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

Olalekan O. Oluwole, MBBS, MPH[1]; Edouard Forcade, MD, PhD[2]; Javier Muñoz, MD, MS, MBA, FACP[3]; Sophie de Guibert, MD[4]; Julie M. Vose, MD, MBA[5]; Nancy L. Bartlett, MD[6]; Yi Lin, MD, PhD[7]; Abhinav Deol, MD[8]; Peter A. McSweeney, MBChB[9]; Andre H. Goy, MD[10]; Marie José Kersten, MD, PhD[11]; Caron A. Jacobson, MD, MMSc[12]; Umar Farooq, MD[13]; Monique C. Minnema, MD, PhD[14]; Catherine Thieblemont, MD, PhD[15]; John M. Timmerman, MD[16]; Patrick Stiff, MD[17]; Irit Avivi, MD[18]; Dimitrios Tzachanis, MD, PhD[19]; Jenny J. Kim, MD, MS[20]; Yan Zheng, MS[20]; Rhine R. Shen, PhD[20]; Saran Vardhanabhuti, PhD[20]; and Tom van Meerten, MD, PhD[21]

[1]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [2]CHU Bordeaux, Bordeaux, France; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]Hématologie Clinique, CHU Rennes, Rennes, France; [5]University of Nebraska Medical Center, Omaha, NE, USA; [6]Washington University School of Medicine and Siteman Cancer Center, St Louis, MO, USA; [7]Mayo Clinic, Rochester, MN, USA; [8]Karmanos Cancer Center, Wayne State University, Detroit, MI, USA; [9]Colorado Blood Cancer Institute, Denver, CO, USA; [10]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [11]Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands on behalf of HOVON/LLPC; [12]Dana-Farber Cancer Institute, Boston, MA, USA; [13]University of Iowa, Iowa City, IA, USA; [14]University Medical Center Utrecht, Utrecht, Netherlands, on behalf of HOVON/LLPC; [15]Université de Paris, Hôpital Saint-Louis, Hemato-Oncology, DMU HI, Paris, France; [16]UCLA David Geffen School of Medicine, Los Angeles, CA, USA; [17]Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA; [18]Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [19]Moores Cancer Center, UCSD, La Jolla, CA, USA; [20]Kite, a Gilead Company, Santa Monica, CA, USA; and [21]University Medical Center Groningen, Groningen, Netherlands, on behalf of HOVON/LLPC

Disclosures

Olalekan O. Oluwole: consultancy or advisory role for Kite, Janssen, Pfizer, Novartis, and Curio Science; and honoraria and research funding from Kite.

Background

- ZUMA-1 is the registrational Phase 1/2 study of axi-cel, an autologous anti-CD19 CAR T-cell therapy, in patients with refractory LBCL[1,2]
- In ZUMA-1 pivotal Cohorts 1+2
  - 83% ORR; 58% CR rate[2]
  - With 63.1 months median follow-up: 25.8 months median OS; 43% 5-year OS rate[3]
  - 13% Grade ≥3 CRS; 28% Grade ≥3 NEs[1]
- Management of CRS and NEs has been under evaluation to optimize safety outcomes
  - In safety management Cohort 4, earlier corticosteroid and/or tocilizumab use appeared to reduce Grade ≥3 CRS and NE rates, without affecting CAR T-cell expansion or ongoing response rates[4]
  - Cohort 6 evaluated the addition of prophylactic corticosteroids to the Cohort 4 toxicity management regimen in further reducing the incidence and severity of CRS and NEs[5]
- At a median follow-up of 8.9 months in Cohort 6 (n=40), no Grade ≥3 CRS was observed, a low rate of Grade ≥3 NEs (13%) was present, and response rates were high (95% ORR, 80% CR rate)[5]
- Here, we present a 1-year updated analysis of Cohort 6 supported by propensity score–based comparison of outcomes in Cohort 6 and Cohorts 1+2 to enable an accurate comparison of patients with highly similar characteristics across cohorts

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Locke FL, et al. *Lancet Oncol*. 2019;20:31-42. 3. Jacobson CA, et al. ASH 2021. Poster #1764. 4. Topp M, et al. *Br J Haematol*. 2021;195:388-398. 5. Oluwole OO, et al. *Br J Haematol*. 2021;194:690-700.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; LBCL, large B-cell lymphoma; NE, neurologic events; ORR, objective response rate; OS, overall survival.

