894 3-Year Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) As First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma (LBCL)

Program: Oral and Poster Abstracts
Type: Oral
Session: 704. Cellular Immunotherapies: Early Phase and Investigational Therapies: Improving CAR-T Therapies for B Cell Malignancies
Hematology Disease Topics & Pathways:
Research, clinical trials, Biological therapies, adult, Lymphomas, non-Hodgkin lymphoma, B Cell lymphoma, Clinical Research, Chimeric Antigen Receptor (CAR)-T Cell Therapies, Diseases, immune mechanism, Therapies, Lymphoid Malignancies, Biological Processes, Study Population, Human
Monday, December 11, 2023: 4:00 PM

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Background:
Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for the treatment of relapsed/refractory (R/R) LBCL. ZUMA-12 (NCT03761056) is a Phase 2,

multicenter, single-arm study of axi-cel as part of first-line treatment in patients with high-risk LBCL. In the primary efficacy analysis (n=37; median follow-up of 15.9 months), axi-cel demonstrated a high rate of investigator-assessed complete response (CR; 78%; 95% CI, 62-90) and an 89% objective response rate (ORR; 95% CI, 75-97). Axi-cel also had a manageable safety profile, with no new safety signals observed in the first-line setting (Neelapu et al. *Nat Med.* 2022). Here, we report updated efficacy and safety outcomes from ZUMA-12 in all patients treated with axi-cel after a median follow-up of ≥40 months.

Methods:

Eligible adults had high-risk LBCL, with *MYC* and *BCL2* and/or *BCL6* rearrangements (double- or triple-hit histology) per investigator or an International Prognostic Index (IPI) score ≥3, plus a positive interim PET per Lugano classification (Deauville score 4/5) after 2 cycles of an anti-CD20 monoclonal antibody and anthracycline-containing regimen. Patients underwent leukapheresis, followed by lymphodepleting chemotherapy (cyclophosphamide and fludarabine) on Days -5, -4, and -3, and a single axi-cel infusion of 2×10^6 CAR T cells/kg on Day 0. Per investigator discretion, non-chemotherapy bridging could be administered. The primary endpoint was investigator-assessed CR rate per Lugano classification (Cheson et al. *J Clin Oncol.* 2014). Secondary endpoints included ORR, duration of response (DOR), event-free survival (EFS), progression-free survival (PFS), overall survival (OS), safety, and levels of CAR T cells in blood and cytokines in serum.

Results:

As of May 3, 2023, 42 patients were enrolled and 40 were treated with axi-cel, with a median follow-up of 40.9 months (range, 29.5-50.2). In total, 37 patients were evaluable for response (centrally confirmed double- or triple-hit histology or IPI score ≥3). The CR rate was 86% (95% CI, 71-95), and 92% (95% CI, 78-98) of patients had an objective response. Patients with centrally confirmed double- or triple-hit histology (n=10) had a CR rate of 90%. Responses were ongoing in 73% of response-evaluable patients at data cutoff. Medians for DOR, EFS, PFS, and OS were not reached. The 36-month estimates for DOR, EFS (Figure 1), PFS, and OS (Figure 2) were 82%, 73%, 75%, and 81%, respectively.

All treated patients (n=40) experienced adverse events (AEs) of any grade and 88% of patients had grade ≥3 AEs. Similar to the primary analysis, the most common any-grade AEs were pyrexia (100%), headache (70%), and neutrophil count decreased (55%). No new cases of cytokine release syndrome (CRS) or neurologic events of any grade occurred since the prior data cut and all cases of CRS and neurologic events reported were resolved by data cutoff. Prolonged cytopenias of any grade (present Day ≥30 post-infusion) occurred in 9 patients (n=7 neutrophil count decreased) and were resolved by data cutoff. There were 8 deaths due to progressive disease (n=5) and other causes not related to axi-cel (1 COVID-19, 1 esophageal adenocarcinoma, 1 septic shock on Days 350, 535, and 287 post axi-cel infusion, respectively).

Two of the 8 deaths (1 progressive disease and 1 esophageal adenocarcinoma) occurred after the primary analysis.

Among treated patients, post-infusion CAR T-cell expansion by peak and area under the curve was 36.9 cells/µL and 368.0 cells/µL×days, respectively, in those with ongoing responses at data cutoff (n=17), 45.1 cells/µL and 413.4 cells/µL×days in those who relapsed (n=6), and 34.7 cells/µL and 566.8 cells/µL×days in non-responders (n=3).

