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ORIGINAL PAPER

Outcome after chimeric antigen receptor (CAR) T-cell therapy failure in large B-cell lymphomas

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Summary

This study retrospectively evaluated the outcome of salvage therapy in 51 patients who failed axicabtagene ciloleucel or tisagenlecleucel for relapsed/refractory large B-cell lymphomas. Of these patients, 22 (43%) were enrolled in clinical trials (glofitamab or loncastuximab tesirine + ibrutinib), whereas 29 received standard therapies (lenalidomide [Len], checkpoint inhibitors [CPIs], ibrutinib [I], chemoimmunotherapy and radiotherapy) or supportive care. Overall, 26 of 39 (67%) treated patients received a treatment based on immunotherapy (glofitamab, CPI, Len) that was mainly represented by bispecific antibody ($n = 18$). In this subgroup, plasma samples were collected and analysed for circulating tumour DNA (ctDNA) using cancer-personalized profiling by deep sequencing (CAPP-seq). The study found that patients with high ctDNA had poor outcomes. At a median follow-up of 11.7 months, the estimated 12-month overall survival (OS) was 35%. Factors adversely affecting the prognosis in the multivariable model were the absence of response to CAR T-cell therapy (HR: 3.08; $p = 0.0109$) and a diagnosis other than PMBCL and t-FL (HR: 4.54; $p = 0.0069$). The outcome of patients failing CAR T cells is poor and requires further investigation.

KEYWORDS
bispecific antibodies, CAR T cells, immunotherapy, refractory large B-cell lymphoma

Carmelo Carlo-Stella and Paolo Corradini are equally contributed.

INTRODUCTION

First-line chemotherapy can cure approximately 60% of patients affected by large B-cell non-Hodgkin lymphomas (LBCLs); however, those with primary refractory disease or relapsing after second-line therapy have a median overall survival (OS) of only 6 months.[1] Autologous chimeric antigen receptor (CAR) T cells targeting CD19 have demonstrated significant efficacy in relapsed LBCL, including diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGL), transformed follicular lymphoma (t-FCL) and primary mediastinal B-cell lymphoma (PMBCL). Based on pivotal trials, three different CD19 CAR T cells, namely axicabtagene ciloleucel (axicel), tisagenlecleucel (tisacel) and llisocabtagene maraleucel (lisocel), have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for patients failing at least two lines of therapy.[2–4] All these trials reported 39%–58% of complete remission and an OS ranging from 40% to 50% at 24 months. Recently, FDA and EMA approved axi-cel and liso-cel as second-line therapy for patients with early relapsed/refractory DLBCL based on the advantage of EFS as compared to platinum-based chemotherapy and salvage autologous stem cell transplantation.[5,6]

Approximately 60% of patients progress or relapse after CAR T-cell therapy, and their treatment remains an unmet clinical need. Many factors are associated with failure, some related to the tumour and its microenvironment, others to the reduced expansion, persistence and cytotoxicity of CAR T cells.[7,8]

Data regarding the clinical outcome after CAR T cells failure are limited.[9–11] Conventional treatment options for these patients include standard chemoimmunotherapy, allogeneic stem cell transplantation or lenalidomide. Recently, novel treatment approaches, including antibody–drug conjugates,[12,13] checkpoint inhibitors (CPIs)[14,15] and bispecific antibodies,[16–19] became available in the setting of clinical trials.

After identifying the recommended phase 2 dose of glofitamab,[16] Dickinson et al.[17] reported the results of the expansion phase of trial NP30179 showing similar complete response (CR) rates for patients who had failed CAR T cells versus those who had not.

In this retrospective study, we evaluated the outcome of patients failing CAR T cells at two haematological departments. Patients were treated with standard care approaches or investigational drugs (glofitamab or loncastuximab-tesirine in combination with ibrutinib). Patients treated with glofitamab were analysed specifically for their clinical characteristics and molecular features, as defined by circulating tumour DNA (ctDNA).

MATERIALS AND METHODS

Study population

Between February 2019 and February 2022, we identified 51 consecutive patients affected by R/R aggressive LBCL who did not respond to or relapsed after CAR T-cell therapy. The patients were treated at Fondazione IRCCS Istituto Nazionale dei Tumori and Humanitas Cancer Center. Inclusion criteria were: (i) therapy with axicel or tisacel; (ii) relapse or progressive disease (PD) after CAR T-cell therapy. At the time of CAR T-cell failure, patients' eligibility for additional treatments was evaluated. If therapeutic slots were available, patients were screened for enrollment in either the phase 1/2 NP30179 glofitamab trial or the phase 2 ADCT-402-103 Loncastuximab-tesirine and Ibrutinib trial (protocols details under Supplementary section). All the remaining patients received commercially available salvage treatments or no therapy according to their clinical conditions.

Patients' characteristics were evaluated before lymphodepletion and at salvage therapy post-CAR T-cell failure. All patients gave written informed consent. The Ethical Committees of participating Institutions approved the study (number 11/22).

Clinical evaluation

Disease response after CAR T cells infusion was assessed by fluorodeoxyglucose positron emission tomography (PET) and computed tomography (CT) at months +1 and +3 and then every 3 months until +12 and every 6 months after that. Relapse or PD were defined according to Cheson criteria.[20] Biopsy was performed only when indicated and clinically feasible. Patients were divided into two groups according to their response to CAR T-cell therapy: non-responders (absence of response to CAR T cells at any time) and transient responders (CR or PR as the best response at any time during the follow-up). We defined early relapse/PD for those who experienced PD ≤30 days and late PD for those who experienced PD after 30 days from CAR T cells.

