Real-World Trends of Cytokine Release Syndrome and Neurologic Events, and Pattern of Their Management Among Patients Receiving Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma in the US: A CIBMTR Report

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CIBMTR® & Kite, a Gilead Company Collaboration Study

Background and Objective

- Axi-cel is an autologous CD19-targeting CAR T-cell therapy approved for patients with R/R LBCL[1,2] that has demonstrated curative potential in the second- and third line or later settings[3,4]
- Efforts have focused on mitigating incidence and severity of CAR T-cell–related AEs, like CRS and ICANS[5]
  - ZUMA-1 (NCT02348216) safety management Cohort 4 and Cohort 6 showed improvement in the incidence and severity of CRS and neurologic events among patients with R/R LBCL who received axi-cel[6,7]
    - Cohort 4 strategy: early use of corticosteroids and tocilizumab intervention[6]
    - Cohort 6 strategy: further addition of prophylactic corticosteroids[7]
  - RWE from Europe showed reduced incidence of CRS and ICANS and higher rates of tocilizumab and corticosteroid use among patients with R/R LBCL who received CAR T-cell therapy in 2020-2022 versus 2019[8]
- There remains a paucity of evidence to understand the trends in the incidence and management of CRS and ICANS following CAR T-cell therapy given the evolution in management strategies over time

Here, we investigated real-world trends in CRS and ICANS and patterns of their management among patients with R/R LBCL who received axi-cel in the United States from 2017 to 2023

1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2024. 2. YESCARTA® (axicabtagene ciloleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2024. 3. Neelapu SS, et al. *Blood*. 2023;141:2307-2315. 4. Westin JW, et al. *N Engl J Med*. 2023;389:148-157. 5. Mitra A, et al. *Front Immunol*. 2023;14:1188049. 6. Topp M, et al. *Br J Haematol*. 2021;195:388-398. 7. Oluwole OO, et al. *Br J Haematol*. 2021;194:690-700. 8. Boyle S, et al. *Br J Haematol*. 2024;204:507-513.
AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; RWE, real-world evidence.

Study Design and Analysis

CIBMTR Data Source	• Patients who received 3L+ commercial axi-cel for R/R LBCL in the United States between 10/2017 and 07/2023 • Key exclusion criteria: prior nontransplant cellular therapy or those with primary CNS lymphoma • Two cohorts from the database were used for the study
Outcomes of Interest	• **Primary safety outcomes**: incidence, maximum grade (per ASTCT consensus grading[1]), treatments, and duration of CRS and ICANS • **Secondary AEs of interest**: prolonged neutropenia,[a] prolonged thrombocytopenia,[b] and clinically significant infection[c]
Statistical Analysis	• Outcomes were descriptively evaluated across 3 study periods: 2017-2019, 2020-2021, and 2022-2023 • Multivariable regressions were used to estimate the association between time periods and safety outcomes while adjusting for other confounding effects

[a] Prolonged neutropenia was defined as failure to recover absolute neutrophil count ≥500/mm^3 and/or sustain 3 consecutive normal lab values within the first 30 days after infusion.
[b] Prolonged thrombocytopenia was defined as failure to recover platelet count ≥20×10^9/L within the first 30 days after infusion.
[c] Clinically significant infection was defined as any infection diagnosed after the initial infusion of axi-cel that required treatment.

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

3L+, third line or later; AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; CNS, central nervous system; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

Study Cohorts

Adult patients who received commercial axi-cel in the United States for 3L+ treatment of R/R LBCL were selected from the CIBMTR database

US PMR Cohort for Axi-Cel n=1217

- Recruited in a PMR study between October 2017 and August 2020

Ex-PMR Cohort n=398

- Random sample of patients outside of the PMR cohort that were treated after August 2020 through August 2023

Final Analysis Set N=1615 from 109 centers

Study periods	2017-2019	2020-2021	2022-2023
Patients treated	n=923	n=486	n=206
Median follow-up[a]	45.6 mo (95% CI, 42.7-47.0)	34.1 mo (95% CI, 25.1-35.3)	12.5 mo (95% CI, 12.4-12.8)

[a] Calculated based on reverse Kaplan-Meier method.

3L+, third line or later; axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; LBCL, large B-cell lymphoma; PMR, post-marketing requirement; R/R, relapsed/refractory.

