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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

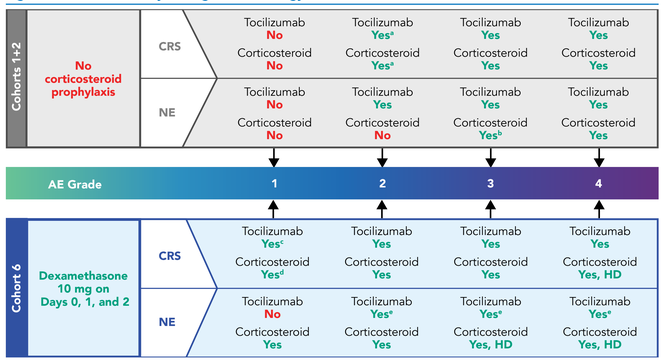
- Axicabtagene ciloleucel (axi-cel) is a CD19-directed genetically modified autologous T-cell immunotherapy with a CD28 co-stimulatory domain that provides rapid and strong expansion and reprograms T cells to trigger target-specific cytotoxicity of cancer cells[1,2]
- Axi-cel is approved for the treatment 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 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, 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

Figure 1. ZUMA-1 Toxicity Management Strategy



[a] Only in case of comorbidities or older age.
[b] Only if no improvement with tocilizumab; use standard dose.
[c] If no improvement after 24 hours of supportive care in Cohort 6.
[d] If no improvement after 3 days.
[e] Only for Grade ≥2 NEs with concurrent CRS in Cohort 6.
AE, adverse event; CRS, cytokine release syndrome; HD, high dose; NE, neurologic event.

- 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 (**Figure 1**)[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 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]
- All 40 patients (100%) had treatment-emergent adverse events (TEAEs)
- All patients reported Grade ≥3 TEAEs, most commonly neutropenia (80%; combined with preferred term neutrophil count decreased), leukopenia (40%; combined with preferred term white blood cell count decreased), and thrombocytopenia (28%; combined with preferred term platelet count decreased)

RESULTS *(continued)*

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 event, 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. The patient was in CR at time of death and died in hospice care; an autopsy was not performed
- Given the Grade 5 event, the incidence of Grade ≥3 NEs increased from 15% to 18% since the 1-year analysis

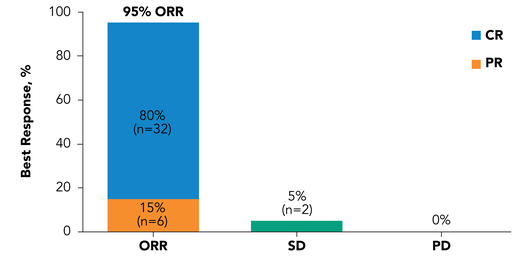
Table 2. Summary of Infections, Hypogammaglobulinemia, and IVIG Use in Cohort 6 Since Start of Study

	Cohort 6 (N=40)
Any grade infection, n (%)	**24 (60)**
Worst Grade 1, n (%)	3 (8)
Worst Grade 2, n (%)	10 (25)
Worst Grade ≥3, n (%)	11 (28)
Median time to onset of any grade infection (range), days	69 (3-638)
Median duration of any grade infection (range), days	28 (7-420)
Any grade hypogammaglobulinemia, n (%)	**8 (20)**
Worst Grade 1, n (%)	2 (5)
Worst Grade 2, n (%)	6 (15)
Worst Grade ≥3, n (%)	0 (0)
Required IVIG therapy,[a] n (%)	**7 (18)**

[a] IVIG therapy was administered at the treating investigator's discretion.
IVIG, intravenous immunoglobulin.

- Since the start of study
  - 24 patients (60%) had any grade infections, and 11 (28%) experienced Grade ≥3 events (**Table 2**)
  - 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])

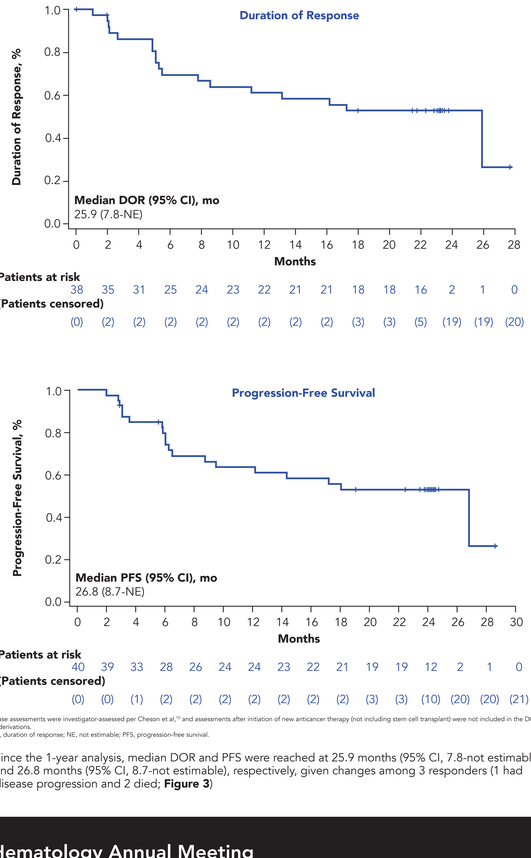
Figure 2. Investigator-Assessed Objective Response Rate



CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- 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] (**Figure 2**)

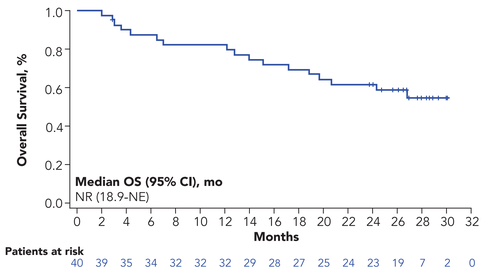
Figure 3. Duration of Response and Progression-Free Survival



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; NE, not estimable; 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 3**)

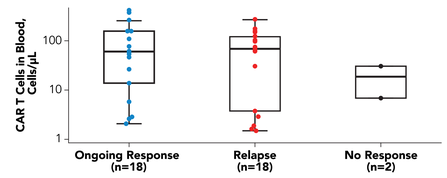
Figure 4. Overall Survival



NE, not estimable; NR, not reached; OS, overall survival.

- Median OS was still not reached (**Figure 4**)
- 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

Figure 5. Associations Between Peak CAR T-Cell Levels and Response at 2 Years



CAR, chimeric antigen receptor.

- Similar to the 1-year analysis,[8] median peak CAR T-cell levels were higher among patients in ongoing response (61 cells/µL [n=18]) or those who relapsed by the 2-year follow-up data cutoff date (68 cells/µL [n=18]), and considerably lower among nonresponders (18 cells/µL [n=2]; **Figure 5**)
- 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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