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Incidence of Cytokine Release Syndrome and Neurological Events in Patients With Relapsed or Refractory Large B-Cell Lymphoma at and Beyond 2 Weeks Following Axicabtagene Ciloleucel Infusion

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BACKGROUND

- Axicabtagene ciloleucel (axi-cel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, is approved for the 2L+ treatment of adult patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) and has become a standard of care providing significant clinical benefit[1–3]
- Cytokine release syndrome (CRS) and neurologic events (NEs) are toxicities associated with CAR T-cell therapies that require close monitoring and prompt intervention[1,2,4]
- In the pivotal ZUMA-1 and ZUMA-7 trials in R/R LBCL (**Table 1**), most patients treated with axi-cel experienced CRS and/or NEs[5,6]
  - In ZUMA-1 (Phase 2 Cohorts 1 and 2, N=101), any-grade CRS and NEs occurred in 93% and 64% of patients, respectively[5]
  - In ZUMA-7 (N=170), 92% and 60% of patients experienced any-grade CRS and NEs, respectively[6]
  - Median time to CRS onset following axi-cel infusion was 2 days in ZUMA-1 and 3 days in ZUMA-7, with a median duration of 8 and 7 days, respectively[5,6]
- Neurologic toxicities may occur concurrently with CRS or after CRS resolution[1]
  - In ZUMA-1 and ZUMA-7, median time to NE onset was 5 and 7 days, respectively, with a median duration of 17 and 9 days, respectively[5,6]
- Currently, patients must remain within close proximity of a certified healthcare facility for 4 weeks after axi-cel infusion and seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur[1,2]
- Although this 4-week monitoring period allows timely intervention for treatment-emergent CRS and NEs, it may be unnecessary for many patients and may represent a barrier to access for CAR T-cell therapy[4]
  - A recent retrospective analysis of real-world data has shown that first onset of CRS or NEs beyond 2 weeks post–CAR T-cell infusion is rare in patients with R/R LBCL[4]

AIM

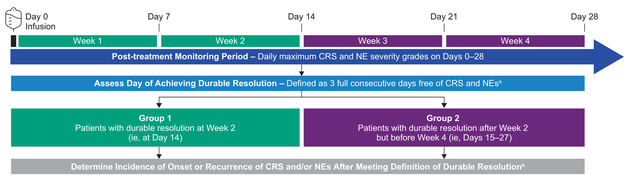
- To understand the patterns of onset and resolution of CRS and NEs within 28 days post–axi-cel infusion and assess the risk of onset or recurrence at 2 weeks after infusion and beyond in patients with R/R LBCL

METHODS

- The highest daily CRS and NE[a] severity grades (using Lee 2014[7] and CTCAE, respectively) were extracted using adverse event data from day of infusion (Day 0) through Day 28 for patients treated with axi-cel in ZUMA-1 (Phase 2, N=182), ZUMA-7, and ZUMA-24 (Phase 2, N=30, **Table 1**)
- Summary statistics were used to describe first onset and recurrent CRS/NEs
- An algorithm (**Figure 1**) was developed using safety data from all patients treated with axi-cel in ZUMA-7 (training cohort, N=170) to classify patients as having durable resolution of CRS/NEs versus not having durable resolution
  - "Durable resolution" of CRS/NEs was defined as 3 full consecutive days free of CRS and NEs, with a minimum monitoring period of 2 weeks
  - Patients who did not experience CRS or NEs during the minimum monitoring period were classified as having durable resolution
- We assessed whether patients who met the definition of durable resolution had any later CRS/NE onset or recurrence
  - Those who achieved durable resolution were considered "low risk" for onset or recurrence within the 28-day monitoring period post–axi-cel infusion

[a]NEs were reported and graded based on individual symptoms and do not reflect the precise definition of the immune effector cell-associated neurotoxicity syndrome (ICANS).

Figure 1. Classification Algorithm for Durable Resolution



[a]With a minimum monitoring period of 2 weeks. [b]Accuracy rate in determining 'durable resolution' for each patient group was calculated using the following equation: (patients correctly classified ÷ total patients classified) ×100.
CRS, cytokine release syndrome; NE, neurologic event.

