Real-World Outcomes of Axicabtagene Ciloleucel for the Treatment of Large B-Cell Lymphoma: Impact of Age and Specific Organ Dysfunction

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Disclosures

Frederick L. Locke: consulting or advisory role with ecoR1, Emerging Therapy Solutions Gerson Lehman Group, Allogene, Amgen, bluebird bio, Bristol Myers Squibb/Celgene, Calibr, Iovance, Kite, a Gilead Company, Janssen, Legend Biotech, Novartis, Umoja, Cowen, Cellular Biomedicine Group, GammaDelta Therapeutics, Wugen; research funding from Kite, a Gilead Company, Allogene and Novartis; and patents, royalties, other intellectual property from several patents held by the institution in his name (unlicensed) in the field of cellular immunotherapy.

Background

- Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved in the US and EU for the treatment of adults with R/R LBCL after ≥2 prior lines of systemic therapy[1,2]

- In a 5-year follow-up analysis of ZUMA-1 (median follow-up, 63.1 months), the median OS was 25.8 months, and the KM estimate of the 5-year OS rate was 43%[3]

- Some patients who would have been ineligible for ZUMA-1 due to comorbidities have been treated with axi-cel in the real-world setting[4,5]
  - Real-world setting safety and efficacy results of axi-cel are comparable to the registrational ZUMA-1 trial, but with complete response rates and duration of response more advantageous in patients eligible for ZUMA-1[4,5]

- **We interrogated the axi-cel postapproval safety study (PASS), which is being conducted by the CIBMTR, to assess the impact of age and comorbidities in the real-world setting**

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1. YESCARTA® (axicabtagene ciloleucel) Prescribing information. Kite Pharma, Inc; 2021. 2. YESCARTA® (axicabtagene ciloleucel) [summary of product characteristics]. Amsterdam, The Netherlands: Kite Pharma EU B.V.; 2021. 3. Jacobson CA, et al. ASH 2021. #1764.
4. Jacobson CA, et al. *J Clin Oncol*. 2020;38(27):3095-3106. 5. Nastoupil LJ, et al. *J Clin Oncol*. 2020;38(27):3119-3128.
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CIBMTR, Center for International Blood and Marrow Transplant Research; EU, European Union; KM, Kaplan-Meier; LBCL, large B-cell lymphoma; OS, overall survival; R/R, relapsed/refractory; US, United States.

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Methods

- Patients who received commercial axi-cel between October 2017 and August 2020, signed informed consent, accrued to PASS, and were followed for at least 6 months with complete data entry by the time of analysis was included
  - Patients with a prior history of non-HCT cell therapy (including CAR T-cell therapy or DLI) were excluded

- Endpoints of interest
  - Efficacy: ORR, CR rate, DOR, PFS, OS
  - Safety: CRS and ICANS

- Outcomes were assessed and compared by age and preselected coexisting disease or organ impairment within 3 months prior to the infusion included in the HCT comorbidity index

- Multivariate logistic and Cox regression models were used to assess the impact of age or coexistent organ dysfunction on outcomes via OR or HR and the corresponding 95% CI

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Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLI, donor lymphocyte infusion; DOR, duration of response; HCT, hematopoietic cell transplantation; HR, hazard ratio; ICANS, immune effector cell-associated neurotoxicity syndrome; OR, odds ratio; ORR, overall response rate; OS, overall survival; PASS, postapproval safety study; PFS, progression-free survival; overall survival.

