HHS Public Access

Author manuscript

Leukemia. Author manuscript; available in PMC 2023 July 01.

Published in final edited form as:

Leukemia. 2023 January ; 37(1): 154–163. doi:10.1038/s41375-022-01739-2.

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Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors.

Previous Publication: This work was presented in part as an oral presentation at the 63rd American Society of Hematology Annual Meeting (Atlanta, GA).

Conflict of Interest

Author	Name of organization	Type of relationship
Roni Shouval	Medexus	Consultancy
Parastoo B. Dahi	Kite/Gilead.	Advisory board
Sergio A. Giralt	Actinnum	Membership on an entity's Board of Directors or advisory committees
	CELGENE	Membership on an entity's Board of Directors or advisory committees
	BMS.	Membership on an entity's Board of Directors or advisory committees
	SANOFI	Membership on an entity's Board of Directors or advisory committees
	AMGEN	Membership on an entity's Board of Directors or advisory committees
	PFIZER	Membership on an entity's Board of Directors or advisory committees
	JENSENN	Membership on an entity's Board of Directors or advisory committees
	GSK.	Membership on an entity's Board of Directors or advisory committees
	JAZZ	Membership on an entity's Board of Directors or advisory committees
Gilles Salles	AbbVie Inc, Allogene Therapeutics, Autolus Therapeutics, BeiGene Ltd, Bristol-Myers Squibb Company, Celgene Corporation, Debiopharm Group, Genmab, Kite, A Gilead Company,	Advisory Committee

Outcomes of first therapy after CD19-CAR-T treatment failure in

Author	Name of organization	Type of relationship
	Incyte Corporation, Janssen Biotech Inc, Miltenyi Biotec, MorphoSys, Novartis, Roche	
	Bristol-Myers Squibb Company, Celgene Corporation, Debiopharm Group, Genmab, Kite, A Gilead Company, Incyte Corporation, Miltenyi Biotec, MorphoSys, Novartis, Roche Laboratories Inc	Consultancy
Craig S. Sauter	Juno Therapeutics	Consultancy and Research Funding
	Sanofi-Genzyme	Consultancy and Research Funding
	Spectrum Pharmaceuticals	Consultancy
	Novartis	Consultancy
	Genmab	Consultancy
	Precision Biosciences	Consultancy
	Kite/Gilead	Consultancy
	Celgene	Consultancy and Research Funding
	Gamida Cell	Consultancy
	GSK.	Consultancy
	Bristol-Myers Squibb	Research Funding
Michael Scordo	McKinsey & Company	Consultancy
	Angiocrine Bioscience	Consultancy and Research Funding
	Omeros Corporation	Consultancy and research funding
	Amgen, Inc.	Research funding
	Kite - A Gilead Company	Advisory Board
	i3 Health	Other: Honorarium, CME activity
	Medscape, LLC	Other: Honorarium, CME activity
Gunjan Shah	Amgen	Research Funding
	Janssen Pharmaceutica	Research Funding
Abraham Avigdor	Takeda	Consultancy and honoraria
	Janseen	Research Funding
	BMS	Research Funding
	Gilead	Consultancy and honoraria
	Pfizer	Consultancy and honoraria
Miguel-Angel Perales	Bristol-Myers Squibb	Honoraria
	Celgene	Honoraria
	Equilium	Honoraria
	Incyte	Honoraria and Other: Clinical trial support to institution
	Karyopharm	Honoraria
	Kite/Gilead	Honoraria and Other: Clinical trial support to institution
	Merck	Honoraria
	Miltenyi Biotec	Honoraria and Other
	MorphoSys	Honoraria

large B-cell lymphoma

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	Omeros	Honoraria
	Takeda	Honoraria
	Cidara Therapeutics	Honoraria
	Medigene	Honoraria
	Sellas Life Sciences	Honoraria
	Servier	Honoraria
	NexImmune	Honoraria
Elad Jacoby	Novartis	Advisory board, Honoraria
Joachim Yahalom	Convergent R.N.R Ltd.	Advisory board
Mikhail Roshal	Celgene	Provision of Services
	Auron Therapeutics, Inc.	Ownership / Equity Interests; Provision of Services
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Abstract

Persistence or recurrence of large B-cell lymphoma after CD19-CAR-T is common, yet data guiding management are limited. We describe outcomes and features following CAR-T treatment failure. Of 305 adults who received CD19-CAR-T, 182 experienced disease recurrence or progression (1-year cumulative incidence 63% [95%CI: 57–69]). Of 52 post-CAR-T biopsies evaluated by flow cytometry, 49 (94%) expressed CD19. Subsequent anti-cancer treatment was administered in 135/182 (74%) patients with CAR-T treatment failure. Median OS from the first post-CAR-T treatment was 8 months (95%CI 5.6–11.0). Polatuzumab-, standard chemotherapy-, and lenalidomide-based treatments were the most common approaches after CAR-T. No complete responses (CRs) were observed with conventional chemotherapy, while CR rates exceeding 30% were seen following polatuzumab- or lenalidomide-based therapies. Factors associated with poor OS among patients treated post-CAR-T were pre-CAR-T bulky disease (HR 2.27 [1.10–4.72]), lack of response to CAR-T (2.33 [1.02–5.29]), age >65 years (HR 2.65 [1.49–4.73]) and elevated LDH at post-CAR-T treatment (HR 2.95 [1.61–5.38]). The presence of ≥2 of these factors was associated with inferior OS compared to ≤1 (56% vs. 19%). In this largest analysis to date of patients who progressed or relapsed after CD19-CAR-T, survival is poor, though novel agents such as polatuzumab and lenalidomide may have hold promise.

