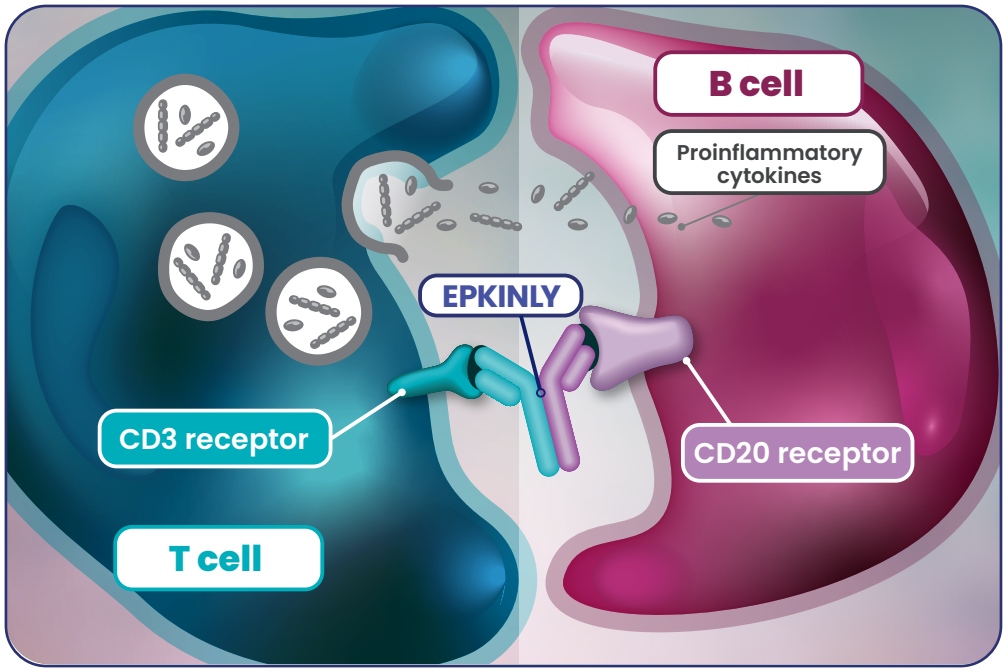
Epcoritamab-bysp is a bispecific CD20-directed CD3 T-cell engager; it is a humanized bispecific immunoglobulin G subclass 1 (IgG1) antibody. Epcoritamab-bysp is manufactured in Chinese hamster ovary (CHO) cells using recombinant DNA technology and has an approximate molecular weight of 149 kDa.[1]

Mechanism of Action[1]

Epcoritamab-bysp binds to the CD3 receptor expressed on the surface of T cells and CD20 expressed on the surface of lymphoma cells and healthy B-lineage cells. Developed using Genmab's innovative DuoBody® platform, EPKINLY helps activate T cells and target CD20.[24]

In vitro, epcoritamab-bysp activated T cells, caused the release of proinflammatory cytokines, and induced lysis of B cells (Figure 3). In nonclinical studies, the combination of epcoritamab-bysp and rituximab resulted in both T-cell mediated cytotoxicity and natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC).

Figure 3: The Mechanism of Action of EPKINLY Targets CD3 and CD20



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Pharmacodynamics[1]

Circulating B-Cell Count

Circulating B cells decreased to undetectable levels (<10 cells/microliter) after administration of the approved recommended dosage of EPKINLY in patients who had detectable B cells at treatment initiation by Cycle 1 Day 15, and the depletion was sustained while patients remained on treatment.

Cytokine Concentrations

Plasma concentrations of cytokines (interleukin [IL]-2, IL-6, IL-10, tumor necrosis factor [TNF]-α, and interferon [IFN]-γ) were measured. Transient elevation of circulating cytokines was observed at dose levels of 0.04 mg and above.

After administration of the approved recommended dosages of EPKINLY, cytokine levels increased within 24 hours after the first dose on Cycle 1 Day 1, generally reached maximum levels after the first 48 mg dose and returned to baseline prior to the second 48 mg full dose.

Pharmacokinetics[1]

Pharmacokinetic (PK) parameters were evaluated at the approved recommended dosage (48 mg) and are presented as geometric mean (CV%) unless otherwise specified.

Epcoritamab-bysp area under the concentration-time curve (AUC) increased more than proportionally over a full dosage range from 1.5 to 60 mg (0.03125 to 1.25 times the approved recommended dosage).

Epcoritamab-bysp maximum concentration (10.2 mcg/mL [43.2%]) is achieved after the first dose of the every 2 weeks (Q2W) regimen (ie, the first dose of Cycle 4). No clinically significant differences in PK parameters were observed between patients with relapsed or refractory large B-cell lymphoma (LBCL) and patients with relapsed or refractory follicular lymphoma (FL). PK exposures are summarized for the recommended dosage of EPKINLY in Table 1.

Table 1: Exposure Parameters of Epcoritamab-bysp in Subjects With Relapsed or Refractory Large B-Cell Lymphoma and Relapsed or Refractory Follicular Lymphoma Following Recommended Dosage

	C_{avg} (mcg/mL)[a]	C_{max} (mcg/mL)[a]	C_{trough} (mcg/mL)[a]
First full 48 mg dose[b]	1.3 (113.3%)	1.7 (106.7%)	1.4 (100.9%)
End of weekly dosing (end of Cycle 3)	9.1 (45.9%)	9.9 (43.4%)	7.8 (52.4%)
End of every 2-week dosing (end of Cycle 9)	5.3 (57%)	6.7 (49.4%)	3.6 (81.5%)
Steady state[c] with every 4-week dosing	2.4 (73.3%)	4.2 (59.8%)	1.1 (134.1%)

[a]Values are geometric mean with geometric CV%.
[b]First full 48 mg dose is on the first day of Week 3 in subjects with relapsed or refractory LBCL and on the first day of Week 4 in subjects with relapsed or refractory FL.
[c]Steady state values are approximated at Cycle 15 (Week 60).

Absorption

The median (range) T_{max} of epcoritamab-bysp after the first full dose and end of the weekly dosing regimen (end of Cycle 3) treatment doses were 4 (0.3 to 7) days and 2.3 (0.3 to 3.2) days, respectively.

Distribution

The apparent total volume of distribution is 25.6 L (82%).

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Elimination

The half-life of full dose epcoritamab-bysp (48 mg) was approximately 22 days (58%) at the end of Cycle 3, with apparent total clearance of approximately 0.53 L/day (40%) after the end of Cycle 3.

Metabolism

Epcoritamab-bysp is expected to be metabolized into small peptides by catabolic pathways.

Specific Populations

No clinically significant differences in the PK of epcoritamab-bysp were observed based on age (20 to 89 years), sex, race (White or Asian), mild to moderate renal impairment (creatinine clearance [CrCL] 30 to <90 mL/min as estimated by Cockcroft-Gault formula), and mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] and aspartate transaminase [AST] > ULN, or total bilirubin 1 to 1.5 times ULN and any AST) after accounting for differences in body weight (BW).

The effects of severe renal impairment (CrCL 15 to <30 mL/min), end-stage renal disease (CrCL <15 mL/min), or moderate-to-severe hepatic impairment (total bilirubin >1.5 times ULN and any AST) on the PK of epcoritamab-bysp are unknown.

Body Weight (BW)

In patients who received the recommended dosage of EPKINLY, geometric mean average concentration following the first full 48 mg dose was 31% lower in the higher BW group (85 to 172 kg) and 13% higher in the lower BW group (39 to 65 kg) compared to patients with BW of 65 to <85 kg.

Drug Interaction Studies

No clinical studies evaluating the drug interaction potential of epcoritamab-bysp have been conducted.

Immunogenicity[1]

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the study described below with the incidence of ADA in other studies, including those of epcoritamab-bysp.

Anti-epcoritamab-bysp antibodies developed in 2.6% of patients (4 of 156) with LBCL and 4.2% of patients (8 of 190) with FL treated with EPKINLY in EPCORE NHL-1 (up to 10 cycles) using an electrochemiluminescence immunoassay (ECLIA). Because of the low occurrence of ADA, the effect of these antibodies on the PK, pharmacodynamics, safety, and effectiveness of epcoritamab-bysp is unknown.

Use in Specific Populations[1]

Pregnancy

Based on the mechanism of action, EPKINLY may cause fetal harm when administered to a pregnant woman. There are no available data on the use of EPKINLY in pregnant women to evaluate for a drug-associated risk. No animal reproductive or developmental toxicity studies have been conducted with epcoritamab-bysp.

About EPKINLY® for DLBCL and FL

Epcoritamab-bysp causes T-cell activation and cytokine release; immune activation may compromise pregnancy maintenance. In addition, based on expression of CD20 on B cells and the finding of B-cell depletion in non-pregnant animals, epcoritamab-bysp can cause B-cell lymphocytopenia in infants exposed to epcoritamab-bysp in utero. Human IgG is known to cross the placenta; therefore, EPKINLY has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to the fetus.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation

There is no information regarding the presence of epcoritamab-bysp in human milk, the effect on the breastfed child, or milk production. Because maternal IgG is present in human milk, and there is potential for epcoritamab-bysp absorption leading to serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with EPKINLY and for 4 months after the last dose.

Females and Males of Reproductive Potential

EPKINLY may cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating EPKINLY.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose.

Pediatric Use

The safety and efficacy of EPKINLY in pediatric patients have not been established.

Geriatric Use

Large B-Cell Lymphoma

In patients with relapsed or refractory LBCL who received EPKINLY in EPCORE NHL-1, 77 (49%) were 65 years of age and older, and 29 (19%) were 75 years of age or older. No clinically meaningful differences in safety or efficacy were observed between patients with relapsed or refractory LBCL who were 65 years of age and older compared with younger adult patients.

Follicular Lymphoma

In patients with relapsed or refractory FL who received EPKINLY in combination with lenalidomide and rituximab in EPCORE FL-1, 88 (36%) were 65 years of age or older, and 20 (8%) were 75 years of age or older. No clinically meaningful differences in safety or efficacy were observed between patients who were 65 years of age and older compared with younger patients.

In patients with relapsed or refractory FL who received EPKINLY in EPCORE NHL-1, 66 (52%) were 65 years of age or older, and 16 (13%) were 75 years of age and older.

In patients with relapsed or refractory FL, there was a higher rate of fatal adverse reactions, primarily infections, including COVID-19, in patients older than 65 years of age compared to younger adult patients. No overall difference in efficacy was observed in patients with relapsed or refractory FL who were 65 years of age and older compared with younger adult patients.

Dosage Forms and Strengths

EPKINLY® for subcutaneous injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, free of visible particles and is supplied as a single-dose 4 mg/0.8 mL glass vial or a single-dose 48 mg/0.8 mL glass vial (Table 2). The single-dose 4 mg/0.8 mL must be diluted prior to use (see Preparation of EPKINLY, pages 21-27).[1]

Table 2: EPKINLY Dosage Forms and How Supplied[1]

Carton Contents	NDC Number
One 4 mg/0.8 mL single-dose vial[a]	NDC 82705-002-01
One 48 mg/0.8 mL single-dose vial[a]	NDC 82705-010-01

[a]The vial stopper is not made with natural rubber latex.

For each step-up dose[a]

One 4 mg per 0.8 mL single-dose vial

[a]See Prescribing Information for step-up dose prep instructions.

For full doses

One 48 mg per 0.8 mL single-dose vial

Images are not to scale; for illustrative purposes only.

Storage and Handling

Store refrigerated at 2°C to 8°C (36°F to 46°F). Keep in the original carton to protect from light. Do not freeze. Do not shake.

Dosage and Administration Overview of EPKINLY®

Important Dosing Information[1]

Administer EPKINLY to well-hydrated patients and premedicate before each dose in Cycle 1 (see Recommended Pre- and Post-Administration Medications, page 18). EPKINLY should only be administered by a qualified healthcare professional with appropriate medical support to manage severe reactions such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). Certain doses of EPKINLY require dilution prior to administration. There are two available methods to prepare diluted EPKINLY: the empty sterile vial method or the sterile syringe methods. Preparation of 3 mg and 48 mg EPKINLY doses does not require dilution.

Administer EPKINLY subcutaneously according to the step-up dosage schedule in Table 3 for patients with DLBCL or high-grade B-cell lymphoma (HGBCL) or Tables 4 or 5 for patients with FL to reduce the incidence and severity of CRS.