Disease assessment according to Cheson criteria[20] for patients receiving salvage therapy after failure of CAR T cells was performed every 2 months until the achievement of the best response of CR or PR and then every 6 months until PD or death (details under the Supplementary section). Plasma samples were isolated and profiled by cancer personalized profiling by deep sequencing (CAPP-Seq) strategy[21] (details under the Supplementary section).

Statistical analyses

Patient and disease characteristics were summarized using descriptive statistics. The Binary association between two categorical variables was evaluated using the non-parametric Fisher–Freeman–Halton test.[22] In contrast, Kruskal–Wallis test[23] was used to study the numerical and categorical variables association. Survival curves were estimated using the Kaplan–Meier method, and group differences were tested using the log-rank test (details are reported under the Supplementary section).

RESULTS

Patients

A total of 51 patients were evaluated. Twenty-nine patients (57%) were diagnosed with DLBCL, seven (14%) with high-grade lymphomas, eight (15%) with t-FCL, and seven (14%) with PMBCL (Table 1). Seventeen patients were infused with axicel (33%) and 34 (67%) with tisacel, with a median time from enrollment to infusion of 48 days (IQR: 39–64.5) [38 days for axicel (IQR: 35–44) and 55.5 days for tisacel (IQR: 47–69)]. A detailed description of patient characteristics can be found in Tables S1–S3). Twenty of 51 patients (39%; $N = 10$ CR, $N = 10$ PR) responded to CAR T cells, whereas 31 (61%) did not. Progression after CAR T-cell therapy occurred at a median time of 49 days (IQR: 31–93 days), with nine patients (18%) experiencing an early PD (PD ≤30 days).

All patients had a documented CT/PET scan at relapse or progression; a lymph node biopsy was performed in 29 (57%). Among these, the lack of CD19 and CD20 expression by immunohistochemistry was found in 12 (41%) and 8 (28%) patients respectively. At the time of CAR T-cell therapy failure, 37 (73%) patients had advanced clinical stage. Most of the relapsed patients presented with extranodal disease ($n = 40$, 78%), bulky disease ($n = 25$, 49%), elevated LDH ($n = 35$, 69%) and increased ferritin levels ($n = 30$, 59%).

TABLE 1 Patient characteristics.

	Overall ($N = 51$)
Age	
Mean (SD)	52.0 (14.1)
Median [Q1, Q3]	57.0 [44.0, 63.0]
ECOG at leukapheresis	
0	25 (49.0%)
≥1	26 (51.0%)
IPI at leukapheresis	
0–1	16 (31.4%)
≥2	35 (68.6%)
Histotype	
DLBLC[a]	29 (56.9%)
HGBL w/o rearrangement	1 (2.0%)
DHL/THL	6 (11.8%)
PMBCL	7 (13.7%)
tFL	8 (15.7%)
Relapsed versus refractory	
Refractory (never CR or CR <6 months)	36 (70.6%)
Relapsed	15 (29.4%)
CAR-T product	
Axicel	17 (33.3%)
Tisacel	34 (66.7%)
LDH before infusion	
Mean (SD)	547 (881)
Median [Q1, Q3]	315 [231, 530]
LDH elevated before infusion	
No	26 (51.0%)
Yes	25 (49.0%)
Response to CAR-T at 30 days	
SD/PD	31 (60.8%)
CR/PR	20 (39.2%)

Abbreviations: CR, complete remission; DHL/THL, double-hit and triple-hit lymphomas; DLBCL, diffuse large B-cell lymphomas; HGBL, high-grade lymphomas without rearrangement; IPI, International Prognostic Index; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphomas; PR, partial remission; SD, stable disease; tFL, transformed follicular lymphomas.

[a]The presence of rearrangements by FISH was evaluated in 33 patients (65%), with single rearrangements found in five patients. The concomitant expression of MYC and BCL2 (DEL) was evaluated in 28 (55%) patients (DEL, $n = 16$ [31%] non-DEL, $n = 12$ [24%]). Immunohistochemical analysis of the cell of origin was performed in 41 patients (80%) ($n = 22$, germinal and $n = 19$, non-germinal centre). Notably, 36 (71%) patients presented with primary refractory disease.

Efficacy of salvage therapy

Twenty-two (43%) patients were enrolled in a clinical trial ($n = 18$, glofitamab; $n = 4$, loncastuximab-tesirine + Ibrutinib), whereas the remaining 29 patients were treated with standard therapies ($n = 17$, 33%) or supportive care only ($n = 12$, 24%). The details of the treated and untreated patients are reported in Table S2. Clinical characteristics before and after CAR T-cell therapy were not different between patients enrolled or not in clinical trials (Table S3).

The median time to treatment after progression was 38 days (IQR: 19–69) and did not differ among the different strategies. The leading causes for not recruiting patients in clinical trials ($n = 29$) were rapidly PD ($n = 3$, 10%), reduced marrow reserve ($n = 4$, 14%), active infections ($n = 3$, 10%), ECOG >2 ($n = 8$, 28%), cardiological problems ($n = 1$, 3%) and patient choice ($n = 10$, 35%).

Among the 17 patients treated with standard therapy, lenalidomide (LEN) was given to 4 (8%), CPIs to 4 (8%), ibrutinib to 2 (4%), chemotherapy to 6 (12%) and radiotherapy to only one (2%). We observed two complete remissions and two progressions in those treated with LEN. CPI were administered to 4 patients with a PMBCL diagnosis: three achieved complete remission. One partial remission was achieved in patients treated with ibrutinib ($n = 2$). Seven patients received chemotherapy ($n = 6$, CT) or radiotherapy ($n = 1$, RT); only one attained complete remission.