INTRODUCTION

CD19-directed chimeric antigen receptor T-cell (CD19-CAR-T) therapy has transformed the care of relapsed or refractory (r/r) large B-cell lymphoma (LBCL). Both FDA-approved and Point-of-Care CD19-CAR-T cell (POC) products have resulted in unprecedented response rates of approximately 70% in this population.[1–7] Unfortunately, over 60% of patients will ultimately progress or relapse following CD19-CAR-T.[8–13]

The treatment landscape for r/r LBCL is expanding. Polatuzumab, tafasitamab, selinexor, and loncastuximab are FDA-approved in this setting.[14–17] Immune checkpoint inhibitors, lenalidomide, bi-specific antibodies, investigational CAR-T products, and allogeneic hematopoietic cell transplantation, as well as salvage chemotherapy, represent additional options. Nevertheless, it is unclear how they should be utilized after exposure to CAR-T.[18, 19] Several groups have reported their experience treating relapses after CAR-T cell therapy, albeit with limited sample sizes and heterogeneous treatment strategies.[11, 13, 19–22],

In this retrospective observational research study, our aims were: 1. Report characteristics and outcomes of LBCL patients whose disease relapsed or progressed after CD19-CAR-T therapy; 2. Characterize response and overall survival of first-line interventions after CAR-T therapy; 3. Identify risk factors for poor outcomes and develop a model for stratifying the mortality risk in patients receiving therapeutic interventions after CAR-T treatment.

MATERIAL AND METHODS

Study Population

This retrospective analysis included patients with r/r LBCL treated at Memorial Sloan Kettering Cancer Center (MSKCC, New York) and Sheba Medical Center (Tel Hashomer, Israel) with CD19-directed CAR-T cell therapy between April 2016 to May 2021 (Figure 1A). We included adults (age ≥ 18 years) treated with one of the following CD19-CAR-T products: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), or a POC CD28-based product (NCT02772198).[6, 7] Axi-cel and tisa-cel were given as standard-of-care therapy, and liso-cel was administered under the TRANSCEND NHL 001 study (NCT02631044). Patients who received additional anti-cancer treatment concomitantly with CAR-T administration were excluded. Patient data were captured in REDCap databases.[23] The Institutional Review Boards of the participating institutions approved the study in accordance with the Declaration of Helsinki.

Definitions

Bulky disease was defined as the presence of any mass with a single diameter > 10 cm. Response assessment was performed locally according to the Lugano criteria.[24] Best response denotes the best response achieved up to 100 days following cell infusion. Disease status before CAR-T infusion was determined according to the most recent disease assessment before infusion. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded using the American Society of Transplant and Cellular Therapy grading criteria.[25] Event-free survival (EFS) was defined as the time from (1) CAR-T infusion (“post-CAR-EFS”) and (2) the initiation of first-line treatment after CAR-T (“post-treatment-EFS”) to the date of first documented progression, death due to any cause, or the initiation of the subsequent line of treatment. Similarly, post-CAR-overall survival (OS) and post-treatment-OS corresponded to time from CAR-T infusion and first-line treatment after CAR-T to vital status at last-follow up. Time to progression or relapse was measured from time of CAR-T infusion. Death without documented relapse or progression was considered a competing event. Table S1 lists additional definitions.

Flow Cytometry

Flow cytometry was performed as previously described[26]. Panels used for B cell analysis and methodology are presented in Table S2.

Statistical Analysis

Descriptive statistics, including median and interquartile range (IQR) for continuous variables and percentages for categorical variables, are provided. OS and EFS were estimated using the Kaplan-Meier method. Fisher’s exact or χ^2 tests evaluated the association between categorical variables. The Wilcoxon rank-sum test or Kruskal-Wallis test was used to assess the difference in a continuous variable between/among patient groups. Clinically relevant variables were included in univariable Cox regression models for post-CAR-EFS and post-treatment-overall survival (OS). Variables meeting a $P \leq .1$ in

univariable models were introduced into multivariable Cox regression models stratified by center. Characteristics associated with adverse post-treatment-OS in the multivariable model were aggregated as a score into a risk-stratification system. An exploratory multivariable Cox regression analysis stratified by center and adjusted for age, response to CAR-T, and pre-treatment LDH was used to compare post-treatment-OS between different post-CAR-T treatment strategies. Data were analyzed using R (version 4.1.2).

RESULTS

Patient characteristics and outcomes

A total of 305 patients (MSKCC n=165 [54%], Sheba n=140 [46%]; Table 1) with a median age of 63 years (range: 20–86) received CD19-CAR-T therapy (axi-cel [n=116, 38%]; tisa-cel [n=83, 27%]; lisocel [n=28, 9%]; POC-CAR-T [n=78, 26%]). The primary histological subtype of LBCL was diffuse large B cell lymphoma not otherwise specified (n=236, 77%). A majority (211, 69%) had received 3 or more previous lines of therapy, 125 patients (41%) were generally heavily pretreated (>3 lines; 125, 41%), most had stage III-IV disease (216, 71%), and 134 (44%) and 43 (14%) had primary refractory disease and bulky disease, respectively.

CRS and ICANS of any grade were observed in 76% and 32% of patients, respectively, with severe (grade ≥2) CRS and ICANS developing in 33% and 23%. Most patients responded to CAR-T treatment (best overall response was 67%, 48% complete response [CR], 19% partial response [PR]). CAR-T product specific toxicity and response are presented in Table S3. With a median follow-up of 20 months (IQR: 10–30), the probability of 1-year post-CAR-OS and post-CAR-EFS was 62% (95% confidence interval [CI] 56–68) and 29% (95% CI 24–35), respectively (Figure 1B). At one year, the cumulative relapse or progression incidence rate was 63% ([95% CI 57–69], Figure 1C).

