Predictors of Early Safety Outcomes With Axicabtagene Ciloleucel (Axi-Cel) in Patients With Relapsed or Refractory Large B-Cell Lymphoma

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Background

- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for adults with R/R LBCL,[1,2] with curative potential demonstrated in the 3L+ (ZUMA-1) and 2L (ZUMA-7) settings[3,4]
  - CRS and neurologic toxicities are adverse events associated with CAR T-cell therapy, as reported in the clinical trials[5-9]
- In the real-world, axi-cel has also been administered in the outpatient setting,[10] which has reduced costs of care[11]
  - The risk for early safety events, such as CRS and ICANS, is a large barrier to widespread outpatient administration
  - Better prediction of early events may lead to improved safety management

%	ZUMA 1			ZUMA 7 (N=170)
	Pivotal Cohorts 1&2 (N=101)	Safety Management Cohort 4 (N=41)	Safety Management Cohort 6 (N=40)	
CRS	93	93	80	92
Grade ≥3	13	2	0	6
Neurologic events	64	61	58	60
Grade ≥3	28	17	13	21

- Here, we identify pre-infusion characteristics associated with high risk for developing early CRS or early ICANS following axi-cel infusion in the real-world setting

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 JR, et al. *N Engl J Med.* 2023;389:148-157. 5. Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638. 6. Neelapu S, et al. *N Engl J Med.* 2017;377:2531-2544. 7. Locke FL, et al. *N Engl J Med.* 2022;386:640-654. 8. Topp MS, et al. *Br J Haematol.* 2021;195:388-398. 9. Oluwole OO, et al. *Br J Haematol.* 2021;194:690-700. 10. Dholaria B, et al. *Br J Haematol.* 2022;198:1073-1075. 11. Lyman GH, et al. *JAMA Network Open.* 2020;3:e202072.
2L, second line; 3L+, third line or later; 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.

Study Design and Analysis

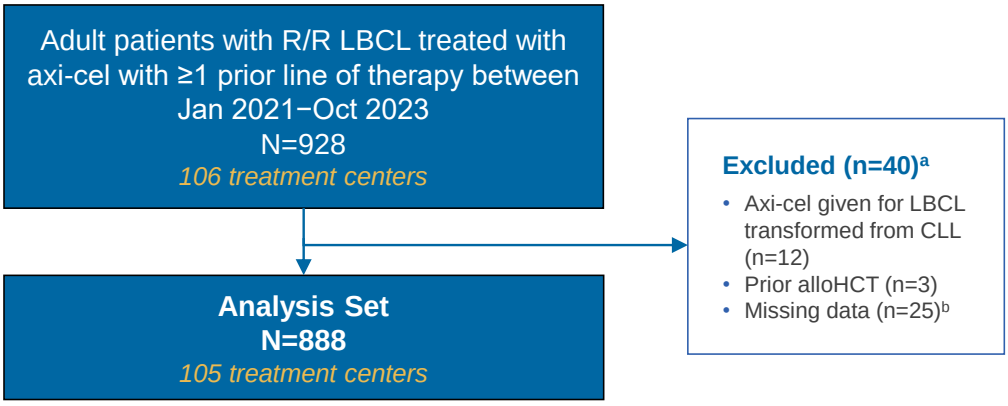
Data Source	• Data were collected from the **CIBMTR** observational database • **Study population:** patients receiving axi-cel for R/R LBCL in the 2L+ setting in the US or Canada (Jan 2021 through Oct 2023)
Outcomes of Interest	• **Primary:** incidence of early CRS and early ICANS of any grade – Early events were those with onset occurring from infusion (Day 0) through end of Day 3 • **Secondary:** Early Grade ≥2 CRS, early Grade ≥3 CRS, and early Grade ≥3 ICANS[1] – Grade of CRS and ICANS was based on maximum grade calculated across total follow-up
Statistical Analysis	• Clinically relevant candidate variables were evaluated by univariate screening (Chi-squared or Fisher exact test)[a] and further selected using the stepwise selection process • Multivariable logistic regression was used to estimate effect of pre-infusion characteristics on early CRS and early ICANS, accounting for other factors

[a] Candidate variables in the multivariate analyses were age, sex, race/ethnicity, ECOG PS prior to infusion, each of the following comorbidities: hepatic (moderate/severe), diabetes or steroid-induced hyperglycemia requiring continuous treatment with insulin or oral hypoglycemics in the last four weeks prior to infusion, disease characteristics at diagnosis (Ann Arbor organ stage, number of extranodal sites), elevated LDH (>ULN prior to infusion), chemo-sensitivity prior to infusion, bulky disease, number of prior lines of therapy (not counting prior HCT), time from leukapheresis to infusion, and year of infusion.