Conclusion:

In this updated analysis of ZUMA-12 with a median follow-up of ≥40 months, axi-cel demonstrated a high rate of durable responses and no new safety signals. Axi-cel may benefit patients exposed to fewer prior therapies and those with high-risk LBCL, a population with high unmet need and poor outcomes after standard first-line chemoimmunotherapy.

Figure 1. Event-Free Survival

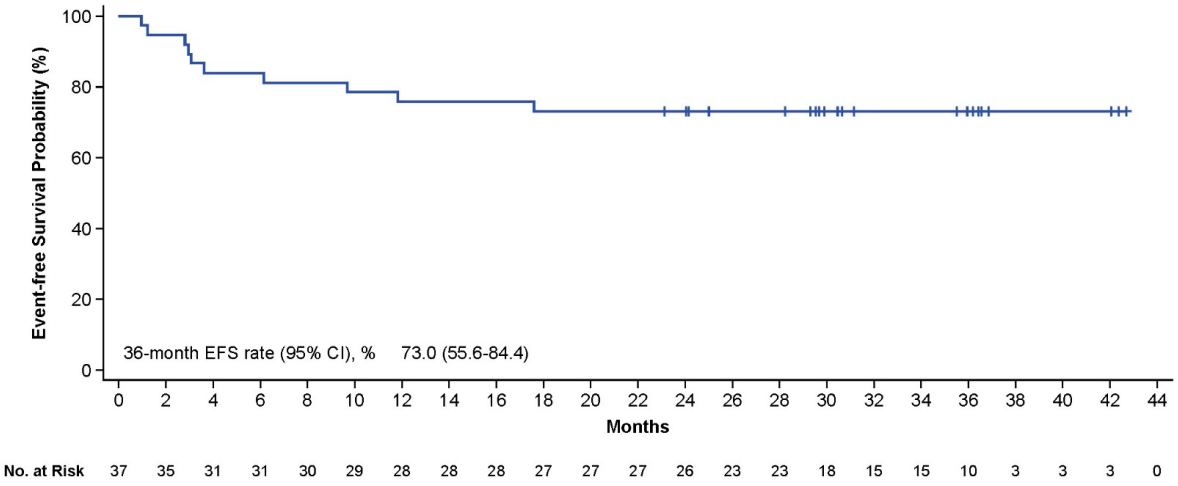
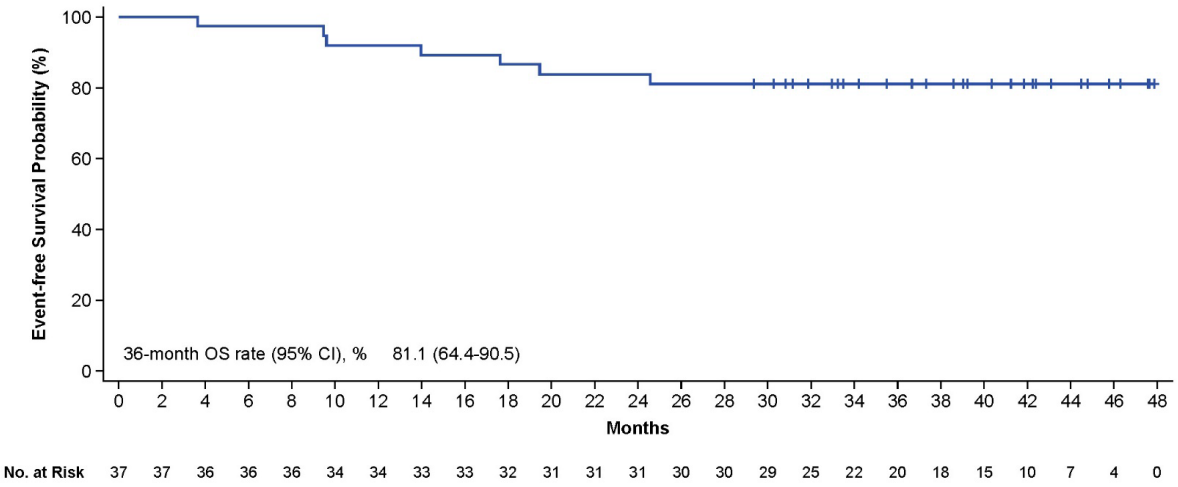


Figure 2. Overall Survival



EFS, event-free survival; No, number; OS, overall survival.

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