- Accuracy and error rates of the classification algorithm were calculated for 2 distinct groups of patients
  - Group 1: patients with durable resolution of CRS/NEs at 2 weeks (ie, Day 14)
  - Group 2: patients with durable resolution after 2 weeks but before 4 weeks (ie, Days 15–27)
- Frequency of patients with either ongoing CRS/NEs or non-durable (<3 days) resolution of CRS/NEs at Day 28 was reported
- The algorithm was trained using ZUMA-7 and validated using 2 independent axi-cel datasets (**Table 1**):
  - A pooled ZUMA-1 cohort (Phase 2 pivotal Cohorts 1 and 2, and safety Cohorts 4 and 6 [early use of tocilizumab/dexamethasone for Grade 1 CRS/NEs without and with prophylactic corticosteroids, respectively])
  - ZUMA-24 cohort (Phase 2 Cohort who received daily prophylactic corticosteroids on Days 0–2 and received axi-cel in the outpatient setting)

Table 1. Details of the Training and Validation Datasets Used for Algorithm Development and Validation

	Training Cohort	Validation Cohorts	
	ZUMA-7[6,8]	Pooled ZUMA-1[5,9–11,a]	ZUMA-24[12,13]
Trial ID	NCT03391466	NCT02348216	NCT05459571
Trial phase	Phase 3, randomized, open-label	Phase 2, single-arm	Phase 2, single-arm
Trial description	Pivotal study to assess efficacy and safety of axi-cel vs SOC	Pivotal study to evaluate efficacy of axi-cel; Safety management study to assess impact of prophylactic regimens or earlier interventions on CRS/NE incidence and severity	Study to evaluate safety and efficacy of axi-cel with concomitant administration of prophylactic corticosteroids in the outpatient setting
Patient population	R/R LBCL	R/R DLBCL, PMBCL, TFL	R/R LBCL
Treatment line	2L	3L+	2L+
Patients who received axi-cel	170	182	30
CRS grading system	Severity: Lee et al.[7]	Severity: Lee et al.[7]	Severity: Modification[b] of Lee 2014 et al.
NE grading system	CTCAE v4.03	CTCAE v4.03	CTCAE v5.0

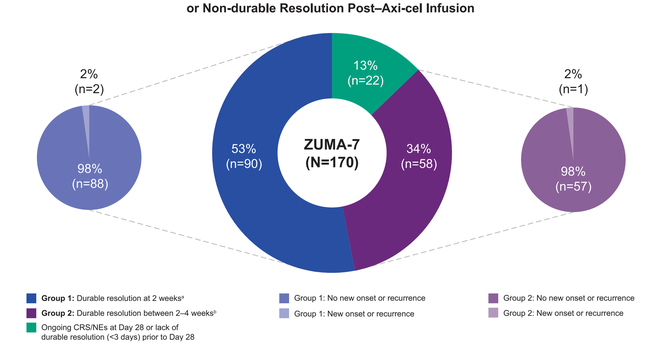
[a]ZUMA-1 validation cohort consisted of pooled Cohorts 1 and 2 from Phase 2 pivotal study and Cohorts 4 and 6 from safety management study. [b]Meaning exclusion of neurologic symptoms from the categorization of the CRS.
Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; CTCAE, common terminology criteria for adverse events; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; NE, neurologic event; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care; TFL, transformed follicular lymphoma.

RESULTS

ZUMA-7 Training Cohort

- In the ZUMA-7 training cohort (N=170), 87% of patients (n=148) achieved durable resolution of CRS/NEs prior to Week 4 and 13% of patients (n=22) had ongoing CRS/NEs at Day 28 or lack of durable resolution prior to Day 28 (**Figure 2**)
  - 98% of the patients who achieved durable resolution (n=145) had no subsequent CRS/NE onset or recurrence within 4 weeks post–axi-cel infusion
- In the 94% of ZUMA-7 patients who experienced CRS and/or NEs within the first 28 days, the maximum day of first onset was Day 12

Figure 2. ZUMA-7 Training Cohort—Descriptive Statistics Based on Classification Algorithm



[a]Three full consecutive days free of CRS and NEs with a minimum monitoring period of 2 weeks (ie, no CRS or NE of any grade on Days 12, 13, and 14). [b]Three full consecutive days free of CRS and NEs with a minimum monitoring period of 2 weeks (ie, patient did not meet criteria for durable resolution at Day 14 but met these criteria between Days 15 and 27 [eg, CRS- and NE-free on Days 13, 14, and 15; Days 14, 15, and 16; etc]).
Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; NE, neurologic event.

