Poster
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Prophylactic Corticosteroid Use With Axicabtagene Ciloleucel in Patients With Relapsed/Refractory Large B-Cell Lymphoma: 2-Year Follow-Up of ZUMA-1 Cohort 6

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BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is a CD19-directed genetically modified autologous T-cell immunotherapy with a CD28 co-stimulatory domain that provides rapid and strong expansion and reprograms T cells to trigger target-specific cytotoxicity of cancer cells[1,2]
- Axi-cel is approved for the treatment of adults with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) after ≥2 lines of systemic therapy and for patients refractory to or who relapsed within 12 months of first-line chemoimmunotherapy[2,3]
- In pivotal Cohorts 1+2 of the registrational ZUMA-1 (NCT02348216) Phase 1/2 study of axi-cel in patients with refractory LBCL (n=101), with a median follow-up of 27.1 months[4]
  - 11% and 31% of patients experienced Grade ≥3 cytokine release syndrome (CRS) and neurologic events (NEs), respectively
  - 38% of patients experienced any grade infections, and 14% of patients had hypogammaglobulinemia
  - The objective response rate (ORR) was 83% and the complete response (CR) rate was 58%
- With a median follow-up of 63.1 months for Cohorts 1+2, the 5-year OS rate was 43%[5]
- Several exploratory safety management cohorts were added to ZUMA-1 to evaluate how safety outcomes can be optimized without compromising efficacy[6,7]
- Safety management Cohort 4 (N=41) evaluated the impact of earlier corticosteroid and tocilizumab intervention on the incidence and severity of CRS and NEs in patients with R/R LBCL[6]
- Cohort 6 (N=40), which evaluated the addition of prophylactic corticosteroids to the Cohort 4 toxicity management strategy, demonstrated reduced Grade ≥3 CRS and NEs (no Grade ≥3 CRS; 15% Grade ≥3 NEs) versus Cohorts 1+2, and high, durable response rates with ≥1 year of follow-up (95% ORR, 80% CR rate, and 53% ongoing response rate)[8]

OBJECTIVE

- To present updated safety, efficacy, and pharmacokinetic outcomes of Cohort 6 with ≥2 years of follow-up

METHODS

- The toxicity management protocols for ZUMA-1 Cohorts 1+2 and Cohort 6 were previously described[7,9]
- Cohort 6 primarily differed from Cohorts 1+2 in that patients in Cohort 6 could receive optional bridging therapy per investigator discretion and all patients received levetiracetam and corticosteroid prophylaxis and earlier corticosteroids and tocilizumab for toxicity management[7,9]
  - Patients in Cohort 6 received once-daily oral dexamethasone 10 mg on Days 0 (before axi-cel), 1, and 2
- No formal hypothesis was tested for Cohort 6 and all endpoints were analyzed descriptively[7]
  - The primary endpoints were incidence and severity of CRS and NEs, which were identified and graded as previously reported[7]
  - Secondary endpoints included investigator-assessed ORR (per International Working Group Response Criteria for Malignant Lymphoma[10]), duration of response (DOR), progression-free survival (PFS), OS, and chimeric antigen receptor (CAR) T-cell levels in blood

RESULTS

- As of the December 16, 2021 2-year data cutoff date, the median follow-up time for the 40 patients treated in Cohort 6 was 26.9 months (range, 24.0-30.1)
- Patient demographics and disease characteristics at baseline were previously reported[7]