Among 22 patients enrolled in clinical trials, 18 received glofitamab for a median of five cycles (IQR: 4.25–7 cycles) (Table S3). The expression of CD20 was evaluated in 12 of 18 patients. The overall response (OR) and CR rates were 61% ($n = 11$) and 33% ($n = 6$) respectively. Interestingly, in the eight patients, who experienced a transient response to CAR T cells, the CR rate was 50% (4 out of 8). The median time to response to glofitamab was 41 days (IQR: 32–43). Seven of the 18 patients receiving glofitamab are alive, and five are in complete remission. The estimated 1-year OS was 47% (95% CI: +21%–24%) for the population treated with glofitamab

and 57% (95% CI: +21%–29%) for patients receiving a target glofitamab dose of 16 mg or 30 mg.

The remaining four patients enrolled in a clinical trial were treated with loncastuximab-tesirine in combination with ibrutinib. By protocol, tumour biopsy was mandatory to assess CD19 expression. All patients were CD19-positive; two responded to therapy by achieving CR ($n = 1$) or PR ($n = 1$).

Among patients who received a post-CAR T-cell salvage therapy, 26 of 39 (67%) were addressed to T-cell-activating treatments, including glofitamab, CPI or LEN, which resulted in an overall CR rate of 42% (Tables S4 and S5).

Circulating tumour DNA assessment in patients treated with glofitamab

Plasma samples collected at baseline ($n = 18$) and before cycle 3 ($n = 11$) were profiled by the CAPP-Seq strategy.[21] At baseline, patients showed a median of 18 (range 0–54) non-synonymous somatic variants in the coding region and a median of 8 mutated genes (range 0–18). Genes recurrently affected by non-synonymous somatic variants were PIM1 (53%), BCL2 and CARD11 (37%), CREBBP (32%), IGLL5, BCL6 and TP53 (26%), SOCS1, EZH2, HIST1H1E and IRF8 (21%) (Figure S1).

The median value of ctDNA was 38 790 (range 6334–496 076) haploid genome equivalents per mL (hGE/mL). The receiver operating characteristic (ROC) curve was built to evaluate the optimal ctDNA value for predicting the achievement of complete remission after salvage. We identified the cut-off value of 593 hGE/mL with a sensitivity and specificity of 100% and 42% respectively. High levels of pretreatment ctDNA were associated with poor OS (estimated 6-month OS: 20% vs. 68%; p-value 0.0035) and PFS (estimated 6-month PFS: 0% vs. 30%; p-value = 0.0023) as compared to those with low levels (Figure 1). Five out of 18 patients bearing mutations of the TP53 gene experienced PD at the end of the treatment. Assessment of ctDNA before cycle three could be performed in 11 patients (61%). Six of 7 patients with negative ctDNA at cycle 3 achieved CR or PR, and 4 of 7 remained in remission at the end of the treatment.

Allogeneic stem cell transplantation

Nine of 51 (17%) patients underwent allogeneic stem cell transplantation (alloSCT). At the time of allografting, patients were in complete ($n = 5$) or partial remission ($n = 4$) following immunotherapy ($n = 5$, glofitamab; $n = 1$, LEN) or standard therapy ($n = 1$, radiotherapy, and $n = 2$, chemotherapy). The donors were as follows: human leukocyte antigen (HLA)-matched related for one patient, HLA-matched unrelated for two patients and haploidentical for six patients. Seven of 9 patients are alive and in CR after alloSCT. Two patients died of PD; both received chemotherapy as a bridge to alloSCT.

Outcome and predictive factors

At a median follow-up of 11.7 months (IQR: 16.8–247), 19 patients were alive, and 32 died ($n = 30$, PD; $n = 1$, coronavirus disease pneumonia; and $n = 1$, infection following autologous stem cell transplantation). The estimated 12-month and 24-month OS rates were 35% [95% confidence interval (CI): 23%–53%] and 27% (95% CI: 16%–47%) respectively. The median OS of the whole population was 8.36 months

