Abstract
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ZUMA-22: A Phase 3, Randomized Controlled Study of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care Therapy in Patients With Relapsed or Refractory Follicular Lymphoma

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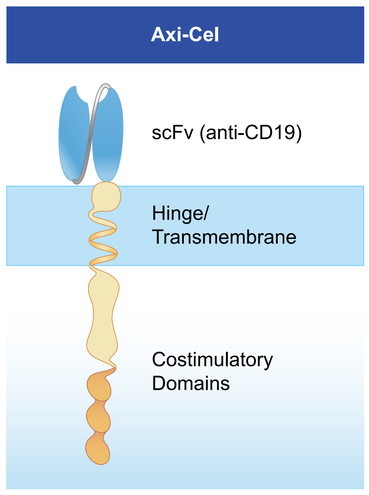
BACKGROUND

- Patients with relapsed or refractory (R/R) follicular lymphoma (FL) experience progressively shorter remissions with each successive line of therapy, and the disease is largely considered incurable[1]
  - In a retrospective analysis between 1998-2009, progression-free survival (PFS) and overall survival (OS) among patients with FL after 3 lines of therapy were 1.1 years and 8.8 years, respectively
- Patients who progressed <24 months after initiating first-line chemoimmunotherapy (POD24) have inferior OS compared with those who did not experience POD24[2,3]
  - This incidence of POD24 is ~20% among patients who receive first-line chemoimmunotherapy[3]
- 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, that results in target-specific cytotoxicity and helps to overcome the limitations of the immune system (**Figure 1**)[4,5]
- In ZUMA-5, the pivotal Phase 2 study of axi-cel in indolent non-Hodgkin lymphoma, outcomes among patients with FL (n=127) were positive after a median follow-up of 41.7 months[6]
  - Median PFS was 40.2 months
  - Median OS was not yet reached
  - Long-term safety was manageable
- In ZUMA-5, POD24 did not adversely affect PFS or OS[6]
- ZUMA-5 supported the approval of axi-cel for the treatment of R/R FL[4,7,8]
- ZUMA-22 is a Phase 3, open-label, multicenter, randomized controlled trial that will evaluate the efficacy and safety of axi-cel compared with standard-of-care therapy in patients with R/R FL

Figure 1. Axi-Cel Structure



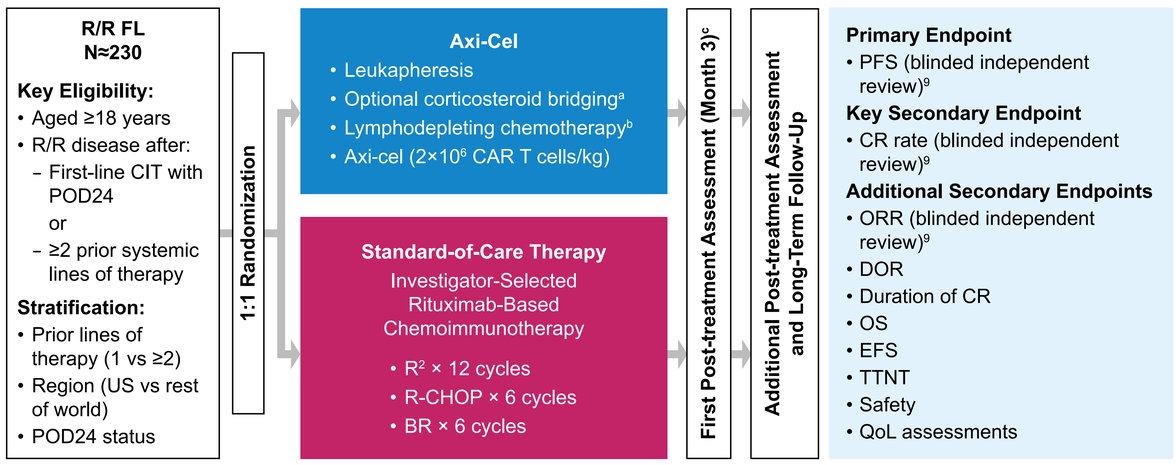
Axi-cel, axicabtagene ciloleucel; scFv, single-chain variable fragment.

OBJECTIVE

- To determine if axi-cel is superior to standard-of-care therapy in patients with R/R FL as measured by PFS per blinded independent review

STUDY DESIGN AND ENDPOINTS

Figure 2. ZUMA-22 Study Design



[a] Bridging corticosteroid therapy will be administered at the discretion of the investigator. [b] Lymphodepleting chemotherapy will consist of cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day), received days –5 to –3 before receiving axi-cel. [c] End of Month 3 after randomization.
Axi-cel, axicabtagene ciloleucel; BR, rituximab + bendamustine; CAR, chimeric antigen receptor; CIT, chemoimmunotherapy; CR, complete response; DOR, duration of response; EFS, event-free survival; FL, follicular lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression within 24 months from initiating first-line chemoimmunotherapy; R², rituximab + lenalidomide; R-CHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; QoL, quality of life; R/R, relapsed/refractory; TTNT, time to next treatment; US, United States.

