Outcomes After Nonresponse and Relapse Post-Tisagenlecleucel in Children, Adolescents, and Young Adults With B-Cell Acute Lymphoblastic Leukemia

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abstract

PURPOSE Nonresponse and relapse after CD19-chimeric antigen receptor (CAR) T-cell therapy continue to challenge survival outcomes. Phase II landmark data from the ELIANA trial demonstrated nonresponse and relapse rates of 14.5% and 28%, respectively, whereas use in the real-world setting showed nonresponse and relapse rates of 15% and 37%. Outcome analyses describing fate after post-CAR nonresponse and relapse remain limited. Here, we aim to establish survival outcomes after nonresponse and both CD19+ and CD19– relapses and explore treatment variables associated with inferior survival.

METHODS We conducted a retrospective multi-institutional study of 80 children and young adults with B-cell acute lymphoblastic leukemia experiencing nonresponse (n = 23) or relapse (n = 57) after tisagenlecleucel. We analyze associations between baseline characteristics and these outcomes and establish survival rates and salvage approaches.

RESULTS The overall survival (OS) at 12 months was 19% across nonresponders (n = 23; 95% CI, 7 to 50). Ninety-five percent of patients with nonresponse had high preinfusion disease burden. Among 156 morphologic responders, the cumulative incidence of relapse was 37% (95% CI, 30 to 47) at 12 months (CD19+; 21% [15 to 29], CD19–; 16% [11 to 24], median follow-up; 380 days). Across 57 patients experiencing relapse, the OS was 52% (95% CI, 38 to 71) at 12 months after time of relapse. Notably, CD19– relapse was associated with significantly decreased OS as compared with patients who relapsed with conserved CD19 expression (CD19– 12-month OS; 30% [14 to 66], CD19+ 12-month OS; 68% [49 to 92], P = .0068). Inotuzumab, CAR reinfusion, and chemotherapy were used as postrelapse salvage therapy with greatest frequency, yet high variability in treatment sequencing and responses limits efficacy analysis across salvage approaches.

CONCLUSION We describe poor survival across patients experiencing nonresponse to tisagenlecleucel. In the post-tisagenlecleucel relapse setting, patients can be salvaged; however, CD19– relapse is distinctly associated with decreased survival outcomes.

BACKGROUND

Chimeric antigen receptor (CAR) therapy targeting CD19 is US Food and Drug Administration–approved for the treatment of patients age < 26 years with refractory B-cell acute lymphoblastic leukemia (B-ALL) or disease in second or greater relapse. Although response and relapse rates have been established across both the clinical trial and commercial settings,[1-6] limited data exist describing the risk factors or the fate of tisagenlecleucel nonresponders or patients who relapse. We aimed to establish survival outcomes after post-tisagenlecleucel nonresponse and relapse. We interrogated if baseline characteristics are associated with risk of relapse and whether certain patterns of relapse confer survival advantage.

The Pediatric Real-world CAR Consortium (PRWCC) previously described outcomes of 185 children and young adults (CAYAs) treated with commercial tisagenlecleucel. We reported a complete morphologic remission (CR) rate of 85% at day 28 (d28) postinfusion,

CONTEXT

Key Objective

Outcomes after post–chimeric antigen receptor (CAR) nonresponse and relapse are yet to be established in the pediatric B-cell acute lymphoblastic leukemia commercial setting. Our key objective was to describe overall survival (OS) and salvage approaches after post-tisagenlecleucel nonresponse and relapse, with distinct analysis across CD19+ and CD19– relapse patterns. To approach this, we extracted data across 80 patients experiencing nonresponse (n = 23) or relapse (n = 57) from the Pediatric Real-world CAR Consortium.

Knowledge Generated

We describe poor survival across patients experiencing post-tisagenlecleucel nonresponse (12 month OS; 19%). On relapse, we report a 12-month OS rate of 52%, yet CD19– disease is distinctly associated with inferior survival (12-month OS; 30%). Although salvage can be achieved after post-CAR relapse, salvage regimens remain highly heterogeneous.

Relevance

We identify patients with CD19– relapse post-tisagenlecleucel to be a high-risk patient population and highlight the need for the systematic study of salvage regimens in the post-tisagenlecleucel nonresponse and relapse setting.

with 37% of complete responders experiencing disease relapse.[2] Center for International Blood and Marrow Transplant Research–generated data reported a similar nonresponse rate of 14.5% after tisagenlecleucel.[6] These real-world reports compare with the phase II landmark trial studying tisagenlecleucel, ELIANA, where a nonresponse rate of 19% and a relapse rate of 28% were reported.[1] Interestingly, although CD19– disease was the predominant relapse pattern in ELIANA, there was comparatively decreased CD19 downregulation on relapse in the real-world reports, possibly related to overall lower disease burden. Here, we describe characteristics and outcomes of CAYA patients who experienced nonresponse and relapse post-tisagenlecleucel and establish survival rates after post-tisagenlecleucel CD19+ and CD19– relapse.

METHODS

Study Design

We established the PRWCC and previously reported outcomes of 185 CAYA patients infused with tisagenlecleucel across 15 US institutions. Centers obtained independent institutional review board approval. Deidentified data were collected retrospectively and stored in a Health Insurance Portability and Accountability Act–compliant REDCap database. Here, we analyze baseline characteristics, salvage strategies, and survival outcomes across patients who experienced nonresponse or relapse after tisagenlecleucel between August 17, 2017, and March 6, 2020. Nonresponse is defined as detectable disease by morphology with > M1 marrow and/or CNS or non-CNS extramedullary (EM) disease at d28 post-tisagenlecleucel infusion. We additionally study patients who achieved morphological remission at d28, yet continued to have detectable minimal residual disease (MRD) by flow cytometry. Although these patients are not included in patients experiencing nonresponse, we independently describe baseline characteristics

in this cohort. We study patients experiencing relapse after tisagenlecleucel, with relapse defined as detectable disease by morphology, CNS/non-CNS EM disease, and/or any level of MRD by flow cytometry or next-generation sequencing disease driving new antileukemia therapy. CD19 status at time of relapse was captured, as defined by institutional reporting. Because of lack of systematic quantification of antigen density, we use CD19 downregulation to include total or partial CD19 loss.