Baseline Patient and Disease Characteristics

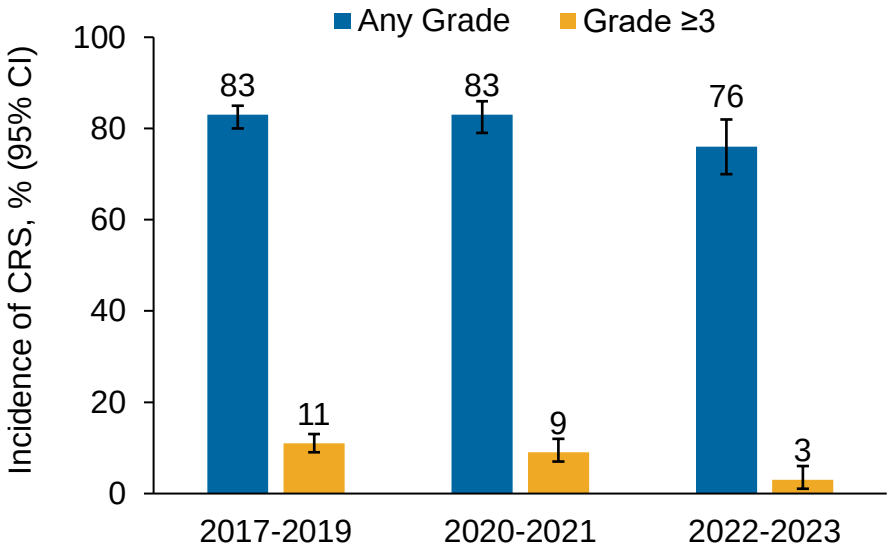
Characteristic	2017-2019 n=923	2020-2021 n=486	2022-2023 n=206
Median age (IQR), years	61.6 (52.9-67.7)	63.1 (55.2-69.6)	63.2 (54.8-70.9)
≥65 years, n (%)	**322 (35)**	**210 (43)**	**91 (44)**
≥70 years, n (%)	163 (18)	116 (24)	59 (29)
ECOG performance status 0-1, n (%)	881 (95)	455 (94)	192 (93)
Clinically significant comorbidity,[a] n/N (%)	684/910 (75)	365/485 (75)	165/206 (80)
Secondary CNS lymphoma, n/N (%)	25/836 (3)	9/456 (2)	9/194 (5)
Number of lines of prior therapies (excluding prior HCT), n (%)			
2 lines	284 (31)	159 (33)	63 (31)
3 lines	311 (34)	155 (32)	70 (34)
4 or more lines	328 (36)	172 (35)	73 (35)
Prior HCT,[b] n (%)	**274 (30)**	**103 (21)**	**40 (19)**
Response to last line of therapy prior to leukapheresis			
Relapse, n/N reported (%)	125/809 (15)	63/401 (16)	32/153 (21)
Refractory, n/N reported (%)	684/809 (85)	338/401 (84)	121/153 (79)
Received bridging therapy, n (%)	**310 (34)**	**203 (42)**	**119 (58)**
Received single-agent bendamustine for lymphodepletion, n (%)	1 (<1)	0 (0)	33 (16)

[a] Defined per HCT-specific comorbidity index (HCT-CI).[1] [b] The majority of patients received prior ASCT, though some received prior alloSCT or both ASCT and alloSCT.

1. Sorror ML, et al. *Blood*. 2005;106:2912-2919.

AlloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; CNS, central nervous system; ECOG, European Cooperative Oncology Group; HCT, hematopoietic cell transplantation; IQR, interquartile range.

