Abstract: PB2319

Title: 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

Abstract Type: Publication Only

Session Title: Aggressive Non-Hodgkin lymphoma - Clinical

Background:

The nearly 40% of patients with large B-cell lymphoma (LBCL) who are refractory to or relapse 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. High International Prognostic Index (IPI) score and the subtype of high-grade B-cell lymphoma are associated with shorter progression-free and overall survival (PFS and OS; Nastoupil LJ and Bartlett NL. *J Clin Oncol*. 2023). Strategies to improve outcomes in these subgroups 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 approved to treat patients with relapsed/refractory LBCL after demonstrating significant clinical benefit as 2L (ZUMA-7; Locke FL, et al. *N Engl J Med*. 2022) and ≥3L (ZUMA-1; Neelapu SS, et al. *N Engl J Med*. 2017) therapy. Additionally, in the Phase 2 ZUMA-12 study in patients with refractory first-line LBCL, axi-cel showed a high rate of durable responses with an objective response rate of 89% (complete response rate, 78%) and an ongoing response rate of 73% (median follow-up, 15.9 months; Neelapu SS, et al. *Nat Med*. 2022).

Aims:

ZUMA-23 is the first Phase 3, randomized controlled study to evaluate CAR T-cell therapy as a first-line regimen for any cancer and will assess axi-cel versus SOC in patients with high-risk LBCL, defined as IPI 4-5.

Methods:

The Phase 3 trial design will enroll approximately 300 adult patients with high-risk, histologically confirmed LBCL based on the 2016 WHO classification, including diffuse large B-cell lymphoma, high-grade B-cell lymphoma, and transformed follicular or marginal zone lymphoma (Swerdlow SH, et al. *Blood*. 2016). Eligible patients will receive 1 cycle of R-chemotherapy and then be randomized 1:1 to receive axi-cel or continue with SOC. Patients in the axi-cel arm will undergo leukapheresis and then receive R-CHOP or DA-EPOCH-R as bridging therapy, followed by lymphodepleting chemotherapy (fludarabine/cyclophosphamide), and a single axi-cel infusion (2×10^6 CAR T cells/kg). Prophylactic corticosteroids may be administered to reduce the incidence and severity of cytokine release syndrome at the investigator's discretion. Patients in the SOC arm will receive 5 additional cycles of R-CHOP or DA-EPOCH-R (investigator's choice).

The primary endpoint is event-free survival by blinded central review. Key secondary endpoints are OS and PFS. Safety, quality of life, and pharmacokinetics will also be assessed. Patients with a history of HIV and/or hepatitis B or C and undetectable viral loads may enroll. Key exclusion criteria include LBCL of the central nervous system.

Results:

ZUMA-23 is open for enrollment (NCT05605899).

Summary/Conclusion:

ZUMA-23 will examine the efficacy and safety of axi-cel versus SOC as first-line therapy in patients with high-risk LBCL.

Keywords: High risk, CD19, CAR-T, Diffuse large B cell lymphoma