ZUMA-1 Study Design

Original AE Management

Phase 2 (n=101)	
Cohort 1 Refractory DLBCL (n=77)	Cohort 2 Refractory PMBCL/TFL (n=24)

Revised AE Management

Phase 2 (n=40)
Cohort 6 R/R LBCL[a] (n=40)

Key eligibility criteria

- Cohorts 1+2: No response to last chemotherapy or relapse ≤12 months post-ASCT
- Cohort 6: R/R LBCL after ≥2 lines of therapy

Optional bridging therapy allowed in Cohort 6 only

- Dexamethasone,[b] high-dose methylprednisolone + rituximab,[c] or bendamustine + rituximab[d]

Conditioning regimen (all cohorts)

- Cyclophosphamide 500 mg/m^2 + fludarabine 30 mg/m^2 for 3 days

Axi-cel (all cohorts)

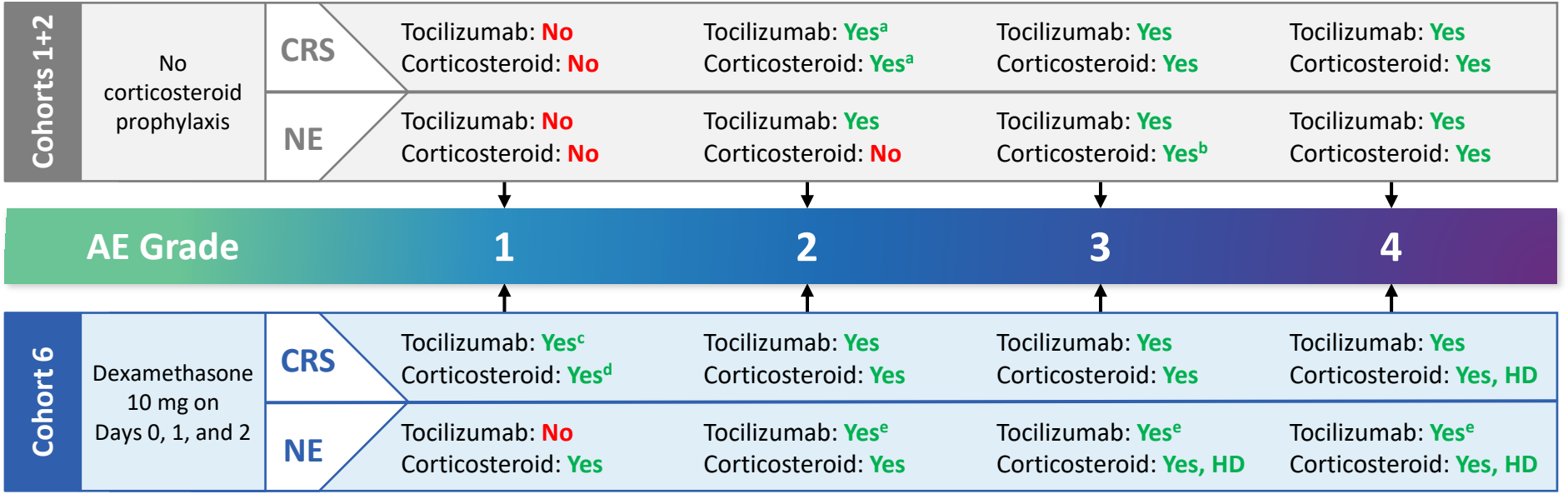
- 2×10^6 CAR+ T cells/kg[e]

Cohort 6 primary endpoint

- Incidence and severity of CRS and NEs

[a] Includes adult patients with DLBCL, PMBCL, TFL, and high-grade B-cell lymphoma after ≥2 systemic lines of therapy.
[b] 20 to 40 mg/day or equivalent daily for 1 to 4 days, completed before conditioning chemotherapy.
[c] Methylprednisolone 1 g/m^2 daily for 3 days + rituximab (375 mg/m^2 weekly), completed at least 7 days before conditioning chemotherapy.
[d] Bendamustine 90 mg/m^2 daily for 2 days + rituximab (375 mg/m^2 for 1 day), completed at least 14 days before conditioning chemotherapy.
[e] Flat dose of 2×10^8 CAR+ T cells/kg for patients with body weight >100 kg.
AE, adverse event; ASCT, autologous stem cell transplantation; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; LBCL, large B-cell lymphoma; NE, neurologic event; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapsed/refractory; TFL, transformed follicular lymphoma.