For patients with LBCL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose (Cycle 1 Day 15) is appropriate based on comorbidities or other situational factors (see Dosage and Administration [2.1]). During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.

For patients with FL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose (Cycle 1 Day 22) is appropriate based on comorbidities or other situational factors (see Dosage and Administration [2.1]). During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.

Dosage and Administration Overview of EPKINLY®

Recommended Dosage[1]

EPKINLY is for subcutaneous injection only. Administer EPKINLY in 28-day cycles until disease progression or unacceptable toxicity.

Table 3: EPKINLY 2-Step Up Dosage Schedule for Patients With Diffuse Large B-Cell Lymphoma or High-Grade B-Cell Lymphoma

Cycle of Treatment[a]	Day of Treatment	Dose of EPKINLY	
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 to 9	1 and 15	48 mg	
Cycle 10 and beyond	1	48 mg	

[a]Cycle=28 days.

Table 4: EPKINLY 3-Step Up Dosage Schedule for Patients With 3L+ Follicular Lymphoma When Given as Monotherapy

Cycle of Treatment[a]	Day of Treatment	Dose of EPKINLY	
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 to 9	1 and 15	48 mg	
Cycle 10 and beyond	1	48 mg	

Table 5: EPKINLY Dosage Schedule in Combination with Lenalidomide and Rituximab for Patients With 2L Follicular Lymphoma

Cycle of Treatment[a]	Day of Treatment	Dose of EPKINLY	
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 to 12	1	48 mg	

[a]Cycle=28 days.

Restarting EPKINLY After Dosage Delay[1]

If a dose of EPKINLY is delayed, restart therapy based on the recommendations made in Table 6 for patients with DLBCL or HGBCL or Table 7 for patients with FL (see Recommended Dosage, pages 13-15).

Table 6: Recommendations for Restarting Therapy With EPKINLY After Dosage Delay for Patients With Diffuse Large B-Cell Lymphoma or High-Grade B-Cell Lymphoma

Last Dose Administered	Time Since Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg (eg, 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 (eg, 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 (eg, 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.

[a]Administer pretreatment medication prior to EPKINLY dose and monitor patients accordingly (see Recommended Pre- and Post-Administration Medications, page 18, and Dosage Modifications and Management of Adverse Reactions, pages 18-21).

Table 7: Recommendations for Restarting Therapy With EPKINLY After Dosage Delay for Patients With Follicular Lymphoma

Last Dose Administered	Time Since Last Dose Administered	Action for Next Dose(s)[a]
0.16 mg (eg, 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 (eg, 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 (eg, 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 (eg, 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.

[a]Administer pretreatment medication prior to EPKINLY dose and monitor patients accordingly (see Recommended Pre- and Post-Administration Medications, page 18, and Dosage Modifications and Management of Adverse Reactions, pages 18-21).

Dosage and Administration Overview of EPKINLY®

Recommended Pre- and Post-Administration Medications[1]

Administer pre- and post-administration medications as outlined in Table 8 to reduce the risk of CRS.

Table 8: EPKINLY Pre- and Post-Administration Medications

Cycle	Patients Requiring Medication	Medication	Administration
Cycle 1	All patients	• Dexamethasone[a] (15 mg oral or IV) or Prednisolone (100 mg oral or IV) or equivalent	• 30-120 min prior to each weekly administration of EPKINLY • And for 3 consecutive days following each weekly administration of EPKINLY in Cycle 1
		• Diphenhydramine (50 mg oral or IV) or equivalent • Acetaminophen (650 mg to 1,000 mg oral)	• 30-120 min prior to each weekly administration of EPKINLY
Cycle 2+	Patients who experienced Grade 2 or 3[b] CRS with previous dose	• Dexamethasone[a] (15 mg oral or IV) or Prednisolone (100 mg oral or IV) or equivalent	• 30-120 min prior to next administration of EPKINLY after a Grade 2 or 3[b] CRS event • And for 3 consecutive days following the next administration of EPKINLY until EPKINLY is given without subsequent CRS of Grade 2 or higher

CRS=cytokine release syndrome; IV=intravenous.
[a]Dexamethasone is the preferred corticosteroid when available.
[b]Patients will be permanently discontinued from EPKINLY after Grade 4 CRS.

Recommended Prophylaxis[1]

Pneumocystis jirovecii Pneumonia

Provide *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis prior to starting treatment with EPKINLY.

Herpes Virus

Consider initiating prophylaxis against herpes virus prior to starting EPKINLY to prevent herpes zoster reactivation.

Thromboprophylaxis

Refer to the lenalidomide prescribing information for recommendations on prophylaxis for venous and arterial thrombotic events.

Dosage Modifications and Management of Adverse Reactions[1]

Cytokine Release Syndrome

Identify CRS based on clinical presentation (see Warnings and Precautions, pages 50-54). Evaluate for and treat other causes of fever, hypotension, and hypoxia.

If CRS is suspected, withhold EPKINLY until CRS resolves. Manage according to the recommendations in Table 9, page 19, and consider further management per current practice guidelines. Administer supportive therapy for CRS, which may include intensive care for severe or life-threatening CRS.

Immune Effector Cell–Associated Neurotoxicity Syndrome

Monitor patients for signs and symptoms of ICANS (see Warnings and Precautions, pages 50-54). At the first sign of ICANS, withhold EPKINLY and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide supportive therapy, which may include intensive care, for ICANS. Manage ICANS according to the recommendations in Table 10, pages 20-21, and consider further management per current practice guidelines.

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

epkinly® epcoritamab-bysp SUBCUTANEOUS INJECTION 4mg|48mg

Dosage and Administration Overview of EPKINLY®

Table 9: Recommendations for Management of Cytokine Release Syndrome (CRS)

Grade[a]	Presenting Symptoms	Actions
Grade 1	Temperature ≥100.4°F (38°C)[b]	• Withhold EPKINLY and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of EPKINLY.[c]
Grade 2	Temperature ≥100.4°F (38°C)[b] with: Hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen[e] by nasal cannula or blow-by.	• Withhold EPKINLY and manage per current practice guidelines. • Ensure CRS symptoms are resolved prior to next dose of EPKINLY.[c] • Administer premedication[d] prior to next dose of EPKINLY. • For the next dose of EPKINLY, monitor more frequently and consider hospitalization.
Grade 3	Temperature ≥100.4°F (38°C)[b] with: Hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen[e] by nasal cannula, face mask, non-rebreather mask, or Venturi mask.	• Withhold EPKINLY and manage per current practice guidelines, which may include intensive care. • Ensure CRS symptoms are resolved prior to the next dose of EPKINLY.[c] • Administer premedication[d] prior to next dose of EPKINLY. • Hospitalize for the next dose of EPKINLY.
		Recurrent Grade 3 CRS • Permanently discontinue EPKINLY. • Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥100.4°F (38°C)[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).	• Permanently discontinue EPKINLY. • Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.

BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure.

[a]Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.

[b]Premedication may mask fever; therefore, if clinical presentation is consistent with CRS, follow these management guidelines.

[c]Refer to Tables 6 and 7 for information on restarting EPKINLY after dosage delays for patients with DLBCL or HGBCL and those with FL.

[d]If Grade 2 or 3 CRS occurs with the second full dose (48 mg) or beyond, administer CRS pre- and post-administration medications with each subsequent dose until an EPKINLY dose is given without subsequent CRS of Grade 2 or higher. Refer to Table 8 for additional information on pre- and post-administration medications.

[e]Low-flow oxygen defined as oxygen is delivered at <6 L/minute; high-flow oxygen is defined as oxygen delivered at ≥6 L/minute.

Dosage and Administration Overview of EPKINLY®

Table 10: Recommendations for Management of Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

Grade[a]	Presenting Symptoms[b]	Actions
1	ICE score 7-9,[c] Or depressed level of consciousness[d]: awakens spontaneously.	• Withhold EPKINLY until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.
2	ICE score 3-6,[c] Or depressed level of consciousness[d]: awakens to voice.	• Withhold EPKINLY until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.
3	ICE score 0-2,[c] Or depressed level of consciousness[d]: awakens only to tactile stimulus, Or seizures,[d] either: • Any clinical seizure, focal or generalized, that resolves rapidly, or • Non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, Or raised intracranial pressure: focal/local edema on neuroimaging.[d]	First occurrence of Grade 3 ICANS • Withhold EPKINLY until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.
		Recurrent Grade 3 ICANS • Permanently discontinue EPKINLY. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.

[a]Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
[b]Management is determined by the most severe event, not attributable to any other cause.
[c]If patient is arousable and able to perform Immune Effector Cell–Associated Encephalopathy (ICE) Assessment, assess: 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 patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS)=0 points.
[d]Not attributable to any other cause.
[e]See Tables 6 or 7 for recommendations on restarting EPKINLY after dosage delays.
[f]All references to dexamethasone administration are dexamethasone or equivalent.

Table 10: Recommendations for Management of Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS) (cont'd)

Grade[a]	Presenting Symptoms[b]	Actions
4	ICE score 0,[c] Or depressed level of consciousness,[d] either: • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • Stupor or coma Or seizures,[d] either: • Life-threatening prolonged seizure (>5 minutes), or • Repetitive clinical or electrical seizures without return to baseline in between, Or motor findings[d]: • Deep focal motor weakness, such as hemiparesis or paraparesis, Or raised intracranial pressure/cerebral edema,[d] with signs/symptoms such as: • Diffuse cerebral edema on neuroimaging, or • Decerebrate or decorticate posturing, or • Cranial nerve VI palsy, or • Papilledema, or • Cushing's triad	• Permanently discontinue EPKINLY. • Administer dexamethasone[f] 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 consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.

[a]Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
[b]Management is determined by the most severe event, not attributable to any other cause.
[c]If patient is arousable and able to perform Immune Effector Cell–Associated Encephalopathy (ICE) Assessment, assess: 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 patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS)=0 points.
[d]Not attributable to any other cause.
[e]See Tables 6 and 7 for recommendations on restarting EPKINLY after dosage delays.
[f]All references to dexamethasone administration are dexamethasone or equivalent.

Other Adverse Reactions

Infections, cytopenias, and other adverse reactions may develop in patients receiving EPKINLY. Table 11 details dose modifications that should be taken should an adverse reaction occur.

Table 11: Recommended Dosage Modifications for Other Adverse Reactions When EPKINLY Is Given as a Monotherapy

Adverse Reaction[a]	Severity[a]	Action
Infections (see Warnings and Precautions, page 53)	Grades 1-4	• Withhold EPKINLY in patients with active infection, until infection resolves.[b] • For Grade 4, consider permanent discontinuation of EPKINLY.
Neutropenia (see Warnings and Precautions, page 53)	Absolute neutrophil count less than 0.5×10^9/L	• Withhold EPKINLY until absolute neutrophil count is 0.5×10^9/L or higher.[b]
Thrombocytopenia (see Warnings and Precautions, page 53)	Platelet count less than 50×10^9/L	• Withhold EPKINLY until platelet count is 50×10^9/L or higher.[b]
Other Adverse Reactions (see Adverse Reactions, pages 33-35, 39-41)	Grade 3 or higher	• Withhold EPKINLY until the toxicity resolves to Grade 1 or baseline.[b]

[a]Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.
[b]See Tables 6 and 7 for recommendations for restarting EPKINLY after dosage delays.

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

epkinly® epcoritamab-bysp SUBCUTANEOUS INJECTION 4mg|48mg

Preparation of EPKINLY®

Certain doses of EPKINLY require dilution prior to administration. Follow the preparation instructions provided on pages 23-27, as improper preparation may lead to improper dose.

EPKINLY is prepared and administered by a healthcare provider as a subcutaneous injection. The administration of EPKINLY takes place over the course of 28-day cycles, following the step-up dosage schedule (see Recommended Dosage, page 16).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use an aseptic technique to prepare EPKINLY. Filtration of the diluted solution is not required.

There are 2 available methods to prepare diluted EPKINLY[1]:

Empty Sterile Vial Method:

- 0.16 mg (Step-up dose 1: DLBCL/HGBCL and FL) requires 2 dilutions
- 0.8 mg (Step-up dose 2: DLBCL/HGBCL and FL) requires 1 dilution

Sterile Syringe Method:

- 0.16 mg (Step-up dose 1: DLBCL/HGBCL and FL) requires 2 dilutions
- 0.8 mg (Step-up dose 2: DLBCL/HGBCL and FL) requires 1 dilution

Preparation of EPKINLY Using the Vial Method[1]

0.16 mg Dose Preparation Instructions (2 Dilutions Required) - Empty Sterile Vial Method

Use an appropriately sized syringe, vial, and needle for each transfer step.