Predictors of post-CAR-EFS

Post-CAR-EFS reflects cases with CAR-T treatment failure due to relapse, progression, or death. Therefore, it is imperative to understand its determinants. We screened for candidate predictors in univariable analysis. Those meeting a significance criteria of $P <$ .1 were introduced to a multivariable Cox regression model (Table 2). Non-germinal center lymphomas (Hazard Ratio [HR], 1.43; 95% CI, 1.04–1.97); P= .026), pre-apheresis primary refractory disease (HR, 1.64; 95% CI, 1.18–2.28); P = .003), elevated pre-CAR-T LDH (HR, 1.89; 95% CI, 1.37–2.60); $P <$ .001), and presence of active disease at time of CAR-T infusion relative to complete metabolic remission (PR [HR, 1.90; 95% CI] and SD/PD [HR, 3.32; 95% CI, 0.80–13.8]; global P = .012). Apart from these traditional risk factors, Tisa-cel was also associated higher risk of treatment failure compared to axi-cel (HR, 2.03; 95% CI, 1.37–3.00, P = .005).

Disease features at CAR-T treatment failure

Of 182 patients with disease recurrence or persistence after CAR-T, 51% had CAR-T refractory disease, and 49% initially responded to CAR-T but then relapsed. Tissue biopsies to confirm disease persistence or recurrence were performed in 77 patients. Since antigen

escape is a potential mechanism of CAR-T resistance,[27–31] we assessed CD19 expression in 52 tumor biopsies. Interestingly, CD19 expression (Figure 2A) was absent in only 3/52 (6%), while the remaining samples had either dim (14/52, 27%) or normal (35/52, 67%) expression.

We compared baseline characteristics between refractory patients versus those relapsing after CAR-T to identify those potentially related to the type of CAR-T treatment failure (Figure 2B, Table S4). Primary refractory disease before apheresis was the only pre-CAR-T that varied between the groups, with a greater percentage in the CAR-T-refractory population (58% vs. 36%, $P = .003$).

To further understand the differences between these two patterns of disease response to CAR-T, we studied additional variables measured after CAR-T infusions. Patients in the refractory group were more likely to have new sites of disease involvement at time of disease assessment compared to the relapse group (30% vs. 14%, $P = .017$). Patients with CAR-T resistance had similar CD19 expression at disease progression to those with relapsed disease, both when considering expression categories (absent/dim/normal; $P = .88$) and MFI ratio (relative to a reference value) as a continuous covariate ($P = .60$). Collectively, our findings suggest that disease resistance and relapse are both common modes of CAR-T treatment failure and that better biomarkers are required to describe the differences in disease biology between them.

Therapy following CAR-T treatment failure

Of 182 patients with relapsed or stable/progressive disease post-CAR-T, 135 patients (74%; Figure 1A) received subsequent anti-cancer therapy at a median of 83 days (IQR: 53–130) after CAR-T infusion. Most patients (75/135, 56%) were treated for disease relapsing after response to CAR-T (CR 32%, PR 24%); the remaining patients (60/135, 44%) were treated for CAR-T-unresponsive disease.

To provide an indirect assessment of considerations underlying the decision to treat after CAR-T treatment failure, we compared patients receiving and not receiving anti-cancer treatment following CAR-T (Table S5). Untreated patients were more likely to be older at the time of CAR-T infusion (median age 65 [IQR: 57–72] vs. 60 [IQR: 49–69], $P = .029$) and have bulky disease before apheresis (28% vs. 12%).

Among patients who received further therapy after CAR-T treatment failure, the overall response rate was 39% (CR 20%; PR 19%). As expected, the median time from CAR-T to next line treatment for patients who had progressive or stable disease after CAR-T was shorter than those who initially responded and then relapsed (50 days [IQR 37–66] vs. 123 days [IQR 92–236], $p<0.001$). Median follow-up from time of first-line therapy after CAR-T was 15 months (IQR: 8–33). Median post-treatment-OS and post-treatment-EFS (Figure 3A) were 8.5 months (95% CI 5.6–11) and 1.9 months (95% CI 1.4–2.3), respectively. These poor outcomes highlight the urgent need for interventions to improve the care of patients requiring anti-cancer treatment after CAR-T.

More than 30 distinct treatment strategies were employed for first-line therapy after CAR-T. Treatments were grouped by major drug classes or agents (Table S6). The predominant treatment categories (Figure 3B) included polatuzumab-based (n=29), chemotherapy approaches (n=17; anthracycline or platinum-based), lenalidomide-based (n=15), involved site radiation therapy (ISRT) monotherapy (n=15), and Bruton's tyrosine kinase inhibitor-based (BTKi; n=14). Treatment assignments were made at the treating physician's discretion and varied by center Monotherapy ISRT was primarily administered for localized diseases (Figure 3C).

Patient characteristics across the various treatment strategies differed meaningfully. Aggressive disease features such as bulky disease, primary refractory disease before apheresis, and lower response rates to CAR-T were more frequently observed in the chemotherapy group. Patients receiving lenalidomide were older and more heavily pretreated than other treatment groups while also having favorable CAR-T responses and lower pre-treatment LDH (i.e., before administration of post-CAR-T treatment). Patients treated with polatuzumab and BTKi-based strategies were typically younger than 60 years old, and over 70% of these patients had elevated pre-treatment LDH (Table S7). CR rates of systemic therapies ranged from 0% with chemotherapy to over 30% with lenalidomide and polatuzumab-based strategies (Figure 3D; Table S8). Patient-level outcome to the most common systemic treatment groups (polatuzumab-based (n=29), chemotherapy approaches (n=17), lenalidomide-based (n=15, and BTKi n=14) are depicted in Figure S1.

