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Outcomes of patients with aggressive B-Cell lymphoma after failure of anti-CD19 CAR T-Cell Therapy. A DESCAR-T analysis.

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Abstract:
Anti-CD19 CAR T-cells represent a major advance in the treatment of relapsed/refractory aggressive B-cell lymphomas. However, a significant number of patients experiences 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 2-3, 18.9% had ECOG 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% high lactate dehydrogenase (LDH). Failure after CAR T-cells occurred after a median of 2.7 months (range, 0.2-21.5). Fifty-four (22.7%) patients 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 (64%) patients received salvage treatment: 38.3% had lenalidomide, 7.1% bispecific antibodies, 21.4% targeted treatment, 11% radiotherapy, and 20% immuno-chemotherapy 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 versus after D30 was 1.7 vs 3.0 months respectively (p=0.0001). 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-cells, highlighting the need for further strategies dedicated to this population.

Conflict of interest: COI declared - see note

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- **Key point 1**: Outcome of patients progressing/relapsing after CAR T-cells is poor, especially in case of relapse within 30 days

- **Key point 2:** Salvage immunomodulatory treatment may offer better outcomes compared to standard immuno-chemotherapy

ABSTRACT

Anti-CD19 CAR T-cells represent a major advance in the treatment of relapsed/refractory aggressive B-cell lymphomas. However, a significant number of patients experiences 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 2-3, 18.9% had ECOG 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% high lactate dehydrogenase (LDH). Failure after CAR T-cells occurred after a median of 2.7 months (range, 0.2-21.5). Fifty-four (22.7%) patients 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 (64%) patients received salvage treatment: 38.3% had lenalidomide, 7.1% bispecific antibodies, 21.4% targeted treatment, 11% radiotherapy, and 20% immuno-chemotherapy 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 versus after D30 was 1.7 vs 3.0 months respectively (p=0.0001). 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-cells, highlighting the need for further strategies dedicated to this population.

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 both in pivotal clinical trials (JULIET, ZUMA 1 and TRANSCEND) and in real-world experience (CIMBTR, CART consortium registry, and French, Spanish and German multi-centric studies). Nonetheless, failure after chimeric antigen receptor (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-cells 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 CIMBTR experience with 60% failure at 6 month after tisagenlecleucel (tisa-cel)[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 cells[8]. Iacoboni et al[9] showed almost 70% relapse rate at 12 months in another Spanish cohort. In a multi-centric French study, more than half of the patients showed failure 6 months after CART cells treatment[10]. These data were collected in the DESCAR-T registry, a French national registry designed by 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 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 DESCAR-T registry if they were eligible for treatment with CAR-T for a hematologic malignancy covered by the French healthcare system, on the basis that a CAR-T indication had been validated during a multidisciplinary tumor board of a CAR-T accredited center. As of August 2018, 680 patients with R/R aggressive B-cell lymphoma (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 DESCAR-T. At the time of the analysis (April 2021), 550 patients had been infused with commercially available CAR T-cell products. D0 was identified as the day of CAR T-cell infusion. Patients were evaluated at D30, 90, 180, 270, 360, then at 18, 24 and 36 months.

Characteristics of treated patients

The following clinical characteristics at time of decision/before lymphodepletion were collected: sex, age, number and type of previous lines of treatment before CAR T-cells, previous autologous or allogeneic transplant, histology, Eastern Cooperative Oncology Group (ECOG) performance status (PS)[13], Ann Arbor stage, International Prognostic Index (IPI), age-adjusted International Prognostic Index (aaIPI)[14], number of extra nodal sites, and lactate dehydrogenase (LDH) levels. The same parameters were evaluated at D0. Albumin, C-reactive protein (CRP), and ferritin were also collected at D0. Three groups of bridging chemotherapy were defined: low-dose regimen (steroids +/- immunotherapy), conventional regimen (chemotherapy +/- immunotherapy), and radiation therapy. Treatments received at failure were grouped in the following classes:

monoclonal antibodies (mainly anti-CD20), immuno-chemotherapy, lenalidomide, bispecific antibodies, immune checkpoint inhibitors.

