Five-Year Follow-Up of Standard-of-Care Axicabtagene Ciloleucel for Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

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ABSTRACT

PURPOSE Axicabtagene ciloleucel (axi-cel) is an autologous CD19 chimeric antigen receptor (CAR) T-cell therapy that is approved for the treatment of relapsed or refractory large B-cell lymphoma. Little is known about the long-term survivorship after CAR T-cell therapy.

METHODS We previously reported the results of 298 patients who were leukapheresed with the intent to receive standard-of-care axi-cel (n = 275 infused) after two or more previous lines of therapy at a median follow-up of 12.9 months. Here, we report extended follow-up of this cohort to a median of 58 months, with a focus on late survivorship events.

RESULTS Among axi-cel–infused patients, progression-free survival at 5 years was 29% and overall survival (OS) at 5 years was 40%. The 5-year lymphoma-specific survival was 53% with infrequent late relapses. However, the 5-year nonrelapse mortality (NRM) was 16.2%, with over half of NRM events occurring beyond 2 years. Patients who were 60 years and older had a lower risk of relapse (P = .02), but a higher risk of NRM compared with patients younger than 60 years (NRM odds ratio, 4.5 [95% CI, 2.1 to 10.8]; P < .001). Late NRM was mainly due to infections and subsequent malignant neoplasms (SMNs). In total, SMNs occurred in 24 patients (9%), including therapy-related myeloid neoplasms (n = 15), solid tumors (n = 7), and unrelated lymphoid malignancies (n = 2).

CONCLUSION In the standard-of-care setting, axi-cel exhibits outcomes consistent with those reported in clinical trials, with sustained, durable responses observed at the 5-year time point. However, late infections and the development of SMN are key survivorship issues that reduce long-term survival after CAR T-cell therapy, particularly in the elderly.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

CD19-directed chimeric antigen receptor (CAR) T-cell therapy may generate durable remissions in patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL). Axicabtagene ciloleucel (axi-cel) was initially approved for the standard-of-care treatment of R/R LBCL after two or more previous lines of therapy on the basis of the ZUMA-1 clinical trial.[1,2] The long-term update of ZUMA-1 reported a 5-year progression-free survival (PFS) of 32% and a 5-year overall survival (OS) of 43%.[3] More recently, the ZUMA-7 randomized clinical trial compared axi-cel with standard-of-care chemotherapy and autologous stem-cell transplant (ASCT) in the second line for patients who relapsed within 12 months of upfront therapy.[5] ZUMA-7 met its primary end point of event-free survival favoring axi-cel and also demonstrated an OS benefit.[5,24] Currently, among CD19 CAR T-cell therapies for R/R LBCL, axi-cel and lisocabtagene maraleucel are approved after one or more previous lines, and tisagenlecleucel is approved after two or more previous lines.[6]

CONTEXT

Key Objective
What are the long-term survivorship risks of patients who previously received chimeric antigen receptor (CAR) T-cell therapy for large B-cell lymphoma?

Knowledge Generated
Nonrelapse mortality (NRM) is primarily driven by infections and secondary malignancies. After CAR T-cell therapy, older patients have a lower risk of relapse, but a higher risk of late NRM.

Relevance *(J.W. Friedberg)*
These data demonstrate the need for future studies to better understand NRM risks post CAR T-cell therapy, and evaluate strategies to mitigate these risks.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

Previously, we reported the standard-of-care outcomes of axi-cel in R/R LBCL after two or more previous lines of therapy at a median follow-up of 12.9 months.[7] Despite 43% of patients not meeting ZUMA-1 trial eligibility criteria for comorbidities, initial outcomes were comparable with the ZUMA-1 trial with a 12-month PFS estimate of 45%.

As more patients are treated with CAR T-cell therapies and attain durable remissions, a greater understanding of long-term survivorship is needed. Here, we report the outcomes of our multicenter cohort of standard-of-care axi-cel patients at a median follow-up of 58 months. We report that infections and subsequent malignant neoplasms (SMNs), particularly among the elderly, are the key long-term survivorship issues for axi-cel patients.

METHODS

The US Lymphoma CAR T-cell Consortium of 17 US academic centers previously reported the baseline characteristics and initial outcomes of leukapheresed (N = 298) and axi-cel–infused (n = 275) patients with R/R LBCL after two or more previous lines of therapy.[7] Patients were leukapheresed between November 3, 2017, and September 30, 2018. For the present study, follow-up data were collected up to July 15, 2023. Approval for the study with waivers of informed consent was granted by each institution's institutional review board. Clinical data were collected retrospectively as available at each center. OS and secondary malignancy data were collected in all patients, regardless of lymphoma relapse. Immune reconstitution and infection data were included before lymphoma relapse or diagnosis of myeloid malignancy and excluded thereafter.

Time-to-event analysis was conducted using the Kaplan-Meier method, and median follow-up was calculated using the reverse Kaplan-Meier method. Cumulative incidence of competing risk comparisons was evaluated using Gray's test. For multivariable modeling, logistic regression was conducted by the LASSO method using the GLMNET statistical package. Analyses were conducted in R v4.13.

RESULTS

Best Overall Response and PFS

Appendix Table A1 (online only) reports baseline characteristics of the cohort of 275 patients who received infusion of axi-cel for the standard-of-care treatment of LBCL after two or more previous lines of therapy. The overall response rate was 82%, with best responses as complete response (CR) in 64%, partial response (PR) in 18%, stable disease (SD) in 3%, and progressive disease (PD) in 14%.

At a median follow-up of 58 months from infusion (range, 0.16-68.7), PFS of patients who received axi-cel is shown in Figure 1A, with a median PFS of 8.7 months (95% CI, 5.9 to 16.6). The landmark 1-, 3-, and 5-year PFS was 47.3 (95% CI, 41.3 to 53), 36.1% (95% CI, 30.4 to 41.8), and 28.5% (95% CI, 23.0 to 34.2), respectively. A total of 191 PFS events occurred, with 151 progression events and 40 deaths due to nonrelapse mortality (NRM). Among the 151 lymphoma progression events, 131 (87%) occurred within the first year after axi-cel, 13 (9%) occurred between 1 and 2 years, and seven (5%) occurred beyond 2 years. The latest identified lymphoma progression occurred at 46 months after infusion. The 5-year cumulative risk of relapse was 55.2%. Baseline characteristics associated with PFS on multivariable analysis are reported in Table 1.