One-year survival following the most common systemic treatment strategies (1-year post-treatment-OS) ranged from 21% (95% CI 8–58) with BTKi and 25% (95% CI 11–59) with chemotherapy-based approaches to 69% (95% CI 48–100) with lenalidomide-based treatment (Figure 3E; Table S9). Polatuzumab-based strategies induced complete or partial responses in 48% of patients (CR n=10/29 [34%], PR n=4/29 [14%]), though these responses did not translate into prolonged 1-year post-treatment-OS (37% [95% CI 22–63]). Given the differences in post-treatment-OS rates, we performed an exploratory analysis to compare the leading treatment strategies. In a multivariable Cox regression model stratified by center and adjusted for potential drivers of treatment selection, including age, LDH at treatment, and previous response to CAR-T (Table S10), lenalidomide-based treatment was associated with improved post-treatment-OS compared to standard chemotherapy (HR 0.25 [0.07–0.85], $P = .027$). Our findings suggest that novel agents may induce remission after CAR-T treatment failure.

Post-CAR-T risk stratification system

Given poor outcomes following first-line treatment after CAR-T treatment failure, we sought to identify key predictors of mortality in this setting. We investigated associations between disease, patient, and therapy-related features with post-treatment-OS in univariable and multivariable Cox regression models. Older age (>65 years), bulky disease at apheresis, elevated LDH pre-treatment, shorter period between CAR-T to treatment (<100 days), advanced disease stage at treatment, and CAR-T refractoriness were candidate predictors of shorter post-treatment-OS in univariable analysis (Table 3). A multivariable Cox model for post-treatment OS, including candidate predictors, confirmed an independent association of

bulky disease (HR 2.27 [95% CI: 1.10–4.72]), older age (HR 2.65 [95% CI 1.49–4.73]), elevated LDH, (HR 2.95 [95% CI 1.61–5.38]) and CAR-T refractoriness (95% CI 2.33 [1.02–5.29]). To stratify the risk of mortality for these patients, we propose a prognostic system including these four factors (pre-apheresis bulky disease, CAR-T refractoriness, age > 65, and pre-treatment LDH). Grouped by the presence of 0–1 versus ≥ 2 of these factors, the corresponding probability of 1-year survival was 56% (95% CI 42–75) vs. 19% (95% CI 11–35, Figure 3F), respectively.

DISCUSSION

We sought to address knowledge gaps related to outcomes and management of patients who were failed by CAR-T therapy. Our results reflect the dismal consequences of lymphoma persistence after CAR-T and highlight the unmet need for therapies with long-lasting effects. Nonetheless, newer agents show activity after CAR-T exposure and should be further explored in this context. Finally, we propose a prognostic tool for identifying patients at the highest risk for early mortality after CAR-T, which may help stratify patients for future investigations in the post-CAR-T setting.

This observational study illustrates the immense contribution of CAR-T cells to our field. However, and in line with the pivotal trials and real-world data,[1–3, 8, 9, 12, 32] 60% of the studied population did not achieve long-term disease control, confirming that disease recurrence or progression represents the most significant challenge in r/r LBCL treated with CAR-T. We identified several risk factors for CAR-T treatment failure concordant with the literature and included treatment-refractory disease, bulky disease before apheresis, and elevated LDH before CAR-T infusion.[1, 11, 12, 33] Notably, non-GCB cell-of-origin, was likewise associated with shorter post-CAR-EFS. To our knowledge, this represents the first report associating COO and adverse outcome after CAR-T. Previous studies have not identified the same effect but may have had less power to detect it or looked at endpoints other than post-CAR-EFS.[10–13] The choice of CAR-T product was also notable. In a multivariable analysis, patients treated with tisa-cel were at increased risk for an EFS event compared to axi-cel. This finding should be interpreted with caution as latent confounders such as performance status may have guided product selection and could underlie worse outcomes. While many of the identified risk factors for treatment failure are fixed, they can be used to identify high-risk populations who could potentially benefit from further interventions such as post-CAR-T maintenance.

Antigen loss is a predominant immune escape mechanism in B-cell acute lymphoblastic leukemia.[27–30] In our cohort, which we believe is the most extensive collection of LBCL post-CAR-T tumor samples reported to date, loss of CD19 was infrequent (only 6%). Furthermore, CD19 expression at CAR-T treatment failure showed no correlation with CAR-T refractoriness versus later relapse. Our findings echo those reported by Plaks *et al.* in suggesting that antigen loss is a minor resistance mechanism in LBCL.[31] The persistence of CD19 may render tumors susceptible to further CD19-directed interventions such as tafasitamab or loncastuximab,[14, 17] Disappointingly, Gauthier et al. have reported low response rates for a second CD19-directed CAR-T infusion.[34] However, bispecific

constructs simultaneously targeting CD19 and CD20 appear to have promising activity among this patient population.[35]

CAR-T use is rapidly growing and is being introduced as an earlier line of treatment,[36–38] leading to greater opportunity for therapeutic decisions in the CAR-T treatment failure setting. Several small patient series have reported outcomes of post-CAR-T interventions.[13, 19–22, 34] While treatment assignments following CAR-T varied, we believe our study provides the most comprehensive experience reported to date.

Overall survival and complete response rates with lenalidomide as first-line therapy after CAR-T treatment failure were encoring (69% and 33%, respectively). Lenalidomide was primarily given as monotherapy (8/15). These results could be driven by the relatively favorable initial responses to CAR-T, along with generally lower pre-treatment LDH, in this group. However, these promising results could also be linked to distinct immunomodulatory activity of lenalidomide in the presence of CAR-T cells. In preclinical models, lenalidomide appears to mitigate T-cell exhaustion and induce CAR-T cell activation.[39–41] Preliminary clinical data suggest that lenalidomide can induce high response rates in LBCL rapidly progressing after CAR-T cell therapy.[42] Polatuzumab treatment, typically administered with bendamustine (n=26), also resulted in promising overall response rates (48%), albeit lower 1-year overall survival in our cohort. Similar results were reported by Liebers et al.[21] Others showed a similar response to polatuzumab but with limited durability.[43] Therefore, polatuzumab may serve as a valuable agent for salvage therapy post-CAR-T. A follow-up study on the CORAL trial demonstrated that salvage chemotherapy, administered as third-line treatment in r/r LBCL, induced CR in approximately 30% of cases.[44] However, chemotherapy-based approaches did not result in CRs in our cohort and OS was poor. In an exploratory comparison of survival between chemotherapy-based treatment and novel agents, the disadvantage of post-CAR-T salvage chemotherapy persisted when adjusting for features that may contribute to treatment selection. Nevertheless, aggressive disease features more prevalent in this subgroup (Table S6) may have driven results in this group. Our results suggest that chemotherapy should be deprioritized in sequencing therapies post-CAR-T in contemporary practice. The proliferation of new treatment options for r/r LBCL complicates the identification of the best sequence of treatments post-CAR-T therapies and warrants the development of prospective trials.

