# Real-World Early Outcomes of Second-Line Axicabtagene Ciloleucel Therapy in Patients With Relapsed or Refractory Large B-Cell Lymphoma

Dasom (Caroline) Lee, MD*[1]; Swetha Kambhampati Thiruvengadam, MD*[2]; Maria Silvina Odstrcil Bobillo, MD*[3]; Babatunde Adedokun, PhD, MBBS[4]; Mazyar Shadman, MD, MPH[5]; Amanda Olson, MD[6]; Alex F. Herrera, MD[2]; Catherine J. Lee, MD, MS[5]; Caron A. Jacobson, MD, MMSc[7]; Matthew Bye, MPH[8]; Mehdi Hamadani, MD[8]; Soyoung Kim, PhD[8]; Saurabh Dahiya, MD, FACP[1]; Zhen-Huan Hu, MPH[4]; Kelly Speth, PhD[4]; Christina To, MD[4]; Debbie L. Mirjah, MD[4]; Timothy Best, PhD[4]; Frederick L. Locke, MD[9]; Nausheen Ahmed, MD[10]; Michael Tees, MD, MPH[11]; Marcelo C. Pasquini, MD, MS[7]; and Sairah Ahmed, MD[6]

* Authors contributed equally

*[1]Division of Hematology, Stanford University, Stanford, CA, USA; [2]City of Hope National Medical Center, Duarte, MA, USA; [3]University of Utah, Salt Lake City, UT, USA; [4]Kite, a Gilead Company, Santa Monica, CA, USA; [5]Fred Hutchinson Cancer Center and Medical Oncology Division, University of Washington, Seattle, WA, USA; [6]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]Dana-Farber Cancer Institute, Boston, MA, USA; [8]Center for International Blood and Marrow Transplant Registry (CIBMTR), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA; [9]H. Lee Moffitt Cancer Center, Tampa, FL, USA; [10]Division of Hematologic Malignances and Cellular Therapeutics, University of Kansas Cancer Center, Westwood, KS, USA; and [11]Colorado Blood Cancer Institute, Sarah Cannon Transplant and Cellular Therapy Network, Denver, CO, USA*

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# Background

- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved in many countries for treating patients with LBCL that is refractory to 1L therapy or relapses within 12 months of 1L therapy[1,2]
  - Axi-cel has demonstrated curative potential in the 2L (ZUMA-7) and 3L+ settings (ZUMA-1) for patients with R/R LBCL[3,4]
- In the Phase 3 ZUMA-7 study, axi-cel showed superior EFS, response rate, and OS versus standard of care in transplant-intended R/R LBCL[3,5]
- The Phase 2 ALYCANTE study (NCT04531046) additionally demonstrated high response and durable remissions in transplant-ineligible patients[6]
- In the real-world setting, patients receiving axi-cel could have a broader range of patient and/or disease characteristics that would have precluded eligibility in these trials; real-world outcomes data are lacking on CAR T-cell therapies to treat R/R LBCL in 2L
- Here we report early real-world effectiveness and safety outcomes of patients in the United States who received axi-cel as a 2L treatment for R/R LBCL

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. Westin JR, et al. *N Engl J Med*. 2023;389:148-157. 4. Neelapu SS, et al. *Blood*. 2023;141:2307-2315.
5. Locke FL, et al. *N Engl J Med*. 2022;386:640-654. 6. Houot R, et al. *Nat Med*. 2023;29:2593-2601.
1L, first line; 2L, second line; 3L+, third line or later; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; EFS, event-free survival; LBCL, large B-cell lymphoma; OS, overall survival; R/R, relapsed or refractory.