1. Per ASTCT Consensus Criteria (Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638).

2L+, second line and greater; ASTCT, American Society for Transplantation and Cellular Therapy; axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; CRP, C-reactive protein; CRS, cytokine release syndrome; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; R/R, relapsed or refractory; ULN, upper limit of normal; US, United States.

Analysis Population



[a] Reasons for exclusion are not mutually exclusive. [b] Missing data included the number of lines of prior therapy (n=23), comorbidities (yes/no, n=1), and prior autologous HCT (yes/no, n=1). AlloHCT, allogeneic hematopoietic cell transplantation; axi-cel, axicabtagene ciloleucel; CLL, chronic lymphocytic leukemia; HCT, hematopoietic cell transplantation; LBCL, large B-cell lymphoma; R/R, relapsed or refractory.

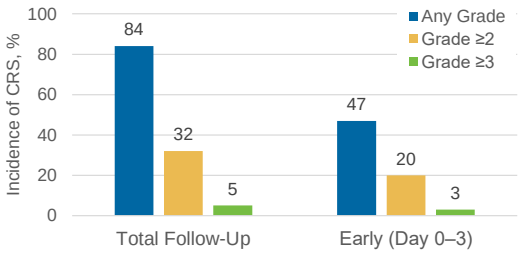
Baseline Characteristics

Characteristic	Patients (N=888)
Median age (IQR), years	63 (54–71)
≥65 years, n (%)	399 (45)
Male sex, n (%)	583 (66)
ECOG PS ≥2 prior to infusion, n (%)	40 (5)
Clinically significant comorbidity, n (%)[a]	625 (70)
Disease stage III-IV at diagnosis, n (%)[b]	606 (68)
Extranodal involvement prior to infusion, n (%)	17 (2)
Bulky disease prior to infusion, n (%)[c]	57 (6)
Elevated LDH prior to infusion, n (%)[d]	387 (44)
1 line of prior therapy, n (%)	448 (50)
Prior autologous HCT, n (%)	92 (10)
Chemoresistance prior to infusion, n (%)[e]	540 (61)
Bridging therapy (any type), n (%)	522 (59)
Median time from leukapheresis to infusion (IQR), days	30 (27–34)
Bendamustine lymphodepletion regimen, n (%)	130 (15)

- Median follow-up post-infusion was 12.3 months (range, 3–38)
- Most patients (73%) had non-Hispanic ethnicity (63% white, 5% Black or African American, 5% Asian race)
- Most patients (81%) had DLBCL at diagnosis
  - 17% had HGBCL (15% with double- or triple-hit lymphoma), and 2% had PMBCL
- 14% were intended to be treated in the outpatient setting

[a] List of comorbidities defined per the HCT–specific Comorbidity Index[1] with the addition of low body mass index (<20 kg/m^2). [b] Per Ann Arbor criteria. [c] Largest size of nodal mass >7.5 cm. [d] LDH greater than ULN at each center. [e] Defined as patients who had stable or progressive disease prior to infusion. 1. Sorror ML, et al. *Blood*. 2005;106:2912-2919.
DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; HGBCL, high-grade B-cell lymphoma; IQR, interquartile range; LDH, lactate dehydrogenase, PMBCL, primary mediastinal B-cell lymphoma; ULN, upper limit of normal.

Incidence of CRS by Grade and Onset[a]



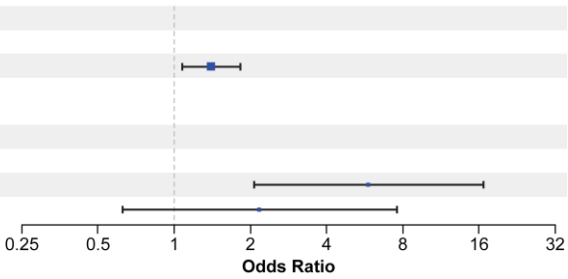
CRS Characteristic	Patients With Any Grade CRS	
	Total Follow-Up (N=748)	Early (N=421)
Median time to onset (IQR), days	4 (2–6)	2 (2–3)
Median duration (IQR), days	4 (3–6)	5 (4–7)
Resolution by day 21 (95% CI), %	99 (98–100)	99 (98–100)

- Early (Days 0–3) Grade ≥3 CRS was rare (3%)
  - Most CRS cases (56%) had onset before Day 3
  - Most early CRS events were Grade 1 (Grade 1 27%, Grade 2 17%, Grade ≥3 3%)
  - The most common early CRS symptom was fever[b] (45%); other early CRS symptoms were reported in <10% of patients
- Nearly all cases of any grade CRS (99%) resolved within 3 weeks after onset

[a] Based on earliest onset and maximum grade. [b] Fever was defined as temperature ≥100.4°F or ≥38°C.
CRS, cytokine release syndrome; IQR, interquartile range.