Table 1. Summary of CRS and Neurologic Events in Cohort 6 Since Start of Study

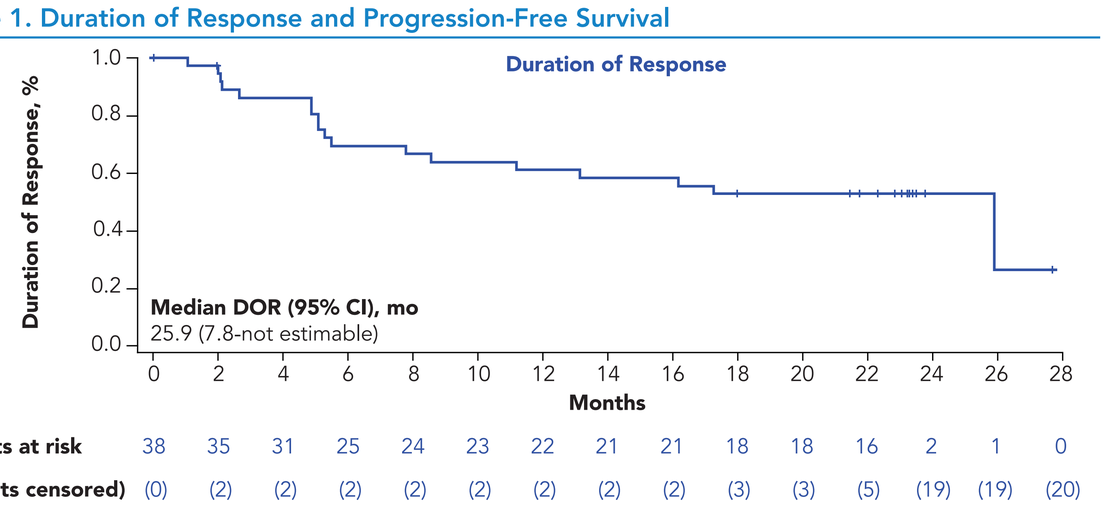
	Cohort 6 (N=40)
CRS, n (%)	**32 (80)**
Worst Grade 1, n (%)	14 (35)
Worst Grade 2, n (%)	18 (45)
Worst Grade ≥3, n (%)	0 (0)
Median time to onset[a] of any grade CRS (range), days	5 (1-15)
Median duration of any grade CRS (range), days	4 (1-11)
Neurologic events, n (%)	**23 (58)**
Worst Grade 1, n (%)	9 (23)
Worst Grade 2, n (%)	7 (18)
Worst Grade ≥3, n (%)	7 (18)
Median time to onset[a] of any grade neurologic event (range), days	6 (2-162)
Median duration of any grade neurologic event (range), days	19 (1-438)

Severity of CRS and neurologic events were graded per Lee et al criteria[11] and Common Terminology Criteria for Adverse Events version 4.03, respectively. Neurologic events were identified using a Medical Dictionary for Regulatory Activities version 24.1 search term list that was developed based on a modification of the specific search strategy by Topp et al.[12]
[a] Time to onset was defined as the time to earliest event onset, including among patients who may have experienced multiple events.
CRS, cytokine release syndrome.

- Since the start of study, no patients experienced Grade ≥3 CRS in Cohort 6 (**Table 1**), and the incidence of CRS did not change since the 1-year analysis[8]
- Since the 1-year analysis, 2 new NEs were observed in 2 patients
  - Patient 1: Grade 2 dementia with onset on Day 685 (unrelated to axi-cel); the event was ongoing at the time of data cutoff
  - Patient 2: axi-cel–related leukoencephalopathy (onset as a Grade 3 event on Day 758) that was ultimately fatal on Day 815. A biopsy performed on Day 802 suggested that the underlying etiology of the leukoencephalopathy was infection versus other malignancy. However, an autopsy was not performed. The patient was in CR at time of death and died in hospice care
- Since the Grade 5 event was coded as a NE, the incidence of Grade ≥3 NEs increased from 15% to 18% since the 1-year analysis
- Since the start of study
  - 24 patients (60%) had any grade infections, and 11 (28%) experienced Grade ≥3 events
  - 5 patients (13%) had COVID-19 infections after axi-cel infusion, and 3 were Grade ≥3 (all events were deemed unrelated to axi-cel by the treating investigator)
  - 8 patients (20%) had hypogammaglobulinemia, all experienced Grade 1 (n=2) or 2 (n=6) events
  - 7 patients (18%) received intravenous immunoglobulin (IVIG) therapy for treatment of adverse events (of these, 1 patient also received IVIG for prophylaxis)
- Since the 1-year analysis, 6 new infections were reported, as follows
  - Grades 1, 2, and 5 COVID-19 infection (n=1 each; unrelated to axi-cel)
  - Grade 3 *Pneumocystis jirovecii* pneumonia (n=1; axi-cel–related)
  - Grade 3 unknown infectious episode with inflammatory syndrome (n=1; axi-cel–related)
  - Grade 2 herpes zoster (n=1; axi-cel–related)
- B-cell recovery was observed among patients in ongoing response, as 1 of 18 evaluable patients (6%) had detectable B cells at Month 3 compared with 5 of 16 evaluable patients (31%) at 2 years after axi-cel infusion
- In total, 8 deaths occurred since the 1-year analysis
  - 5 due to progressive disease
  - 3 due to adverse events (leukoencephalopathy [n=1] and COVID-19 [n=2])
- The ORR was 95% (95% CI, 83-99) and the CR rate was 80% (95% CI, 64-91), both of which were unchanged from the 1-year analysis[8]