Endpoints

The study was designed to identify the outcomes of patients associated with failure after CAR T-cells (D0) in terms of next progression, death, or last follow-up. We calculated progression-free survival 2 (PFS-2), defined as the lapse of time from first failure after CAR-T infusion to next progression/relapse after further treatment, and overall survival 2 (OS-2), defined as the lapse of time from failure after CAR-T infusion to death or last follow-up. Failure after CAR T-cells was defined as progression and relapse after treatment according to Cheson 2014 response assessment criteria[12]. Patients with stable disease were excluded. The primary endpoint of the study was to determine OS-2 of R/R BCL patients enrolled in the DESCAR-T registry. Secondary endpoints were to describe PFS-2, the baseline characteristics of the patients, treatment proposed at failure, response to the salvage treatment, and the prognostic factors associated with PFS-2 and OS-2. Outcomes were analyzed according to time of relapse D0-D30 (very early), D31-90 (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 addition, the event rates at specific time points were computed, along with 95% confidence intervals (CI). Cox proportional hazard regression models were used to estimate the hazard ratios (HR) 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 axicabtagene-ciloleucel (axi-cel, n=350) or tisagenlecleucel (tisa-cel, n=200).

After a median follow-up of 7.9 months, 312 patients were considered non-progressive, showing complete remission (CR, n=181; 58%), partial remission (PR, n=35; 11%), or stable disease (SD, n=3; 1%). The remaining 238 patients were considered progressive/relapsing after anti-CD19 CAR T-cells treatment and represent the patient population for this analysis; 136 patients progressed/relapsed after axi-cel (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 (DLBCL), a high aaIPI of 2 or 3 (n=126, 57.0%), and had received more than three lines of therapy prior to CAR T-cells (n=136, 57.1%), including 48 (20.1%) transplanted patients (46 autologous hematopoietic stem cell transplantation 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 (PD) determined by PET scan and LDH levels were elevated in 72 patients (38.9%).

Of 238 patients with relapse/progressive disease after CAR T-cells, 54 patients (22.7%) relapsed before day 30 (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-cells 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-cells, 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**). It is of note that at failure, patients who had had received axi-cel (n=136) presented higher rates of grade 3/4 cytopenia at D30 and at D90 than those who had tisa-cel (n=102) (Chi-square test, p <0.001). Cytopenia at D30 did not impact the choice of the subsequent treatment (Fisher Exact, p=0.812).

Response to treatment was available for 120 of the 154 patients relapsing/progressing after CAR T-cells (77.9%). Overall response (CR + PR) was observed in 14.1% patients (17/120); the CR rate was 6.6% (8/120), PR rate was 7.5% (9/120), 0.8% (1/120) of

patients presented SD, and 70.8% (85/120) 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 immuno-chemotherapy 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=0.104). Median OS-2 rate for patients treated with bispecific antibodies, lenalidomide, targeted therapy, and immuno-chemotherapy 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=0.32). Radiation therapy was proposed only to patients presenting localized disease (n=12). Median PFS-2 was 3.7 months (95% CI 2.9-NR) and median OS-2 was 9.6 months (95% CI 6.7-NR).

Outcomes

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

Median DOR for the 356 responders on 550 treated patients was 11.1 months (DoR at 6 months was 57.7%).

For the 238 patients at failure, median progression-free survival (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% patients had progressed/relapsed respectively (**Figure 2**). Overall survival (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**).

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. 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-D90, p<0.0001 and 4.2 months (95%CI, 2.9-7.5) for patients relapsing after D90 (**Figure 4**). Similarly, median OS-2 for patients presenting very early progression/relapse was 1.9 months (95% CI, 1.1-3.2), whilst median OS-2 for patients presenting CAR T-cell failure between D31-D90 was 6.1 months (95% CI, 3.8-8.1), p<0.0001. Patients relapsing after D90 presented a median OS-2 at 9.6 months (95%CI, 6.0 – NR) (**Figure 5**)

Prognostic Factors

In a univariate model, factors significantly associated with worse PFS-2 were high LDH at infusion (p<0.0001, HR 2.66, 95% CI 1.74-4.0.6), ECOG PS ≥2 at infusion (p=0.0067, HR 1.94, 95% CI 1.20-3.13), very early progression (D0-D30, p=0.0002, HR 1.98, 95% CI 1.38-2.82), and abnormal levels of CRP and ferritin at infusion (CRP: p=0.0187, HR 1.03, 95% CI 1.01-1.06; ferritin: p=0.0002, HR 1.01, 95% CI 1.01-1.02). There was no significant association regarding treatment type proposed after CAR T-cells and PFS-2,

for immunotherapy by bispecific antibodies (p=0.07 HR 0.45, 95% CI 0.19;1.09), lenalidomide (p=0.10, HR 0.66, 95% CI 0.41;1.08), or targeted therapy (p=0.8, HR 0.95, 95% CI 0.5;1.66).