- Standard-of Care-Therapy Options (**Figure 2**)
  - R² × 12 cycles (28-day cycle)
    - Cycle 1: lenalidomide (20 mg/day) on Days 1-21; rituximab (375 mg/m²) on Days 1, 8, 15, and 22
    - Cycle 2 through Cycle 5: lenalidomide (20 mg/day) on Days 1-21; rituximab (375 mg/m²) on Day 1
    - Cycle 6 through Cycle 12: lenalidomide 20 mg/day on Days 1-21
  - R-CHOP × 6 cycles (21-day cycle)
    - Rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), vincristine (1.4 mg/m², maximum 2 mg) on Day 1
    - Prednisone (40 mg/m²) on Days 1-5
  - BR × 6 cycles (28-day cycle)
    - Rituximab (375 mg/m²) on Day 1
    - Bendamustine (90 mg/m²) on Days 1-2
- QoL Endpoints (**Figure 2**)
  - Changes from baseline in the Global Health Status Quality of Life scale and the physical functioning domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30 and the Low-Grade Non-Hodgkin Lymphoma-20
  - Changes from baseline in the EuroQoL 5-Dimension 5-Level and visual analog scale

PATIENT ELIGIBILITY

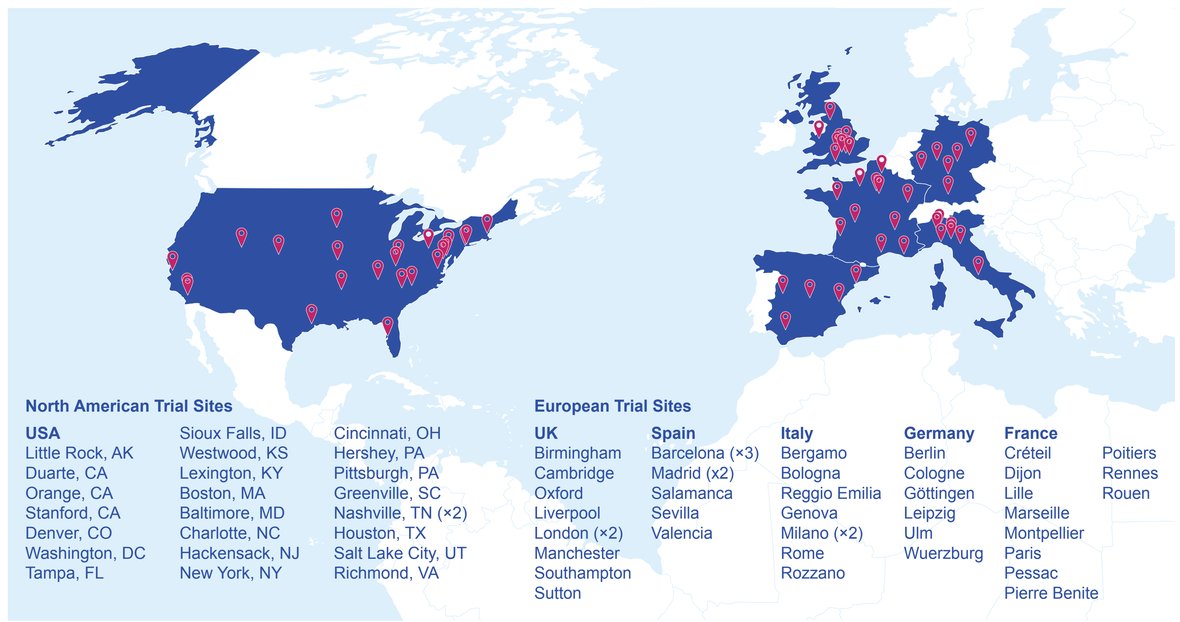
Table 1. ZUMA-22 Key Inclusion Criteria and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Histologically confirmed FL, Grades 1-3a • R/R disease after one of the following: – First-line CIT with POD24[a] – ≥2 prior systemic lines of therapy • ECOG PS 0-1 • Clinical indication for treatment • At least 1 measurable lesion per the Lugano Classification[9] • Adequate renal, hepatic, pulmonary, and cardiac function	• History of LBCL or TFL • FL Grade 3b • Prior CD19-targeted therapy • Prior CAR therapy or other genetically modified T-cell therapy • Uncontrolled fungal, bacterial, viral, or other infection • Active infection with HIV or hepatitis B or C – Note: Those with HIV or hepatitis B or C and an undetectable viral load are eligible • Known history or CNS lymphoma involvement • History of clinically significant cardiac disease within 6 months of randomization • Neuropathy greater than Grade 1

[a] Patients who received anti-CD20 mAb monotherapy prior to the initial line of CIT are eligible and POD24 will be counted from initiation of CIT.
CAR, chimeric antigen receptor; CIT, chemoimmunotherapy; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; POD24, progression within 24 months from initiating first-line chemoimmunotherapy; R/R, relapsed/refractory; TFL, transformed follicular lymphoma.

STATUS

Figure 3. Map of ZUMA-22 Clinical Trial Sites



- This study opened to accrual in June 2022 and is currently recruiting participants at several sites globally

REGISTRATION

- This study is registered at ClinicalTrials.gov (NCT05371093)

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DISCLOSURES

- Author disclosure information is available from the abstract online
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