# Study Design and Analysis

| | |
|---|---|
| **Data Source** | • Data were collected from the CIBMTR database<br>• **Study population:** consecutive, consenting adult patients with R/R LBCL (including DLBCL, HGBCL, FL Grade 3B, PMBCL) who received axi-cel in 2L between April 2022 and July 2023 from 89 centers in the United States and enrolled in the CIBMTR data registry |
| **Outcomes of Interest** | • **Effectiveness:** OR and CR rate, DOR, EFS, OS<br>• **Safety:** CRS, ICANS, cytopenias, infections, non-relapse mortality, cause of death, therapies to manage CRS and ICANS |
| **Statistical Analysis** | • Descriptive statistics summarized baseline patient characteristics and outcomes in the overall population, by ZUMA-7 eligibility among patients with DLBCL, HGBCL, and FL Grade 3B (ineligible vs eligible/unknown),[a] and in patients with PMBCL<br>– Patients with PMBCL were ineligible for ZUMA-7 and were analyzed separately<br>• Time-to-event outcomes were assessed using Kaplan–Meier methodology<br>– When sufficient data were available, 12-month data were reported; otherwise, 6-month data were reported |

[a] Patients were considered ineligible if they met at least one available ZUMA-7 exclusion criterion and eligible otherwise, regardless of covariate missingness. PMBCL patients (ZUMA-7 ineligible) were summarized as a separate category.

2L, second line; axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival; FL, follicular lymphoma; HGBCL, high grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; OR, objective response; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; R/R, relapsed or refractory.

# Baseline Patient and Disease Characteristics

| Characteristic | All Patients N=446 |
|---|---|
| **Median age, years (range)** | 63.9 (19.5-86.0) |
| ≥65 to <70, n (%) | 74 (17) |
| ≥70, n (%) | 137 (31) |
| **Male sex, n (%)** | 285 (64) |
| **ECOG performance status 0-1,[a] n (%)** | 401 (97) |
| **Disease type, n (%)** | |
| DLBCL | 349 (78) |
| PMBCL | 13 (3) |
| HGBCL | 79 (18) |
| FL Grade 3B | 5 (1) |
| **Elevated lactate dehydrogenase levels pre-infusion,[a] n (%)** | 199 (48) |
| **Response to last line of therapy pre-leukapheresis,[a,b] n (%)** | 228 (51) |
| **Median vein-to-vein time, days,[c] (IQR)** | 29.0 (27.0-35.0) |
| **Bridging therapy,[a,d] n (%)** | 286 (66) |

- A total of 446 patients with R/R LBCL received axi-cel in 2L between April 2022 and July 2023
- Most patients had non-Hispanic ethnicity (White, 72%; Black, 5%; Asian, 6%); 12% were Hispanic
- Median follow-up for all patients was 12.0 months (95% CI, 11.5-12.1)
  - ZUMA-7 ineligible: 11.8 months (95% CI, 7.2-12.1)
  - ZUMA-7 eligible/unknown: 12.1 months (95% CI, 11.8-12.3)
  - PMBCL: 10.3 months (95% CI, 6.1-12.3)

[a] Unknown or not reported was excluded from the denominator in percentage calculations. [b] Response defined as complete response (25%) or partial response (36%).
[c] Vein-to-vein time is defined as the time from leukapheresis to axi-cel infusion. [d] Most common bridging therapies were systemic (53%) or radiation (16%).
2L, second line; axi-cel, axicabtagene ciloleucel; ECOG, Eastern Cooperative Oncology Group; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCT-CI, hematopoietic cell transplantation comorbidity index; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; PMBCL, primary mediastinal B-cell lymphoma.

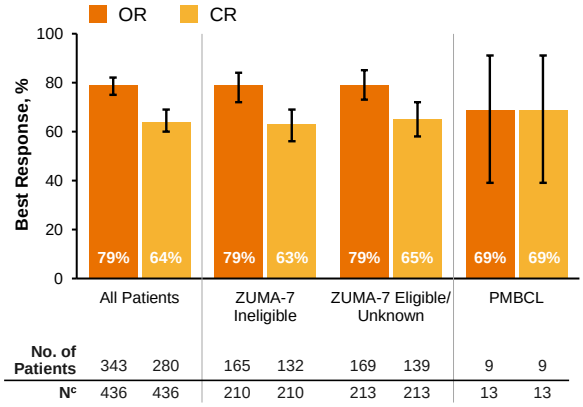
# ZUMA-7 Eligibility and Transplant Ineligibility