AE Management Strategy in ZUMA-1



- Patients in Cohort 6 received once-daily oral dexamethasone 10 mg on Days 0 (before axi-cel), 1, and 2
- Corticosteroids and tocilizumab were started earlier in Cohort 6 than in Cohorts 1+2 for toxicity management[1,2]

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Oluwole OO, et al. *Br J Haematol*. 2021;194:690-700.

[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; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; HD, high dose; Mgmt, management; NE, neurologic event.

Tocilizumab and Corticosteroid Guidelines for AE Management in Cohort 6

CRS Grade	Tocilizumab Dose[a]	Corticosteroid Dose[a]
1	If no improvement after 24 hours of supportive care, 8 mg/kg over 1 hour[b]; repeat every 4-6 hours as needed	If no improvement after 3 days, dexamethasone 10 mg ×1
2	8 mg/kg over 1 hour[b]; repeat every 4-6 hours as needed	Dexamethasone 10 mg ×1
3	Per Grade 2	Methylprednisolone 1 mg/kg IV twice daily or equivalent dexamethasone dose
4	Per Grade 2	Methylprednisolone 1000 mg/d IV for 3 days
NE Grade	**Tocilizumab Dose**	**Corticosteroid Dose**
1	N/A	Dexamethasone 10 mg ×1
2	Only in the case of concurrent CRS; 8 mg/kg over 1 hour; repeat every 4-6 hours as needed	Dexamethasone 10 mg 4 times/day
3	Per Grade 2	Methylprednisolone 1 g once daily
4	Per Grade 2	Methylprednisolone 1 g twice daily

[a] Therapy to be tapered on improvement of symptoms at investigator's discretion. [b] Not to exceed 800 mg.
AE, adverse event; CRS, cytokine release syndrome; IV, intravenous; N/A, not applicable; NE, neurologic event.

Analyses and Follow-Up Time

1-Year Analysis	**Data Cutoff Dates** • Cohorts 1+2[1]: Aug 11, 2017 • Cohort 6: Dec 16, 2020	**Median Follow-Up Times** • Cohorts 1+2[1]: 15.4 months • Cohort 6: 14.9 months

Exploratory Propensity Score Analysis	• Propensity score–matched comparisons[2] were performed to compare clinical safety, efficacy, and PK profiles of patients in Cohort 6 and Cohorts 1+2 after balancing for known baseline disease characteristics
	  ○ Tumor burden
	  ○ IPI score
	  ○ No. of prior lines of chemotherapy
	  ○ Disease stage
	  ○ LDH level
	• Propensity score matching was used to select matching patient subgroups from Cohorts 1+2 and Cohort 6	

1. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531-2544. 2. Rosenbaum PR, Rubin DB. *Biometrika*. 1983;70:41-55.
IPI, International Prognostic Index; LDH, lactate dehydrogenase; PK, pharmacokinetic.

Cohort 6: Patient Disposition and Baseline Characteristics

- As of December 16, 2020, 40 patients with relapsed/refractory LBCL were treated with axi-cel, and all 40 were eligible for efficacy and safety analyses

- The median patient age was 64.5 years (range, 37-85 years; ≥65 years, 50%); 55% of patients had ECOG performance status score of 1, 65% had stage III or IV disease, and 38% had received ≥3 prior therapies

Axi-cel, axicabtagene ciloleucel; ECOG, Eastern Cooperative Oncology Group; LBCL, large B-cell lymphoma.