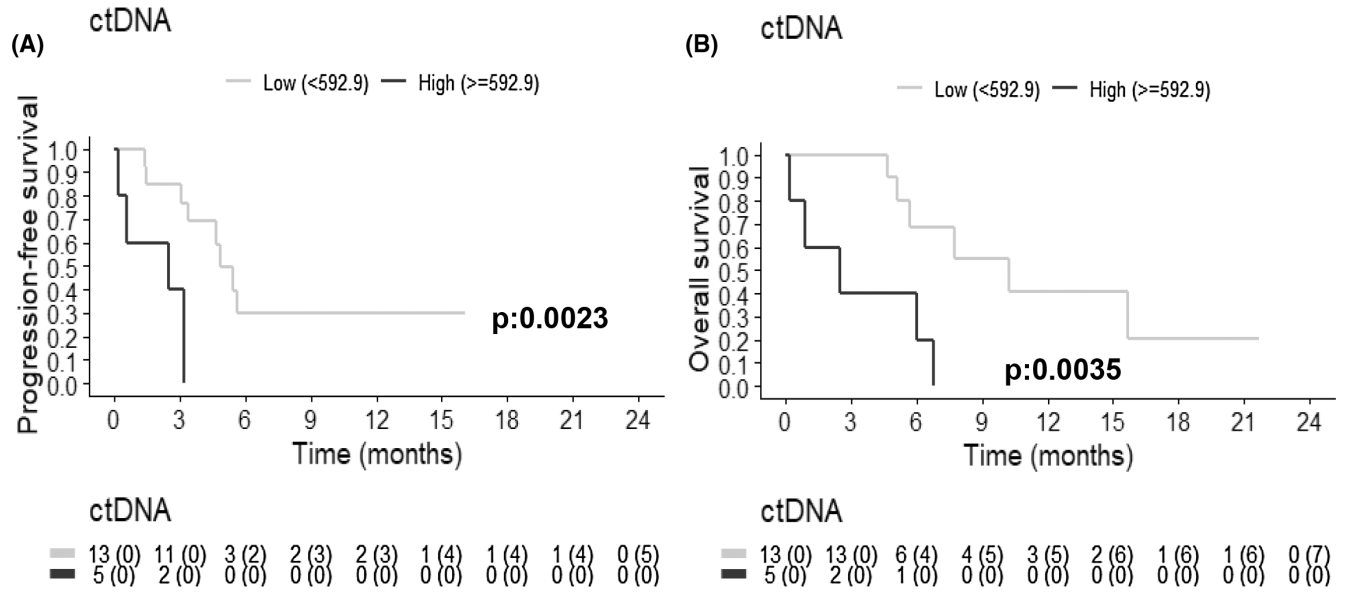

FIGURE 1 PFS (A) and OS (B) according to high pretreatment ctDNA threshold identified by the Jouden method. ctDNA, circulating tumour DNA; OS, overall survival; PFS, progression-free survival.

(IQR: 2.43-NA) (Figure 2). In treated versus untreated patients, the estimated 12-month OS was 45% (95% CI: 31%–66%) versus 0% ($p < 0.0001$) respectively (median OS of 11.74 vs. 1.88; respectively).

In addition, the estimated 1-year overall survival was significantly different for those treated with Axicel versus Tisacel [50% vs. 27%, p-value 0.0483]. As reported in Table S1, patients treated with Tisacel were older and with higher IPI.

First, we studied the prognostic factors on the whole population of treated and untreated patients. Univariable Cox analyses for OS are shown in Table 2. A diagnosis other than t-FCL and PMBCL, age ≥60 years, and IPI ≥2 (evaluated at the time of CAR T cells infusion) were significantly associated with poor outcomes. In addition, no response to CAR T cells and early relapse was associated with inferior OS. Patients not responding to CAR T-cell therapy had the worst OS (12-month OS for non- vs. transient responders: 17%

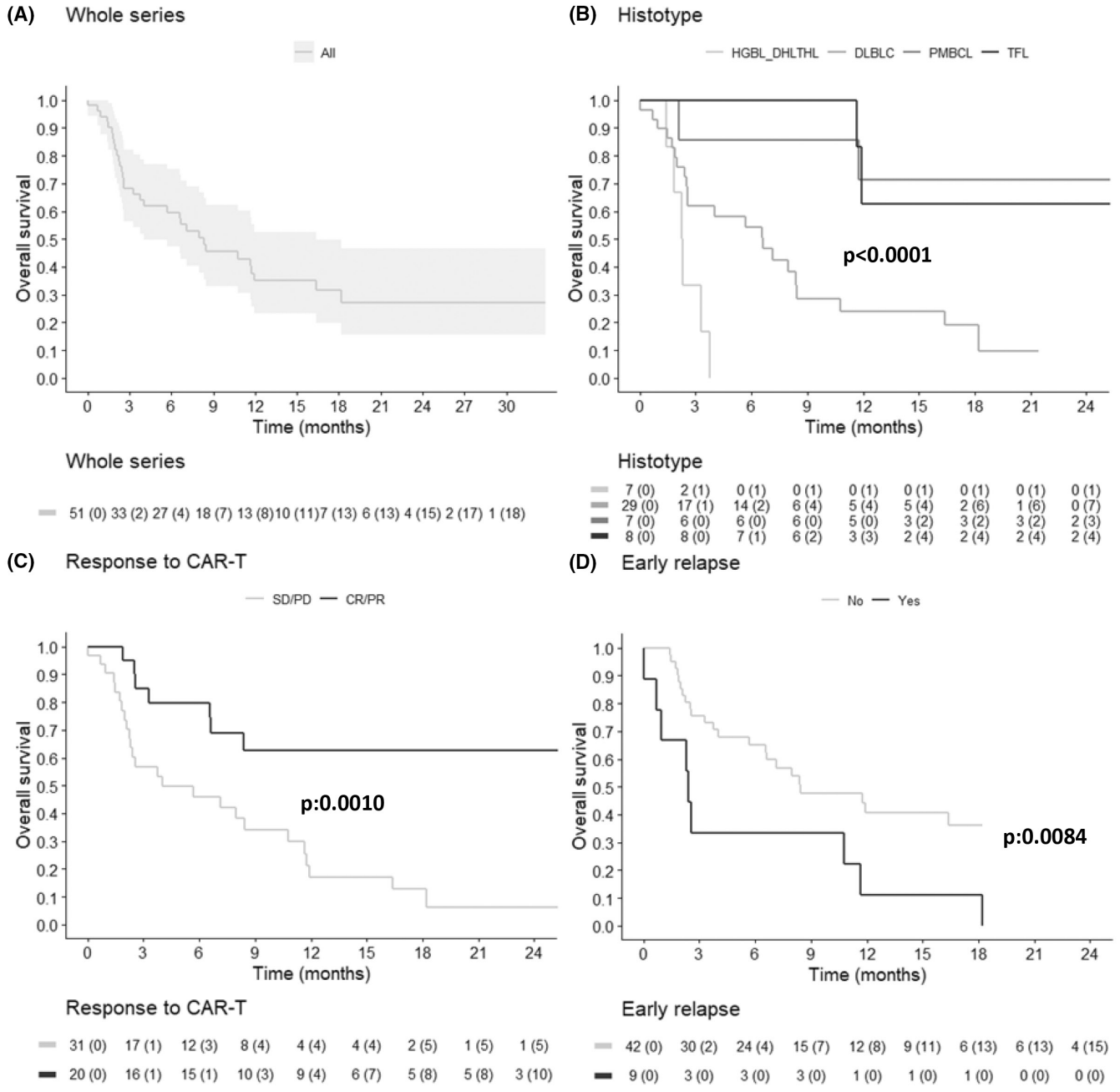

FIGURE 2 Intention-to-treat analysis: Overall survival for all patients who failed CAR T cells (A); overall survival according to the histotype ($p < 0.0001$) (B); overall survival in patients transient responders (CR/PR) versus never responding (PD/SD) to CAR T cells ($p = 0.0010$) (C); overall survival according to time to relapse (early vs. late, $p = 0.0084$) (D). CAR-T, chimeric antigen receptor T cell; CR, complete remission; DHL/THL, double-hit and triple-hit lymphomas; DLBCL, diffuse large B-cell lymphomas; HGBL, high-grade lymphomas without rearrangement; PD, progressive disease; PMBCL, primary mediastinal B-cell lymphomas; PR, partial remission; SD, stable disease; tFL, transformed follicular lymphomas.