1. Prepare EPKINLY vial
- a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
- b. Allow the vial to come to room temperature for no more than 1 hour.
- c. Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Perform first dilution
- a. Label an appropriately sized empty vial as "**Dilution A**."
- b. Transfer **0.8 mL of EPKINLY** into the **Dilution A** vial.
- c. Transfer **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** vial. The initially diluted solution contains 0.8 mg/mL of EPKINLY.
- d. Gently swirl the **Dilution A** vial for 30 to 45 seconds.

3. Perform second dilution
- a. Label an appropriately sized empty vial as "**Dilution B**."
- b. Transfer **2 mL of solution** from the **Dilution A** vial into the **Dilution B** vial. The **Dilution A** vial is no longer needed.
- c. Transfer **8 mL of 0.9% Sodium Chloride Injection** into the **Dilution B** vial to make a final concentration of 0.16 mg/mL.
- d. Gently swirl the **Dilution B** vial for 30 to 45 seconds.

4. Withdraw dose
- a. Withdraw **1 mL of the diluted EPKINLY** from the **Dilution B** vial into a syringe.

5. Label syringe
- a. Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the vial containing unused EPKINLY.

Preparation of EPKINLY®

Preparation of EPKINLY Using the Vial Method[1]

0.8 mg Dose Preparation Instructions (1 Dilution Required) - Empty Sterile Vial Method

Use an appropriately sized syringe, vial, and needle for each transfer step.

1. Prepare EPKINLY vial
- a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
- b. Allow the vial to come to room temperature for no more than 1 hour.
- c. Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Perform dilution
- a. Label an appropriately sized empty vial as "**Dilution A**."
- b. Transfer **0.8 mL of EPKINLY** into the **Dilution A** vial.
- c. Transfer **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** vial to make a final concentration of 0.8 mg/mL.
- d. Gently swirl the **Dilution A** vial for 30 to 45 seconds.

3. Withdraw dose
- a. Withdraw **1 mL of the diluted EPKINLY** from the **Dilution A** vial into a syringe.

4. Label syringe
- a. Label the syringe with the dose strength (0.8 mg) and the time of day.

Discard the vial containing unused EPKINLY.

Preparation of EPKINLY Using the Syringe Method[1]

0.16 mg Dose Preparation Instructions (2 Dilutions Required) - Sterile Syringe Method

Use an appropriately sized syringe and needle for each transfer step.

1. Prepare EPKINLY vial
- a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
- b. Allow the vial to come to room temperature for no more than 1 hour.
- c. Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Perform first dilution
- a. Label an appropriately sized syringe as "**Dilution A**."
- b. Withdraw **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** syringe. Include approximately 0.2 mL air in the syringe.
- c. In a new syringe labeled as **"Syringe 1,"** withdraw **0.8 mL of EPKINLY**.
- d. Connect the two syringes and push the **0.8 mL of EPKINLY** into the **Dilution A** syringe. The initially diluted solution contains 0.8 mg/mL of EPKINLY.
- e. Gently mix by inverting the connected syringes 180 degrees 5 times.
- f. Disconnect the syringes and discard **Syringe 1**.

3. Perform second dilution
- a. Label an appropriately sized syringe as **"Dilution B."**
- b. Withdraw **8 mL of 0.9% Sodium Chloride Injection** into the **Dilution B** syringe. Include approximately 0.2 mL air in the syringe.
- c. Label another appropriately sized syringe as **"Syringe 2."**
- d. Connect **Syringe 2** to the **Dilution A** syringe and transfer **2 mL of solution** into **Syringe 2**. The **Dilution A** syringe is no longer needed.
- e. Connect **Syringe 2** to the **Dilution B** syringe and push the **2 mL of solution** into the **Dilution B** syringe to make a final concentration of 0.16 mg/mL.
- f. Gently mix by inverting the connected syringes 180 degrees 5 times.
- g. Disconnect the syringes and discard **Syringe 2**.

4. Withdraw dose
- a. Connect and transfer **1 mL of the diluted EPKINLY** from the **Dilution B** syringe into a new syringe. The **Dilution B** syringe is no longer needed.

5. Label syringe
- a. Label the syringe with the dose strength (0.16 mg) and the time of day.

Discard the vial containing unused EPKINLY.

Preparation of EPKINLY Using the Syringe Method[1]

0.8 mg Dose Preparation Instructions (1 Dilution Required) - Sterile Syringe Method

Use an appropriately sized syringe and needle for each transfer step.

1. Prepare EPKINLY vial
- a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
- b. Allow the vial to come to room temperature for no more than 1 hour.
- c. Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Perform first dilution
- a. Label an appropriately sized syringe as "**Dilution A**."
- b. Withdraw **4.2 mL of 0.9% Sodium Chloride Injection** into the **Dilution A** syringe. Include approximately 0.2 mL air in the syringe.
- c. In a new syringe labeled as **"Syringe 1,"** withdraw **0.8 mL of EPKINLY**.
- d. Connect the two syringes and push the **0.8 mL of EPKINLY** into the **Dilution A** syringe to make a final concentration of 0.8 mg/mL.
- e. Gently mix by inverting the connected syringes 180 degrees 5 times.
- f. Disconnect the syringes and discard **Syringe 1**.

3. Withdraw dose
- a. Connect a new syringe to the **Dilution A** syringe and transfer **1 mL of the diluted EPKINLY** into the new syringe. The **Dilution A** syringe is no longer needed.

4. Label syringe
- a. Label the syringe with the dose strength (0.8 mg) and the time of day.

Discard the vial containing unused EPKINLY.

Preparation of 3 mg and 48 mg EPKINLY Doses[1]

3 mg Dose Preparation Instructions (No Dilution Required)

EPKINLY 3 mg dose is required for patients with FL only.

1. Prepare EPKINLY vial
- a. Retrieve one 4 mg/0.8 mL EPKINLY vial from the refrigerator.
- b. Allow the vial to come to room temperature for no more than 1 hour.
- c. Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Withdraw dose
- a. Withdraw **0.6 mL of EPKINLY** into a syringe.

3. Label syringe
- a. Label the syringe with the dose strength (3 mg) and the time of day.

Discard the vial containing unused EPKINLY.

48 mg Dose Preparation Instructions (No Dilution Required)

EPKINLY 48 mg/0.8 mL vial is supplied as ready-to-use solution that does not need dilution prior to administration.

1. Prepare EPKINLY vial
- a. Retrieve one 48 mg/0.8 mL EPKINLY vial from the refrigerator.
- b. Allow the vial to come to room temperature for no more than 1 hour.
- c. Gently swirl the EPKINLY vial.

DO NOT invert, vortex, or vigorously shake the vial.

2. Withdraw dose
- a. Withdraw **0.8 mL of EPKINLY** into a syringe.

3. Label syringe
- a. Label the syringe with the dose strength (48 mg) and the time of day.

Discard the vial containing unused EPKINLY.

Storage and Administration[1]

Storage of EPKINLY Solution in the Syringe

Use EPKINLY solution in the syringe immediately. If not used immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature at 20°C to 25°C (68°F to 77°F) for up to 12 hours. The total storage time from the start of dose preparation to administration should not exceed 24 hours. Protect from direct sunlight. Discard unused EPKINLY solution beyond the allowable storage time.

Administration of EPKINLY

To minimize injection pain, allow EPKINLY solution to equilibrate to room temperature for no more than 1 hour before administration. Inject the required volume of EPKINLY into the subcutaneous tissue of the lower part of the abdomen (preferred injection site) or the thigh.

Change of injection site from the left or right side or vice versa is recommended, especially during the weekly administrations (Cycles 1 to 3). Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard, or not intact.

EPKINLY® in Clinical Trials (DLBCL/HGBCL)

Pivotal Clinical Trial Details

Study Design

The efficacy of EPKINLY was evaluated in EPCORE NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multi-cohort, multicenter, single-arm clinical trial in 157 patients with relapsed or refractory LBCL after 2 or more lines of systemic therapy. The efficacy population includes 148 patients with DLBCL, not otherwise specified (NOS), including DLBCL arising from indolent lymphoma, and HGBCL.[1]

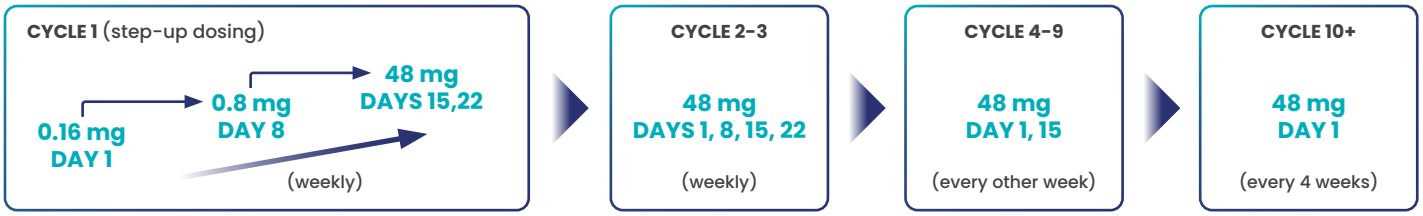
Primary endpoint:

Overall response rate (ORR), includes complete response (CR) and partial response (PR).[1]

Select secondary endpoints:

CR rate, duration of response (DOR), duration of complete response (DOCR), and time to response.[25]

Patients received EPKINLY subcutaneously according to the following 28-day cycle schedule[1]:



Strategies to minimize occurrence and severity of CRS:

- Step-up dosage: step-up dose 1 of 0.16 mg on Cycle 1 Day 1; step-up dose 2 of 0.8 mg on Cycle 1 Day 8; and full dose of 48 mg on Cycle 1 Day 15
- For patients with LBCL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose (Cycle 1 Day 15) is appropriate based on comorbidities or other situational factors (see Dosage and Administration [2.1]). During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.

Key inclusion criteria for the study were[25]:

- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2
- Prior chimeric antigen receptor (CAR) T-cell therapy allowed
- ≥2 prior lines of antineoplastic therapy, including ≥1 anti-CD20 monoclonal antibody (mAb)

Key exclusion criteria for the study were[1]:

- Central nervous system (CNS) involvement of lymphoma
- Allogeneic hematopoietic stem cell transplant (HSCT) or solid organ transplant
- Ongoing active infection
- Any patient with known impaired T-cell immunity

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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EPKINLY® in Clinical Trials (DLBCL/HGBCL)

Patient Characteristics

As shown in Table 12, EPKINLY was studied in a population of patients with complex treatment histories. The diagnosis was DLBCL NOS in 86% of patients, including 27% with DLBCL transformed from indolent lymphoma, and HGBCL in 14% of patients. Table 12 outlines the select patient characteristics.[1]

Table 12: Patient Characteristics and Disease Parameters for Patients With Diffuse Large B-Cell Lymphoma or High-Grade B-Cell Lymphoma (Efficacy Population)[1]

Characteristic	(N=148)
Age (median)	65 y (range: 22-83)
Sex (male)	62%
Race	
White	61%
Asian	20%
Native Hawaiian or other Pacific Islander	0.7%
Black, African American, Hispanic, Latino	0%
ECOG PS	
0 or 1	97%
2	3%
DLBCL NOS	86%
DLBCL transformed from indolent lymphoma, %	27%
HGBCL, %	14%
Treatment History	
Median no. of prior therapies	3 (range: 2-11)
2 prior therapies	30%
3 prior therapies	30%
4+ prior therapies	40%
Primary refractory[25,a]	**60%**
Refractory to last therapy	**82%**
Refractory to ≥2 consecutive lines of therapy	76%
Prior ASCT	18%
Prior CAR T	**39%**
Refractory to CAR T	29%

ASCT=autologous hematopoietic stem cell transplant; CAR T=chimeric antigen receptor T-cell therapy; DLBCL=diffuse large B-cell lymphoma; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HGBCL=high-grade B-cell lymphoma; NOS=not otherwise specified.
[a]A patient is considered to be primary refractory if their disease is refractory to first-line antilymphoma therapy.

