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Impact of SCHOLAR-1 Criteria on Chimeric Antigen Receptor T Cell Therapy Efficacy in Aggressive B Lymphoma: A Real-World GELTAMO/GETH Study

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A B S T R A C T

In the pre-chimeric antigen receptor T cell (CAR-T) therapy era, the SCHOLAR-1 study identified a group of patients with refractory aggressive B cell lymphoma (ABCL) with particularly poor prognoses. We recently published our real-world data from Spain, focused on this SCHOLAR-1 refractory group, and compared patients who underwent CAR-T therapy with the previous standard of care. In this study, we found that the efficacy of CAR-T therapy in refractory patients, in terms of progression-free survival (PFS) and overall survival (OS), was superior to that of the treatments available in the pre-CAR-T era. The main objective of these new analyses was to analyze treatment efficacy in terms of response rates and survival for patients with ABCL with or without the SCHOLAR-1 criteria. In addition, we analyzed the prognostic impact of each SCHOLAR-1 criterion independently. Our study aimed to assess the prognostic impact of SCHOLAR-1 criteria on ABCL patients treated with CAR-T therapy in Spain. This multicenter, retrospective, observational study. We included all adult patients treated with commercially available CAR-T cell products and diagnosed with ABCL different from primary mediastinal large B cell lymphoma between February 2019 and July 2022. Patients meeting any SCHOLAR-1 criteria (progressive disease as the best response to any line of therapy, stable disease as the best response to $\geq$4 cycles of first-line therapy or $\geq$2 cycles of later-line therapy, or relapse at $<$12 months after autologous stem cell transplantation [auto-SCT]) in the line of treatment before CAR-T therapy (SCHOLAR-1 group) were compared with those not meeting any of these criteria (non-SCHOLAR-1 group). To analyze the prognostic impact of individual SCHOLAR-1 criteria, all the patients who met any of the SCHOLAR-1 criteria at any time were included to assess whether these criteria have the same prognostic impact in the CAR-T era. In addition, patients were grouped according to whether they were refractory to the first line of treatment, refractory to the last line of treatment, or relapsed early after auto-SCT. The PFS and OS were calculated from the time of appearance of the SCHOLAR-1 refractoriness criteria. Of 329 patients treated with CAR-T (169 with axi-cel and 160 with tisa-cel), 52

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were in the non-SCHOLAR-1 group and 277 were in the SCHOLAR-1 group. We found significantly better outcomes in the non-SCHOLAR-1 patients compared with the SCHOLAR-1 patients (median PFS of 12.2 and 3.3 months, respectively; P = .009). In addition, axi-cel showed better results in terms of efficacy than tisa-cel for both the non-SCHOLAR-1 group (hazard ratio [HR] for PFS, 2.7 [95% confidence interval (CI), 1.1 to 6.7; P = .028]; HR for OS, 7.1 [95% CI, 1.5 to 34.6; P = .015]) and SCHOLAR-1 group (HR for PFS, 1.8 [95% CI, 1.3 to 2.5; P < .001]; HR for OS, 1.8 [95% CI, 1.2 to 2.6; P = .002]), but also significantly more toxicity. Finally, separately analyzing the prognostic impact of each SCHOLAR-1 criterion revealed that refractoriness to the last line of treatment was the variable with the most significant impact on survival. In conclusion, SCHOLAR-1 refractoriness criteria notably influence the efficacy of CAR-T therapy. In our experience, axi-cel showed better efficacy than tisa-cel for both SCHOLAR-1 and non-SCHOLAR-1 patients. Refractoriness to the last line of treatment was the variable with the most significant impact on survival in the CAR-T therapy era.

INTRODUCTION

Chimeric antigen receptor (CAR) T cell therapy is becoming the standard of care for patients with aggressive B cell lymphoma (ABCL), including diffuse large B cell lymphoma (DLBCL), transformed follicular lymphoma, primary mediastinal large B cell lymphoma (PMLBCL), and high-grade B cell lymphoma (HGBCL) pretreated with 2 lines. Currently, 3 CAR-T products targeting CD19 are available in Europe and the United States for treating ABCL after at least 2 lines of systemic therapy: axicabtagene ciloleucel (axi–cel), tisagenlecleucel (tisa-cel) [1–3], and lisocabtagene maraleucel (liso-cel) [4]. The 3 pivotal single-arm phase II clinical trials provided highly encouraging results, showing complete response (CR) rates of 40% to 58% and prolonged remission in 30% to 40% of patients [1–4]. In addition, various studies from the United States [5–7] and Europe [8–14] have shown the efficacy of these treatments in the real-world setting. The response and survival rates were similar to those found in pivotal studies and also identified important factors related to outcome as well as to toxicity, such as elevated lactate dehydrogenase levels, Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥2, a need for and response to bridging therapy, and disease status pre-CAR-T infusion. More recently, axi-cel and liso-cel have even positioned themselves in previous lines, given their approval for use after first relapse if it occurred within 12 months or if refractory to front-line chemoimmunotherapy, having shown superior results to the standard of care in patients with ABCL [15,16].

In the pre-CAR-T era, the SCHOLAR-1 study identified a group of refractory patients with especially poor prognoses [17]. This study pooled data from 2 separate phase III clinical trials (the Lymphoma Academic Research Organization CORAL study and the Canadian Cancer Trials Group LY.12 study) and 2 observational cohorts (MD Anderson Cancer Center and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence). Patients with DLBCL refractory to first-line or subsequent lines of therapy or relapsing within 1 year after autologous stem cell transplantation (auto-SCT) had a very low probability of responding to the next line of treatment (26% overall response rate and 7% CR rate) and a median overall survival (OS) of only 6.3 months [17]. We recently published our real-world data from Spain, focused on this SCHOLAR-1 refractory group, and compared patients who underwent CAR-T therapy with the previous standard of care. In this study, we found that the efficacy of CAR-T therapy in refractory patients, in terms of progression-free survival (PFS) and OS, was superior to that of the treatments available in the pre-CAR-T era. We also found that axi-cel appeared to be more effective than tisa-cel in refractory patients according to SCHOLAR-1 criteria.