[95% CI: 7%–41%] vs. 63% [95% CI: 44%–89%], $p = 0.0010$) (Figure 2C).

Secondly, we analysed OS and PFS only for the cohort of treated patients. Overall, 39 patients were treated, and their observed 12- and 24-month OS, starting from the treatment, were 37% (95% CI: 22%–63%) and 30% (95% CI: 15%–59%) respectively. Furthermore, the PFS at 12 and 24 months was 30% (95% CI: 17%–52%), with 23 of 39 (59%) patients experiencing progression after salvage, and only one died without progression (Figure 3A,B, Table 3).

Multivariate analysis for OS starting at the time of relapse/progression after CAR T-cell administration is shown in Table 4, and for OS and PFS starting at the time of salvage therapy (performed only for 39 patients) is shown in Table 5. The factors that negatively influenced OS were the absence of response to previous CAR T-cell administration (HR: 3.08; 95% CI: 1.29–7.31; $p = 0.0109$) and a histotype different from t-FCL and PMBCL (HR: 4.54; 95% CI: 1.51–13.61; $p = 0.0069$). For patients who underwent salvage treatment, the only factor that significantly influenced OS and PFS at multivariable analysis was an IPI ≥2 at the time of starting salvage therapy (OS: HR: 10.20; 95% CI: 1.19–87.21; $p = 0.0340$; PFS: HR: 6.83; 95% CI: 1.40–33.38; $p = 0.0176$).

TABLE 2 Univariable Cox models for OS for all patients.

Variable	HR	Lower 0.95	Upper 0.95	*p*-value
Response to CAR-T—SD/PD versus CR/PR	3.75	1.61	8.73	0.0022
Early relapse—Yes versus No	2.73	1.26	5.92	0.0112
IPI (at apheresis)—≥2 versus 0–1	2.94	1.25	6.9	0.0131
Histotype—Other versus PMBCL/tFL	6.48	2.23	18.84	0.0006
Age at enrolment—≥60 versus <60	2.07	1.02	4.21	0.0448

Abbreviations: CAR-T, chimeric antigen receptor T cells; IPI, International Prognostic Index; OS, overall survival; PMBCL, primary mediastinal B-cell lymphomas; t-FCL, transformed follicular lymphomas.

Toxicity of salvage therapy

Six of 39 (15%) treated patients experienced grade 3–4 and two grade 5 infections while in CR. Six infectious complications were bacterial, and one was caused by severe acute respiratory coronavirus syndrome. In the 18 cases treated with glofitamab, the incidence of CRS was 78%, with only 27% of grade ≥2. Immune effector cell-associated neurotoxicity syndrome was not reported. We did not observe immune-mediated adverse events for those treated with CPIs. Patients treated with loncastuximab-tesirine plus Ibrutinib did not have grade 3–4 adverse events. Nine patients were allografted, and a grade 3 graft-versus-host disease (GVHD) was observed in only one patient. No patient died of non-relapse mortality after alloSCT.

DISCUSSION

In this retrospective study, we evaluated the outcome of a consecutive series of patients, mostly treated with immune-based therapies, after CAR T-cell therapy failure. The peculiarity of our population was that a significant proportion of patients