Tools for risk stratification in a population with CAR-T-resistant LBCL could inform clinical trial design and goals of care discussion. We identified four key predictors of OS in patients receiving treatment for relapse or progressive disease after CAR-T therapy: (1) bulky disease at apheresis, (2) refractoriness to CAR-T, (3–4) age, and elevated LDH at the time of subsequent therapy. Notably, bulky disease was the only factor preceding CAR-T, suggesting it is a biomarker of disease biology. We propose a simple prognostic tool incorporating these factors for identifying patients at the highest risk of early adverse outcomes after post-CAR-T therapy and should be used for stratifying or selecting clinical trial participants in the post-CAR-T setting. The proposed system is intended to be a research instrument, not a clinical decision-making tool.

Several limitations of the analysis should be noted. First, treatment decisions post-CAR-T varied considerably and were not protocol-driven. Therefore, selection bias and latent confounders such as pre-existing hematological toxicities, performance status, comorbidities, and health insurance complicate comparisons between the treatments. However, we have extensively characterized the differences among the groups and restricted comparisons to only the most common treatments while adjusting for key known confounders to mitigate this bias. Second, despite describing what we believe is the largest cohort of post-CAR-T relapse and progression to date, the sample size remains limited and spread across varied treatment groups. Third, the intent of treatments administered after CAR-T was not captured. Treatment goals are essential for interpreting results in interventions such as monotherapy ISRT. Imber et al. recently reported ISRT as an effective bridging treatment for patients relapsing with localized disease after CAR-T.[20] However, a portion of patients in our cohort likely received monotherapy ISRT for palliation. Therefore, we only describe outcomes with radiation therapy and avoid comparisons. Finally, biological biomarkers such as the continued presence of CAR-T cells at relapse or progression are lacking.

In conclusion, the poor outcomes following CAR-T treatment failure suggest that the community should focus first and foremost on relapse prevention. In patients treated with curative intent after CAR-T therapy failure, our findings indicate that definitive approaches are needed as the vast majority progress. Future trials should aim to tailor post-CAR-T management strategies based on patient and disease features as well as exposure to previous therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment:

This research was supported in part by the Memorial Sloan Kettering Cancer Center Core grant (P30 CA008748) from the National Institutes of Health/National Cancer Institute. RS was supported by the American Society of Transplantation and Cellular Therapy New Investigator Award, the American Society of Hematology Fellow Scholar Award, a grant from the Long Island Sound Chapter, Swim Across America, the Robert Hirschhorn Award, and the Memorial Sloan Kettering Steven Greenberg Lymphoma Research Award. A.A.T was supported by a grant from the Alfonso Martín Escudero. JAF was supported by an HONORS Award from the American Society of Hematology.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available due to protect study participant privacy but are available from the corresponding author upon reasonable request.

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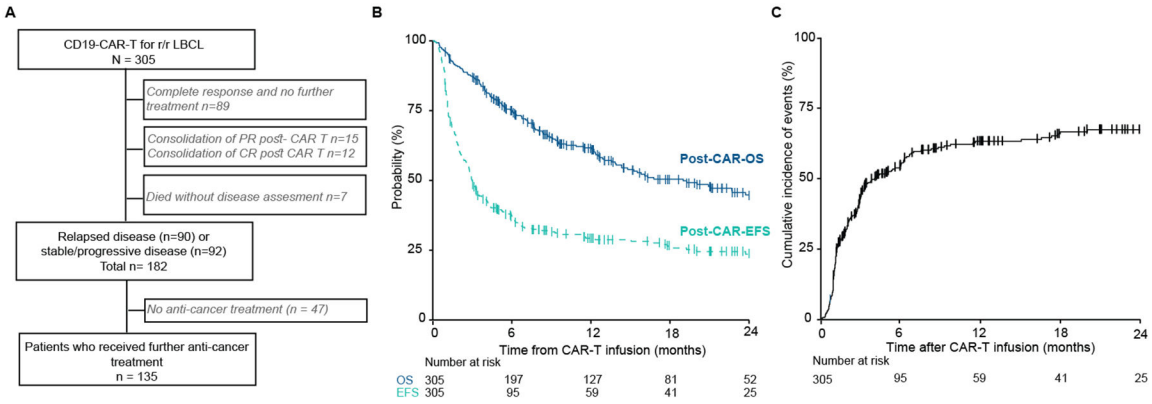

Figure 1. Outcomes following CD19-CAR-T in LBCL.

(**A**) A study flow diagram describing the population. Three hundred five patients were included; 165 patients were treated at MSKCC and 140 at Sheba Medical Center. One hundred thirty-five patients received subsequent anti-cancer treatment for relapsed or progressive or stable disease post-CAR-T therapy. (**B**) Post-CAR-overall survival (OS) and post-CAR-event-free survival (EFS) from the day of CAR-T infusion across the entire cohort. (**C**) Cumulative incidence of relapse or progression after CD19-CAR-T therapy. MSKCC – Memorial Sloan Kettering Cancer Center; r/r – relapsed/refractory; LBCL – large B-cell lymphoma; PR – partial response; CR – complete response.