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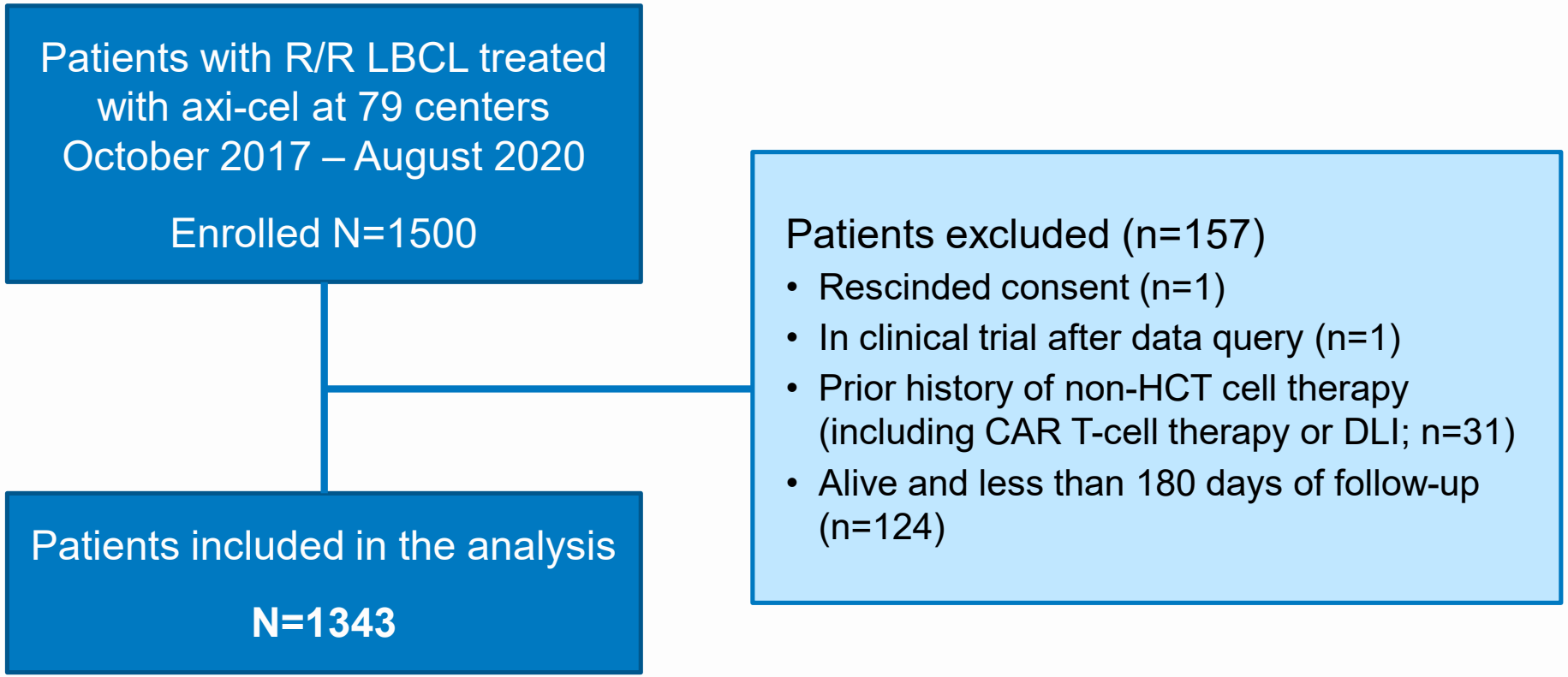
Analysis Population

- As of June 22, 2021, a total of 1500 patients were enrolled and **1343** were included in the analysis



Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; DLI, donor lymphocyte infusion; HCT, hematopoietic cell transplantation; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

