Universitat Autònoma de Barcelona

Prognostic factors and outcome of patients with lymphoproliferative disorders who receive treatment with chimeric antigen receptor T-cells

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To my parents, Cristina and Anthony

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ABBREVIATIONS

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aaIPI, age adjusted international prognostic index

ABC, activated B-cell-like subtype of diffuse large B-cell lymphoma

ADC, antibody-drug conjugate

AKI, acute kidney injury

APC, antigen-presenting cell

ASCT, autologous stem cell transplant

ASTCT, American Society for Transplantation and Cellular Therapy

CAR, Chimeric Antigen Receptor

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone

CRP, C-reactive protein

CRS, Cytokine Release Syndrome

DHAP, Cisplatin, High-Dose Ara-C, Dexamethasone

DLBCL, diffuse large B-cell lymphoma

DoR, duration of response

EBV, Epstein-Barr virus

ECOG, Eastern Cooperative Oncology Group

EFS, event-free survival

EMA, European Medicines Agency

FDA, Food and Drug Administration

FFS, failure-free survival

FL, follicular lymphoma

GDP, Gemcitabine, Dexamethasone, and Cisplatin

GELTAMO, Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea

HCT, Hematopoietic cell transplantation

HGBL, high-grade B-cell lymphoma

HR, Hazard Ratio

ICANS, Immune effector-Cell Associated Neurotoxicity Syndrome

ICE, ifosfamide, carboplatin and etoposide

ICU, intensive care unit

IPI, International Prognostic Index

LBCL, large B-cell lymphoma

LD, lymphodepletion

LDH, Lactate Dehydrogenase

LVEF, left ventricular ejection fraction

m, media

MAb, monoclonal antibody

MHC, major histocompatibility complex

mo, months

MoA, mechanism of action

MR, maintenance Rituximab

N, number of patients

NA, not available

NK, natural killer

non-GCB, non-germinal center B-cell DLBCL

NR, not reached

Obs, Observation

ORR, overall response rate

OS, overall survival

PET/CT, positron emission tomography/computed tomography

PFS, progression-free survival

PMBL, primary mediastinal large B-cell lymphoma

PS, performance status

R, rituximab

Ref, reference

SOC, standard of care

ULN, upper limit of normal

WHO, World Health Organization

wks, weeks

y, years

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ABSTRACT

ABSTRACT

The dismal prognosis of patients with relapsed/refractory large B-cell lymphoma has significantly improved since the advent of CAR T-cell therapy. Despite these enormous advances, approximately 60% of infused patients will eventually progress, which is associated with a median overall survival of 6 months and response rates to salvage strategies inferior to 25%. Finally, CAR T-cell therapy is not devoid of short and/or long-term toxicity that diminish the survival of some patients. Altogether, it is beyond doubt that a careful patient selection is key to identify which candidates have a higher chance of benefitting from CAR-T therapy.

The Doctoral Thesis presented herein is composed by three clinical studies analyzing real-world data of axi-cel and tisa-cel CAR-T therapies. In all of them, a similar safety profile to the pivotal trials was observed, although a higher use of tocilizumab and steroids led to a lower incidence of severe CRS and ICANS. Among products, patients treated with axi-cel had higher rates of CRS and ICANS then tisa-cel recipients, leading to an increased use of immunosuppressive agents, hospital stay and infections. Patients with increased serum LDH, more than 2 prior lines of treatment or those harboring a poor PS presented an increased risk of severe CRS and/or ICANS.

Regarding efficacy, the response rates and survival outcomes were comparable to the pivotal trials. There were no significant differences in survival between both products in the modified intention to treat analysis. Among pretreatment characteristics associated with efficacy, we identified high LDH levels, TMTV values and a poor PS to be associated with a worse PFS. The 1-month post-infusion assessment was predictive of CAR T-cell outcomes and identified patients in partial remission at high risk of disease progression.

In conclusion, the three studies that represent the body of this doctoral thesis accomplished to identify variables that prior or after CAR-T infusion are able to predict the outcome of patients receiving these therapies.

RESUMEN

El pronóstico sombrío de los pacientes con linfoma difuso de células B grandes en recaída o refractario ha mejorado significativamente desde la incorporación de la terapia de células T-CAR. A pesar de estos enormes avances, aproximadamente el 60% de los pacientes infundidos progresarán, lo que se asocia con una mediana de supervivencia aproximada de 6 meses y tasas de respuesta a las estrategias de rescate inferiores al 25%. Finalmente, la terapia con linfocitos T-CAR no está exenta de toxicidad a corto y/o largo plazo que disminuye la supervivencia de algunos pacientes. En conjunto, no cabe duda de que una cuidadosa selección de pacientes es clave para identificar qué candidatos tienen una mayor probabilidad de beneficiarse de esta terapia.

Esta Tesis Doctoral está compuesta por tres estudios clínicos que analizan datos de vida real de las terapias T-CAR axi-cel y tisa-cel. En todos ellos se observó un perfil de seguridad similar al de los ensayos pivotales, aunque un mayor uso de tocilizumab y corticoides condujo a una menor incidencia de síndrome de liberación de citocinas (SLC) y neurotoxicidad (NT) graves. Entre los productos, los pacientes tratados con axi-cel presentaron tasas más altas de SLC y NT que los receptores de tisa-cel, lo que llevó a un mayor uso de agentes inmunosupresores, hospitalización e infecciones. Los pacientes con LDH sérica elevada, más de 2 líneas de tratamiento previas o aquellos con mal estado general presentaron un mayor riesgo de SLC y/o NT grave.

En cuanto a la eficacia, las tasas de respuesta y los resultados de supervivencia fueron comparables a los de los ensayos pivotales. No hubo diferencias significativas en la supervivencia entre ambos productos en el análisis por intención de tratar modificado. Entre las características previas al tratamiento asociadas con eficacia, identificamos que niveles elevados de LDH y volumen metabólico tumoral, junto a un estado general deteriorado, se asociaron a una peor supervivencia libre de progresión. La evaluación

de respuesta al mes post-infusión predijo los resultados de la terapia T-CAR e identificó a los pacientes en remisión parcial con alto riesgo de progresión.

En conclusión, los tres estudios que integran esta tesis doctoral lograron identificar variables que, antes o después de la infusión de linfocitos T-CAR, son capaces de predecir el resultado de los pacientes que reciben estas terapias.

1 INTRODUCTION

1.1 Overview of mature lymphoid neoplasms

1.1.1 Definition and epidemiology

Lymphoid neoplasms are a diverse group of clonal tumors of B cells, T cells and natural killer (NK) cells at various stages of differentiation. They can be further classified as precursor lymphoid neoplasms (lymphoblastic leukemia) and mature lymphoid neoplasms(1).

Mature B-cell neoplasms constitute approximately 90% of lymphoid malignancies worldwide(2). They usually mimic normal stages of B-cell differentiation, enabling their classification and nomenclature. The most common B-cell lymphoma subtypes in adults are DLBCL (37%) and FL (29%) (Figure 1)(3). Other less frequent subtypes include small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), mucosa-associated lymphoid tissue (MALT) lymphoma and mantle cell lymphoma (MCL). These relative frequencies vary across different geographic regions, with a higher incidence in developed countries.

The median patient age for all types of mature B-cell neoplasms is between the sixth and seventh decade of life, except for PMBL, with a median patient age of 35 years. Only Burkitt and DLBCL occur with any significant frequency in children. Most subtypes have a male predominance but FL and PMBL are more frequent in female patients.

Even though most lymphomas have an unknown etiology, certain risk factors have been identified, such as primary or acquired immunodeficiencies (HIV infection, immunosuppressive agents)(4, 5), autoimmune diseases (Sjögren syndrome, Hashimoto thyroiditis)(6), environmental exposures (pesticides), and infectious agents (Epstein-Barr virus, human herpesvirus 8, human T-cell leukemia virus type I, hepatitis C virus, Helicobacter pylori)(7, 8, 9, 10, 11).