Study Aims, Clinical Outcomes Assessment, and Statistical Approach

Our primary aim was to establish the overall survival (OS) rate after post-tisagenlecleucel relapse. We first characterize relapse patterns using cumulative incidence curves for overall relapse and relapse with CD19+ and CD19– diseases. We measure OS from time of post-CAR relapse to occurrence of death by any cause or censored at last follow-up. Our secondary aim was to assess whether distinct relapse patterns are associated with improved OS. Postrelapse OS was measured for patients relapsing with CD19+ and CD19– disease. We additionally compare OS in patients experiencing post-CAR relapse with patients who remain relapse-free, using a 6-month landmark time point, with the 6-month time point chosen to capture the majority of relapses while minimizing sample attrition from postrelapse death. Our exploratory aims include analysis of associations between baseline patient and disease characteristics and nonresponse or relapse and characterization of salvage regimens used in the post-tisagenlecleucel relapse setting.

The cumulative incidence of relapse, CD19+ and CD19– relapse, was estimated using the Aalen-Johansen estimator. For overall relapse, death is treated as a competing event. For relapse with CD19+ and CD19– disease, relapse with the other disease type and death are treated as competing
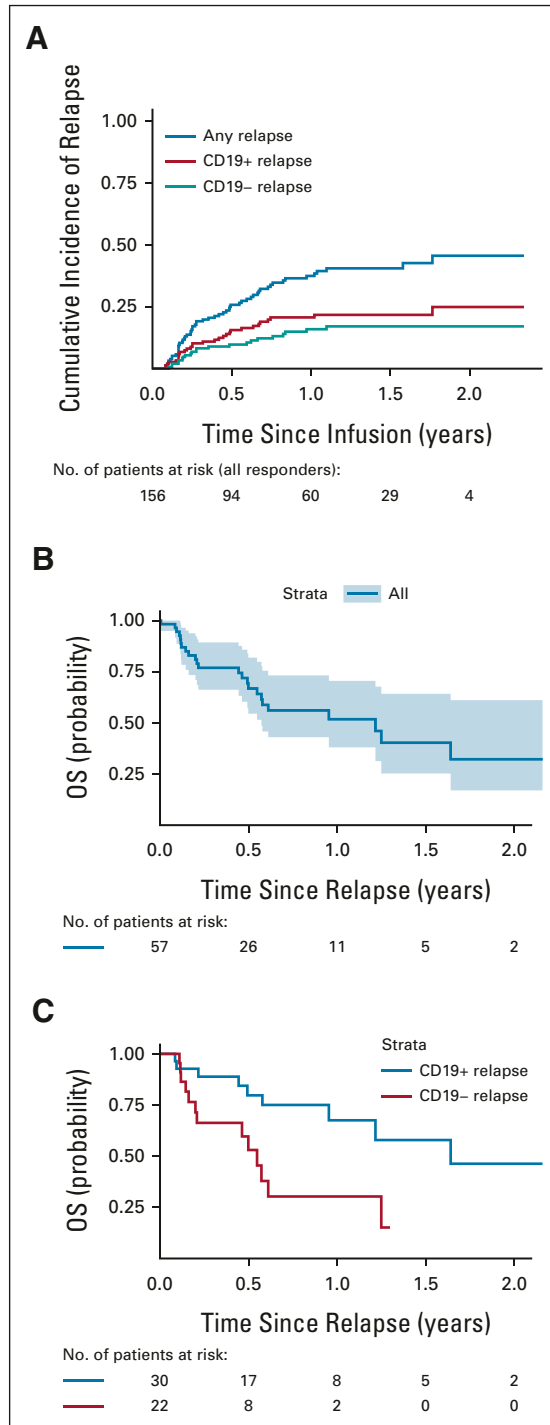
FIG 1. (A) Cumulative incidence of relapse and OS after relapse in (B) the overall cohort and (C) patients with CD19+ and CD19− relapse. OS, overall survival.

events. Baseline covariates investigated for association with nonresponse and relapse include the following: sex, age at diagnosis, age at infusion, race/ethnicity, cytogenetics, number of pre-CAR relapses, prior therapy lines, prior CD19-directed therapy, prior hematopoietic stem-cell transplantation

(HSCT), disease burden at CAR T infusion (high burden defined as > 5% bone marrow [BM] lymphoblasts, CNS3/EM, or peripheral blood lymphoblasts before lymphodepleting chemotherapy; low burden includes patients with detectable disease, not meeting high burden criteria), CAR T-cell viability, percent CAR expression, time from diagnosis to CAR T infusion, and refractory/relapse status. We conducted univariate analyses examining these baseline characteristics to determine whether they are associated with relapse, CD19+ relapse and CD19− relapse, and OS postrelapse. Associations between patient and disease characteristics and relapse and death were assessed using Cox proportional hazards models. For the analysis of relapse, death was considered as a competing risk, and for CD19+ and CD19− relapses, the other type of relapse and death were treated as competing events, and cause-specific hazards were modeled using Cox models. Multivariate analysis of factors associated with OS after post-CAR relapse was performed using variables achieving significance in the univariate model.

OS for the overall relapse cohort and patients distinctly relapsing with CD19+ and CD19− diseases was estimated using Kaplan-Meier (KM) curves, with CD19+ and CD19− cohorts compared using the log-rank test. OS across patients receiving secondary CAR infusions because of relapse was estimated using KM curves. OS on the basis of timing from infusion to relapse was estimated using KM curves, analyzing 0-60, 60-180, and > 180 days to relapse as categorical variables, with cohorts compared using the log-rank test. Landmark analysis was used to compare OS in patients who relapse versus remained relapse-free at the 180-day landmark time point. Clinical course after nonresponse and relapse is descriptively illustrated. Characterization of lines of salvage therapies and respective responses is reported descriptively, using response by morphology and flow cytometry MRD, as reported by the treating physician. *P* values < .05 were considered significant.

