Abstract
P7509

Real-World Early Outcomes of Axicabtagene Ciloleucel for Relapsed or Refractory Follicular Lymphoma

Caron A. Jacobson, MD, MMSc[1,a,b]; Michael T. Hemmer, MS[2,b]; Zhen-Huan Hu, MPH[2]; Matthew Joshua Frank, MD[3]; Leslie Popplewell, MD[4]; Nausheen Ahmed, MD[5]; Yi Lin, MD, PhD[6]; Timothy Best, PhD[2]; Sara Beygi, MD[2]; Harry H. Miao, MD, PhD[2]; Christine Fu, PhD[2]; Fang Sun, MD, PhD[2]; Hairong Xu, MD, PhD[2]; Marcelo C. Pasquini, MD, MS[7]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Kite, a Gilead Company, Santa Monica, CA, USA; [3]Stanford University School of Medicine, Stanford, CA, USA; [4]City of Hope National Medical Center, Duarte, CA, USA; [5]The University of Kansas Medical Center, Westwood, KS, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

[a]Presenting author
[b]Co-primary authors contributed equally to this work

BACKGROUND

- Axicabtagene ciloleucel (axi-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, which includes a CD28 costimulatory domain to elicit rapid and robust expansion, that results in target-specific cytotoxicity and helps to overcome the limitations of the immune system[1,2]
- In the United States, axi-cel is approved for the treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) after ≥2 lines of systemic therapy based on the outcomes from the pivotal ZUMA-5 study[1]
- ZUMA-5 is a multicenter, single-arm, phase 2 trial of axi-cel in patients with R/R indolent non-Hodgkin lymphoma including FL and marginal zone lymphoma[3]
  - In the primary analysis of the ZUMA-5 trial, 94% of patients who received axi-cel to treat R/R FL achieved an overall response with a 79% complete response (CR) rate[3]
  - Grade ≥3 cytokine release syndrome (CRS) occurred in 6% of patients[3]
  - Grade ≥3 neurologic events occurred in 15% of patients[3]
- In the real world, patients receiving axi-cel for R/R FL may have broader demographics, disease characteristics, and comorbidities that would otherwise have made them ineligible for the ZUMA-5 trial
- The post-authorization safety study (PASS) of axi-cel aims to enroll 300 patients with R/R FL for long-term follow-up of 15 years
- Here, we present the first report of real-world safety and effectiveness outcomes of patients from the PASS receiving axi-cel for R/R FL, including those who would have been ineligible for ZUMA-5

OBJECTIVE

- To describe the early effectiveness and safety outcomes of axi-cel for the treatment of patients with R/R FL in the real-world setting, including outcomes in the elderly (aged ≥65 years) and those who would have been ineligible for ZUMA-5

METHODS

Eligibility

- Patients treated with commercial axi-cel for R/R FL between March 2021 and September 2022, with informed consent and enrolled in the PASS, were eligible

Key exclusion criteria for the analysis set

- Receiving axi-cel in a clinical trial or other noncommercial setting
- FL grade 3B or 3A/3B unspecified or other B-cell malignancies
- Received prior nontransplant cellular therapy (including prior CAR T-cell therapy)
- Follow-up not due or not reported

Endpoints of interest

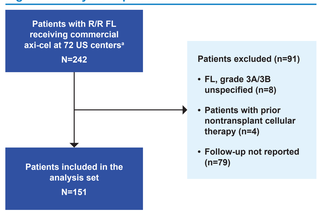
- **Effectiveness:** Overall response rate per investigator (defined as CR or partial response [PR]), CR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
- **Safety:** CRS (graded per American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading[a]), immune effector cell-associated neurotoxicity syndrome (ICANS; graded per ASTCT consensus grading[a]), and prolonged cytopenias (including neutropenia and thrombocytopenia)

Statistical methods

- Percentages and 95% Clopper-Pearson exact CIs were calculated for dichotomous outcomes
- DOR, PFS, and OS were described using the Kaplan-Meier estimator
- Time to resolutions of CRS and ICANS were estimated by cumulative incidence functions

RESULTS

Figure 1. Analysis Population



[a] Identified from the CIBMTR registry.
Axi-cel, axicabtagene ciloleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; FL, follicular lymphoma; R/R, relapsed or refractory; US, United States.