PFS based on best overall response is shown in Figure 1D, and patients without a CR had poor outcomes. Responses in the first 6 months after axi-cel infusion and status at last follow-up are represented in Figure 1F. Among patients who

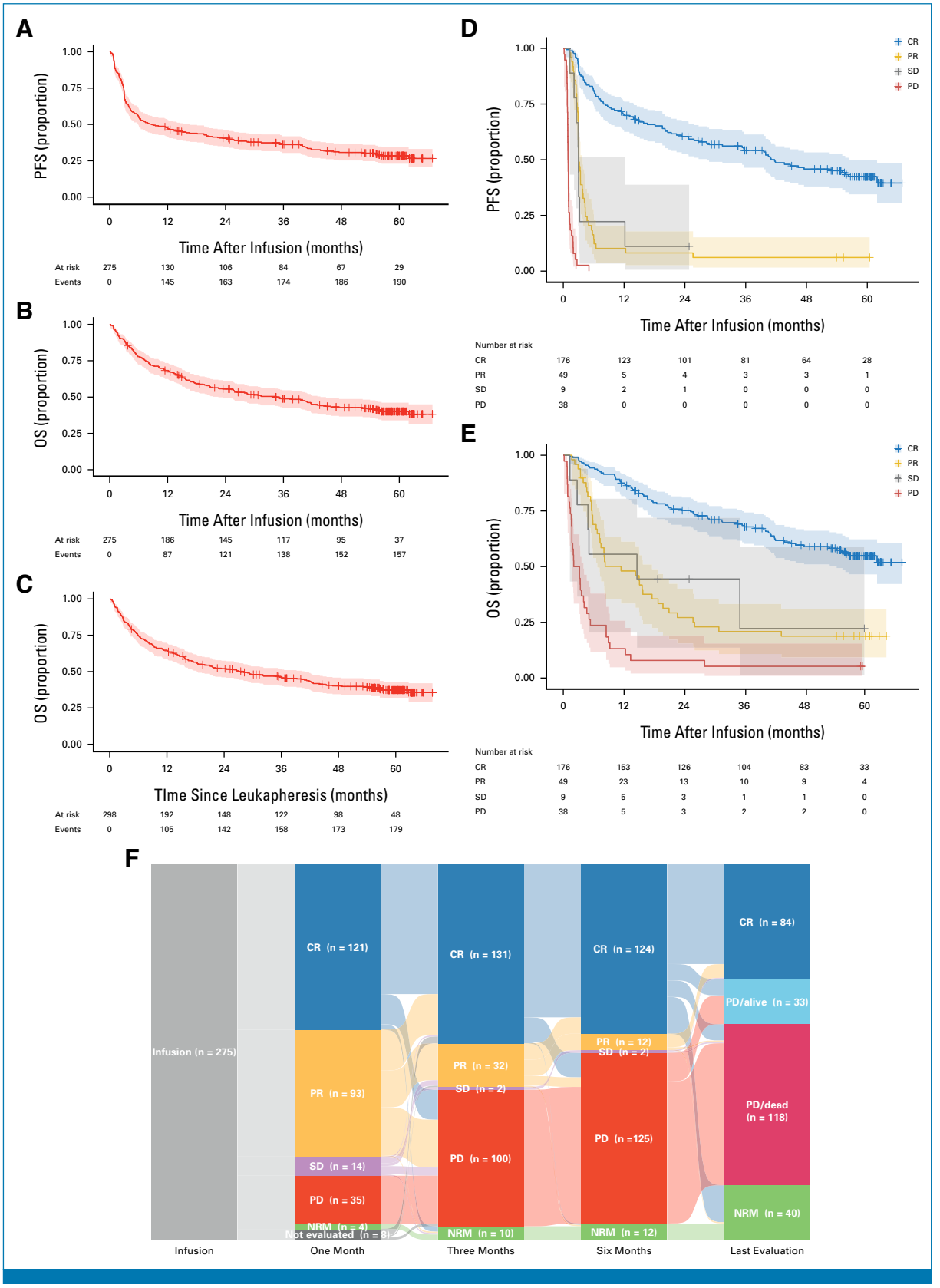

FIG 1. Five-year outcomes following standard-of-care axi-cel for R/R DLBCL after two or more previous lines of therapy. (A) PFS and (B) OS among patients infused with axi-cel (n = 275). (C) OS among patients leukapheresed with intention to treat with axi-cel (N = 298). (D) PFS and (E) OS stratified by best overall response. (F) Visualization of (continued on following page)

FIG 1. (Continued). lymphoma response and clinical outcomes between infusion and last known evaluation. axi-cel, axicabtagene ciloleucel; CR, complete response; DLBCL, diffuse large B cell lymphoma; NRM, nonrelapse mortality; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R/R, relapsed or refractory; SD, stable disease.

were in CR at 3 months, ongoing PFS and OS at last follow-up were 46.6% (95% CI, 36.4 to 54.5) and 61.1% (95% CI, 51.5 to 69.4), respectively. For those in CR at 6 months, ongoing PFS and OS at last follow-up were 54.4% (95% CI, 44.1 to 63.6) and 64.7% (95% CI, 54.3 to 73.3), respectively.

Survival Outcomes and Causes of Death

Among axi-cel–treated patients (n = 275), the median OS was 34.9 months (95% CI, 23.4 to 44.8) with an OS at 1, 3, and 5 years of 68.6% (95% CI, 62.8 to 73.8), 49.1% (95% CI, 42.9 to 54.9), and 40.3% (95% CI, 34.2 to 46.4), respectively (Fig 1B). OS of all leukapheresed patients (N = 298) is shown in Figure 1C. Baseline characteristics associated with OS are reported in Table 1. OS was highest in patients who attained CR, and patients with a best response of PD had dismal survival (Fig 1E).