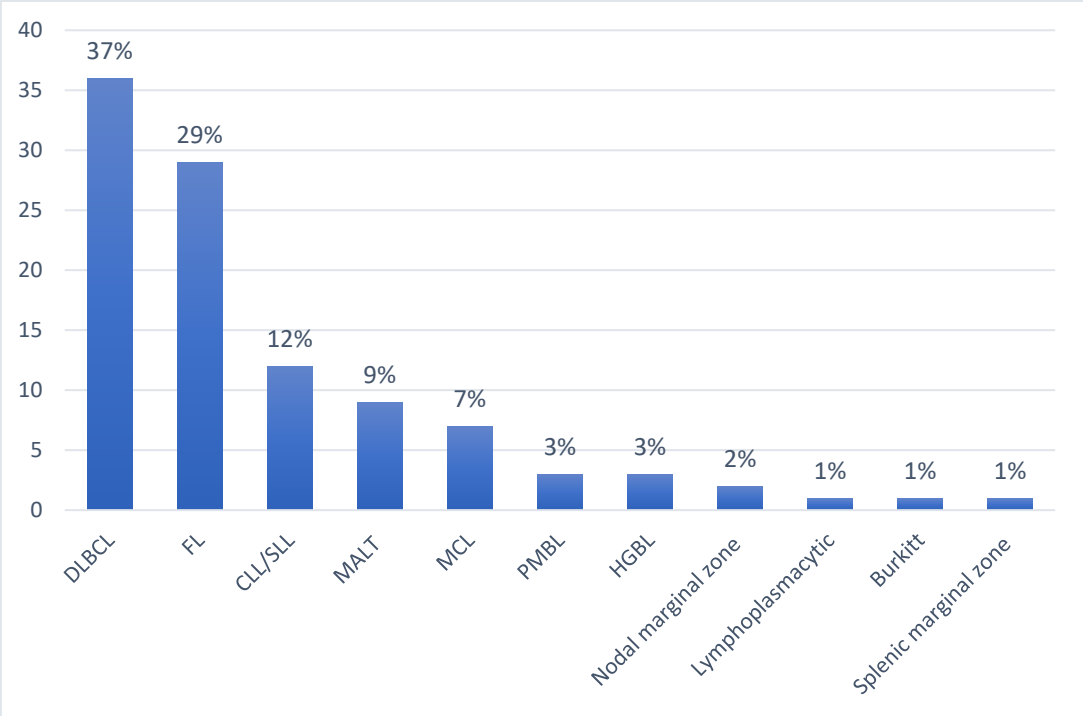

Figure 1.- Distribution of mature B-cell neoplasms according to their prevalence. Adapted from the Non-Hodgkin Lymphoma Classification Project(3).

1.1.2 Classification

The currently accepted classification is established by the World Health Organization (WHO). This system takes into account multiple parameters, such as morphology, immunophenotype, cytogenetics and molecular features, as well as clinical behavior and etiology data to establish each category.

The classification here described is the 2016 update of the 4th Edition *of the WHO classification of tumours of the haematopoietic and lymphoid tissues* (Table 1)(1).

Table 1. WHO classification of lymphoid neoplasms (1).

Mature B-cell lymphomas
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Lymphoplasmacytic lymphoma / Waldenström macroglobulinemia
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Follicular lymphoma
Pediatric-type follicular lymphoma
Large B-cell lymphoma with IRF4 rearrangement
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), NOS
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV^+ DLBCL, NOS
EBV^+ mucocutaneous ulcer
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK^+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
$HHV8^+$ DLBCL, NOS
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration
High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
High-grade B-cell lymphoma, NOS
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Adapted from the 2016 revision of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (1). Provisional entities are listed in italics.

1.2 Diffuse large B-cell lymphoma

1.2.1 Concept and epidemiology

DLBCL is the most common B-cell non-Hodgkin lymphoma. Median age at diagnosis is 60-70 years, with a male predominance. In some cases, it can be the result of a transformation from an indolent B-cell lymphoma, such as FL, SLL/CLL or marginal zone lymphoma.

It is a heterogeneous entity from a biological and clinical perspective. Established morphological variants are centroblastic, immunoblastic, anaplastic and other rare variants. Defined molecular subtypes include germinal center B-cell (GCB, ~60%) and activated B-cell (ABC, ~25–30%); about 10–15% are unclassifiable. These subtypes are believed to arise from a different cell of origin and carry prognostic implications; patients with GCB subtype have superior survival outcomes in comparison with ABC (1, 12).

1.2.2 Pathology features and genetics

On pathology assessment, there is a diffuse proliferation of large lymphoid B cells usually expressing CD19, CD20, CD22, CD79a, PAX5, and surface or cytoplasmic immunoglobulin. Given the lack of widespread molecular techniques in clinical practice, subtypes are usually established based on immunohistochemical (IHC) staining algorithms (13). The Hans algorithm divides DLBCL patients into GCB and non-GCB; the latter includes ABC and most of the unclassifiable cases.

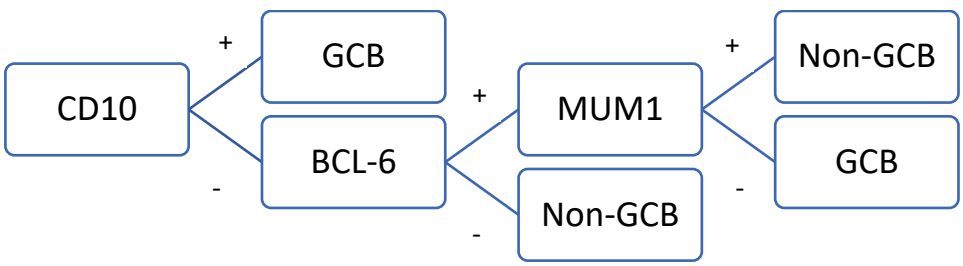

Figure 2. Algorithm for DLBCL IHC classification according to cell of origin(13)

The most common genetic rearrangement detected by fluorescence in situ hybridization (FISH) is *BCL6* (30%), usually in the ABC subtype. Oher common translocations include *BCL2* (20-30%), predominantly in the GCB subtype, and *MYC* (8-14%). Approximately 50% of patients with *MYC* rearrangements also include *BLC2* or *BCL6* and are included in the category of high-grade B-cell lymphoma. However, patients with a single *MYC* translocation and DLBCL morphology are considered part of DLBCL category. Often, patients with a *MYC* rearrangement also have a high IHC expression of MYC (≥40%) and BCL2 (≥50%), termed as "double-expressor lymphoma". This coexpression is more frequent in the ABC subtype.

The mutational landscape of DLBCL is complex and highly variable depending on the cell of origin subtype. Some of the most frequent mutations are found in genes involved in epigenetic modification, such as *KMT2D* (also called *MLL2*), *CREBBP* or *EP300*, immune escape, such as *B2M*, *CD58* or *HLA,* and DNA damage response, mainly *TP53.* Regarding molecular subtypes, the GCB subtype includes frequent mutations of *BCL2, EZH2, GNA13* and *TNFRSF14*. In the ABC subtype, the most frequent mutations affect the NF-κB/BCR signaling, including *MYD88*, *TNFAIP3*, *CD79A/B*, and *CARD11(14)*. A summary of the main mutations and their relative frequencies is presented in Table 2.

Finally, based on molecular data, distinct DLBCL subsets have been described. These subtypes explain differences in pathogenesis, entail a prognostic impact and could lead to a tailored management approach according to actionable targets. (15, 16, 17)

GCB,	%	ABC,	%	GCB and ABC,	%
BCL2	34	TNFAIP3	30	KMT2D	35
EZH2	22	MYD88	30	CREBBP	30
GNA13	21	PRDM1	25	B2M	25
TNFRSF14	20	CD79A/B	20	TP53	20
BCL6	15	CARD11	9	MEF2B	15

Table 2. Genetic mutations according to cell of origin. Adapted from Pasqualucci L and Dalla-Favera R. (14)

1.2.3 Clinical presentation and staging

Most patients will have a nodal presentation at diagnosis, but up to 40% can have exclusive extranodal disease. The most frequent extranodal site is the gastrointestinal tract, followed by bone, testes, spleen, Waldeyer ring, salivary glands, thyroid, liver, kidneys and adrenal glands. The last two are associated with an increased risk of central nervous system (CNS) dissemination. Clinical behavior is usually aggressive with rapid tumor dissemination. Therefore, most patients will have an advanced disease at diagnosis. Symptoms will be largely dependent on the location of the tumor mass and can be associated with fever, night sweats and weight loss (B symptoms)(1).