RESULTS

Characteristics and Outcomes of Patients With Nonresponse Post-Tisagenlecleucel

Across 184 patients evaluable for response, 23 (12.5%) did not achieve CR to tisagenlecleucel, as defined by morphologic or EM disease at d28. Five additional patients (3%) had detectable MRD by flow cytometry at this time, despite morphologic remission. Baseline characteristics of responders and nonresponders are reported in Appendix Table A1 (online only). Notably, 20 of 23 (95%) patients experiencing nonresponse had high baseline disease burden. At time of nonresponse, 22 of 23 (96%) patients had high disease burden with morphologic disease or EM (Appendix Table A2, online only). At time of nonresponse, three patients had CD19

TABLE 1. Characteristics of Patients With Overall Relapse and Across CD19 Expression Patterns

Characteristic	Overall (N = 57)	CD19– Relapse (n = 22)	CD19+ Relapse (n = 30)
Sex, No. (%)			
Female	26 (46)	10 (45)	13 (43)
Male	31 (54)	12 (55)	17 (57)
Age at diagnosis, years, median (IQR)	12 (4-15)	12 (5-15)	12 (3-16)
Age at infusion, years, median (IQR)	13 (9-19)	14 (10-18)	13 (8-18)
Race/ethnicity, No. (%)			
Asian	3 (5.4)	1 (4.8)	2 (6.7)
Black	2 (3.6)	1 (4.8)	1 (3.3)
Hispanic	19 (34)	7 (33)	11 (37)
More than one race	1 (1.8)	1 (4.8)	0 (0)
Non-Hispanic White	31 (55)	11 (52)	16 (53)
Unknown	1	1	0
Initial cytogenetic risk, No. (%)			
Favorable	5 (11)	3 (17)	2 (8.0)
Intermediate	19 (40)	10 (56)	8 (32)
Unfavorable	23 (49)	5 (28)	15 (60)
Unknown	10	4	5
No. of relapses pre-CAR, median (IQR)	2.00 (1.00-2.00)	2.00 (1.00-2.00)	1.00 (1.00-2.00)
No. of additional lines of therapy pre-CAR, median (IQR)	2.00 (1.00-3.00)	2.00 (2.00-3.75)	2.00 (1.00-2.75)
Prior CD19-directed therapy, No. (%)	12 (21)	7 (32)	4 (13)
Pre-CAR HSCT, No. (%)	11 (19)	5 (23)	5 (17)
Preinfusion disease burden overall, No. (%)			
High disease burden	35 (61)	14 (64)	17 (57)
Low disease burden	9 (16)	4 (18)	5 (17)
No detectable disease	13 (23)	4 (18)	8 (27)
CAR viability, %, median (IQR)	89 (85-93)	92 (85-94)	88 (85-92)
Unknown	1	1	0
Determination of CAR expression (% CAR-positive viable cells), median (IQR)	14.5 (8.7-19.7)	14.4 (9.5-18.7)	13.9 (9.1-20.1)
Unknown	4	2	2
Months from diagnosis to CAR T infusion, median (IQR)	30 (16-52)	30 (19-51)	32 (12-58)
Relapsed or refractory indication, No. (%)			
Refractory	9 (16)	1 (4.5)	6 (20)
Relapsed	48 (84)	21 (95)	24 (80)

Abbreviations: CAR, chimeric antigen receptor; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range.

antigen downregulation, one additional patient developed mixed phenotype acute leukemia (CD19+/myeloid), and remaining 19 patients had conserved CD19 expression. Details of salvage therapies after nonresponse are included in Appendix Table A2. Among nonresponders, 16 of 23 experienced death before last follow-up and the OS at 3, 6, and 12 months was 59% (95% CI, 41 to 84), 43% (95% CI, 26 to 71), and 19% (95% CI, 7 to 50), respectively. The median survival was 160 days (95% CI, 76 to 333).

Characteristics of Patients Experiencing Relapse Post-Tisagenlecleucel

Of 156 patients achieving a CR, with a median follow-up of 380 days postinfusion, 57 experienced relapse disease post-tisagenlecleucel. The cumulative incidence of relapse among responders was 16% (95% CI, 11 to 23), 26% (95% CI, 20 to 34), and 37% (95% CI, 30 to 47) at 3, 6, and 12 months, respectively (Fig 1A). Baseline characteristics of patients who relapsed after tisagenlecleucel are included in
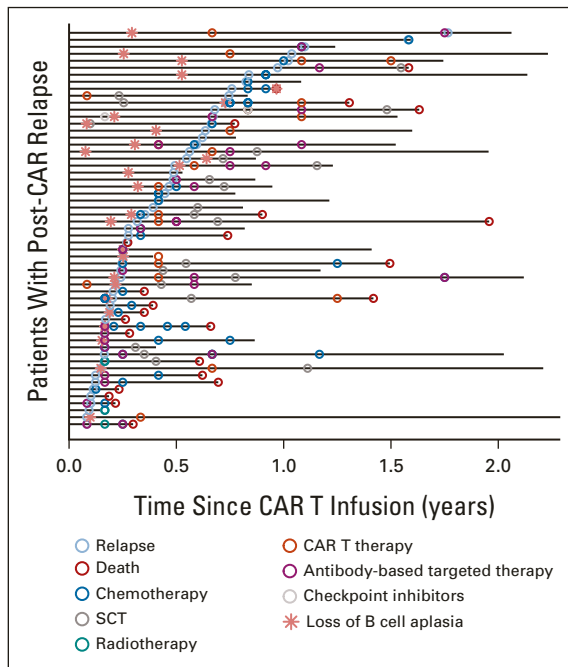
FIG 2. Interventions and outcomes across individual patients after relapse post-CAR T-cell therapy (swimmer's plot). CAR, chimeric antigen receptor.

Table 1. As previously reported, the median time from infusion to relapse among those who relapsed was 101 (range 30-645) days. The median time from relapse to last follow-up was 176 (range 2-806) days.

Of 57 relapses, 48 (84%) had BM involvement (> M1morphologic marrow [n = 26]), flow-positive/morphology-negative (n = 14), flow-positive/morphology unknown (n = 3), and next-generation sequencing–positive/flow-negative (n = 5). Of 48 patients with BM involvement, 10 patients (21%) had combined BM and EM diseases (CNS: n = 3, testicular: n = 1, skin: n = 1, ocular: n = 1, and others: n = 4). Six (11%) had isolated EM disease (CNS: n = 5 and skin: n = 1). Relapse site was not reported in three patients.

Relationship between loss of B-cell aplasia (BCA) and relapse was available for 25 relapsed patients (Fig 2). In 15 patients, loss of BCA preceded relapse with the median time between loss of BCA and relapse of 84 (range 4-538) days. Seven patients relapsed concurrently with loss of BCA, and three patients had ongoing documented BCA at time of relapse (CD19+: n = 2 and CD19–: n = 1).

