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

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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
- relapsed or refractory (R/R) follicular lymphoma (FL) after ≥2 lines of systemic therapy based on the outcomes from the pivotal ZUMA-5 study¹
- 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
- 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) rate³
- Grade ≥3 cytokine release syndrome (CRS) occurred in 6% of patients³ Grade ≥3 neurologic events occurred in 15% of patients³
- 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,

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
- Follow-up not due or not reported

Endpoints of interest

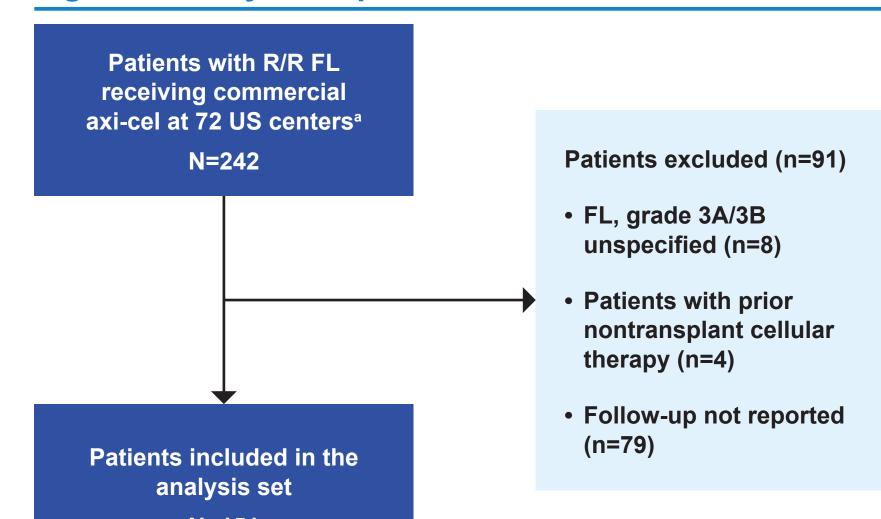
- Effectiveness: Overall response rate per investigator (defined as CR or partial response [PR]), CR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS)
- Safety: CRS (graded per American Society for Transplantation and Cellular Therapy [ASTCT] consensus grading⁴), immune effector cell-associated neurotoxicity syndrome (ICANS; graded per ASTCT consensus grading4), and prolonged cytopenias (including neutropenia and thrombocytopenia)

Statistical methods

- Percentages and 95% Clopper-Pearson exact Cls 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



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)

Error bars denote 95% Cls.

Shaded bands denote 95% C

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

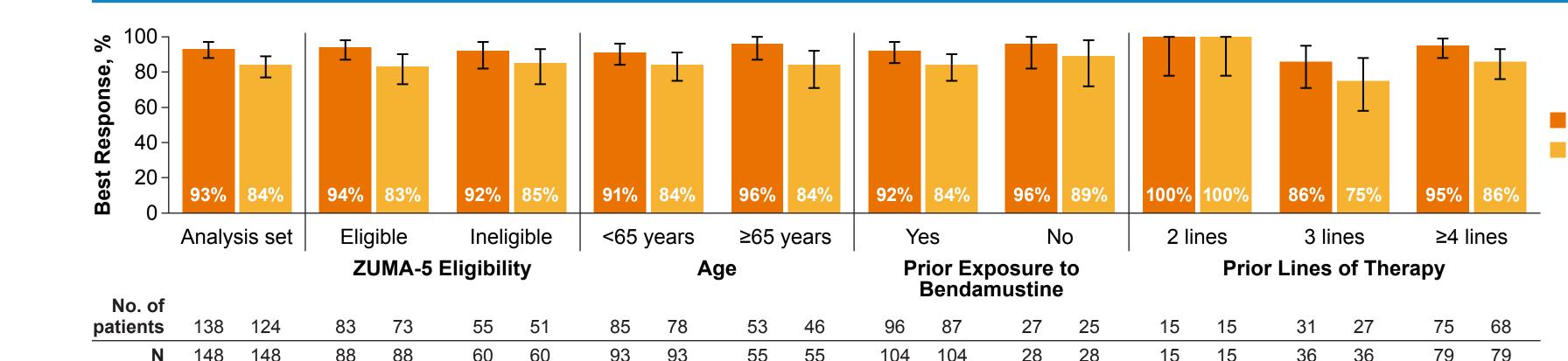
Key Variable of Interest	Enrolled Patients	ZUMA-5 Eligibility ^a		Age	
	in Analysis Set N=151	Eligible n=90	Ineligible n=61	<65 years n=95	≥65 years n=56
Median age (IQR), years	61 (55-68)	60 (54-68)	62 (55-69)	57 (51-61)*	70 (68-74)*
Age ≥65 years, n (%)	56 (37)	33 (37)	23 (38)	0	56 (100)
Male sex, 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,g} n (%)	26 (28)	15 (26)	11 (32)	15 (26)	11 (32)
PR/SD/PD to last line of therapy before leukapheresis, ^h n (%)	97 (64)	53 (59)*	44 (72)*	63 (66)	34 (61)
Chemoresistant prior to infusion, 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 ^j : 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-Cl and included a body mass index <20.5 d Forty-seven patients did not report disease stage at initial diagnosis. ^c Sixteen patients did not report prior bendamustine exposure. Elevated LDH is defined as above the upper limit of normal. Fifty-nine patients did not report best response to last line of therapy before leukapheresis. Chemoresistance is defined as patients who had SD or PD prior to