Primary Endpoint: Incidence and Severity of CRS and Neurologic Events

	Cohort 6 (N=40)
CRS, n (%)	**32 (80)**
Worst Grade 1	14 (35)
Worst Grade 2	18 (45)
Worst Grade ≥3	0 (0)
Median time to onset (range), days	5 (1–15)
Median duration (range), days	4 (1–11)
Neurologic event, n (%)	**23 (58)**
Worst Grade 1	10 (25)
Worst Grade 2	7 (18)
Worst Grade ≥3	6 (15)
Median time to onset (range), days	6 (2–162)
Median duration (range), days	19 (1–438[a])

- No Grade ≥3 CRS occurred in Cohort 6
- Grade ≥3 neurologic events were reported in 15% of patients

Severity of CRS and neurologic events were graded per Lee et al criteria[1] and Common Terminology Criteria for Adverse Events version 4.03, respectively.

1. Lee DW, et al. *Blood.* 2014;124:188-195.

[a] Duration is defined as the end date of the last neurologic event minus the onset date of the first neurologic event +1. The maximum value is due to a late onset neurologic event that occurred on Day 441 and resolved on Day 442; if not for this late event, the maximum duration would be 79 days as the patient's second to last neurologic event ended on Day 83 (lasted 3 days).

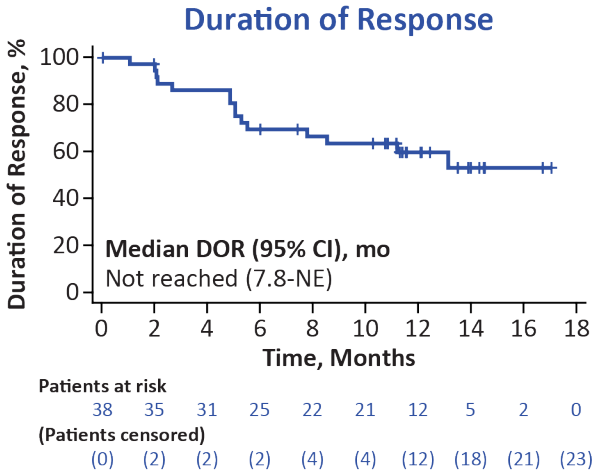
CRS, cytokine release syndrome.

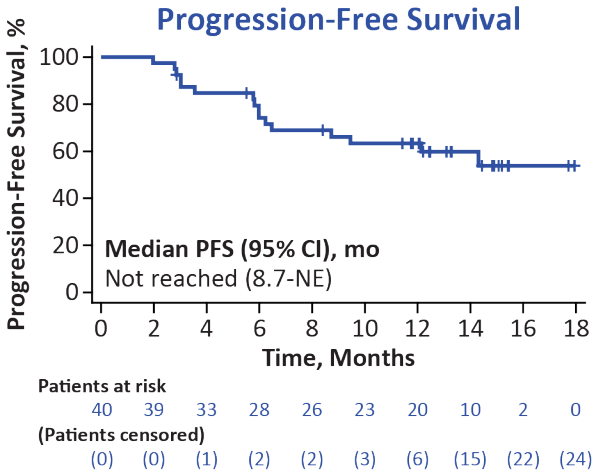
Safety Update Since the Previous Cohort 6 Analysis[1]

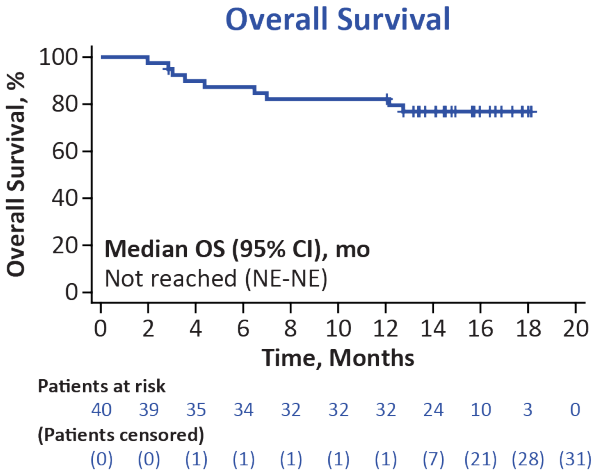
- No new cases of CRS
- Four new axi-cel–related neurologic events in 2 patients
  - Patient 1: Grade 2 mental status changes and seizure-like phenomena both on Day 441 (duration, 2 days and 1 day, respectively)
  - Patient 2: Grade 1 dementia (occurred on Day 93 but was reported late; duration, 277 days) and Grade 5 toxic encephalopathy on Day 369 (resultant from a Grade 4 event that started on Day 351)
    - Investigator believed that a mild case of dementia may have predated the study
    - Workup was limited on the Grade 5 AE due to family refusal for diagnostic testing and autopsy; however, magnetic resonance imaging showed leukoencephalopathy but was not confirmed with lumbar puncture. The investigator suspected that the outcome may have resulted from an opportunistic infection due to prolonged immunosuppression
- Two new infections of Grade 2 pneumonia on Day 474 (resolved on Day 479; unrelated to axi-cel) and Grade 1 bronchitis on Day 459 (resolved on Day 459; related to axi-cel)
- One death due to progressive disease