| Characteristic | All Patients N=446 |
|---|---|
| **ZUMA-7 eligibility,[a] n (%)** | |
| Eligible | 214 (48) |
| Not eligible[b] | 219 (49) |
| Organ impairment | 150 (34) |
| Pulmonary (moderate/severe) | 81 (18) |
| Cardiac | 49 (11) |
| Bone marrow (platelets, ANC, and/or ALC) | 37 (8) |
| Arrhythmia | 26 (6) |
| Cerebrovascular disease | 14 (3) |
| Renal (moderate/severe) | 5 (1) |
| Heart valve disease | 4 (<1) |
| Hepatic (moderate/severe) | 1 (<1) |
| Prior malignancy | 70 (16) |
| Other causes for ineligibility[c] | 48 (11) |
| PMBCL | 13 (3) |
| **Transplant ineligible,[d] n (%)** | 226 (52) |

- About half the patients would have been ineligible for ZUMA-7, mainly due to organ impairment (34%) and prior malignancy (16%)

[a] Patients were considered eligible regardless of any missingness, unless they were identified as ineligible (for each separate criterion and overall). [b] Not mutually exclusive. [c] Other causes for ZUMA-7 ineligibility included infection (n=17, 4%), ECOG performance score >1 (n=12, 3%), autoimmune disease (n=12, 3%), non-DLBCL/HGBCL (n=5, 1%), CNS involvement (n=5, 1%).
[d] Derived using the following criteria: age ≥70 years (n=137), HCT-CI score ≥3 (n=141), or prior hematopoietic cell transplantation (n=0).
ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic cell transplantation comorbidity index; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma.

# Objective Response

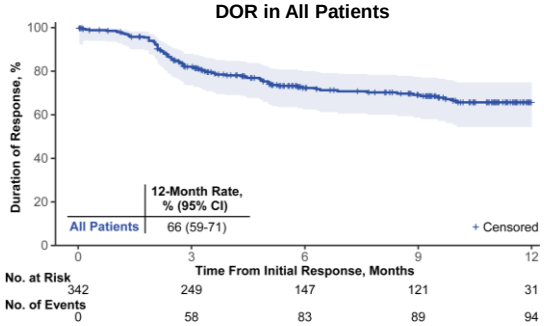



- ORs and CRs were similar across all patient groups[a,b]
- Median time to OR in all patients was 2.1 months (IQR, 1.0-3.6)
  - ZUMA-7 ineligible: 1.8 months (IQR, 1.0-3.4)
  - ZUMA-7 eligible/unknown: 2.4 months (IQR, 1.0-3.7)
  - PMBCL: 3.0 months (IQR, 1.2-NE)
- Median time to CR in all patients was 3.1 months (IQR, 1.1-NE)
  - ZUMA-7 ineligible: 3.2 months (IQR, 1.1-NE)
  - ZUMA-7 eligible/unknown: 3.1 months (IQR, 1.1-NE)
  - PMBCL: 3.0 months (IQR, 1.2-NE)

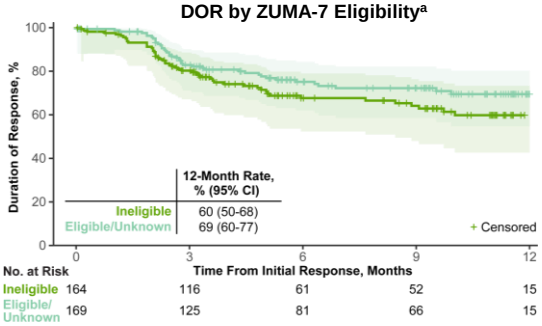
Error bars denote 95% CIs.
[a] Patients with missing response assessment were excluded.
[b] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately. [c] Total number of evaluable patients.
CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; NE, not estimable; OR, objective response; PMBCL, primary mediastinal B-cell lymphoma.