Multivariate Analyses for Early CRS

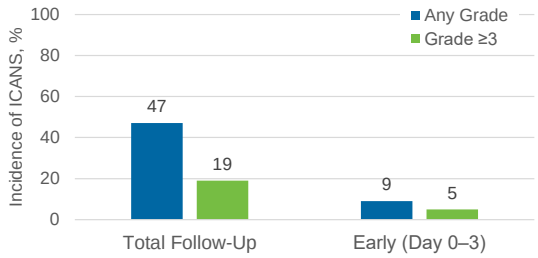
	Event/N (%)	OR (95% CI)
Any Grade CRS		
Number of lines of prior therapy		
≥2	190/440 (43)	Ref.
1	231/448 (52)	1.40 (1.08-1.82)
Grade ≥3 CRS		
ECOG PS		
0-1	19/778 (2)	Ref.
≥2	5/39 (13)	5.87 (2.07-16.7)
Not reported	3/58 (5)	2.18 (0.63-7.59)



- One prior line of therapy was associated with greater risk for early any-grade CRS
  - Notably, 47% and 52% of patients with ≥2 vs 1 prior line of therapy, respectively, had early Grade 1 CRS (fever only)
- ECOG PS ≥2 was associated with greater risk for early Grade ≥3 CRS
- No tested factors associated with early Grade ≥2 CRS; comorbidities were not associated with early CRS

All candidate variables in the multivariate analyses are described in the Study Design and Analysis.
CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

Incidence of ICANS by Grade and Onset[a]



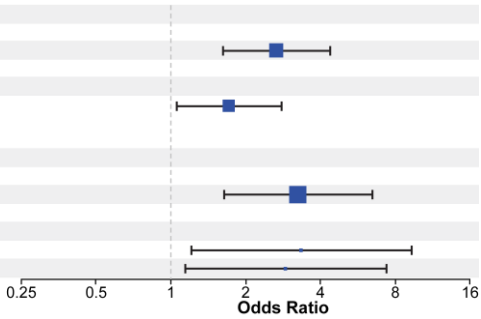
ICANS Characteristic	Patients With Any Grade ICANS	
	Total Follow-Up (N=405)	Early (N=76)
Median time to onset (IQR), days	7 (5–9)	3 (2–4)
Median duration (IQR), days	5 (2–9)	10 (5–18)
Resolution by day 21 (95% CI), %	93 (90–95)	84 (71–91)

- Early (Days 0–3) Grade ≥3 ICANS was rare (5%)
  - Over 80% of ICANS cases occurred after Day 3
- Most cases of early any grade ICANS (84%) resolved within 3 weeks after onset

[a] Based on earliest onset and maximum grade.
ICANS, immune effector cell-associated neurotoxicity syndrome; IQR, interquartile range.

Multivariate Analyses for Early ICANS

	Event/N (%)	OR (95% CI)
Any Grade ICANS		
Age at infusion		
<65	26/483 (5)	Ref.
≥65	50/391 (13)	2.66 (1.62-4.36)
Number of lines of prior therapy		
1	30/440 (7)	Ref.
≥2	46/434 (11)	1.71 (1.05-2.78)
Grade ≥3 ICANS		
Age at infusion		
<65	12/482 (2)	Ref.
≥65	30/389 (8)	3.26 (1.64-6.47)
ECOG PS		
0-1	31/775 (4)	Ref.
≥2	5/39 (13)	3.36 (1.21-9.31)
Not reported	6/57 (11)	2.90 (1.14-7.38)



- Age ≥65 years and ≥2 prior lines of therapy were associated with greater risk for early any-grade ICANS
- Age ≥65 years and ECOG PS ≥2 were associated with greater risk for early Grade ≥3 ICANS
- Comorbidities were not associated with early ICANS

All candidate variables in the multivariate analyses are described in the Study Design and Analysis.
ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell-associated neurotoxicity syndrome; OR, odds ratio.

Conclusions

- In this real-world cohort of patients with R/R LBCL receiving axi-cel, incidences of early CRS and early ICANS (within 3 days of infusion) were 47% and 9%, respectively
  - Early Grade ≥3 CRS and ICANS occurred in 3% and 5% of patients, respectively
- After adjustment for other factors, age ≥65 years was associated with a greater risk of early ICANS (any grade and Grade ≥3), and ECOG PS ≥2 was associated with a greater risk of early Grade ≥3 CRS and early Grade ≥3 ICANS
  - There was no association between any comorbidity and early CRS nor early ICANS
- This analysis was limited to readily-available demographic and clinical variables; future work may evaluate risks associated with other disease characteristics (eg, tumor burden) for CRS and ICANS following axi-cel administration
- These findings, with future evaluation of early safety endpoints, may help clinicians identify patients who need prophylactic safety management prior to administration of axi-cel, facilitating its outpatient administration

Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; ECOG PS, Eastern Cooperative Oncology Group performance status; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; R/R, relapsed or 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