The main objective of these new analyses, performed with a larger number of patients and longer follow-up, was to analyze treatment efficacy in terms of response rates and survival for patients with ABCL with or without the SCHOLAR-1 criteria, comparing both axi-cel and tisa-cel in these 2 subgroups. In addition, we analyzed the prognostic impact of each SCHOLAR-1 criterion.

METHODS

Study Design and Patients

This was a multicenter retrospective observational study conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Hospital Universitario Gregorio Marañón. We included all adult patients treated with commercially available CAR-T cell products and diagnosed with ABCL different from PMLBCL. All patients were registered in the GELTAMO/GETH-TC (Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea/Grupo Español de Trasplante Hematopoyético y Terapia Celular [Spanish Lymphomas and Autologous Bone Marrow Transplant Group/Spanish Hematopoietic and Cellular Transplant Group]) database. These patients were treated with CAR-T therapy in 12 Spanish centers between February 2019 and July 2022. All patients were deemed eligible according to homogeneous criteria by the Expert Committee of the Spanish National Health System. Patients meeting any of the SCHOLAR-1 criteria [17]—progressive disease as best response to any line of therapy, stable disease as best response to ≥4 cycles of first-line therapy or ≥2 cycles of later-line therapy, or relapse <12 months after auto-SCT—in the line of treatment prior to CAR-T therapy (SCHOLAR-1 group) were compared with those not meeting any of these criteria (non-SCHOLAR-1 group). Primary refractory patients who subsequently responded to the next treatment were included in the non-SCHOLAR-1 group, as were primary refractory patients who relapsed late after auto-SCT. Patient selection, supportive care, toxicity management, and response assessment followed institutional practices. Cytokine release syndrome (CRS) and neurotoxicity were graded according to the American Society of Transplantation and Cellular Therapy consensus criteria [18].

Statistical Analysis

The present analysis was based on a data cutoff of September 15, 2022. We obtained descriptive statistics, including median and interquartile range (IQR) for the continuous variables and percentages for the categorical variables. The

association between 2 categorical variables was analyzed using the Fisher exact test or chi-square test. The median follow-up time (in months) was calculated by the reverse Kaplan-Meier method. Time to event, OS, and PFS were estimated using the Kaplan-Meier method, and comparisons between variables of interest were performed using the log-rank test. The OS for the infused populations was calculated from the date of infusion until the date of death from any cause, censoring for patients alive at last contact. The PFS for the infused populations was calculated from the date of infusion until the date of relapse, progression, or death from any cause, censoring for patients who were alive and progression-free at last contact. This analysis was exploratory, and *P* values were not corrected for multiple testing. The specific cutoffs for quantitative variables, such as time to approval, apheresis, or infusion, were calculated using receiver operating characteristic curves. We performed multivariable logistic regression to assess the effect of important covariates on response and toxicity. We also performed a multivariate survival analysis including the variables that appeared to be significant in the univariate analysis ($P < .05$), as well as potential confounders according to the Cox proportional hazard regression model. All reported *P* values were 2-sided, and statistical significance was set at $P < .05$. Analyses were performed using SPSS version 29 (IBM, Armonk, NY). In addition, considering the imbalance between cohorts, we created a balanced covariate distribution considering an exhaustive list of covariates that could generate confusion between cohorts or significantly influence PFS or OS in the whole series, including previous lines of therapy (0 or 1 versus ≥2), age at apheresis (18 to 60 years versus >60 years), bulky disease at infusion (largest tumor diameter ≥7.5 cm), histology (transformed follicular lymphoma versus DLBCL versus HGBCL), SCHOLAR-1 criteria, previous auto-SCT, ECOG-PS preapheresis (0/1 versus 2 to 4), bridging therapy, disease status preinfusion (CR/partial response [PR] versus stable disease [SD]/progressive disease [PD]), ECOG-PS at infusion (0/1 versus 2 to 4), Ann Arbor stage at infusion (I/II versus III/IV), and revised International Prognostic Index (R-IPI) at infusion (0 to 2 versus 3 to 5). Matching was done at a 1:1 ratio without replacement and with optimal matching, applying a caliper width of the propensity score set at .2.

Analysis of the prognostic impact of individual SCHOLAR-1 criteria included all the patients who met any of the SCHOLAR-1 criteria at any time, with the aim of assessing whether these criteria have the same prognostic impact in the CAR-T therapy era. Patients were grouped according to whether they were refractory to the first line of treatment, were refractory to the last line, or relapsed early after auto-SCT. The PFS and OS were calculated from the time of appearance of the SCHOLAR-1 refractoriness criteria.

RESULTS

Patient Characteristics

From the initial population of 407 patients registered in the GELTAMO/GETH-TC database, 54 were excluded, 31 owing to a diagnosis of PMLBCL and 23 for lack of data or follow-up. A total of 353 patients underwent apheresis, 181 with axi-cel and 172 with tisa-cel. Twenty-four patients were not infused, 18 due to disease progression, 5 due to severe infection, and 1 because of production failure. Ultimately, 329 patients were infused, 169 with axi-cel and 160 with tisa-cel, including 52 in the non-SCHOLAR-1 group and 277 in the SCHOLAR-1 group (Figure 1).