Group 1

- 53% of patients (n=90) achieved durable resolution of CRS/NEs at **2 weeks**
  - 98% of these patients (n=88) had no subsequent onset of CRS/NEs (**Figure 2**)
  - 2 patients experienced a Grade 1 NE prior to the 4-week timepoint **(Figures 2 and 4)**

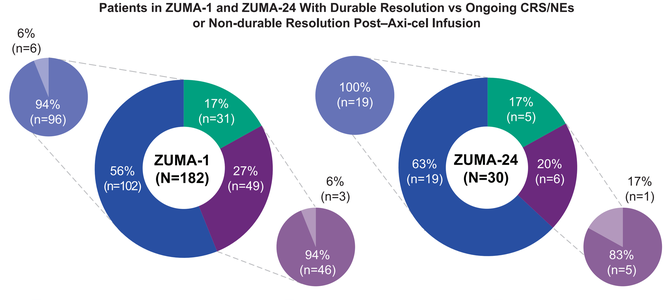
Group 2

- An additional 34% of patients (n=58) achieved durable resolution of CRS/NEs **between 2–4 weeks**
  - 98% of these patients (n=57) had no subsequent onset of CRS/NEs (**Figure 2**)
  - 1 patient later had Grade 1 NEs (**Figures 2 and 4**)

ZUMA-1 and ZUMA-24 Validation Cohorts

- In both the ZUMA-1 (N=182) and ZUMA-24 (N=30) validation cohorts, 83% of patients achieved durable resolution of CRS/NEs prior to Week 4 (**Figure 3**)
  - 94% and 96% of patients in ZUMA-1 and ZUMA-24, respectively, had no subsequent onset of CRS/NEs
- 17% had ongoing CRS/NEs at Day 28 or lack of durable resolution prior to Day 28 (**Figure 3**)
- In the 91% of ZUMA-1 patients who experienced CRS and/or NEs within the first 28 days, the maximum day of first onset was Day 11
- In the 93% of ZUMA-24 patients who experienced CRS and/or NEs within the first 28 days, the maximum day of first onset was Day 8

Figure 3. ZUMA-1 and ZUMA-24 Validation Cohorts—Descriptive Statistics Based on Classification Algorithm



[a]Three full consecutive days free of CRS and NEs with a minimum monitoring period of 2 weeks (ie, no CRS or NE of any grade on Days 12, 13, and 14). [b]Three full consecutive days free of CRS and NEs with a minimum monitoring period of 2 weeks (ie, patient did not meet criteria for durable resolution at Day 14 but met these criteria between Days 15 and 27 [eg, CRS- and NE-free on Days 13, 14, and 15; Days 14, 15, and 16; etc]).
Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; NE, neurologic event.

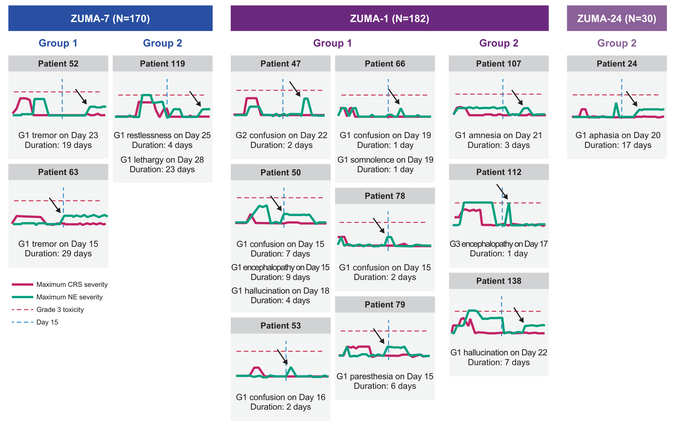
Group 1

- 56% (n=102) and 63% (n=19) of patients in the ZUMA-1 and ZUMA-24 cohorts achieved durable resolution of CRS/NEs **at 2 weeks**, respectively (**Figure 3**)
  - 94% of patients (n=96) who achieved durable resolution in ZUMA-1 had no subsequent CRS/NE onset or recurrence prior to Day 28 (**Figure 3**)
  - 6 patients in ZUMA-1 (Cohorts 1, 2, and 4: n=1 each; Cohort 6: n=3) subsequently had Grade ≥1 NEs prior to the 4-week timepoint (**Figures 3 and 4**)
  - 100% of patients (n=19) showing durable resolution in ZUMA-24 had no subsequent CRS/NE onset or recurrence prior to Day 28 (**Figure 3**)

Group 2

- An additional 27% of patients (n=49) in the ZUMA-1 cohort and 20% of patients (n=6) in the ZUMA-24 cohort achieved durable resolution of CRS/NEs **between 2–4 weeks** (**Figure 3**)
  - 94% of the patients (n=46) in ZUMA-1 had no subsequent CRS/NE onset or recurrence (**Figure 3**)
  - 3 patients in ZUMA-1 later had Grade ≥1 NEs (**Figures 3 and 4**)
  - 83% of the patients (n=5) in ZUMA-24 had no subsequent CRS/NE onset or recurrence (**Figure 3**)
  - 1 patient in ZUMA-24 later had a Grade 1 NE (**Figures 3 and 4**)
- The records for 13 patients across the 3 cohorts who were misclassified as low risk but later experienced NEs prior to Day 28 after achieving durable resolution are depicted using longitudinal plots (**Figure 4**)
- As shown in **Figure 4**, the majority of these NEs were of Grade 1 severity