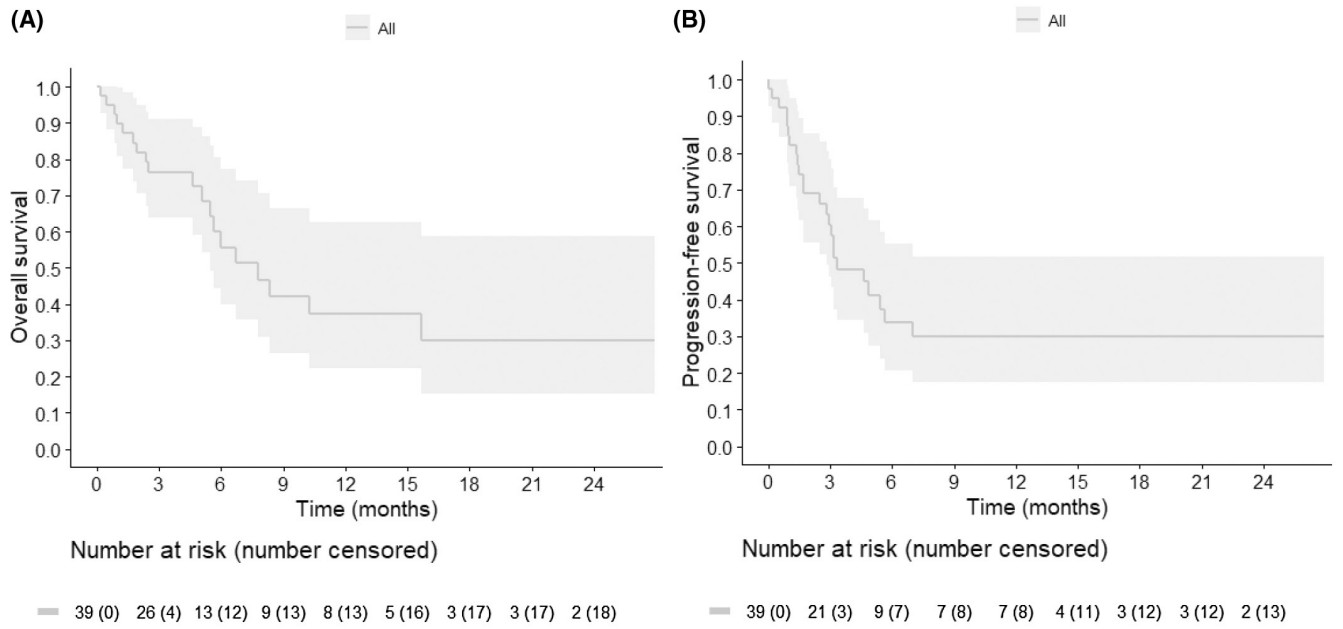

FIGURE 3 Intention-to-treat analysis: overall survival (A) and progression-free survival (B) for patients treated with a salvage therapy.

TABLE 3 Univariable Cox models for OS and PFS for patients receiving salvage therapy.

	OS				PFS			
Variable	**HR**	**Lower 0.95**	**Upper 0.95**	***p*-value**	**HR**	**Lower 0.95**	**Upper 0.95**	***p*-value**
Response to CAR-T—SD/PD versus CR/PR	3.64	1.30	10.20	0.0140	3.54	1.43	8.80	0.0064
Early relapse—yes versus no	2.33	0.76	7.08	0.1376	1.63	0.55	4.81	0.3740
IPI (at salvage)—≥2 versus 0–1	20.66	2.66	160.32	0.0038	11.89	2.59	54.51	0.0014
Histotype—others versus PMBCL/tFCL	5.28	1.52	18.34	0.0088	3.65	1.35	9.87	0.0106
Immunotherapy—no versus yes	2.12	0.82	5.5	0.1217	1.79	0.75	4.26	0.1878
Time to salvage—2.6 versus 1.63 months	0.88	0.61	1.27	0.4949	1	0.75	1.34	0.9987
Age – ≥60 versus <60 years	2.36	0.93	6.00	0.0723	2.73	1.17	6.37	0.0206

Abbreviations: CAR-T, chimeric antigen receptor T-cell; CR/PR, complete remission and partial remission; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphomas; SD/PD, stable disease and progressive disease; t-FCL, transformed follicular lymphomas.

TABLE 4 Multivariable Cox model for OS for all patients.

Variable	**HR**	**Lower 0.95**	**Upper 0.95**	***p*-value**
Response to CAR-T—SD/PD versus CR/PR	3.08	1.29	7.31	0.0109
IPI (at apheresis)—≥2 versus 0–1	2.18	0.91	5.20	0.0801
Histotype—other versus PMBCL/tFL	4.54	1.51	13.61	0.0069

Abbreviations: CAR-T, chimeric antigen receptor T cell; CR/PR, complete remission and partial remission; IPI, International Prognostic Index; OS, overall survival; PMBCL, primary mediastinal B-cell lymphomas; SD/PD, stable disease and progressive disease; t-FCL, transformed follicular lymphomas.

TABLE 5 Multivariable Cox models for OS and PFS for patients receiving salvage therapy.

	OS				PFS			
Variable	**HR**	**Lower 0.95**	**Upper 0.95**	***p*-value**	**HR**	**Lower 0.95**	**Upper 0.95**	***p*-value**
Response to CAR-T—SD/PD versus CR/PR	1.80	0.61	5.27	0.2841	2.19	0.86	5.61	0.1009
IPI (at salvage)—≥2 versus 0–1	10.20	1.19	87.21	0.0340	6.83	1.40	33.38	0.0176
Histotype—others versus PMBCL/tFL	2.98	0.83	10.61	0.0926	2.15	0.78	5.95	0.1391

Abbreviations: CAR-T, chimeric antigen receptor T cell; CR/PR, complete remission and partial remission; IPI, International Prognostic Index; OS, overall survival; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphomas; SD/PD, stable disease and progressive disease; t-FCL, transformed follicular lymphomas.

(43%) was included in clinical trials. We observed an estimated 12-month OS of 35%, which was favourable considering that most of these patients (61%) were refractory to CAR T cells.

Patients progressing after CAR T cells have limited treatment options, and there is no consensus on the best strategy to adopt.

Two retrospective studies reporting the outcome after CAR T cells failure showed an overall response rate of 14%–39% with a 1-year OS of 25%.[10,11] These studies are fundamental as they demonstrated the ineffectiveness of standard chemotherapy in this setting. Despite the short follow-up, both studies showed an OS advantage for patients treated with lenalidomide, given the potential effect on the expansion of CAR T cells.

Another interesting strategy, not available in Italy at time of this retrospective analysis, was using polatuzumab-based regimens. This combination was investigated retrospectively in 57 patients failing CAR T cells with an overall response rate of 44% and a CR rate of only 14%, which explains the limited OS survival of only 17 weeks.[12]

Recently, several bispecific antibodies have been explored in phase 1–2 studies,[16–19] including patients failing CAR T-cell therapy. Interestingly, the response rate in these patients was similar to that observed in patients not previously exposed to CAR T cells. Herein, we report the clinical characteristics before and after CAR T-cell infusion and the prognostic role of ctDNA in 18 patients enrolled in the phase 1/2 NP30179 trial. In our cohort, the overall response and CR rates following glofitamab were 61% and 33%, respectively, superimposable to those described for epcoritamab.[19] Interestingly, the CR rate increased in transient CAR T-cell responders (CR rate 50%) without detectable expansion of circulating CAR T cells (data not shown).