The current staging system for LBCL is the Ann Arbor classification. Even though it was initially established for Hodgkin's disease(18), it later extended to NHL and was revised at the Lugano 2014 conference (19).

Table 3. Ann Arbor staging system (18)

Stage	Nodal Involvement	Extranodal (E) Involvement
Limited		
Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Advanced		
Stage III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Nodal involvement with additional noncontiguous extralymphatic involvement	Not applicable

Adapted from Cheson et al, JCO 2014. The disease extension is assessed with PET/CT in LBCL.

1.2.4 Prognostic index score

The classic prognostic index score used in DLBCL is the International Prognostic Index (IPI), published in 1993, to predict outcomes and long term prognosis for aggressive non-Hodgkin lymphoma patients after first-line chemotherapy(20). It takes into account pretreatment clinical and laboratory parameters, assigning 1 point each to patients with >60 years of age, serum LDH >ULN, Ann Arbor stage III-IV, ECOG >1, and >1 site of extranodal involvement.

After the addition of rituximab to the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) regimen, the scoring system was re-evaluated to confirm its prognostic power in the new immunochemotherapy era. The R-IPI (revised IPI) score incorporated the same factors, with the same scoring for each one, but re-classified the prognostic groups (21).

Table 4. Risk scores for DLBCL.

IPI risk groups		
Scoring system	***Risk groups***	***OS at 5 years (%)***
Low	0-1	73
Low-intermediate	2	51
High-intermediate	3	43
High	4-5	26
R-IPI risk groups		
Scoring system	***Risk groups***	***OS at 4 years (%)***
Very good	0	94
Good	1-2	79
Poor	3-5	55

1.2.5 PET-based response criteria in lymphoma

For FDG-avid histologies, such as DLBCL, PET/CT scan is the recommended tool to perform staging at diagnosis and to evaluate response at end-of-treatment. The latter should be performed according to the 5-point Deauville scale (Table 5), with mediastinum and liver uptake as reference points. An interim PET, after 2-4 cycles of

treatment, can hold prognostic value but should not alter the course of treatment, unless progressive disease is observed(22, 23). Surveillance scans, after achieving a complete response, have not shown to improve patients' outcomes and should not be performed routinely(19).

Table 5. Response categories in lymphoma patients evaluated with PET scan.

Response category	Definition
Complete metabolic response (CMR)	• Deauville score 1, 2, or 3 (with or without a residual mass) • No new lesions
Partial metabolic response (PMR)	• Score 4 or 5 with reduced uptake compared with baseline and residual mass of any size • No new lesions
No metabolic response	• Score 4 or 5 with no significant change in FDG uptake from baseline • No new lesions
Progressive metabolic disease (PMD, PD)	• Score 4 or 5 with an increase in uptake from baseline and/or • New FDG-avid foci consistent with lymphoma
PET 5-point scale: 1, no uptake above background 2, uptake ≤ mediastinum 3, uptake > mediastinum but ≤ liver 4, uptake moderately > liver 5, uptake markedly higher than liver and/or new lesions X, new areas of uptake unlikely to be related to lymphoma.	

Adapted from Cheson BD et al, The Lugano Classification(19).

1.2.6 Treatment

1.2.6.1 First line treatment

The CHOP chemotherapy schema was the established SOC for first-line DLBCL. Randomized trials with more intensive chemotherapy combinations failed to show an improved survival over CHOP, confirming its leading role in this setting(24, 25).

Rituximab was added to CHOP after clinical trials in younger and older patients with newly diagnosed DLBCL confirmed superior outcomes in patients receiving the immunochemotherapy arm (Table 6). Thorough the years, modifications of the R-CHOP regimen were tested, including a more frequent administration (every 2 weeks vs 3 weeks) an increased number of cycles (8 vs 6) and the addition of rituximab maintenance after responding to induction. None of them yielded superior survival outcomes in comparison with R-CHOP. Therefore, R-CHOP remained the standard first-line treatment for DLBCL. This immunochemotherapy regimen cures approximately 60% of newly diagnosed DLBCL patients, so 40% will require further therapy. This latter group includes refractory patients (lack of achieving a complete response or progression in the first 6 months after the last rituximab dose) (26) and relapsed patients (progression after achieving an initial complete response)(12).

Table 6. Phase III trials for untreated DLBCL patients which evaluated the impact of adding rituximab to the first-line setting.

Study	N	Study arms	Patients	Primary endpoint	OS
LNH-98.5 (27, 28)	399	8xCHOP21 8xR-CHOP21	60-80y	EFS	10 year- R-CHOP: 44% CHOP: 28%
RICOVER-60 (29)	1222	8xCHOP14 8xR-CHOP14 6xCHOP14 6xR-CHOP14	61-80y	EFS (3y)- 6xCHOP: 47% 8xCHOP: 53% 6xRCHOP: 67% 8xRCHOP: 63%	3-year 6xCHOP: 68% 8xCHOP: 66% 6xRCHOP: 78% 8xRCHOP: 73%
MInT (30)	824	6xCHOP21 6xR-CHOP21	18-60y aaIPI 0-1	EFS (3y)- 6xCHOP: 59% 6xRCHOP: 79%	3-year 6xCHOP: 84% 6xRCHOP: 93%
US Intergroup (31)	632	1st Random.: 6-8xCHOP21 6-8x RCHOP21 2nd Random.: (CR/PR) MR vs Obs.	≥ 60y	FFS (2y from 2nd) RCHOP: 77% RCHOP+MR: 79% CHOP: 45% CHOP+MR: 74%	3-year R-CHOP: 67% CHOP: 58%

In the last years, many randomized phase III trials have tried to improve the R-CHOP results in DLBCL by adding a new agent to this regimen which had previously shown efficacy in single-arm phase II studies. None of these randomized trials confirmed a statistically significant improvement in PFS of the experimental arm in comparison with R-CHOP (Table 7)(32).

Recently, the POLARIX trial compared R-CHOP with polatuzumab-RCHP (replacing vincristine with polatuzumab vedotin) in intermediate-risk or high-risk DLBCL. The primary endpoint of PFS was met. However, overall survival was not significantly different and the subgroup analysis revealed several subpopulations which did not benefit from this novel regimen, such as patients younger than 60 years, female patients, patients with bulky disease or a GCB subtype(33).

Table 7. Randomized phase III trials comparing R-CHOP with an experimental arm for patients with untreated DLBCL.

Study	N	Patients	Experimental arm	Primary endpoint
MAIN (34)	787	DLBCL, any subtype	Bevacizumab-RCHOP	PFS; HR 1.09, **p=0.49** Increased cardiotoxicity
GOYA (35)	1418	DLBCL, any subtype	Obinutuzumab-CHOP	PFS; HR 0.92 (0.76-1.11), **p=0.39**
REMoDL-B (36)	918	DLBCL, any subtype	Bortezomib-RCHOP	30 mo-PFS; HR 0.86 (0.65-1.13), **p=0.28**
PHOENIX (37)	838	nonGCB-DLBCL	Ibrutinib-RCHOP	EFS; HR 0.95 (0.70 to 1.28), **p=0.73**
ROBUST (38)	570	ABC-DLBCL	Lenalidomide-RCHOP	PFS; HR 0.85 (0.63 to 1.14), **p=0.29**
POLARIX (33)	879	intermediate or high-risk DLBCL	Polatuzumab-RCHP	PFS; HR 0.73 (0.57-0.95), **p=0.02**

For patients with HGBL, retrospective series suggest that R-CHOP may be insufficient. This prompted the use of more intensive therapies, such as dose-adjusted etoposide,

prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab (DA-EPOCH-R), which seem to be associated with improved outcomes and are currently recommended in these LBCL subtypes (39, 40).