Efficacy Results

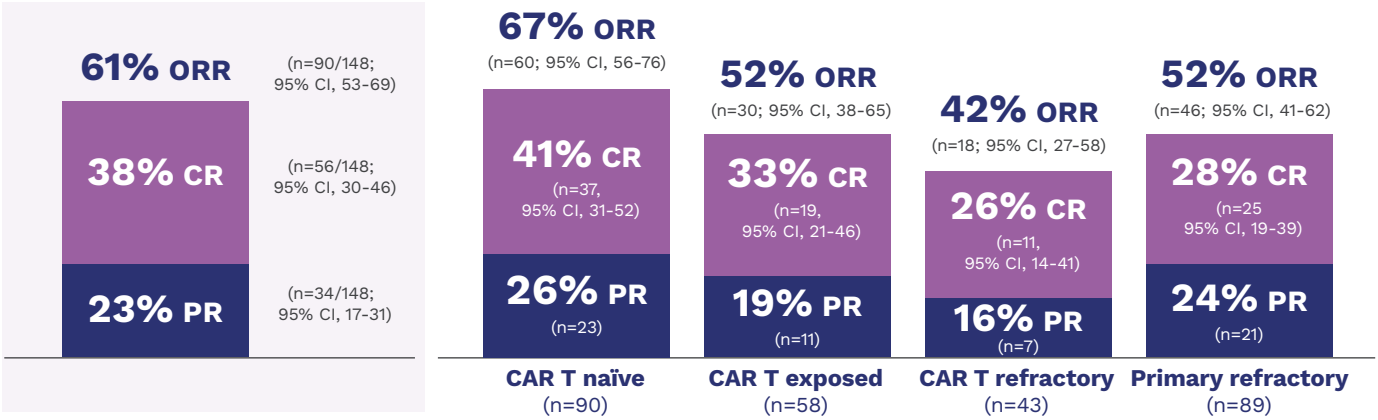
Efficacy was established based on ORR, determined by Lugano 2014 criteria as assessed by Independent Review Committee (IRC) and DOR.[1] The efficacy results are summarized in Figure 4.

EPKINLY® in Clinical Trials (DLBCL/HGBCL)

Response Rates

The median time to response was 1.4 months (range: 1 to 8.4 months). The overall response rate was 61%, with 38% of patients achieving a complete response and 23% achieving a partial response. More than half (62%) of all responders achieved a complete response (Figure 4).[1] The response in select prespecified subgroups was consistent with the overall population.[26]

Figure 4: Efficacy Results and Responses in Prespecified Subgroups in EPCORE NHL-1 in Patients With Diffuse Large B-Cell Lymphoma and High-Grade B-Cell Lymphoma[1,26]



Data limitation: Study was not powered to evaluate these prespecified subgroups. Data are exploratory and descriptive in nature. No formal inferences can be drawn.

CAR T=chimeric antigen receptor T-cell therapy; CI=confidence interval; CR=complete response; ORR=overall response rate; PR=partial response.

Duration of Responses

In overall responders (61%, n=90/148), EPKINLY delivered durable responses in heavily pretreated 3L+ DLBCL, NOS patients[1]

RAPID	DURABLE	SUSTAINED
1.4 months median time to response (range: 1.0-8.4)	mDOR[a] **15.6 months** (95% CI, 9.7 mo-NR)	**63%** still responding at 9 months[a] (estimated; 95% CI, 52-72)

- Among responders, the median follow-up for DOR was 9.8 months (range: 0 to 17.3 months).

In a pre-specified analysis of complete responders (38%, n=56/148)[1,26]

2.6 months median time to complete response (range: 1.2-10.2)	mDOCR[a] **NOT REACHED** (95% CI, 14.3 mo–NR)	**89%** still responding at 9 months[a] (estimated; 95% CI, 75-95)

- Complete responses were achieved as late as 10.2 months.[26]
- Among complete responders, the median follow-up for DOCR was 9.7 months (range: 8.3 to 12.1 months).[26]

3L=third line; CI=confidence interval; DOR=duration of response; mDOCR=median duration of complete response; mDOR=median duration of response; NOS=not otherwise specified; NR=not reached.

[a]Based on Kaplan-Meier estimate.

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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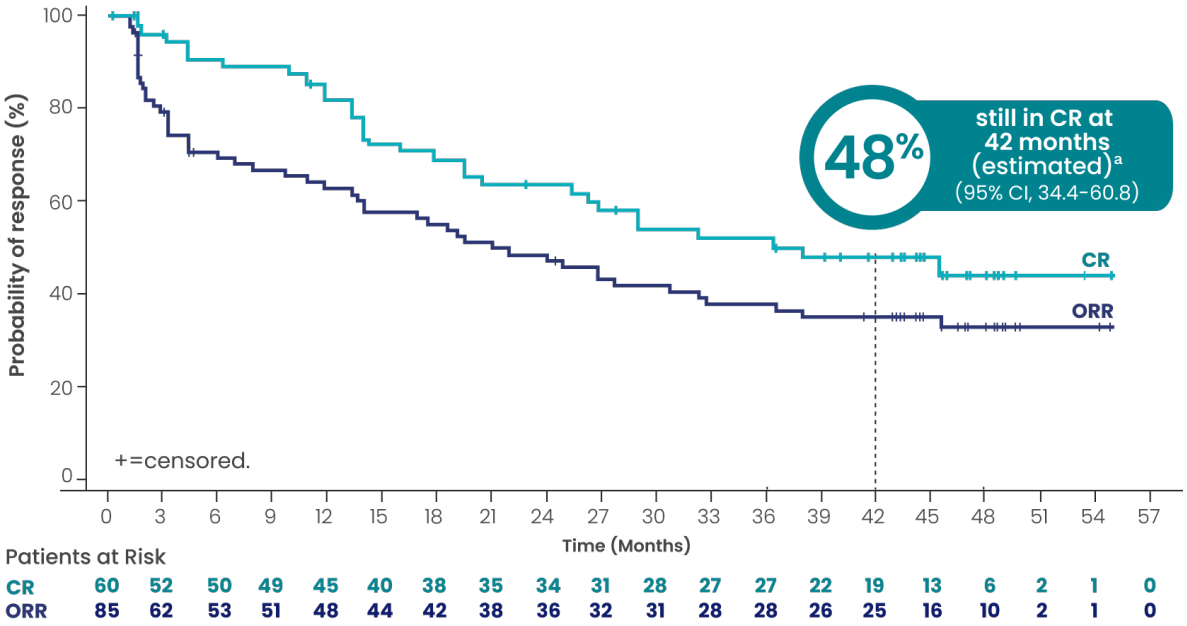
Long-Term Follow-Up Data

The DOR and DOCR have been studied for a median study follow-up of 4 years (49.2 months, range: 47.8, 50.2)[a] (Figure 5).[27]

Observations were consistent with the known epcoritamab safety profile (see Adverse Reactions, pages 33-35). Discontinuation due to an adverse reaction occurred in 7.6% of patients. Serious infections were reported in 33% of patients, with serious infections (including COVID-19[b] and pneumonia) occurring in ≥5% of patients. Fatal infections occurred in 16 patients, of which 12 were COVID-19 events.[27]

Figure 5: Long-Term Follow-Up Data[27]



ORR=57.4%
(n=85/148; 95% CI, 49.0-65.5)

CR=40.5%
(n=60/148; 95% CI, 32.6-48.9)

PR=16.9%
(n=25/148; 95% CI, 11.2-23.9)

mDOCR[a,b]
37.7 months
(95% CI, 20.2-NR)

mDOR[a,b]
20.8 months
(95% CI, 13.0-32.0)

No inference can be drawn from this data set. Follow-up analysis is exploratory and data are descriptive in nature. The Kaplan-Meier estimates may be unreliable at the tail end of the curve due to a smaller number of patients at risk.

CI=confidence interval; CR=complete response; DOCR=duration of complete response; DOR=duration of response; mDOCR=median duration of complete response; mDOR=median duration of response; NR=not reached; ORR=overall response rate; PR=partial response.
[a]Based on Kaplan-Meier estimate.
[b]Median follow-up for DOR was 46.2 months (range: 43.0-48.1 months). Median follow-up for DOCR was 44.1 months (range: 41.3 -46.6 months).[c]
[c]Based on reverse Kaplan-Meier estimate.

EPKINLY® in Clinical Trials (DLBCL/HGBCL)

Adverse Reactions[1]

The safety of EPKINLY was evaluated in 157 patients with relapsed or refractory LBCL after 2 or more lines of therapy in EPCORE NHL-1. The median duration of exposure for patients receiving EPKINLY was 5 cycles (range: 1 to 20 cycles).

Serious adverse reactions occurred in 54% of patients who received EPKINLY. Serious adverse reactions occurring in ≥2% of patients included CRS, infections (including sepsis, COVID-19, pneumonia, and upper respiratory tract infections), pleural effusion, febrile neutropenia, fever, and ICANS. Fatal adverse reactions occurred in 3.8% of patients who received EPKINLY, including COVID-19 (1.3%), hepatotoxicity (0.6%), ICANS (0.6%), myocardial infarction (0.6%), and pulmonary embolism (0.6%).

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 3.8% of patients. Adverse reactions which resulted in permanent discontinuation of EPKINLY included COVID-19, CRS, ICANS, pleural effusion, and fatigue.

Dosage interruptions of EPKINLY due to an adverse reaction occurred in 34% of patients who received EPKINLY. Adverse reactions which required dosage interruption occurring in ≥3% of patients included CRS, neutropenia, sepsis, and thrombocytopenia.

The most common (≥20%) adverse reactions were CRS, fatigue, musculoskeletal pain, injection site reactions, pyrexia, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets.

Table 13 summarizes the adverse reactions in EPCORE NHL-1.

Clinically relevant adverse reactions in <10% of patients who received EPKINLY included ICANS, sepsis, pleural effusion, COVID-19, pneumonia (including pneumonia and COVID-19 pneumonia), tumor flare, febrile neutropenia, upper respiratory tract infections, and tumor lysis syndrome.

Table 14 summarizes the laboratory abnormalities in EPCORE NHL-1.

EPKINLY® in Clinical Trials (DLBCL/HGBCL)

Table 13: Adverse Reactions (≥10%) in Patients With Relapsed or Refractory Large B-Cell Lymphoma Who Received EPKINLY in EPCORE NHL-1[1]

	EPKINLY (N=157)	
Adverse Reaction[a]	**All Grades (%)**	**Grade 3 or 4 (%)**
Immune System Disorders		
Cytokine release syndrome[b]	51	2.5[c]
General Disorders and Administration Site Conditions		
Fatigue[d]	29	2.5[c]
Injection site reactions[e]	27	0
Pyrexia	24	0
Edema[f]	14	1.9[c]
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[g]	28	1.3[c]
Gastrointestinal Disorders		
Abdominal pain[h]	23	1.9[c]
Diarrhea	20	0
Nausea	20	1.3[c]
Vomiting	12	0.6[c]
Skin and Subcutaneous Disorders		
Rash[i]	15	0.6[c]
Nervous System Disorders		
Headache	13	0.6[c]
Metabolism and Nutrition Disorders		
Decreased appetite	12	0.6[c]
Cardiac Disorders		
Cardiac arrhythmias[j]	10	0.6[c]

[a]Adverse reactions were graded based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[b]Cytokine release syndrome was graded using ASTCT consensus criteria (Lee et al, 2019).
[c]Only Grade 3 adverse reactions occurred.
[d]Fatigue includes asthenia, fatigue, lethargy.
[e]Injection site reactions include injection site erythema, injection site hypertrophy, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling, injection site urticaria.
[f]Edema includes edema, edema peripheral, face edema, generalized edema, peripheral swelling.
[g]Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, spinal pain.
[h]Abdominal pain includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.
[i]Rash includes dermatitis bullous, erythema, palmar erythema, penile erythema, rash, rash erythematous, rash maculo-papular, rash pustular, recall phenomenon, seborrheic dermatitis, skin exfoliation.
[j]Cardiac arrhythmias include bradycardia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia.

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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EPKINLY® in Clinical Trials (DLBCL/HGBCL)

Table 14: Select Laboratory Abnormalities (≥20%) That Worsened From Baseline in Patients With Relapsed or Refractory Large B-Cell Lymphoma Who Received EPKINLY in EPCORE NHL-1[1]

Laboratory Abnormality[a]	EPKINLY[b]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocyte count decreased	87	77
Hemoglobin decreased	62	12
White blood cells decreased	53	22
Neutrophils decreased	50	32
Platelets decreased	48	12
Chemistry		
Sodium decreased	56	2.6
Phosphate decreased[c]	56	NA
Aspartate aminotransferase increased	48	4.6
Alanine aminotransferase increased	45	5.3
Potassium decreased	34	5.3
Magnesium decreased	31	0
Creatinine increased	24	3.3
Potassium increased	21	1.3

[a]Laboratory abnormalities were graded based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

[b]The denominator used to calculate the rate varied from 146 to 153, based on the number of patients with a baseline value and at least 1 post-treatment value.

[c]CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value < lower limit of normal (LLN).

EPKINLY® in Clinical Trials (2L+ FL)

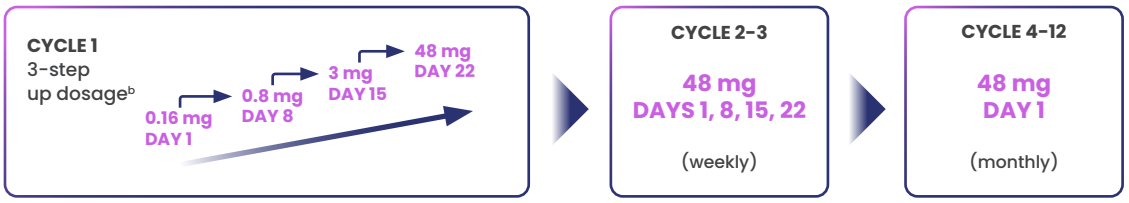
Pivotal Clinical Trial Details

EPKINLY in Combination With Lenalidomide and Rituximab Study Design

The efficacy of EPKINLY in combination with lenalidomide and rituximab (n=243) vs lenalidomide and rituximab alone (n=238) was evaluated in EPCORE FL-1, an open-label, randomized, multicenter, global trial that included patients with relapsed or refractory FL after at least 1 line of systemic therapy.[1,28,29]

- **Dual primary endpoints:** PFS and ORR[a]
- **Select secondary endpoints:** CR, OS, and minimal residual disease negativity

Patients received EPKINLY via subcutaneous injection according to the following 28-day cycle schedule[1]:



In both treatment arms, lenalidomide was given orally at a dose of 20 mg once daily from Days 1 to 21 for 12 cycles. Rituximab was administered intravenously at a dose of 375 mg/m^2 on Days 1, 8, 15, and 22 of Cycle 1, followed by administration on Day 1 of Cycles 2 to 5.

Key inclusion criteria for the study were[29]:

- Patients with relapsed or refractory FL after at least 1 line of systemic therapy
- Histologically confirmed classic FL (Grades 1-3A)
- ECOG PS 0-2

Key exclusion criteria for the study were[1]:

- Known CNS involvement by lymphoma
- Prior allograft
- Known active infection

[a]Efficacy results determined by Lugano criteria (2014) as assessed by Independent Review Committee.

[b]N=131 patients who received 3-step up dosage.

EPKINLY® in Clinical Trials (2L+ FL)

Patient Characteristics

Table 15 outlines select patient characteristics of EPCORE FL-1.

Table 15: Demographics and Disease Parameters for Patients With Follicular Lymphoma (Intent-to-treat Population)[29]

Demographics (All patients randomized, N=488)	
Age	
Median	61 (24-89)
≥65 years	**40%**
Gender	
Male	57%
Race	
White	72%
Asian	24%
Black	2%
Ann Arbor stage III-IV	83%
Bulky disease (≥7 cm)	22%
ECOG PS 0 or 1	98%
ECOG PS 2	2%
FLIPI score 3-5	44%

Treatment History (All patients randomized, N=488)	
Median number of prior lines of therapy (range)	1 (1-7)
Prior lines of therapy	
1	59%
2	24%
≥3	17%
Anti-CD20 antibody	100%
Anti-CD20 antibody with chemotherapy	98%
Refractory to first-line therapy	34%
Refractory to both anti-CD20 and alkylator therapy	37%
POD24	41%

1L=first line; CD20=cluster of differentiation 20; ECOG PS=Eastern Cooperative Oncology Group Performance Status; FLIPI=Follicular Lymphoma International Prognostic Index; POD24=progression of disease 2 years or less from the date of initiation of first-line chemoimmunotherapy.

Efficacy Results

Efficacy was established based on progression free survival (PFS) and overall response rate (ORR) as assessed by IRC using Lugano 2014 criteria. The efficacy results are summarized in Table 16[1] and in Figure 6,[1] which shows the Kaplan-Meier plot of PFS. The results are based on a median duration of follow-up of 10.4 months in the intention-to-treat population.

Table 16: Efficacy Results in EPCORE FL-1 in Patients With Follicular Lymphoma[1]

Endpoint[a]	EPKINLY + Lenalidomide and Rituximab (N=243)	Lenalidomide and Rituximab (N=245)
PFS Number of events, n (%) Progressive disease Death Median (95% CI), months	 23 (9) 19 (83) 4 (17) NR (21.9, NR)	 75 (31) 63 (84) 12 (16) 11.2 (10.5, NR)
Hazard ratio (95% CI)[a] *P*-value[b]	0.21 (0.13, 0.33) < 0.0001	
ORR, n (%) (95% CI)	216 (89) (84, 93)	181 (74) (68, 79)
P-value[c,d]	< 0.0001	
CR, n (%) (95% CI)	181 (74) (69,80)	106 (43) (37, 50)
P-value[d]	< 0.0001	

CI=confidence interval; CR=complete response; NR=not reached; ORR=overall response rate; PFS=progression free survival.
[a]Cox proportional hazards hazard ratio stratified by disease history and region.
[b]Log-rank p-value (one sided) stratified by disease history and region.
[c]*P*-value is based on a prespecified analysis of the first 232 patients randomized.
[d]*P*-value (one sided) is from a Cochran-Mantel-Haenszel test stratified by disease history and region.

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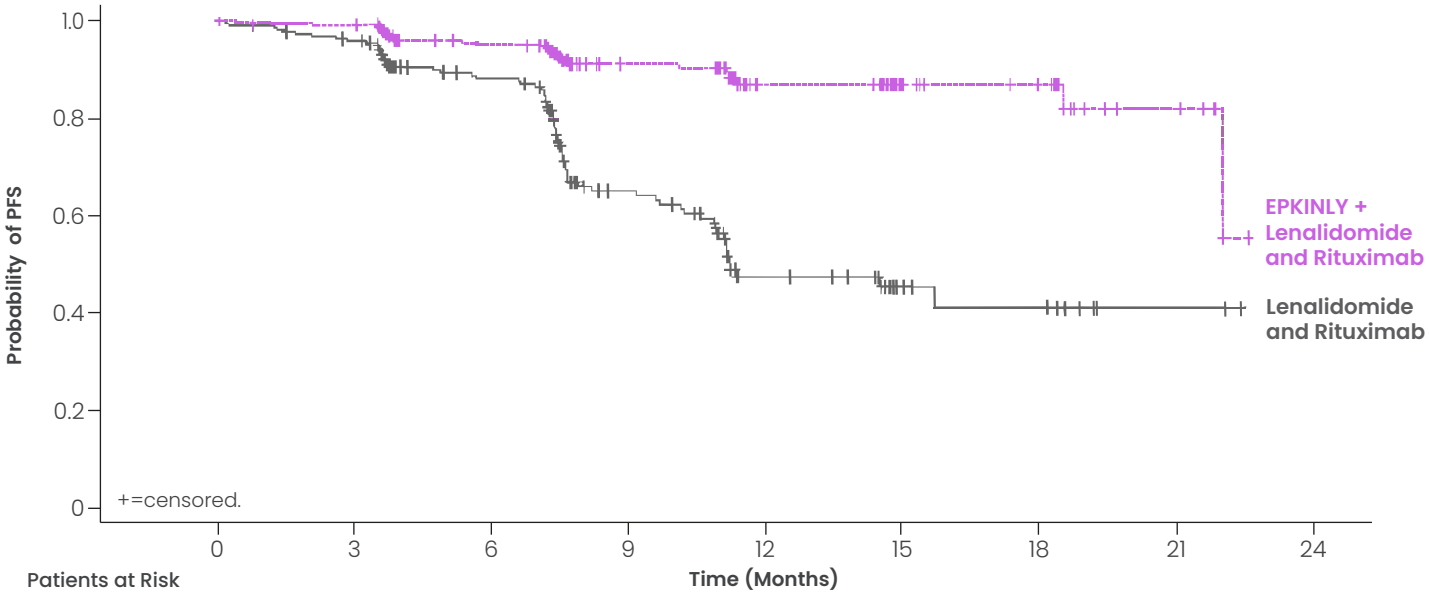
EPKINLY® in Clinical Trials (2L+ FL)

Figure 6: Reduction in the Risk of Disease Progression or Death[1,a,b] (HR=0.21[c]; 95% CI, 0.13-0.33; *P*<0.0001[d])



Patients at Risk									
EPKINLY + Lenalidomide and Rituximab	243	224	182	103	57	29	24	8	0
Lenalidomide and Rituximab	245	203	149	68	28	11	9	2	0

Median PFS[1,a,b]

NOT REACHED
with EPKINLY + lenalidomide and rituximab
(95% CI, 21.9 months-NR)

11.2 months
with lenalidomide and rituximab
(95% CI, 10.5 months-NR)

CI=confidence interval; ITT, intention to treat; NR=not reached.

[a]Efficacy results determined by Lugano criteria (2014) as assessed by IRC and based on prespecified interim analysis.
[b]The median duration of study follow-up was 10.4 months in the ITT population.
[c]Cox proportional hazards hazard ratio stratified by disease history and region.
[d]Log-rank P-value (one-sided) stratified by disease history and region.

EPKINLY® in Clinical Trials (2L+ FL)

Adverse Reactions[1,29]

Safety results are based on all 243 patients who received EPKINLY, with the exception of data for CRS and ICANS, which are based on patients who received EPKINLY at the recommended dosage schedule (n=131). The median duration of exposure in this arm was 10 cycles for EPKINLY and 9 cycles for lenalidomide.

Serious adverse reactions occurred in 51% of these patients, including serious infections in 28% of patients and serious CRS in 12% of patients. Fatal adverse reactions within 60 days of last treatment occurred in 0.8% of patients.

Adverse reactions led to permanent discontinuation of EPKINLY in 6% of patients and dose interruption in 75% of patients, with infection as a leading cause. Adverse reactions leading to interruption of EPKINLY in ≥5% of patients included respiratory tract infections, CRS, and rash.

In the EPKINLY arm, adverse reactions led to lenalidomide dose interruption in 72%, dose reduction in 22%, and permanent discontinuation in 15%.

The most common (≥20%) adverse reactions in the EPKINLY arm were rash, upper respiratory tract infections, fatigue, injection site reactions, constipation, diarrhea, CRS, pneumonia, COVID-19, and fever (Table 17). The most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreases in neutrophil count, lymphocyte count, and platelets (Table 18).