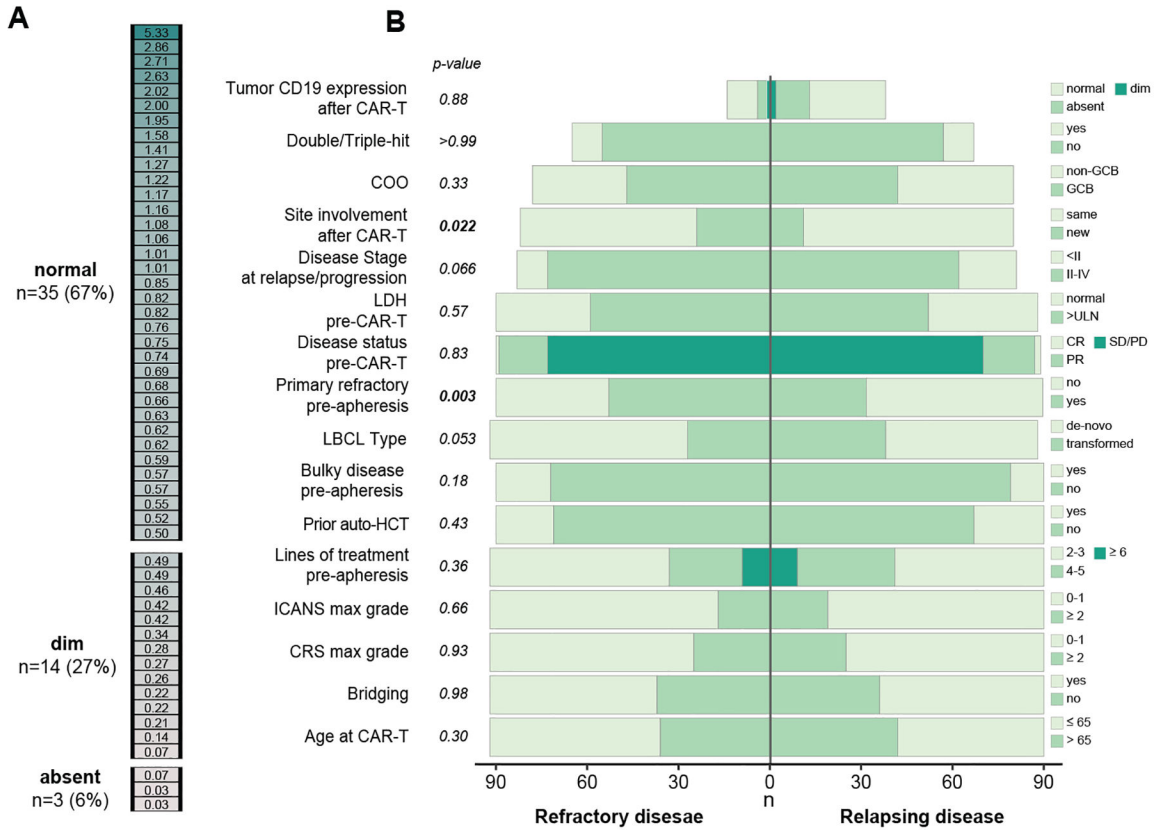

Figure 2. Characteristics at time of CAR-T treatment failure

(**A**) CD19 expression was assessed by flow cytometry in 52 tumor biopsies that were performed after CD19-CAR-T therapy. The color intensity represent CD19 expression intensity as measured by the MFI ratio (see methods). Expression was categorized into dim and normal based on the MFI ratio level. Absent (**B**) A divergent bar plot representing differences between pre- and post-CAR-T features of LBCL refractory to CAR-T vs. LBCL that initially responded to CAR-T and then relapsed (Table S2). P-values represent Pearson's Chi-squared test or Fisher's exact test.

COO– Cell of origin; LDH – lactate dehydrogenase; LBCL – large B-cell lymphoma; auto-HCT – autologous hematopoietic stem cell transplantation; PR – partial response; CR – complete response; CRS–Cytokine release syndrome (CRS); ICANS– Central Nervous System (CNS); GCB– Germinal center B cells; ULN–Upper Limit of Normal; PR– Partial response; CR– Complete response; PD– Progressive disease; SD– Stable disease.