1.2.6.2 Treatment in the relapsed/refractory setting

Patients who are refractory to first-line treatment, or relapse after achieving an initial response, are in urgent need of salvage treatment. These patients can be divided in two groups: those who are candidates for an autologous stem cell transplant (auto-HCT), taking into account age, performance status and comorbidities, and those who are not.

Salvage treatment as a bridge to an autologous stem cell transplant

For young, fit patients, salvage treatment is based on platinum-containing immunochemotherapy regimens (R-GDP, R-ESHAP, R-DHAP and R-ICE)(41, 42). If patients are chemotherapy-sensitive and achieve a complete or partial response, consolidation with an auto-HCT is carried out. The type of salvage regimen is heterogenous among centers given the similar results observed in 2 randomized trials (Table 8).

Table 8. Phase III trials for relapsed/refractory DLBCL patients.

Study	N	Study arms	Primary endpoint	OS
NCIC-CTG LY.12 (41)	619	R-GDP ± ASCT R-DHAP ± ASCT	GDP vs DHAP ORR → 45.2% vs 44.0% Transplant rate → 52.1% vs 49.3%	HR 1.03 **p=0.78**
CORAL (42)	396	R-ICE ± ASCT R-DHAP ± ASCT	ICE vs DHAP ORR → 63.5% vs 62.8%	ICE vs DHAP (3y) 47% and 51% **p=0.4**

The auto-HCT consolidation is based on data proving a survival benefit of high-dose chemotherapy with an autologous stem cell rescue in comparison with prolonged conventional chemotherapy (43).

The main parameters with a prognostic impact on outcome after second-line treatment are tumor burden at relapse, chemotherapy sensitivity before auto-HCT and time from diagnosis to relapse(44).

Other treatment options for relapsed/refractory DLBCL patients

Patients who are not auto-HCT candidates and progress after R-CHOP have limited treatment options and low response rates with conventional chemotherapy-based strategies, such as R-GEMOX (rituximab, gemcitabine and oxaliplatin) (45, 46, 47, 48). Also, patients who progress after an auto-HCT have a similar dismal outcome (49).

Until recently, the only approved drug in the relapsed/refractory setting for patients who were not auto-HCT candidates or had progressed after transplant was pixantrone, based on the results of a randomized phase 3 trial which showed a significantly higher CR rate in comparison with other single chemotherapy agents (20% vs 5.7%) (50). Recently, some novel agents have become available for R/R DLBCL patients, including R-polatuzumab-bendamustine, tafasitamab-lenalidomide and loncastuximab tesirine (Table 9). Even though reported CR rates for these agents are close to 40% in the registration trials, the durability of these responses is not clear and longer follow-up is needed. If patients respond to these therapeutic options, an allogeneic HCT (allo-HCT) should be considered(51, 52, 53, 54).

Another drug class with a potential impact in the therapeutic landscape of R/R DLBCL are bispecific antibodies. Although none of them are yet EMA-approved, these anti-CD20/CD3 agents have very promising results in large phase I trials. Main data is summarized in Table 10.

Table 9. Available EMA-approved agents in R/R DLBCL.

	Pixantrone	Polatuzumab-R-Bendamustine	Tafasitamab-Lenalidomide	Loncastuximab Tesirine*
MoA	Inhibits topoisomerase II	ADC anti-CD79b	MAb anti-CD19 /Immunomodulator	ADC anti-CD19
Trial	Phase III PIX301	Phase II GO29365	Phase II L-MIND	Phase II LOTIS-2
N	140 (1:1)	80 (1:1)	81 (single-arm)	145 (single-arm)
ORR	40%	45%	58%	48%
CR	24%	40%	40%	24%
mPFS	5.0 mo	9.2 mo	11.6 mo	4.9 mo
mDoR	-	12.6 mo	43.9 mo	10.3 mo
mOS	7.5 mo	12.4 mo	33.5 mo	9.9 mo
Ref	(50)	(55, 56)	(57)	(58)

** EMA has recommended conditional marketing authorization (15 September 2022).*

Table 10. Main CD20/CD3 bispecific antibody trials in aggressive B-cell lymphoma.

	Mosunetuzumab	Glofitamab	Odronextamab*	Epcoritamab
Patients (N)	129	154	82	157
mFollow-up	11.9 mo	12.6 mo	2.9 mo	10.7 mo
Dosing	IV, e/21 days	IV, e/21 days	IV, e/21 days	SC, e/28 days
ORR	35%	52%	33-39%	63%
CR	19%	39%	24%	39%
mPFS	1.4 mo	4.9 mo	2.0-11.5	4.4 mo
mDoR	7.6 mo	18.4 mo	4.4-6.7 mo	12.0 mo
CRS, any/≥G3	27% - 1%	63% - 4%	61% - 7%	50% - 3%
NT, any/≥G3	44% - 4%	8% - 3%	NA - 3%	6% - 1%
Reference	(59)	(60)	(61)	(62)

**Data with Odronextamab was reported separately for patients who received a previous CAR-T. **≥ 10mg cohorts*

In this scenario, Chimeric Antigen Receptor (CAR) T-cells have emerged as a potentially curative therapeutic option for R/R DLBCL patients. With the available trial and real-world data, they have become the standard salvage strategy for patients who progressed after 2 or more lines of treatment. This is further developed in the next section.

1.3 Chimeric antigen receptor T-cells

1.3.1 Background

The normal immune system has two main subsystems:

- **Innate immune system**. This is a non-specific first line of defense on mucosal and cutaneous surfaces. The cells involved include NK cells, gamma delta T cells, macrophages and granulocytes, amongst others. This system does not require the presentation of antigens by the major histocompatibility complex (MHC) in order to initiate an immune response.
- **Adaptive immune system**. It includes the exclusive features of antigen specificity and memory. In this system, B cells and T cells recognize pathogens through immunoglobulins (B-cell receptor, BCR) and the T-cell receptor (TCR), respectively.

    - The TCR complex is integrated by an α and β chain with a variable (target-recognition) and constant region each. The intracellular signaling capacity is provided by the CD3 complex, specially the ζ chain which has the largest intracytoplasmatic domain. For an effective T cell activation, antigen presentation through the MHC class II molecule on antigen-presenting cells (APCs) is required, together with a second signal, usually CD28 (T cell) with CD80 (APC) or 4-1BB (T cell) with 4-1BBL (APC) (Figure 3)(63).

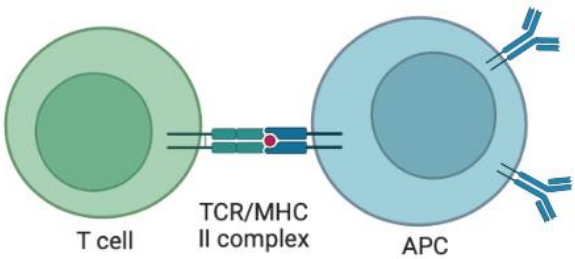

Figure 3. T cells recognize tumor antigens presented by APCs through the interaction of their TCR and the MHC-II on the APC. Image constructed with *https://biorender.com*

1.3.2 Concept and mechanism of action of CAR T-cells

CARs are synthetic receptors that provide a defined specificity to an immune effector cell, typically a T cell, and augment its function, allowing it to recognize antigens in an MHC-independent manner. Currently available CAR T-cells for commercial use have a defined structure, including (Figure 4):

- **Antigen-binding domain**. Extracellular region capable of recognizing a defined target. It is built from a single-chain variable fragment (scFv), containing the variable regions of the heavy and light chain of an immunoglobulin. Commercial CAR T-cells in LBCL target CD19; this protein is mainly restricted to normal B-cells (across all stages of differentiation, from Pro-B to plasma cell) and preserved in most B-cell malignancies. Therefore, on-target off-tumor toxicity is mainly restricted to B-cell aplasia and secondary hypogammaglobulinemia (64, 65). Other CAR-T targets under research for LBCL include CD20 and CD22.
- **Spacer.** The length and composition of the spacer or hinge domain (HD) is crucial for optimal *in vivo* activity of CAR T-cells. Some of the usual spacers include CD8, CD28 and IgG4. (66, 67)
- **Transmembrane domain (TD).** The different types of TD can modulate CAR T-cell activities. Noteworthy, the 3 EMA-approved CAR T-cells differ in their HD and TM: CD28-HD/TD for axi-cel, CD8-HD/TD for tisa-cel, and IgG4-HD/CD28-TD for liso-cel. (67, 68, 69, 70, 71, 72)
- **Costimulatory domain**, usually 4-1BB or CD28. This intracytoplasmic region was added to first-generation CARs in order to increase cytokine production and promote T-cell proliferation and survival, turning them into second-generation CAR T-cells. Second-generation CAR constructs (Figure 4) mimic physiologic T-cell activation, as described above.
- **Activation domain** derived from the CD3ζ chain. (73).