Patient characteristics are shown in Table 1. Interestingly, all cases of HGBCL occurred in the SCHOLAR-1 group (n = 38). There were no statistically significant differences between the SCHOLAR-1 and non-SCHOLAR-1 groups in R-IPI, bulky disease, or Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI). Two hundred sixty-four patients (71%) required bridging therapy, including 204 (71%) with classical immunochemotherapy, 17 (6%) with R-bendamustine-polatuzumab, 40 (15%) with radiotherapy with or without chemotherapy, 11 (4%) with steroids with or without monoclonal antibodies, and 9 (3%) with molecular targeting therapy, with no difference in bridging therapy frequency between the SCHOLAR-1 group (80%) and the non-SCHOLAR-1 group (77%). The rate of lymphodepletion with stable or progressive disease was higher in the SCHOLAR-1 group (87% versus 75%; $P = .044$).

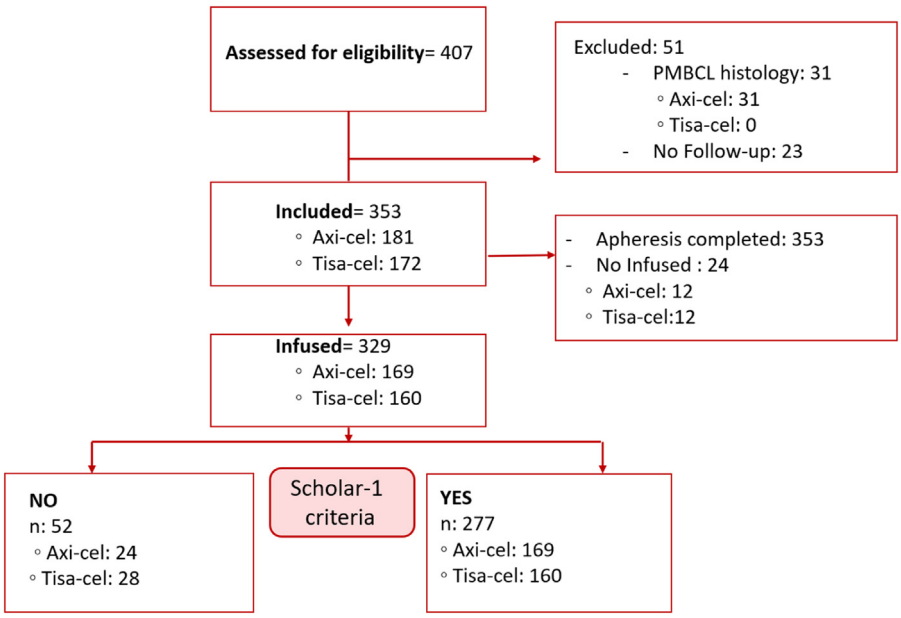

Figure 1. Flow chart of the study.

Table 1
Patient Characteristics

Characteristic	Non-SCHOLAR-1 Group (N = 52)	SCHOLAR-1 Group (N = 277)	*P* Value
At diagnosis			
Sex, n (%)			
Male	33 (63)	175 (63)	1
Female	19 (36)	102 (37)	
Diagnosis, n (%)			.093
DLBCL NOS	47 (92)	212 (77)	
HGL DH/TH	0	33 (12)	
HGL NOS	0	5 (2)	
T cell-rich LBCL	2 (4)	11 (4)	
Follicular transformed	1 (2)	12 (4)	
Other	1 (2)	3 (1)	
Missing	1	1	
Cell of origin, n (%)			.74
GCB	28 (60)	149 (63)	
Non-GCB	19 (40)	88 (37)	
Missing	5	40	
MYC rearrangement, n (%)			.65
Yes	5 (12)	42 (17)	
No	37 (88)	211 (83)	
Missing	10	24	
BCL2 rearrangement			.008
Yes	4 (10)	74 (29)	
No	37 (90)	182 (71)	
Missing	11	21	
BCL6 rearrangement			1
Yes	5 (12)	32 (13)	
No	35 (87)	222 (87)	
Missing	12	23	
AA stage, n (%)			.22
I-II	12 (24)	44 (16)	
III-IV	38 (76)	230 (84)	
Missing	2	3	
R-IPI, n (%)			.74
0-2	19 (43)	100 (41)	
3-5	25 (57)	146 (59)	
Missing	8	31	
Treatment			
CAR-T product, n (%)			.45
Tisa-cel	28 (54)	132 (48)	
Axi-cel	24 (46)	145 (52)	
Primary refractory, n (%)			<.001
Yes	16 (31)	170 (61)	
No	36 (69)	107 (38)	
Refractory to last therapy, n (%)			<.001
Yes	0	254 (92)	
No	52 (100)	23 (8)	
Early relapse post-auto-SCT, n (%)			<.001
Yes	0	57 (21)	
No	52 (100)	220 (79)	
Previous auto-SCT (%), n (%)			.003
Yes	25 (48)	73 (26)	
No	27 (52)	204 (74)	
Previous lines of therapy, n (%)			.88
0-2	31 (61)	172 (62)	
>2	20 (39)	105 (38)	
Status before lymphodepletion			
Disease status at CAR-T, n (%)			.044
CR/PR	12 (24)	34 (13)	
SD/PD	37 (75)	235 (87)	
Missing	3	8	
Bridge therapy, n (%)			.25
Yes	39 (75)	225 (82)	
No	13 (25)	50 (18)	
Missing		2	
HCT-CI at CAR-T, n (%)			1
0-2	32 (67)	169 (67)	
3-7	16 (33)	84 (32)	
Missing	3	24	
ECOG PS at CAR-T, n (%)			.14
0-1	50 (100)	256 (94)	
2-4	0	17 (6)	
Missing	2	4	
AA stage at CAR-T, n (%)			.17
I-II	10 (22)	34 (14)	
III-IV	35 (78)	215 (86)	
Missing	7	28	
Bulky mass at CAR-T, n (%)			.074
Yes	12 (25)	105 (39)	
No	36 (75)	164 (61)	
Missing	4	8	
LDH, n (%)			.03
Normal	33 (66)	127 (49)	
Elevated	17 (34)	134 (51)	
Missing	2	16	
R-IPI at CAR-T, n (%)			1
0-2	18 (41)	105 (41)	
3-5	26 (59)	151 (59)	
Missing	8	21	