In the follow-up period of axi-cel–treated patients, 158 deaths occurred, of which 118 deaths were due to lymphoma relapse and 40 deaths were NRM events. Causes of death by year are listed in Table 2, with 21 NRM deaths due to infection, nine due to secondary malignancy, three due to early CAR T-cell–associated toxicities, one due to suicide, and six due to unknown causes in patients who were in remission at last follow-up. Overall, the 5-year NRM was 16.2%, with competing risk of lymphoma relapse shown in Figures 2A and 2B. Although relapse was almost always early after CAR T-cell therapy and rare thereafter, NRM continued to occur over time. Lymphoma-specific survival at 5 years was 53.3%

TABLE 1. Multivariable Analysis of PFS and OS

	OS		PFS	
Characteristic	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex				
Female	—		—	
Male	1.52 (1.05 to 2.20)	.026	1.68 (1.20 to 2.37)	.003
Age, years				
<60	—		—	
≥60	1.03 (0.74 to 1.43)	.9	0.87 (0.65 to 1.18)	.4
LDH ≥ ULN				
Below ULN	—		—	
Above ULN	1.57 (1.10 to 2.25)	.014	1.82 (1.31 to 2.53)	<.001
ECOG				
0-1	—		—	
2-4	2.00 (1.32 to 3.04)	.001	1.93 (1.30 to 2.86)	.001
Bridging therapy				
No	—		—	
Yes	1.25 (0.88 to 1.78)	.2	1.08 (0.78 to 1.49)	.6
Elevated bilirubin (≥1.5 g/dL)				
No	—		—	
Yes	5.61 (2.18 to 14.5)	<.001	3.68 (1.45 to 9.37)	.006
Previous lines of therapy				
<3	—		—	
≥3	1.43 (0.95 to 2.15)	.084	1.49 (1.03 to 2.13)	.032
Disease status at referral				
Relapsed			—	
Primary refractory			1.15 (0.77 to 1.74)	.5
Refractory			1.39 (0.95 to 2.02)	.087

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal for the laboratory.

TABLE 2. Causes of Death by Year After Axi-Cel Infusion

Cause of Death	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6 or Later	Total
Progressive disease	74	28	11	4	1	0	118
Infection	8	2	4	6	1	0	21
Secondary malignancy	0	3	1	3	1	1	9
CAR-T toxicity[a]	3	0	0	0	0	0	3
Unknown/Other[b]	2	1	1	1	2	0	7

NOTE. Infectious causes of death (n = 21) included unclassified infection (n = 6), pneumonia (n = 5), bacterial sepsis (n = 4), COVID-19 disease (n = 2), candidemia (n = 2), candidemia and concomitant pneumocystis jiroveci pneumonia (n = 1), and JC viral encephalitis (n = 1).
Abbreviations: axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; HLH, hemophagocytic lymphohistiocytosis.
[a]Includes HLH, cerebral edema, and intracranial hemorrhage.
[b]Unknown = 6, suicide = 1.

(95% CI, 46.8 to 59.3; Fig 2C), similar to that reported previously for the ZUMA-1 trial (51.1%).[3] On univariable analysis of baseline characteristics, age 60 years and older was associated with NRM (odds ratio, 4.5 [95% CI, 2.1 to 10.9]; $P < .001$). Other baseline factors such as sex, previous lines of therapy, use of bridging therapy, and LDH did not demonstrate an association with NRM (Appendix Table A2). As previously noted by MVA (Table 1), age was not associated with OS, but the finding that older patients had a higher risk of late NRM suggested that the causes of death after CAR T-cell therapy differ by age. Causes of death in patients younger than 60 years (n = 132 patients, 72 deaths) versus those who were 60 years and older (n = 143 patients, 86 deaths) were lymphoma (64 *v* 54 deaths), acute CAR T-cell toxicity (1 *v* 2 deaths), infection (4 *v* 17 deaths), secondary malignancy (3 *v* 6 deaths), and unknown/other (0 *v* 7 deaths). Patients who were 60 years and older had a lower incidence of lymphoma progression ($P = .02$) but a higher risk of NRM ($P < .001$) compared with younger patients (Fig 2D).

Immune Reconstitution and Late Infections

We evaluated immune reconstitution and late infections between 6 months and 2 years after axi-cel in patients whose lymphoma did not relapse at the time of evaluation. This time period was chosen because acute CAR T-cell therapy toxicities resolve by 6 months, whereas patients continue to be closely followed with clinical documentation at the providing centers.

Between 6 and 12 months after axi-cel, infections were reported in 31.2% (34/109) of patients, of whom 17% (18/109) had severe infections, as defined by the need for either hospitalization or IV antibiotics. Between 1 and 2 years after axi-cel, infections were reported in 23.6% (21/89) of patients, of whom 10% (9/89) had severe infections (Fig 3A). Two patients had more than one severe infection event between 6 and 24 months. Of the 21 NRM events that were due to infection, six infection deaths occurred in the first 6 months, four infection deaths occurred between 6 and 24 months, and 11 infection deaths occurred beyond 2 years. Severe infection events between 6 and 24 months, their mortality outcome, and immune status (if known) at the time of the infection event are case-reported in Appendix (Table A3). The majority of cases were respiratory (but not COVID-19 disease, which was infrequent), with pneumonia being the most commonly diagnosed clinical syndrome. Among severe infection events with available data, 5 of 19 reported absolute neutrophil counts below 1,000/μL at the onset of the infection, and 6 of12 reported IgG levels below 400 mg/dL.

Cytopenias were common after CAR T-cell therapy, and typically, neutropenia co-occurred with thrombocytopenia and anemia within the same patient (Fig 3B). Prolonged grade 3 or higher neutropenia (absolute neutrophil count <1,000/μL) occurred at 1 and 2 years in 9.2% and 10%, respectively. Prolonged grade 2 or higher thrombocytopenia (platelet count <75 k/μL) occurred at 1 and 2 years in 9.2% (10/109) and 3.6% (3/84) of patients, respectively. Prolonged grade 2 anemia (hemoglobin <10 g/dL) occurred at 1 and 2 years in 9.2% (10/109) and 6.0% (5/84) of patients, respectively. Compared with pre–CAR T-cell therapy levels, neutrophil counts decreased over time, whereas hemoglobin levels increased, and platelet counts were largely unchanged (Fig 3C). A limited number of centers evaluated CD4 T-cell reconstitution and B-cell aplasia as standard of care after axi-cel. Among patients who did not subsequently relapse, 36% (12/33) of patients had low CD4 counts (≤200/μL) before CAR T-cell therapy, and the rates of poor CD4 reconstitution after CAR T-cell therapy (≤200/μL) were 62% (23/37) and 27% (7/26) at 1 and 2 years (Fig 3D), respectively. Recovery of B cells was observed in 54% (15/28) and 57% (13/23) at 1 and 2 years after infusion (Fig 3E). IgG levels similarly decreased over time (Fig 3F). Among evaluable patients, 45 patients (42%) received IVIG between 6 and 12 months, and 33 patients (38%) received IVIG between 1 and 2 years. Patients who were provided IVIG during this period after CAR T-cell therapy had lower pre–CAR T-cell IgG levels compared with patients who did not receive subsequent IVIG ($P = .033$; Fig 3G).