Unadjusted Incidence of CRS Over Time

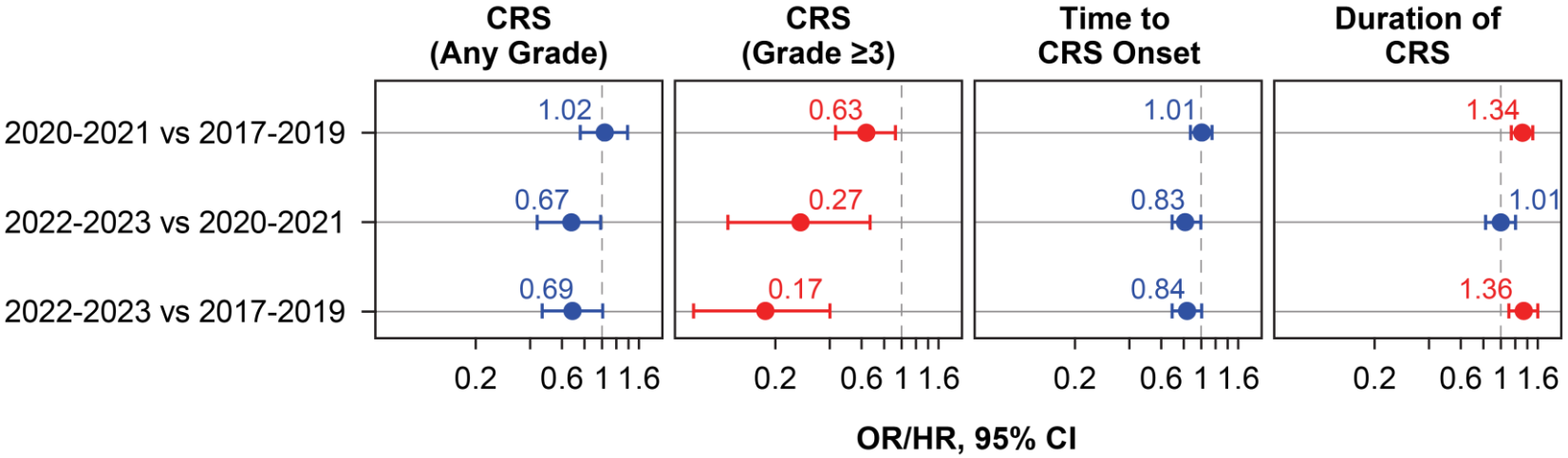


	2017-2019 n=923	2020-2021 n=486	2022-2023 n=206
Patients with any-grade CRS, n (%)	765 (83)	403 (83)	157 (76)
Median time to onset (IQR), days	4 (2-6)	4 (2-6)	4 (2-6)
Median duration (IQR), days	7 (4-10)	6 (4-8)	5 (4-8)
Resolution within 3 weeks since onset, % (95% CI)	91 (89-93)	95 (92-97)	95 (90-97)
Patients with Grade ≥3 CRS, n/N (%)	103/923 (11)	43/481 (9)	6/202 (3)

- In univariate analysis, the incidence of any-grade and Grade ≥3 CRS decreased over time, with only 3% of patients treated in 2022-2023 experiencing Grade ≥3 events
- Median duration of CRS was reduced from 7 days in 2017-2019 to 5 days in 2022-2023

Missing data were excluded from the calculations.
CRS, cytokine release syndrome; IQR, interquartile range.

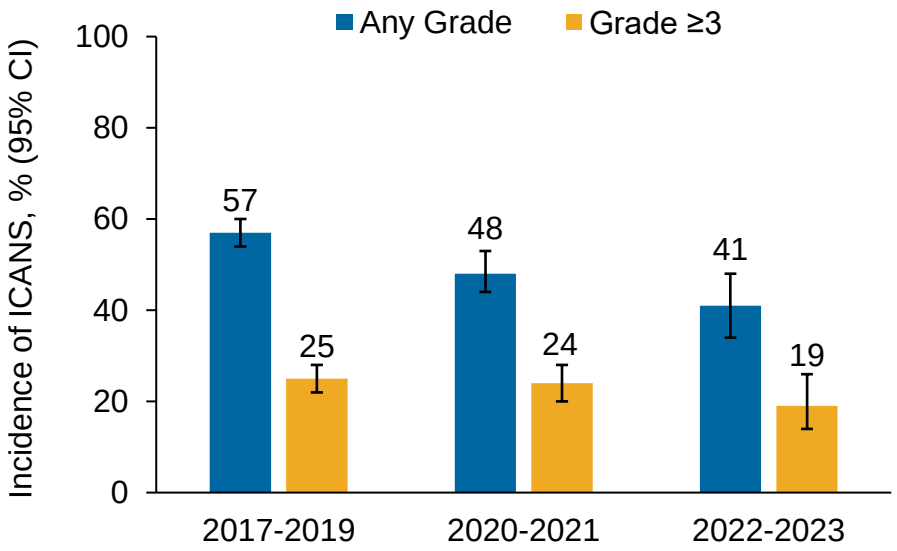
Adjusted Relative Risks (OR/HR) Comparing CRS Outcomes Over the Study Periods