Fifty-two patients had CD19 status evaluable at relapse. Forty-one percent (22 of 52) relapsed with CD19 loss or down-regulation, and 59% (30 of 52) relapsed with conserved CD19 expression. Cumulative incidence of CD19+ relapse was 9% (95% CI, 5 to 15), 16% (95% CI, 11 to 23), and 21% (95% CI, 15 to 29) at 3, 6, and 12 months, respectively. The cumulative incidence of CD19– relapse was 7% (95% CI, 4 to 12), 10% (95% CI, 6 to 16), and 16% (95% CI, 11 to 24) at 3, 6, and 12 months, respectively (Fig 1A). Median duration

from infusion to relapse was similar across patients relapsing with CD19+ (median 104 days, range 30-645) and CD19– (median 101 day, range 37-401) diseases. Baseline characteristics across patients relapsing with CD19+ and CD19– diseases are included in Table 1. Univariate analysis studying risk of relapse across baseline characteristics identified high disease burden to associate with increased risk of overall relapse (hazard ratio [HR] 2.11 [95% CI, 1.08 to 4.11] for high burden versus no detectable disease, P = .026, Table 2). Univariate analysis studying baseline characteristics as predictors of CD19+ and CD19– relapse identified the number of relapses pre-CAR to associate with post-CAR CD19– relapse (HR 1.59 [95% CI, 1.12 to 2.25], P = .010). Preinfusion high disease burden (HR 2.98 [95% CI, 0.98 to 9.05], P = .078), relapse compared with refractory status (HR 5.06 [95% CI, 0.68 to 37.6]; P = .11), and prior CD19-targeted therapy (HR 1.91 [95% CI, 0.78 to 4.68]; P = .16) were estimated to have large HRs for CD19– relapse risk, yet do not achieve significance. Variables distinctly predictive of CD19+ relapse were not identified with significance.

Outcomes After Post-Tisagenlecleucel Relapse

OS rates at 3, 6, and 12 months post-tisagenlecleucel relapse were 77% (95% CI, 66 to 89), 67% (95% CI, 55 to 82), and 52% (95% CI, 38 to 71), respectively (Fig 1B). Notably, CD19– post-tisagenlecleucel relapse is associated with significantly decreased OS rates, with 3-, 6-, and 12-month OS rates of 66% (95% CI, 49 to 90), 53% (95% CI, 34 to 82), and 30% (14 to 66), as compared with 3-, 6-, and 12-month OS rates of 90% (95% CI, 78 to 100), 80% (95% CI, 655 to 98), and 68% (95% CI, 49 to 92) after CD19+ post-tisagenlecleucel relapse (P = .0068; Fig 1C). Univariate analysis of factors associated with survival after post-tisagenlecleucel relapse identifies the number of additional lines of pre-CAR therapy (HR 128 [95% CI, 1.04 to 1.57]; P = .021) and relapse with CD19– disease (HR, 3.25 [95% CI, 1.32 to 7.99], P = .010) to significantly associate with decreased survival (Table 3). Multivariate analysis across variables with univariate significance confirms that CD19– relapse is associated with greater risk of death postrelapse (HR, 2.83 [95% CI, 1.11 to 7.20]; P = .03, Table 3). Timing of relapse after tisagenlecleucel (0-60, 60-180, or > 180 days) did not significantly affect OS after relapse (P = .37; Appendix Fig A1 [online only]).

To evaluate the impact of relapse by 6 months on survival, we conducted a 6-month landmark OS analysis across 119 patients with a minimum follow-up of 6 months. Of these, 20% (n = 24) relapsed before 6 months and 80% (n = 95) were relapse-free at 6 months postinfusion. Nine of 24 (38%) and nine of 95 (9%) patients in respective relapse and nonrelapse cohorts experienced post-tisagenlecleucel death. We demonstrate that relapse before 6 months post-tisagenlecleucel is strongly associated with an increased risk of death (HR, 4.75 [95% CI, 1.86 to 12.1]; P = .001; Fig 3). Notably, in patients who survive to 6 months post-tisagenlecleucel without

TABLE 2. Univariate Analysis Examining Factors Associated With Any Relapse, CD19+ Relapse, and CD19– Relapse

Characteristic	Any Relapse				CD19+ Relapse				CD19– Relapse			
	No.	HR	95% CI	P	No.	HR	95% CI	P	No.	HR	95% CI	P
Sex	156				151				151			
Female		—	—			—	—			—	—	
Male		0.73	0.42 to 1.26	.260		0.76	0.37 to 1.56	.45		0.67	0.29 to 1.56	.360
Age at diagnosis, years	156	1.03	0.99 to 1.07	.200	151	1.03	0.97 to 1.08	.37	151	1.04	0.98 to 1.11	.200
Age at infusion, years	156	1.02	0.98 to 1.06	.380	151	1.02	0.96 to 1.07	.59	151	1.04	0.97 to 1.11	.280
Race/ethnicity	150			.910	145			.73	145			.930
Asian		—	—			—	—			—	—	
Black		1.06	0.18 to 6.34			0.81	0.07 to 8.97			1.53	0.10 to 24.5	
Hispanic		0.62	0.18 to 2.09			0.58	0.13 to 2.61			0.71	0.09 to 5.81	
More than one race		0.56	0.06 to 5.39			0.00	0.00 to Inf			1.57	0.10 to 25.2	
Non-Hispanic White		0.72	0.22 to 2.37			0.68	0.16 to 2.95			0.90	0.12 to 6.96	
Initial cytogenic risk	119			.410	115			.21	115			.190
Favorable		—	—			—	—			—	—	
Intermediate		1.89	0.70 to 5.10			2.09	0.44 to 9.85			1.82	0.50 to 6.60	
Unfavorable		1.58	0.59 to 4.22			3.09	0.71 to 13.5			0.70	0.17 to 2.92	
No. of relapses pre-CAR	156	1.08	0.89 to 1.31	.450	151	0.91	0.63 to 1.31	.61	151	**1.59**	1.12 to 2.25	**.010**
No. of additional lines of therapy pre-CAR	156	1.03	0.88 to 1.20	.730	151	0.94	0.75 to 1.18	.60	151	1.17	0.94 to 1.45	.160
Prior CD19-directed therapy	156				151				151			
No		—	—			—	—			—	—	
Yes		1.08	0.55 to 2.10	.820		0.64	0.22 to 1.83	.41		1.91	0.78 to 4.68	.160
Pre-CAR HSCT	156				151				151			
Pre-CAR HSCT		0.65	0.32 to 1.29	.220		0.56	0.21 to 1.46	.23		0.79	0.29 to 2.15	.650
Preinfusion disease burden overall	154			**.026**	149			.18	149			.078
No detectable disease		—	—			—	—			—	—	
Low disease burden		0.98	0.41 to 2.33			0.78	0.25 to 2.37			1.31	0.33 to 5.26	
High disease burden		**2.11**	1.08 to 4.11			1.74	0.75 to 4.03			2.98	0.98 to 9.05	
CAR viability, %	155	1.02	0.97 to 1.06	.430	150	1.01	0.96 to 1.07	.63	150	1.03	0.96 to 1.10	.440
Determination of CAR expression (% of CAR-positive viable cells)	151	1.00	0.95 to 1.04	.850	146	1.01	0.94 to 1.07	.87	146	0.99	0.92 to 1.06	.710
Months from diagnosis to CAR T infusion	156	1.00	0.99 to 1.00	.210	151	1.00	0.99 to 1.01	.38	151	0.99	0.98 to 1.01	.400
Relapsed or refractory indication	156				151				151			
Refractory		—	—			—	—			—	—	
Relapsed		1.65	0.74 to 3.66	.220		0.97	0.40 to 2.38	.95		5.06	0.68 to 37.6	.110