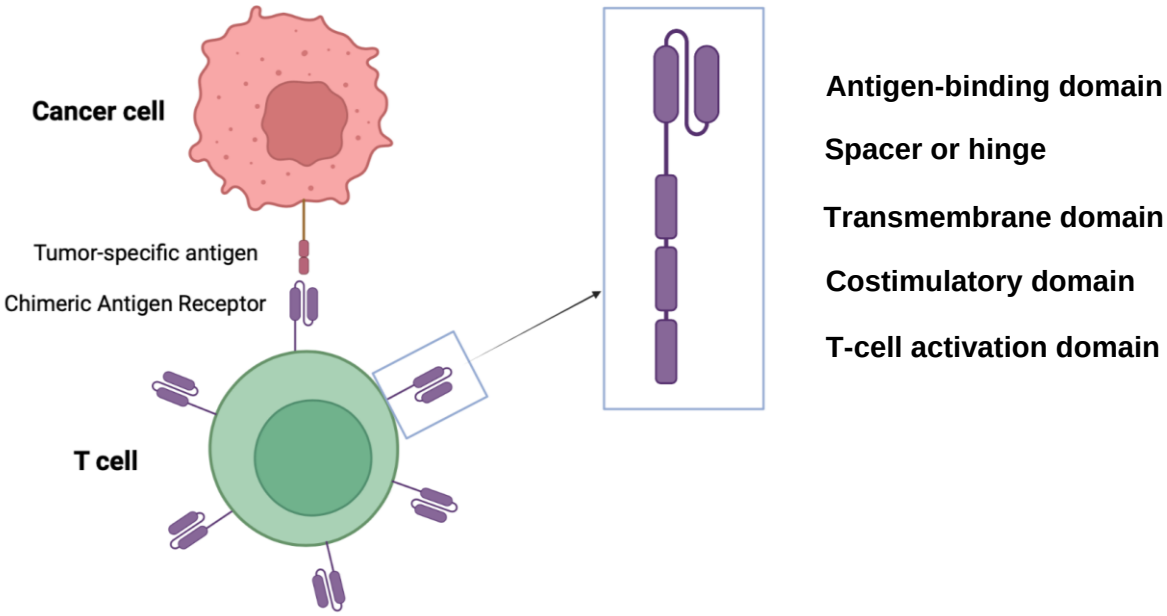

Figure 4. Interaction between the tumor-specific antigen on the cancer cell surface and a Chimeric Antigen Receptor (CAR) T-cell. On the right, a second-generation CAR construct. Image built with *https://biorender.com*

1.3.3 Patient journey

The patient journey for CAR T-cell therapy includes:

1. **Lymphocyte apheresis** → The apheresis requirements for each product are different and should be scheduled in advance.
2. **CAR T-cell manufacturing** includes:
    - Isolation and activation of T cells
    - CAR gene transfer through a viral vector
    - Expansion of CAR-expressing T cells
    - Quality check for product release: This is a key step to ensure that each CAR product meets the specification list and acceptance criteria, such as number of CAR+ cells, viability and sterility, amongst others. If any of these label-required criteria are not met, the product will be termed “Out-of-Specification” (OOS).

3. **Bridging treatment** (BT) → This term refers to whatever regimen the patient receives between apheresis and CAR T-cell therapy. Most patients (approximately 85%) will require some type of BT due to the aggressive nature of the underlying disease. BT can be local, with radiation, or systemic, with chemotherapy or novel agents (lenalidomide, ibrutinib, polatuzumab, monoclonal antibodies). In the pivotal trials and real-world publications, reported data are very heterogeneous and country-dependent. In general, patients who require a more intensive BT show worse outcomes after CAR T-cell therapy, probably as a surrogate marker of the rapid disease kinetics. However, patients who respond to BT have an improved survival in comparison to patients who do not receive BT or progress as best response to BT. (74, 75, 76, 77)
4. **Lymphodepleting (LD) chemotherapy** → Before cell infusion, patients receive a conditioning regimen to gain disease control and favor CAR-T expansion. The latter is achieved through multiple effects including endogenous lymphocyte depletion, removal of immunosuppressive elements such as regulatory T cells and myeloid-derived suppressor cells, and modulation of the patients' cytokine profile, amongst others(78, 79, 80, 81, 82). This schema usually includes cyclophosphamide and fludarabine(83, 84, 85), even though other drugs have been tested in this setting, such as bendamustine (84, 86). After LD, patients require at least 2 days of washout before they can receive the cell infusion.
5. **CAR T-cell infusion** → The possibility of outpatient management will largely depend on the product, hospital structure and available resources.

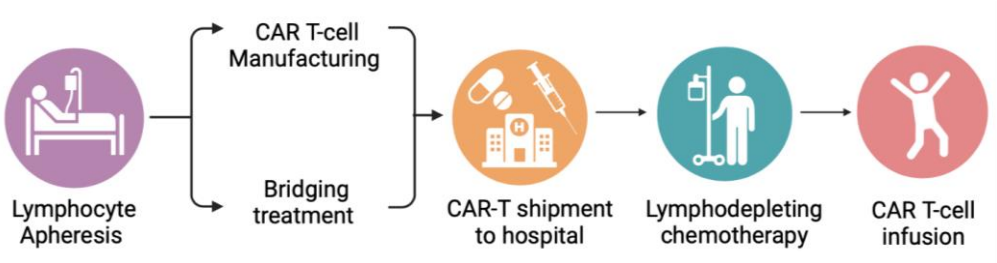

Figure 5. Patient journey for CAR T-cell patients (https://biorender.com)

1.3.4 Main toxicity profile

1.3.4.1 Short term toxicity

Short-term adverse events are considered those that take place within the first month after CAR T-cell infusion(87). Even though the CAR is directed against a specific target, it also binds to non-tumor cells that share this antigen, like normal B lymphocytes (on-target off-tumor effect) and the cytokine release can reach other cells (off-target effect).

These adverse events mainly include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), macrophage activation syndrome (MAS), tumor lysis syndrome (TLS), cytopenias and infectious complications, amongst others(88).

Cytokine release syndrome

Cytokine release syndrome is due to the massive release of cytokines (IL-6, IL-1, IL-10, IFNγ, MCP-1, GM-CSF, TNFα, IL-2 and IL-8) mediated by CAR T-cells and can cause fever, hypotension, and hypoxia. In addition, CRS can also be associated with coagulopathy and organ dysfunction (hepatic, renal or cardiac, among others) (89).

The median onset of CRS is between days 2 to 3 after the CAR-T infusion and usually has a duration of 7 to 8 days, depending on the product and the underlying disease. The currently accepted guidelines to assess the degree of severity are established by the American Society for Transplantation and Cellular Therapy (ASTCT)(90). Both the grading and management of CRS are summarized in the following tables(91).

Table 11. Grading of cytokine release syndrome(90).

	Grade 1	Grade 2	Grade 3	Grade 4
Fever	T ≥ 38ºC	T ≥ 38ºC	T ≥ 38ºC	T ≥ 38ºC
Hypotension	None	No vasopressors	Requiring a vasopressor	Requiring >1 vasopressor
Hypoxia	None	Low-flow (≤6 L/min)	High-flow (>6 L/min)	Positive pressure or intubation

The degree of CRS is defined by the most serious event. Grade 5 is death due to CRS after excluding other causes. Abbreviations: T – Temperature; L/min – liters/minute.