RESULTS *(Continued)*

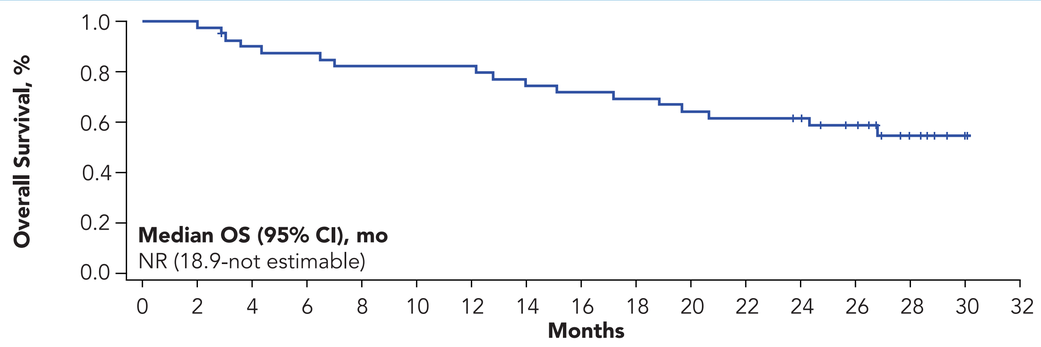
Figure 1. Duration of Response and Progression-Free Survival



Disease assessments were investigator-assessed per Cheson et al,[10] and assessments after initiation of new anticancer therapy (not including stem cell transplant) were not included in the DOR or PFS derivations.
DOR, duration of response; PFS, progression-free survival.

- Since the 1-year analysis, median DOR and PFS were reached at 25.9 months (95% CI, 7.8-not estimable) and 26.8 months (95% CI, 8.7-not estimable), respectively, given changes among 3 responders (1 had disease progression and 2 died; **Figure 1**)

Figure 2. Overall Survival



NR, not reached; OS, overall survival.

- Median OS was still not reached (**Figure 2**)
- Kaplan-Meier estimates of the 2-year DOR, PFS, and OS rates were 53%, 53%, and 62%, respectively
- At data cutoff, 18 patients (45%) were in ongoing response, and all had achieved CR as the best response
- CAR T-cell expansion was comparable between patients in Cohort 6 and ZUMA-1 pivotal Cohorts 1+2

CONCLUSIONS

- With ≥2 years of follow-up, the ZUMA-1 Cohort 6 toxicity management strategy of prophylactic corticosteroids and earlier corticosteroid and/or tocilizumab intervention continued to demonstrate reduced Grade ≥3 CRS without adversely affecting CAR T-cell pharmacokinetics or compromising efficacy outcomes for patients with R/R LBCL treated with axi-cel
  - No Grade ≥3 CRS has been reported in Cohort 6 since start of study
  - The incidence of Grade ≥3 NEs increased slightly from the prior 1-year analysis,[8] though the value remains numerically lower than that reported in Cohorts 1+2[4]
- Responses remained high, durable, and similar to those observed in Cohorts 1+2[4]

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DISCLOSURES

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