DLBCL, NOS indicates diffuse large B cell lymphoma not otherwise specified; HGL DH/TH, high-grade B cell lymphoma double and triple hit; HGL, NOS, high-grade B cell lymphoma not otherwise specified; GCB, germinal center B cell-like; SD, stable disease; PD, progressive disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; AA, Ann Arbor stage; R-IPI, revised International Prognostic Index; LDH, lactate dehydrogenase.

Overall series

Considering the global series, with a median follow up of 12.2 months (95% CI, 12.1 to 12.2 months), the median OS and PFS were 15.4 months (95% CI, 10.8 to 20 months) and 3.5 months (95% CI, 2.3 to 4.6 months), respectively, and the estimated 12-month OS and PFS were 56% (95% CI, 50 to 62 months) and 36% (95% CI, 31 to 42 months), respectively. In

Table 2
Univariate and Multivariate Analysis of Non-SCHOLAR-1 Group (N = 52)

Variable	1-yr OS, % (95% CI)/HR (95% CI)*	*P* Value	1-yr PFS, % (95% CI)/HR (95% CI)*	*P* Value
Univariate analysis				
Diagnosis		.001		.12
DLBCL NOS	81 (69-93)		56 (41-71)	
T cell-rich LBCL	0 (NA)		50 (0-100)	
tFL	100 (NA)		100 (NA)	
Other	100 (NA)		100 (NA)	
ECOG PS preapheresis		<.001		.013
0-1	84 (73-95)		59 (45-74)	
2-4	0 (NA)		0 (NA)	
AA stage preapheresis		.10		.047
I-II	100 (NA)		89 (68-100)	
III-IV	76 (61-91)		51 (34-67)	
CAR-T type		.068		.10
Tisa-cel	69 (50-87)		43 (24-63)	
Axi-cel	90 (77-100)		70 (51-88)	
Disease status at CAR-T		.042		.33
CR/PR	100 (NA)		83 (62-100)	
SD/PD	74 (59-89)		51 (34-68)	
AA stage at CAR-T		.29		.076
I-II	90 (71-100)		80 (55-100)	
III-IV	77 (61-92)		49 (31-66)	
LDH at CAR-T		.36		.15
Normal	83 (69-97)		60 (43-98)	
Elevated	75 (53-96)		47 (23-71)	
R-IPI at CAR-T		.03		.3
0-2	94 (83-100)		59 (36-83)	
3-5	70 (51-89)		52 (32-72)	
Multivariate analysis				
Tisa-cell CAR-T product	11.79 (1.45-95.89)	.021	2.74 (1.12-6.72)	.028
R-IPI 3-5	7.12 (1.46-34.63)	.015	—	—
AA stage III-IV	—	—	7.79 (1.03-58.71)	.046

NA indicates not applicable; tFL, transformed follicular lymphoma.
* OS for univariate analysis, HR for multivariate analysis.

the multivariate analysis, the CAR-T product (tisa-cel: HR, 1.73; 95% CI, 1.24 to 2.42; $P = .001$), need for bridging therapy (HR, 1.81; 95% CI, 1.16 to 2.82; $P = .008$), ECOG PS >1 at CAR-T (HR, 1.97; 95% CI, 1.15 to 3.37; $P = .013$), and refractoriness to last therapy (HR, 2.23; 95% CI, 1.44 to 3.44; $P < .001$) were independent predictors of poorer PFS, whereas the independent factors associated with poorer OS were the type of CAR-T (tisa-cel: HR, 1.73; 95% CI, 1.19 to 2.52; $P = .004$), need for bridging therapy (HR, 2.18; 95% CI, 1.22 to 3.91; $P = .009$), ECOG PS >1 at apheresis (HR, 3.08; 95% CI, 1.46 to 6.51; $P = .003$), and previous ASCT (HR, 2.3; 95% CI, 1.44 to 3.65; $P < .001$).

Non-SCHOLAR-1 cohort

Of the 52 patients in the non-SCHOLAR-1 group, 24 were infused with axi-cel and 28 received tisa-cel. As shown in Supplementary Table S1, we found no significant baseline differences at diagnosis, apheresis, or CAR-T infusion between the patients infused with axi-cel and those given tisa-cel. With a median follow-up of 12.2 months (95% CI, 10.5 to 13.8 months), the median OS and PFS were not reached and 12.2 months, respectively, and the estimated 12-month OS and PFS were 79% (95% CI, 67% to 90%) and 56% (95% CI, 42% to 70%), respectively (Supplementary Figure S1). Table 2 presents the results of univariate and multivariate analyses for OS and PFS. In the multivariate analysis, the variables that maintained an independent prognostic role were the type of CAR-T for both OS (tisa-cel:, HR 7.12; 95% CI, 1.46 to 34.63; $P = .015$) and PFS (tisa-cel: HR, 2.74; 95% CI, 1.12 to 6.72; $P = .028$) (Figure 2A), Ann Arbor stage III-IV preapheresis for PFS (HR, 7.79; 95% CI, 1.03 to 58.71; $P = .046$), and R-IPI preapheresis for OS (HR, 11.79; 95% CI, 1.45 to 95.89; $P = .021$) Table 3.