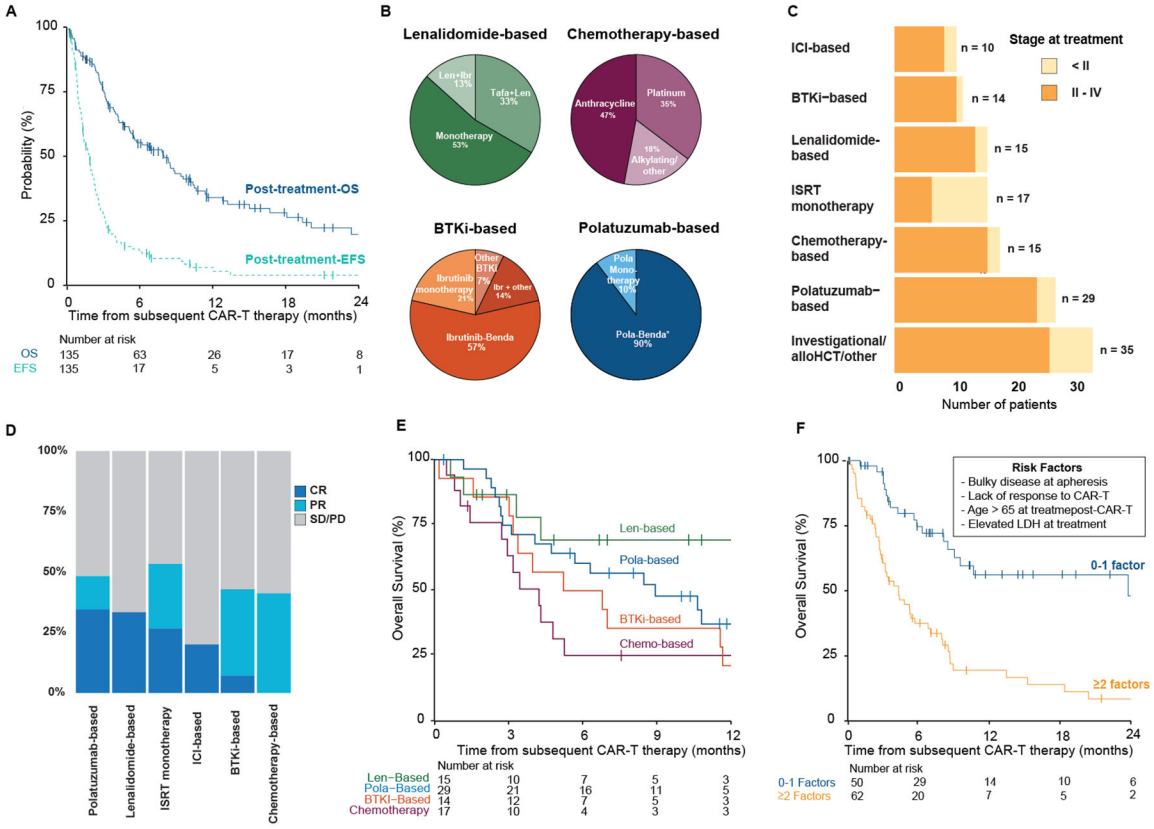

Figure 3. Outcomes among patients receiving first treatment after CD19-CAR-T.

(**A**) Post-treatment-overall survival (OS) and post-treatment-event-free survival (EFS) from initiation of first-line treatment post-CD19-CAR-T. (**B**) Treatment components among the most common treatments groups. Treatment strategies of the remaining treatment groups are listed in Table S3. (**C**) First-line treatment strategies, by disease stage at time of relapse or progression, after CD19-CAR-T treatment failure. (**D**) Response rates by treatment group. (**E**) Post-treatment-OS by leading treatment strategies. (**F**) Overall survival by prognostic strata.

AutoSCT – autologous stem cell transplantation; GCB – germinal center B-cell; CRS – cytokine release storm; ICANS – immune effector cell-associated neurotoxicity syndrome; LDH – lactate dehydrogenase; ICI – immune checkpoint inhibitor; BTKi – Bruton's tyrosine kinase inhibitor; ISRT – involved site radiation therapy; alloHCT – allogeneic hematopoietic stem cell transplantation; Ibr - Ibrutinib; Tafa – tafasitimab; Benda - bendamustine; CR – complete response; PR – partial response; SD/PD – stable disease/progressive disease

Table 1.

Population characteristics

Characteristic	Overall, N = 305[1]
Age (years) at infusion	63 (IQR: 51 – 71)
≤ 65	176 (58%)
> 65	129 (42%)
Patient sex	
Female	112 (37%)
Male	193 (63%)
LBCL origin	
De novo	191 (63%)
Transformed low-grade	111 (37%)
Unknown	3
Primary diagnosis	
DLBCL NOS	236 (77%)
High-grade b-cell lymphoma[2]	42 (14%)
Primary mediastinal B-cell lymphoma	21 (7%)
Other[3]	6 (2%)
Cell of origin	
Germinal Center B cells	125 (47%)
non- Germinal Center B cells	139 (53%)
Unknown	41
Double/triple hit	32 (15%)
Unknown	92
Number of prior lines of therapy	
2 lines	94 (31%)
3 lines	86 (28%)
4–5 lines	94 (31%)
6 or more lines	31 (10%)
Prior autologous transplantation	76 (25%)
Prior allogeneic transplantation	14 (5%)
Primary refractory disease up to apheresis	134 (44%)
Unknown	1
Bulky disease at apheresis	43 (14%)
Stage at apheresis	
≤ II	87 (29%)
III-IV	216 (71%)
Unknown	2
Bridging therapy	172 (56%)
Pre-CAR-T LDH	
Normal range	138 (46%)

Characteristic	Overall, N = 305[1]
> ULN	160 (54%)
Unknown	7
Disease status at the time of CAR-T infusion	
Complete response	13 (4%)
Partial response	60 (20%)
Stable/Progressive disease	229 (76%)
Unknown	3
Days from diagnosis to CAR-T	456 (286 – 810)
Unknown	2
CAR-T product	
Axicabtagene ciloleucel	116 (38%)
Lisocabtagene maraleucel	28 (9%)
POC-CAR-T	78 (25%)
Tisagenlecleucel	83 (27%)

[1] Median (IQR); n (%)

[2] High-grade b-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangement (n =30, 10%), High-grade B-cell lymphoma, NOS (n=12, 4%)

[3] EBV-positive DLBCL, T-cell rich DLBCL, Intravascular large B-cell lymphoma

Abbreviations: Large B cell lymphoma (LBCL), Diffuse large B cell lymphoma Not otherwise specified (DLBCL NOS) Germinal Center B cells (GCB), Lactate dehydrogenase (LDH), Upper Limit of Normal (ULN), Point-of-Care CD19-CAR-T cell (POC)

Table 2.