1. Oluwole OO, et al. *Br J Haematol*. 2021;194:690-700.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome.

Duration of Response, Progression-Free Survival, and Overall Survival



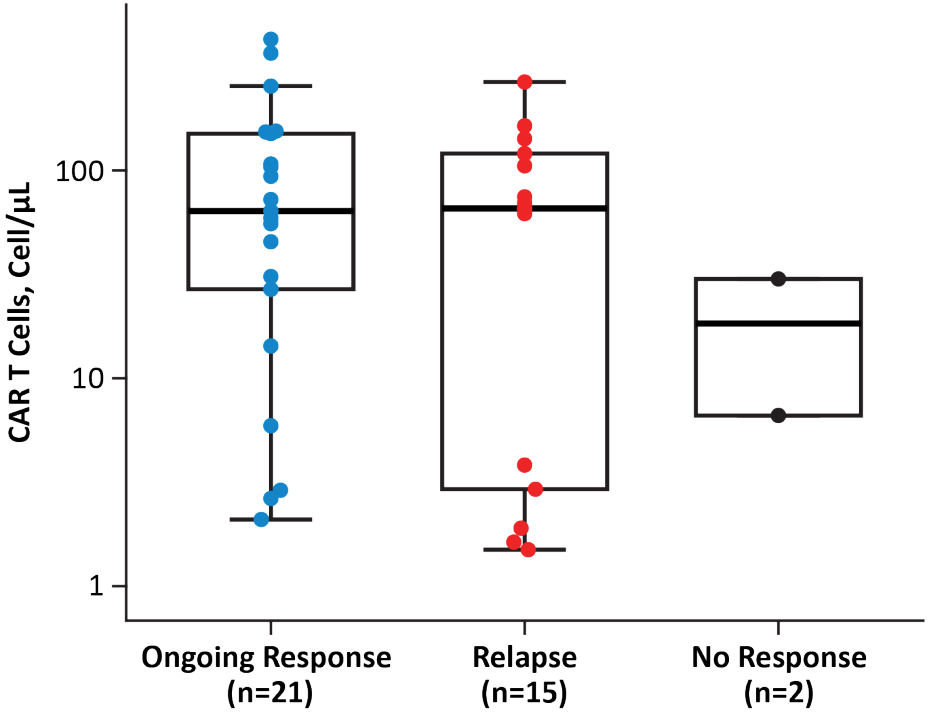




- Median DOR, PFS, and OS were not reached
- KM estimates of the 12-mo DOR, PFS, and OS rates were 60%, 63%, and 82%, respectively
- The investigator-assessed ORR remained 95% (80% CR rate) with a median follow-up of 14.9 months
  - At data cutoff, 21 patients (53%) were in ongoing response

CR, complete response; DOR, duration of response; KM, Kaplan-Meier; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Associations Between Peak CAR T-Cell Levels and Response at 12 Months



- Median peak CAR T-cell levels were comparably high in patients with ongoing response and relapse (64 cells/µL [n=21] and 66 cells/µL [n=15], respectively) at 12 months and considerably lower in nonresponders (18 cells/µL [n=2])
  - A similar trend was observed with CAR T-cell expansion by area under the curve from Day 0 to 28

CAR T cells were quantified using quantitative polymerase chain reaction.
CAR, chimeric antigen receptor.