Table 12. Treatment of cytokine release syndrome according to grade(91).

Grade 1	• Rule out infection by performing blood and urine cultures, chest X-ray and initiating empirical antimicrobial treatment. • If infectious cause has been ruled out and grade 1 CRS is persistent (>72 hours) and/or the patient has significant comorbidities or fragility, assess treatment as if grade 2.
Grade 2	• Administer tocilizumab 8 mg/kg (maximum 800 mg). • If no resolution, tocilizumab administration can be repeated every 8 hours up to 4 doses. • In case of refractory CRS, consider dexamethasone 10 mg every 6 hours.
Grade 3	• Same tocilizumab regimen as grade 2. • In case of refractory CRS, consider dexamethasone 10-20 mg every 6 hours.
Grade 4	• Same tocilizumab regimen as grade 2. • In case of refractory CRS, consider methylprednisolone 1000 mg every 24 hours. • Consider other third-line options, such as siltuximab (11mg/kg) and anakinra (8mg/kg). • Other experimental options include dasatinib and ruxolitinib.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

The pathophysiology of ICANS is not clearly established, although it is also suggested that cytokine release together with an increased permeability of the blood-brain barrier may be involved, leading to a wide range of symptoms that include encephalopathy, aphasia, apraxia, tremor, dysgraphia, lethargy and seizures (92, 93).

The median onset of ICANS is from days 4 to 6 after CAR T-cell infusion, usually following CRS. Duration is between 7 to 17 days, depending on the product and the underlying disease. The degree of severity is defined in the guidelines of the American Society for Transplantation and Cellular Therapy (ASTCT)(90). The grading and detailed management of ICANS is summarized in the following tables.

Table 13. Grading of neurotoxicity(90).

	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (unarousable)
Depressed level of consciousness	Awakens spontaneous	Awakens to verbal stimulus	Awakens only to tactile stimulus	Stupor or coma
Seizure	None	None	Any clinical seizure or nonconvulsive seizures on EEG that resolve rapidly	Prolonged (>5 min) or repetitive seizures
Motor findings	None	None	None	Deep focal motor weakness
Elevated ICP/ cerebral edema	None	None	Focal edema on imaging	Cerebral edema; VI cranial nerve palsy; Cushing's triad

The degree of neurotoxicity is defined by the most serious event. Grade 5 is death due to ICANS after excluding other possible causes. Abbreviations: ICE - Immune Effector Cell-Associated; EEG – electroencephalogram; min – minutes; ICP Intracranial pressure

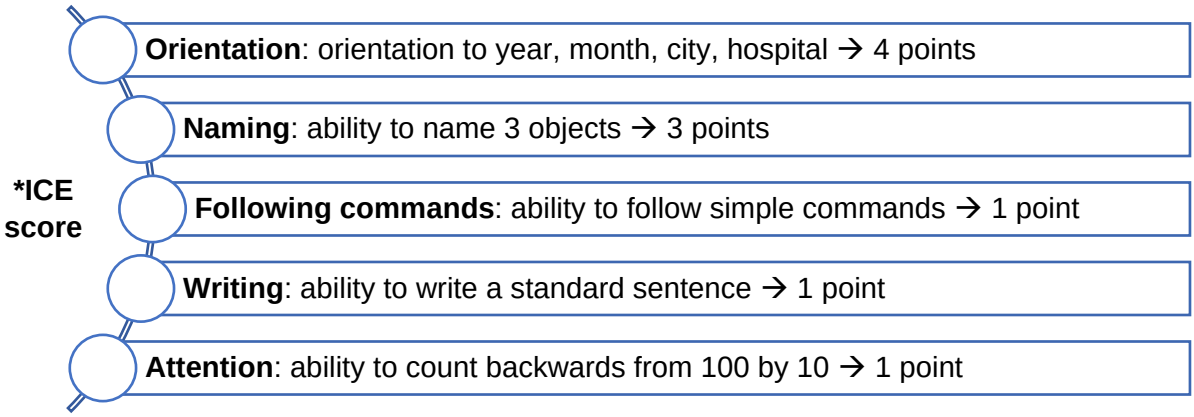

Table 14. Treatment of ICANS according to grade(91).

Grade 1	• Perform a brain CT and MRI, electroencephalogram and optional lumbar puncture to rule out other possible causes. • Steroid therapy is not routinely recommended. Small studies have explored the role of early or prophylactic steroids (94, 95)
Grade 2	• Steroid treatment with doses equivalent to dexamethasone 10 mg/6h until ICANS resolves to, at least, grade 1. • In case of refractory ICANS, treat as ICANS grade 3.
Grade 3	• Steroid treatment with dexamethasone 10-20 mg/6h until ICANS resolves to, at least, grade 1. • In case of refractory ICANS, treat as ICANS grade 4.
Grade 4	• Steroids treatment with methylprednisolone 1000 mg/day until ICANS resolves to, at least, grade 1. • In case of refractory ICANS, the use of anakinra and siltuximab may be considered. • Other experimental approaches include dasatinib and ruxolitinib, as well as intrathecal chemotherapy (methotrexate, cytarabine and corticosteroids).

Macrophage activation syndrome (MAS)

MAS is characterized by uncontrolled macrophage and lymphocyte activation associated with supraphysiological secretion of proinflammatory cytokines, lymphohistiocytic tissue infiltration and immune-mediated organ damage. It usually includes fever, hyperferritinemia, hypertriglyceridemia, elevated liver enzymes, coagulopathy and pancytopenia. In the context of CAR-T, there are 2 MAS modalities:

- **Early MAS**: its onset and characteristics can overlap with CRS and the management is similar.
- **Late MAS**: it has a very low incidence (around 1%) and a later onset, after the second week post-CAR T-cell infusion. It usually doesn't respond to CRS-directed therapy and has a very high mortality rate (around 80%).

Table 15. Diagnostic criteria for MAS related to CAR-T therapy(96).

Peak ferritin >10,000 ng/mL and ≥2 of the following	- Grade ≥3 increase in serum bilirubin, AST or ALT * - Oliguria or increased creatinine grade ≥3 * - Pulmonary edema grade ≥3 * - Presence of hemophagocytosis in the bone marrow or organs according to histopathological evaluation by morphology and/or immunohistochemistry (CD68)

** Scored according to the Common Terminology Criteria for Adverse Events, version 4.03.*

Table 16. Therapeutic management of MAS related to CAR-T therapy.

First line	Manage according to CRS protocol
Second line	If no improvement after 48 hours consider: - Etoposide (+/- doxorrubicine and methylprednisolone) - Anakinra 8 mg/kg/day - Antithymocyte globulin - Methylprednisolone 1g/day for 3-5 days plus immunoglobulins 1g/kg during 2 days.

1.3.4.2 Long term toxicity

Hypogammaglobulinemia

It is defined as an immunoglobulin G (IgG) level <400 mg/dL or the need for replacement therapy with immunoglobulins (IVIG) due to recurrent infections. It is the most frequent late adverse effect and is due to the prolonged B-cell aplasia. A significant proportion of patients will already have baseline hypogammaglobulinemia secondary to the underlying disease and previous treatments(97, 98).

In adults with non-Hodgkin lymphoma, IVIG replacement is recommended when serum IgG is <400 mg/dL and the patient has recurrent or severe infections(99, 100). In patients with recurrent infections despite an IgG level >400 mg dL, IgG subtypes should be analyzed. The half-life of administered IgG is 3 to 4 weeks, so there should be monthly monitoring. Recovery from B-cell aplasia is not always associated with recovered IgG levels; therefore, it is important to monitor the serum IgG levels and discontinue IVIG once the trough level is persistently >400 mg/dL without replacement(101).

Prolonged cytopenias

In the setting of CAR T-cell therapy, persistent cytopenias (beyond the first month post-infusion) have been reported, including significant rates of severe neutropenia (30-38%), thrombocytopenia (21-29%), and anemia (5-17%)(98, 102, 103, 104). The underlying mechanism is not clear, but identified risk factors include baseline hematopoietic reserve and inflammatory status at time of lymphodepletion (C-reactive protein and ferritin) (105, 106). Patients can present a biphasic course of cytopenias, with initial recovery and subsequent development of severe cytopenias in the following weeks(102). Late cytopenias are more common in patients who developed severe CRS and/or ICANS (102).