- 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%)

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.

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



- 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

Among 148 patients evaluable for

CR, complete response; ORR, overall response rate.

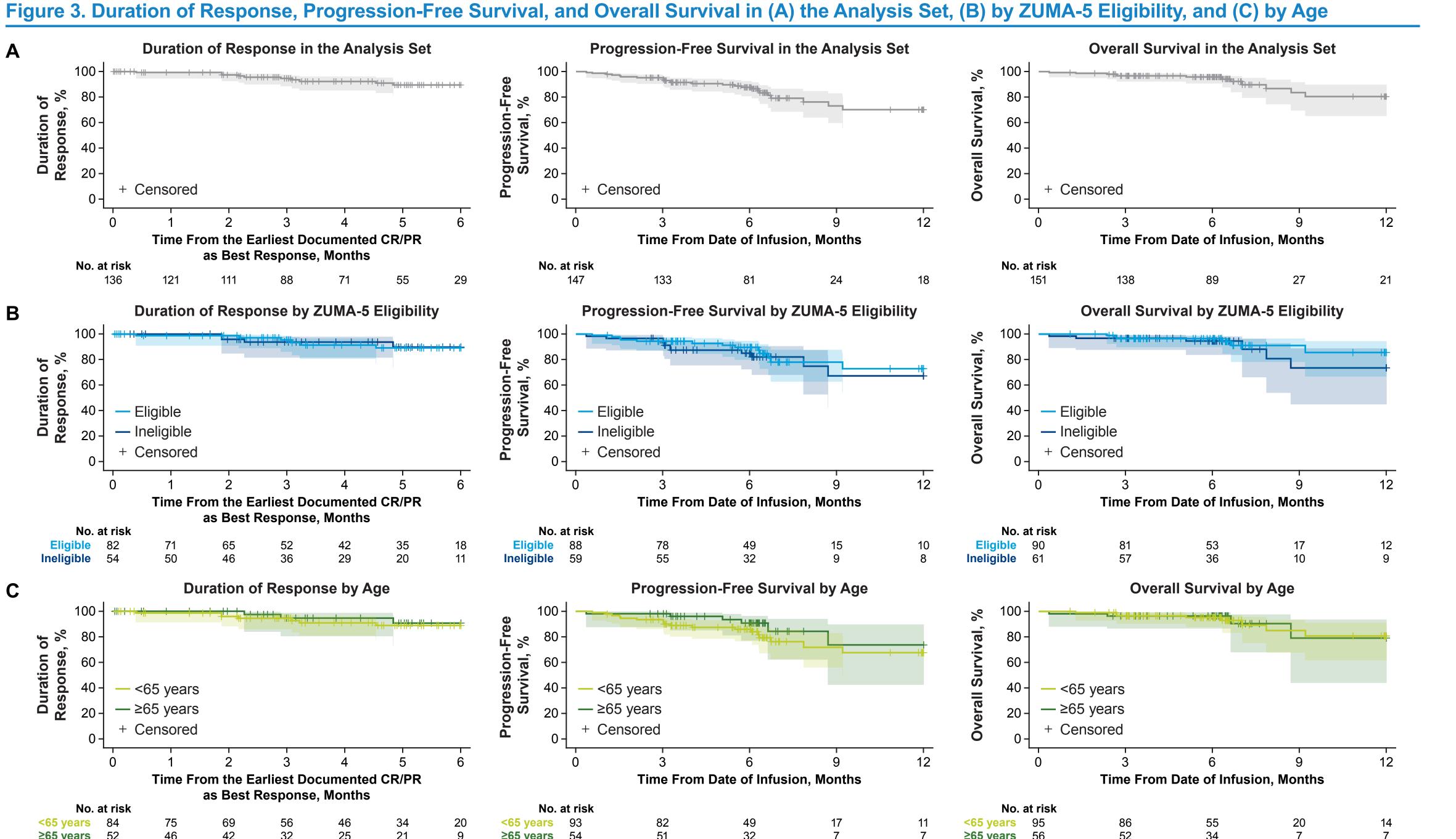
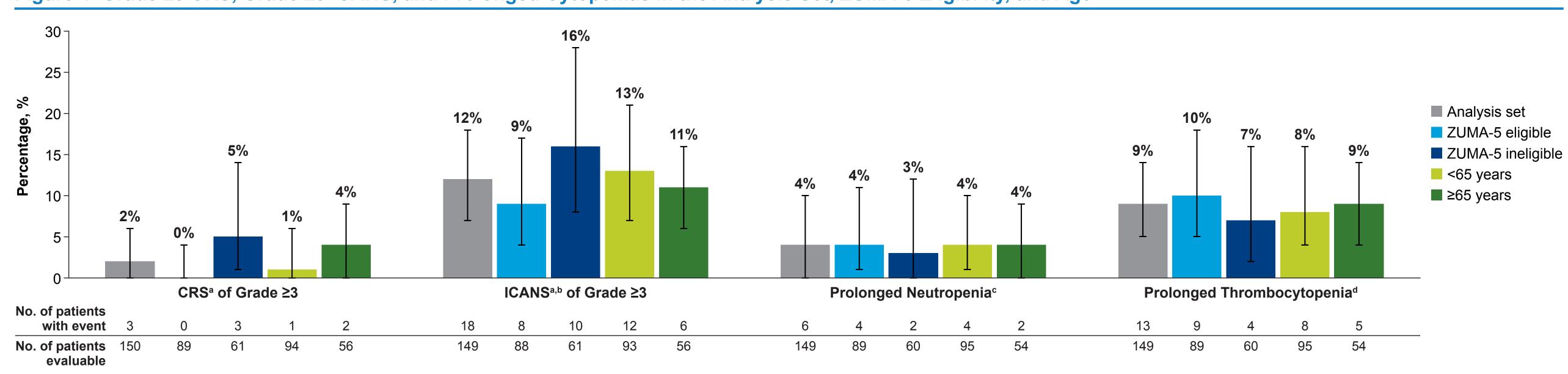


Figure 4. Grade ≥3 CRS, Grade ≥3 ICANS, and Prolonged Cytopenias in the Analysis Set, ZUMA-5 Eligibility, and Age



- 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

		ZUMA-5 Eligibility		Age	
Parameter	All Patients (N=151)	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 CRSb	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.⁵ 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.

a Among patients experiencing CRS onset within 30 days post-infusion. The date of CRS resolution was not reported for 1 patient. Among patients experiencing ICANS onset within 100 days post-infusion