NOTE. Parameters achieving statistical significance appear in bold.

Abbreviations: CAR, chimeric antigen receptor; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation.

relapse, OS rates are remarkably high in this historically high-risk relapsed acute lymphoblastic leukemia cohort, with 6-month and 1-year survival rates of 94% (95% CI, 89 to 99) and 92% (95% CI, 86 to 99), respectively.

Salvage Therapies After Relapse

Of 57 patients who relapsed post-tisagenlecleucel, 88% (n = 50) received salvage therapy (initial salvage therapy line: chemotherapy, n = 19; inotuzumab, n = 15; blinatumomab, n = 3; nivolumab, n = 1; CAR, n = 10; and HSCT, n = 2) and seven received supportive care (Appendix Fig A2, online only).

Fifty-six percent (20 of 36) of evaluable patients achieved CR by flow cytometry with their first salvage therapy. When used as an initial salvage regimen, 9 of 14 (64%) evaluable patients treated with inotuzumab and 7 of 9 (78%) evaluable patients treated with CD19-CAR reinfusion (3 of 5 tisagenlecleucel reinfusion, 3 of 3 humanized CD19-CAR, and 1 of 1 tandem tisagenlecleucel/nivolumab/radiation) received CR by flow cytometry. Although chemotherapy was used as the most common salvage strategy, variable utilization and reporting limit analysis. Of nonchemotherapy-based salvage approaches, CAR reinfusion and inotuzumab emerge as most

TABLE 3. Univariate and Multivariate Analyses of Factors Associated With Overall Survival After Relapse

Characteristic	No.	HR	95% CI	P
Univariate analysis				
Sex	57			
Female		—	—	
Male		0.79	0.35 to 1.76	.560
Age at diagnosis, years	57	1.01	0.96 to 1.07	.720
Age at infusion, years	57	1.01	0.95 to 1.07	.760
Race/ethnicity	56			.900
Asian		—	—	
Black		0.93	0.08 to 10.4	
Hispanic		0.83	0.18 to 3.87	
More than one race		0.00	0.00 to Inf	
Non-Hispanic White		0.73	0.16 to 3.26	
Initial cytogenic risk	47			.850
Favorable		—	—	
Intermediate		1.19	0.25 to 5.67	
Unfavorable		0.90	0.19 to 4.24	
No. of relapses pre-CAR	57	1.38	0.98 to 1.94	.066
No. of additional lines of therapy pre-CAR	57	1.28	1.04 to 1.57	**.021**
Prior CD19-directed therapy	57			
No		—	—	
Yes		0.97	0.36 to 2.62	.960
Pre-CAR HSCT	57			
Pre-CAR HSCT		1.51	0.56 to 4.05	.420
Preinfusion disease burden overall	57			.250
High disease burden		—	—	
Low disease burden		0.92	0.31 to 2.74	
No detectable disease		0.34	0.08 to 1.47	
CAR viability, %	56	0.99	0.92 to 1.06	.760
Determination of CAR expression (% of CAR-positive viable cells)	53	0.96	0.90 to 1.03	.230
Months from diagnosis to CAR T infusion	57	0.99	0.98 to 1.01	.400
Relapsed or refractory indication	57			
Refractory		—	—	
Relapsed		2.25	0.52 to 9.63	.280
Time from infusion to relapse, days	57			
0-60		—	—	
60-180		0.79	0.31 to 1.97	.610
180-700		0.45	0.14 to 1.40	.170
CD19 downregulation at relapse	52	3.25	1.32 to 7.99	**.010**
Multivariate analysis				
No. of additional lines of therapy pre-CAR	57	1.21	0.97 to 1.51	.084
CD19 downregulation at relapse	52	2.83	1.11 to 7.20	**.030**

NOTE. Parameters achieving statistical significance appear in bold.

Abbreviations: CAR, chimeric antigen receptor; HR, hazard ratio; HSCT, hematopoietic stem cell transplantation.
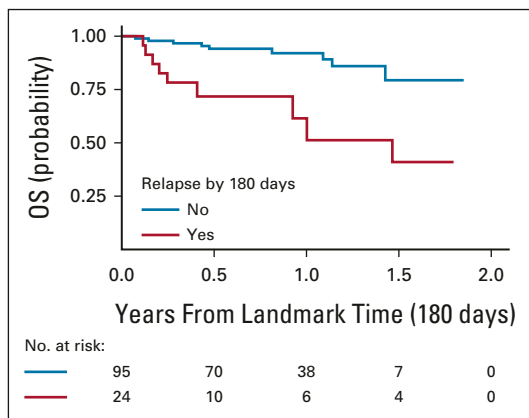
FIG 3. One hundred eighty–day landmark overall survival analysis post-tisagenlecleucel.

widely adopted initial salvage regimens. Expectedly, blinatumomab was less commonly used as post–CD19-CAR initial salvage therapy (n = 3, two progressive disease and one CR when combined with tyrosine kinase inhibitor).