- Patients who received axi-cel during 2022-2023 and 2020-2021 had significantly lower incidences of Grade ≥3 CRS compared with those treated during 2017-2019
- Durations of CRS during 2022-2023 and 2020-2021 were significantly shorter compared with 2017-2019

A stepwise selection at *P*<.2 was used to select covariates for the multivariate models; candidate variables included patient characteristics, treatment history, disease status at diagnosis and prior to infusion, and infusion-related characteristics. Adjusted ORs for CRS incidence, and adjusted HRs for time to CRS onset and duration. Red font/line indicates statistical significance.
Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; HR, hazard ratio; OR, odds ratio.

Unadjusted Incidence of ICANS Over Time

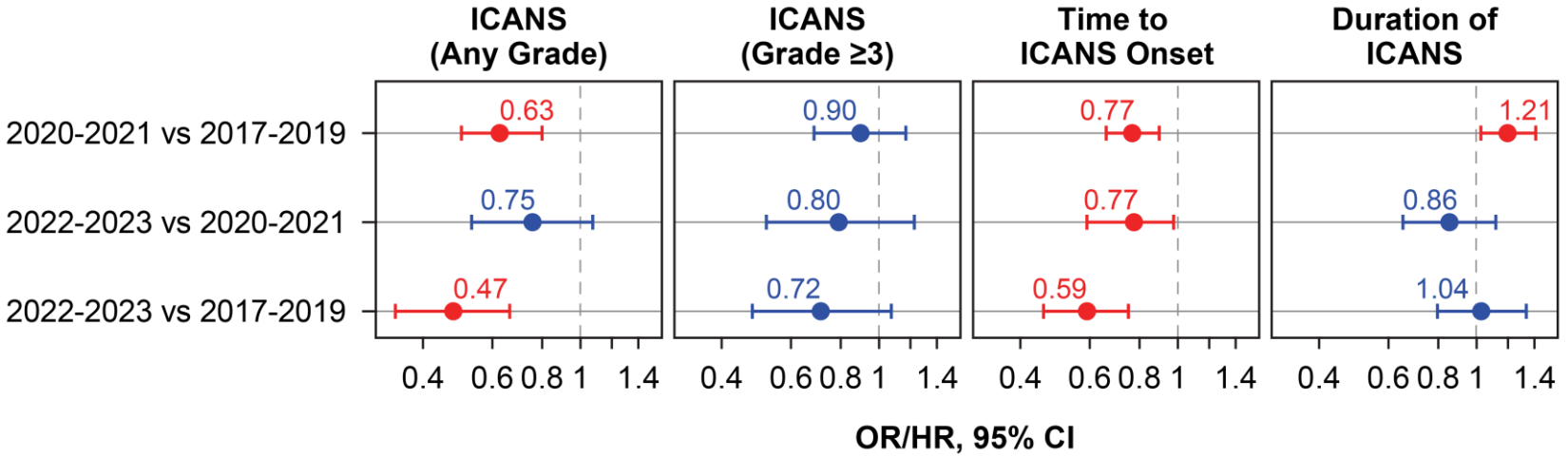


	2017-2019 n=923	2020-2021 n=486	2022-2023 n=206
Patients with any-grade ICANS, n (%)	527 (57)	234 (48)	85 (41)
Median time to onset (IQR), days	7 (5-9)	6 (4-9)	7 (5-10)
Median duration (IQR), days	7.5 (4-13)	7.0 (4-12)	6.0 (4-11)
Resolution within 3 weeks since onset, % (95% CI)	77 (73-80)	81 (76-86)	72 (61-80)
Patients with Grade ≥3 ICANS, n/N (%)	224/907 (25)	113/476 (24)	38/197 (19)

- In univariate analysis, the incidence of any-grade and Grade ≥3 ICANS decreased over time, with a greater reduction in any-grade events over the 3 study periods
- Median duration of ICANS was reduced from 7.5 days in 2017-2019 to 6 days in 2022-2023

Missing data were excluded from the calculations.
ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range.