Figure 3H shows that severe infection events did not typically coincide with the presence of late neutropenia measured

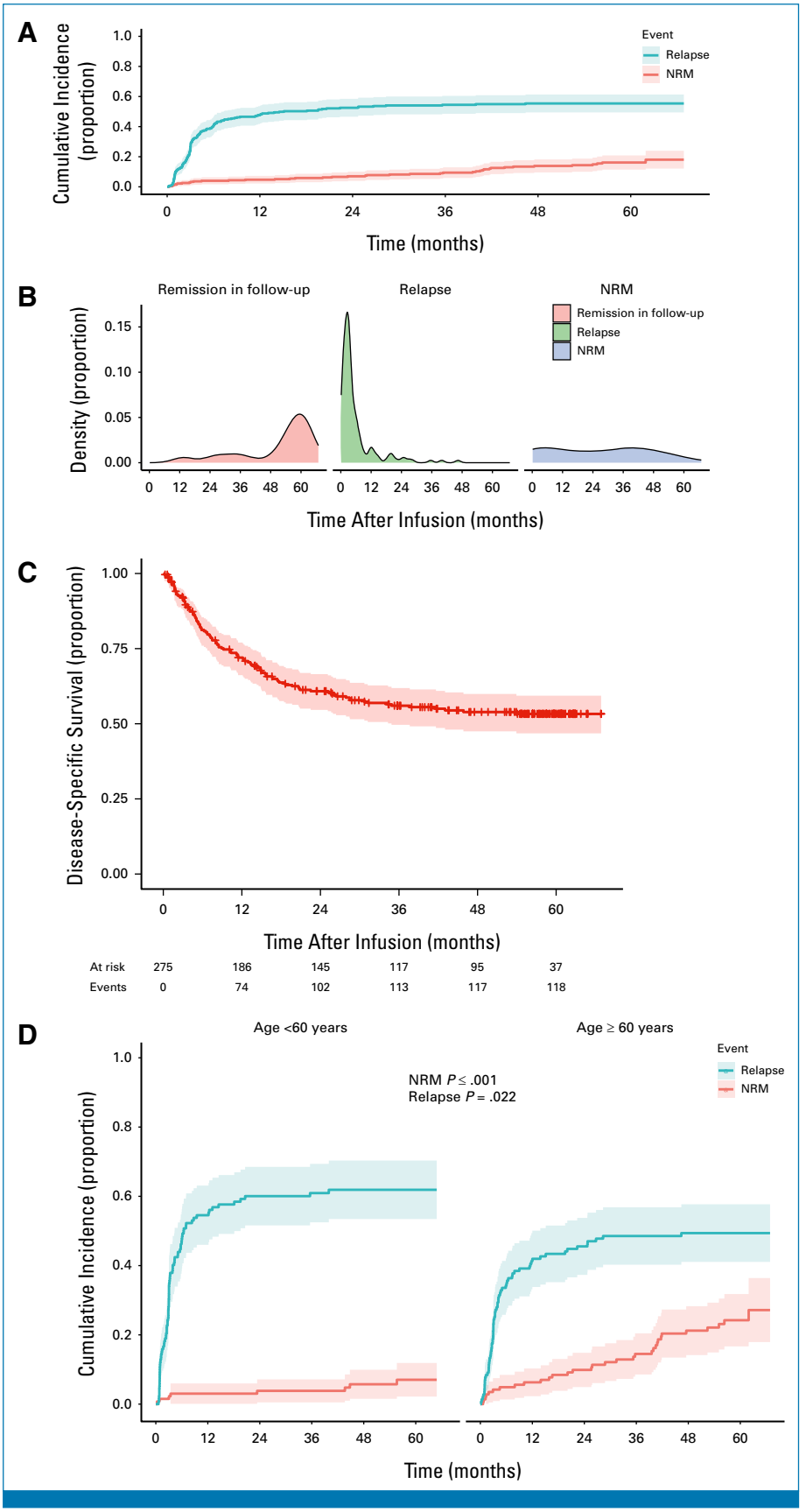

FIG 2. NRM and relapse after standard-of-care axi-cel. (A) Competing-risk curve indicating the cumulative incidence of death due to relapse and NRM over time. (B) Density plot with incidence from time since infusion. Left panel, patients (continued on following page)

FIG 2. (Continued). in remission with last known follow-up indicated. Middle panel, incidence of lymphoma relapse marked at the time of relapse after axi-cel. Right panel, incidence of deaths due to NRM. (C) Disease-specific survival, censoring patients who died of NRM. (D) Competing-risk curves indicating the cumulative incidence of death due to relapse and NRM. Left, age < 60 years at the time of CAR T-cell apheresis. Right, age ≥ 60 years. *P* values using Gray's test comparing patients who were 60 years and older with those younger than 60 years for relapse and NRM. axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; NRM, nonrelapse mortality.

routinely at 1 and 2 years, although as noted in Appendix (Table A3), patients sometimes had suppressed neutrophil counts at the onset of infections. We did not find any association between the development of severe infections between 6 and 24 months with baseline clinical factors (age, sex, or previous therapies) or pre–CAR T-cell immune parameters (hemoglobin, neutrophils, platelets, CD4 counts, or IgG levels). However, as noted previously, deaths due to infection across the entirety of the follow-up period were concentrated among patients who were 60 years and older compared with patients younger than 60 years (17 *v* 4 deaths).

SMNs

Excluding nonmelanoma skin cancers, 24 (9%) of 275 patients were diagnosed with SMN after axi-cel treatment: 15 (5.4%) of 275 patients were diagnosed with therapy-related myeloid malignancies (myelodysplastic syndrome [n = 11], AML [n = 2], chronic myelomonocytic leukemia [n = 1], mast cell leukemia [n = 1]); other malignancies occurred in a single patient each and included anal cancer, prostate cancer, endometrial cancer, lung cancer, metastatic Merkel cell carcinoma, mesothelioma, histiocytic sarcoma, B-cell acute lymphoblastic leukemia, and angioimmunoblastic T-cell lymphoma (AITL). The case of T-cell lymphoma occurred in a patient who had evidence of PD on PET/CT at 17 months after axi-cel infusion while in local care away from the CAR T-cell center. The patient was not biopsied at that time and received lenalidomide and rituximab for over a year until further disease progression was identified. This was biopsied and demonstrated AITL, but tissue samples to test for CAR signatures were not available.

The characteristics of therapy-related myeloid neoplasms (tMN) after CAR T-cell therapy are shown in Table 3. The median time from axi-cel infusion to tMN diagnosis was 16.2 months (IQR, 8.5-29.7). Four of 15 patients with tMN had progression of lymphoma at the time of tMN diagnosis. Patients with tMN had a median age of 62 years at axi-cel apheresis (IQR, 56-70), and 73% were male and had received a median 3.5 lines of previous therapy (IQR, 3-5.5), including one-third with a previous ASCT. Karyotype showed monosomy 7 or complex cytogenetics in most cases, consistent with tMN. Only three of 15 patients underwent allogeneic transplant after the tMN diagnosis, all of whom died. At the time of data cutoff, two of 15 patients with tMN were alive; however, one died shortly thereafter in hospice care.