Baseline Characteristics of the Study Population

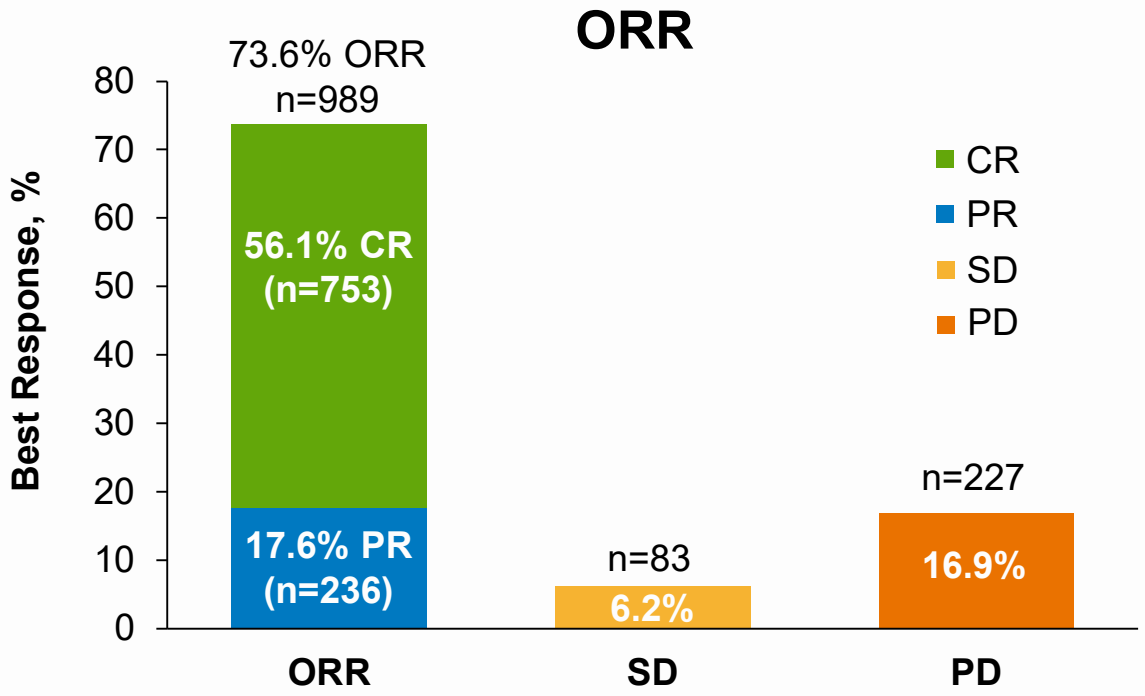
Key Variables of Interest, n (%)	N=1343
Age ≥65 years	509 (38)
ECOG PS score ≥2 at infusion	59 (4)
Comorbidities	
Pulmonary	368 (27)
Prior cancer	213 (16)
Cardiac / cerebrovascular / heart valve	168 (13)
Obesity	117 (9)
Renal	30 (2)
Hepatic	28 (2)

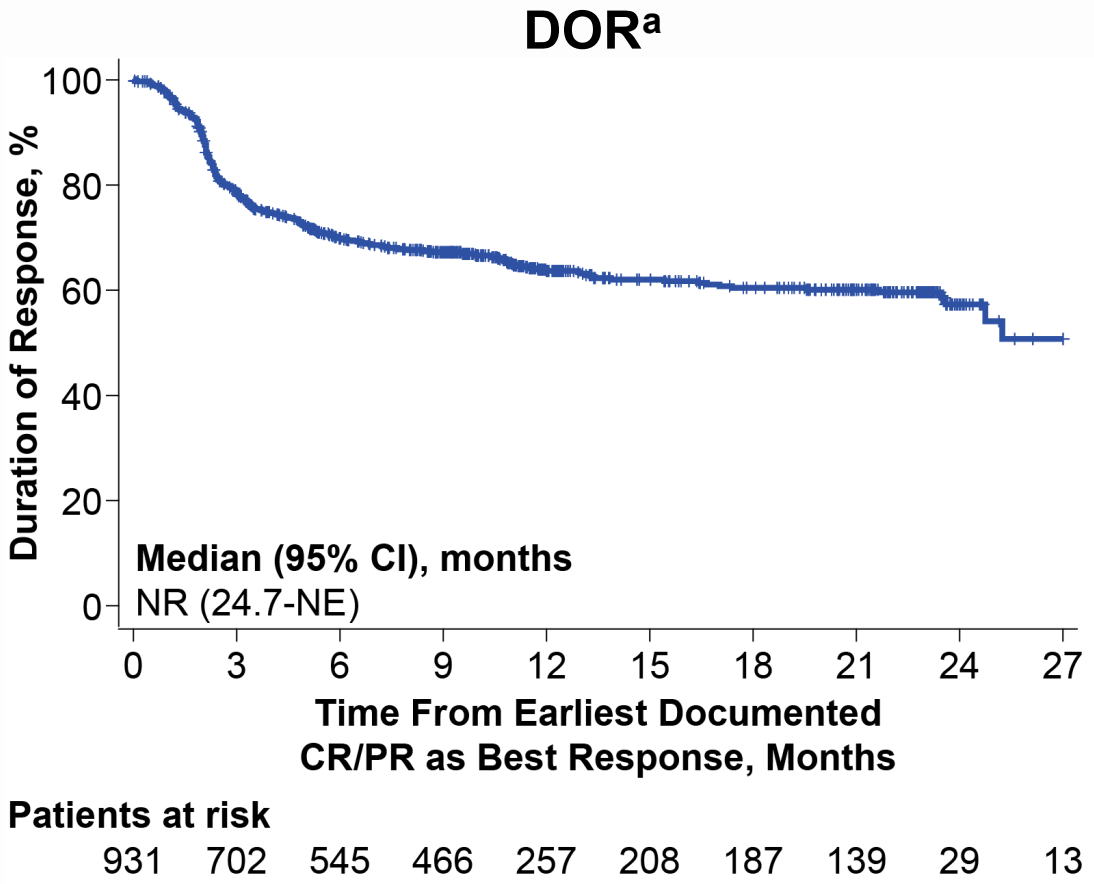
- Efficacy and safety outcomes were assessed and compared by the above key variables
- 682 patients (51%) had ECOG ≥2, and/or comorbidities, and/or CNS lymphoma/CNS metastasis that would have made them otherwise ineligible for ZUMA-1 trial

