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CME Article

Outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy: a DESCAR-T analysis

Roberta Di Blasi,[1] Steven Le Gouill,[2] Emmanuel Bachy,[3] Guillaume Cartron,[4] David Beauvais,[5] Fabien Le Bras,[6] François-Xavier Gros,[7] Sylvain Choquet,[8] Pierre Bories,[9] Pierre Feugier,[10] Olivier Casasnovas,[11] Jacques Olivier Bay,[12] Mohamad Mohty,[13] Magalie Joris,[14] Thomas Gastinne,[15] Pierre Sesques,[3] Jean-Jacques Tudesq,[4] Laetitia Vercellino,[16] Franck Morschhauser,[5] Elodie Gat,[17] Florence Broussais,[18] Roch Houot,[19] and Catherine Thieblemont[1]

[1]University of Paris APHP, Saint-Louis Hospital, Hemato-oncology, DMU DHI, Paris, France; [2]Institut Curie, Paris, France; [3]HCL, Hematology, Lyon, France; [4]CHU Montpellier, Hematology Department, UMR CRNS 5535, Montpellier, France; [5]CHU de Lille, Hematology, Lille, France; [6]APHP, CHU Créteil, Hematology, Creteil, France; [7]CHU de Bordeaux, Hematology, Bordeaux, France; [8]APHP, Hopital La Pitié Salpetrière, APHP, Hematology, Paris, France; [9]Oncopole Toulouse, Hematology, Toulouse, France; [10]Centre Hospitalier Universitaire Nancy and INSERM 1256, Nancy, France; [11]CHU Dijon, Bourgogne, France; [12]CHU de Clermont–Ferrand, Hematology, Clermont-Ferrand, France; [13]APHP, Hopital Saint-Antoine, Sorbonne University, Paris, France; [14]CHU Amiens, Hematology, Amiens, France; [15]CHU Nantes, Hematology, Nantes, France; [16]Assistance Publique–Hôpitaux de Paris, Hôpital Saint-Louis Service de médecine nucléaire, Paris, France; [17]Institut Carnot CALYM, Lyon, France; [18]LYSARC CHU, Lyon Pierre Bénite, Lyon, France; and [19]CHU Rennes, Rennes, France

KEY POINTS

- Outcome of patients progressing/relapsing after CAR T-cell treatment is poor, especially in case of relapse within 30 days.
- Salvage immunomodulatory treatment may offer better outcomes compared to standard immuno-chemotherapy.

Anti-CD19 chimeric antigen receptor (CAR) T-cells represent a major advance in the treatment of relapsed/refractory aggressive B-cell lymphomas. However, a significant number of patients experience failure. Among 550 patients registered in the French registry DESCAR-T, 238 (43.3%) experienced progression/relapse, with a median follow-up of 7.9 months. At registration, 57.0% of patients presented an age-adjusted International Prognostic Index of 2 to 3, 18.9% had Eastern Cooperative Oncology Group performance status ≥2, 57.1% received >3 lines of treatment prior to receiving CAR T-cells, and 87.8% received bridging therapy. At infusion, 66% of patients presented progressive disease, and 38.9% had high lactate dehydrogenase (LDH). Failure after CAR T-cell treatment occurred after a median of 2.7 months (range: 0.2-21.5). Fifty-four patients (22.7%) presented very early failure (day [D] 0-D30); 102 (42.9%) had early failure (D31-D90), and 82 (34.5%) had late (>D90) failure. After failure, 154 patients (64%) received salvage treatment: 38.3% received lenalidomide, 7.1% bispecific antibodies, 21.4% targeted treatment, 11% radiotherapy, and 20% immunochemotherapy with various regimens. Median progression-free survival was 2.8 months, and median overall survival (OS) was 5.2 months. Median OS for patients failing during D0-D30 vs after D30 was 1.7 vs 3.0 months, respectively (P = .0001). Overall, 47.9% of patients were alive at 6 months, but only 18.9% were alive after very early failure. In multivariate analysis, predictors of OS were high LDH at infusion, time to CAR-T failure <D30, and high C-reactive protein at infusion. This multicentric analysis confirms the poor outcome of patients relapsing after CAR T-cell treatment, highlighting the need for further strategies dedicated to this population.

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Disclosures

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Learning objectives

Upon completion of this activity, participants will:

1. Describe outcomes for patients with relapsed/refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (BCL) after anti-cluster of differentiation (CD)19 chimeric antigen receptor (CAR) T-cell infusion, according to a follow-up study of 550 patients registered in the French registry DESCAR-T
2. Determine prognostic markers and post–CAR-T options for patients with R/R aggressive BCL after anti-CD19 CAR T-cell infusion, according to a follow-up study of 550 patients registered in the French registry DESCAR-T
3. Identify clinical implications of outcomes for patients with R/R aggressive BCL after anti-CD19 CAR T-cell infusion, according to a follow-up study of 550 patients registered in the French registry DESCAR-T

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Introduction

Anti-CD19 chimeric antigen receptor (CAR) T cells are a major therapeutic advance in the management of patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (R/R aggressive BCL). Valuable response rates have been observed in both pivotal clinical trials (JULIET, ZUMA 1, and TRANSCEND) and real-world experience (Center for International Blood and Marrow Transplant Research; CAR T consortium registry; and French, Spanish, and German multicentric studies). Nonetheless, failure after CAR T-cell treatment remains a major issue, representing an unmet medical need. In the JULIET trial, nearly 60% of patients showed progression at 6 months after CAR T-cell infusion.[1] Similarly, the ZUMA 1 and TRANSCEND trials showed that approximately 50% of patients had relapsed at 6 months.[2-4] These data were confirmed in several real-world series. Pasquini et al reported the Center for International Blood and Marrow Transplant Research experience, with 60% failure at 6 months after tisagenlecleucel (tisa-cel) treatment.[5] Likewise, for axicabtagene ciloleucel (axi-cel), Nastoupil et al reported, in the US CAR T consortium registry, an approximate 45% failure rate after infusion.[6] Bethge et al reported in a German experience that 26% of patients presented progressive disease, with 64% of patients relapsing at 6 months.[7] In the Spanish report by Kwon et al, almost 30% of patients presented with failure after CAR T-cell treatment.[8] Iacoboni et al[9] showed an almost 70% relapse rate at 12 months in another Spanish cohort.

In a multicentric French study, more than half of the patients showed failure 6 months after CAR T-cell treatment.[10] These data were collected in the DESCAR-T (Dispositif d'Enregistrement et de Suivi des CAR-T) registry, a French national registry designed by the Lymphoma Study Association/Lymphoma Academic Research Organization (LYSA/LYSARC) to collect real-world data with commercial CAR T cells (axi-cel and tisa-cel) for up to 15 years after CAR T-cell infusion.[11]

The aim of the present study was to describe the outcome for patients registered in DESCAR-T who progress/relapse after CAR T-cell infusion, and to identify prognostic markers and post–CAR-T treatment options for this population. The relationship between treatment strategies at relapse, and the outcomes following CD19-CAR-T failure, was investigated in depth.

Patients and methods

Population

Patients were included in the DESCAR-T registry if they were eligible for treatment with CAR T-cells for a hematologic malignancy covered by the French healthcare system, on the basis that a CAR-T indication had been validated by a multidisciplinary tumor board of a CAR-T accredited center. As of August 2018, 680 patients with R/R aggressive BCL were registered in the DESCAR-T national registry. All patients or their representatives provided informed consent to non-interventional use of personal data prior to inclusion in the DESCAR-T registry. At the time of the analysis (April 2021), 550 patients had been infused with commercially available CAR T-cell products. D0 (for day 0) was identified as the day of CAR T-cell infusion. Patients were evaluated at D30, 90, 180, 270, and 360, and then at 18, 24, and 36 months.

Characteristics of treated patients

The following clinical characteristics at the time of decision/before lymphodepletion were collected: sex, age, number and type of previous lines of treatment before CAR T-cell treatment, previous autologous or allogeneic transplant, histology, Eastern

Table 1. Baseline patient and CAR T-cell therapy characteristics of all patients, according to timing of relapse/progression

	All (n = 238)	D0-D30 (n = 54)	D30-D90 (n = 102)	>D90 (n = 82)
Sex, male	160 (67.2)	37 (68.5)	75 (73.5)	48 (58.5)
Age ≥65 y	91 (38.2)	29 (53.7)	37 (36.3)	35 (42.6)
Histology				
DLBCL, NOS	178 (74.8)	36 (66.7)	82 (80.4)	60 (73.3)
PMBL	11 (4.6)	3 (5.6)	2 (2.0)	6 (7.3)
HGBCL	3 (1.3)	2 (3.7)	1 (1.0)	0 (0)
Transformed FL	31 (13.0)	7 (13.0)	13 (12.7)	11 (13.4)
Other*	15 (6.3)	6 (11.1)	4 (3.9)	5 (6.1)
>3 lines of prior therapy	136 (57.1)	40 (74.1)	49 (48.0)	47 (57.3)
Prior autologous transplant	46 (19.3)	9 (16.7)	21 (20.6)	16 (19.5)
ECOG PS at registration ≥2	28 (12.2)	12 (23.1)	13 (13.5)	3 (3.7)
LDH prior to infusion > UNL	72 (38.9)	31 (67.4)	27 (35.1)	14 (22.6)
Bulky disease (>5 cm)	53 (38.7)	16 (51.6)	24 (43.6)	13 (25.5)
aaIPI 2-3	126 (57.0)	8 (15.7)	7 (7.6)	1 (1.3)
Bridging therapy	209 (87.8)	49 (90.7)	89 (87.2)	71 (86.5)
Neutropenia prior to infusion (<1 G/L)	31 (13.5)	9 (18.8)	13 (13.0)	9 (11.1)
Lymphopenia prior to infusion (<1 G/L)	168 (99.4)	36 (100)	73 (98.6)	59 (100.0)
Ferritin prior to infusion > UNL	133 (84.7)	37 (88.1)	57 (85.1)	39 (81.3)
Median CRP prior to infusion, mg/L (range)	20 (6-50)	39 (0-349)	18 (1-376)	12.5 (0-204)
CAR T-cell product				
Tisagenlecleucel	102 (42.9)	33 (61.1)	40 (39.2)	29 (35.3)
Axicabtagene ciloleucel	136 (57.1)	21 (38.9)	62 (60.7)	53 (64.7)

Values are n (%), unless otherwise indicated.

aaIPI, age-adjusted International Prognostic Index; CRP, C-reactive protein; D, day; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HGBCL, high grade B-cell lymphoma; LDH, lactate dehydrogenase; NOS, not otherwise specified; PMBL, primary mediastina B-cell lymphoma; UNL, upper normal limit.

*3B-FL n = 2; primary central nervous system lymphoma n = 1; transformed marginal zone lymphoma n = 3; unclassifiable Hodgkin/DLBCL n = 9.

Cooperative Oncology Group (ECOG) performance status (PS),[12] Ann Arbor stage, International Prognostic Index (IPI), age-adjusted IPI,[13] number of extra nodal sites, and lactate dehydrogenase (LDH) levels. The same parameters were evaluated at D0. Albumin, C-reactive protein (CRP), and ferritin levels were also collected at D0. Three groups of bridging chemotherapy were defined, as follows: low-dose regimen (steroids ± immunotherapy), conventional regimen (chemotherapy ± immunotherapy), and radiation therapy. Treatments received at failure were grouped into the following classes: monoclonal antibodies (mainly anti-CD20), immunochemotherapy, lenalidomide, bispecific antibodies, and immune checkpoint inhibitors.

End points

The study was designed to identify the outcomes of patients associated with failure after CAR T-cell treatment (D0), in terms of next progression, death, or last follow-up. We calculated progression-free survival 2 (PFS-2), defined as the time elapsed from first failure after CAR-T infusion to next progression/relapse after further treatment, and overall survival 2 (OS-2), defined as the time elapsed from failure after CAR-T infusion to death or last follow-up. Failure after CAR T-cell treatment was defined as progression and relapse after treatment according to the Cheson et al 2014 response assessment criteria.[14] Patients with stable disease were excluded. The primary end point of the study was to determine OS-2 of R/R BCL patients enrolled in the DESCAR-T registry. Secondary end points were to describe PFS-2, the baseline characteristics of the patients, the treatment proposed at failure, the response to the salvage treatment, and the prognostic factors associated with PFS-2 and OS-2. Outcomes were analyzed according to time of relapse, as follows: D0–D30 (very early); D31–D90 (early); and after D90 (late).

Statistical considerations

Estimates of survival were calculated according to the Kaplan-Meier method and compared using the log-rank test. In

Table 2. Treatments administered at CAR T-cell progression/relapse

Treatment	n = 154
IMID lenalidomide*	59 (38.3)
Bispecific antibodies anti-CD20-CD3	11 (7.1)
Target therapy†	33 (21.4)
Nivolumab	11 (7.1)
Pembrolizumab	4 (2.6)
Ibrutinib	3 (1.9)
Ibrutinib + lenalidomide + rituximab	2 (1.3)
Ibrutinib + corticosteroids	2 (1.3)
Ibrutinib + lenalidomide	1 (0.6)
Nivolumab + brentuximab vedotin	1 (0.6)
Pembrolizumab + lenalidomide	1 (0.6)
Lenalidomide + polatuzumab vedotin	1 (0.6)
Busulfan + fludarabine + nivolumab + thiotepa	1 (0.6)
Clinical trial LYM 1002‡	1 (0.6)
MALT-1 inhibitor	1 (0.6)
Anti-CD20 monoclonal antibody	3 (1.9)
Other monoclonal antibody (anti-CD38, anti-CD30, anti-CD79b)	1 (0.6)
Radiotherapy	17 (11.0)
Immunochemotherapy	31 (20.1)
Palliative corticosteroids	1 (0.6)

Values are n (%). A total of 7% of patients (n = 17) did not receive any treatment because their disease was too advanced.

IMID, immunomodulatory drug; MALT-1, mucosa-associated lymphoid tissue lymphoma translocation protein 1.

*Ten patients received lenalidomide alone; 49 received lenalidomide in combination, including 46 with rituximab.

†Among the 33 patients who received targeted therapies, 24 received monotherapy, and 9 received combination therapy (all with different drugs).

‡MALT-1 inhibitor + ibrutinib.

addition, the event rates at specific time points were computed, along with 95% confidence intervals (CIs). Cox proportional hazard regression models were used to estimate the hazard ratios (HRs) and associated 95% CIs. All analyses were performed using SAS 9.3.

Results

Demographic and baseline characteristics

From August 2018 until 12 April 2021, 680 consecutive patients with R/R aggressive BCL were registered in the DESCAR-T registry, 550 of whom were infused at the time of analysis. Patients received either axi-cel (n = 350) or tisa-cel (n = 200).

After a median follow-up of 7.9 months, 312 patients were considered nonprogressive, showing either complete remission (CR, n = 181; 58%), partial remission (PR, n = 35; 11%), or stable disease (n = 3; 1%). The remaining 238 patients were considered progressive/relapsing after anti-CD19 CAR T-cell treatment and represent the patient population for this analysis; 136 patients progressed/relapsed after axi-cel treatment (median follow-up: 9.0 months [95% CI 5.1-9.7]) and 102 patients after tisa-cel (median follow-up: 7.8 months [95% CI 5.9-10.4]). Demographic characteristics are summarized in Table 1. At the time of decision/before lymphodepletion, most patients (n = 178; 74.8%) presented with diffuse large B-cell lymphoma, a high age-adjusted IPI of 2 or 3 (n = 126; 57.0%), and had received more than 3 lines of therapy prior to CAR T-cell treatment (n = 136; 57.1%), including 48 (20.1%) transplanted patients (46 autologous hematopoietic stem cell transplants and 2 allogeneic hematopoietic stem cell transplants). Bridging therapy was administered to 209 patients (87.8%), including conventional immune-chemotherapy for 176 patients (84.2%), lighter regimens (corticosteroids, monoclonal antibodies without chemotherapy) for 24 patients (11.5%), and radiotherapy for 9 patients (4.3%). At the time of infusion, 138 patients (66%) presented progressive disease, as determined by positron emission tomography scan, and LDH levels were elevated in 72 patients (38.9%).

Of 238 patients with relapse/progressive disease after CAR T-cell treatment, 54 patients (22.7%) relapsed before D30 (very early), 102 patients (42.9%) presented early (D31-D90) progression/relapse, and 82 patients (34.5%) presented late (>D90) progression/relapse. Failure after CAR T-cell treatment occurred after a median time of 2.7 months (range: 0.2; 21.5).

Treatment at time of failure and response

To characterize the management of the patients relapsing/progressing after CAR T-cell treatment, we analyzed treatment administration and type. Of the 238 patients with failure after anti-CD19 CAR T-cell therapy, data for a new line of treatment were available for 154 patients (64.7%). Treatments administered alone or in combination were lenalidomide in 59 patients (38.3%), bispecific antibodies in 11 patients (7.1%), targeted treatment in 33 patients (21.4%), radiotherapy in 17 patients (11%), and combined immune-chemotherapy with various regimens (R-DHAX, R-ICE, Pola-R-Benda, etc) for 31 patients (20%; Table 2). Of note, at failure, patients who had had received axi-cel (n = 136) presented higher rates of grade 3/4 cytopenia at D30 and D90 than those who had received tisa-cel (n = 102; χ^2 test, $P < .001$). Cytopenia at D30 did not impact the choice of subsequent treatment (Fisher's exact test, $P = .812$).

Response to treatment was available for 120 of the 154 patients relapsing/progressing after CAR T-cell treatment (77.9%). Overall response (CR + PR) was observed in 14.1% patients (17 of 120); the CR rate was 6.6% (8 of 120), and the PR rate was 7.5% (9 of 120). A total of 1 of 120 patients (0.8%) presented stable disease, and 70.8% (85 of 120) presented progressive disease as best response.

Efficacy outcomes by treatment type after failure on CAR-T therapy

We further analyzed response rates and survival outcomes after CAR-T relapse, grouping treatments by class (Figure 1). Median PFS-2 after treatment with bispecific antibodies, lenalidomide, targeted therapy, and immunochemotherapy were 3.7 months (95% CI 2.3-not reached [NR]), 3.8 months (95% CI 2.2-4.6), 2.1 months (95% CI 1.7-2.8), and 2.4 months (95% CI 1.8-3.0), respectively. No statistically significant advantage was found comparing the different treatment strategies ($P = .104$).

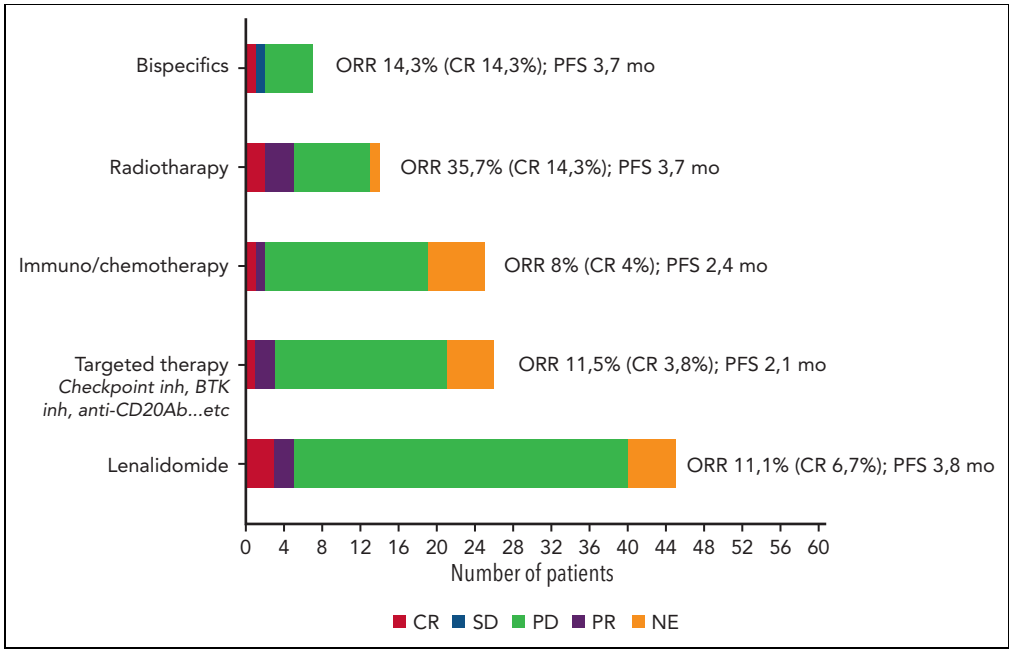


Figure 1. Overall response rate (ORR), best overall response (n = 120), and median progression-free survival (PFS; n = 154) after CAR-T relapse, according to treatment type. BTK inh, Bruton tyrosine kinase inhibitors; CR, complete response; NE, not evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

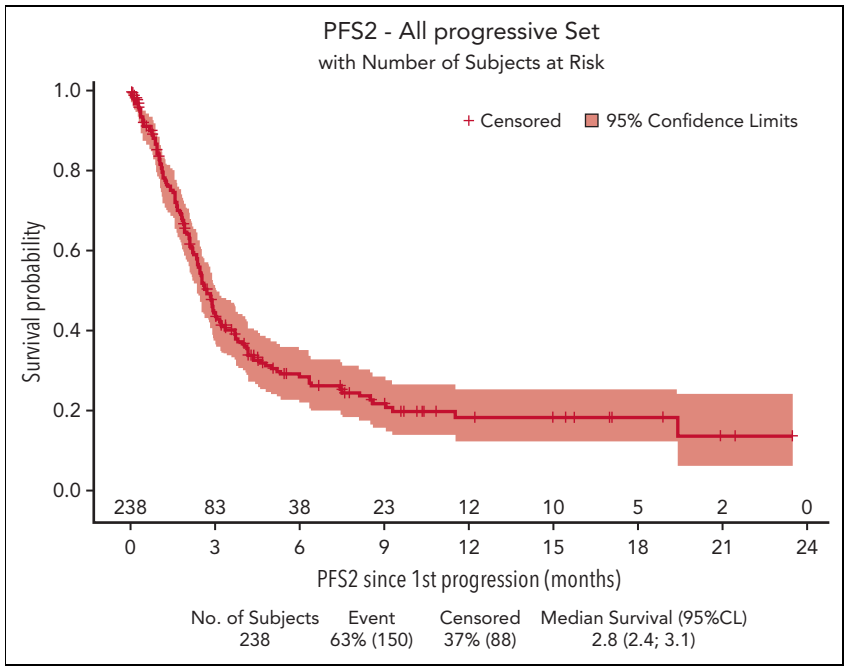
The median OS-2 rates for patients treated with bispecific antibodies, lenalidomide, targeted therapy, and immunochemotherapy were 8.5 months (95% CI 2.9-NR), 7.5 months (95% CI 4.8-9.6), 4.5 months (95% CI 1.7-7.4), and 3.7 months (95% CI 2.6-6.0), respectively (*P*=.32). Radiation therapy was proposed to only those patients presenting localized disease (n = 12). The median PFS-2 was 3.7 months (95% CI 2.9-NR), and the median OS-2 was 9.6 months (95% CI 6.7-NR).

Outcomes

In the overall population of patients treated using CAR T-cells and with data collected in the DESCAR-T registry, the median PFS was 4.6 months (PFS at 6 months was 44.5%).

The median duration of response for the 356 responders on 550 treated patients was 11.1 months (duration of response at 6 months was 57.7%).

Figure 2. Progression-free survival of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy (n = 238). CL, confidence limit.



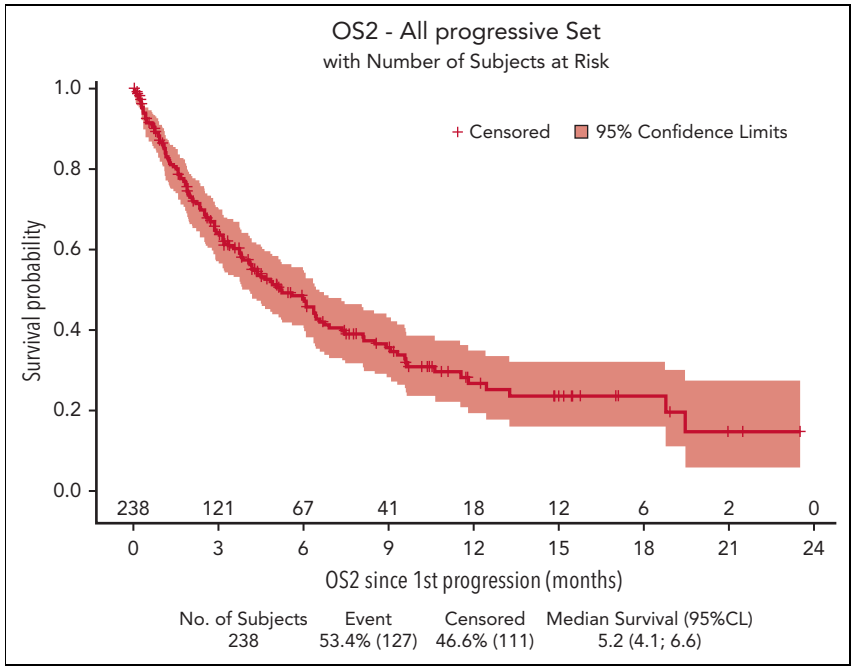


Figure 3. Overall survival of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy (n = 238).

For the 238 patients at failure, median PFS-2 was 2.8 months (95% CI 2.4-3.1) from the time of relapse/progression after CAR T-cell infusion. At 6 months and 12 months, 71.6% and 81.8% of patients had progressed/relapsed, respectively (Figure 2). OS-2 from the time of relapse/progression after CAR T-cell infusion was consistently poor, with a median of 5.2 months (95% CI 4.1-6.6 months) in the overall population (238 patients). At 6 months, only 47.9% of patients were alive, and at 12 months, 26.9% of patients were alive (Figure 3).

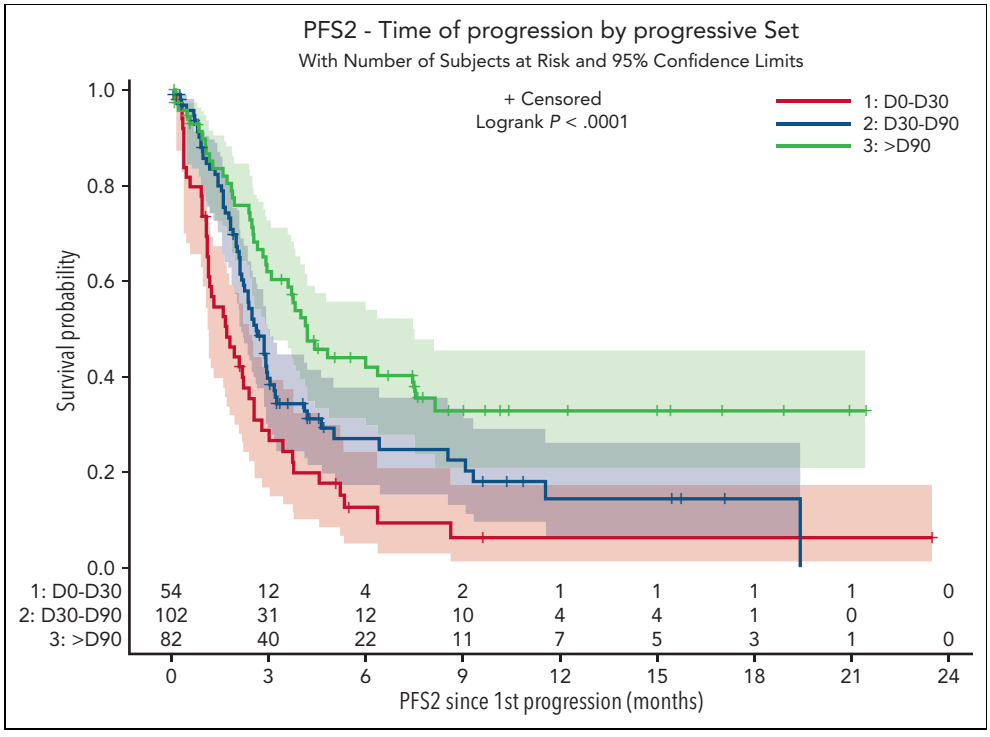


Figure 4. Progression-free survival of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy according to time of failure: relapse/progression between D0-D30 (red), between D30 and D90 (blue), and after D90 (green).

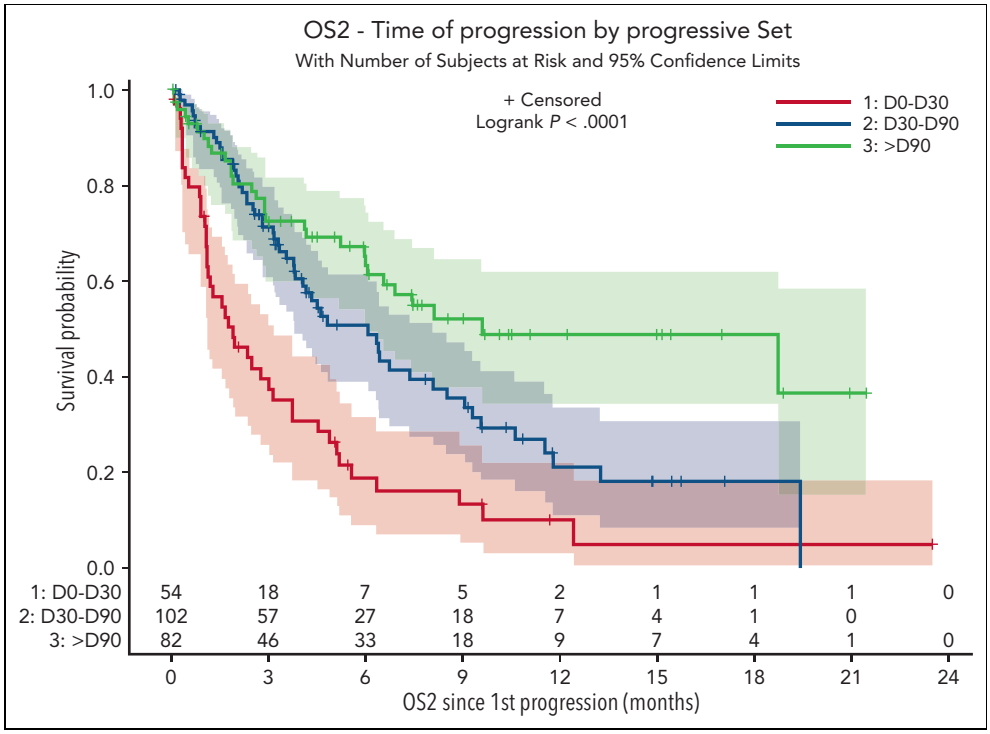


Figure 5. Overall survival of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy, according to time of failure: relapse/progression between D0 and D30 (red), between D30 and D90 (blue), and after D90 (green).

PFS-2 and OS-2 from the time of relapse/progression after CAR T-cell infusion were also analyzed according to the timing of failure. The median PFS-2 for very early progression/relapse patients was 1.7 months (95% CI 1.1-2.4); 2.6 months (95% CI 2.1-3.0) for patients in failure between D31 and D90, $P < .0001$; and 4.2 months (95% CI 2.9-7.5) for patients relapsing after D90 (Figure 4). Similarly, the median OS-2 for patients presenting very early progression/relapse was 1.9 months (95% CI 1.1-3.2), and the median OS-2 for patients presenting CAR T-cell failure between D31 and D90 was 6.1 months (95% CI 3.8-8.1), $P < .0001$. Patients relapsing after D90 presented a median OS-2 of 9.6 months (95% CI 6.0-NR; Figure 5).

Table 3. Multivariable analysis of factors impacting survival outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell therapy

	HR, 95% CI	*P*
Progression-free survival		
LDH prior to infusion > UNL	3.42 [1.93-6.05]	<.0001
Progression/relapse D0-D30	1.74 [0.93-3.25]	.0815
T-cell engagers	NA	.9878
Lenalidomide	0.55 [0.29-1.07]	.0789
Targeted therapy	0.69 [0.33-1.45]	.3228
Ferritin prior to infusion > UNL	1.02 [1.00-1.03]	.0173
Overall survival		
LDH prior to infusion > UNL	2.10 [1.16-3.78]	.0136
Progression/relapse D0-D30	2.93 [1.56-5.50]	.0009
Bispecific antibodies	0.22 [0.03-1.80]	.1566
Lenalidomide	0.42 [0.21-0.82]	.0116
Targeted therapy	0.47 [0.21-1.07]	.0729
CRP prior to infusion > UNL	1.11 [1.04-1.19]	.0027

CI, confidence interval; CRP, C-reactive protein; D, day; HR, hazard ratio; LDH, lactate dehydrogenase; NA, not applicable; UNL, upper normal limit.

Prognostic factors

In a univariate model, factors significantly associated with worse PFS-2 were high LDH at infusion ($P < .0001$, HR 2.66, 95% CI 1.74-4.0.6), ECOG PS ≥2 at infusion ($P = .0067$, HR 1.94, 95% CI 1.20-3.13), very early progression (D0-D30, $P = .0002$, HR 1.98, 95% CI 1.38-2.82), and abnormal levels of CRP and ferritin at infusion (CRP: $P = .0187$, HR 1.03, 95% CI 1.01-1.06; ferritin: $P = .0002$, HR 1.01, 95% CI 1.01-1.02). No significant association was found of treatment type proposed after CAR T-cell treatment and PFS-2, for immunotherapy by bispecific antibodies ($P = .07$, HR 0.45, 95% CI 0.19-1.09), lenalidomide ($P = .10$, HR 0.66, 95% CI 0.41-1.08), or targeted therapy ($P = .8$, HR 0.95, 95% CI 0.5-1.66).

Factors associated with worse OS-2 were as follows: high LDH level ($P < .0001$, HR 2.66, 95% CI 1.74-4.06,); ECOG PS ≥2 at infusion ($P = .0008$, HR 2.37, 95% CI 1.43-3.92); very early progression (D0-D30, $P < .0001$, HR 2.59, 95% CI 1.78-3.76); and abnormal levels of CRP and ferritin at infusion (CRP: $P = .0006$, HR 1.05, 95% CI 1.02-1.08; ferritin: $P = .0002$, HR 1.01, 95% CI 1.01-1.02). No significant association occurred regarding treatment type proposed after CAR T-cell treatment and OS-2, for immunotherapy with bispecific antibodies ($P = .2$ HR 0.51, 95% CI 0.18;1.49), lenalidomide ($P = .06$, HR 0.60, 95% CI 0.35-1.02), or targeted therapy ($P = .7$, HR 0.91, 95% CI 0.5-1.65).

A multivariate analysis identified factors associated with worse PFS-2 as high LDH level at the time of infusion ($P < .0001$, HR

3.42, 95% CI 1.93-6.05), and abnormal levels of ferritin at the time of infusion (P = .01, HR 1.02, 95% CI 1.00-1.03; Table 3). No significant association occurred regarding treatment type proposed after CAR T-cell treatment and PFS-2, for immunotherapy by bispecific antibodies (P = .98 HR = not reached), lenalidomide (P = .07, HR 0.55, 95% CI 0.29-1.07) or target therapy (P = .3, HR 0.69, 95% CI 0.33-1.45). Multivariate analysis of OS-2 identified the following factors as being associated with worse outcome (Table 3): high LDH level (P = .01, HR 2.10, 95% CI 1.16-3.78), elevated CRP levels (P = .003, HR 1.11, 95% CI 1.04-1.19), and very early progression (D0-D30, P = .0009, HR 2.93, 95% CI 1.56-5.50). No significant association occurred regarding treatment type proposed after CAR T-cell treatment and OS-2, for immunotherapy by bispecific antibodies (P = .15, HR 0.22, 95% CI 0.03-1.8) or target therapy (P = .078, HR 0.47 95% CI 0.21–1.07). Treatment by lenalidomide was significantly associated with better OS-2 (P = .01, HR 0.42, 95% CI 0.21-0.82).

Discussion

Anti-CD19 CAR T-cell therapy represents a major advance in the treatment of R/R aggressive BCL. Despite this advancement, failure after infusion is not unexpected, and registered relapse rates reach 66% in pivotal clinical trials and real-world series.[1-9] Much effort has been put into defining the characteristics of patients at high risk of relapse, reflecting the clinical and biological elements corresponding to uncontrolled disease, and those that are potentially relevant (including total metabolic tumor volume, LDH, PS, and CD19 status).[15-19] CAR T-cell product properties, such as kinetics and dose, can also be taken into account,[20] along with tumoral intrinsic factors.[21-23]

Chow et al previously reported a poor outcome in 61 patients presenting progression or relapse after CAR T-cell treatment.[24] The DESCAR-T registry offers a unique opportunity to gather data about a large European cohort. In our series, the outcomes of patients experiencing failure after CAR T-cell treatment are poor, with a median PFS-2 of only 2.8 months (95% CI 2.4-3.1). In our experience, outcomes for patients showing very early failure are even worse (median PFS-2 was 1.7 months, 95% CI 1.1-2.4). These results mirror those that occur with considerably uncontrolled disease that is difficult to manage regardless of the treatment proposed. Preliminary data were recently presented by Alarcon Tomas et al, who reported similar results concerning progression/relapse rates post–CAR T-cell treatment.[25] Interesting to note is that, in their study, the overall response rate after failure was 47% (including 25% CR), which is higher than that in our cohort. This result might be explained by the fact that not all responses were reported in the DESCAR-T registry, and more importantly, by the differing availability across countries of treatments proposed. Polatuzumab-vedotin (Pola) was administered mainly in the former study, whereas in France, this molecule was available for compassionate use only from January 2020 to January 2021, and its cost is not reimbursed; hence, only a few of our patients received Pola after CAR T-cell treatment failure. Similarly, Zurko et al demonstrated in their population the highest response rates after R-Pola-Benda regimen (73% overall response rate and 40% CR, respectively).[26] Other studies suggest a role for anti–programmed cell death protein 1 drugs[27,28] in this setting. In our experience, as well as that of Alarcon Tomas et al[25] and Zurko et al,[26] no advantage of use of this class of molecules was found. Lenalidomide showed beneficial effect in in vivo models in the case of CAR T-cell treatment failure.[29] In our population, lenalidomide was thus used to reinforce immunomodulation. Moreover, previous studies suggest a potential efficacy in this subset of patients.[30,31] A significant advantage was confirmed in our DESCAR-T subset (P = .045).

In our study, statistically significant benefit after lenalidomide treatment was found regarding OS (P = .011), but not PFS (P = .078). This finding is probably related to the groups being small in size, but still, a trend can be observed (Figure 1). We hypothesize that lenalidomide allows partial control of the disease, and thereby aids longer survival. The use of bispecific antibodies seems promising for R/R aggressive BCL patients, even after CAR T-cell treatment failure.[32] Similar results have been reported in a US series,[26] suggesting that bispecific antibodies are a valid option. In our study, only a small sample of the patients (n = 11) received this therapeutic strategy, and longer follow-up is needed for these patients, limiting any conclusions that can be drawn. From our observations, standard chemo-immunotherapy does not seem to offer an advantage in terms of OS or PFS, and available evidence backs this up.[25,26] In our experience, the acceptable response to radiotherapy after CAR T-cell treatment failure is likely explained by the localized progression/relapse of the patients to whom this option was proposed.

Although it has the benefit of being multicenter, our study has some limitations, with longer follow-up needed to better evaluate the long-term responses, and data at the time of relapse potentially missing for some patients in registries. Evaluation of the biology of the tumor and the microenvironment should also bring valuable information to help us better understand these relapses.

In conclusion, this DESCAR-T registry study confirms that outcomes of patients following failure of CAR T-cell treatment remain extremely poor, and outcomes are worse in the event of failure within the first month. Alternative therapeutic strategies (immunotherapy by bispecific antibodies, lenalidomide) may improve PFS in these patients. Nevertheless, treatment of patients with R/R aggressive BCL after failure of anti-CD-19 CAR T-cell constitutes an unmet medical need, and further innovative strategies are needed to improve outcomes for such patients.

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Authorship

Contribution: R.D.B. and C.T. conceived and designed the study; R.D.B., E.G., and C.T. wrote the article; and all authors provided study material and patients, collected and assembled data, performed data analysis and interpretation, provided final approval for the article, and are accountable for all aspects of the work.

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ORCID profiles: R.D.B., 0000-0001-9001-573X; S.L.G., 0000-0001-9840-2128; E.B., 0000-0003-2694-7510; G.C., 0000-0003-0659-9635; D.B., 0000-0003-1866-828X; F.-X.G., 0000-0001-8998-3039; S.C., 0000-0002-7791-0470; J.-J.T., 0000-0003-4879-8106; F.M., 0000-0002-3714-9824; R.H., 0000-0003-1729-8213.

Correspondence: Catherine Thieblemont, Hôpital Saint-Louis, APHP, Hémato-oncologie, 1, ave Claude Vellefaux, Paris 75010, France; email: catherine.thieblemont@aphp.fr.

Footnotes

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For original data, please contact catherine.thieblemont@aphp.fr.

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