Real-World and Clinical Trial Outcomes in Large B-cell Lymphoma with Axicabtagene Ciloleucel Across Race and Ethnicity

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DATA SUPPLEMENT

SUPPLEMENTAL METHODS

Race and Ethnicity Definitions

- Asian: Includes persons with ancestors in any of the original peoples of the Far East, the Indian subcontinent including Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, Philippine Islands, Thailand, Vietnam, Hmong, East India, Laos, Bangladesh, Indonesia, Sri Lanka, Nepal, Bhutan, Sikh, Burma and other South and Southeast Asian.
- Black or African American: Includes persons having origins in any of the Black racial groups of Africa, including Black Americans, Africans, Haitians, and residents of Caribbean Islands of African descent.
- Hispanic/Latino: Hispanic or Latino refers to people whose ancestors or descendants originated in Central and South America and in the Caribbean, who follow the customs and cultures of these areas and who may speak Spanish. The phrase Hispanic or Latino excludes people born in Europe whose language is Spanish or Portuguese, and non-Spanish speaking people born in Brazil, Belize, French Guyana, Guyana, Surinam, and other non-Spanish speaking territories.
- Other/Unknown: Includes persons whose race is American Indian or Alaska Native (having origins in any of the original people of North, South, or Central America), Native Hawaiian and other Pacific Islander (having origins in any of the original peoples of the Hawaiian Islands, Guam or Samoa, or having origins in any of the peoples of the Pacific Islands), or with multi-race and unknown race.
- white: Includes persons who indicate their race as White such as Canadian, German, Italian, Lebanese, Near Easterner, Arabian, Eastern European, etc.

Covariates Used in Multivariable Modeling

A stepwise variable selection process was used to determine the final models, both for the logistic and Cox regressions (summarized below). The complete list of covariates subject to stepwise selection included:

- Age at infusion: ≥65 years and <65 years
- Sex: male versus female
- Eastern Cooperative Oncology Group performance status (converted from Karnofsky performance score) at infusion: 0 or 1 versus ≥2
- Comorbidities prior to infusion:
    - Pulmonary, moderate to severe: yes versus no
    - Cardiac, cerebrovascular, and/or heart valve disease: yes versus no
    - Hepatic, moderate to severe: yes versus no
    - Renal, moderate to severe: yes versus no
    - Obesity, with body mass index ≥35 kg/m^2: yes versus no
    - Prior malignancy other than non-melanoma skin carcinoma (ie, basal or squamous cell carcinoma): yes versus no
- Disease characteristics at initial diagnosis
    - Histologic transformation: yes versus no
    - Double/triple-hit: yes versus no
    - Ann Arbor stage of organ involvement: I or II versus III or IV
    - Elevated lactate dehydrogenase level above upper limit of normal: yes versus no
    - Number of extra-nodal involvement site(s): 0 or 1 versus ≥ 2

- Presence of bulky disease (ie, maximum nodal size ≥10 cm) prior to infusion: yes versus no
- Disease sensitivity prior to infusion: sensitive versus resistant versus untreated or sensitivity unknown
- Number of prior lines of therapy (excluding hematopoietic cell transplantation [HCT]): 1 or 2 versus ≥ 3
- Time from last prior HCT to infusion: no prior HCT versus prior HCT to infusion ≤12 months versus prior HCT to infusion >12 months
- Time from initial diagnosis to axicabtagene ciloleucel (axi-cel) infusion: <12 months versus ≥12 months
- Time from leukapheresis to axi-cel infusion: <28 days versus ≥28 days
- Use of bridging therapy: yes versus no

Multivariable Logistic Regression

A multivariable logistic regression model was used to evaluate efficacy and safety endpoints including overall response rate (ORR) and complete response (CR) among all treated patients, cytokine release syndrome (CRS; any grade and grade ≥3) and immune effector cell-associated neurotoxicity syndrome (ICANS; any grade and grade ≥3). Odds ratios along with 95% CIs was estimated and patients with missing value were excluded from the denominator. The main variables of interest forced into the model were race/ethnicity (non-Hispanic white vs non-Hispanic Black vs non-Hispanic Asian vs Hispanic or Latino). A stepwise variable selection process was used to determine the final model. The overall model fitness was assessed using