We performed univariable analysis to identify baseline factors associated with the subsequent development of tMN and did not find an association with age, sex, previous lines of therapy, or previous stem-cell transplant (Appendix Table A4). On evaluation of complete blood count data from the time of apheresis, hemoglobin (P = .039) and platelet counts (P = .004) were lower in patients who went on to develop a tMN compared with patients who did not (Fig 3I).

DISCUSSION

In this study, we report the long-term follow-up of 275 patients infused with standard-of-care axi-cel for R/R LBCL after two or more lines of therapy across 17 US academic centers. The median follow-up was 58 months. Estimates of 5-year OS and PFS are 40% and 29%, respectively. The 5-year disease-specific survival estimate is 53%. These results are similar to the registrational ZUMA-1 clinical trial, which reported 5-year OS and PFS estimates of 43% and 32%, respectively, and a 5-year disease-specific survival estimate of 51%.[3] These similarities are remarkable given that 43% of patients in our cohort would not have met eligibility criteria for trial entry.[7] In our cohort, relapses beyond 1 year were uncommon. However, we report a 5-year NRM of 16%, with over half of the NRM events occurring beyond 2 years, mainly caused by infections and SMNs, and concentrated among patients older than 60 years. These data suggest that the care of CAR T-cell therapy survivors should focus on cancer screening, infection prevention, and principles of geriatric oncology.[8,9]

Cytopenias, B-cell aplasia, and poor CD4 T-cell reconstitution occur in many patients after CAR T-cell therapy.[1,10-13] Here, we found that approximately 10% of patients have significant neutropenia even after 2 years of CAR T-cell infusion. Deaths due to infection continued to contribute to NRM beyond 2 years, particularly among the elderly, highlighting long-term immunosuppression. Approximately 40% of patients were provided IVIG, and additional work is needed to optimize prophylaxis and monitoring. In our cohort, only two patients died of COVID-19 disease; however, all the patients in our cohort were at least 12 months —after axi-cel infusion at the time of the first wave of COVID-19 disease.

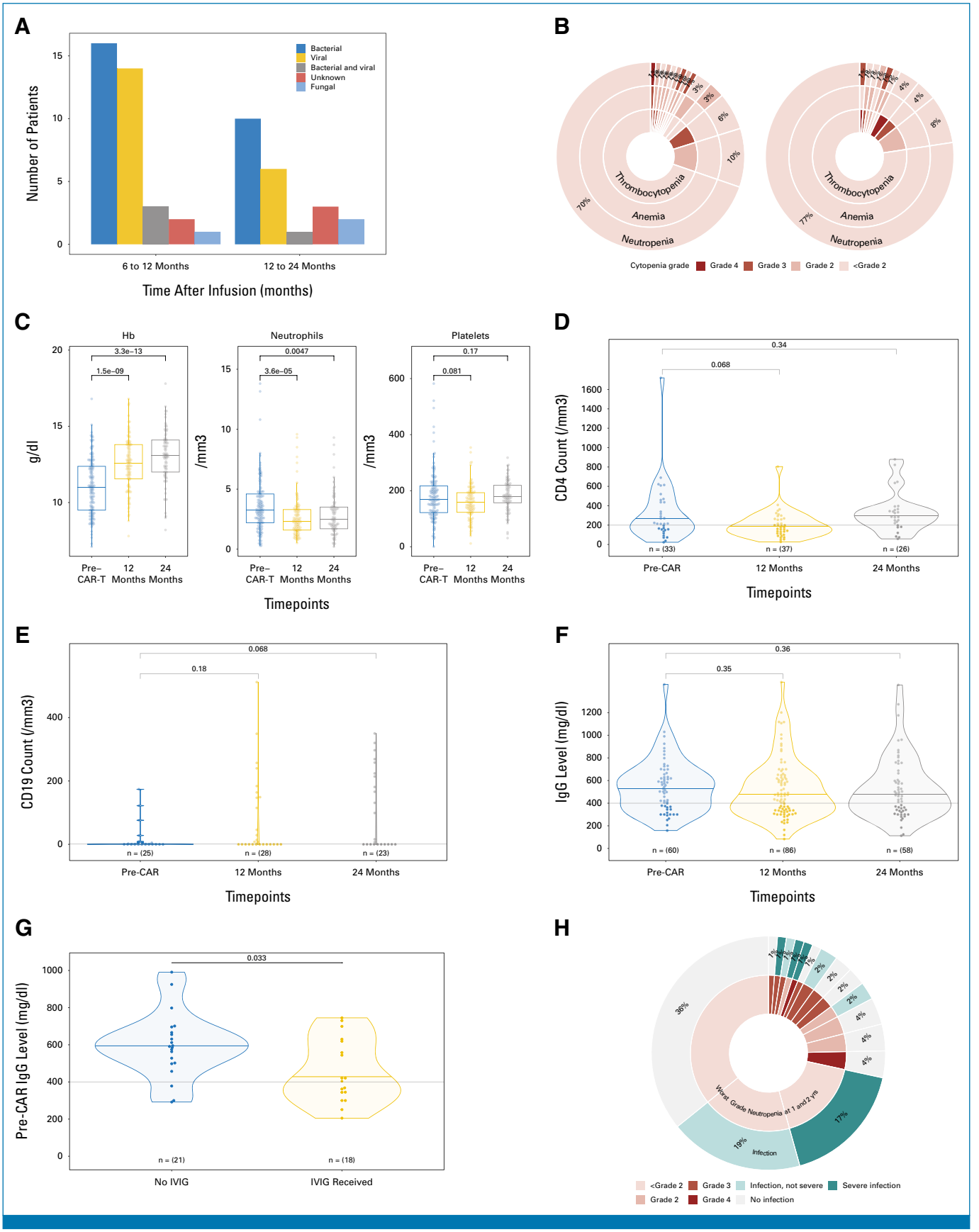

FIG 3. Immune reconstitution and infections after standard-of-care axi-cel. (A) Infection events (severe and nonsevere) occurring between 6 months and 2 years after axi-cel. (B) Incidence of cytopenias at 1 year (left) and 2 years (right) after axi-cel. Grading by CTCAE 5.0. Grade 3 is Hb <8 g/dL, or ANC between 500 and 1,000/mm^3, or Plt between 25,000 and 50,000/mm^3. (continued on following page)