Across all salvage lines after nonresponse and post-tisagenlecleucel relapse, 28% of patients (16 of 57, one nonresponder and 15 relapses) received additional CAR infusions (seven same CAR construct, nine alternative CAR constructs [four, CD22; four, CD19 clinical trial; and one, CD19-bispecific/CD22-bispecific]) within reported follow-up. One patient received two subsequent CAR infusions. The single patient receiving CAR reinfusion after nonresponse had progressive morphologic disease. After relapse, 10, four, and two CAR products were infused as first, second, and fifth salvage lines, respectively. Of patients receiving CD22-targeting CARs (monospecific CD22, n = 3; bispecific CD19/CD22, n = 1), 2 of 4 achieved CR by flow cytometry. Overall, of 15 patients with post-tisagenlecleucel relapse receiving subsequent CAR, 67% (10 of 15) achieved CR by flow cytometry, demonstrating the utility of subsequent CAR infusions to reinstate remission. OS analysis after second CAR infusion used to salvage post-CAR nonresponse or relapse is demonstrated in Appendix Fig A3 (online only).

Of 57 patients who relapsed, 19 patients were successfully bridged to allogeneic HSCT, of which 37% (7 of 19) experienced death. Of 38 patients who did not go to HSCT, 45% (17) experienced death within reported follow-up. Longer follow-up is warranted to establish if HSCT in the post-tisagenlecleucel relapse setting is protective of death. Swimmer plot demonstrates individual patient clinical courses postrelapse (Fig 2). Details of sequenced salvage therapy lines and responses are shown across 57 relapse patients, with the varying sequencing and permutations highlighting that salvage approaches in post-CAR relapse are yet to be standardized (Appendix Fig A2).

DISCUSSION

We conduct a retrospective analysis across 80 pediatric and young adult patients who experienced nonresponse (n = 23) or relapse (n = 57) after tisagenlecleucel. Overall, we demonstrate that patients with nonresponse have poor survival outcomes (12 month OS; 19%) and patients who relapse post-tisagenlecleucel have an increased risk of death as compared with patients who sustain durable remissions (HR, 4.75; 95% CI, 1.86 to 12.1; $P = .001$). Furthermore, in a landmark analysis of patients who remain alive at 6 months post-tisagenlecleucel without relapse (n = 95), we report a remarkably high OS rate of 92% at 18 months post-CAR infusion.

Antigen downregulation has emerged as a major barrier challenging the durability of post-CAR remissions.[1,7,8] Here, we conduct an outcome analysis across patients relapsing with distinct antigen expression patterns. We identify that relapse with CD19– disease is associated with poor OS (12 months; 30%), highlighting the need to address CD19– relapse as a major clinical gap. Therapeutics targeting alternative antigens to CD19 are under clinical development, with CD22-specific agents most advanced. Inotuzumab, a CD22-specific antibody-calicheamicin conjugate, achieved a 58% CR rate in CAYAs with B-ALL (phase II; n = 48).[9] CD22-specific CAR T cells achieved a 70% CR rate (phase I; n = 58) in CAYAs with B-ALL.[10] To our knowledge, this is the first CAR targeting an alternative antigen to CD19 to successfully achieve comparable efficacy. CD22 antigen density was, however, decreased upon nonresponse and relapse, highlighting that antigen downregulation is not a CD19-specific phenomenon.

Mitigation strategies to avert, rather than manage, antigen downregulation have driven CAR T-cell development with multispecificity. Phase I studies of bispecific CARs simultaneously targeting CD19 and CD22 are being clinically explored in pediatric B-ALL (ClinicalTrials.gov identifier: NCT03241940 and NCT03448393) and adult B-ALL and large B-cell lymphoma. The adult experience demonstrated an MRD-negative CR rate of 88% (n = 17). Relapse patterns, however, favored CD19– disease (50%), in the absence of CD22 antigen downregulation, supporting increased potency of the CD19 arm of this construct.[11] Alternative approaches to bispecific targeting include cotransduction of distinct CD19 and CD22 CAR vectors to yield a mixed mono- and multispecific CAR cocktail product and bicistronic vector transduction.[12,13] These respective efforts have been challenged by selective expansion of dominant monospecific CAR T-cell populations and limited persistence. These experiences showcase the challenges in developing equipotent, persisting, and multitargeting CARs.

Analysis of nonresponders highlights that 95% of nonresponders had high preinfusion disease burden. Disease burden is additionally associated with overall increased risk of relapse, supporting the growing body of literature identifying baseline high disease burden to associate with inferior survival outcomes.[2,14,15] Although our data do not identify treatment with prior blinatumomab to be predictive

of CD19– relapse, it has been shown that prior nonresponse to blinatumomab, rather than treatment itself, is a vital predictor of CD19-CAR outcomes.[14] The PRWCC previously published outcomes using tisagenlecleucel for the treatment of EM disease and described that the presence of baseline EM disease versus BM-only disease was not a risk factor for nonresponse or relapse.[16] Here, we identify that the number of preinfusion lines of therapy is associated with increased likelihood of relapse, possibly explained by more recalcitrant tumor biology, and compromised T-cell fitness or cumulative toxicity. Clinical studies evaluating CD19-CAR in the upfront MRD+ refractory setting are ongoing (ClinicalTrials.gov identifier: NCT03876769).

Analysis of individual patient's postrelapse treatment paths illustrates the heterogeneity of salvage strategies used. With the development of antibody-based therapies and cellular therapy, the therapeutic armamentarium for relapsed leukemia has expanded beyond traditional chemotherapy and HSCT. These agents have overlapping indications, yet optimized sequencing has not been standardized to date. Across 57 relapsed patients in our cohort, many distinct treatment permutations and response patterns are reported after post-CAR relapse. Chemotherapy, inotuzumab, and CAR reinfusion are used with greatest frequency as initial salvage regimens and can be used effectively to reinstate remission. The OS in this high-risk cohort of patients experiencing relapse post-tisagenlecleucel is 52% at 1 year and 32% at 2 years. This supports the need for relapse mitigation strategies, yet demonstrates the possibility of salvage in the relapse post-tisagenlecleucel setting and supports the systematic study in this window to establish treatment algorithms for post-tisagenlecleucel relapse.