EPKINLY® in Clinical Trials (2L+ FL)

Table 17: Adverse Reactions (≥10% All Grade and ≥5% Grade 3 or 4) in Patients With Relapsed or Refractory FL Who Received EPKINLY in Combination With Lenalidomide and Rituximab in EPCORE FL-1[1]

Adverse Reactions[a]	All Grades (%)	Grades 3 or 4 (%)
N=131		
Immune System Disorders		
Cytokine release syndrome	24[b]	0
N=243		
Skin and Subcutaneous Disorders		
Rash[c]	46	11[d]
Injections and Infestations		
Upper respiratory tract infections[e]	33	3.3
Pneumonia[f]	24	16[d]
COVID-19[g]	23	5[d]
General Disorders and Administration Site Conditions		
Fatigue[h]	31	4.9[d]
Injection site reactions	27	0
Fever	23	0.4[d]
Gastrointestinal Disorders		
Constipation	26	0.8[d]
Mucositis[i]	12	0
Nervous System Disorders		
Neurological changes[j]	15	1.2[d]
Headache	11	0
Psychiatric Disorders		
Insomnia	14	0

[a]Adverse reactions were graded using CTCAE Version 5.0. CRS was graded using ASTCT consensus criteria.
[b]The frequency of CRS among the 243 patients who received either the 2-step up or 3-step up dosage schedule was the following: Any grade CRS 35%; Grade 1 CRS: 28%; Grade 2 CRS: 7%. The frequency of CRS is based on 131 patients who received EPKINLY at the recommended dosage schedule was the following: Grade 1 CRS: 19%; Grade 2 CRS: 5%.
[c]Rash includes blister, dermatitis, erythema, rash, skin exfoliation, skin reaction, toxic skin eruption, urticaria and related terms.
[d]Only Grade 3 adverse reactions occurred.
[e]Upper respiratory tract infections include sinusitis, laryngitis, nasopharyngitis, pharyngitis, rhinitis, rhinovirus infection, upper respiratory tract infection, and related terms.
[f]Pneumonia includes pneumonia, COVID-19 pneumonia, pneumonia fungal, Pneumocystis jirovecii pneumonia, pneumonia cytomegaloviral, and related terms.
[g]COVID-19 includes COVID-19, COVID-19 pneumonia, coronavirus infection, coronavirus pneumonia.
[h]Fatigue includes asthenia, fatigue, lethargy, malaise.
[i]Mucositis includes gingival pain, glossitis, mouth ulceration, mucosal infection, mucosal inflammation, oral discomfort, oral mucosal exfoliation, oropharyngeal pain, stomatitis.
[j]Neurological changes include brain fog, cognitive disorder, confusional state, disturbance in attention, dysphonia, epilepsy, essential tremor, gait disturbance, hypoacusis, lethargy, loss of consciousness, memory impairment, somnolence, syncope, tremor, vertigo, and ICANS.

EPKINLY® in Clinical Trials (2L+ FL)

Table 18: Select Laboratory Abnormalities (≥30% All Grade and ≥10% Grade 3 or 4) That Worsened From Baseline in Patients With Relapsed or Refractory FL Who Received EPKINLY in Combination With Lenalidomide and Rituximab in EPCORE FL-1[1]

Laboratory Abnormality[a]	EPKINLY (N=243)	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Neutrophils decreased	86	67
Lymphocytes decreased	86	62
Hemoglobin decreased	60	7
Platelets decreased	50	10
Chemistry		
Alanine aminotransferase increased	58	7
Phosphate decreased[b]	49	NA
Sodium decreased	43	4.1
Potassium decreased	41	9
Aspartate aminotransferase increased	40	2.9

NA=not applicable.

Laboratory abnormalities were graded based on CTCAE Version 5.0.

[a]The denominator used to calculate the rate varied from 240 to 242 in the EPKINLY arm based on the number of patients with a baseline value and at least one post-treatment value.

[b]CTCAE Version 5.0 does not include numeric thresholds for grading of hypophosphatemia; all grades represent patients with lab value less than lower limit of normal.

EPKINLY® in Clinical Trials (3L+ FL)

Pivotal Clinical Trial Details

EPKINLY Monotherapy Study Design

The efficacy of EPKINLY was evaluated in EPCORE NHL-1 (Study GCT3013-01; NCT03625037), an open-label, multi-cohort, multicenter, single-arm trial that included patients with relapsed or refractory FL after at least 2 lines of systemic therapy.[1]

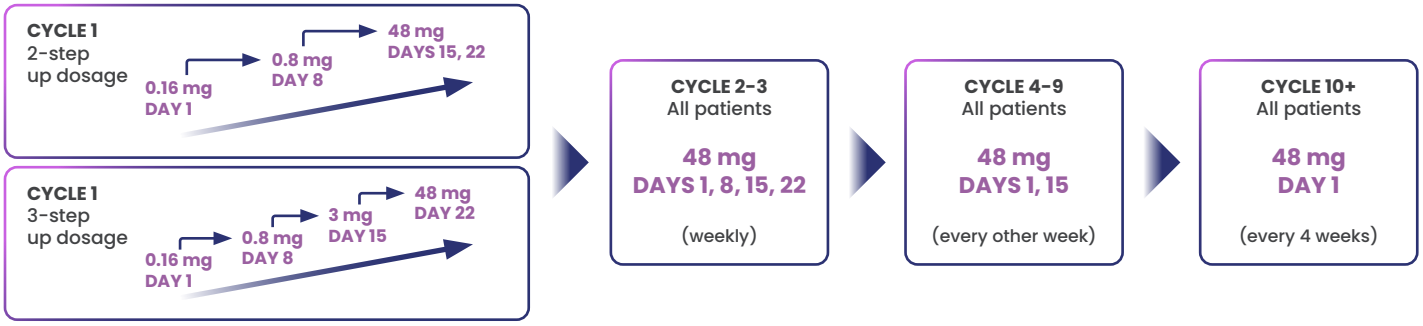
In the 2-step up dosage schedule cohort of 127 patients:

- **Primary endpoint:** Overall response rate (ORR), included complete response (CR) and partial response (PR)[1]
- **Select secondary endpoints:** CR, DOR, DOCR, and time to response (TTR)[30]

In the 3-step up dosage schedule cohort of 86 patients[30,31]:

- **Primary endpoint:** Percentage of ≥Grade 2 CRS events and all-grade CRS events
- **Select secondary endpoint:** ORR (CR and PR)

Patients received EPKINLY subcutaneously according to the following 28-day cycle schedule[1]:



Patients continued to receive subcutaneous EPKINLY until disease progression or unacceptable toxicity.

The 3-step up dosage schedule is the recommended dosage for patients with 3L+ FL.

A separate dose optimization cohort evaluated the recommended 3-step up dosage schedule for CRS mitigation.

Key inclusion criteria for the study were[30,31]:

- ECOG PS 0-2
- Prior CAR T and/or autologous HSCT allowed
- Patients who received 2 or more therapies, including an anti-CD20 mAb containing chemotherapy combination regimen

Key exclusion criteria for the study were[1]:

- CNS involvement of lymphoma
- Allogeneic HSCT or solid organ transplant
- Ongoing active infection
- Known impaired T-cell immunity
- Creatinine clearance <45 mL/min
- Alanine aminotransferase >3× ULN
- Cardiac ejection fraction <45%

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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EPKINLY® in Clinical Trials (3L+ FL)

Patient Characteristics

As shown in Table 19, EPKINLY was studied in a population that included challenging-to-treat patients with relapsed or refractory FL.[1,32-34] Table 19 outlines the select patient characteristics.

Table 19: Demographics and Disease Parameters for Patients With Follicular Lymphoma (Efficacy Population)[1,35]

Demographics (N=127, 2-step up dosage cohort)	
Age	
Median	65 (range: 39-84)
≥65 years	**52%**
Stage III-IV disease	85%
Bulky disease (>6 cm)	25%
ECOG performance status	
0 or 1	95%
2	6%
FLIPI scores 3-5	61%
Treatment History (N=127, 2-step up dosage cohort)	
Double refractory[a]	**70%**
Refractory[b] to last therapy	**69%**
Refractory to ≥2 consecutive lines of antilymphoma therapy	55%
Refractory to prior anti-CD20 monoclonal antibody therapy	79%
Median no. of prior therapies	3 (range: 2-9)
2 prior therapies	36%
3 prior therapies	32%
4+ prior therapies	32%
POD24 from any 1L therapy	52%
Prior therapy	
Anti-CD20 mAb	100%
Alkylating agent	100%
Autologous HSCT	19%
CAR T-cell therapy	5%
Rituximab + lenalidomide	21%

1L=first line; CAR=chimeric antigen receptor; CD20=cluster of differentiation 20; ECOG=Eastern Cooperative Oncology Group; FLIPI=Follicular Lymphoma International Prognostic Index; HSCT=hematopoietic stem cell transplantation; mAb=monoclonal antibody; POD24=progression of disease within 2 years of 1L systemic therapy.

[a]Defined as refractory to both anti-CD20 monoclonal antibody and alkylator therapy.[33]

[b]Refractory: Patient with no response or relapse within 6 months after completing therapy.[33]

Efficacy Results

Efficacy was established based on ORR determined by Lugano 2014 criteria as assessed by Independent Review Committee (IRC) and DOR. The median follow-up for DOR was 14.8 months. The efficacy results are summarized in Table 20.[1]

Response Rates

In responders (n=104/127), the median time to first response was 1.4 months (range: 1 to 3 months). In a prespecified analysis of complete responders (n=76/127), the median time to complete response was 1.5 months (range: 1.2 to 11.1 months).[33] The overall response rate was 82%, with 60% of patients achieving a complete response and 22% achieving a partial response. The majority of patients who achieved a response had a complete response.[1]

The efficacy results of the 86 patients who received the recommended 3-step up dosage schedule in the EPCORE NHL-1 dose optimization cohort were comparable to the primary efficacy population.[1]

Table 20: Efficacy Results in EPCORE NHL-1 in Patients With Follicular Lymphoma[1]

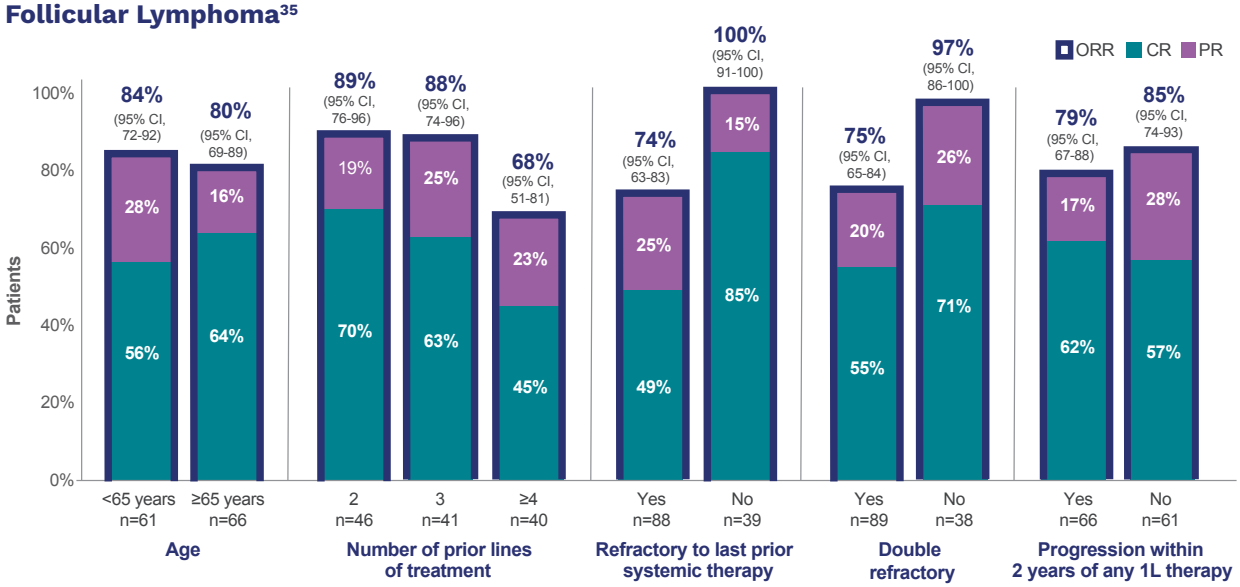
Endpoint[a]	EPKINLY (N=127)
Overall Response Rate	82% (n=104/127; 95% CI, 74.1-88.2)
Complete Response	60% (n=76/127; 95% CI, 50.8-68.4)
Partial Response	22% (n=28/127; 95% CI, 15.2-30.3)
Duration of Response	
Median (months)	NR (95% CI, 13.7-NR)
12-month estimate[b]	68.4% (95% CI, 57.6-77.0)

Majority of patients achieved a CR

CI=confidence interval; NR=not reached.
[a]Determined by Lugano criteria (2014) as assessed by independent review committee (IRC).
[b]Kaplan-Meier estimate.

Subgroup Analyses

Figure 7: Responses Demonstrated Across Prespecified Subgroups Among Patients With Follicular Lymphoma[35]



Data limitation: Study was not powered to evaluate these prespecified subgroups. Data are exploratory and descriptive in nature. No formal inferences can be drawn.

1L=first line; CI=confidence interval; CR=complete response; ORR=overall response rate; PR=partial response.