# Duration of Response

**DOR in All Patients**



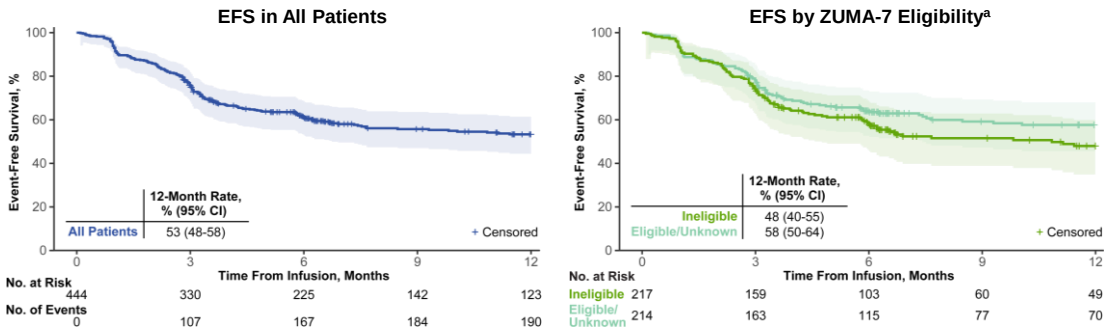

**DOR by ZUMA-7 Eligibility[a]**




- Among all patients (median follow-up, 12 months), the 12-month DOR rate was 66%
  - Among patients who were ZUMA-7 ineligible, the 12-month DOR rate was 60%
  - Among patients who were ZUMA-7 eligible/unknown, the 12-month DOR rate was 69%
  - Among patients with PMBCL, the 6-month DOR rate was 100%

Shaded areas represent confidence bands.
[a] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately.
DOR, duration of response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma.

## Event-Free Survival




- Among all patients, the 12-month EFS rate was 53%
  - Among patients who were ZUMA-7 ineligible, the 12-month EFS rate was 48%
  - Among patients who were ZUMA-7 eligible/unknown, the 12-month EFS rate was 58%
  - Among patients with PMBCL, the 6-month EFS rate was 68% (95% CI, 36-87)

Shaded areas represent confidence bands.
[a] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately.
DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma.

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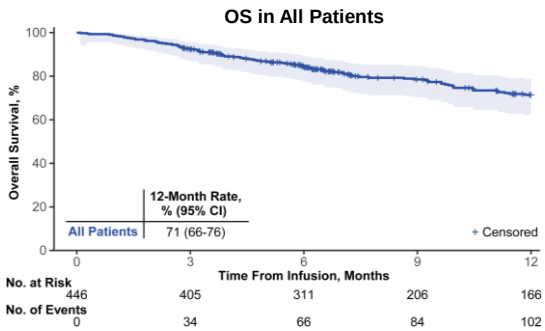
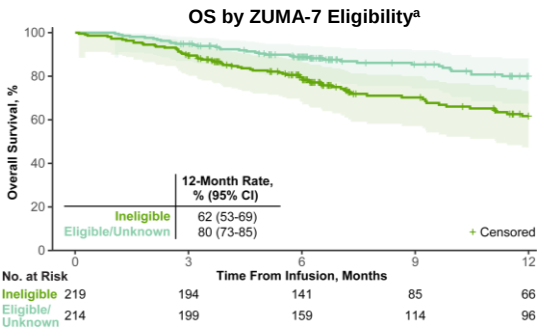
Notes for Dr. Lee: The difference between the ZUMA-7 definition and EFS and the one in this analysis is that the event “Stable disease at day 150” not obtainable as follow up times were at 100 days, 6mths, and yearly in CIBMTR.