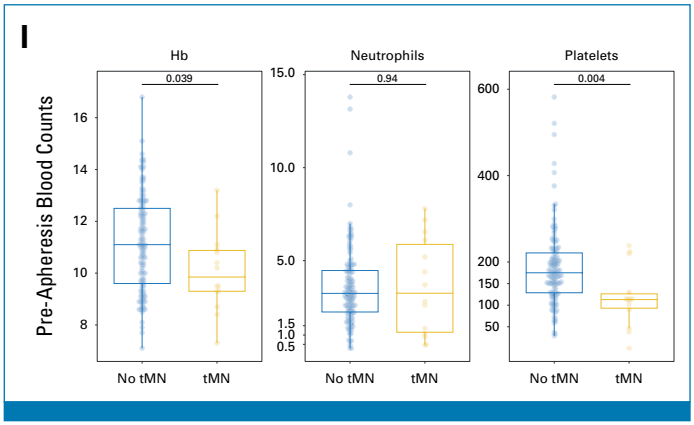

FIG 3. (Continued). Grade 4 is ANC <500/mm^3 or Plt <25,000/mm^3. Each ring of the sunburst chart represents the cytopenia indicated. Each ray of the sunburst chart represents patient(s) with that unique combination of cytopenias. (C-F) Plots comparing indicated immune parameters at baseline, 12 months, and 24 months after CAR T-cell therapy among patients with available data. (G) Comparison of patients who did or did not receive IVIG between 6 and 24 months after CAR T-cell therapy on the basis of baseline IgG levels. (H) Cumulative incidence of infections occurring between 6 months and 2 years (outer circle) compared with incidence of neutropenia at 1 and 2 years (inner circle). Each ray of the sunburst plot indicates co-occurrence of neutropenia and infections within the same patient(s), indicating that the majority of infections occurred in patients without neutropenia. (I) Comparison of patients who went on to develop a tMN and those that did not. Hemoglobin, absolute neutrophil counts, and platelets were obtained at the time of apheresis. ANC, absolute neutrophil count; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CTCAE, Common Terminology Criteria for Adverse Events; Hb, hemoglobin; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; Plt, platelets; tMN, therapy-related myeloid neoplasms.

Although the typical finding in CAR T-cell–associated neutropenia is an aplastic marrow that recovers over time, we also identified patients with tMN, occurring at a median of 16.2 months after axi-cel. Nearly all patients had complex karyotype and/or chromosomal deletions and translocations, similar to tMN after cytotoxic therapies. CAR T-cell therapy is now approved for use in the second line, and its use in patients with lower previous exposure to chemotherapy might reduce the risk of SMN among survivors. In addition to myeloid neoplasms, we also identified patients with subsequent solid tumor malignancies. Additional studies are needed to identify whether risks of these cancers are different in patients receiving CAR T-cell therapy compared with other therapies. Finally, we identified a case of T-cell malignancy but were unable to obtain tissue to test for CAR sequences. However, it should be noted that in the absence of CAR T-cell therapy, patients with DLBCL are at a nearly 10-fold higher risk of developing AITL than patients without DLBCL.[14] With only one observed case, T-cell lymphoma after axi-cel (whether CAR-related or unrelated) was a minor cause of mortality, in agreement with other recent reports.[15]

Limitations of this study include the reliance on data extraction from clinical records. This includes local assessment of PET/CT response, and many cases of early PR or SD did not represent treatment failure, but instead converted to durable responses over the long term. Recent studies have reported that circulating tumor DNA measurements can be used to improve relapse prediction after CAR T-cell therapy, but these are not yet widely used for standard-of-care practices.[16,17] Another limitation of the retrospective design is the underestimation of adverse events such as infections, and we do not have complete immune reconstitution data on all patients, limiting the identification of risk factors for these events. Overall, it is challenging to quantify the specific effect of the CAR T-cell therapy on late events. Our data support that many patients have significant immune deficits before CAR T-cell infusion and are elderly and/or heavily pretreated. Indeed, older patients are at the highest risk of NRM, indicating that patient-related factors may combine with treatment factors to produce the overall long-term risk for an individual patient. Similarly, we found that patients who went on to experience SMNs after CAR T-cell therapy had lower baseline platelet and

TABLE 3. tMN After Axi-Cel

Patient	Diagnosis	Lymphoma Progression	Time to tMN Diagnosis From Axi-Cel, months	Mutations	Karyotype	Marrow Blasts, %	Risk Stratification	Therapy for tMN	First tMN Regimen	Response to First tMN Regimen	HSCT	OS From tMN Diagnosis (months)	Vital Status
1	CMML	Yes	29.7	KRAS, RUNX1	Monosomy 7	3	High risk (CPSS mol 5)	Yes	Azacitadine	HI	No	13.3	Dead
2	MDS	No	16.2	TP53, IDH2	Complex	1	6.5	Yes	Decitabine	SD	Yes	7.2	Dead
3	MDS	No	12.6	PPM1D, PM1D, and BCOR	Del 4q	0.5	2.5	No	Epoetin alfa	HI	No	47.9	Dead
4	MDS	No	8.7	KRAS, SRSF2, and PPM1D	NA	1.5	3	No	Sargramostim	NR	No	8.8	Dead
5	MDS	No	8.5	TP53	Complex	1	Low risk (score = 2)	Yes	Decitabine	SD	Yes	19.2	Dead
6	AML	No	11.5	KMT2A, STAG2, and SF1	t(11:19); MLL2	88	Adverse risk per ELN	Yes	Decitabine + venetoclax	CR	Yes	14.1	Dead
7	MDS-EB2	Yes	2.7	PPM1D	Deletion 7	10	Very high	Yes	Decitabine	SD	No	5.5	Dead
8	MDS-MLD	No	1	NA	20q-	2	Low risk (score = 2)	No	Observation	NA	No	34.3	Dead[a]
9	MDS	Yes	18.3	TP53	Complex	2	NA	Yes	Azacitadine	NA	No	1.9	Dead
10	MDS	No	20	NA	Monosomy 7	2	NA	Yes	Azacitadine	SD	No	58.9	Alive
11	MDS	Yes	4.2	NA	Complex	2	NA	Yes	Azacitdine + venetoclax	SD	No	23.7	Dead
12	MDS	No	18.5	NA	Complex	2	NA	Yes	Azacitadine	CR	No	13	Dead
13	Mast cell leukemia	No	64	NA	Monosomy 7	NA	NA	No	NA	NA	No	2	Alive[b]
14	MDS	No	41	NA	Complex	NA	NA	No	NA	NA	No	0.7	Dead
15	AML	No	61.1	NA	Monsomy 7	NA	Adverse risk per ELN	No	NA	NA	No	0.5	Dead