In the first weeks after infusion, patients often require transfusion of irradiated blood products and G-CSF support. However, if cytopenias persist beyond 3 months, or transfusion-requirements are high, a differential diagnosis must be carried out. Laboratory studies should include iron metabolism, folic acid, vitamin B12, parvovirus B19 and CMV, amongst others. A bone marrow study should be performed to rule out a myelodysplastic syndrome(98). If other causes are ruled out, erythropoietin and/or thrombopoietin receptor agonists can be considered(107). If there is no recovery despite these measures, a stem cell boost could be considered, if available (108, 109).

Late infections

One of the key aspects regarding late infections is prevention and early detection. As mentioned above, immunoglobulin replacement and G-CSF for neutropenic patients should be considered to reduce the risk of infection. Main risk factors for late infections and prophylaxis recommendations are summarized in the following tables(99).

Table 17. Prophylaxis recommendations for patients receiving CAR T-cells.

Type	Indication	Drugs	Duration
Bacterial	No routine prophylaxis		
Viral	HSV seropositive patients	Acyclovir	Minimum 1 year
Fungal	Fluconazole in all and prophylaxis of filamentous fungi if ≥2 risk factors: 1. ≥ 4 prior lines 2. Baseline neutropenia (<500/mm3) 3. High CAR-T dose 4. Previous IFI 5. Tocilizumab and/or steroids	Fluconazole For filamentous fungi: - Posaconazole - Nebulized liposomal amphotericin B - Micafungin	Until neutrophil recovery
Pneumocystis jirovecii	All cases	Trimethoprim sulfamethoxazole or pentamidine	1 year, prolong if CD4 <200 cells/µL

Adapted from Los-Arcos I et al(99). *Abbreviations: h: hours; HSV: herpes simplex virus; IFI: invasive fungal infection; iv: intravenous; MD: maximum dose, po: oral dosing, pw: per week, TMP: trimethoprim µL: microliter*

Table 18. Main factors which increase the risk of infection.

Factors that increase the risk of infection
- Acute lymphoid leukemia as the underlying disease - More than 3 previous lines of treatment - B-cell aplasia and hypogammaglobulinemia - Baseline cytopenias, mainly neutropenia and CD4+ lymphopenia - Severe complications after infusion (CRS and neurotoxicity) that require treatment with tocilizumab and/or corticosteroids

Second neoplasms

In the long-term follow-up of the ZUMA-1 trial, 1 patient developed a myelodysplastic syndrome (MDS) at 19 months post-infusion(83, 110). In a study of the FHCRC(98), subsequent hematological neoplasms were observed in 5 patients, including 4 cases of MDS and 1 case of multiple myeloma (MM). However, 2 of the 4 MDS patients had pre-existing cytogenetic abnormalities, and the MM patient had a prior monoclonal gammopathy of uncertain significance. Also, 8 (9%) patients developed solid tumors, including 6 cases of skin cancer (non-melanoma), 1 melanoma, and 1 bladder cancer. Since these patients had received extensive prior cytotoxic therapies, it is unclear whether these neoplasms can be attributed to CAR-T therapy. In a recent publication reporting a large cohort of commercial axi-cel patients, 4% (50 patients) were diagnosed with secondary neoplasms, including 15 of MDS, 11 of squamous cell skin carcinoma, and 4 of myelodysplastic/myeloproliferative neoplasms, amongst others (111).

Insertional oncogenesis due to insertion of the viral vector near an oncogene in the engineered T cells is a possibility, but no such cases have been reported to date(112). Because secondary malignancies are rare events with a long latency, long-term follow-up is recommended to better estimate the incidence and evolution.

Other late adverse events

Immune-related late effects

The development of an autoimmune disease or the exacerbation of a pre-existing one is a potential concern after CAR-T therapy. Among the pivotal clinical trials, no late autoimmune reactions were reported. However, in a study carried out in FHCRC in lymphoid neoplasms, late autoimmune adverse events were observed in 7 patients (8%) at a median of 234 days after infusion(98). Definitive attribution of these complications to CAR T-cell therapy remains difficult.

Late neurologic events

Neurological events past the first 3 months have been described, including cases of stroke, transient ischemic attack, Alzheimer's dementia and peripheral neuropathy(98). However, the predisposing factors for these events are not clear.

Cardiovascular toxicity

One study observed elevated troponin levels in 54% of CAR T-cell infused patients, with a higher incidence in patients experiencing CRS grade ≥2. Additionally, 30% of patients had a significant reduction in LVEF. Finally, cardiovascular (CV) events were reported, including 6 CV-related deaths, 6 cases of congestive heart failure and 5 arrhythmias. A longer period between CRS onset and tocilizumab administration was associated with a higher risk of CV events. This study highlighted the role of troponin as a biomarker of CV toxicity and the potential cardioprotective role of tocilizumab(113, 114).

Kidney toxicity

Transient AKI after CAR T-cell infusion has been reported in up to 20% of children and young adults with B-ALL, especially those with grade ≥3 CRS. In adults, the incidence is higher (30%). Risk factors include prior HCT, admission to the ICU and high-grade CRS. Long-term follow-up is required to confirm whether a subset of these patients is at risk of developing chronic kidney disease(115, 116).

1.4 CAR T-cell therapy in aggressive B-cell lymphoma

1.4.1 Background

Currently, axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) are the EMA-approved CAR-T products for relapsed or refractory LBCL after two or more lines of treatment. The former is also approved in second-line for primary refractory and early relapsed (<12 months) LBCL patients. All three are second-generation CD19-targeted CAR-T constructs. Main differences lie in the costimulatory domain and the hinge/transmembrane regions.

These approvals were based on the results of non-randomized phase 2 registration trials (ZUMA-1, JULIET and TRANSCEND, respectively) which supported their outcome benefit on the survival results of historical cohorts. The main comparator was the retrospective SCHOLAR-1 study(49), which analyzed long term results of patients with LBCL who were refractory to first or second-line, or had relapsed in the first 12 months after an auto-HCT. Patients who met this profile from the CORAL and LY.12 studies, together with 2 additional US cohorts, were included. These patients received heterogeneous treatment approaches, obtaining a 26% overall response rate. Only 7% achieved a complete remission and median overall survival was 6.3 months. After propensity score matching for populations included in SCHOLAR-1 and ZUMA-1 studies, there was a significant benefit for the latter in terms of durable responses and overall survival(117). The results from the JULIET trial were also compared with a similar patient population from the CORAL study(118), confirming an improved response rate and survival for CAR T-cell recipients.

1.4.2 Available data in third or later line of treatment

1.4.2.1 Clinical trials

Axicabtagene ciloleucel

Axicabtagene ciloleucel (axi-cel) is a second-generation CD19-targeted autologous CAR-T with a CD28 costimulatory domain, which confers greater expansion and limited persistence. Hinge and transmembrane regions are also CD28 in this construct.

The ZUMA-1 registry study(83, 110) evaluated the efficacy and safety of axi-cel in patients with chemotherapy-refractory DLBCL, PMBL and transformed follicular lymphoma (tFL). A total of 111 patients were included, of which 101 (91%) were infused, 77 with DLBCL and 24 with PMBL or tFL. In this study, patients were not allowed to receive bridging treatment between apheresis and lymphodepleting chemotherapy.

Regarding toxicity, 93% developed CRS (13% grade ≥3) with a median onset of 2 days after CAR T-cell infusion. Sixty-four percent of the patients presented any grade of ICANS (28% grade ≥3) with a median onset of 5 days after infusion. To manage these complications, 43% of the patients received tocilizumab and 27% steroids.

In terms of efficacy, 54% of infused patients achieved a CMR, with a median duration of response of 8.1 months. No significant differences were observed based on age, disease stage, IPI score, presence of bulky mass, cell of origin, use of tocilizumab or steroids. An association was observed between *in vivo* CAR-T expansion and response; however, the persistence of CAR T-cells did not seem to have a significant impact on duration of response.