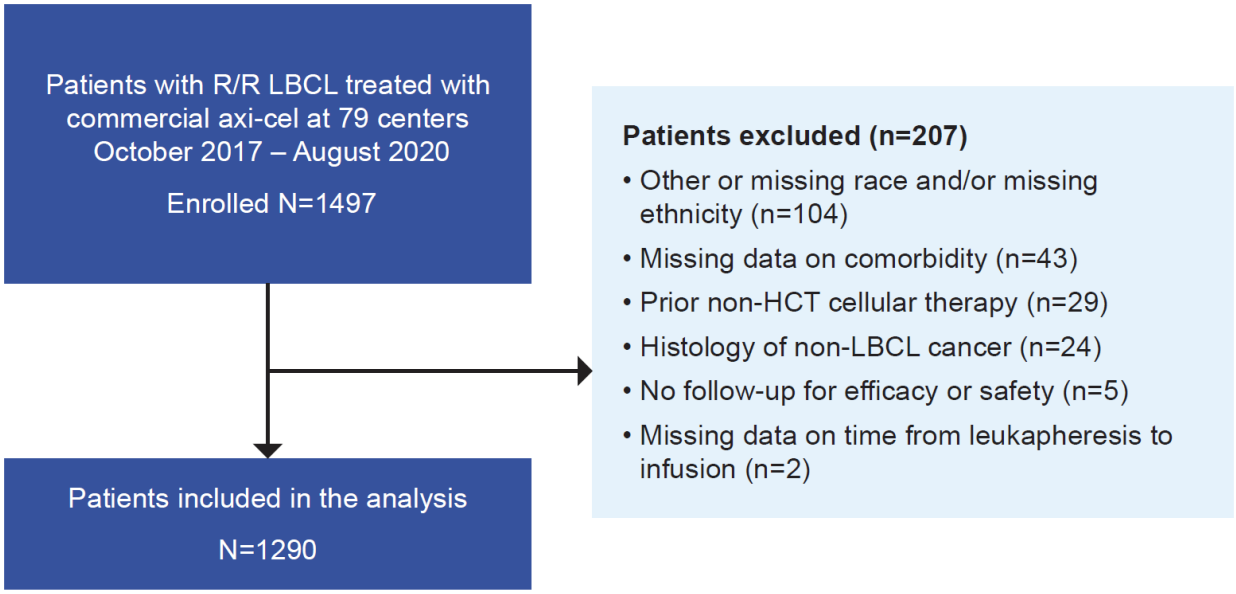
the area under the Receiver Operating Characteristic (ROC) curve for logistic regression. Pairwise correlations among covariates were investigated to prevent collinearity in the multivariable model.

Multivariable Cox Proportional Hazards Model

A multivariable Cox proportional hazards model was used to evaluate duration of response (DOR; as defined in the primary descriptive analysis), progression-free survival (PFS), and overall survival (OS). Hazard ratios (HR) with 95% CIs were estimated. Patients with missing outcome status or missing data were censored at Day 1 for PFS and OS, and at the time of initial response for DOR. The proportionality assumption for the Cox model was first tested using time-dependent covariates for the main risk factors of interest (ie, interaction terms between bridging therapy and its response and logarithm of time). The proportionality assumption was then further tested. Once the proportionality assumption was satisfied, a stepwise selection process was used to determine the final model. The overall model fitness was assessed using Harrell's C-index (ie, the concordance index) for Cox proportional hazards model.[1] Pairwise correlations among covariates were investigated to prevent collinearity in the multivariable model. Adjusted survival estimates at 6, 9 and 12 months since the first documented CR/partial response (PR) for DOR and at Month 6, 12, 18, and 24 for PFS and OS along with 95% CIs were summarized using the direct adjusted survival function from a stratified Cox proportional hazards model.[2,3] The main variables of interest (ie, race and ethnicity) were stratified, while the remaining covariates from the stepwise selection process were adjusted in the stratified Cox model. Direct adjusted survival curves were plotted by the main variables of interest.