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APPENDIX
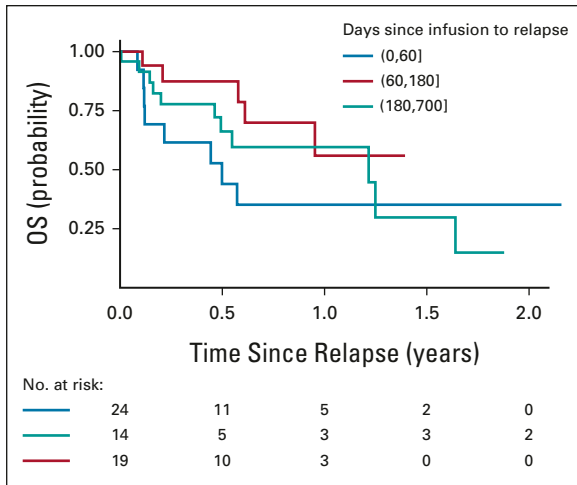
FIG A1. OS after relapse by time from infusion to relapse. OS, overall survival.
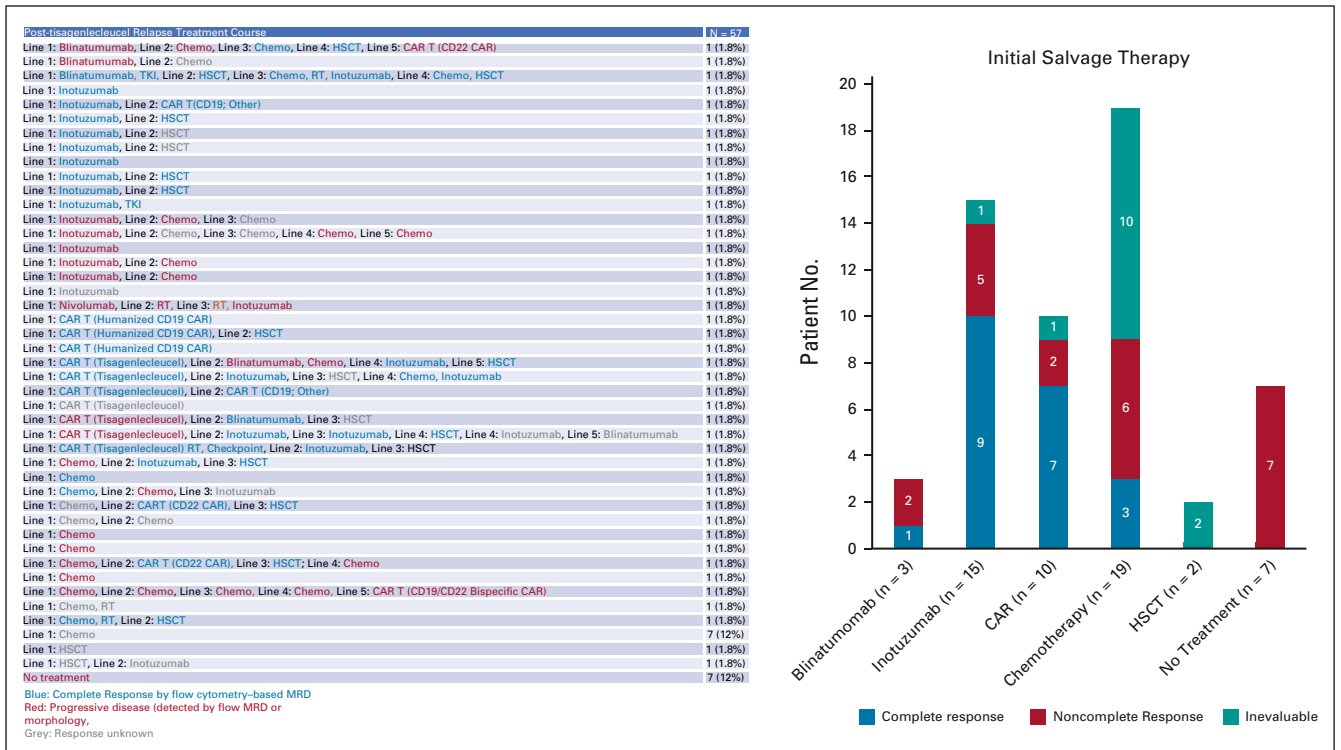
FIG A2. Salvage therapies and responses in the post-tisagenlecleucel relapse setting. CAR, chimeric antigen receptor; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; RT, radiotherapy; TKI, tyrosine kinase inhibitor.

FIG A3. OS across patients who received secondary salvage CAR infusion after tisagenlecleucel nonresponse or relapse. Time 0 is the day of the second CAR infusion. CAR, chimeric antigen receptor; OS, overall survival.