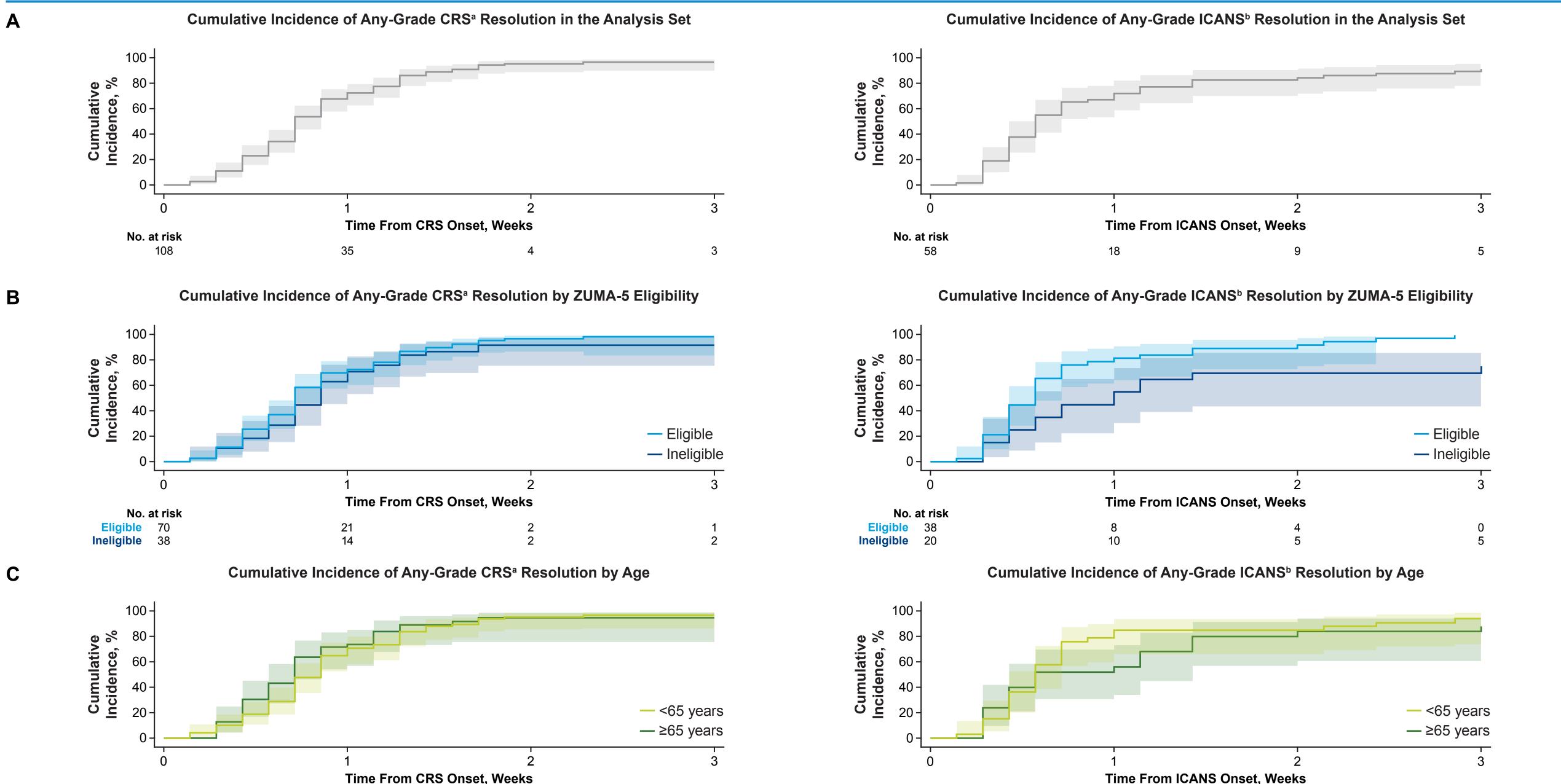
Table 3. Other Treatment-Emergent Adverse Events of Interest by ZUMA-5

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

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 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 ingal 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.

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:

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



<65 years 33

≥65 years

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 trial³
- 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-5³
- 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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<65 years 69

≥65 years 39

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome