Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of aggressive B-cell lymphoma

Mi Kwon,[1,2*] Gloria Iacoboni,[3,4*] Juan Luis Reguera,[5] Lucía López Corral,[6] Rafael Hernani Morales,[7] Valentín Ortiz-Maldonado,[8] Manuel Guerreiro,[9] Ana Carolina Caballero,[10] María Luisa Guerra Domínguez,[11] Jose Maria Sanchez Pina,[12] Alberto Mussetti,[13] Juan Manuel Sancho,[14] Mariana Bastos-Oreiro,[1,2] Eva Catala,[3,4] Javier Delgado,[5] Hugo Luzardo Henriquez,[11] Jaime Sanz,[9] María Calbacho,[12] Rebeca Bailén,[1,2] Cecilia Carpio,[3,4] Jose Maria Ribera,[14] Anna Sureda,[13] Javier Briones,[10] Juan Carlos Hernandez-Boluda,[7] Nuria Martínez Cebrián,[8] Jose Luis Diez Martin,[1,2,15] Alejandro Martín[6] and Pere Barba[3,4] on behalf of GETH-TC (Spanish Group of Stem Cell Transplantation and Cell Therapy) and GELTAMO (Spanish Group of Lymphoma and Autologous Stem Cell Transplantation)

[1]Department of Hematology, Hospital General Universitario Gregorio Marañón, Madrid; [2]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid; [3]Department of Hematology, Vall d'Hebron University Hospital, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona; [4]Department of Medicine, Universitat Autònoma de Barcelona, Bellaterra; [5]Department of Hematology, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, Sevilla; [6]Department of Hematology, Hospital Clínico Universitario de Salamanca, IBSAL, Salamanca; [7]Department of Hematology, Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria INCLIVA, Valencia; [8]Department of Hematology, Hospital Clínic, Barcelona; [9]Department of Hematology, Hospital Universitario y Politécnico La Fe, Valencia; [10]Department of Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona; [11]Department of Hematology, Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria; [12]Department of Hematology, Hospital Universitario 12 de Octubre, Madrid; [13]Department of Hematology, Hospital Duran i Reynals, Instituto Catalán de Oncología, Barcelona; [14]Department of Hematology, Hospital Universitari Germans Trias i Pujol, Instituto Catalán de Oncología, Josep Carreras Research Institute, Badalona and [15]Universidad Complutense de Madrid, Madrid, Spain

MK and GI contributed equally as co-first authors.

Correspondence: M. Kwon
mi.kwon@salud.madrid.org

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Abstract

Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are CD19-targeted chimeric antigen receptor (CAR) T cells approved for relapsed/refractory (R/R) large B-cell lymphoma (LBCL). We performed a retrospective study to evaluate safety and efficacy of axi-cel and tisa-cel outside the setting of a clinical trial. Data from consecutive patients with R/R LBCL who underwent apheresis for axi-cel or tisa-cel were retrospectively collected from 12 Spanish centers. A total of 307 patients underwent apheresis for axi-cel (n=152) and tisa-cel (n=155) from November 2018 to August 2021, of which 261 (85%) received a CAR T infusion (88% and 82%, respectively). Median time from apheresis to infusion was 41 days for axi-cel and 52 days for tisa-cel (P=0.006). None of the baseline characteristics were significantly different between both cohorts. Both cytokine release syndrome and neurologic events (NE) were more frequent in the axi-cel group (88% *vs.* 73%, P=0.003, and 42% *vs.* 16%, P<0.001, respectively). Infections in the first 6 months post-infusion were also more common in patients treated with axi-cel (38% *vs.* 25%, P=0.033). Non-relapse mortality was not significantly different between the axi-cel and tisa-cel groups (7% and 4%, respectively, P=0.298). With a median follow-up of 9.2 months, median PFS and OS were 5.9 and 3 months, and 13.9 and 11.2 months for axi-cel and tisa-cel, respectively. The 12-month PFS and OS for axi-cel and tisa-cel were 41% and 33% (P=0.195), 51% and 47% (P=0.191), respectively. Factors associated with lower OS in the multivariate analysis were increased lactate dehydrogenase, ECOG ≥2 and progressive disease before lymphodepletion. Safety and efficacy results in our real-world experience were comparable with those reported in the pivotal trials. Patients treated with axi-cel experienced more toxicity but similar non-relapse mortality compared with those receiving tisa-cel. Efficacy was not significantly different between both products.

Introduction

Patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) after two lines of therapy have a very poor outcome with currently available conventional therapies. Only a small proportion of patients will eventually achieve prolonged disease-free survival with subsequent treatments.[1,2] Axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) are CD19-targeted chimeric antigen receptors (CAR) T cells commercially available in Europe for R/R LBCL after two or more lines of systemic therapy. In the registration ZUMA-1 trial, 58% of patients who received axi-cel achieved a complete response (CR), with a progression-free survival (PFS) at 24 months of 36%.[3,4] The pivotal JULIET trial with tisa-cel showed a CR rate of 40%, with a PFS at 24 months of 33%.[5,6] Several joint efforts among United States' centers have shown similar overall real-world results to those obtained in the pivotal trials.[7–9] However, European data is heterogenous, with 3-month CR rates ranging from 37% to 21% for axi-cel and 29% to 17% for tisa-cel.[10,11,12,13,14] These differences may be explained by multiple factors including patient selection, country-specific administrative issues and manufacturing turnaround time, among others. Taking into account the absence of randomized trials comparing both products and the significant differences in patient inclusion criteria and trial design that preclude direct comparisons between the ZUMA-1 and JULIET results, mainly regarding patient selection and bridging strategies, there is scarce data available to guide product selection.[15,16] We performed a multicenter, retrospective study to compare efficacy and safety results of axi-cel and tisa-cel in the real-world setting.

Methods

Study design

Data from all consecutive patients who underwent apheresis for axi-cel or tisa-cel between November 2018 and August 2021 were retrospectively collected from electronical medical records at 12 Spanish institutions. Three centers contributed with patients treated only with tisa-cel (n=13). All treatments were approved after review of patients' diagnoses and medical charts by a national expert panel of the Ministry of Health. Primary mediastinal lymphoma cases were excluded from this study since they were treated exclusively with axi-cel. Selection of axi-cel or tisa-cel did not follow predefined uniform criteria and was performed according to each centers' guidelines. Patients included for safety and response analysis had a minimum post-infusion follow-up of 30 days and at least one imaging response assessment. Survival outcomes were assessed in all patients who underwent leukapheresis (intention-to-treat analysis, ITT) and in patients who received a CAR T-cell infusion. All patients provided informed consent for CAR T-cell therapy. The study was approved by the ethical committee of the Hospital General Universitario Gregorio Marañón and conducted in accordance with the Declaration of Helsinki.

Patient management

Patients received lymphodepleting chemotherapy with fludarabine (30 mg/m^2 for axi-cel and 25 mg/m^2 for tisa-cel) and cyclophosphamide (500 mg/m^2 for axi-cel and 250 mg/m^2 for tisa-cel) for 3 consecutive days. After 2 to 4 days of washout, patients received the CAR T-cell infusion in a hospitalization regimen to guarantee a close monitoring of adverse events. Grading of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) followed the American Society for Transplantation and Cellular Therapy (ASTCT) recommendations.[17] Management of CRS and ICANS followed local institutional guidelines, based on national guidelines.[18] Briefly, tocilizumab was used for the treatment of CRS grade ≥2, but considered in cases of persistent CRS grade 1. Steroids were the second line for CRS if two to three doses of tocilizumab were unsuccessful. For ICANS, steroids were the first line of treatment (dexamethasone 10 mg 4 times each day [QID]), started at grade ≥2 and considered for cases of persistent grade 1. Severe ICANS was treated with anakinra or siltuximab as per local protocol. Tocilizumab was only considered in cases of concurrent CRS. For the reporting of other adverse events, Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used. Infectious complications were treated following the Spanish consensus guidelines.[19] Infection severity was classified as mild, moderate, severe, life-threatening, or fatal as previously established.[20] All reported cytopenias were recorded from salvage therapy-naïve patients. All patients underwent a baseline positron emission tomography and computed tomography (PET/CT) scan immediately before the start of LD chemotherapy (after the last bridging regimen). Response assessment after CAR T-cell therapy was performed at 1, 3, 6, 12 and 18 months post-infusion and graded according to the 2014 Lugano recommendations.[21]

Definition and endpoints

Overall response rate (ORR) was defined as the percentage of patients who achieved a partial response (PR) or CR after CAR T-cell therapy. Progression-free survival (PFS) was defined as the time from apheresis (ITT population) or CAR T-cell infusion until relapse, progression or death from any cause. Overall survival (OS) was defined as the time from apheresis (ITT) or CAR T-cell infusion until death of any cause. Duration of response (DOR) was defined as the time from CR or PR to relapse, progression

or death from any cause, whichever occurred first. Non-relapse mortality (NRM) was defined as any death event not associated to relapse/progression since leukapheresis to last follow-up and computed as time-to-event outcome.

Statistical methods

Descriptive statistics included mean, standard deviation, median, range and interquartile range (IQR) for continuous variables, and percentages for categorical variables. Fisher's exact test or Chi-squared test was used to evaluate the association between two categorical variables. Comparability of the two groups (axi-cel and tisa-cel) for the main prognostic features was tested with *t* test or Mann-Whitney test. Kaplan-Meier method was used to estimate PFS and OS rates, including 95% confidence interval (95% CI), and log-rank test was used to evaluate the difference in PFS or OS between patient groups. Cox proportional hazards regression models were used for univariable and multivariable analysis to include significant covariates. Variables with at least marginal association with PFS/OS from the univariable analysis (P<0.2) were included in the initial multivariable model. A univariable and multivariable logistic regression model was performed to study the association with CRS and ICANS grade ≥3. A P value <0.05 was considered statistically significant. The data analyses were carried out using SPSS (IBM, SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA).

Results

Patient characteristics

Between November 2018 and August 2021, 307 patients with R/R LBCL underwent apheresis for axi-cel (n=152) and tisa-cel (n=155) in 12 centers, of which 261 (85%) received a CAR T-cell infusion (n=134, 88% and n=127, 82%, respectively). The main reason for not receiving an infusion was progressive disease in both groups (n=12, 66% in axi-cel and n=25, 89% in tisa-cel) (*Online Supplementary Figure S1*). Median time from apheresis to infusion was 41 days (interquartile range [IQR], 36-56) for axi-cel and 52 days (IQR, 46-63) for tisa-cel (P=0.006).

Patient and disease characteristics at apheresis are shown in Table 1. Median age was 61 years (range, 23-79). The most frequent subtype was diffuse LBCL NOS (70%), followed by high grade B-cell lymphoma (15%) and transformed follicular lymphoma (14%). Patient and disease characteristics at apheresis were similar for the axi-cel and tisa-cel cohorts (Table 1). Infused patients´ characteristics are detailed in the *Online Supplementray Table S1*. Of the 261 infused patients, 210 (80%) received bridging therapy (BT) before infusion, chemotherapy-based in most cases (n=127, 60%; *Online Supplementary Table S2A*). The proportion of patients who received BT before axi-cel and tisa-cel was similar (78% *vs.* 83%, respectively). Thirty (14%) patients achieved a response to BT (21 PR, 9 CR), most of them after chemotherapy (*Online Supplementary Table S2B*). Baseline characteristics at the time of lymphodepletion (LD) therapy were similar between patients treated with axi-cel and tisa-cel (*Online Supplementary Table S1*). Median follow-up from infusion for patients receiving axi-cel and tisa-cel was 8.2 months (IQR, 6-13.7) and 12.4 months (IQR, 6-20), respectively.

Safety

Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome

For all infused patients, any grade of CRS and ICANS occurred in 211 (81%) and 78 (30%) patients. Median time to onset was 2 days for CRS (range, 0-10) and 7 days for ICANS (range, 2-65) (Table 2).

When comparing axi-cel and tisa-cel toxicity, frequency of all grade CRS but not severe (grade ≥3) CRS was higher in the axi-cel group (88% *vs.* 73%, P=0.003), (8% *vs.* 6%, P=0.637). Use of tocilizumab and corticosteroids for CRS was more common in axi-cel treated patients (Table 2). Any grade and grade ≥3 ICANS were significantly more frequent in the axi-cel group (42% *vs.* 16%, P<0.001, and 18% *vs.* 5%, P=0.001, respectively). Corticosteroids, siltuximab and tocilizumab for ICANS were also used more often in the axi-cel group (Table 2). There were no differences in times of onset and duration of CRS and ICANS between axi-cel ant tisa-cel (Table 2; *Online Supplementary Figure S2*). Macrophage activation syndrome (MAS) occurred in four patients, one treated with axi-cel and three with tisa-cel (one of them fatal).[22]

In the multivariable analysis, Eastern Cooperative Oncology Group (ECOG) performance status (PS) score ≥2 at start of LD was the only factor associated with an increased risk of CRS grade ≥3 (P=0.046). The use of axi-cel (P=0.027) and having received >2 prior lines of therapy (P=0.015) were associated with an increased risk of ICANS grade ≥3 (Table 3; *Online Supplementary Table S3*).

Hematological toxicity and infections

Among the 220 evaluable patients, neutropenia and thrombocytopenia grade 3-4 at 1 month after infusion were reported in 53 (24%) and 95 (43%) patients, respectively. At 3 months post-infusion, of the 123 evaluable patients, these cytopenias persisted in 12 (10%) and 18 (15%), respectively. There were no significant differences in the rate of persistent cytopenias between patients treated with axi-cel and tisa-cel (Table 2).

Eighty-three (32%) infused patients presented 91 infectious episodes during the first 6 months after CAR T-cell infusion, mainly bacterial (n=54, 59%) followed by viral (n=31, 34%) and fungal (n=6, 7%). Six patients presented

human herpes virus 6 reactivation, all of them after axi-cel infusion. Two patients presented a SARS-CoV-2 infection during the first 6 months post-infusion, one of them fatal. Of note, three additional patients died from SARS-CoV-2 infection after 6 months (*Online Supplementary Table S4*). In general, infections in the first 6 months post-

Table 1. Baseline patients and disease characteristics at apheresis.

	Total ITT N=307	Axi-cel ITT N=152	Tisa-cel ITT N=155	*P*
Age in years, median (range)	61 (23-79)	59 (29-79)	62 (23-76)	0.078
Sex, N (%) Male	186 (61)	89 (59)	97 (63)	0.486
HCT-CI, N (%) 0-2 3 or more Not available	 236 (77) 66 (21) 5 (2)	 121 (80) 30 (19) 1 (1)	 115 (74) 36 (23) 4 (3)	0.486
ECOG, N (%) 0-1 2-3	 288 (94) 19 (6)	 144 (95) 8 (5)	 144 (93) 11 (7)	0.637
Histology, N (%) DLBCL, NOS DH/TH HGBCL Transformed FL Transformed from other indolent	 214 (70) 45 (15) 43 (14) 5 (1)	 114 (75) 20 (13) 17 (11) 1 (1)	 100 (64) 25 (16) 26 (17) 4 (3)	0.178
Cell of origin, N (%) GCB Non-GCB Unknown	 173 (57) 90 (29) 44 (14)	 84 (55) 41 (27) 27 (18)	 89 (57) 49 (32) 17 (11)	0.697
Disease stage, N (%) I-II III-IV	 73 (24) 234 (76)	 35 (23) 117 (77)	 38 (25) 117 (75)	0.789
R-IPI score, N (%) 0-2 3-5 NA	 143 (46) 150 (49) 14 (5)	 73 (48) 76 (50) 3 (2)	 70 (45) 74 (48) 11 (7)	 0.648 0.732
Bulky disease*, N (%)	75 (24)	40 (26)	35 (23)	0.688
Primary refractory, N (%)	178 (58)	90 (59)	88 (57)	0.729
Previous lines, median (range)	2 (2-7)	2 (2-6)	2 (2-7)	0.124
Prior ASCT, N (%)	88 (29)	45 (30)	43 (28)	0.801
Prior Allo-SCT, N (%)	3 (1)	1 (1)	2 (1)	1.000
Disease status, N (%) Progressive disease Stable disease Partial response Complete response	 276 (90) 21 (6) 9 (3) 1 (1)	 138 (91) 10 (7) 4 (3) 0 (0)	 138 (89) 11 (7) 5 (3) 1 (1)	1.000
LDH >ULN, N (%)	185 (60)	84 (54)	101 (66)	0.385
CRP >ULN, N (%)	154 (50)	62 (41)	92 (59)	0.105
Lymphocytes x10^3/µL, median (range)	0.9 (0.1-11)	0.88 (0.1-6.3)	0.9 (0.1-11.0)	0.711
Platelets x10^3/µL, median (range)	157 (11-1,000)	165 (27-1,000)	146 (11-523)	0.119

ITT: intention-to-treat; HCT-CI: hematopoietic cell transplantation-comorbidity index; DLBCL NOS: diffuse large B-cell lymphoma not otherwise specified; HGBCL: high grade B-cell lymphoma; FL: follicular lymphoma; GCB: germinal center B-cell like; R-IPI: revised international prognostic index; NA: not available; ASCT: autologous stem cell transplantation; LDH: lactate dehydrogenase; CRP: c-reactive protein; >ULN: upper limit of normal. *Bulky disease (>7 cm).

infusion were more frequent in patients treated with axi-cel than with tisa-cel (Table 2; *Online Supplementary Table S4*).

Hospitalization, intensive care unit admission and non-relapse mortality

Median length of hospitalization was 22 days (IQR, 20-29) for the axi-cel cohort and 18 days (IQR, 14-22) for the tisa-cel cohort (*P*<0.001). Admission to the intensive care unit (ICU) was needed in 22% of patients in the axi-cel group and 15% in the tisa-cel group (*P*=0.154) with a median stay of 4 days (IQR, 2-7) and 3 days (IQR, 1-5), respectively (*P*<0.001).

Non-relapse mortality for all infused patients was 5% (Table 2) and similar between both groups (P=0.298). In the axi-cel cohort, nine patients (7%) died due to infection (2 bacterial, 1 SARS-CoV-2, 1 fungal, 1 not specified), ICANS (2), CRS (1) and tumor lysis syndrome (1). In the tisa-cel group, five patients (4%) died due to SARS-CoV-2 infection (2), CRS (1), ICANS (1) and MAS (1) (*Online Supplementary Figure S3*).

Efficacy

Disease response

Among all infused patients, the ORR was 57% (38% CR, 19% PR) (*Online Supplementary Figure S4*). Thirteen (17%)

Table 2. Safety analysis of infused patients.

	All infused patients N=261	Axi-cel infused N=134	Tisa-cel infused N=127	*P*
CRS, N (%) CRS grade ≥3, N (%)	211 (81) 19 (7)	118 (88) 11 (8)	93 (73) 8 (6)	**0.003** 0.637
CRS onset day, median (range)	2 (0-10)	3 (0-10)	2 (0-10)	0.154
CRS duration days, median (range)	5 (1-35)	5 (1-15)	5 (1-35)	0.574
CRS treatment, N (%) Tocilizumab Steroids	 120 (46) 52 (20)	 81 (60) 41 (31)	 39 (31) 11 (9)	 **<0.001** **<0.001**
ICANS, N (%) ICANS grade ≥3, N (%)	78 (30) 30 (11)	57 (42) 24 (18)	21 (16) 6 (5)	**<0.001** **0.001**
ICANS onset day, median (range)	7 (2-65)	7 (2-65)	6 (2-35)	0.214
ICANS duration days, median (range)	4.5 (1-83)	4 (1-44)	7 (1-83)	0.119
ICANS treatment, N (%) Tocilizumab Steroids Anakinra Siltuximab	 2 (1) 65 (25) 15 (6) 14 (5)	 2 (1) 48 (36) 12 (9) 11 (8)	 0 (0) 17 (13) 3 (2) 3 (2)	 **<0.001** **<0.001** **<0.001** **<0.001**
Hospitalization days, median (IQR)	20 (17-27)	22 (20-29)	18 (14-22)	**<0.001**
ICU admission, N (%) median stay, days (IQR)	49 (18) 3 (2-7)	30 (22) 4 (2-7)	19 (15) 3 (1-5)	0.154 **<0.001**
Infections during first 6 months, N (%)	83 (32)	51 (38)	32 (25)	**0.033**
Persistent cytopenias by day 28, N (%)* Neutropenia grade 3-4 Thrombocytopenia grade 3-4	 53 (24) 95 (43)	 31 (28) 49 (47)	 22 (19) 46 (40)	 0.082 0.278
Persistent cytopenias by day 90, N (%)* Neutropenia grade 3-4 Thrombocytopenia grade 3-4	 12 (10) 18 (15)	 6 (10) 10 (16)	 6 (10) 8 (13)	 1.000 0.799
Persistent cytopenias by day 180, N (%)* Neutropenia grade 3-4 Thrombocytopenia grade 3-4	 2 (3) 4 (6)	 1 (3) 3 (8)	 1 (3) 1 (3)	 1.000 0.625
Non-relapse mortality, N (%)	13 (5)	9 (7)	4 (3)	0.298

CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: intensive care unit: *Evaluable patients: 220 at day 28, 123 at day 90, 66 at day 180.

patients in PR at 1 month converted to CR (10 at day 90 and 3 at day 180) and four (13%) patients in stable disease at 1 month achieved CR (3 at day 180 and 1 at 1 year). Median duration of response was 14.1 months (95% CI: 5.8 to not reached) for all infused patients and was not reached for those who achieved CR. In the axi-cel cohort, ORR was 60% (CR 42% and PR 18%) with a median DOR of 12.5 months (95% CI: 5.7 to not reached). In the tisa-cel group, ORR was 54% (n=68) (34% CR and 19% PR), with a median DOR of 14.1 months (95% CI: 2.5 to not reached). Median DOR was not significantly different between both cohorts (*P*=0.494).

Progression-free survival and overall survival

In the ITT analysis, with a median follow-up of 9.2 months (IQR, 5-15), median PFS and OS were 4.8 months (95% CI: 4.5-5.6) and 11.7 months (95% CI: 10.2-14.3), respectively. The estimated 12-month PFS and OS were 34% (95% CI: 27-39) and 48% (95% CI: 41-54), respectively (Figure 1). Regarding each cohort, the 12-month PFS and OS for patients intended to be treated with axi-cel and tisa-cel were 41% and 27% (*P*=0.091), 50% and 45% (*P*=0.07) (*Online Supplementary Figure S5*), respectively.

Focusing on infused patients with axi-cel or tisa-cel, median PFS was 5.9 months and 3 months, respectively, and median OS was 13.9 months and 11.2 months, respectively (Figure 1). The estimated 12-month PFS was 41% and 33% (*P*=0.195), and 12-month OS was 51% and 47% (*P*=0.191), respectively.

Regarding factors with an impact on efficacy, an increased lactate dehydrogenase (LDH) before apheresis (*P*=0.003), ECOG PS ≥2 before LD therapy (*P*<0.001) and progressive disease before LD therapy (*P*=0.018) were associated with a worse PFS in the multivariable analysis (Table 4; Figure 2; *Online Supplementary Table S3*). Factors independently associated with a worse OS included high LDH at apheresis, (*P*=0.023), ECOG PS ≥2 at apheresis (*P*=0.021), progressive disease at apheresis (*P*=0.018) and ECOG PS ≥2 before LD therapy (*P*=0.001). Patients with very high LDH elevation (>2x upper limit of normal [ULN]) showed worse PFS (hazard ration [HR] 2.5, *P*<0.001) and OS (HR 2.1, *P*<0.001) than patients with mild (1-2x ULN) increase.

Noteworthy, 15 of the 19 patients with EOCG PS > or =2 at the time of apheresis died, 13 due to disease progression (8 of them did not receive the CAR T infusion) and two due to toxicity.

Discussion

We report herein one of the largest European cohort of patients with R/R aggressive B-cell lymphoma treated with commercial CAR T cells, including a detailed comparison between axi-cel and tisa-cel, which has been very little addressed in previous real-world studies.[23,24,25,26]

In our study, patient and disease characteristics at apher-

Table 3. Factors significantly associated with cytokine release syndrome grade ≥3 and immune effector cell-associated neurotoxicity syndrome grade ≥3 in the logistic regression analysis of axicabtagene ciloleucel and tisagenlecleucel–treated patients.

	CRS grade 3	
	OR (95% CI)	***P***
ECOG PS at LD, 2-3 *vs.* 0-1	3.528 (1.021-12.186)	0.046
R-IPI at LD, 0-2 *vs.* >2	1.530 (0.419-5.590)	0.520
LDH at LD, >UNL *vs.* normal	2.978 (0.580-15.284)	0.191
	ICANS grade 3	
	OR (95% CI)	***P***
CAR T type axi-cel *vs.* tisa-cel	3.545 (1.156-10.870)	0.027
Number prior lines, >2 *vs.* 2	2.000 (1.150-3.503)	0.015
ECOG PS at LD, 2-3 *vs.* 0-1	1.812 (0.418-7.878)	0.427
R-IPI at LD, 0-2 *vs.* >2	2.414 (0.868-6.711)	0.091

OR: odds ratio; CRS: cytokine release syndrome; ECOG PS: Eastern Cooperative Group performance status; LD: lymphodepletion; R-IPI: revised international prognostic index; LDH: lactate dehydrogenase; ULN: upper limit of normal; ICANS: Immune effector cell-associated neurotoxicity syndrome; CI: confidence interval.

esis were similar between both cohorts, suggesting that CAR T selection was likely driven by other factors including logistical aspects, manufacturing slot availability and expected turnaround time. More patients in the axi-cel group received the CAR T infusion, probably influenced by the shorter turnaround time. Although other possible unintended bias in product selection are yet to be identified, the fact that both populations were comparable, provides the opportunity to compare outcomes after treatment with axi-cel and tisa-cel from patients with similar features.

In terms of toxicity, rates of CRS and ICANS were lower than the pivotal trials and in line with other contemporary real-world studies.[3,5,7,9] A better understanding of these adverse events together with an earlier administration of specific treatments (i.e., tocilizumab, steroids) could explain these lower rates. Notably, CRS and, especially, ICANS were more frequent and severe in patients treated with axi-cel compared with tisa-cel. Accordingly, the use of tocilizumab, corticosteroids, and siltuximab was also more common in the former group. Patients who received axi-cel presented a longer median hospitalization, an increased infection rate and a higher likelihood of being transferred to the ICU. Since prolonged neutropenia was similar in both cohorts, potential reasons which could justify the increased infection rate observed with axi-cel could be the rate of CRS, ICANS and the higher use of immunosuppressive therapies for these adverse events.[27] Non-relapse mortality was similar to previous real-world studies in patients with R/R LBCL.[7–9] Noteworthy, four patients died of SARS-CoV-2 infection, mostly in the early months of the pandemic and before the wide implementation of vaccines.[27,28] Despite these relatively low numbers, our study highlights the significant morbidity burden of CAR T-cell therapies and the potential associated costs derived from health resource utilization which

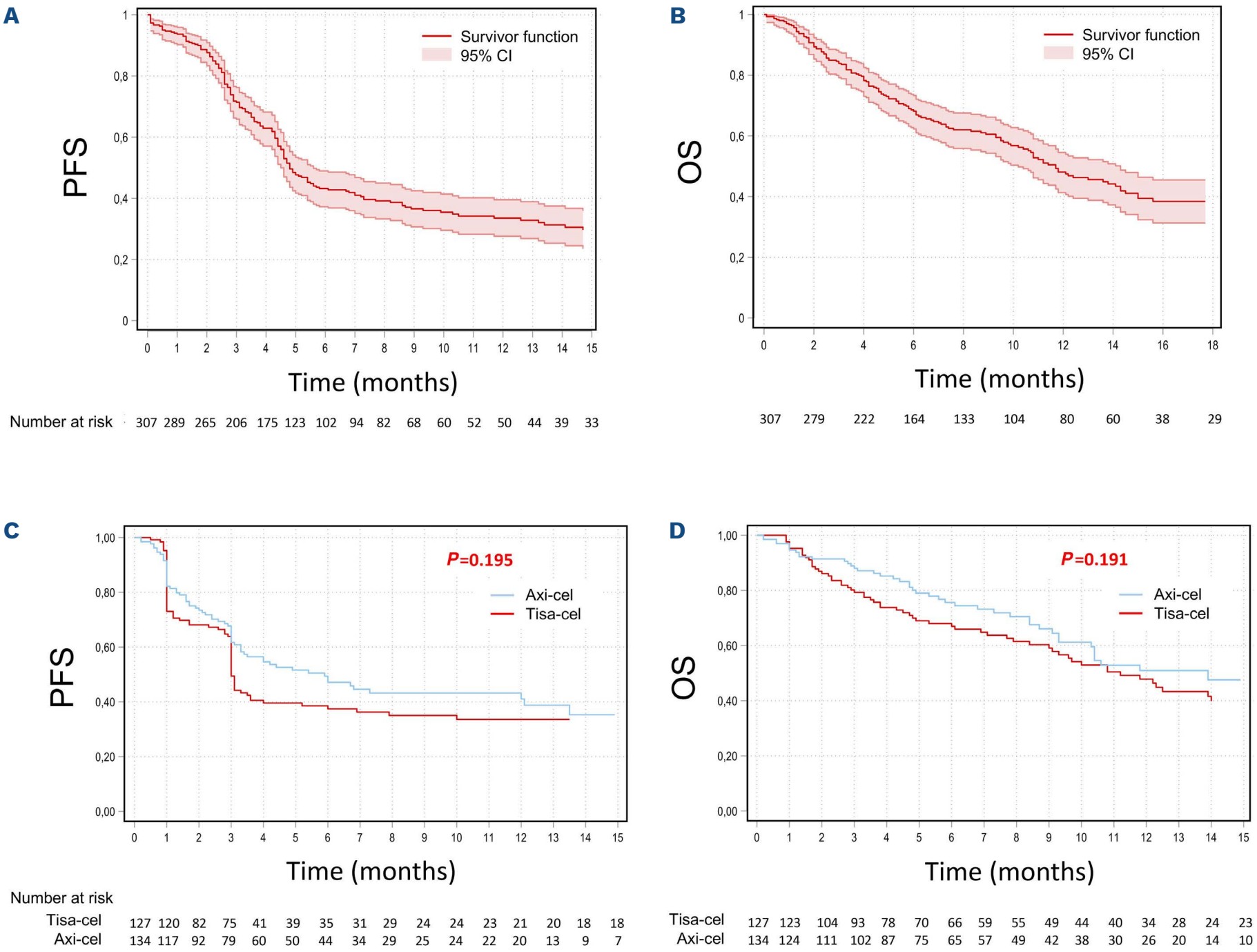

Figure 1. Progression-free survival and overal survival of patients treated with axicabtagene ciloleucel and tisagenlecleucel. (A) Progression-free survival (PFS) from apheresis for the intention-to-treat (ITT) population. (B) Overall survival (OS) from apheresis for the ITT population. (C) PFS from infusion according to product infused. (D) OS from infusion according to product infused.

Table 4. Characteristics significantly associated with progression-free survival and overall survival in the multivariable analysis of axicabtagene ciloleucel and tisagenlecleucel–treated patients.

	Progression-free survival	
	HR (95% CI)	***P***
CAR T type, axi-cel *vs.* tisa-cel	0.888 (0.576-1.370)	0.592
Cell of origin, CGB *vs.* non-CGB	0.726 (0.460-1.147)	0.170
Primary Refractory, yes *vs.* no	1.371 (0.806-2.331)	0.244
Prior ASCT, yes *vs.* no	0.957 (0.550-1.666)	0.877
Disease status, PD *vs.* other	**1.804 (1.096-3.507)**	**0.018**
ECOG at apheresis, 2-3 *vs.* 0-1	0.731 (0.208-2.572)	0.626
Disease stage, III-IV *vs.* I-II	0.494 (0.159-1.539)	0.244
R-IPI at apheresis	1.156 (0.824-1.621)	0.402
Bulky size at apheresis, yes *vs.* no	0.770 (0.401-1.477)	0.431
LDH at apheresis, >UNL *vs.* normal	**2.181 (1.303-3.651)**	**0.003**
CRP at apheresis, >UNL *vs.* normal	1.489 (0.925-2.398)	0.101
Platelets at apheresis, $x10^9$	0.998 (0.995-1.001)	0.130
ECOG at LD, 2-3 *vs.* 0-1	**5.446 (2.354-12.597)**	**<0.001**
	Overall survival	
	HR (95% CI)	***P***
ECOG at apheresis, 2-3 *vs.* 0-1	**2.113 (1.122-3.980)**	**0.021**
LDH at apheresis, >UNL *vs.* normal	**1.809 (1.084-3.021)**	**0.023**
Bridging therapy, yes *vs.* no	1.791 (0.817-3.930)	0.146
Disease status at LD, PD *vs.* other	**2.561 (1.812-3.999)**	**0.018**
Bulky (>7 cm) prior to LD, yes *vs.*no	1.495 (0.794-2.816)	0.212
Extranodal at LD >2 sites, yes *vs.* no	1.158 (0.951-1.411)	0.145
ECOG at LD, 2-3 *vs.* 0-1	**4.306 (1.841-10.071)**	**0.001**
R-IPI at LD	0.827 (0.476-1.437)	0.500
LDH at LD, >UNL *vs.* normal	1.304 (0.565-3.013)	0.581
CRP at LD, >UNL *vs.* normal	1.235 (0.455-3.353)	0.679
LDH at infusion, >UNL *vs.* normal	1.235 (0.520-2.938)	0.632
CRP at infusion, >UNL *vs.* normal	1.501 (0.487-4.629)	0.479
CRS grade 3-4, yes *vs.* no	1.939 (0.726-5.177)	0.186
CRS tocilizumab, yes *vs.* no	0.914 (0.539-1.548)	0.737
ICANS grade 3-4, yes *vs.* no	1.066 (0.316-3.589)	0.918
ICANS tocilizumab, yes *vs.* no	1.148 (0.462-2.852)	0.766
ICANS steroids, yes *vs.* no	1.090 (0.503-2.362)	0.827

HR: hazard ratio; GCB: germinal center B-cell like; ASTC: autologous stem cell transplantation; PD: progressive disease; ECOG PS: Eastern Cooperative Group performance status; R-IPI: revised international prognostic index; LD: lymphodepletion; LDH: lactate dehydrogenase; NA: not applicable (characteristic not a part of the multivariable-adjusted model for the listed outcome); ULN: upper limit of normal; CRP: c-reactive protein.

need to be studied in more depth.[29] Efforts should be made to decrease toxicity in future trials, including design of CAR T cells with an improved safety profile together with prophylactic or preemptive strategies for CRS and ICANS.[30,31] Moreover, real-world studies like ours might help identify patients at high risk of developing severe adverse events, improving patient selection and management. Several models for predicting CAR T-cell related toxicity have been proposed. External validation of these models in independent cohorts is warranted to assess their implementation in routine clinical practice.[32,33]

Regarding efficacy, median PFS and OS in the ITT analysis were comparable to the pivotal trials, despite a longer turnaround time in our study.[3,5] Our results were also similar to other real-world data, albeit some differences in patients characteristics and logistical country-specific aspects.[7–9,13,23] Both for the ITT and the infused population, PFS and OS were similar between axi-cel and tisa-cel. Noteworthy, there was a trend towards a higher PFS and OS in the ITT analysis in favor of the axi-cel cohort (PFS at 9 months 41% and 27%, *P*=0.091, and OS 67% *vs*. 54%, *P*=0.07). These trends could be explained by a shorter turnaround time in patients receiving axi-cel which could have led to slightly fitter population at the time of CAR T infusion. Also, the number of apheresed patients who finally did not receive the infusion was higher in the tisa-

cel group. Finally, complete responses were more frequently seen in patients treated with axi-cel. Whether these trends towards higher PFS and OS are driven by a different efficacy of each product, as suggested by differences on the results of the phase III clinical trials in second-line therapy,[34,35] or by patient selection and/or logistic

Figure 2. Progression-free survival and overall survival from CAR T-cell infusion stratified by prognostic factors. (A) Progression-free survival (PFS) by disease status at lymphodepletion. (B) PFS by lactate dehydrogenase (LDH) at leukapheresis. (C) PFS by LDH at lymphodepletion. (D) Overall survival (OS) by LDH at leukapheresis. (E) OS by Eastern Cooperative Group performance status (ECOG PS) at lymphodepletion.

reasons warrants further studies. Outstanding prognostic factors included LDH and ECOG PS, in line with previous reports.[8,13,36,37] Even though the use of BT has been associated with worse outcomes, especially the use of systemic therapy,[38] there is scarce data regarding the impact of disease status at time of LD therapy. In our study, progressive disease as best response to BT was associated with a worse PFS. Noteworthy, more than half of our patients, without significant differences between both cohorts, had PD as best response to BT. Given the availability of novel therapies for LBCL, future studies should address the optimal bridging strategy for patients intending to receive a CAR T-cell infusion. Although patients with high LDH and progressive disease showed worse PFS, whether these cases should not be eligible for CAR T-cell therapy is arguable, since these high-risk populations still performed better than with standard therapies.[1,2] However, very few patients with very high LDH and ECOG PS score seemed to benefit from the therapy, highlighting the need of careful selection of patients harboring adverse prognostic factors. In all, our findings support the inclusion of selected patients with such baseline characteristics in prospective studies that would not only improve access but also better characterize the risk factors for safety and efficacy.

There are some limitations to this study. The data was collected retrospectively and some previously reported prognostic factors were not collected in this dataset including albumin levels, total metabolic tumor volume and CAR T-cell kinetics.[13,36,37] The patient population treated includes a relatively small proportion of high-risk patients in terms of comorbidity and performance status scores. Previous real-world reports showed superior results with axi-cel for patients who would had met eligibility criteria for the ZUMA-1 trial than those individuals that would have been ineligible.[7] Further analysis to confirm our observations in patient populations with greater comorbidities are granted. In contrast, patients were infused in a small number of centers and treatment-related complications were managed homogenously.[19] Also, the CAR T therapy approval process was carried out by a single national Expert Committee, ensuring uniform selection criteria of the patients.[39] Given the lack of direct comparisons between CAR T-cell products within prospective randomized clinical trials, we consider that retrospective comparisons can provide clinically meaningful insight to physicians managing these patients. In conclusion, safety and efficacy results in our real-world experience were comparable with those reported in the pivotal clinical trials. Patients treated with axi-cel experienced more toxicity but similar non-relapse mortality compared with those receiving tisa-cel while efficacy was similar between both products.

Disclosures

MK has received honoraria from Gilead, Novartis, BMS and Pfizer. GI has received honoraria from BMS/Celgene, Gilead, Novartis, Janssen, AstraZeneca, Abbvie and Roche. LLC has received honoraria from Gilead and Novartis, and research funding from Gilead. JB has received honoraria from Roche, Takeda, Celgene, Novartis, Gilead, and research funding from Celgene, Roche. JS has received honoraria from Kite and Novartis. MBO has received honoraria from Roche, Takeda, Kite, Novartis, Janssen, Incyte, and research funding from Roche. AM has received honoraria from Takeda, Novartis, BMS, MSD, and research funding from GILEAD. MG has received honoraria from Gilead and Novartis. AS has received honoraria from Takeda, BMS, MSD, Sanofi, Roche, Novartis, Gilead Kite, Janssen, Sanofi, consultancy fees from Takeda, BMS, MSD, Novartis, Janssen, Gilead Kite and speaker's bureau for Takeda. JMS has received honoraria from Roche, Janssen, Gilead-Kite, Novartis, BMS-Celgene, Takeda, Incyte, Lilly, Beigene. PB has received honoraria from Amgen, BMS, Gilead, Incyte, Jazz Pharmaceuticals, Miltenyi biotech, Novartis and Pfizer.

