ZUMA-5: Phase 2 Multicenter Study Evaluating Efficacy of Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

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Background

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T cell therapy (Figure 1)\(^1\)
  - Composed of an anti-CD19 single-chain variable fragment region, a CD28 costimulatory domain, and CD3ζ signaling domain
- Approved by the United States Food and Drug Administration for the treatment of adult patients with relapsed/refractory (R/R) large B cell lymphoma after ≥ 2 prior lines of systemic therapy\(^2\)
  - Axi-cel is not indicated for the treatment of patients with primary central nervous system lymphoma
- Each year, approximately 75,000 new cases of non-Hodgkin lymphoma (NHL) are diagnosed in the United States\(^3\)
- Follicular lymphoma (FL) is the second most common NHL, with an annual incidence rate of 2.6 per 100,000 people in the United States and 5 per 100,000 people in Western Europe\(^3,4\)

Structure of Axi-Cel

scFv (anti-CD19)
Hinge/Transmembrane
Signal 2: CD28
Signal 1: CD3ζ

scFv, single-chain variable fragment.
Background

- Many agents are under investigation for treatment of R/R FL, but no standard of care exists\(^5\)
- FL is generally considered incurable and most patients experience multiple relapses of increasing frequency and aggressiveness\(^6\)
- Despite advances in management and improvements in survival, outcomes remain varied for patients with FL\(^7\)
- Patients with FL receive upfront treatment with an anti-CD20 antibody-containing immunochemotherapy regimen; however, approximately 20% progress soon after first-line therapy\(^8\)
- New therapies are needed for patients with indolent NHL (iNHL), including FL and marginal zone lymphoma, that is refractory to immunochemotherapy regimens\(^8,9\)
- ZUMA-5 is a Phase 2, multicenter, single-arm study investigating the efficacy and safety of axi-cel in patients with R/R iNHL
ZUMA-5 STUDY SCHEMA

Phase 2

Relapsed/Refractory iNHL (n = 80)

Screening

Enrollment/Leukapheresis

Manufacturing 6-8 Days

Lymphodepleting Chemotherapy\(^{a}\)

Axi-Cel Infusion\(^{a}\)

First Tumor Assessment

Day −5 to −3

Day 0

Day 7

Day 28

Follow-Up Period (post-treatment assessment and long-term follow-up)

Investigational Product Hospitalization Period

\(^{a}\)Axi-cel treatment consists of lymphodepleting chemotherapy of 500 mg/m\(^2\) cyclophosphamide and 30 mg/m\(^2\) fludarabine on Day −5, Day −4, Day −3 followed by a target of 2 × 10\(^6\) CAR T cells/kg on Day 0. For patients weighing > 100 kg, a maximum flat dose of 2 x 10\(^8\) CAR T cells will be administered.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; iNHL, indolent non-Hodgkin lymphoma.
ENDPOINTS

**Primary Endpoint**: Objective response rate (ORR), defined as complete response (CR) + partial response (PR) per the Lugano Classification\(^\text{10}\) as determined by central review

**Secondary Endpoints**:
- CR rate, defined per the Lugano Classification\(^\text{10}\) by central review
- Incidence of adverse events (AEs) and clinically significant changes in laboratory values
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Levels of anti-CD19 CAR T cells in blood
- Levels of cytokines in serum
- Incidence of antibodies to axi-cel

**Exploratory Endpoints**:
- Biomarker analyses
### Key Inclusion Criteria

- Histologically proven iNHL:
  - FL, Grade 1, 2, and 3a
  - MZL, nodal or extranodal
- Relapsed or refractory disease after ≥ 2 prior lines of therapy
  - Must have included an anti-CD20 monoclonal antibody combined with an alkylating agent
- ≥ 1 measurable lesion
- Prior systemic therapy at the time of leukapheresis
  - ≥ 2 weeks or 5 half-lives, whichever is shorter
  - ≥ 3 half-lives for systemic inhibitory/stimulatory immune checkpoint therapy
- Age ≥ 18 years
- ECOG PS 0-1
- Adequate renal, hepatic pulmonary, and cardiac function

### Key Exclusion Criteria

- Histological Grade 3b FL or transformed FL/MZL
- Splenic MZL, SLL, or lymphoplasmacytic lymphoma
- Prior allogeneic stem cell transplant
- Prior CD19 targeted therapy
- Prior CAR T therapy
- Clinically significant infection
- Detectable CSF malignant cells or brain metastases
- History or presence of non-malignant CNS disorder
- Clinically significant cardiac disease
- History of autoimmune disease

STATISTICAL ANALYSES

• The incidence and exact 2-sided 95% CIs will be generated for ORR
• The incidence and exact 2-sided 95% CIs will be generated for CR
• Kaplan-Meier estimates and 2-sided 95% CIs will be generated for DOR, PFS, and OS
• Incidence rates of AEs (Common Terminology Criteria for AEs [CTCAE] version 4.03) Grade ≥ 3 and treatment-emergent AEs reported throughout the conduct of the study will be tabulated
• All patients will be followed for survival for up to ≈15 years after the last patient receives their last axi-cel infusion
Ab, antibody; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; IL-2, interleukin-2; PBMC, peripheral blood mononuclear cell.
STATUS

- The study opened to accrual in May 2017 and is currently enrolling participants at 19 sites in the United States and France
  - 55 patients have been treated
Registration

- This study was sponsored by Kite, a Gilead Company, and is registered at ClinicalTrials.gov (NCT03105336)
References


2. YESCARTA® (axicabtagene ciloleucel) [prescribing information]. Santa Monica, CA: Kite Pharma; 2017.


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