In recent years, cancer personalized profiling by deep sequencing (CAPP-Seq) has been recognized to have a role in identifying mutations, disease burden and minimal residual disease after treatment.[24] ctDNA has become an independent prognostic marker following standard chemotherapy and after CAR T cells.[25,26] Our study showed that pretreatment

ctDNA before glofitamab was significantly associated with PFS and OS. In particular, low ctDNA was associated with a very favourable outcome (estimated 6-month PFS and OS: 30% and 68% respectively). Considering the limited sample size, this interesting observation requires validation in a larger sample.

The long-term follow-up of novel drugs has yet to be defined in this setting. In fact, for young patients attaining a response to salvage therapy, alloSCT could be an option. Recently, Zurko reported the outcome of 88 patients allografted after a previous CAR T-cell failure showing a 1-year OS and PFS of 59% and 45% respectively.[27] In our cohort, we allografted nine patients, including five following glofitamab, and we did not observe an increase in GVHD incidence or non-relapse mortality.

We analysed different prognostic factors in the entire population and in treated patients. In agreement with other studies, significant prognostic factors were CAR T-cell refractoriness and IPI at salvage.[9–11] In addition, not previously reported, salvage therapy following CAR T-cell failure was less efficient for patients with double-hit/triple-hit (DH/TH) lymphomas and DLBCL other than PMBCL and tFCL. Six out of seven patients diagnosed with DH/TH lymphoma died, and only one patient is alive but with a rapidly progressive disease. Given the rarity of high-grade lymphomas, it is not easy to conclude. The recent ZUMA-12 data suggested that these patients might benefit from an early switch to an immunotherapeutic approach.[28]

In this heavily pretreated population, infectious complications remained a significant issue. These complications might be related to previous treatment with CAR T cells and the associated B-cell aplasia and hypogammaglobulinaemia that lead to a higher risk of infections despite extensive antimicrobial prophylaxis.[29]

Our study demonstrated that novel drugs might improve the outcome of patients failing CAR T cells, especially in the subset of transient responders.

AUTHOR CONTRIBUTIONS

Anna Dodero and Stefania Bramanti designed research and wrote the paper. Martina Pennisi, Annalisa Chiappella, Magagnoli Massimo, Anna Guidetti, Francesco Corrado, Paulina Maria Nierychlewska, Alice Di Rocco and Chiara De Philippis collected the data. Silva Ljevar performed the statistical analyses. Annalisa Chiappella and Rahal Daoud performed the histological analyses. Armando Santoro, Carmelo Carlo-Stella and Paolo Corradini reviewed the paper.

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CONFLICT OF INTEREST STATEMENT

C.C.S. reported research funding from Roche, ADC Therapeutics and Sanofi; served as consultant/advisor for Roche, Celgene/Bristol-Myers Squibb, ADC Therapeutics, Sanofi, Scenic Biotech; and received honoraria from Roche, ADC Therapeutics, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen Oncology, AstraZeneca, Incyte, Novartis, Takeda. A.C. served the Advisory boards from Celgene-BMS, Gilead-Sciences, Ideogen, Roche, SecuraBIO and Takeda. In addition, she also received honoraria for lectures/educational activities: Astrazeneca, Celgene-BMS, Clinigen, Gilead-Sciences, Incyte, Janssen, Novartis, Roche, Takeda. P.C. has honoraria paid by for-profit health care companies during the past 3 years: AbbVie, ADC Therapeutics, Amgen, Celgene, Daiichi Sankyo, Gilead/Kite, GSK, Incyte, Janssen, KyowaKirin, Nerviano Medical Science, Novartis, Roche, Sanofi, Takeda (Consulting, Advisory role or Lecturer). He has travel and accommodations paid by for-profit health care companies during the past 3 years: Novartis, Janssen, Celgene, BMS, Takeda, Gilead/Kite, Amgen and AbbVie. A.S. served as advisor for Bristol-Myers-Squibb, Servier, Gilead, Pfizer, Eisai, Bayer, Merck Sharp & Dohme. He served as consultant for Sanofi and Incyte. He is also part of the Speaker's Bureau for Takeda, Bristol-Myers-Squibb, Roche, Abb-vie, Amgen, Celgene, Servier, Gilead, Astra-Zeneca, Pfizer, Lilly, Sandoz, Eisai, Novartis, Bayer, Merck Sharp & Dohme. S.B. received Honoraria for lectures from Novartis, Gilead, Astra-Zeneca, Roche, Kiova, Bristol-Myers-Squibb. A.D., M.D.T., M.D., S.L., M.M., A.G., F.C., P.M.N., A.D.R., D.L., R.D. and C.D.P. have nothing to disclose.

DATA AVAILABILITY STATEMENT

Data will be available upon request to anna.dodero@istitutotumori.mi.it.

ETHICS STATEMENT

The ethical committees of participating Institutions approved the study (number 11/22).

PATIENT CONSENT STATEMENT

All patients gave written informed consent according to the Helsinki declaration.