Other Characteristics/Demographics, n (%)	N=1343
Female sex	471 (35)
White race	1,097 (82)
Hispanic ethnicity	213 (16)
Histology: transformed	377 (28)
Double/triple hit	198 (15)
Ann Arbor stage at diagnosis: I-II / III-IV	249 (19) / 773 (58)
Elevated LDH at diagnosis	375 (28)
>1 Extranodal involvements	330 (25)
CNS lymphoma / CNS metastasis	19 (1)
Chemosensitive / resistant	308 (23) / 880 (66)
No. of lines of prior therapies: 1 or 2 / 3 / 4 / ≥5	374 (28) / 421 (31) / 238 (18) / 251 (19)
Prior HCT (any type) / prior auto-HCT	384 (29) / 359 (27)
Systemic bridging therapy	232 (17)
≥12 Months since diagnosis	780 (58)
≥28 Days since leukapheresis	659 (49)

CNS, central nervous system; ECOG PS Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; LDH, lactate dehydrogenase.

ORR and DOR Were Favorable With Axi-Cel





- The median DOR was not yet reached, and the estimated 1-year and 2-year DOR rates were 64% and 57%, respectively

[a] Among patients who achieved CR/PR as best response. DOR is censored at subsequent cell therapy/HCT; patients with unknown relapse/progression status, or unknown time to relapse/progression, were excluded in the analysis.
Axi-cel, axicabtagene ciloleucel; CR, complete response; DOR, duration of response; HCT, hematopoietic cell transplantation; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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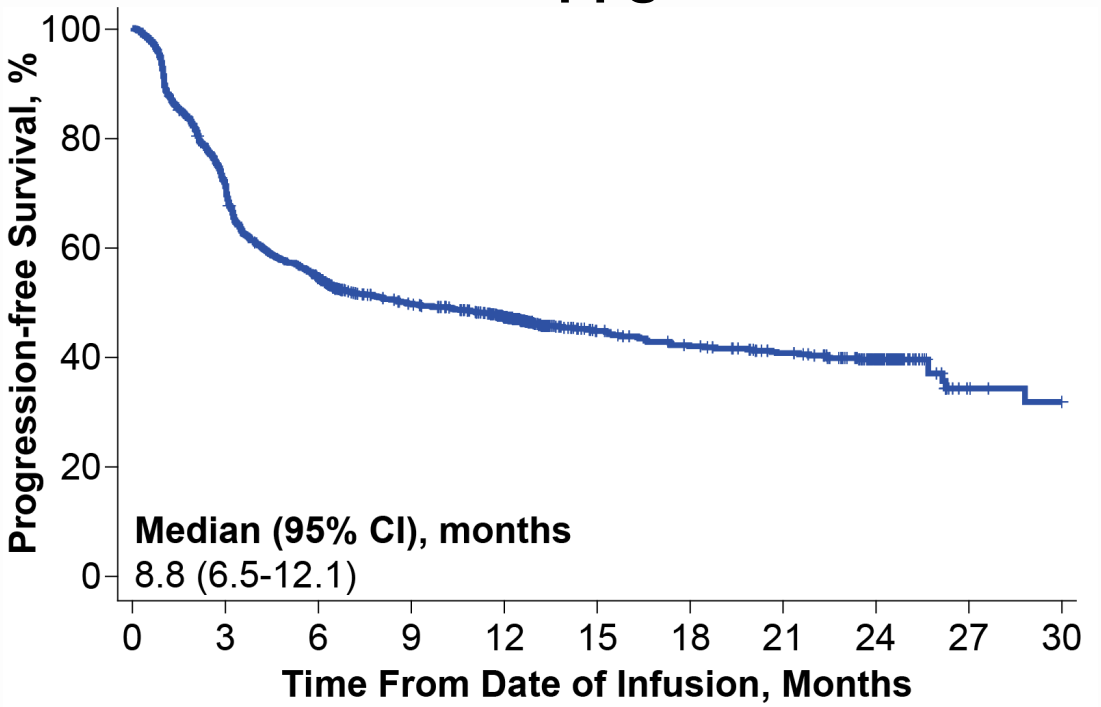
Survival Outcomes With Axi-Cel