# Overall Survival

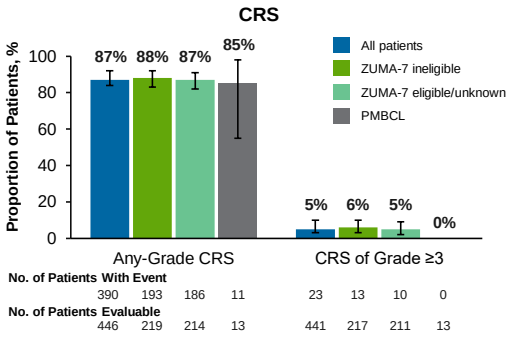



- Among all patients, the 12-month OS rate was 71%
  - Among patients who were ZUMA-7 ineligible, the 12-month OS rate was 62%
  - Among patients who were ZUMA-7 eligible/unknown, the 12-month OS rate was 80%
  - Among patients with PMBCL, the 6-month OS rate was 100%

Shaded areas represent confidence bands.
[a] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately.
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; OS, overall survival; PMBCL, primary mediastinal B-cell lymphoma.

# Incidence of CRS

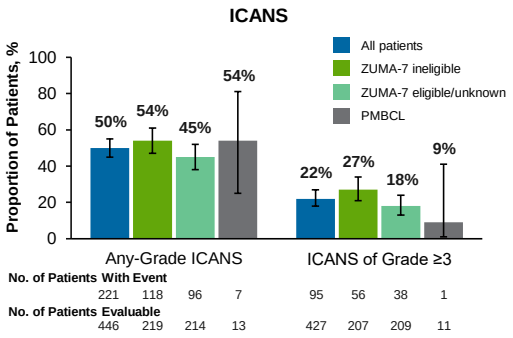



| Characteristic | All Patients N=446 | ZUMA-7 Eligibility[a] | | Patients With PMBCL n=13 |
|---|---|---|---|---|
| | | Ineligible n=219 | Eligible/ Unknown n=214 | |
| **Any-grade CRS, n (%)** | 390 (87) | 193 (88) | 186 (87) | 11 (85) |
| Median time from infusion to CRS onset, days (IQR) | 4 (2-6) | 4 (2-5) | 4 (2-6) | 4 (2-6) |
| Median time from CRS onset to resolution, days (IQR) | 5 (4-7) | 5 (4-7) | 5 (4-7) | 7 (4-8) |
| Cumulative incidence of CRS resolution at 3 weeks since onset, % (95% CI) | 98 (96-99) | - | - | - |

- Incidence of any-grade CRS and Grade ≥3 CRS were similar across patient groups[b,c]
- Among all patients, 390 (87%) had any-grade CRS; Grade ≥3 CRS occurred in 5%

Error bars denote 95% CIs.
[a] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately.
[b] CRS and ICANS were graded per ASTCT consensus criteria. [c] Missing were excluded.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range; PMBCL, primary mediastinal B-cell lymphoma.

# Incidence of ICANS

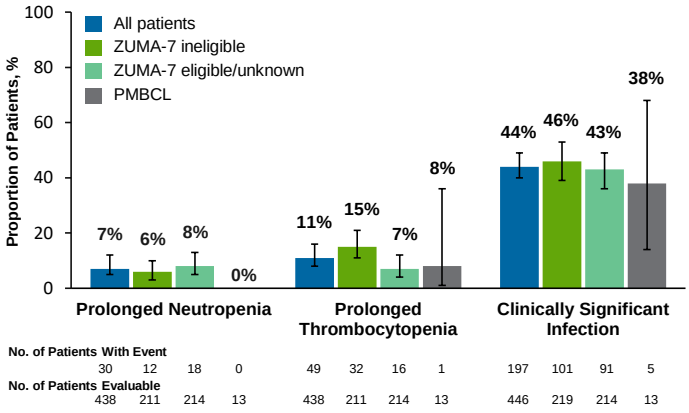



| Characteristic | All Patients N=446 | ZUMA-7 Eligibility[a] | | Patients With PMBCL n=13 |
|---|---|---|---|---|
| | | Ineligible n=219 | Eligible/ Unknown n=214 | |
| **Any-grade ICANS, n (%)** | 221 (50) | 118 (54) | 96 (45) | 7 (54) |
| Median time from infusion to ICANS onset, days (IQR) | 7 (5-9) | 7 (5-9) | 7 (5-8) | 10.5 (8-11) |
| Median time from ICANS onset to resolution, days (IQR) | 6 (3-10) | 5 (3-10) | 6 (3-10) | 3.5 (2-6) |
| Cumulative incidence of ICANS resolution at 3 weeks since onset, % (95% CI) | 88 (83-92) | - | - | - |