Factors associated with worse OS-2 were high LDH (p<0.0001, HR 2.66 95% CI 1.74-4.06,), ECOG PS ≥2 at infusion (p=0.0008, HR 2.37, 95% CI 1.43-3.92), very early progression (D0-D30, p<0.0001, HR 2.59, 95% CI 1.78-3.76), abnormal levels of CRP and ferritin at infusion (CRP: p=0.0006, HR 1.05, 95% CI 1.02-1.08; ferritin: p=0.0002, HR 1.01, 95% CI 1.01-1.02). There was no significant association regarding treatment type proposed after CAR T-cells and OS-2, for immunotherapy with bispecific antibodies (p=0.2 HR 0.51, 95% CI 0.18;1.49), lenalidomide (p=0.06, HR 0.60, 95% CI 0.35-1.02), or targeted therapy (p=0.7, HR 0.91, 95% CI 0.5;1.65).

A multivariate analysis identified factors associated with worse PFS-2 as high LDH at time of infusion (p<0.0001, HR 3.42, 95% CI 1.93-6.05), and abnormal levels of ferritin at time of infusion (p=0.01, HR 1.02, 95% CI 1.00-1.03) (**Table 3**). There was no significant association regarding treatment type proposed after CAR T-cells and PFS-2, for immunotherapy by bispecific antibodies (p=0.98 HR=not reached), lenalidomide (p=0.07, HR 0.55, 95% CI 0.29;1.07) or target therapy (p=0.3, HR 0.69, 95% CI 0.33;1.45). Multivariate analysis of OS-2 identified the following factors as associated with worse outcome (**Table 3**): high LDH (p=0.01, HR 2.10, 95% CI 1.16-3.78), elevated CRP levels (p=0.003, HR 1.11, 95% CI 1.04-1.19), very early progression (D0-D30, p=0.0009, HR 2.93, 95% CI 1.56-5.50). There was no significant association regarding treatment type proposed after CAR T-cells and OS-2 for immunotherapy by bispecific antibodies (p=0.15, HR 0.22, 95% CI 0.03-1.8) or target therapy (p=0.078, HR 0.47 95%

CI 0.21;1.07). Treatment by lenalidomide was significantly associated with better OS-2 (p=0.01, HR 0.42, 95% CI 0.21;0.82).

DISCUSSION

Anti-CD19 CAR T-cells represent a major advance in the treatment of R/R aggressive BCL. Despite this, 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 that are potentially relevant (including total metabolic tumor volume, LDH, PS, CD19 status)[15-19]. CAR T-cell product properties such kinetics and dose, can also be taken into account[20] along with tumoral intrinsic factors[21-23].

Chow et al previously reported a ~~dismal~~ 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 outcome of patients experiencing failure after CAR T-cells is poor, with a median PFS-2 of only 2.8 months (95% CI, 2.4-3.1). In our experience, outcome of patients showing very early failure, is even worse (median PFS-2 was 1.7 months, 95% CI, 1.1-2.4). These results mirror 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-cells[25]. Interestingly, in their study, ORR after failure was 47% (including 25% CR), which is higher than in our cohort. This 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 largely administered in the former study, whereas in France this molecule only had been available for compassionate use from January 2020 to January 2021 and

is not reimbursed, hence only a few of our patients had received Pola after CAR T-cell failure. Similarly, Zurko et al. demonstrated in their population the highest response rates after R-Pola-Benda regimen (73% ORR and 40% CR respectively)[26]. Other studies suggest a role for anti-PD1 drugs[27,28] in this setting. In our experience, as well as that of Alarcon Tomas et al and Zurko et al, no advantage was found for the use of this class of molecules. Lenalidomide showed beneficial effect in *in vivo* models in case of CAR T-cell failure[29]. In our population it was thus used to reinforce immunomodulation. Moreover, previous studies suggested a potential efficacy in this subset of patients[30,31]. A significant advantage was confirmed in our DESCAR-T subset (p=0.045).