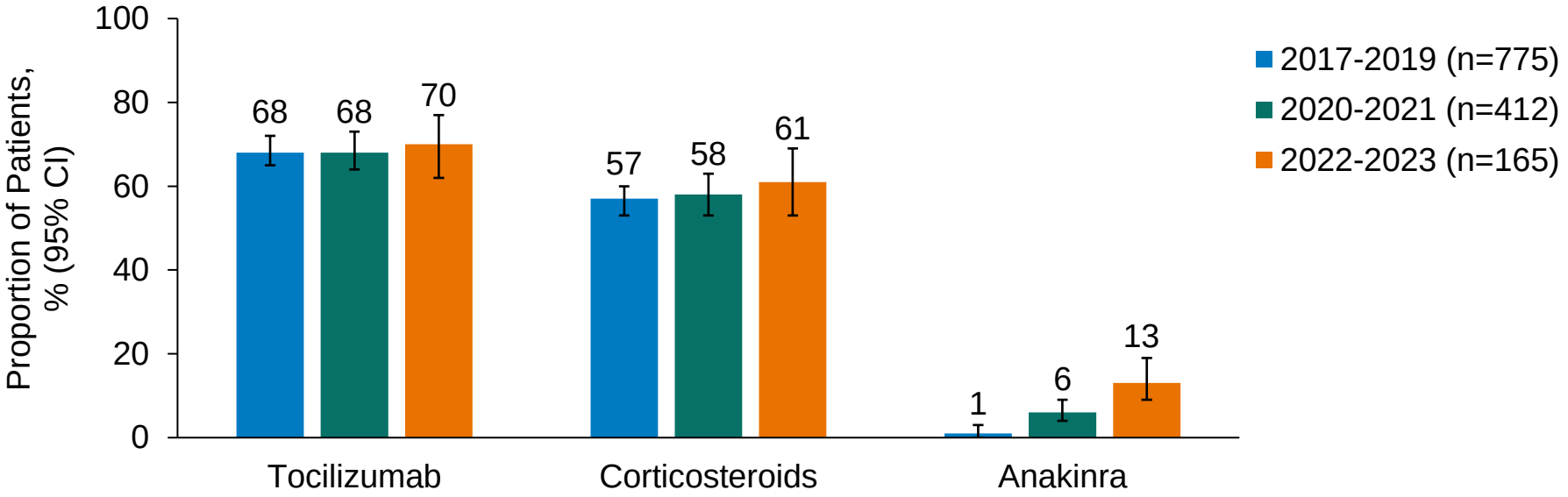
Adjusted Relative Risks (OR/HR) Comparing ICANS Outcomes Over the Study Periods



- Patients who received axi-cel during 2022-2023 and 2020-2021 had significantly lower incidences of any-grade ICANS compared with those treated during 2017-2019, and significantly delayed time to ICANS onset, though the latter was not significant in univariate analysis
- Duration of ICANS during 2020-2021 was significantly shorter compared with 2017-2019

A stepwise selection at *P*<.2 was used to select covariates for the multivariate models; candidate variables included patient characteristics, treatment history, disease status at diagnosis and prior to infusion, and infusion-related characteristics. Adjusted ORs for ICANS incidence, and adjusted HRs for time to ICANS onset and duration. Red font/line indicates statistical significance.
Axi-cel, axicabtagene ciloleucel; ICANS, immune effector cell-associated neurotoxicity syndrome; HR, hazard ratio; OR, odds ratio.

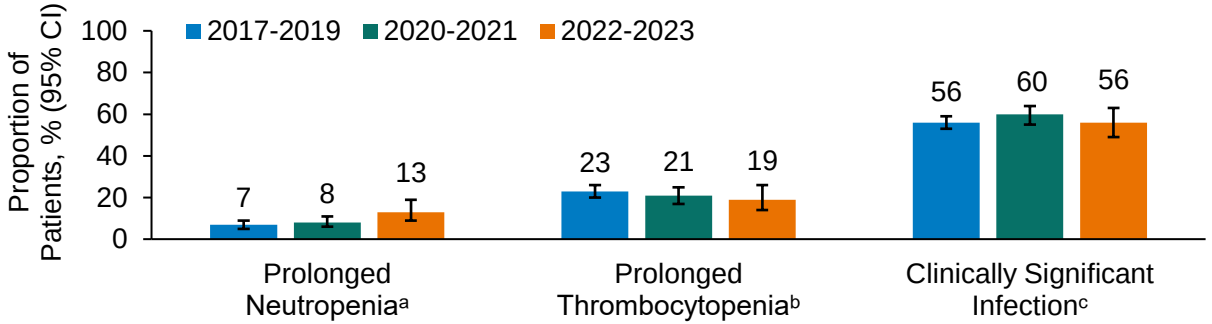
Treatment Trends for CRS/ICANS Across Study Periods