SCHOLAR-1 cohort

Of the 277 patients included in the SCHOLAR-1 group, 145 were infused with axi-cel and 132 received tisa-cel. The patients treated with tisa-cel were older and more heavily pretreated than those treated with axi-cel (Table 3 and Supplementary Table S1). In contrast, more patients in the axi-cel group had bulky disease at the time of CAR-T infusion. With a median follow-up of 12.2 months (95% CI, 12.1 to 12.2 months), the median OS and PFS were 13.3 months and 3.3 months, respectively, and the estimated 12-month OS and PFS were 52% (95% CI, 45% to 59%) and 33% (95% CI, 27% to 38%), respectively. Table 4 shows the results of univariate and multivariate analyses for OS and PFS. The type of CAR-T showed an independent prognostic role for PFS (tisa-cel: HR, 1.73; 95% CI, 1.24 to 2.42; $P = .001$) and OS (tisa-cel: HR, 1.82; 95% CI, 1.21 to 2.75; $P = .004$) (Figure 2B). Other variables that independently impacted PFS were nonreceipt of ASCT (HR, 1.73; 95% CI, 1.15

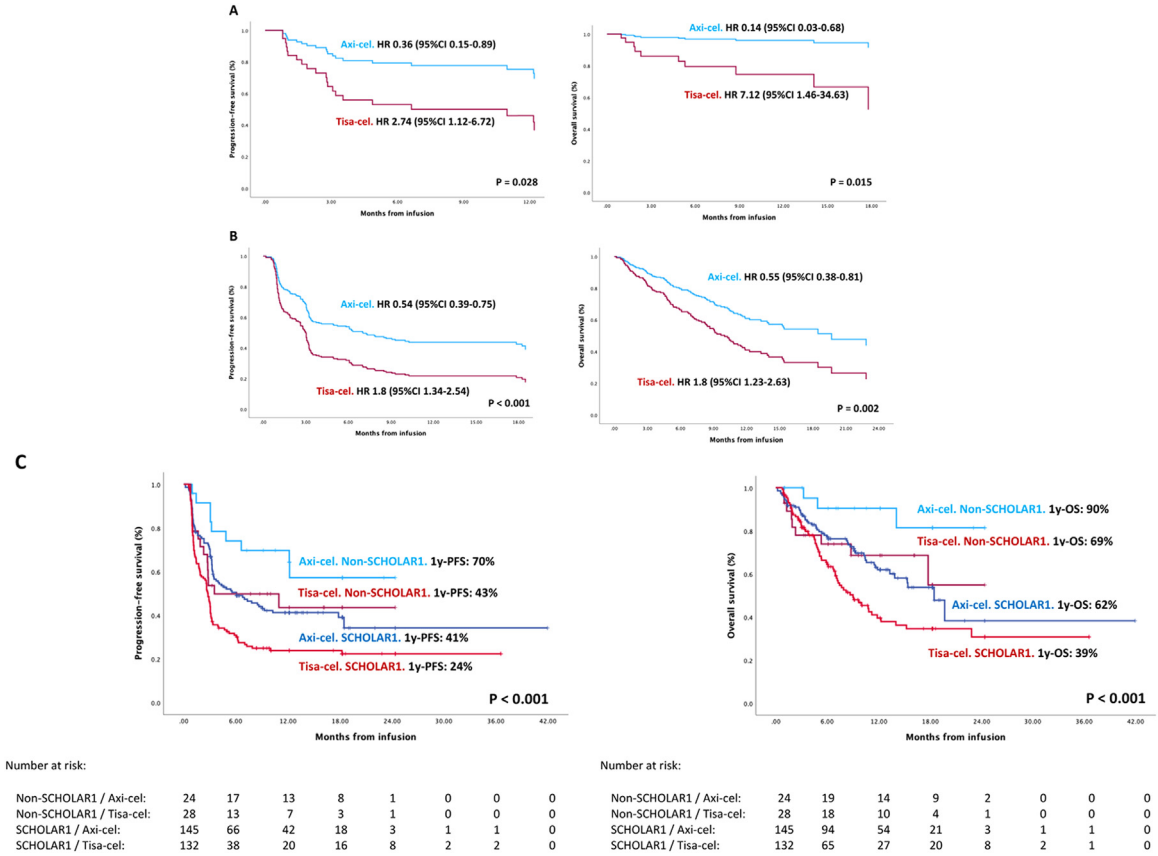

Figure 2. PFS and OS according to type of CAR-T. (A) Multivariate plots for non-SCHOLAR-1 cases. (B) Multivariate plots for SCHOLAR-1 cases. (C) Kaplan-Meier plots comparing Non-SCHOLAR-1 and SCHOLAR-1 cases according to type of CAR-T.

to 2.62; $P = .009$), HCT-CI at CAR-T >2 (HR, 1.6; 95% CI, 1.15 to 2.24; $P = .006$), and elevated LDH at CAR-T (HR, 1.66; 95% CI, 1.18 to 2.33; $P = .033$). Variables that independently impacted OS included nonreceipt of ASCT (HR, 2.47; 95% CI, 1.41 to 4.32; $P = .002$), HCT-CI at CAR-T >2 (HR, 2.15; 95% CI, 1.43 to 3.23; $P < .001$), and elevated LDH at CAR-T (HR, 1.89; 95% CI, 1.23 to 2.89; $P = .003$). The 4 SCHOLAR-1 and non-SCHOLAR-1 groups treated with tisa-cel or axi-cel are compared in Figure 2C.