Contributions

MK, GI and PB developed the concept, designed the study and wrote the manuscript. MK, GI, RB and PB collected and assembled data. All authors provided study materials or patients, analyzed and interpreted data, and approved the final version of the manuscript.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-1808.
2. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016;51(1):51-57.
3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
4. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31-42.
5. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.
6. Jaeger U, Bishop MR, Salles G, et al. Myc expression and tumor-infiltrating T cells are associated with response in patients (Pts) with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) treated with tisagenlecleucel in the Juliet Trial. Blood. 2020;136(Suppl 1):S48-49.
7. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. J Clin Oncol. 2020;38(27):3119-3128.
8. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. J Clin Oncol. 2020;38(27):3095-3106.
9. Pasquini MC, Hu Z-H, Curran K, et al. Real-world evidence of tisagenlecleucel for pediatric acute lymphoblastic leukemia and non-Hodgkin lymphoma. Blood Adv. 2020;4(21):5414-5424.
10. Kuhnl A, Roddie C, Martinez-Cibrian N, et al. Real-world data of high-grade lymphoma patients treated with CD19 CAR-T in England. Blood. 2019;134(Suppl 1):S767.
11. Bethge WA. Standard-of-care CAR-T cell therapy for large B-cell lymphoma: real world data Germany. Bone Marrow Transplantation. 2021;56(1):20.
12. Iacoboni G, Villacampa G, Martinez-Cibrian N, et al. Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. Cancer Med. 2021;10(10):3214-3223.
13. Vercellino L, Di Blasi R, Kanoun S, et al. Predictive factors of early progression after CAR T-cell therapy in relapsed/refractory diffuse large B-cell lymphoma. Blood Adv. 2020;4(22):5607-5615.
14. Kwon M, Bailen R, Corral LL, et al. Real world of experience axicabtagene ciloleucel for the treatment of relapsed or refractory large B-cell lymphoma in Spain. Bone Marrow Transplant. 2021;56:37-39.
15. Oluwole OO, Jansen JP, Lin VW, et al. Comparing efficacy, safety, and preinfusion period of axicabtagene ciloleucel versus tisagenlecleucel in relapsed/Rrfractory large B cell lymphoma. Biol Blood Marrow Transplant. 2020;26(9):1581-1588.
16. Zhang J, Li J, Ma Q, et al. A review of two regulatory approved anti-CD19 CAR T-cell therapies in diffuse large B-cell lymphoma: why are indirect treatment comparisons not feasible? Adv Ther. 2020;37(7):3040-3058.
17. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
18. https://www.sanidad.gob.es/profesionales/farmacia/pdf/20190508_Protocolo_manejo_efectos_adversos_CAR_T.pdf.
19. Los-Arcos I, Iacoboni G, Aguilar-Guisado M, et al. Recommendations for screening, monitoring, prevention, and prophylaxis of infections in adult and pediatric patients receiving CAR T-cell therapy: a position paper. Infection. 2021;49(2):215-231.
20. Young J-AH, Logan BR, Wu J, et al. Infections after transplantation of bone marrow or peripheral blood stem cells from unrelated donors. Biol Blood Marrow Transplant. 2016;22(2):359-370.
21. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
22. Martín-Rojas RM, Gómez-Centurión I, Bailén R, et al. Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) following treatment with tisagenlecleucel. Clin Case Rep. 2022;10(1):e05209.
23. Sesques P, Ferrant E, Safar V, et al. Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. Am J Hematol. 2020;95(11):1324-1333.
24. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR-T cell therapies for large B-cell lymphoma in Germany. Blood. 2022;140(4):349-358.
25. Riedell PA, Walling C, Nastoupil LJ, et al. A multicenter retrospective analysis of outcomes and toxicities with commercial axicabtagene ciloleucel and tisagenlecleucel for relapsed/refractory aggressive B-cell lymphomas. Biol Blood Marrow Transplant. 2020;26(Suppl 3):S41-42.
26. Gauthier J, Gazeau N, Hirayama AV, et al. Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL. Blood. 2022;139(26):3722-3731.
27. Meir J, Abid MA, Abid MB. State of the CAR-T: risk of infections with chimeric antigen receptor T-cell therapy and determinants of SARS-CoV-2 vaccine responses. Transplant Cell Ther. 2021;27(12):973-987.
28. Spanjaart AM, Ljungman P, de La Camara R, et al. Poor outcome of patients with COVID-19 after CAR T-cell therapy for B-cell malignancies: results of a multicenter study on behalf of the European Society for Blood and Marrow Transplantation (EBMT) Infectious Diseases Working Party and the European Hematology Association (EHA) Lymphoma Group. Leukemia. 2021;35(12):3585-3588.
29. Maziarz RT, Yang H, Liu Q, et al. Real-world healthcare resource utilization and costs associated with tisagenlecleucel and axicabtagene ciloleucel among patients with diffuse large B-cell lymphoma: an analysis of hospital data in the United States. Leuk Lymphoma. 2022;0(0):1-11.
30. Roddie C, Dias J, O'Reilly MA, et al. Durable responses and low toxicity after fast off-rate CD19 chimeric antigen receptor-T therapy in adults with relapsed or refractory B-cell acute lymphoblastic leukemia. J Clin Oncol. 2021;39(30):3352-3363.
31. Oluwole OO, Bouabdallah K, Muñoz J, et al. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021;194(4):690-700.
32. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138(24):2499-2513.

33. Pennisi M, Sanchez-Escamilla M, Flynn JR, et al. Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells. Blood Adv. 2021;5(17):3397-3406.
34. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. N Engl J Med. 2022;386(7):629-639.
35. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.
36. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv. 2020;4(19):4898-4911.
37. Awasthi R, Pacaud L, Waldron E, et al. Tisagenlecleucel cellular kinetics, dose, and immunogenicity in relation to clinical factors in relapsed/refractory DLBCL. Blood Adv. 2020;4(3):560-572.
38. Pinnix CC, Gunther JR, Dabaja BS, et al. Bridging therapy prior to axicabtagene ciloleucel for relapsed/refractory large B-cell lymphoma. Blood Adv. 2020;4(13):2871-2883.
39. Carpio C, Iacoboni G, Villacampa G, et al. Selection process and causes of non-eligibility for CD19 CAR-T cell therapy in patients with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma in a European center. Leuk Lymphoma. 2021;62(9):2288-2291.