In our study, statistically significant benefit after Lenalidomide treatment was found regarding OS (p=0.011), but not PFS (p=0.078). This finding is probably related to groups small in size. Despite that, a trend can be observed (**Figure 1**). We could hypothesize that Lenalidomide could allow to achieve partial control on the disease, and then longer survivals. The use of bispecific antibodies seems promising for R/R aggressive BCL patients, even after CAR T-cells 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 censored patients (11patients) 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-cells failure is likely explained by the localized progression/relapse of the patients to whom this option was proposed.

Despite its multicentric character, our study has some limitations, with longer follow-up needed to better evaluate the long-term responses, and data at the time of relapse may be missing for some patients in registries. Evaluation of the biology of the tumor and the microenvironment should also bring valuable information to help us to better understand these relapses.

In conclusion, this DESCAR-T registry study confirms that the outcome of patients at the time of failure after CAR T-cells treatment remains extremely poor, and that this outcome is worse in the event of failure within the first month. Alternative therapeutic strategies (immunotherapy by bispecific antibodies, lenalidomide) may improve PFS rates in these patients. Patients with R/R aggressive BCL failing after anti-CD-19 CAR T-cells treatment constitute an unmet medical need, and further innovative strategies are needed to improve the outcome of such patients.

Authorship Contributions

Conception and design: RDB and CT

Provision of study material or patients: all authors

Collection and assembly of data: all authors

Data analysis and interpretation: all authors

Manuscript writing: RB, EG, CT

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Disclosure of Conflicts of Interest

R Di Blasi: Honoraria, travel support, and membership of advisory boards from Novartis, Kite/Gilead, Janssen, Pfizer, Celgene.
S Le Gouill: Honoraria, travel support, and membership of advisory boards from Novartis, Kite/Gilead, Janssen
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D Beauvais: Honoraria and advisory boards from Gilead, boards from Celgène
F Le Bras: Honoraria Kite/Gilead
FX Gros: Honoraria: Kite/Gilead, BMS, Milteny, Novartis.
S Choquet: served on the scientific advisory board for Gilead, Novartis, Roche, Abbvie, Sandoz, Sanofi, Janssen, Celgene-BMS, Takeda, Atara, Astra Zeneca,
P Bories: Honoraria and membership of advisory boards from Novartis, Kite/Gilead, BMS-Celgene, Abbvie
P Feugier: Janssen: Consultancy, Honoraria; Gilead: Consultancy, Honoraria; Abbvie: Consultancy, Honoraria; Amgen: Honoraria; Astrazeneca: Consultancy, Honoraria.
RO Casasnovas: Honoraria for consultancy and advisory board :Roche, Takeda, BMS, MSD, Gilead/Kite, Janssen, ADC Therapeutics, Incyte ; Research funding : Roche, Gilead, Takeda
JO Bay: no conflict to declare
M Mohty: Honoraria: Amgen, Astellas, BMS, Celgene, Gilead, Janssen, Jazz, Takeda, Novartis, Pfizer, Sanofi, Adaptive Biotechnologies. Research Funding: Celgene, Janssen, Jazz, Sanofi
M Joris: no conflict to declare
T Gastinne: honoraria from Gilead/kite, Novartis, Takeda
P Sesques: Honoraria, Advisory/Consultancy from Janssen, Roche, BMS, Chugai; Novartis and Kite/Gilead
JJ Tudesq: honoraria from BMS, Gilead; travel support from Gilead.
L Vercellino: no conflict to declare
F Morschhauser: Advisory boards pour Gilead, Novartis, BMS, épizyme, miltenyi, Abbvie, genmab, Roche, AstraZeneca; Consultancy: gilead, roche; Scientific lectures: Roche, Chugai,
E Gat: no conflict to declare
F Broussais: no conflict to declare

R Houot: Honoraria from Bristol-Myers Squibb, Celgene, Gilead Sciences, Incyte, Janssen, Kite, MSD, Novartis and Roche

C Thieblemont. Board /Consultancy/honoraria: Novartis, BMS/Celgene, Bayer, AbbVie, Gilead Sciences, Roche, Janssen, Kite, Incyte, Amgen Educational activities: Janssen, Roche, BMS/ Celgene, Novartis