To confirm these results, and taking into account the imbalance between the SCHOLAR-1 cohorts, we performed a propensity score analysis in the entire cohort, taking into account 12 covariates listed in Methods. Patient characteristics after matching are shown in Supplementary Table S2. Supplementary Table S3 shows the results of an efficacy analysis based on response rate comparing axi-cel and tisa-cel in the matched populations. Axi-cel was superior to tisa-cel in terms of response rate (overall response rate, 71% versus 57%; CR, 52% versus 35%; $P = .018$), 1-year PFS (43% versus 24%; $P < .001$), and 1-year OS (63% versus 41%; $P = .008$) (Supplementary Figure S3).

Table 3
Comparison of Axi-Cel and Tisa-Cel Patients in the SCHOLAR-1 Group

Parameter	Tisa-Cel (N = 132)	Axi-Cel (N = 145)	*P* Value
Previous lines of treatment, median (range)	2 (1-7)	2 (1-6)	.066
More than 2 previous lines of treatment, n (%)	59 (45)	46 (32)	.035
Age at apheresis, yr, median (range)	62 (23-79)	57 (21-80)	.003
Age >60 yr at apheresis, n (%)	76 (58)	59 (41)	.006
Bulky mass at CAR-T, n (%)	38 (29)	67 (48)	.003

SCHOLAR-1 Criteria in the CAR-T Era

This analysis included all the patients who met any of the SCHOLAR-1 criteria at any time (n = 293; Supplementary Figure S2). The median OS for this group after CAR-T infusion was 14 months (95% CI, 9 to 19 months), with an estimated 18-month OS of 45% (95% CI, 38% to 53%) (Figure 2A). When the analysis was performed from the time of appearance of the SCHOLAR-1 refractoriness criteria, the median OS was 24 months (95% CI, 18 to 30 months), with an estimated 2-year OS of 51% (95% CI, 44% to 58%) (Figure 3B). In this second analysis, when we analyzed the variables of the SCHOLAR-1 criteria individually, we found that the variable the greatest impact on survival in the CAR-T era was refractoriness to the last line (response to last treatment: median OS not reached versus no response to last treatment: median OS, 22 months; 95% CI, 18 to 25 months; $P = .007$) (Figure 3C).

Toxicity Analysis

Table 5 summarizes the data on adverse events of special interest, CRS, and immune effector cell-associated neurotoxicity syndrome (ICANS). Axi-cel was more toxic than tisa-cel in both the SCHOLAR-1 and non-SCHOLAR-1 cohorts. In multivariate analysis, the type of CAR-T product maintained an independent influence on global CRS (axi-cel: risk ratio [RR], 4.89; 95% CI, 2.52 to 9.51; $P < .001$), global ICANS (axi-cel: RR,

Table 4
Univariate and Multivariate Analysis Of SCHOLAR-1 Group

Variable	1-yr OS, % (95% CI)/HR (95% CI)*	*P* Value	1-yr PFS, % (95% CI)/HR (95% CI)*	*P* Value
Univariate analysis				
Primary refractory		.044		.17
Yes	47 (39-56)		31 (24-39)	
No	60 (48-71)		35 (25-44)	
Refractory to last therapy		.046		.003
Yes	50 (43-57)		30 (24-36)	
No	67 (44-90)		63 (43-84)	
Early relapse after ASCT		.004		.007
Yes	67 (53-81)		48 (34-61)	
No	48 (40-55)		29 (22-35)	
Previous ASCT (%)		<.001		.003
Yes	67 (54-80)		45 (33-57)	
No	46 (38-54)		28 (22-35)	
ECOG preapheresis		<.001		.028
0-1	53 (46-60)		34 (28-39)	
2-4	0 (NA)		10 (0-29)	
Bridging therapy		.008		.005
Yes	48 (41-56)		29 (23-35)	
No	69 (54-84)		50 (36-65)	
CAR-T product		.004		<.001
Tisa-cel	39 (29-50)		24 (16-31)	
Axi-cel	62 (53-71)		41 (33-50)	
Disease status at CAR-T		.1		.03
CR/PR	65 (44-87)		48 (31-65)	
SD/PD	49 (42.57)		30 (24-36)	
HCT-CI at CAR-T		<.001		.017
0-2	60 (51-68)		39 (32-47)	
3-7	39 (26-52)		23 (13-33)	
ECOG PS at CAR-T		.013		.001
0-1	53 (46-60)		34 (28-41)	
≥2	26 (0-53)		9 (0-24)	
LDH at CAR-T		<.001		<.001
Normal	62 (52-73)		42 (33-51)	
Elevated	40 (30-49)		23 (16-31)	
Multivariate analysis				
Tisa-cell CAR-T product	1.82 (1.21-2.75)	.004	1.73 (1.24-2.42)	.001
No previous auto-SCT	2.47 (1.41-4.32)	.002	1.73 (1.15-2.62)	.009
HCT-CI >2 at CAR-T	2.15 (1.43-3.23)	<.001	1.60 (1.15-2.24)	.006
Elevated LDH at CAR-T	1.89 (1.23-2.89)	.003	1.66 (1.18-2.33)	.003

* OS for univariate analysis, HR for multivariate analysis.

5.57; 95% CI, 3.27 to 9.5; $P < .001$), and severe ICANS (axi-cel: RR, 5.97; 95% CI, 2.4 to 14.83; $P < .001$). Other factors independently associated with severe CRS were ECOG-PS ≥2 (RR, 7.11; 95% CI, 1.94 to 26.01; $P = .003$) and bulky disease preapheresis (RR, 3.19; 95% CI, 1.19 to 8.54; $P = .021$). Nonrelapse mortality (NRM) was 5% for tisa-cel and 7% for axi-cel ($P = .64$). Causes of NRM were infection (n = 5; 62%), CRS (n = 1; 12%), and unknown (n = 2; 25%) for tisa-cel and infection (n = 8; 73%), ICANS (n = 2; 18%), and CRS (n = 1; 9%) for axi-cel.