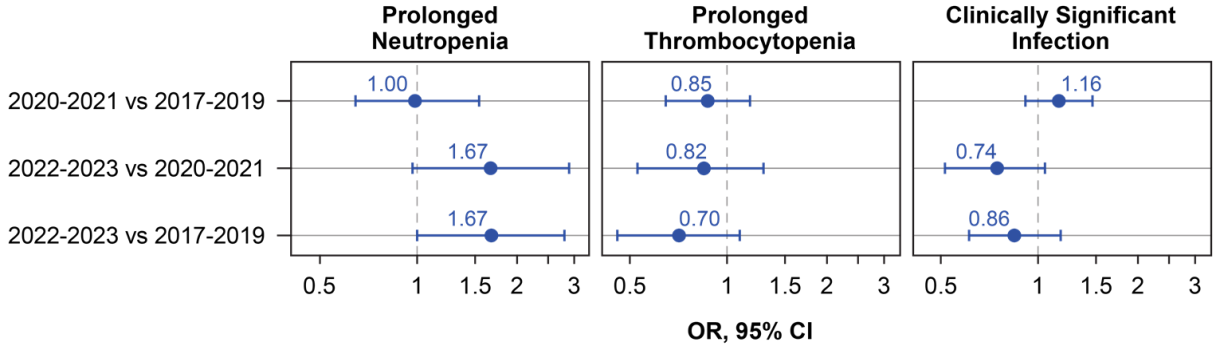
- In univariate analysis, rates of tocilizumab and corticosteroid use were consistent for the 3 periods, with a trend for increased anakinra use (1%, 6%, and 13%, respectively)

Percentages reflect the proportion of patients who experienced CRS/ICANS and had treatment reported (yes or no).
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

Trends of AEs of Interest



- In unadjusted univariate analysis, incidence of prolonged thrombocytopenia and clinically significant infection were consistent over the 3 time periods, with a significant increase in the incidence of prolonged neutropenia (from 7% in 2017-2019 to 13% in 2022-2023)



- However, the increased incidence of prolonged neutropenia became insignificant after multivariable adjustment[d]

[a] Prolonged neutropenia was defined as failure to recover absolute neutrophil count ≥500/mm^3 and/or sustain 3 consecutive normal lab values within the first 30 days after infusion. [b] Prolonged thrombocytopenia was defined as failure to recover platelet count ≥20×10^9/L within the first 30 days after infusion. [c] Clinically significant infection was defined as any infection diagnosed after the initial infusion of axi-cel that required treatment. The grade of the infection was not captured within the registry. [d] A stepwise selection at P<.2 was used to select covariates for the multivariate models; candidate variables included patient characteristics, treatment history, disease status at diagnosis and prior to infusion, and infusion-related characteristics.
AE, adverse event; axi-cel, axicabtagene ciloleucel.

Conclusions

- In this analysis of patients with R/R LBCL who received 3L+ axi-cel in real-world settings in the United States,

Improvements were observed in CAR T-cell–related toxicities over time	Evolving clinical practices were identified
• Decreases in incidence of Grade ≥3 CRS and duration of any-grade CRS • Decreases in incidence and duration of any-grade ICANS	• Increased use of bridging therapy • Increased use of anakinra for treatment of CRS/ICANS

Study limitations	
	• Timing of treatment initiation for CRS/ICANS was not collected in the registry, precluding analysis of the adaptation of early safety intervention on outcomes • Potential underreporting of prophylactic corticosteroid use within the CIBMTR registry

- Although the study indicates that the improvement in incidence and severity of CAR T-cell–related toxicities over time may be attributed to evolving clinical practice and greater experience, further study is warranted to validate this observation

3L+, third line or later; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CIBMTR, Center for International Blood and Marrow Transplant Research; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

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Additional Resources

- Full author disclosures are available through the virtual meeting platform
- A plain language summary of the key results from this presentation is available through the Quick Response (QR) code