SUPPLEMENTAL RESULTS

Supplemental Figure 1. Real-World Cohort Analysis Population



Data cutoff date: May 4, 2022.

Axi-cel; axicabtagene ciloleucel; LBCL, large B-cell lymphoma; R/R relapsed or refractory.

Supplemental Table 1. Baseline Characteristics by Race and Ethnicity in Clinical Trials

Key Variable of Interest, n (%) unless otherwise specified	Hispanic	Non-Hispanic Asian	Non-Hispanic Black	Non-Hispanic white
ZUMA-1[a]	**n=19**	**n=3**	**n=5**	**n=79**
Age, median (range), years	51.0 (38.0-72.0)	27.0 (23.0-65.0)	37.0 (25.0-60.0)	59.0 (28.0-76.0)
≥65 years	3 (16)	1 (33)	0 (0)	22 (28)
Male sex	11 (58)	2 (67)	0 (0)	59 (75)
Disease histology per investigator				
DLBCL	17 (89)	0 (0)	4 (80)	62 (78)
HGBL	0 (0)	2 (67)	1 (20)	5 (6)
HGBL-NOS	2 (11)	1 (33)	0 (0)	12 (15)
Baseline ECOG PS 1[b]	7 (37)	3 (100)	4 (80)	47 (59)
≥3 of lines of prior therapies	14 (74)	2 (67)	4 (80)	55 (70)
Prior HCT (any type)	6 (32)	2 (67)	3 (60)	18 (23)
≥28 Days from leukapheresis to infusion	5 (26)	2 (67)	1 (20)	18 (23)
ZUMA-7[a]	**n=10**	**n=12**	**n=10**	**n=137**
Age, median (range), years	60.5 (33.0-80.0)	57.5 (30.0-71.0)	52.0 (21.0-62.0)	59.0 (23.0-77.0)
≥65 years	3 (30)	2 (17)	0 (0)	44 (32)
Male sex	5 (50)	7 (58)	7 (70)	84 (61)
Disease histology per investigator				
DLBCL	6 (60)	10 (83)	8 (80)	89 (65)
HGBCL	3 (30)	2 (17)	2 (20)	32 (23)
HGBL-NOS	1 (10)	0 (0)	0 (0)	16 (12)

Baseline ECOG PS 1[b]	7 (70)	8 (67)	8 (80)	55 (40)
Bridging therapy	4 (40)	6 (50)	3 (30)	46 (34)
≥28 Days from leukapheresis to infusion	2 (20)	3 (25)	4 (40)	53 (39)

[a] Study procedures and eligibility criteria for ZUMA-1 and ZUMA-7 were previously reported.[4,5]

[b] Patients with ECOG PS ≥2 were not eligible and excluded from ZUMA-1 and ZUMA-7.

Axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; ECOG; Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplantation; HGBL, high-grade B-cell lymphoma; LBCL, large b-cell lymphoma; NOS; not otherwise specified; R/R, relapsed or refractory.

Supplemental Table 2. Cumulative Incidences of Relapse and Non-Relapse Mortality in the Real-World

	Hispanic (n=152)	Non-Hispanic Asian (n=78)	Non-Hispanic Black (n=68)	Non-Hispanic white (n=992)
Relapse/PD[a]				
Estimate at 12 months (95% CI), %	48 (40-56)	39 (28-50)	61 (48-71)	47 (44-51)
Estimate at 24 months (95% CI), %	53 (44-61)	39 (28-50)	64 (51-75)	51 (48-55)
Non-relapse mortality[a]				
Estimate at 12 months (95% CI), %	4 (2-9)	6 (2-13)	5 (1-12)	5 (4-6)
Estimate at 24 months (95% CI), %	11 (6-18)	11 (5-21)	6 (2-14)	9 (7-11)

[a] Subsequent cellular therapy/HCT were censored.

HCT, hematopoietic cell transplantation; PD, progressive disease.