NOTE. Risk stratification for MDS is per R-IPSS, AML per ELN, and CMML per CMML-specific scoring system with molecular features (CPSS Mol).
Abbreviations: axi-cel, axicabtagene ciloleucel; CMML, chronic myelomonocytic leukemia; CR, complete response; ELN, European Leukemia Network; HI, hematologic improvement; HSCT, hematopoetic stem cell transplant; MDS, myelodysplastic syndrome; MLD, multilineage dysplasia; NA, not available; NR, no response; R-IPSS, revised international prognostic scoring system; SD, stable disease; tMN, therapy-related myeloid neoplasms.
[a]Died of trauma.
[b]In hospice at data cutoff.

hemoglobin counts, suggesting underlying myeloid dysfunction before CAR T-cell infusion and supportive of recent studies indicating a link between SMNs and baseline clonal hematopoiesis (CH), which increases with age and previous therapy.[18,19] That said, older patients do appear to benefit from CAR T-cell therapy, with lower risks of lymphoma relapse than younger patients and similar long-term PFS and OS despite greater late NRM. Finally, risks of CAR T-cell therapy in our study (5-year NRM of 16%) appear similar to those of autologous stem-cell transplantation, which has reported a long-term NRM of 15%-25% and higher risks in patients with baseline CH.[20-23]

In summary, 29% of patients with R/R LBCL in our cohort remained alive and in remission at a median of 58 months after standard-of-care infusion with axi-cel. Key survivorship issues in CAR T-cell–treated patients include immune reconstitution, infection, and SMNs. Long-term lymphoma relapse prevention, infection risk management, and cancer screening in this unique population need to be developed.

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REFERENCES

1. Locke FL, Ghobadi A, Jacobson CA, et al: Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): A single-arm, multicentre, phase 1-2 trial. Lancet Oncol 20:31-42, 2019
2. Neelapu SS, Locke FL, Bartlett NL, et al: Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 377:2531-2544, 2017
3. Neelapu SS, Jacobson CA, Ghobadi A, et al: Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood 141:2307-2315, 2023
4. Reference deleted
5. Locke FL, Miklos DB, Jacobson CA, et al: Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med 386:640-654, 2022
6. Singh AK, McGuirk JP: CAR T cells: Continuation in a revolution of immunotherapy. Lancet Oncol 21:e168-e178, 2020
7. Nastoupil LJ, Jain MD, Feng L, et al: Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: Results from the US Lymphoma CAR T Consortium. J Clin Oncol 38: 3119-3128, 2020
8. Kent EE, Park EM, Wood WA, et al: Survivorship care of older adults with cancer: Priority areas for clinical practice, training, research, and policy. J Clin Oncol 39:2175-2184, 2021
9. Rosko AE, Cordoba R, Abel G, et al: Advances in management for older adults with hematologic malignancies. J Clin Oncol 39:2102-2114, 2021
10. Logue JM, Zucchetti E, Bachmeier CA, et al: Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. Haematologica 106:978-986, 2020

11. Baird JH, Epstein DJ, Tamaresis JS, et al: Immune reconstitution and infectious complications following axicabtagene ciloleucel therapy for large B-cell lymphoma. Blood Adv 5:143-155, 2021
12. Strati P, Varma A, Adkins S, et al: Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma. Haematologica 106:2667-2672, 2021
13. Cordeiro A, Bezerra ED, Hirayama AV, et al: Late events after treatment with CD19-targeted chimeric antigen receptor modified T cells. Biol Blood Marrow Transplant 26:26-33, 2020
14. Chihara D, Dores GM, Flowers CR, et al: The bidirectional increased risk of B-cell lymphoma and T-cell lymphoma. Blood 138:785-789, 2021
15. Ghilardi G, Fraietta JA, Gerson JN, et al: T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. Nat Med 30:984-989, 2024
16. Dean EA, Kimmel GJ, Frank MJ, et al: Circulating tumor DNA adds specificity to PET after axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv 7:4608-4618, 2023
17. Frank MJ, Hossain NM, Bukhari A, et al: Monitoring of circulating tumor DNA improves early relapse detection after axicabtagene ciloleucel infusion in large B-cell lymphoma: Results of a prospective multi-institutional trial. J Clin Oncol 39:3034-3043, 2021
18. Saini NY, Swoboda DM, Greenbaum U, et al: Clonal hematopoiesis is associated with increased risk of severe neurotoxicity in axicabtagene ciloleucel therapy of large B-cell lymphoma. Blood Cancer Discov 3:385-393, 2022
19. Hamilton MP, Sworder BJ, Alig SK, et al: CAR19 therapy drives expansion of clonal hematopoiesis and associated cytopenias. Blood 142:360, 2023
20. Bhatia S, Dai C, Landier W, et al: Trends in late mortality and life expectancy after autologous blood or marrow transplantation over three decades: A BMTSS report. J Clin Oncol 40:1991-2003, 2022
21. Gibson CJ, Lindsley RC, Tchekmedyian V, et al: Clonal hematopoiesis associated with adverse outcomes after autologous stem-cell transplantation for lymphoma. J Clin Oncol 35:1598-1605, 2017
22. Lackraj T, Ben Barouch S, Medeiros JJF, et al: Clinical significance of clonal hematopoiesis in the setting of autologous stem cell transplantation for lymphoma. Am J Hematol 97:1538-1547, 2022
23. Hill BT, Rybicki L, Bolwell BJ, et al: The non-relapse mortality rate for patients with diffuse large B-cell lymphoma is greater than relapse mortality 8 years after autologous stem cell transplantation and is significantly higher than mortality rates of population controls. Br J Haematol 152:561-569, 2011
24. Westin JR, Oluwole OO, Kersten MJ, et al: Survival with axicabtagene ciloleucel in large B-cell lymphoma. N Engl J Med 389:148-157, 2023

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APPENDIX

TABLE A1. Baseline Characteristics of Standard-of-Care Axi-Cel–Infused Patients

Characteristic	N = 275
Age, years, median (range)	60 (21-83)
<60, No. (%)	132 (48)
≥60, No. (%)	143 (52)
ECOG PS, No. (%)	
0	76 (28)
1	155 (56)
2	35 (13)
3	8 (2.9)
4	1 (0.4)
Disease type, No. (%)	
DLBCL	188 (68)
PMBCL	19 (6.9)
TFL	68 (25)
Disease stage,[a] No. (%)	
I/II	51 (19)
III/IV	222 (81)
Cell of origin,[b] No. (%)	
ABC-like	97 (40)
GCB-like	148 (60)
Unknown	30
Disease status at referral, No. (%)	
Primary refractory	89 (32)
Refractory	117 (43)
Relapsed	69 (25)
Previous autologous SCT, No. (%)	89 (32)
Bulky disease (≥10 cm), No. (%)	58 (21)
≥Three lines of therapy, No. (%)	201 (73)
Elevated bilirubin (≥1.5 g/dL), No. (%)	5 (1.8)

Abbreviations: ABC, activated B-cell; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell; PMBCL, primary mediastinal B cell lymphoma; SCT, stem cell transplant; TFL, transformed follicular lymphoma.
[a]n = 273 cases with available staging information.
[b]n = 245 cases with adjudicated cell of origin.