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Tables

Table 1: Baseline patient and CAR T-cell therapy characteristics of all patients and 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 years	**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	**168 (99.4)**	**36 (100)**	**73 (98.6)**	**59 (100.0)**

infusion (< 1 G/L)				
Ferritin prior to infusion > UNL	**133 (84.7)**	**37 (88.1)**	**57 (85.1)**	**39 (81.3)**
Median CRP prior to infusion (range)	**20 mg/L (6-50)**	**39 mg/L (0-349)**	**18 mg/L (1-376)**	**12.5 mg/L (0-204)**
CAR T-cell product				
Tisagenlecleucel	**102 (42.9)**	**21 (38.9)**	**40 (39.2)**	**29 (35.3)**
Axicabtagene-ciloleucel	**136 (57.1)**	**33 (61.1)**	**62 (60.7)**	**53 (64.7)**

aaIPI: ; CRP: C-reactive protein; DLBCL: diffuse large B-cell lymphoma; ECOG PS: ; NOS : not otherwise specified ; PMBL: primary mediastina B-cell lymphoma; HGBCL: high grade B-cell lymphoma; FL: follicular lymphoma; LDH: lactate dehydrogenase; UNL: upper normal limit; G/L: Giga/Liter.

**: 3B-FL n=2, Primary central nervous system lymphoma n=1, transformed marginal zone lymphoma n=3, unclassifiable Hodgkin/DLBCL n=9*

Table 2: Treatments administered at CAR T progression/relapse

TREATMENT	n=154 (%)
IMID∞ lenalidomide°	**59 (38.3)**
Bispecific antibodies anti-CD20-CD3	**11 (7.1)**
Target therapy § Nivolumab Pembrolizumab Ibrutinib Ibrutinib + lenalidomide + rituximab Ibrutinib + corticosteroids Ibrutinib + lenalidomide Nivolumab + brentuximab vedotin Pembrolizumab + lenalidomide Lenalidomide + polatuzumab vedotin Busulfan + fludarabine + nivolumab + thiotepa Clinical trial LYM 1001* MALT-1 inhibitor Anti-CD20 monoclonal antibody Other monoclonal antibody (anti-CD38, anti-CD30, anti-CD79b)	**33 (21.4%)** 11 (7.1%) 4 (2.6%) 3 (1.9%) 2 (1.3%) 2 (1.3%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 1 (0.6%) 3 (1.9%) 1 (0.6%)
Radiotherapy	**17 (11.0)**
Immuno-chemotherapy	**31 (20.1)**
Palliative corticosteroids	**1 (0.6)**

∞*IMID, immunomodulatory drug*

°10 patients received lenalidomide alone, 49 received lenalidomide in combination, including 46 with rituximab

§ *Among the 33patients who received targeted therapies: 24 received as monotherapy, 9 in combinations (all with different drugs).*

**MALT-1 inhibitor + ibrutinib*

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

Table 3: Multivariable analysis of factors impacting survival outcomes of patients with aggressive B-cell lymphoma after failure of anti-CD19 CAR T-cell Tterapy. Progression-free survival (PFS) and overall survival OS) are analyzed.

	HR, 95%CI	P-value
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]	**0.0815**
T-cell engagers	NA	**0.9878**
Lenalidomide	0.55 [0.29;1.07]	**0.0789**
Targeted therapy	0.69 [0.33;1.45]	**0.3228**
Ferritin prior to infusion > UNL	1.02 [1.00;1.03]	**0.0173**
Overall Survival		
LDH prior to infusion > UNL	2.10 [1.16;3.78]	**0.0136**
Progression/relapse D0-D30	2.93 [1.56;5.50]	**0.0009**
Bispecific antibodies	0.22 [0.03;1.80]	**0.1566**
Lenalidomide	0.42 [0.21;0.82]	**0.0116**
Targeted therapy	0.47 [0.21;1.07]	**0.0729**
CRP prior to infusion > UNL	1.11 [1.04;1.19]	**0.0027**

HR, hazard ratio; LDH, lactate dehydrogenase; UNL

Figure Legends

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. CR, complete response; PR, partial response, SD, stable disease,

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

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

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-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-D30 (red), between D30-D90 (blue), and after D90 (green).

Figure 1.