- Data cutoff date: September 23, 2022
- Median follow-up: 6.2 months (95% CI, 6.0-6.3)

RESULTS *(continued)*

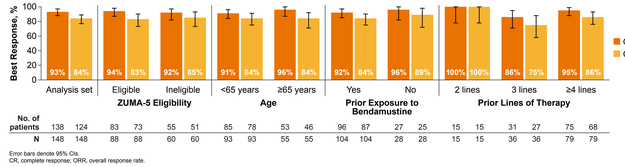
Table 1. Baseline Characteristics for Analysis Set, by ZUMA-5 Eligibility, and by Age

Key Variable of Interest	Enrolled Patients in Analysis Set N=151	ZUMA-5 Eligibility[a]		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Median age (IQR), years	61 (55-68)	60 (54-68)	62 (55-69)	57 (51-61)*	70 (68-74)*
Age ≥65 years, n (%)	56 (37)	33 (37)	23 (38)	0	56 (100)
Male sex, n (%)	94 (62)	50 (56)*	44 (72)*	66 (69)*	28 (50)*
White race, n (%)	132 (87)	80 (89)	52 (85)	82 (86)	50 (89)
Hispanic ethnicity, n (%)	12 (8)	8 (9)	4 (7)	8 (9)	4 (7)
ECOG PS 0-1 at infusion,[b] n (%)	143 (98)	87 (100)	56 (95)	88 (97)	55 (100)
Clinically significant comorbidities,[c] n (%)	113 (75)	56 (62)*	57 (93)*	69 (73)	44 (79)
Disease stage at diagnosis[d]: III-IV, n (%)	79 (76)	46 (78)	33 (73)	57 (78)	22 (71)
Median no. of lines of prior therapies (IQR)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)
Prior bendamustine[e], n (%)	107 (79)	62 (78)	45 (80)	69 (79)	38 (79)
Prior ASCT, n (%)	20 (13)	12 (13)	8 (13)	16 (17)	4 (7)
Elevated LDH prior to infusion,[f] n (%)	26 (28)	15 (26)	11 (32)	15 (26)	11 (32)
PR/SD/PD to last line of therapy before leukapheresis,[g] n (%)	97 (64)	53 (59)*	44 (72)*	63 (66)	34 (61)
Chemoresistant prior to infusion,[f] n (%)	101 (80)	61 (82)	40 (77)	65 (78)	36 (84)
Median time from last line of therapy to infusion (IQR), months	7.1 (3.0-19.3)	7.9 (3.1-20.0)	5.8 (3.0-18.8)	5.6 (2.7-11.1)*	13.7 (4.6-25.7)*
Median time from leukapheresis to infusion (IQR), days	28 (26-33)	28 (26-32)	28 (26-35)	28 (26-33)	28 (26-33)
Bridging therapy[i]: any type / systemic / radiation, n (%)	12 (9) / 10 (8) / 2 (2)	6 (8) / 5 (6) / 1 (1)	6 (11) / 5 (9) / 1 (2)	7 (8) / 7 (8) / 0	5 (10) / 3 (6) / 2 (4)
Outpatient, n (%)	22 (15)	16 (18)	6 (10)	13 (14)	9 (16)

[a] Reasons for ZUMA-5 ineligibility are not mutually exclusive. [b] The remaining 2% pertain to patients with an ECOG PS >1 or missing information. [c] Comorbidities were defined per the HCT-CI and included a body mass index <20.1 [d] Forty-seven patients did not report disease stage at initial diagnosis. [e] Sixteen patients did not report prior bendamustine exposure. [f] Elevated LDH is defined as above the upper limit of normal. [g] Fifty-nine patients did not report LDH prior to infusion. [h] Thirty-seven patients did not report best response to last line of therapy before leukapheresis. [i] Chemoresistance is defined as patients who had SD or PD prior to infusion. Twenty-five patients did not report chemoresistant status prior to infusion. * Nineteen patients did not report the presence or absence of bridging therapy.
*P<0.05 per Fisher's exact test.
ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT-CI, hematopoietic cell transplantation-specified comorbidity index; IQR, interquartile range; LDH, lactate dehydrogenase; PD, progressive disease; PR, partial response; SD, stable disease.

- Of 151 patients enrolled in the analysis set, 61 (40%) would have been considered ineligible for ZUMA-5 (**Table 1**)
  - Reasons for ineligibility included comorbidities (70%), history of prior malignancy (18%), platelet count <75,000/μL (15%), pleura extranodal involvement (15%), cerebrovascular disease (11%), and Eastern Cooperative Oncology Group performance status ≥2 (5%)