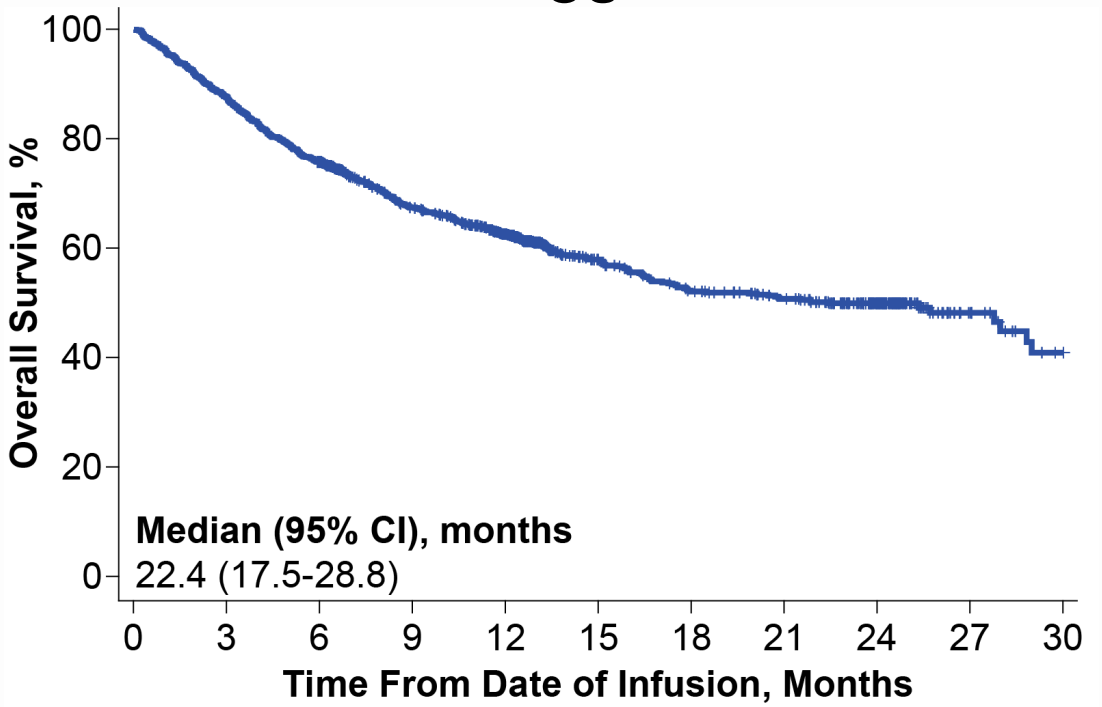
PFS[a]



Patients at risk

1292	918	694	557	549	228	208	188	123	17	13

OS



Patients at risk

1343	1176	1008	786	637	324	282	258	169	34	19

- With a median follow-up of 13 months, median PFS was 8.8 months, and median OS was 22.4 months

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[a] PFS is censored at subsequent cell therapy/HCT; patients with unknown relapse/progression status, or unknown time to relapse/progression, were excluded in the analysis.

Axi-cel, axicabtagene ciloleucel; HCT, hematopoietic cell transplantation; PFS, progression-free survival; OS, overall survival.