- Incidence of any-grade ICANS and Grade ≥3 ICANS were similar across patient groups[b,c]
- The most common treatments given for CRS and/or ICANS were tocilizumab (80%), corticosteroids (65%), antiepileptics (19%), and anakinra (18%)

Error bars denote 95% CIs.
[a] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately.
[b] CRS and ICANS were graded per ASTCT consensus criteria. [c] Missing were excluded.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range; PMBCL, primary mediastinal B-cell lymphoma.

# Prolonged Cytopenias and Infections




- Incidence of prolonged cytopenia and infections were similar across patient groups[a,b]
- Prolonged neutropenia and thrombocytopenia occurred in 7% and 11% of all patients, respectively
- Almost half the patients (44%) had clinically significant infections

Error bars denote 95% CIs.
[a] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately.
[b] 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. Prolonged thrombocytopenia was defined as failure to recover platelet count ≥20×10$^9$/L within the first 30 days after infusion.
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma.

# Patient Deaths

| Characteristic | All Patients N=446 | ZUMA-7 Eligibility[a] | | Patients With PMBCL n=13 |
|---|---|---|---|---|
| | | Ineligible n=219 | Eligible/ Unknown n=214 | |
| **Deaths, n (%)** | 110 (25) | 71 (32) | 38 (18) | 1 (8) |
| **Primary cause of death among those who died during follow-up,[b] n (%)** | | | | |
| Primary disease | 81 (18) | 48 (22) | 32 (15) | 1 (8) |
| CRS | 1 (<1) | 1 (<1) | 0 | 0 |
| Neurotoxicity | 3 (1) | 3 (1) | 0 | 0 |
| Infection | 7 (2) | 6 (3) | 1 (<1) | 0 |
| Pulmonary | 2 (<1) | 1 (<1) | 1 (<1) | 0 |
| Organ failure | 8 (2) | 6 (3) | 2 (1) | 0 |
| Secondary malignancy | 2 (<1) | 1 (<1) | 1 (<1) | 0 |
| Other | 5 (1) | 5 (2) | 0 | 0 |
| **Cumulative incidence of non-relapse mortality at 6 months,[c] % (95% CI)** | 4 (2-6) | 7 (4-10) | 1 (<1-4) | 0 (NE-NE) |

- Across all patient populations (median follow-up, 12 months), the primary cause of death was primary disease

[a] Analysis by ZUMA-7 eligibility was among patients with DLBCL, HGBCL, and FL Grade 3B; patients with PMBCL were analyzed separately.
[b] Unknown or not reported was excluded from the denominator in percentage calculations. [c] REL/PD and treatment for REL/PD was treated as a competing risk; HSCT was censored.
CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma;
HSCT, hematopoietic stem cell transplantation; NE, not estimable; PMBCL, primary mediastinal B-cell lymphoma; REL/PD, relapsed or progressive disease.

# Conclusions

- This is the largest real-world analysis of patients with R/R LBCL who received 2L commercial axi-cel
  - About half of patients (52%) would have been ineligible for ZUMA-7
- Despite a broader patient population beyond the ZUMA-7 trial, effectiveness and safety outcomes at median follow-up of 12 months were consistent with those observed in ZUMA-7
- A limitation of this study is that some patients receiving bridging therapy may have been misclassified as third line or later by the algorithm used to define line of therapy and therefore excluded from this analysis
- Future work will assess real-world outcomes with a longer follow-up
- Overall, these findings support the use of axi-cel as a 2L therapy for patients with R/R LBCL, including many patients who would have been considered ineligible for ZUMA-7, in the real-world setting

2L, second line; axi-cel, axicabtagene ciloleucel; LBCL, large B-cell lymphoma; R/R, relapsed or refractory.

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*This study is a collaboration between CIBMTR and Kite.*
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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