Figure 4. Longitudinal Plots of CRS and NEs for Patients Misclassified as Low Risk



Patient numbers are arbitrary for the purposes of this presentation. Longitudinal toxicities were plotted using a random jitter in order to view CRS and NEs concurrently. For each graph, the x-axis represents time in days (range, 0–28) and the y-axis represents toxicity grade (range, 0–5).
CRS, cytokine release syndrome; G, grade; NE, neurologic event.

- For the 13 patients across all 3 cohorts who were considered low risk but later experienced NEs, the type of NEs, severity, timing of onset, and duration are summarized in **Table 2**
- Rates of recurrent or new-onset NEs:
  - 85% (n=11) had Grade 1 events
  - 92% of patients (n=12) had Grade ≤2 events
  - 8% of patients (n=1) had a Grade 3 event (encephalopathy that resolved within 1 day)
- None of these 13 misclassified patients experienced any recurrent or new-onset CRS events

Table 2. Summary of NEs Experienced by Patients After Meeting the Criteria for Durable Resolution

Meetings	Group	Patient	NE[a]	Grade	Onset	Duration
ZUMA-7 training cohort	1	52	Tremor[b]	1	Day 23	19 days
		63	Tremor[b]	1	Day 15	29 days
	2	119	Restlessness Lethargy	1 1	Day 25 Day 28	4 days 23 days
ZUMA-1 validation cohort	1	47	Confusion	2	Day 22	2 days
		50	Confusion Encephalopathy Hallucination	1 1 1	Day 15 Day 15 Day 18	7 days 9 days 4 days
		53	Confusion	1	Day 16	2 days
		66	Confusion Somnolence	1 1	Day 19 Day 19	1 day 1 day
		78	Confusion	1	Day 15	2 days
		79	Paresthesia[b]	1	Day 15	6 days
	2	107	Amnesia	1	Day 21	3 days
		112	Encephalopathy	3	Day 17	1 day
		138	Hallucination	1	Day 22	7 days
ZUMA-24 validation cohort	2	24	Aphasia	1	Day 20	17 days

[a]Based on individual NE signs/symptoms that do not use the ICANS-specific framework. [b]Per updated ICANS definitions, Grade 1 NEs such as tremor and paresthesia would not qualify as Grade 1 ICANS.
ICANS, immune effector cell-associated neurotoxicity syndrome; NE, neurologic event.

KEY FINDINGS

- Patients with R/R LBCL treated with axi-cel in the 2L+ setting who achieve durable resolution (3 full consecutive days) of CRS/NEs, with a minimum monitoring period of 2 weeks, are at low risk for CRS/NE onset or recurrence
- 55% of patients (211/382) across all datasets analyzed in this study achieved durable resolution of CRS/NEs by Week 2 regardless of the timing of the initial onset
  - 96% of these patients (n=203) had no subsequent CRS/NE onset or recurrence beyond Week 2
- 85% of patients (324/382) across all datasets achieved durable resolution of CRS/NEs by Week 4
- 13 patients with durable resolution had recurrent events
  - 12 of these 13 patients experienced recurrent events that were low grade and non-serious, and 1 patient experienced a serious adverse event that resolved the same day

LIMITATIONS

- Although not a focus of the Risk Evaluation and Mitigation Strategy (REMS) requirements for axi-cel administration, other complications such as infections may occur beyond 2 weeks following infusion
- These data represent patients enrolled and treated under a clinical trial protocol and, therefore, are not fully representative of patients receiving axi-cel in the commercial setting
- The ZUMA-24 sample size is small relative to the ZUMA-1 and ZUMA-7 cohorts; caution is advised if making direct comparisons between cohorts

CONCLUSIONS

- Our data show that patients who achieve durable resolution of CRS/NEs, with a minimum monitoring period of 2 weeks, are at low risk for later onset or recurrence and may be appropriate for a reduced monitoring period that is shorter than 4 weeks as currently prescribed[1,2]
- A risk-based monitoring approach can help maintain patient safety while reducing patient burden and disparities in access to CAR T-cell therapy associated with the need for relocation near authorized treatment centers

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