Supplemental Table 3. Sensitivity Analysis of Efficacy Outcomes by Race and Ethnicity as Separate Variables in the Real World

	Asian (n=79)	Black or African American (n=70)	white (n=1097)	Hispanic or Latino (n=152)	Not Hispanic or Latino (n=1138)
ORR, n (%)	55 (70)	39 (56)	823 (75)	111 (73)	835 (73)
CR	45 (57)	32 (46)	644 (59)	86 (57)	657 (58)
Median DOR[a] (95% CI), mo	NE (25.3-NE)	22.6 (6.5-NE)	23.0 (17.8-30.0)	21.3 (16.4-NE)	25.2 (19.8-NE)
Estimate at 12 months (95% CI), %	78 (63-87)	57 (40-71)	59 (56-63)	64 (54-73)	60 (56-63)
Median PFS[a] (95% CI, mo)	21.7 (3.2-NE)	3.8 (2.9-8.5)	10.3 (7.0-12.8)	7.8 (4.1-17.4)	9.1 (6.5-12.3)
Estimate at 24 months (95% CI), %	49 (37-60)	30 (19-41)	40 (36-43)	36 (28-44)	40 (37-43)
Median OS (95% CI, mo)	24.7 (16.0-NE)	30.4 (9.4-NE)	25.7 (20.7-31.3)	19.3 (13.6-29.3)	26.0 (21.0-31.4)
Estimate at 24 months (95% CI), %	51 (39-62)	55 (43-66)	51 (47-54)	44 (35-52)	51 (48-55)

[a] Subsequent cellular therapy/HCT were censored.

CR, complete response; DOR, duration of response; HCT, hematopoietic cell transplantation; NE, not evaluable; PFS, progression-free survival; ORR, overall response rate; OS, overall survival.

Supplemental Table 4. Sensitivity Analysis of Responses by Race and Ethnicity as Separate Variables in Clinical Trials

n (%)	Asian	Black or African American	white	Hispanic or Latino	Not Hispanic or Latino
ZUMA-1	n=3	n=4	n=87	n=18	n=83
ORR, n (%)	2 (67)	4 (100)	64 (74)	14 (78)	61 (73)
CR	2 (67)	4 (100)	47 (54)	8 (44)	47 (57)
ZUMA-7	n=12	n=11	n=145	n=10	n=167
ORR, n (%)	10 (83)	9 (82)	120 (83)	8 (80)	139 (83)
CR	7 (58)	8 (73)	94 (65)	5 (50)	109 (65)

CR, complete response; ORR, overall response rate.

Supplemental Table 5. Safety Outcomes by Race and Ethnicity as Separate Variables in the Real World

n (%)	Asian (n=79)	Black or African American (n=70)	white (n=1097)	Hispanic or Latino (n=152)	Not Hispanic or Latino (n=1138)
Any-grade CRS	71 (90)	58 (83)	904 (82)	123 (81)	950 (83)
Grade ≥3 CRS	8 (10)	4 (6)	94 (9)	7 (5)	101 (9)
Any-grade ICANS	35 (44)	29 (41)	633 (58)	65 (43)	646 (57)
Grade ≥3 ICANS	16 (20)	14 (20)	306 (28)	24 (16)	314 (28)
Management of CRS and/or ICANS					
Tocilizumab	55 (70)	40 (57)	629 (57)	94 (62)	663 (58)
Corticosteroids	42 (53)	21 (30)	547 (50)	55 (36)	570 (50)
Prolonged cytopenia[a]	25 (35) (n=71)	13 (19) (n=68)	262 (25) (n=1058)	37 (25) (n=148)	272 (25) (n=1093)
Neutropenia	5 (7)	3 (4)	74 (7)	11 (7)	75 (7)
Thrombocytopenia	23 (32)	11 (16)	242 (23)	35 (24)	249 (23)

CRS was graded per Lee et al[6] and ICANS were graded per ASTCT consensus grading.[7]

[a] Defined as failure to resolve within the first 30 days after infusion, measured among patients who survived day 30 post-infusion.