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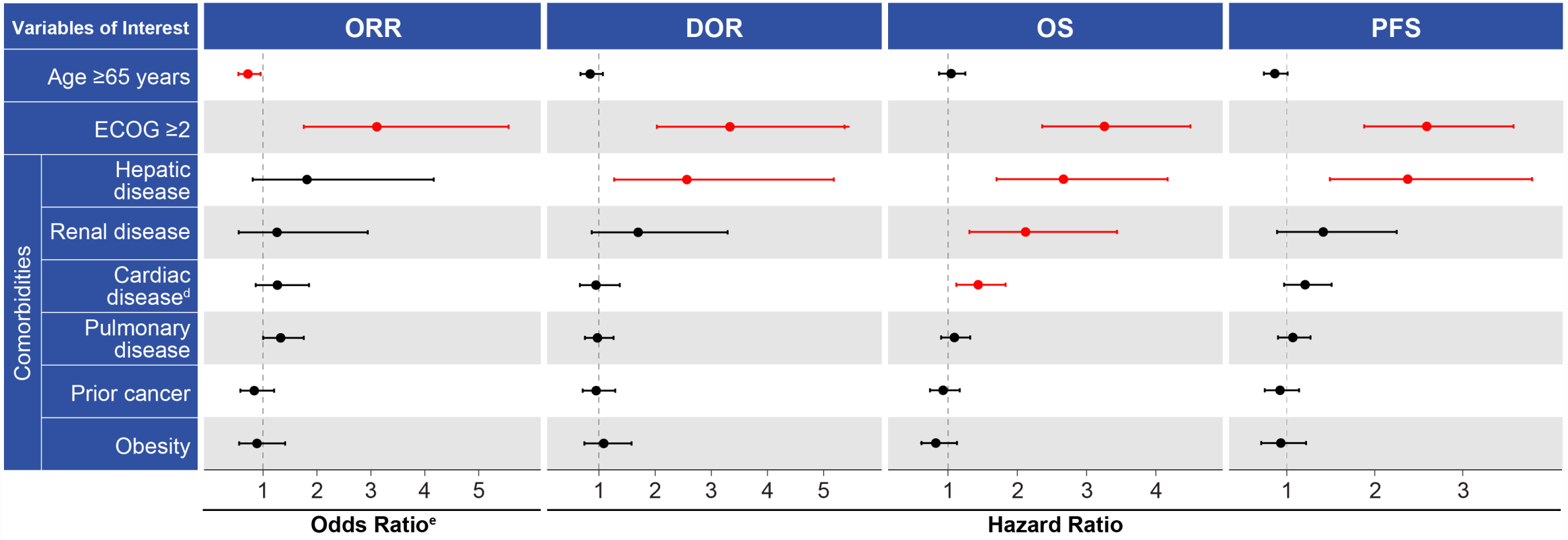
Associations Among Key Factors of Interest and Efficacy Outcomes

Multivariate Model Effect Estimates[a,b,c]



[a] Variables with multivariate *P*<.05 are highlighted in red. [b] Male sex, chemo resistance, ≥3 lines of prior therapies, <12-month disease duration, elevated LDH, >1 extranodal involvements, stage III/IV, and non-White race were also associated with worse outcomes (data not shown). [c] Hepatic disease, moderate or severe, defined as liver cirrhosis, bilirubin >1.5 × upper limit of normal, or AST/ALT >2.5 × upper limit of normal; cardiac/cerebrovascular/heart valve diseases defined as any history of coronary artery disease, congestive heart failure, myocardial infarction, and/or ejection fraction ≤50% on the most recent test; and renal disease, moderate or severe, defined as serum creatinine, >2 mg/dL or >177 µmol/L, on dialysis during the 4 weeks prior to axi-cel infusion or prior renal transplantation. [d] Cardiac disease includes cardiac, cerebrovascular, and heart valve disease. [e] Inverse of OR is plotted for ORR.

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Rates of CRS and ICANS Were Consistent With Prior Reporting for Axi-Cel in R/R LBCL

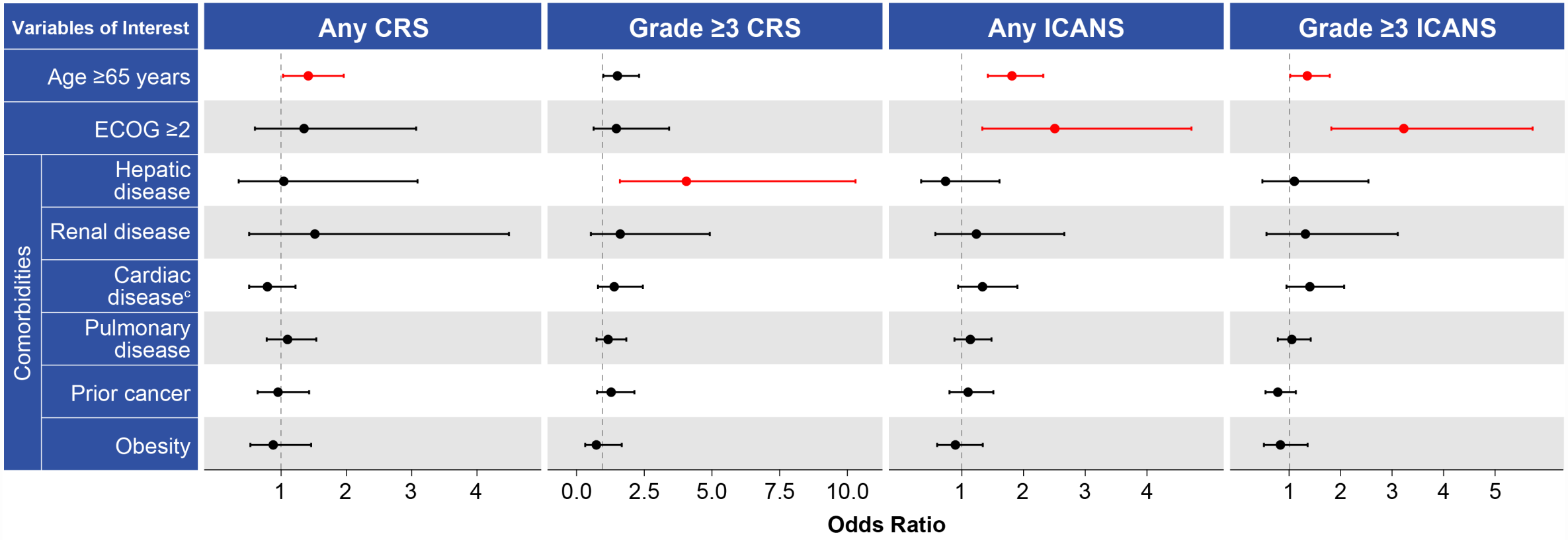
- CRS was reported in 83% of patients, with Grade ≥3 CRS in 8%
- ICANS was reported in 55% of patients, with Grade ≥3 ICANS in 25%

Safety Endpoints	N=1343
CRS, n (%)	1115 (83)
Grade ≥3, n (%)	109 (8)
Median time to onset (range), days	4 (1-28)
Median of duration of CRS (range), days	6 (1-121)
ICANS, n (%)	743 (55)
Grade ≥3, n (%)	331 (25)
Median time to onset (range), days	7 (1-36)
Median of duration of ICANS (range), days	8 (1-115)

Axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; R/R, relapsed/refractory.

Associations Among Key Factors of Interest and CRS and ICANS

Multivariate Model Effect Estimates[a,b]



[a] Variables with multivariate *P*<.05 are highlighted in red. [b] Female sex, chemo resistance, <28 days cell production time, >1 extranodal involvements, nontransformed histology, ≥3 lines of prior therapies, no prior HCT, use of bridging therapy, non-Hispanic, and White race were also associated with worse outcomes for CRS and ICANS (data not shown). [c] Cardiac disease includes cardiac, cerebrovascular, and heart valve disease.

CRS, cytokine release syndrome; ECOG PS Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; ICANS, immune effector cell-associated neurotoxicity syndrome.

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Conclusions

- The findings from this study on efficacy and safety endpoints aligned with and extended data from ZUMA-1, validating the use of real-world evidence for postapproval evaluation of CAR T-cell therapy outcomes
- Advanced age (≥65 years) did not impact efficacy outcomes; however, older patients had higher rates of CRS and ICANS
- Performance status should be considered in patient selection and treatment decisions with axi-cel
- Patients with coexistent organ dysfunction had generally favorable outcomes with axi-cel, although the presence of moderate to severe hepatic, renal, and cardiac diseases were associated with lower OS

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; OS, overall survival.

Acknowledgments

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and healthcare staff at each study site
- The authors also thank Michelle Hooper and Jun Kawashima for their contributions to this analysis
- Medical writing support was provided by Nexus Global Group Science, funded by Kite, a Gilead Company
- This study was funded by the National Cancer Institute (CIDR [U24 CA233032]) and Kite, a Gilead Company

On behalf of the CIBMTR® Cellular Immunotherapy for Cancer Working Committee; CIBMTR® is a research collaboration between National Marrow Donor Program®/Be The Match® and the Medical College of Wisconsin, and operates the Cellular Immunotherapy Data Resource (CIDR)

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