Univariable and multivariable Cox regression model for predictors of post-CAR-EFS

	Univariable analysis				Multivariable analysis*			
Characteristic	**N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**HR[1]**	**95% CI[1]**	**p-value**
Age at infusion (binary)	305			0.36				
≤ 65		—	—					
> 65		0.88	0.67, 1.15					
LBCL type	302			0.061				
De novo		—	—					
Transformed low-grade		0.77	0.58, 1.02					
Cell of origin	264			0.052	255			0.026
Germinal Center B cells		—	—			—	—	
non- Germinal Center B cells		1.33	1.00, 1.77			1.43	1.04, 1.97	
Double/triple hit[2]	213			0.62				
No		—	—					
Yes		1.12	0.72, 1.75					
Number of prior lines of therapy	305			0.36				
2 lines		—	—					
3 lines		1.19	0.84, 1.68	1.19				
4–5 lines		0.88	0.62, 1.25	0.88				
6+ lines		1.15	0.71, 1.85	1.15				
Prior autologous transplantation	305			0.14				
No		—	—					
Yes		0.79	0.58, 1.09					
Prior allogeneic transplantation	305			0.77				
No		—	—					
Yes		1.10	0.60, 2.01					
Primary refractory disease up to apheresis	304			<0.001	255			0.003
No		—	—			—	—	
Yes		1.70	1.30, 2.22			1.64	1.18, 2.28	
Bulky disease at apheresis	305			0.003	255			0.007
No		—	—			—	—	
Yes		1.81	1.26, 2.59			1.82	1.18, 2.82	
Stage at apheresis	303			0.035	255			0.31
≤ II		—	—			—	—	
III-IV		1.38	1.01, 1.88			1.21	0.84, 1.73	
Bridging therapy	305			0.50				
No		—	—					
Yes		1.10	0.84, 1.44					
Pre-CAR-T LDH	298			<0.001	255			<0.001
Normal range		—	—			—	—	

		Univariable analysis				Multivariable analysis*		
Characteristic	**N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**HR[1]**	**95% CI[1]**	**p-value**
> ULN		2.03	1.53, 2.69			1.89	1.37, 2.60	
Disease status at the time of CAR-T infusion	302			<0.001	255			0.012
Complete response		—	—			—	—	
Partial response		2.46	0.88, 6.90			1.90	0.44, 8.18	
Stable/Progressive disease		3.72	1.38, 10.0			3.32	0.80, 13.8	
CART product	305			0.002	255			0.005
Axicabtagene ciloleucel		—	—			—	—	
Lisocabtagene maraleucel		1.15	0.71, 1.88			1.32	0.79, 2.23	
POC-CAR-T		1.88	1.33, 2.65			1.64	0.98, 2.74	
Tisagenlecleucel		1.56	1.11, 2.20			2.03	1.37, 3.00	

*Multivariable cox regression analysis were stratified by center

[1]HR = Hazard Ratio, CI = Confidence Interval

[2]Double/triple hit is defined by two or three recurrent chromosome translocations; MYC/8q24 loci in combination with the t (14; 18) (q32; q21) bcl-2 gene or/and BCL6/3q27 chromosomal translocation.

Abbreviations: Large B cell lymphoma (LBCL), Lactate dehydrogenase (LDH), Upper Limit of Normal (ULN), Point-of-Care CD19-CAR-T cell (POC).

Table 3.

Univariable and multivariable Cox regression models for post-treatment-OS in patients receiving anti-cancer treatment after CAR-T

	Univariable analysis				Multivariable analysis*			
Characteristic	**N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**HR[1]**	**95% CI[1]**	**p-value**
Age at infusion (years)	135			0.035	112			<0.001
≤ 65		—	—			—	—	
> 65		1.60	1.04, 2.47			2.65	1.49, 4.73	
LBCL type	133			0.64				
De novo		—	—					
Transformed low-grade		0.90	0.56, 1.43					
Cell of origin	119			0.88				
Germinal Center B cells		—	—					
non- Germinal Center B cells		1.04	0.66, 1.63					
Double/triple hit cytogenetics translocations	98			0.15				
No		—	—					
Yes		1.62	0.87, 3.00					
Prior autologous transplantation	135			0.39				
No		—	—					
Yes		0.81	0.49, 1.33					
Primary refractory disease up to apheresis	135			0.15				
No		—	—					
Yes		1.37	0.89, 2.10					
Bulky disease at apheresis	135			0.090	112			0.027
no		—	—			—	—	
yes		1.73	0.96, 3.12			2.27	1.10, 4.72	
Bridging therapy	135			0.31				
No		—	—					
Yes		1.25	0.81, 1.94					
CART costimulatory domain	135			0.85				
41bb		—	—					
CD28		0.96	0.63, 1.47					
Maximal CRS grade	135			0.42				
0–1		—	—					
≥ 2		1.23	0.75, 2.03					
Maximal ICANS grade	135			0.30				
0–1		—	—					
≥ 2		1.37	0.77, 2.44					
Overall response to CAR-T	135			0.058	112			0.044
Responder		—	—			—	—	
Nonresponder		1.51	0.99, 2.32			2.33	1.02, 5.29	
Pre-treatment LDH	116			<0.001	112			<0.001

		Univariable analysis				Multivariable analysis*		
Characteristic	**N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**HR[1]**	**95% CI[1]**	**p-value**
Normal range		—	—			—	—	
> ULN		2.94	1.72, 5.02			2.95	1.61, 5.38	
Disease stage at relapse or progression	126			0.013	112			0.52
Stage I		—	—			—	—	
Stages II-IV		2.07	1.11, 3.83			1.32	0.56, 3.08	
Time from CAR-T to next treatment- 100 (days)	135			0.058	112			0.73
>100		—	—			—	—	
0–100		1.54	0.98, 2.42			0.88	0.42, 1.83	

*Multivariable cox regression model stratified by center

[1]HR = Hazard Ratio, CI = Confidence Interval

Abbreviations: Large B cell lymphoma (LBCL), Lactate dehydrogenase (LDH), Upper Limit of Normal (ULN), Point-of-Care CD19-CAR-T cell (POC), Immune effector cell-associated neurotoxicity syndrome (ICANS), Cytokine release syndrome (CRS), Central Nervous System (CNS) Immunohistochemistry (IHC).