Abstract
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ZUMA-23: A Global, Phase 3, Randomized Controlled Study of Axicabtagene Ciloleucel Versus Standard of Care as First-Line Therapy in Patients With High-Risk Large B-Cell Lymphoma

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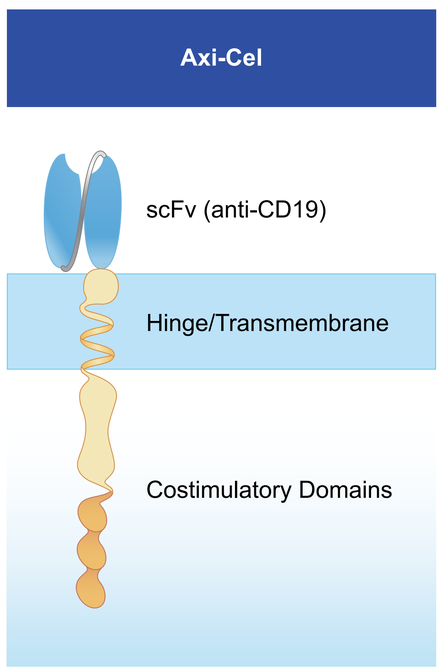
BACKGROUND

- The nearly 40% of patients with large B-cell lymphoma (LBCL) who relapse or are refractory after current first-line standard-of-care (SOC) regimens, such as R-CHOP (rituximab [R] + cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]) and DA-EPOCH-R (dose-adjusted etoposide [DA-E]), have poor prognoses[1]
- High International Prognostic Index score and the high-grade B-cell lymphoma subtype of LBCL are associated with shorter progression-free survival and overall survival[1,2]
  - Strategies to improve outcomes with first-line therapy in these patients have been largely unsuccessful; therefore, therapeutic options with a different mechanism of action are needed
- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, which includes a CD28 costimulatory domain to elicit rapid and robust expansion (**Figure 1**)[3,4]
- Axi-cel is approved to treat patients with relapsed/refractory LBCL after demonstrating significant clinical benefit as second-line (ZUMA-7) and third-line and higher (ZUMA-1) therapy[3,5-7]
- The Phase 2 ZUMA-12 study assessed axi-cel as part of first-line therapy in patients with high-risk LBCL who were positron emission tomography (PET)+ after 2 cycles of chemoimmunotherapy[8]
  - Axi-cel showed a complete response rate of 78% (89% objective response rate)
  - Responses were ongoing in 73% of patients after a median follow-up of 15.9 months
  - No new safety signals were reported in the first-line treatment setting
- ZUMA-23 is the first Phase 3, randomized controlled study conducted in any cancer to evaluate CAR T-cell therapy as a first-line regimen and will assess axi-cel versus SOC in patients with high-risk LBCL

Figure 1. Axi-Cel Structure



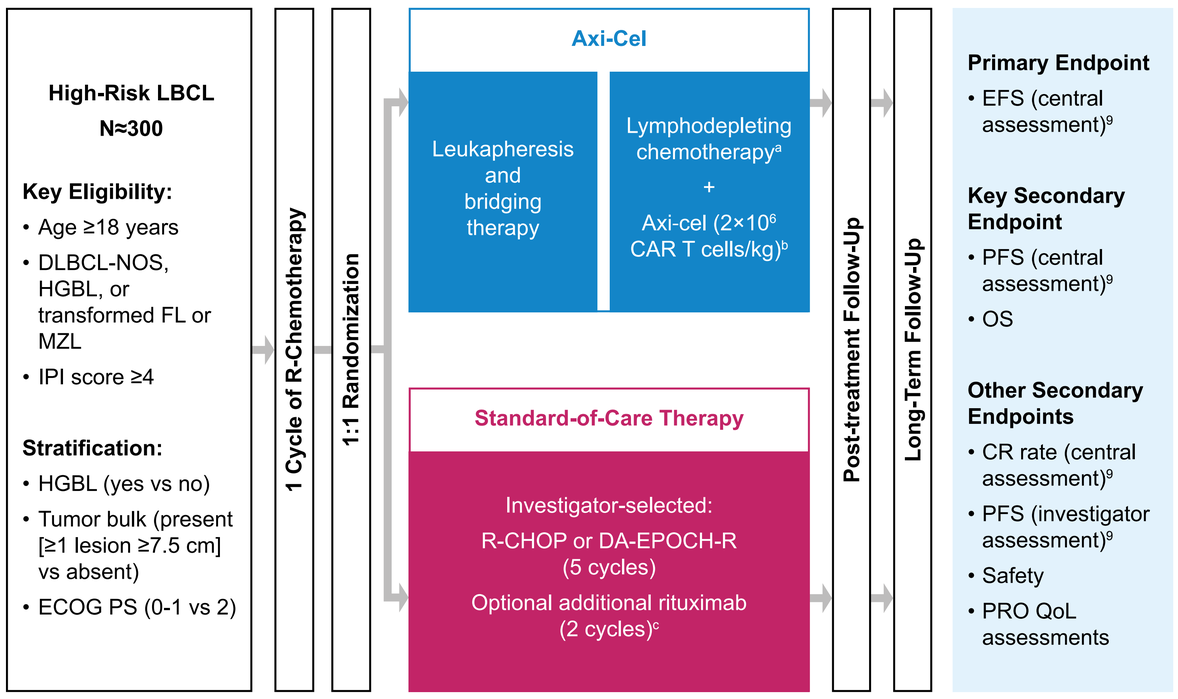
Axi-cel, axicabtagene ciloleucel; scFv, single-chain variable fragment.

