Primary Analysis of ZUMA-7: A Phase 3 Randomized Trial of Axicabtagene Ciloleucel (Axi-Cel) Versus Standard-of-Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma

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Background:

The standard of care (SOC) treatment (Tx) in the curative setting for patients (pts) with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) after 1st-line (1L) chemoimmunotherapy (CIT) is high-dose therapy with autologous stem cell rescue (HDT-ASCT) if responsive to 2L CIT; however, as many pts do not respond to or cannot tolerate 2L CIT, or are not intended for HDT-ASCT, outcomes remain poor. Axi-cel is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved for R/R LBCL after ≥2 prior systemic therapies. Since CAR T-cell therapy may benefit pts in earlier lines of therapy, we conducted ZUMA-7 (NCT03391466), a global, randomized, Phase 3 trial of axi-cel vs SOC in pts with 2L R/R LBCL, and report here the results of the primary analysis (PA).

Methods:

Eligible pts were ≥18 y with LBCL, ECOG PS 0-1, R/R disease ≤12 mo of adequate 1L CIT (including anti-CD20 monoclonal antibody and an anthracycline), and intended to proceed to HDT-ASCT. Pts were randomized 1:1 to axi-cel or SOC, stratified by 1L Tx response and 2L age-adjusted IPI (sAAIPI). In the axi-cel arm, pts received a single infusion of 2×10 6 CAR T cells/kg after conditioning (3 d; cyclophosphamide 500 mg/m 2/day and fludarabine 30 mg/m 2/day). Optional bridging Tx was limited to corticosteroids (CIT was not allowed). In the SOC arm, pts received 2-3 cycles of an investigator-selected, protocol defined, platinum-based CIT regimen; pts with partial response or complete response (CR) proceeded to HDT-ASCT. Disease assessments by PET-CT per Lugano Classification occurred at timepoints specified from randomization. Although there was no planned trial crossover between arms, pts not responding to SOC could receive CAR T-cell therapy off protocol. Axi-cel was hypothesized to result in a 50% improvement in event-free survival (EFS: time to earliest date of disease progression, death from any cause, or new lymphoma Tx) vs SOC. The PA was event-driven, and the primary endpoint was EFS by blinded central review. Key secondary endpoints, tested hierarchically, were objective response rate (ORR) and overall survival (OS; interim analysis); safety was also a secondary endpoint. Level of CAR T cells was an exploratory endpoint.

Results:

As of 3/18/21, 359 pts were enrolled globally. The median age was 59 y (range, 21-81; 30% ≥65 y). Overall, 74% of pts had primary refractory disease and 46% had high sAAIPI (2-3). Of 180 pts randomized to axi-cel, 170 (94%) were infused; of 179 pts randomized to SOC, 64 (36%) reached HDT-ASCT after 2L CIT. The primary endpoint of EFS was met (HR: 0.398; P<.0001). At 24.9 mo median follow-up, median EFS was significantly longer with axi-cel vs SOC (8.3 mo [95% CI: 4.5-15.8] vs 2 mo [95% CI: 1.6-2.8], respectively), and Kaplan-Meier estimates of the 24-mo EFS rates were significantly higher with axi-cel (41% vs 16%). Among randomized pts, ORR and CR rates were higher with axi-cel vs SOC (ORR: 83% vs 50%, odds ratio: 5.31 [95% CI: 3.1-8.9; P<.0001]; CR: 65% vs 32%). Median OS, evaluated as a preplanned interim analysis, favored axi-cel vs SOC, although it did not meet statistical significance (not reached vs 35.1 mo, respectively; HR: 0.730; P=.027). In the SOC arm, 100 (56%) received commercially available or investigational CAR T-cell therapy off protocol as subsequent Tx. Grade ≥3 treatment-emergent adverse events occurred in 155 (91%) and 140 (83%) pts, and Tx-related deaths occurred in 1 and 2 pts in the axi-cel and SOC arms, respectively. In pts treated with axi-cel, grade ≥3 cytokine release syndrome (CRS) occurred in 11 (6%) pts (median time to onset 3 d; median duration 7 d) and grade ≥3 neurologic events (NEs) occurred in 36 (21%) pts (median time to onset 7 d; median duration 8.5 d). No grade 5 CRS or NEs occurred. Median peak CAR T-cell level was 25.8 cells/µL; median time to peak was 7 d after infusion.

Conclusion:

ZUMA-7, the first randomized, global, multicenter Phase 3 study of axi-cel vs 2L SOC in R/R LBCL, demonstrated a statistically significant and clinically meaningful improvement in EFS. Axi-cel showed superiority over SOC with >4-fold greater median EFS, 2.5-fold greater EFS at 2 y, double the CR rate, and more than double the percentage of pts receiving definitive Tx. Safety of axi-cel was manageable and at least consistent with 3L axi-cel therapy. Axi-cel may replace CIT/HDT-ASCT as the SOC for 2L R/R LBCL.