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REFERENCES

1. Crump M, Neelapu SS, Farooq U, van den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800–8. https://doi.org/10.1182/blood-2017-03-769620

2. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531–44. https://doi.org/10.1056/NEJMoa1707447
3. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45–56. https://doi.org/10.1056/NEJMoa1804980
4. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839–52. https://doi.org/10.1016/S0140-6736(20)31366-0
5. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene ciloleucel as second- line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640–54. https://doi.org/10.1056/NEJMoa2116133
6. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675–84. https://doi.org/10.1182/blood.2022018730
7. Lemoine J, Ruella M, Houot R. Overcoming intrinsic resistance of cancer cells to CAR T-cell killing. Clin Cancer Res. 2021;27(23):6298–306. https://doi.org/10.1158/1078-0432.CCR-21-1559
8. Monfrini C, Stella F, Aragona V, Magni M, Ljevar S, Vella C, et al. Phenotypic composition of commercial anti-CD19 CAR T cells affects *in vivo* expansion and disease response in patients with large B-cell lymphoma. Clin Cancer Res. 2022;28(15):3378–86. https://doi.org/10.1158/1078-0432.CCR-22-0164
9. Spiegel JY, Dahiya S, Jain MD, Tamaresis JS, Nastoupil L, Jacobs MT, et al. Outcomes of patients with large B-cell lymphoma progressing after axicabtagene ciloleucel. Blood. 2021;137(13):1832–5. https://doi.org/10.1182/blood.2020006245
10. Alarcon Tomas A, Fein JA, Fried S, Flynn JR, Devlin SM, Fingrut WB, et al. Outcomes of first therapy after CD19-CAR-T treatment failure in large B-cell lymphoma. Leukemia. 2023;37(1):154–63. https://doi.org/10.1038/s41375-022-01739-2
11. Di Blasi R, Le Gouill S, Bachy E, Cartron G, Beauvais D, Le Bras F, et al. Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis. Blood. 2022;140(24):2584–93. https://doi.org/10.1182/blood.2022016945
12. Gouni S, Rosenthal AC, Crombie JL, Ip A, Kamdar MK, Hess B, et al. A multicenter retrospective study of polatuzumab vedotin in patients with large B-cell lymphoma after CAR T-cell therapy. Blood Adv. 2022;6(9):2757–62. https://doi.org/10.1182/bloodadvances.2021006801
13. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790–800. https://doi.org/10.1016/S1470-2045(21)00139-X
14. Crombie JL, Nastoupil LJ, Redd RA, Tang K, Shouse G, Herrera AF, et al. Real-world outcomes of axicabtagene ciloleucel in adult patients with primary mediastinal B-cell lymphoma. Blood Adv. 2021;5(18):3563–7. https://doi.org/10.1182/bloodadvances.2021004880
15. Chong EA, Alanio C, Svoboda J, Nasta SD, Landsburg DJ, Lacey SF, et al. Pembrolizumab for B-cell lymphomas relapsing after or refractory to CD19-directed CAR T-cell therapy. Blood. 2022;139(7):1026–38. https://doi.org/10.1182/blood.2021012634
16. Hutchings M, Morschhauser F, Iacoboni G, Carlo-Stella C, Offner FC, Sureda A, et al. Glofitamab, a novel, bivalent CD20-targeting T-cell–engaging bispecific antibody, induces durable complete remissions in relapsed or refractory B-cell lymphoma: a phase I trial. J Clin Oncol. 2021;39(18):1959–70. https://doi.org/10.1200/JCO.20.03175
17. Dickinson MJ, Carlo-Stella C, Morschhauser F, Bachy E, Corradini P, Iacoboni G, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2022;387(24):2220–31. https://doi.org/10.1056/NEJMoa2206913
18. Hutchings M, Mous R, Clausen MR, Johnson P, Linton KM, Chamuleau MED, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet. 2021;398(10306):1157–69. https://doi.org/10.1016/S0140-6736(21)00889-8
19. Thieblemont C, Phillips T, Ghesquieres H, Cheah CY, Clausen MR, Cunningham D, et al. Epcoritamab, a novel, subcutaneous CD3xCD20 bispecific T-cell–engaging antibody, in relapsed or refractory large B-cell lymphoma: dose expansion in a phase I/II trial. J Clin Oncol. 2023;41(12):2238–47. https://doi.org/10.1200/JCO.22.01725
20. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–67. https://doi.org/10.1200/JCO.2013.54.8800
21. Spina V, Bruscaggin A, Cuccaro A, Martini M, di Trani M, Forestieri G, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. Blood. 2018;131(22):2413–25. https://doi.org/10.1182/blood-2017-11-812073
22. Freeman GH, Halton JH. Note on an exact treatment of contingency, goodness of fit and other problems of significance. Biometrika. 1951;38(1/2):141. https://doi.org/10.2307/2332323
23. Kruskal WH, Wallis WA. Use of ranks in one-criterion variance analysis. J Am Stat Assoc. 1952;47:583–621.
24. Roschewski M, Rossi D, Kurtz DM, Alizadeh AA, Wilson WH. Circulating tumor DNA in lymphoma: principles and future directions. Blood Cancer Discov. 2022;3(1):5–15. https://doi.org/10.1158/2643-3230.BCD-21-0029
25. Kurtz DM, Scherer F, Jin MC, Soo J, Craig AFM, Esfahani MS, et al. Circulating tumor DNA measurements as early outcome predictors in diffuse large B-cell lymphoma. J Clin Oncol. 2018;36(28):2845–53. https://doi.org/10.1200/JCO.2018.78.5246
26. Frank MJ, Hossain NM, Bukhari A, Dean E, Spiegel JY, Claire GK, 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. 2021;39(27):3034–43. https://doi.org/10.1200/JCO.21.00377
27. Zurko J, Ramdial J, Shadman M, Ahmed S, Szabo A, Iovino L, et al. Allogeneic transplant following CAR T-cell therapy for large B-cell lymphoma. Haematologica. 2023;108(1):98–109. https://doi.org/10.3324/haematol.2022.281242
28. Neelapu SS, Dickinson M, Munoz J, Ulrickson ML, Thieblemont C, Oluwole OO, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. Nat Med. 2022;28(4):735–42. https://doi.org/10.1038/s41591-022-01731-4
29. Wudhikarn K, Palomba ML, Pennisi M, Garcia-Recio M, Flynn JR, Devlin SM, et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. Blood Cancer J. 2020;10(8):79. https://doi.org/10.1038/s41408-020-00346-7

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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