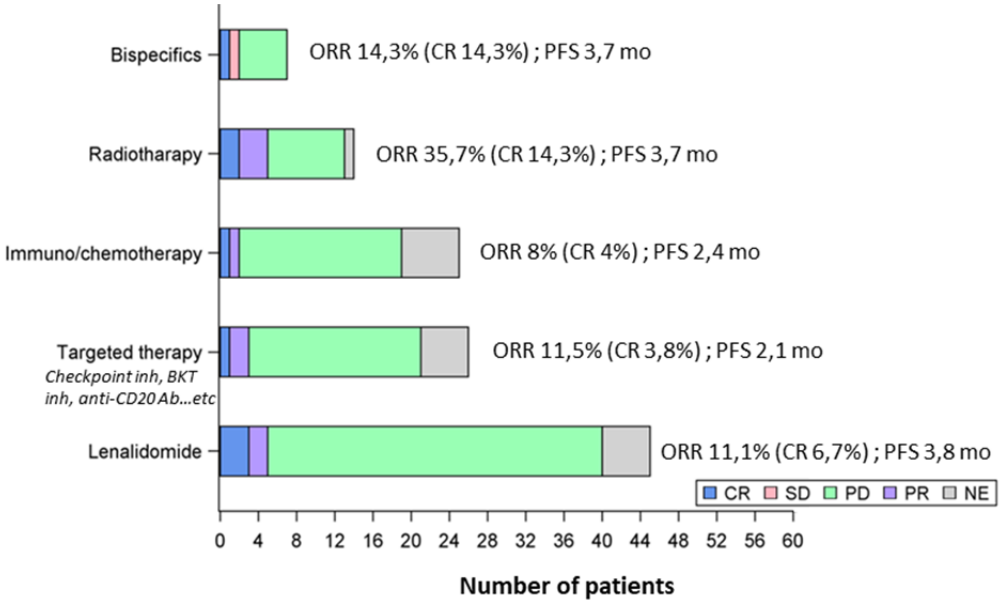
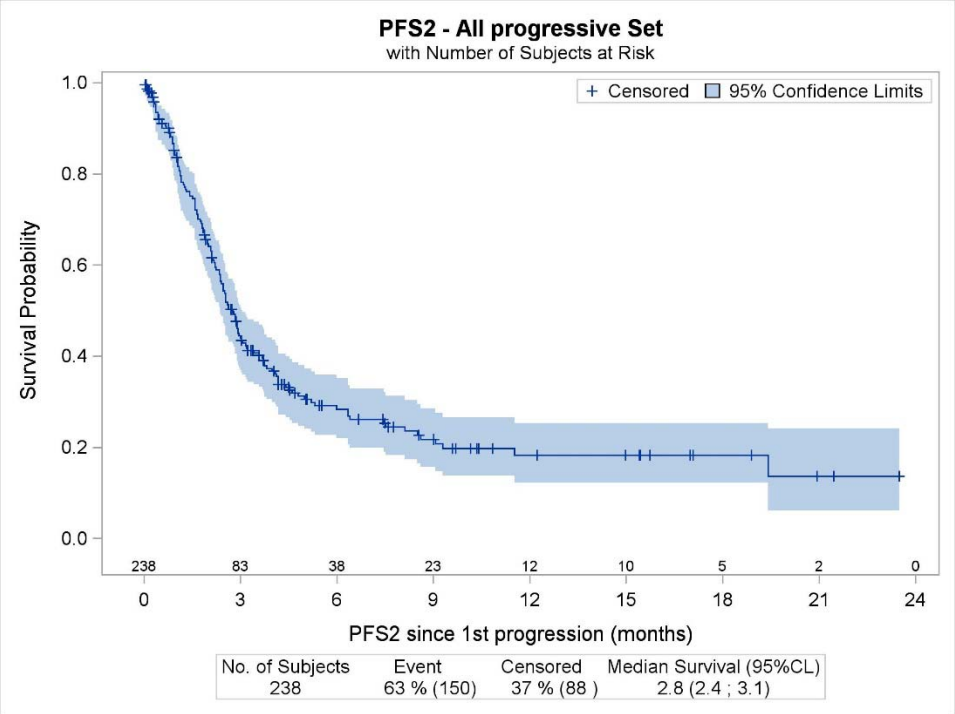


Figure 2.



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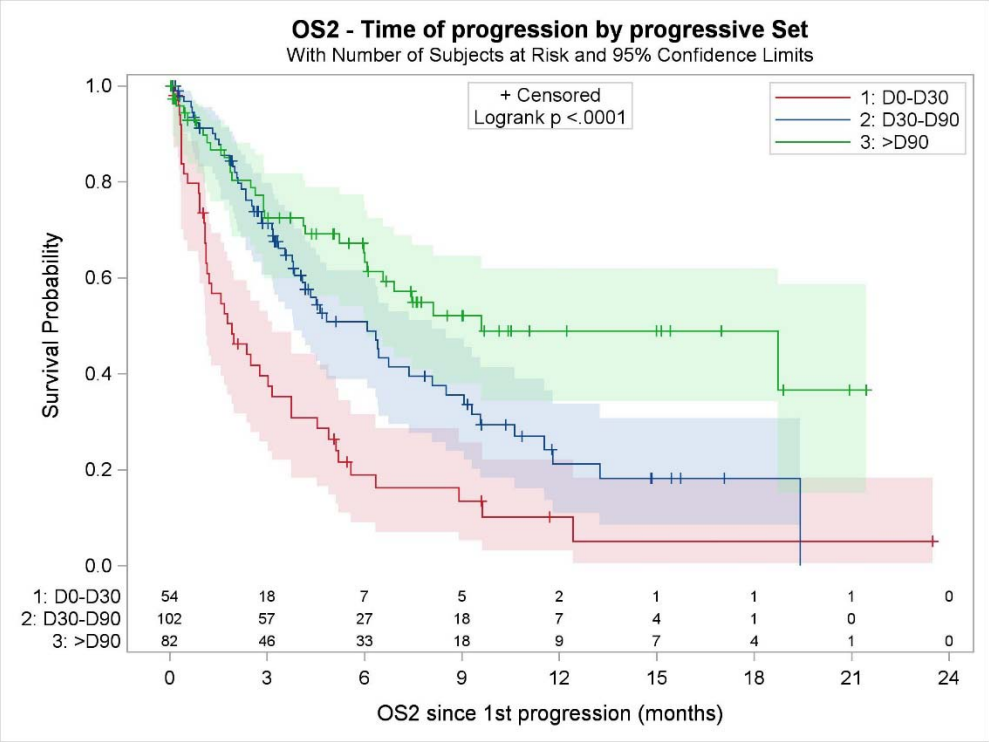

Figure 4.

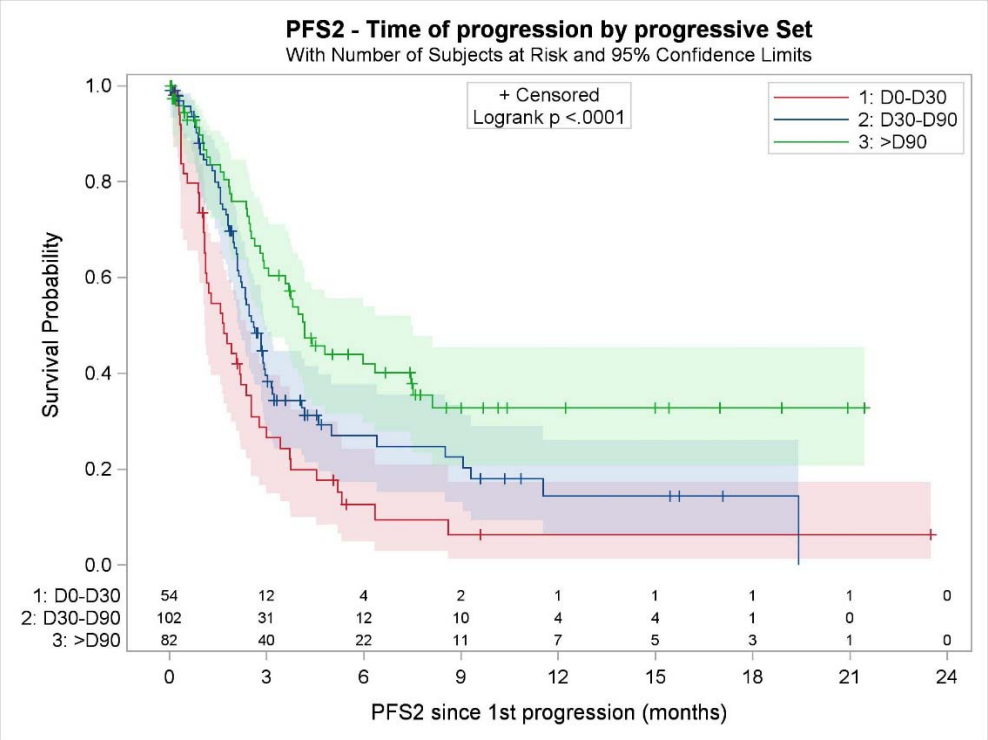

Figure 3.