OBJECTIVE

- To compare the efficacy and safety of axi-cel versus first-line SOC in patients with high-risk LBCL

STUDY DESIGN AND ENDPOINTS

Figure 2. ZUMA-23 Phase 3 Study Design



[a] Lymphodepleting chemotherapy will consist of cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day), received days -5 through -3 before receiving axi-cel.
[b] Prophylactic corticosteroids may be administered after axi-cel infusion per investigator discretion. [c] If standard of care per local clinical practice, patients may also receive 2 additional cycles of rituximab monotherapy.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; DA-EPOCH-R, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; NOS, not otherwise specified; MZL, marginal zone lymphoma; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; QoL, quality of life.

PATIENT ELIGIBILITY

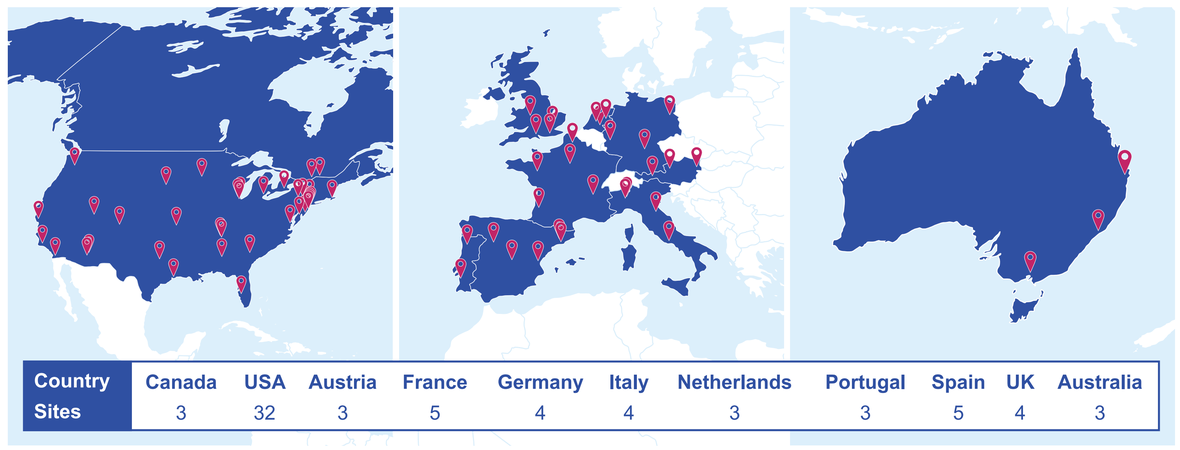
Table 1. ZUMA-23 Key Inclusion Criteria and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Histologically confirmed LBCL, based on WHO 2016 classification[10] by local assessment, including the following: – DLBCL-NOS – HGBL (*MYC* + *BCL2*/*BCL6* rearrangements and NOS) – Note: Transformed DLBCL from FL or MZL is eligible if there was no prior treatment with anthracycline-containing regimen • High-risk disease defined as an IPI score of 4-5 at initial diagnosis • Have received only 1 cycle of R-chemotherapy • Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function	• The following WHO 2016[10] subcategories by local assessment: – T-cell/histiocyte-rich LBCL – Primary DLBCL of the CNS – PMBCL – B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical HL – Burkitt lymphoma • Presence of detectable CSF-malignant cells, brain metastases, or a history of CNS involvement of lymphoma • Presence of CNS disorder; history of stroke, transient ischemic attack, or PRES <12 months prior to enrollment • History of acute or chronic active hepatitis B or C infection unless the viral load is undetectable by PCR and/or nucleic acid testing • HIV-positive unless taking appropriate anti-HIV medications, with an undetectable viral load by PCR and with a CD4 count >200 cells/μL

CNS, central nervous system; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; HL, Hodgkin lymphoma; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; PMBCL, primary mediastinal (thymic) B-cell lymphoma; PCR, polymerase chain reaction; PRES, posterior reversible encephalopathy syndrome; R-chemotherapy, rituximab plus chemotherapy; WHO, World Health Organization.

STATUS

Figure 3. ZUMA-23 Clinical Trial Sites



Country	Canada	USA	Austria	France	Germany	Italy	Netherlands	Portugal	Spain	UK	Australia
Sites	3	32	3	5	4	4	3	3	5	4	3

- This study is currently recruiting participants globally

REGISTRATION

- This study is registered at ClinicalTrials.gov (NCT05605899)

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DISCLOSURES

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