Propensity Score Matching Analysis: Baseline Characteristics

- In total, 32 matched patients each in Cohort 6 and Cohorts 1+2 were identified in propensity score matching analysis[1]
  - Eight patients from Cohort 6 were not included due to nonavailability of matched patients in Cohorts 1+2
- Baseline characteristics were comparable between the 32 matched patients[1]

1. Oluwole OO, et al. *Br J Haematol*. 2021;194:690-700.

Propensity Score Comparison of Outcomes: Efficacy

	Cohorts 1+2 Overall (N=101)	Cohort 6 Overall (N=40)	Cohorts 1+2 After Matching (n=32)	Cohort 6 After Matching (n=32[a])
Objective response, n (%)	**84 (83)**	**38 (95)**	**30 (94)**	**30 (94)**
Complete response, n (%)	59 (58)	32 (80)	25 (78)	24 (75)
Ongoing response at data cutoff date,[b] n (%)	**42 (42)**	**21 (53)**	**19 (59)**	**15 (47)**
Median duration of response (95% CI), mo	11.1 (3.9, NE)	NR (7.8, NE)	NR (8.1, NE)	13.1 (5.5, NE)
KM 12-month (95% CI), %	49 (37, 59)	60 (41, 74)	65 (45, 80)	56 (36, 72)
Median progression-free survival (95% CI), mo	5.9 (3.3, NE)	NR (8.7, NE)	NR (5.6, NE)	14.3 (6.5, NE)
KM 12-month (95% CI), %	44 (34, 54)	63 (46, 77)	61 (42, 76)	61 (41, 76)
Median overall survival (95% CI), mo	NR (12.8, NE)	NR (NE, NE)	NR (15.4, NE)	NR (NE, NE)
KM 12-month (95% CI), %	60 (50, 69)	82 (66, 91)	81 (63, 91)	78 (59, 89)

- Clinical efficacy remained comparable between patients in Cohort 6 and Cohorts 1+2 before and after propensity score–based matching

[a] Eight patients were excluded due to nonavailability of matched patients in the pivotal cohorts. [b] Represents the number of patients in response at the data cutoff date among all treated patients.
KM, Kaplan-Meier; NE, not estimable; NR, not reached.

Propensity Score Comparison of Outcomes: Safety

	Cohorts 1+2 Overall (N=101)	Cohort 6 Overall (N=40)	Cohorts 1+2 After Matching (n=32)	Cohort 6 After Matching (n=32[a])
CRS				
Worst Grade ≥2, n (%)	57 (56)	18 (45)	19 (59)	15 (47)
Worst Grade ≥3, n (%)	**12 (12)**	**0**	**4 (13)**	**0**
Median time to onset of any grade CRS (Q1, Q3), days	**2 (2, 3)**	**5 (4, 6)**	**2 (2, 4)**	**5 (4, 6)**
NEs				
Worst Grade ≥2, n (%)	43 (43)	13 (33)	12 (38)	13 (41)
Worst Grade ≥3, n (%)	**29 (29)**	**6 (15)**	**7 (22)**	**6 (19)**
Median time to onset of any grade NE (Q1, Q3), days	5 (3, 7)	6 (5, 9)	6 (3, 7)	6 (5, 8)
Median time to onset of Grade ≥3 NE (Q1, Q3), days	**7 (5, 7)**	**12 (6, 30)**	**7 (6, 11)**	**12 (6, 30)**
Infections				
Worst any grade, n (%)	37 (37)	20 (50)	12 (38)	15 (47)
Worst Grade ≥3, n (%)	23 (23)	8 (20)	6 (19)	8 (25)[b]

- Incidence of Grade ≥3 CRS was lower in Cohort 6 compared with Cohort 1+2 before and after PSM
- Median time to onset of any-grade CRS was delayed in Cohort 6 versus Cohorts 1+2 before and after PSM
- Median time to onset of Grade ≥3 NEs appeared to be delayed in Cohort 6 versus Cohorts 1+2 before and after PSM

[a] Eight patients were excluded due to nonavailability of matched patients in the pivotal cohorts. [b] Worst Grade 4 or 5 infections occurred in 3 patients (patient 1: Grade 4 sepsis [unrelated to treatment]; patient 2: Grade 4 human herpesvirus 6 encephalitis [related to conditioning chemotherapy] and Grade 5 urosepsis [unrelated to treatment]; and patient 3: Grade 4 *Aspergillus* infection and respiratory tract infection [related to conditioning chemotherapy and axi-cel]).

Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; NE, neurologic event; PSM, propensity score–based matching; Q, quartile.

Propensity Score Comparison of Outcomes: Corticosteroid and Tocilizumab Use

	Cohorts 1+2 Overall (N=101)	Cohort 6 Overall (N=40)	Cohorts 1+2 After Matching (n=32)	Cohort 6 After Matching (n=32[a])
Cumulative cortisone-equivalent corticosteroid dose (including prophylaxis), n	25	40	6	32
Median (Q1, Q3), mg	**6390 (2817, 15760)**	**1252 (939, 6291)**	**7418 (2504, 11579)**	**1252 (939, 6604)**
Cumulative tocilizumab use, n	43	23	11	19
Peak median (Q1, Q3), mg	1300 (800, 1800)	1000 (700, 1760)	1339 (772, 3310)	1000 (600, 1680)

- Median cumulative corticosteroid dose including prophylaxis was ≈6-fold lower in Cohort 6 versus Cohorts 1+2 (1252 mg versus 7418 mg, respectively) after matching
- Although more patients in Cohort 6 versus Cohorts 1+2 required tocilizumab after matching, median peak cumulative tocilizumab dose was lower in Cohort 6 versus Cohorts 1+2 (1000 mg versus 1339 mg, respectively)

[a] Eight patients were excluded due to nonavailability of matched patients in the pivotal cohorts.
Q, quartile.

Propensity Score Comparison of CAR T-Cell and Cytokine Levels

Median (Q1, Q3)	Cohorts 1+2 Overall (N=101)	Cohort 6 Overall (N=40)	Cohorts 1+2 After Matching (n=32)	Cohort 6 After Matching (n=32[a])
Peak CAR T-cell levels				
CAR T-cell expansion, cells/µL	38 (15, 83)	64 (6, 131)	43 (14, 107)	65 (18, 146)
Peak cytokine levels				
IFN-γ, pg/mL	477 (196, 1097)	208 (87, 446)	481 (120, 1096)	227 (103, 424)
IL-2, pg/mL	22 (10, 38)	8 (3, 23)	23 (10, 58)	8 (3, 16)
GM-CSF, pg/mL	7 (2, 16)	2 (2, 5)	9 (2, 21)	2 (2, 4)
Ferritin, ng/mL	3001 (1326, 6683)	904 (489, 1529)	2312 (1225, 4777)	809 (489, 1529)
CRP, mg/L	214 (141, 353)	76 (39, 136)	175 (124, 345)	78 (44, 131)

- Peak CAR T-cell levels were comparable and peak inflammatory biomarkers associated with CAR T-cell treatment-related AEs, including IFN-γ, IL-2, GM-CSF, and ferritin, were lower in Cohort 6 versus Cohorts 1+2 before and after propensity score matching, supporting clinical outcomes

[a] Eight patients were excluded due to nonavailability of matched patients in the pivotal cohorts.
CAR, chimeric antigen receptor; CRP, C-reactive protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon, IL, interleukin; Q, quartile.

Conclusions

- With ≥1-year follow-up for ZUMA-1 Cohort 6, prophylactic and earlier corticosteroid and/or tocilizumab intervention for toxicity management continued to demonstrate potential to improve the benefit/risk profile of axi-cel with no negative impact on pharmacokinetics and/or efficacy outcomes
- Although limited by retrospective and cross-cohort comparisons, findings were corroborated by propensity score–based matching analysis versus pivotal Cohorts 1+2
- Overall, these findings suggest that the Cohort 6 toxicity management strategy can improve long-term safety of axi-cel in relapsed/refractory LBCL, without compromising the durability of responses

Axi-cel, axicabtagene ciloleucel; LBCL, large B-cell lymphoma.

Acknowledgments

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and health care staff at each study site
- Medical writing support was provided by Ashley Skorusa, PhD, of Nexus Global Group Science LLC, funded by Kite, a Gilead Company
- These data were previously presented at the 2021 Annual Meeting of the American Society of Hematology[1]

Oluwole OO, et al. ASH 2021. Abstract 2832.