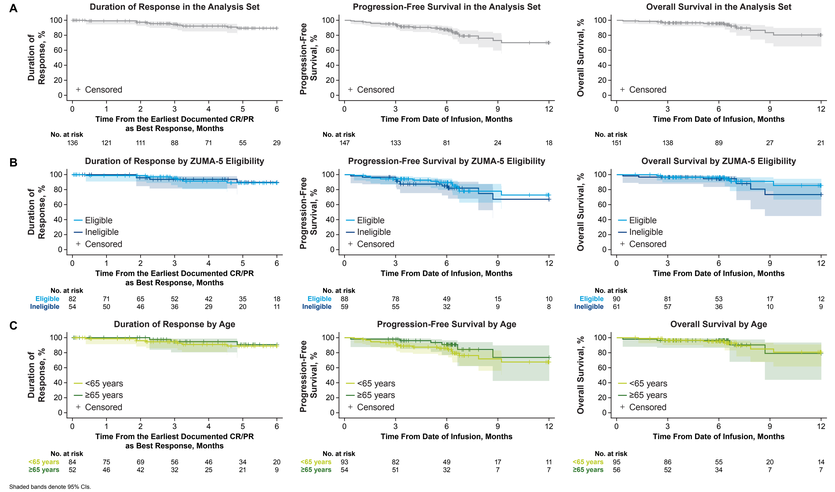
Figure 2. Overall Response in the Analysis Set, by ZUMA-5 Eligibility, by Age, by Prior Exposure to Bendamustine, and by Prior Lines of Therapy



Error bars denote 95% CIs.
CR, complete response; ORR, overall response rate.

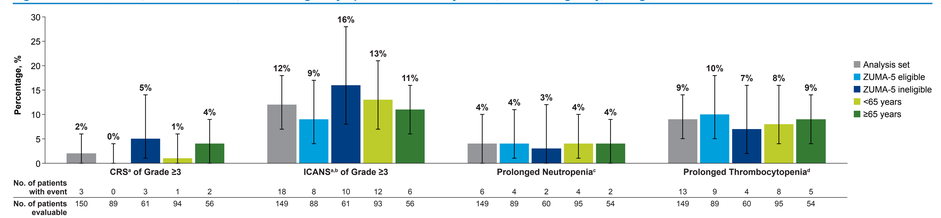
- Among 148 patients evaluable for response, for whom the median follow-up was 6.2 months, **138 (93%; 95% CI, 88-97) had an overall response, with 124 patients (84%; 95% CI, 77-89) achieving a CR (Figure 2)**
- Overall response was comparable regardless of ZUMA-5 eligibility, age, prior exposure to bendamustine, and prior lines of therapy

Figure 3. Duration of Response, Progression-Free Survival, and Overall Survival in (A) the Analysis Set, (B) by ZUMA-5 Eligibility, and (C) by Age



Shaded bands denote 95% CIs.

Figure 4. Grade ≥3 CRS, Grade ≥3 ICANS, and Prolonged Cytopenias in the Analysis Set, ZUMA-5 Eligibility, and Age



[a] CRS and ICANS were graded per ASTCT consensus criteria.[1] [b] Among patients who developed any-grade ICANS by Day 100. [c] Prolonged neutropenia is defined as failure to recover ANC ≥500/mm³ and/or sustain 3 lab values within the first 30 days after infusion. [d] Prolonged thrombocytopenia is defined as failure to recover platelet count ≥20×10⁹/L within the first 30 days after infusion.
ANC, absolute neutrophil count; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

- Any-grade CRS occurred in 79% of ZUMA-5 eligible and 64% of ineligible patients; 74% of patients <65 years and 70% of patients ≥65 years experienced any-grade CRS (**Table 2**)
- Any-grade ICANS was observed in 43% of eligible and 33% of ineligible patients for ZUMA-5; any-grade ICANS was observed in 35% of patients <65 years of age and 45% of patients ≥65 years of age (**Table 2**)

Table 2. CRS and ICANS by ZUMA-5 Eligibility and Age

Parameter	All Patients (N=151)	ZUMA-5 Eligibility		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Any-grade CRS,[a] n (%)	109 (73)	70 (79)	39 (64)	70 (74)	39 (70)
Median time from infusion to CRS, any grade, days (range)	5 (1-15)	6 (2-12)	5 (1-15)	5 (1-12)	6 (2-15)
Corticosteroids to treat CRS[b]	43 (39)	26 (37)	17 (44)	23 (33)	20 (51)
Tocilizumab use to treat CRS[b]	84 (77)	53 (76)	31 (79)	52 (74)	32 (82)
Any-grade ICANS,[a] n (%)	58 (39)	38 (43)	20 (33)	33 (35)	25 (45)
Median time from infusion to ICANS, any grade, days (range)	8 (2-19)	8 (2-16)	8 (6-19)	8 (3-16)	8 (2-19)
Corticosteroids use to treat ICANS[b]	48 (83)	33 (87)	15 (75)	26 (79)	22 (88)
Tocilizumab use to treat ICANS[b]	7 (12)	2 (5)	5 (25)	5 (15)	2 (8)

