Epcoritamab plus rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin induces deep and durable responses in transplant-eligible patients with relapsed or refractory diffuse large B-cell lymphoma: results from the EPCORE NHL-2 trial

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Received: October 21, 2025.
Accepted: February 19, 2026.
Early view: March 5, 2026.

https://doi.org/10.3324/haematol.2025.300086

SUPPLEMENTAL METHODS

Patient eligibility criteria

In Arm 4 of the EPCORE® NHL-2 trial, eligible patients were adults (≥18 years of age) with histologically confirmed CD20+ diffuse large B cell lymphoma (DLBCL) that was de novo or histologically transformed from follicular lymphoma or nodal marginal zone lymphoma, based on World Health Organization 2016 classification[1] (DLBCL not otherwise specified; double-hit or triple-hit DLBCL classified as HGBCL with *MYC* and *BCL2* and/or *BCL6* translocations; follicular lymphoma grade 3B; or T-cell/histiocyte-rich DLBCL).

Dosing regimen

In the dose escalation, patients received subcutaneous epcoritamab in 2 step-up doses, followed by either 24- or 48-mg full doses, administered weekly in 21-day cycles (C) during C1–3; patients could continue epcoritamab monotherapy (once weekly [QW] during a 21-day C4, then in 28-day C: Q2W in C5–9; Q4W in C10+) until high-dose therapy and autologous stem cell transplantation or progressive disease (PD). Rituximab, dexamethasone, cytarabine, oxaliplatin/carboplatin (R-DHAX/C) was administered every C, in 21-day C (C1–3): rituximab at 375 mg/m^2 intravenously (IV); dexamethasone at 40 mg/d IV or orally on days 1–4; cytarabine 2 g/m^2 IV repeated after 12 hours; carboplatin AUC=5 mg/mL x min (Calvert[2] formula) or oxaliplatin 100 mg/m^2 IV.

Endpoints

Additional secondary endpoints assessed in Arm 4 of the EPCORE NHL-2 study were safety and tolerability, including incidence and severity of adverse events (AE), serious AE (SAE), and AE of special interest (i.e., cytokine release syndrome [CRS], immune effector cell-associated neurotoxicity syndrome, clinical tumor lysis syndrome).

Assessments

Tumor response was assessed by fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT), or by CT/magnetic resonance imaging (MRI) and FDG PET if PET-CT is not available at weeks 6, 12, 18, 24, 36, and 48, and every 24 weeks thereafter until PD.

AE were coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.[3] CRS and immune effector cell-associated neurotoxicity syndrome were graded using American Society for Transplantation and Cellular Therapy consensus grading criteria.[4] Clinical tumor lysis syndrome was graded according to Cairo–Bishop criteria.[5] AE were

assessed throughout the study from the first treatment dose until the maximum of 60 days after the last dose of epcoritamab and 30 days after the last dose of standard of care, or start of new therapy, whichever occurred first. All SAE were reported over the duration of the study until the safety follow-up visit (>60 days after the last dose), after which only SAE considered by the investigator as related to epcoritamab were reported.

Statistical analysis

All analyses were descriptive and based on the full analysis set, which included all patients who received ≥1 dose of study treatment. Time-to-event endpoints (duration of response, duration of complete response (CR), progression-free survival, overall survival [OS], and time to next anti-lymphoma therapy [TTNT]) were analyzed using Kaplan–Meier methods; time to response and time to CR were analyzed with descriptive methods. For duration of response, duration of CR, and progression-free survival, progression at the date of PD scan and death prior to progression on the date of death were considered events. Date of PD is defined as the earliest date of documented progression after which there is no more partial response or CR assessment. Patients were censored at the first dosing date if there were no or incomplete baseline tumor assessments or no post-baseline assessments and the patient was alive. Patients were censored at the last adequate disease assessment date if they had no progression, death, or, if they had PD or died after 2 or more consecutive missing disease assessments. Patients were also censored at the last adequate disease assessment date before start of subsequent anti-cancer therapy if they started subsequent anti-cancer therapy prior to PD or death.

OS was defined as the time from C1D1 to death from any cause. For OS analysis, patients for whom death was not reported were censored at the latest date they were known to be alive.

For TTNT, death due to PD was considered an event and death due to other reasons was censored at the death date. The subsequent anti-lymphoma therapies for TTNT events consisted of systemic anti-lymphoma therapy, stem cell transplantation, CAR T-cell therapy, surgery to target lesions and radiotherapy to target lesion(s), with the exception of censoring subjects with partial response or CR while receiving subsequent stem cell transplantation after responding to epcoritamab, to be consistent with the intent to measure duration of clinical benefit using TTNT. Patients who were alive and without initiation of subsequent anti-lymphoma therapy were censored at the last known alive date.

Safety analyses were conducted in the safety population, which included all patients who received ≥1 dose of study treatment. AE, including treatment-emergent AE (TEAE), SAE, grade ≥3 AE, AE of special interest, and AE leading to dose modifications or treatment

discontinuation, were summarized descriptively by frequency, severity (grade), and relationship to study treatment. AE incidence was additionally evaluated by analysis period, where applicable.

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Supplementary Table S1. Treatment-emergent adverse events leading to epcoritamab discontinuation or dose modification of any drug

	All TEAE
TEAE leading to epcoritamab treatment discontinuation, n (%)	3 (10.3)[a]
Guillain–Barré syndrome	1 (3.4)
ICANS	1 (3.4)
Thrombocytopenia	1 (3.4)
Lower respiratory tract infection bacterial	1 (3.4)
Pneumonia	1 (3.4)
TEAE leading to dose modification of any drug, n (%)	18 (62.1)
Thrombocytopenia	9 (31.0)
Neutropenia	4 (13.8)
COVID-19	2 (6.9)
Fatigue	2 (6.9)
Febrile neutropenia	2 (6.9)
Platelet count decreased	2 (6.9)
Acute pulmonary oedema	1 (3.4)
Alanine aminotransferase increased	1 (3.4)
Anemia	1 (3.4)
Blood creatinine increased	1 (3.4)
Bronchitis	1 (3.4)
Cholecystitis	1 (3.4)
Coronary artery disease	1 (3.4)
Cough	1 (3.4)
Cushingoid	1 (3.4)
Cytokine release syndrome	1 (3.4)
Cytomegalovirus colitis	1 (3.4)
Eczema	1 (3.4)
Heart failure with reduced ejection fraction	1 (3.4)
Infusion related reaction	1 (3.4)
Insomnia	1 (3.4)
Mucosal inflammation	1 (3.4)
Neutrophil count decreased	1 (3.4)
Pancytopenia	1 (3.4)
Periodontitis	1 (3.4)
Pneumonia	1 (3.4)
Pneumonia pseudomonal	1 (3.4)
Post procedural hemorrhage	1 (3.4)
Rash maculo-papular	1 (3.4)
Sepsis	1 (3.4)
Streptococcal endocarditis	1 (3.4)
Tumor associated fever	1 (3.4)
Upper respiratory tract infection	1 (3.4)
Vomiting	1 (3.4)

Percentages are calculated based on number of patients in the safety analysis set. Adverse events are classified using MedDRA v27.1 and are counted only once per SOC and only

once per preferred term. [a]Two patients discontinued epcoritamab in Cycle 1; one patient discontinued epcoritamab after long-term treatment.

COVID 19: coronavirus disease 2019; ICANS: Immune effector cell-associated neurotoxicity syndrome; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class; TEAE: treatment emergent adverse events.