TABLE A1. Characteristics of All Infused Patients, by d28 Response

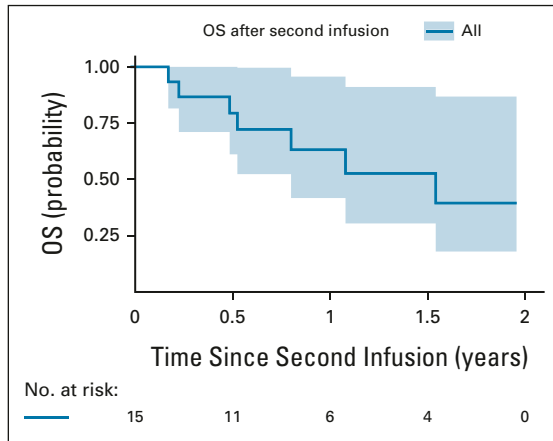| Characteristic	No Morphologic CR (n = 23)	CR by Flow (n = 148)[a]	Detectable Flow MRD (n = 5)[a]	Death Pre-d28 (n = 5)
Sex, No. (%)				
Female	8 (35.0)	58 (39.0)	4 (50)	3 (60)
Male	15 (65.0)	90 (61.0)	4 (50)	2 (40)
Age at diagnosis, years, median (IQR)	10 (2-14)	8 (3-15)	8 (7-14)	8 (8-12)
Age at infusion, years, median (IQR)	13 (5-17)	12 (8-18)	15 (13-16)	12 (11-12)
Race/ethnicity, No. (%)				
Asian	1 (4.5)	5 (3.5)	0 (0)	0 (0)
Black	2 (9.1)	3 (2.1)	1 (20)	1 (20)
Hispanic	11 (50.0)	56 (39.0)	0 (0)	2 (40)
More than one race	0 (0.0)	4 (2.8)	0 (0)	0 (0)
Non-Hispanic White	8 (36.0)	74 (52.0)	4 (80)	2 (40)
Unknown	1	6	0	0
Initial cytogenic risk, No. (%)				
Favorable	5 (31.0)	17 (15.0)	2 (40)	0 (0)
Intermediate	4 (25.0)	42 (37.0)	2 (40)	1 (25)
Unfavorable	7 (44.0)	54 (48.0)	1 (0)	3 (75)
Unknown	7	35	0	1
No. of relapses pre-CAR, median (IQR)	2.00 (1.00-2.00)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	1.00 (1.00-1.00)
No. of additional lines of therapy pre-CAR, median (IQR)	2.00 (1.50-3.00)	2.00 (1.00-3.00)	2.00 (2.00-4.00)	3.00 (2.00-4.00)
Prior CD19-directed therapy, No. (%)	8 (35.0)	29 (20.0)	1 (20)	0 (0)
Pre-CAR HSCT, No. (%)	10 (43.0)	33 (22.0)	2 (40)	1 (20)
Preinfusion disease burden overall, No. (%)				
High disease burden	**20 (95.0)**	63 (43.0)	4 (80)	**5 (100)**
Low disease burden	1 (4.8)	40 (27.0)	0 (0)	0 (0)
No detectable disease	0 (0.0)	44 (30.0)	1 (20)	0 (0)
Unknown	2	1	0	0
CAR viability, %, median (IQR)	85 (83-88)	88 (84-93)	94 (92-96)	90 (90-92)
Unknown	1	1	0	0
Determination of CAR expression (% of CAR-positive viable cells), median (IQR)	13.6 (8.2-18.2)	14.3 (10.0-18.9)	10.1 (9.9-11.2)	16.8 (14.8-18.8)
Unknown	1	5	0	0
Months from diagnosis to CAR T infusion, median (IQR)	22 (14-38)	35 (11-58)	37 (35-94)	23 (18-30)
Relapsed or refractory indication, No. (%)				
Refractory	2 (8.7)	29 (20.0)	0 (0)	0 (0)
Relapsed	21 (91.0)	119 (80.0)	5 (100)	5 (100)

NOTE. Parameters with clinical significance appear in bold.

Abbreviations: CAR, chimeric antigen receptor; CR, complete remission; d28, day 28; HSCT, hematopoietic stem cell transplantation; IQR, interquartile range; MRD, minimal residual disease.

[a]Three patients with unknown response by flow.

TABLE A2. Characteristics of Disease at Time of Nonresponse, Salvage Regimens, and Outcomes After Post-tisagenlecleucel Nonresponse

Patient No.	Disease Status at Progression (% BM Lymphoblasts with or without EM)	Antigen Expression at Progression	Pre-CAR HSCT	No. of Post-CAR Salvage Regimens	Disposition (alive/deceased)	Time of Last Follow-Up/Death	First Salvage Regimen	Second Salvage Regimen	Third Salvage Regimen	Fourth Salvage Regimen	Fifth Salvage Regimen	Sixth Salvage Regimen
1	EM (maxilla/mandible)	CD19+	No	0	Alive	85	No treatment					
2	90%	CD19+	No	0	Death	43	No treatment					
3	18%	CD19+	Yes	0	Death	44	No treatment					
4	Mixed phenotype	CD19+/ myeloid	No	0	Death	57	No treatment					
5	0.01%	CD19+	Yes	1	Death	104	Inotuzumab[PD]					
6	95%	CD19+	Yes	1	Alive	44	Chemo[(unknown)]					
7	EM (CNS3)	CD19+	Yes	1	Death	298	IT[PD]					
8	0.014%/EM (CNS3/ kidney/ pancreas)	CD19–	Yes	1	Alive	188	Inotuzumab[(resolution of EM)a]					
9	59%	CD19+	No	1	Death	188	Chemo[PD]					
10	83%	CD19+	Yes	1	Death	60	Chemo[PD]					
11	90%/EM (CNS2/ testes/liver)	CD19+	No	1	Death	45	Chemo[PD]					
12	98%	CD19+	Yes	1	Death	42	Chemo[PD]					
13	EM (R gluteal mass)	CD19+	No	1	Death	86	Radiation[PD]					
14	55%/EM (CNS3)	CD19+	No	1	Death	107	Pembrolizumab[PD]					
15	15%	CD19+	No	2	Alive	536	Chemo[CR (vinc/asp/venetoclax/navitoclax)a]	HSCT				
16	93%	CD19+	No	2	Death	198	Chemo[PD]	Blinatumomab[PD]				
17	34%	CD19+	Yes	2	Death	132	Chemo[PD]					
18	Peripheral blasts	CD19–	No	3	Alive	253	Inotuzumab[PD]	Chemo[PD]	Chemo[PD]			
19	Peripheral blasts	CD19+	No	3	Death	343	Chemo[PD]	Chemo[PD]	Inotuzumab[PD]			
20	EM (CNS3)	CD19–	Yes	3	Alive	863	IT[BM Relapse]	Inotuzumab[(CR)a]	HSCT			
21	24%	CD19+	No	4	Death	313	Chemo[PD]	Chemo[PD]	CAR[PD (Humanized-CD19)]	Inotuzumab[PD]		
22	96%	CD19+	No	5	Death	361	Chemo[Unknown]	Inotuzumab[CR(flow–/NGS+)a]	Blinatumomab[CR(flow–/rising NGS)]	Chemo/RT[PD]	Chemo[PD]	
23	95%/EM (skin)	CD19+	No	6	Alive	389	Chemo[PD]	Chemo[CR(morph–/flow+)]	Blinatumomab[CR) (flow–/NGS+)a]	HSCT	Chemo[PD]	Chemo[PD]

Abbreviations: asp, asparaginase; BM, bone marrow; CAR, chimeric antigen receptor; Chemo, chemotherapy; CR, complete remission; EM, extramedullary; HSCT, hematopoietic stem-cell transplantation; IT, intrathecal; NGS, next-generation sequencing; PD, progressive disease; RT, radiotherapy; vinc, vincristine.

[a]Complete remission achieved after the annotated regimen.