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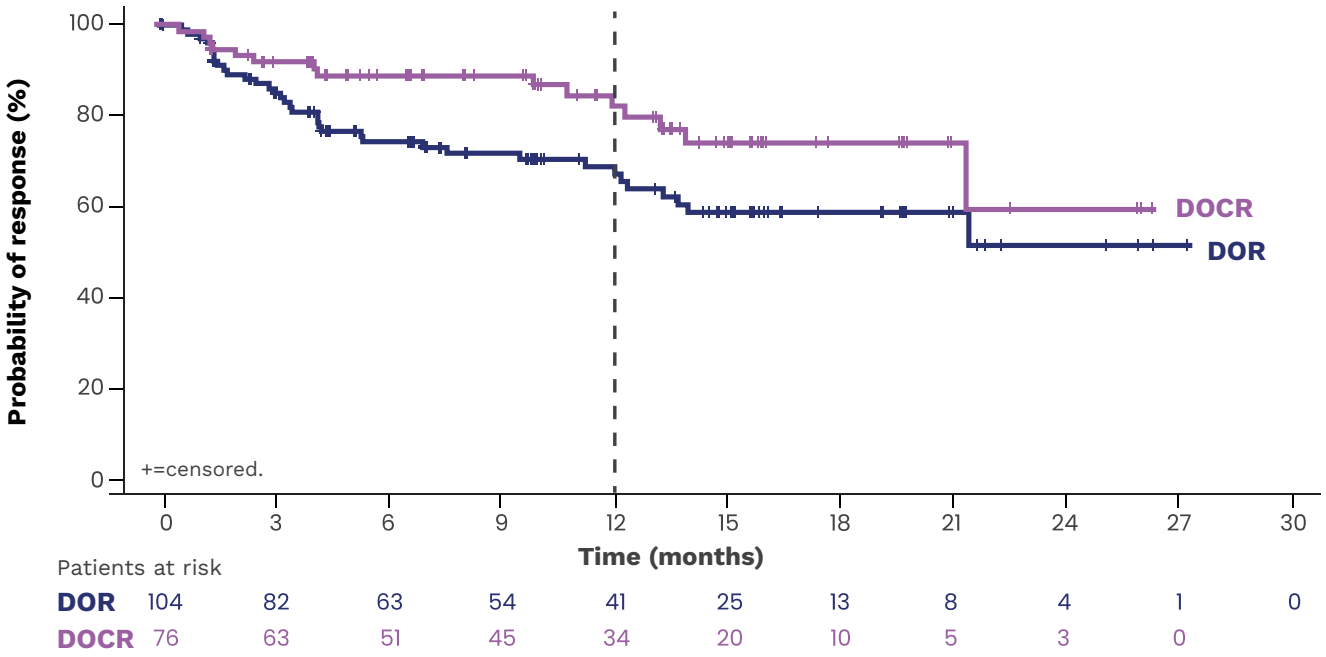
Duration of Responses

In overall responders (82%, n=104/127), 68% of patients were expected to continue responding to treatment at 12 months (95% CI, 57.6-77.0), while in a prespecified analysis of complete responders (60%, n=76/127), 84% of patients were expected to continue responding to treatment at 12 months (95% CI, 72.3-91.4). The follow-up for DOR was up to 27.2 months with a median of 14.8 months (Figure 8).[35]

Figure 8: Response Achieved With EPKINLY in Patients With Follicular Lymphoma[35,a,b]



In overall responders (82%, n=104/127)[a]

mDOR **NOT REACHED**
(95% CI, 13.7-NR)

68% Still responding at 12 months (estimated) (95% CI, 57.6-77.0)

- The median follow-up for DOR was 14.8 months (range: 0.0+, 27.2+)[b]

In a prespecified analysis of complete responders (60%, n=76/127)[a]

mDOCR **NOT REACHED**
(95% CI, 21.4-NR)

84% Still in CR at 12 months (estimated) (95% CI, 72.3-91.4)

- The median follow-up for DOCR was 13.2 months (range: 0.0+, 26.3+)[b]

CI=confidence interval; DOR=duration of response; DOCR=duration of complete response; mDOR=median duration of response; mDOCR=median duration of complete response; NR=not reached.

[a]Based on Kaplan-Meier estimate.

[b]Both lower and upper limits of the range indicate a censored value.

Adverse Reactions[1]

With the exception of CRS, the safety results presented below and in Tables 21 and 22 represent data from patients who received the 2-step up dosage schedule in EPCORE NHL-1 (N=127). The data presented for CRS reflects the 86 patients who received the recommended 3-step up dosage schedule.

Recommended 3-Step Up Dosage Schedule

Of the 86 patients with relapsed or refractory FL who received EPKINLY following the recommended 3-step up dosage schedule, the median duration of exposure was 5 cycles (range: 1 to 12 cycles). CRS occurred in 49% of patients, with Grade 1 CRS occurring in 45% and Grade 2 in 9% of patients. Serious adverse reactions due to CRS occurred in 28% of patients who received EPKINLY. Dose interruptions due to CRS occurred in 19% of patients who received EPKINLY.

2-Step Up Dosage Schedule

Of the 127 patients with relapsed or refractory FL who received EPKINLY following a 2-step up dosage schedule, the median duration of exposure for patients receiving EPKINLY was 8 cycles (range: 1 to 33 cycles).

Serious adverse reactions occurred in 66% of patients who received EPKINLY. Serious adverse reactions in ≥5% of patients included CRS, COVID-19, pneumonia, and second primary malignancies.

Fatal adverse reactions occurred in 9% of patients who received EPKINLY, including COVID-19 (5%), pneumonitis (1.6%), cardiac failure (0.8%), pneumonia (0.8%), and sepsis (0.8%).

Permanent discontinuation of EPKINLY due to an adverse reaction occurred in 19% of patients who received EPKINLY. Adverse reactions which resulted in permanent discontinuation of EPKINLY in ≥2% of patients included COVID-19, hepatitis E, pneumonitis, and second primary malignancy.

Dosage interruptions of EPKINLY due to an adverse reaction occurred in 59% of patients who received EPKINLY. Adverse reactions which required dosage interruption in ≥5% of patients included COVID-19, CRS, pneumonia, upper respiratory tract infection, and fatigue.

The most common (≥20%) adverse reactions were injection site reactions, CRS, COVID-19, fatigue, upper respiratory tract infection, musculoskeletal pain, rash, diarrhea, pyrexia, cough, and headache. The most common Grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, and decreased hemoglobin.

Table 21 summarizes the adverse reactions in EPCORE NHL-1.

Clinically relevant adverse reactions in <10% of patients (N=127) who received EPKINLY included vomiting, pruritus, hepatotoxicity, ICANS, lower respiratory tract infections, cardiac arrhythmias, respiratory tract infections, pneumonitis, second primary malignancy, vision changes, cellulitis, febrile neutropenia, cardiac failure, cytomegalovirus infection and sepsis.

Table 22 summarizes laboratory abnormalities in EPCORE NHL-1.

EPKINLY® in Clinical Trials (3L+ FL)

Table 21: Adverse Reactions (≥10%) in Patients With Relapsed or Refractory Follicular Lymphoma Who Received EPKINLY in EPCORE NHL-1[1]

Adverse Reactions[a]	All Grades (%)	Grades 3 or 4 (%)
N=86[b]		
Immune System Disorders		
Cytokine release syndrome[c,d]	49	0
N=127		
General Disorders and Administration Site Conditions		
Injection site reactions[f]	58	0
Fatigue[f]	37	5[e]
Pyrexia[f]	26	2[e]
Edema[f]	17	0
Injections and Infestations		
COVID-19[g]	40	19
Upper respiratory tract infection[h]	29	2[e]
Pneumonia[i]	17	13[e]
Urinary tract infection[f]	13	5[e]
Herpes virus injection[j]	12	1.6[e]
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[f]	28	0.8[e]
Arthralgia	14	0.8[e]
Skin and Subcutaneous Disorders		
Rash[f]	28	0
Gastrointestinal Disorders		
Diarrhea	26	1.6[e]
Nausea	17	0
Abdominal pain[f]	17	0.8[e]
Constipation	16	0
Mucositis[k]	12	0
Respiratory Disorders		
Cough[f]	20	0
Dyspnea[f]	17	0
Nervous System Disorders		
Headache	20	0
Neurological changes[l]	13	0
Peripheral neuropathy and paresthesia[m]	13	1.6[e]
Dizziness	11	0
Psychiatric Disorders		
Insomnia	13	0
Renal and Urinary Disorders		
Renal insufficiency[n]	10	1.6[e]

[a]Adverse reactions were graded based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[b]The frequency of CRS is based on 86 patients with FL who received the recommended 3-step up dosage schedule in EPCORE NHL-1.
[c]CRS was graded using ASTCT consensus criteria (Lee et al., 2019).
[d]The frequency of CRS based on the 127 patients with FL who received the 2-step up dosage schedule in EPCORE NHL-1 was the following: Any grade CRS 66%; Grade 1 CRS: 50%; Grade 2 CRS: 26%; Grade 3 CRS: 1.6%.
[e]Only Grade 3 adverse reactions occurred.
[f]Includes related grouped terms.
[g]COVID-19 includes COVID-19, COVID-19 pneumonia, SARS-CoV-2 test positive.
[h]Upper respiratory tract infection includes preferred terms with upper respiratory infection and sinusitis, laryngitis viral, nasopharyngitis, oropharyngitis fungal, pharyngitis, rhinitis, rhinovirus infection, tonsillitis.
[i]Pneumonia includes preferred terms with pneumonia, bronchopulmonary aspergillosis, infectious pleural effusion, infective exacerbation of bronchiectasis, *Pneumocystis jirovecii* pneumonia, pneumonia respiratory syncytial viral.
[j]Herpes virus infection includes herpes simplex, herpes simplex reactivation, herpes virus infection, herpes zoster, oral herpes, varicella zoster virus infection.
[k]Mucositis includes aphthous ulcer, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, stomatitis, tongue ulceration.
[l]Neurological changes include amnesia, aphasia, balance disorder, brain fog, confusional state, dysphonia, encephalopathy, extrapyramidal disorder, hallucination, hypoacusis, memory impairment, mental status changes, tremor, vertigo.
[m]Peripheral neuropathy and paresthesia includes bell's palsy, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, polyneuropathy.
[n]Renal insufficiency includes acute kidney injury, blood creatinine increased, renal impairment.

Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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Table 22: Select Laboratory Abnormalities (≥20%) That Worsened From Baseline in Patients With Relapsed or Refractory Follicular Lymphoma Who Received EPKINLY in EPCORE NHL-1[1]

Laboratory Abnormality[a]	EPKINLY (N=127)[b]	
	All Grades (%)	Grade 3 or 4 (%)
Hematology		
Lymphocytes decreased	94	82
Hemoglobin decreased	59	10
White blood cells decreased	58	19
Neutrophils decreased	55	30
Platelets decreased	49	8
Chemistry		
Sodium decreased	51	1.6
ALT increased	47	8
AST increased	44	6
Creatinine increased	36	0.8
Alkaline phosphatase increased	29	0
Bilirubin increased	28	1.6
Potassium decreased	20	3.1
Magnesium decreased	20	0.8

ALT=alanine aminotransferase; AST=aspartate transaminase.

[a]Laboratory abnormalities were graded based on Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

[b]The denominator used to calculate the rate varied from 123 to 127 based on the number of patients with a baseline value and at least one post-treatment value.

Patient Counseling

Advise patients to read the FDA-approved patient labeling (Medication Guide).[1]

Cytokine Release Syndrome

Inform patients of the risk of CRS and to immediately contact their healthcare provider should signs and symptoms associated with CRS (e.g., pyrexia, hypotension, hypoxia, chills, tachycardia, headache, and dyspnea) occur at any time. Advise all patients who experience symptoms that impair consciousness not to drive and refrain from operating heavy or potentially dangerous machinery until events resolve (see Warnings and Precautions, pages 50-54).

Immune Effector Cell–Associated Neurotoxicity Syndrome

Advise patients of the risk of ICANS and to immediately contact their healthcare provider if they experience signs and symptoms associated with ICANS, which may manifest, for example, as confusional state, lethargy, tremor, dysgraphia, aphasia, and nonconvulsive status epilepticus and explain that the onset of events may be delayed. Advise patients who experience symptoms of ICANS that impair consciousness to refrain from driving or operating heavy or potentially dangerous machinery until symptoms of ICANS resolve (see Warnings and Precautions, pages 50-54).

Infections

Advise patients of the risk of serious infections and to contact their healthcare professional if they experience signs or symptoms of serious infection (see Warnings and Precautions, pages 50-54).