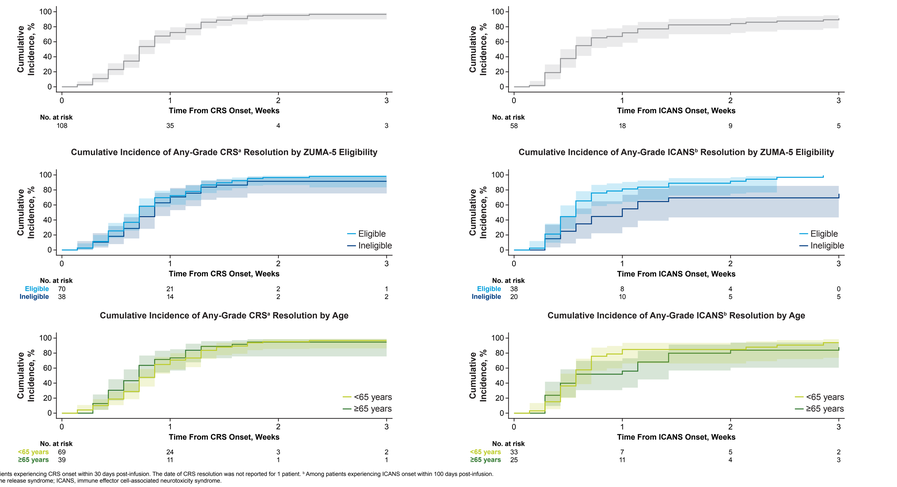
[a] CRS and ICANS were graded per ASTCT consensus criteria.[1] [b] Among patients who developed any-grade CRS/ICANS by Day 100.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

Table 3. Other Treatment-Emergent Adverse Events of Interest by ZUMA-5 Eligibility and Age

Parameter	Enrolled Patients in the Analysis Set (N=151)	ZUMA-5 Eligibility		Age	
		Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Clinically significant infection,[a] n (%)	51 (34)	29 (32)	22 (36)	35 (37)	16 (29)
Bacterial	19 (13)	13 (14)	6 (10)	11 (12)	8 (14)
Fungal	2 (1)	0	2 (3)	1 (1)	1 (2)
Viral	38 (25)	17 (19)	21 (34)	28 (29)	10 (18)
Subsequent neoplasms,[b] n (%)	3 (2)	1 (1)	2 (3)	3 (3)	0
Deaths, n (%)	12 (8)	6 (7)	6 (10)	8 (8)	4 (7)
Primary disease	3 (2)	2 (2)	1 (2)	3 (3)	0
CRS	2 (1)	0	2 (3)	1 (1)	1 (2)
COVID-19	4 (3)	3 (3)	1 (2)	3 (3)	1 (2)
Organ failure[c]	2 (1)	1 (1)	1 (2)	0	2 (4)
Prior malignancy	1 (1)	0	1 (2)	1 (1)	0

[a] Clinically significant infection is defined as any infection diagnosed after the date of infusion that requires treatment. However, the following were not considered as events: culture-negative neutropenic fever without clear source; upper respiratory infections that are presumed viral, but no virus has been identified; candida detected in oral or stool samples (including oral thrush); toenail fungus; yeast infection in the groin, vagina, or under the breasts; surveillance cultures in which normal flora is present and the recipient is asymptomatic; infections persisting from a prior reporting period (including infections that have progressed to new sites since the last report); or certain bacterial, viral, and/or fungal infections recurring within prespecified time frames. [b] Subsequent neoplasms were basal cell skin malignancy (n=1), basal cell skin malignancy + melanoma + squamous cell skin malignancy (n=1), and myelodysplasia (n=1). [c] One patient died due to renal failure and the other patient died due to multiple organ failure.
CRS, cytokine release syndrome.

Figure 5: Cumulative Incidence Rate of CRS Resolution and ICANS Resolution in (A) the Analysis Set, (B) by ZUMA-5 Eligibility, and (C) by Age



[a] Among patients experiencing CRS onset within 30 days post-infusion. The date of CRS resolution was not reported for 1 patient. [b] Among patients experiencing ICANS onset within 100 days post-infusion.
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

CONCLUSIONS

- Among the 151 patients with R/R FL treated with axi-cel in the real-world setting, 61 (40%) had a broad range of demographics, disease characteristics, and treatment history that could have made them ineligible for enrollment in the ZUMA-5 trial[3]
  - The most common reasons for ZUMA-5 ineligibility were comorbidities
- Despite the broader patient population in the real-world setting, axi-cel demonstrated high effectiveness and a manageable safety profile that were comparable with outcomes from ZUMA-5[3]
  - Outcomes were comparable regardless of ZUMA-5 eligibility, age, prior exposure to bendamustine, and prior lines of therapy
- Future work will assess real-world outcomes with a longer follow-up and in a larger patient population
- Overall, findings from the real-world setting support broader use of axi-cel to treat R/R FL

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ACKNOWLEDGMENTS

- The patients, families, friends, and caregivers
- The study investigators, coordinators, and healthcare staff at each study site
- Medical writing support was provided by Laura S. Moye, PhD, of 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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Presented at the 2023 American Society of Clinical Oncology Annual Meeting