DISCUSSION

In this retrospective analysis, we analyzed the outcomes of patients with ABCL who underwent CAR-T therapy in terms of the presence or absence of the SCHOLAR-1 criteria. To our knowledge, no previous study has evaluated the impact of these criteria on this population treated with CAR-T therapy. The results of our multivariable and propensity score analysis indicate better efficacy results for axi-cel compared with tisa-cel but with increased toxicity in both the SCHOLAR-1 and non-SCHOLAR-1 groups. In addition, we also found significantly improved outcomes in the SCHOLAR-1 group in the CAR-T era compared with the historical data [12,17] and identified refractoriness to the last treatment as the most crucial factor related to survival in this group.

Several previous studies have reported real-world data on patients with large B cell lymphoma treated with axi-cel or tisa-cel, but few studies compared the 2 products [8,9,12,14], and only one used a statistical approach matching the cohorts to balance covariates between the axi-cel and tisa-cel groups [9]. This latter study identified the axi-cel construct as providing better disease control than tisa-cel in relapsed or refractory ABCL after 2 lines of previous therapy; however, despite including 14 variables to match the cohorts, the authors did not consider any of the SCHOLAR-1 criteria at that time to

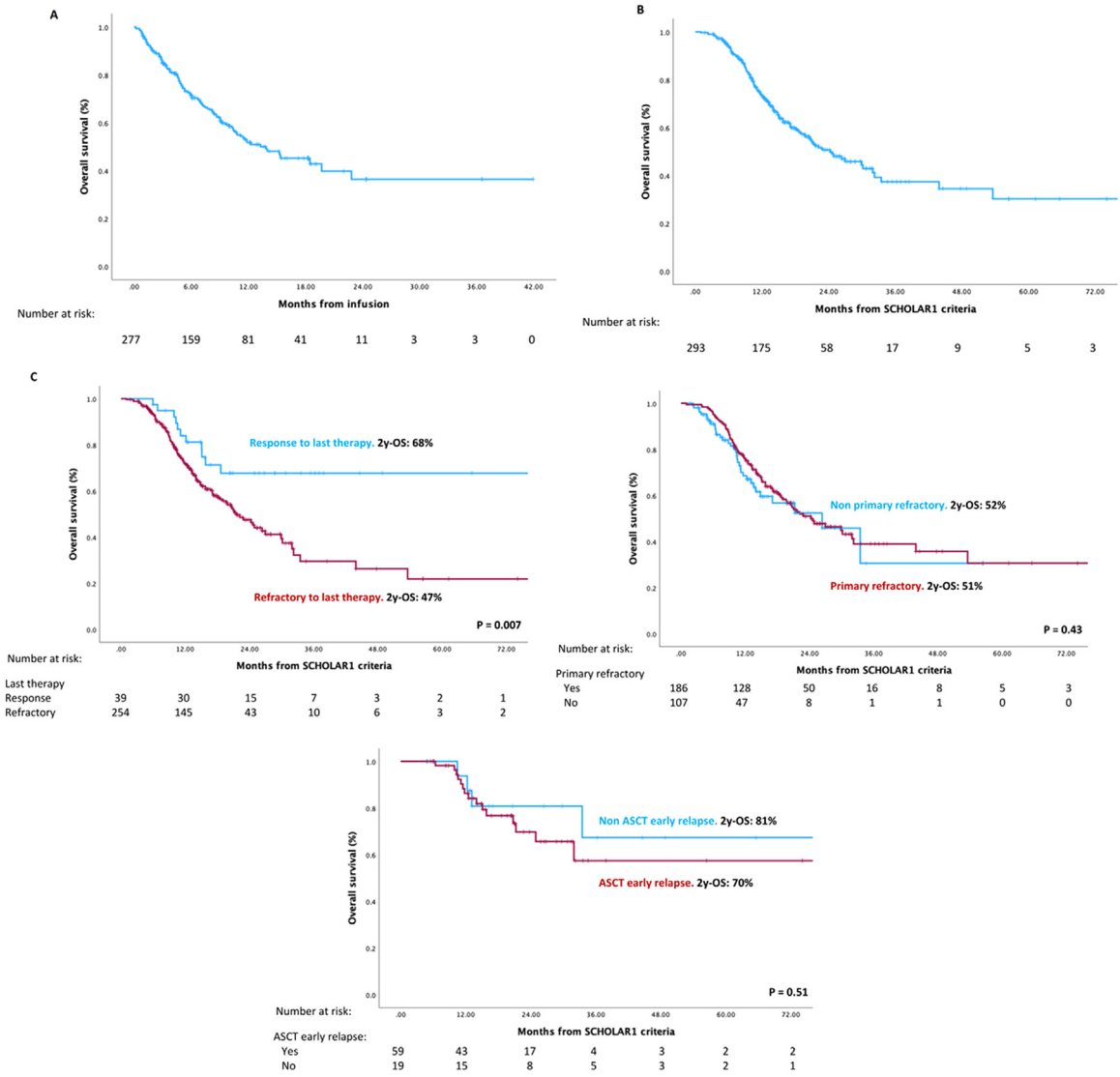

Figure 3. OS of the global SCHOLAR-1 patients. (A) OS from CAR-T infusion. (B) OS from SCHOLAR-1 refractoriness event. (C) OS according to the particular SCHOLAR-1 refractoriness event.

balance the groups, and as we show in the present study, this is a relevant prognostic factor.

Although the outcomes for the non-SCHOLAR-1 group were notably better than those for the refractory group (Figure 1C), the patients infused with axi-cel showed better results than those treated with tisa-cel (OS: HR, 11.8; 95% CI, 1.4 to 95.9; $P = .021$; PFS: HR, 2.74; 95% CI, 1.12 to 6.72; $P = .028$). However, taking into account the higher toxicity with axi-cel for this group, our results could be of special interest when selecting the optimal product to use in some patients. In this sense, in the nonrefractory group of patients, for situations in which the risk of developing severe ICANS could be elevated (ECOG-PS >1 or age >65 years) [14,19], the use of tisa-cel could be considered. For the remaining population, however, axi-cel should be considered the first choice, given the significantly better PFS and OS.

Focusing on the refractory SCHOLAR-1 group, when evaluating the cohorts to compare axi-cel and tisa-cel, we found several baseline differences between the 2 groups, with older and more heavily pretreated patients in the tisa-cel group and a higher rate of patients with bulky disease in the axi-cel group. However, in the multivariate analysis, none of those factors was found to impact OS or PFS, and tisa-cel was identified as an adverse factor for PFS and OS (PFS: HR, 1.73; 95% CI, 1.24 to 2.42; $P = .001$; OS: HR, 1.82; 95% CI, 1.21 to 2.75; $P = .004$).

Our group recently published real-world evidence of outcome in the SCHOLAR-1 groups, comparing CAR-T with the previous standard of care and also analyzing the use of other products in the CAR-T cohort [12], and we found better disease control for axi-cel in this group of refractory patients. In this new analysis, with more patients included, we were able to improve our comparison by including cohort matching, which confirms our previous results. In addition, we report better efficacy for axi-cel in nonrefractory patients.

Considering the toxicity analysis, as previously reported [8,9,14], axi-cel was associated with more global CRS and global and severe ICANS, with no differences between the non-SCHOLAR-1 and SCHOLAR-1 groups.

Finally, if we consider all the patients who met any of the SCHOLAR-1 criteria at any time (n = 293), it is important to highlight the significant improvement that this group

Table 5
Comparative Analysis of Adverse Events of Special Interest

Parameter	Tisa-Cel, n (%)	Axi-Cel, n (%)	*P* Value
Non-SCHOLAR-1 group (N = 52)	N = 28	N = 24	
CRS			.003
Yes	17 (61)	23 (96)	
No	11 (39)	1 (4)	
CRS grade			.008
None	11 (39)	1 (4)	
1-2	15 (54)	22 (92)	
3-4	2 (7)	1 (4)	
ICANS			<.001
Yes	5 (18)	18 (75)	
No	23 (82)	6 (25)	
ICANS grade			<.001
No	23 (82)	6 (25)	
1-2	4 (14)	14 (58)	
3-4	1 (4)	4 (17)	
SCHOLAR-1 group (N = 277)	N = 132	N = 145	
CRS			<.001
Yes	96 (73)	133 (92)	
No	36 (27)	12 (8)	
CRS grade			<.001
None	36 (27)	12 (8)	
1-2	91 (69)	120 (83)	
3-4	5 (4)	13 (9)	
ICANS			<.001
Yes	20 (15)	66 (45)	
No	112 (85)	79 (54)	
ICANS grade			<.001
None	112 (85)	79 (54)	
1-2	15 (11)	39 (27)	
3-4	5 (4)	27 (19)	

experienced compared with data from the pre-CAR-T era. Not only from CAR-T infusion (median OS, 14 months), but also from the occurrence of the SCHOLAR-1 event (median OS, 24 months), survival in these patients was almost 4-fold what was seen in the SCHOLAR-1 study published in 2017, in which OS slightly exceeded 6 months [17]. Our results are consistent with those published by Neelapu et al. [20], who compared data from the pivotal ZUMA-1 study with SCHOLAR-1 data and found a 73% reduction in the risk of death in the former compared with the latter. As noted previously, our group also recently published an indirect comparison, in a real-world evidence setting focusing on patients meeting the SCHOLAR-1 criteria, between CAR-T-treated patients and a historical cohort of patients, considering the survival analysis from failure to the last therapy and from CAR-T infusion, with a similar improvement seen in the CAR-T arm [12]. On the other hand, and unlike what was seen in the SCHOLAR-1 study, in our current cohort of CAR-T recipients, not all the variables that define the SCHOLAR-1 criteria appear to have had the same impact, with refractoriness to the last line of treatment the factor with the greatest weight on efficacy ($P = .03$). This outcome could be explained by the fact that some primary refractory patients could be rescued with other new treatment strategies, as occurred with patients who experienced early relapse after auto-SCT. However, it also could mean that CAR-T therapy better rescues patients who could undergo auto-SCT because of their chemosensitivity.

Our study has some limitations. First, it is a retrospective registry-based study, with the biases that this entails. It is very likely that the number of patients on apheresis but not infused is underestimated, because centers might not register these cases in their entirety. On the other hand, patients for whom CAR-T therapy was considered as a therapeutic option but which was not ultimately requested were not included in the analysis. Another weakness of the analysis is that we do not know how many patients treated with axi-cel were managed according to cohort 6, which could significantly reduce toxicity. The cohort 6 approach showed that corticosteroid administration on days 0, 1, and 2 could decrease the total cumulative corticosteroid dose and reduce the incidence of all-grade CRS and of severe grade CRS, with some benefits for neurotoxicity [21]. Finally, it is also important to mention that in our analysis, we do not know why each center chose to use axi-cel or tisa-cel, and we also recognize this as a weakness.

CONCLUSION

Our data show that SCHOLAR-1 refractoriness criteria influence the efficacy of CAR-T therapy. In our experience, axi-cel showed better results in terms of efficacy than tisa-cel in this population, but with significantly greater toxicity. Results for nonrefractory patients were significantly better with both products, but even better with axi-cel. Survival for SCHOLAR-1 refractory patients has improved notably in the CAR-T era, with refractoriness to the last line of treatment the variable with the greatest impact on survival.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.08.026.

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