Cytopenias

Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia (see Warnings and Precautions, pages 50-54).

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider if they are pregnant or become pregnant. Advise females of reproductive potential to use effective contraception during treatment with EPKINLY® (epcoritamab-bysp) and for 4 months after the last dose (see Use in Specific Populations, pages 12-13).

Lactation

Advise women not to breastfeed during treatment with EPKINLY and for 4 months after the last dose.

Warnings & Precautions

WARNING: CYTOKINE RELEASE SYNDROME AND IMMUNE EFFECTOR CELL–ASSOCIATED NEUROTOXICITY SYNDROME

Cytokine release syndrome (CRS), including serious or life-threatening reactions, can occur in patients receiving EPKINLY. Initiate treatment with the EPKINLY step-up dosage schedule to reduce the incidence and severity of CRS. Withhold EPKINLY until CRS resolves or permanently discontinue based on severity.

Immune effector cell–associated neurotoxicity syndrome (ICANS), including life-threatening and fatal reactions, can occur with EPKINLY. Monitor patients for neurological signs or symptoms of ICANS during treatment. Withhold EPKINLY until ICANS resolves or permanently discontinue based on severity.

Cytokine Release Syndrome

Relapsed or Refractory Large B-Cell Lymphoma

EPKINLY can cause CRS, including serious or life-threatening reactions.

CRS occurred in 51% (80/157) of patients with LBCL receiving EPKINLY at the recommended dosage schedule in EPCORE NHL-1, with Grade 1 CRS occurring in 37%, Grade 2 in 17%, and Grade 3 in 2.5% of patients. Recurrent CRS occurred in 31% of these patients. Most CRS events (92%) occurred during Cycle 1. In Cycle 1, CRS events occurred in 6% of patients after the 0.16 mg dose, 12% after the 0.8 mg dose, 43% after the first 48 mg dose, and 5% after the next 48 mg dose. The median time to onset of CRS from the most recent EPKINLY dose was 24 hours (range: 0 to 10 days). The median time to onset after the first 48 mg dose was 21 hours (range: 0 to 7 days).

For patients with LBCL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose (Cycle 1 Day 15) is appropriate based on comorbidities or other situational factors (see Dosage and Administration [2.1]). During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.

Table 23: Rate of Cytokine Release Syndrome in Patients With Large B-Cell Lymphoma During EPCORE NHL-1

Cytokine Release Syndrome According to Grade	
Grade	**Percentage of Patients With LBCL**
Any	51%
1	37%
2	17%
3	2.5%
Recurrent	31%
Cytokine Release Syndrome After EPKINLY Dose During Cycle 1	
EPKINLY Dose	**Percentage of Events Among Patients With LBCL**
0.16 mg Day 1	6%
0.8 mg Day 8	12%
48 mg Day 15	43%
48 mg Day 22	5%

Follicular Lymphoma

CRS occurred in 49% (42/86) of patients with FL receiving EPKINLY monotherapy at the recommended dosage schedule in EPCORE NHL-1, with Grade 1 CRS occurring in 45% and Grade 2 in 9% of patients. Recurrent CRS occurred in 48% of patients. Most CRS events (88%) occurred during Cycle 1. In Cycle 1, CRS events occurred in 12% of patients after the 0.16 mg dose, 6% after the 0.8 mg dose, 15% after the 3 mg dose, and 37% after the first 48 mg dose. The median time to onset of CRS from the most recent EPKINLY dose was 59 hours (range: 0.1 to 7 days). The median time to onset after the first 48 mg dose was 61 hours (range: 0.1 to 7 days).

CRS occurred in 24% (32/131) of patients with FL receiving EPKINLY at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1, with Grade 1 CRS occurring in 19%, Grade 2 in 5% of patients, and serious adverse reactions due to CRS in 12%. Recurrent CRS occurred in 41% of patients. Most CRS events (88%) occurred during Cycle 1. In Cycle 1, CRS occurred in 5% of patients after the 0.16 mg dose, 3.8% after the 0.8 mg dose, 2.3% after the 3 mg dose, and 18% after the first 48 mg dose. The median time to onset of CRS from the most recent EPKINLY dose was 78 hours (range: 0.2 to 12 days). The median time to onset after the first 48 mg dose was 41 hours (range: 0.3 to 12 days).

For patients with FL, assess whether hospitalization or outpatient monitoring for the first 48 mg dose is appropriate based on comorbidities or other situational factors [see Dosage and Administration (2.1)]. During outpatient monitoring after the first 48 mg dose, patients should remain in proximity to a healthcare facility that can assess and manage CRS.

Among patients with LBCL or FL who experienced CRS, signs and symptoms included pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia. CRS resolved in 98% of patients, after a median duration of 2 days (range: <1 to 27 days). Concurrent neurological adverse reactions associated with CRS occurred in 2.5% of patients with LBCL, 4.7% of patients with FL receiving EPKINLY monotherapy, and 1.5% of patients receiving EPKINLY in combination with lenalidomide and rituximab. Concurrent neurological adverse reactions included headache, confusional state, tremors, dizziness, and ataxia

Initiate therapy according to EPKINLY step-up dosing schedule. Administer pretreatment medications to reduce the risk of CRS and monitor patients for potential CRS following EPKINLY accordingly. At the first signs or symptoms of CRS, immediately evaluate patients for hospitalization, manage per current practice guidelines, and administer supportive care as appropriate. Withhold or discontinue EPKINLY based on the severity of CRS (see Dosage Modifications and Management of Adverse Reactions, pages 17-20).

Patients who experience CRS (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.

Table 24: Rate of Cytokine Release Syndrome in Patients With Follicular Lymphoma During EPCORE NHL-1

Cytokine Release Syndrome According to Grade	
Grade	**Percentage of Patients With FL**
Any	49%
1	45%
2	9%
Recurrent	48%
Cytokine Release Syndrome After EPKINLY Dose During Cycle 1	
EPKINLY Dose	**Percentage of Events Among Patients With FL**
0.16 mg Day 1	12%
0.8 mg Day 8	6%
3 mg Day 15	15%
48 mg Day 22	37%

Immune Effector Cell-Associated Neurotoxicity Syndrome

Relapsed or Refractory Large B-Cell Lymphoma

EPKINLY can cause life-threatening and fatal ICANS. ICANS occurred in 6% (10/157) of patients with LBCL receiving EPKINLY at the recommended 2-step up dosage schedule in EPCORE NHL-1, with Grade 1 ICANS in 4.5% and Grade 2 ICANS in 1.3% of patients. There was one (0.6%) fatal ICANS occurrence. Of the 10 ICANS events, 9 occurred within Cycle 1 of EPKINLY treatment, with a median time to onset of ICANS of 16.5 days (range: 8 to 141 days) from the start of treatment. Relative to the most recent administration of EPKINLY, the median time to onset of ICANS was 3 days (range: 1 to 13 days). The median duration of ICANS was 4 days (range: 0 to 8 days) with ICANS resolving in 90% of patients with supportive care.

Follicular Lymphoma

EPKINLY can cause life-threatening and fatal ICANS.

ICANS occurred in 6% (8/127) of patients with FL receiving EPKINLY following the 2-step up dosage schedule in EPCORE NHL-1, with Grade 1 ICANS in 3.9% and Grade 2 ICANS in 2.4% of patients. The median time to onset of ICANS was 22 days (range 14 to 66 days) from the start of treatment. Relative to the most recent administration of EPKINLY, the median time to onset of ICANS was 3 days (range: 0.4 to 7 days). The median duration of ICANS was 2 days (range: 1 to 7 days) with ICANS resolving in 100% of patients.

Among patients with FL who received EPKINLY at the recommended dosage schedule in combination with lenalidomide and rituximab in EPCORE FL-1, ICANS occurred in 0.8% (1/131, Grade 1).

For patients with LBCL or FL, clinical manifestations of ICANS included, but were not limited to, confusional state, lethargy, tremor, dysgraphia, aphasia, and non-convulsive status epilepticus. The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. Monitor patients for potential ICANS following EPKINLY. At the first signs or symptoms of ICANS, immediately evaluate patient and provide supportive therapy based on severity. Withhold or discontinue EPKINLY per recommendations and consider further management per current practice guidelines.

Patients who experience signs or symptoms of ICANS or any other adverse reactions that impair cognition or consciousness should be evaluated, including potential neurology evaluation, and patients at increased risk should be advised not to drive and to refrain from operating heavy or potentially dangerous machinery until resolution.

Warnings & Precautions

Infections

EPKINLY can cause serious and fatal infections. Serious infections, including opportunistic infections, were reported in 15% of patients with LBCL receiving EPKINLY at the recommended 2-step up dosage schedule in EPCORE NHL-1 and were most commonly due to sepsis (4.5%) and pneumonia (3.2%). Fatal infections occurred in 1.3% of patients and included COVID-19 (1.3%).

Serious infections, including opportunistic infections, were reported in 40% of patients with FL receiving EPKINLY following the 2-step up dosage schedule in EPCORE NHL-1 and were most commonly due to COVID-19 (20%), pneumonia (13%), and urinary tract infections (3%). Fatal infections occurred in 6% of patients and included COVID-19 (5%), pneumonia (0.8%), and sepsis (0.8%).

Among 243 patients with FL who received EPKINLY in combination with lenalidomide and rituximab in EPCORE FL-1, serious infections occurred in 28% of patients. The most common serious infections were pneumonia (15%), COVID-19 (7%), opportunistic infections (5%) and upper respiratory infections (3.3%). 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 in patients treated with EPKINLY. Across a broader clinical trial population, PML was reported in 0.4% (11/3072) of patients, including in the first-line treatment setting. Of the 11 cases of PML, six resulted in fatal outcomes and one was unresolved at the time of death.

Monitor patients for signs and symptoms of infection prior to and during treatment with EPKINLY and treat appropriately. Avoid administration of EPKINLY in patients with active infections. Provide *pneumocystis jirovecii* pneumonia (PJP) prophylaxis prior to initiating treatment with EPKINLY; consider initiating prophylaxis against herpes virus prior to starting EPKINLY (see Recommended Prophylaxis, page 18).

Consider monitoring immunoglobulin levels during treatment and administration of immunoglobulin treatment as appropriate.

Withhold or consider permanent discontinuation of EPKINLY based on severity (see Dosage Modifications and Management of Adverse Reactions, pages 18-21).

Cytopenias

EPKINLY can cause serious or severe cytopenias, including neutropenia, anemia, and thrombocytopenia.

Among LBCL patients who received EPKINLY at the recommended 2-step up dosage schedule in EPCORE NHL-1, 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%. In patients with FL who received EPKINLY following the 2-step up dosage schedule in EPCORE NHL-1, 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%. In patients with FL who received EPKINLY in combination with lenalidomide and rituximab, Grade 3 or 4 decreased neutrophils occurred in 67% (Grade 4, 41%), decreased lymphocytes in 62% (Grade 4, 13%), decreased hemoglobin in 7%, and decreased platelets in 10% (Grade 4, 4.1%) of patients. Febrile neutropenia occurred in 6% (Grade 4, 2.1%). Monitor complete blood counts throughout treatment. Based on the severity of cytopenias, temporarily withhold or permanently discontinue EPKINLY (see Dosage Modifications and Management of Adverse Reactions, pages 18-21). Consider prophylactic granulocyte colony-stimulating factor administration as applicable.

Warnings & Precautions

Embryo-Fetal Toxicity

Based on its mechanism of action, EPKINLY may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment with EPKINLY and for 4 months after the last dose (see Use in Specific Populations below).

Contraindications[1]

None.

Nonclinical Toxicology[1]

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with epcoritamab-bysp. No dedicated studies have been conducted to evaluate the effects of epcoritamab-bysp on fertility.

Drug Interactions[1]

For certain cytochrome P450 (CYP) substrates, minimal changes in the concentration may lead to serious adverse reactions. Monitor for toxicity or drug concentrations of such CYP substrates when co-administered with EPKINLY.

Epcoritamab-bysp causes release of cytokines that may suppress activity of CYP enzymes, resulting in increased exposure of CYP substrates. Increased exposure of CYP substrates is more likely to occur after the first dose of EPKINLY and up to 14 days after the first 48 mg dose, and during and after CRS.

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Please see additional Important Safety Information, including Boxed Warnings for CRS and ICANS, on pages 2-4 and full Prescribing Information.

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