TABLE A2. Baseline Associations With NRM

Characteristic	Odds Ratio (95% CI)	*P*
NRM		
Sex		
Female	—	
Male	0.9 (0.4 to 1.8)	.67
Age, years		
<60	—	
≥60	4.5 (2.1 to 10.8)	<.001
Previous lines of therapy		
<3	—	
≥3	1.6 (0.7 to 3.8)	.29
Baseline LDH		
Below ULN	—	
Above ULN	1.0 (0.5 to 2.0)	.97
Bridging therapy		
No	—	
Yes	1.3 (0.7 to 2.6)	.45

NOTE. Among 275 patients followed for a median of 58 months, 40 NRM events occurred.
Abbreviations: LDH, lactate dehydrogenase; NRM, nonrelapse mortality; ULN, upper limit of normal for the laboratory.

TABLE A3. Cases of Severe Infection Between 6 and 24 Months After Axi-Cel

Patient	How Long After CAR-T Did Infection Occur?	Type of Infection[a]	Syndrome	Specific Organism[a]	Infection Fatal?	Age	IgG	Hb	WBC	ANC	ALC	Plt
LSI1	6-12 months	Bacterial	Pneumonia		No	58	<300	9.3	8.4	6.9	0.2	147
LSI2	6-12 months	Bacterial	Pneumonia		No	66	<300	10.9	3.3	2.7	0.3	177
LSI3	6-12 months	Bacterial	Pneumonia		No	64						
LSI4	6-12 months	Viral	Oral ulcer	HSV	No	61	461	13.2	1.1	0.01	0.1	183
LSI5	6-12 months	Bacterial	Colitis		No	65		16.3	9.5	8.7	0.7	157
LSI6	6-12 months	Viral	Rash	VZV	No	65	764		7.2		0.5	133
LSI7[b,c]	6-12 months	Unknown	Pneumonitis		No	64						
LSI8	6-12 months	Bacterial	Cholecystitis		No	51	360		1	0.5	0.3	68
LSI9[b]	6-12 months	Viral	Pneumonia		No	54		11	9.6	9.1	0.4	104
LSI10	6-12 months	Viral	Pneumonia	COVID-19 disease	No	64		11.3	6.6			88
LSI11	6-12 months	Bacterial	Abscess	*B. fragilis*	No	64	535	8.7	2.4	1.3	1.1	10
LSI12	6-12 months	Bacterial	Pneumonia		No	73	216	12.5	4.5	3.8	0.1	85
LSI13	6-12 months	Viral	Encephalitis (PML)	JC virus	Yes	70	648	10.9	1.5	0.7	0.4	100
LSI14	6-12 months	Bacterial, viral	Pneumonia; colitis	RSV, *H. flu*, Campylobacter	No	55	311	7.1	4.9			18
LSI15	6-12 months	Bacterial, viral	Pneumonia	Rhinovirus, norovirus, MAI	No	34						
LSI16	6-12 months	Viral	URI		No	39						
LSI17	6-12 months	Bacterial, viral	Pneumonia	Rhinovirus	Yes	68						
LSI18	6-12 months	Bacterial	Sinusitis		No	64						
LSI19	12-24 months	Bacterial, viral	Pneumonia	Influenza A	No	49	606	13.1	11	8.7	1.3	260
LSI20	12-24 months	Bacterial	Cellulitis		No	66	774	13.7	4.5	3.1	0.6	174
LSI21	12-24 months	Bacterial	Pneumonia	Pseudomonas	No	61	<300	9.3	10.4	9.3	0.3	252
LSI22	12-24 months	Bacterial	Colitis	*C. difficile*	No	57			0.9	0.29	0.6	29
LSI23	12-24 months	Bacterial	Pneumonia		Yes	70			0.4	0.36		10
LSI7[b,c]	12-24 months	Unknown	Pneumonitis		No	64						
LSI9[b]	12-24 months	Viral	Pneumonia	Influenza A	No	54		12	5.1	2.1	2	219
LSI24	12-24 months	Viral	Pneumonia	RSV	No	71		12.7	11.7			359
LSI25	12-24 months	Bacterial	Sepsis		Yes	69						

NOTE. Laboratory values are at the time of diagnosis of the severe infection event, except for IgG which is at the last measured time point before the infection occurred. Age is at the time of CAR T-cell infusion. Blanks indicate unknown or unavailable data.

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; Hb, hemoglobin; HSV, herpes simplex virus; IgG, immunoglobulin G; LSI, late severe infection; MAI, mycobacterium avium intracellulare; Plt, platelets; PML, progressive multifocal leukoencephalopathy; RSV, respiratory syncytial virus; URI, upper respiratory infection; VZV, varicella zoster virus.

[a]Type of infection considers the clinical syndrome; specific organism only includes those positively identified by microbiological testing.

[b]Patient had more than one severe infection event.

[c]Pneumonitis treated with antibiotics and corticosteroids on each occasion.

TABLE A4. Baseline Associations With tMN

Characteristic	Odds Ratio (95% CI)	*P*
tMN		
Sex		
Female	—	
Male	1.5 (0.5 to 5.5)	.5
Age, years		
<60	—	
≥60	1.4 (0.5 to 4.3)	.5
Previous lines of therapy		
<3	—	
≥3	1.5 (0.5 to 6.7)	.5
Previous ASCT		
No	—	
Yes	1.4 (0.5 to 4.1)	.5
Bridging therapy		
No	—	
Yes	0.6 (0.2 to 1.7)	.3

NOTE. Among 275 patients followed for a median of 58 months, 15 tMN events occurred.
Abbreviations: ASCT, autologous stem-cell transplant; tMN, therapy-related myeloid neoplasms.