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

Supplemental Table 6. Sensitivity Analysis of Safety Outcomes by Race and Ethnicity as Separate Variables in Clinical Trials

n (%)	Asian	Black or African American	white	Hispanic or Latino	Not Hispanic or Latino
ZUMA-1	**n=3**	**n=5**	**n=92**	**n=19**	**n=89**
Any-grade CRS	2 (67)	5 (100)	86 (93)	18 (95)	82 (92)
Grade ≥3 CRS	0	2 (40)	10 (11)	0	12 (13)
Any-grade NEs	1 (33)	4 (80)	64 (70)	9 (47)	63 (71)
Grade ≥3 NEs	0	3 (60)	29 (32)	4 (21)	31 (35)
ZUMA-7	**n=11**	**n=9**	**n=138**	**n=8**	**n=159**
Any-grade CRS	11 (100)	8 (89)	127 (92)	8 (100)	146 (92)
Grade ≥3 CRS	1 (9)	0	7 (5)	1 (13)	9 (6)
Any-grade NEs	5 (45)	5 (56)	83 (60)	8 (100)	92 (58)
Grade ≥3 NEs	2 (18)	3 (33)	28 (20)	2 (25)	33 (21)

CRS was graded per Lee et al[6,7] and NEs were graded per ASTCT consensus grading.[7]

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; NE, neurologic event.

Supplemental Table 7. Univariate OR/HR for Real-World Efficacy and Safety Outcomes

Est (95% CI)	NHB vs NHW	NHA vs NHW	Hispanic vs NHW	NHB vs NHA	NHB vs Hispanic	NHA vs Hispanic
ORR	0.40[a] (0.24-0.66)	0.81 (0.48-1.36)	0.89 (0.60-1.31)	0.49[a] (0.24-0.98)	0.45[a] (0.24-0.82)	0.91 (0.50-1.69)
CR	0.57[a] (0.35-0.95)	0.95 (0.59-1.52)	0.89 (0.63-1.26)	0.61 (0.31-1.18)	0.65 (0.36-1.16)	1.07 (0.61-1.86)
DOR	1.03 (0.65-1.63)	0.56[a] (0.34-0.94)	0.97 (0.71-1.32)	1.83 (0.93-3.60)	1.06 (0.62-1.82)	0.58 (0.32-1.05)
PFS	1.36[a] (1.01-1.83)	0.86 (0.61-1.20)	1.10 (0.88-1.37)	1.58[a] (1.03-2.45)	1.24 (0.87-1.77)	0.78 (0.53-1.15)
OS	1.07 (0.75-1.52)	0.99 (0.70-1.39)	1.10 (0.87-1.40)	1.08 (0.67-1.74)	0.97 (0.65-1.45)	0.90 (0.60-1.33)
CRS (any grade)	0.95 (0.50-1.81)	1.78 (0.84-3.78)	0.86 (0.56-1.34)	0.53 (0.20-1.39)	1.10 (0.52-2.31)	2.06 (0.89-4.76)
CRS (grade ≥3)	0.63 (0.23-1.78)	1.16 (0.54-2.49)	0.49 (0.22-1.08)	0.55 (0.16-1.90)	1.29 (0.37-4.58)	2.37 (0.83-6.79)
ICANS (any grade)	0.46[a] (0.28-0.76)	0.57* (0.36-0.90)	0.52[a] (0.37-0.74)	0.81 (0.42-1.56)	0.88 (0.49-1.58)	1.09 (0.63-1.89)
ICANS (grade ≥3)	0.59 (0.32-1.09)	0.64 (0.36-1.13)	0.46[a] (0.29-0.72)	0.92 (0.40-2.08)	1.28 (0.61-2.71)	1.40 (0.69-2.82)
Prolonged neutropenia	0.63 (0.19-2.06)	1.03 (0.40-2.66)	1.06 (0.55-2.06)	0.61 (0.14-2.66)	0.59 (0.16-2.20)	0.97 (0.32-2.92)

Prolonged thrombocytopenia	0.69 (0.35-1.34)	1.76[a] (1.04-2.97)	1.07 (0.71-1.60)	0.39[a] (0.17-0.89)	0.65 (0.30-1.37)	1.65 (0.88-3.10)

[a] Variables with univariate P<.05.

CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; HR, hazard ratio; ICANS, immune effector cell-associated neurotoxicity syndrome; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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