Tisagenlecleucel

Tisagenlecleucel (tisa-cel) is a second-generation autologous CD19-targeted CAR-T construct with a 4-1BB costimulatory domain, which confers a prolonged persistence after infusion. Hinge and transmembrane regions are CD8α.

The pivotal JULIET trial (84, 119, 120) evaluated tisa-cel in adult patients with relapsed or refractory DLBCL after 2 or more lines of treatment. Apheresis was performed in 165 patients, of which 111 received the infusion. Bridging with any local or systemic treatment was allowed.

Regarding toxicity, 22% of patients presented a grade ≥3 CRS according to UPenn criteria(121), with a median onset on day 3 post-infusion. Neurological events grade ≥3 occurred in 10% of patients. Fourteen percent required administration of tocilizumab and 10% received tocilizumab and steroids.

In terms of efficacy, 40% of infused patients achieved a CMR. The estimated 12-month PFS was 83% in patients who achieved a complete response and median OS of all infused patients was 12 months. Patients with an early relapse had limited expansion and persistence of CAR T-cells compared to those who achieved a CMR.

Lisocabtagene maraleucel

Lisocabtagene maraleucel (liso-cel) is a second generation CD19-targeted autologous CAR-T with a 4-1BB costimulatory domain. The hinge and transmembrane regions are IgG4 and CD28, respectively. The main difference from the previously described CAR-T constructs is the separate infusion of equivalent doses of CD8+ and CD4+ T-cells.

The registry study TRANSCEND-NHL-001 included patients in progression after 2 or more lines of treatment with DLBCL (de novo or transformed from any indolent lymphoma), PMBL and grade 3B FL. In this study, there was greater flexibility in the inclusion criteria, allowing patients with a previous allogeneic HCT, CNS infiltration, moderate comorbidities (creatinine clearance ≥30 ml/min, LVEF ≥40%) and any blood count values. Of the 344 patients who underwent apheresis, 269 received liso-cel.

Regarding toxicity, 113 (42%) developed CRS of any grade, grade ≥3 in 6 (2%) patients. Treatment included tocilizumab, steroids or both in 53 (20%) patients. Neurological

events were described in 80 (30%) patients (grade ≥3 in 27 [10%] patients). Among the seven patients with secondary CNS infiltration, 2 had neurological events (both grade 3). In terms of efficacy, overall response rate was 73%, complete in 53% of infused patients. At 12 months, 55% of the patients maintained the response. The CAR T-cells showed a prolonged persistence of up to 1 year in 52% of patients with available samples.

Table 19. Pivotal studies in third-line LBCL (not intended to compare these treatments).

	ZUMA-1	JULIET	TRANSCEND
Main characteristics			
Apheresis, n	111	165	344
Infusion, n	101	111	269
Infused ≥ 65 years, n (%)	24 (24)	25 (23)	112 (42)
ECOG	0-1	0-1	0-2
Autologous stem cell transplant (%)	21	49	33
Allogeneic stem cell transplant (%)	0	0	3
≥3 prior lines (%)	69	52	51
Bridging (%)	0*	92	59
Efficacy			
Objective response (%)**	82	52	73
Complete response (%)	54	40	53
PFS, median (months)	5.9	3.0	6.8
OS, median (months)	NR	12	21.1
Safety			
CRS, any grade (%)***	93	58	42
CRS grade ≥3 (%)	13	22	2
ICANS, any grade (%)***	64	21	30
ICANS grade ≥3 (%)	28	12	10

**No bridging chemotherapy was allowed. **Objective response includes partial and complete response. ***The studies used different grading scales for CRS and ICANS.*

1.4.2.2 Real-world evidence

Since the approval of CAR T-cell therapy in LBCL, many studies have addressed real-world outcomes, outside the context of controlled clinical trials. Overall, the published efficacy and safety data are similar to the pivotal trials, with an increased use of tocilizumab and steroids. The available data from the United States (US) and Europe (EU) will be discussed separately.

United States

Concerning the use of axi-cel, 2 retrospective studies included 275 and 122 infused patients, respectively. These reports confirmed the efficacy results of the pivotal trials, with complete responses ranging from 64-50%. In terms of toxicity, similar rates of ICANS grade ≥3 (31-35%) were observed with a slight reduction of CRS grade ≥3 (7-16%) in comparison with the ZUMA-1 trial (122, 123). Recently, a larger study reported the outcomes of 1297 patients infused with commercial axi-cel in the US; of note, 57% would have been ineligible for the ZUMA-1 trial. Efficacy outcomes overlapped with previous publications, with an ORR of 73% (CMR in 56%) and median PFS of 8.6 months. Duration of response was similar for ZUMA-1 eligible and ineligible patients(111).

As per tisa-cel, a registry study from the International Center for Bone Marrow Transplantation and Cellular Therapy (CIBMTR) reported efficacy and safety data in 155 LBCL patients(124). Approximately 40% of infused patients achieved a CMR, with a 12-month PFS of 26%. In terms of toxicity, CRS and ICANS grade ≥3 was 5% in each case, according to Lee 2019 criteria (90). Another retrospective report including 260 patients who underwent apheresis for axi-cel (65%) and tisa-cel (35%) identified significant differences in median age (older patients in the tisa-cel group) and manufacturing time (longer with tisa-cel) between both cohorts. Patients who received axi-cel developed

significantly higher rates of CRS and ICANS grade ≥3, conditioning an increased rate of inpatient management. Complete response rate and survival outcomes were not significantly different between both products(125).

Table 20. Published CART real-world data studies in United States.

	(123)	(122)	(111)	(124)	(125)	
	Axi-cel	**Axi-cel**	**Axi-cel**	**Tisa-cel**	**Axi-cel**	**Tisa-cel**
Apheresis, n	298	-	-	-	168	92
Infusion, n	275	122	1297	155	156	84
ORR (%)	82	70	73	62	52	41
CMR (%)	64	50	56	40	44	35
PFS, median (mo)	8.3	4.5	8.6	4.2	42% (12-mo)	32% (12-mo)
OS, median (mo)	NR	NR	21.8	13.1	62% (12-mo)	59% (12-mo)
Follow-up, median mo	12.9	10.4	12.9	11.9	12.4	13.8
CRS, any grade (%)	91	93	83	45	85	39
CRS grade ≥3 (%)	7	16	8	11.6	9	1
ICANS, any grade (%)	69	70	55	18	56	11
ICANS grade ≥3 (%)	31	35	24	8	39	1
ICU admission (%)	33	28	-	-	38	5

Europe

Several European countries have published their national experience with CAR T-cells in third or later line of treatment. The United Kingdom (UK) published their joint experience with axi-cel and tisa-cel. With respect to toxicity, any grade CRS and ICANS were more frequent in axi-cel recipients, together with tocilizumab and steroid use. Noteworthy, 1-year NRM was 8.7% and 3.1% for axi-cel and tisa-cel, respectively.

Efficacy data was similar to the pivotal trials. Interestingly, they identified LDH and extranodal sites (≥3) as prognostic factors with a significant impact on PFS(126).

From Spain, there are 3 publications reporting real-world data with axi-cel and tisa-cel. Two of these studies are part of this Doctoral Thesis and will be explained in *Results (76, 127)*. A third publication focused on the CAR-T recipients who met SCHOLAR-1 criteria(49) and compared them to a historical SOC cohort from the GELTAMO database. Both axi-cel and tisa-cel showed superior survival outcomes in comparison to the historical cohort (128).

The German study included 356 patients treated with CAR T-cell therapy. Turnaround was significantly longer for tisa-cel in comparison to axi-cel. Toxicity was comparable to the pivotal trials and other real-world data reports. Noteworthy, NRM was significantly higher in the axi-cel cohort and mainly driven by infections in patients with prolonged neutropenia and/or severe neurotoxicity. Regarding efficacy, PFS was significantly shorter in patients who progressed to bridging treatment, had an increased baseline LDH and received tisa-cel (75).

From the French group, some small reports (129, 130) preceded their large publication from the multicenter DESCAR-T registry(131). Out of 729 infused patients, they carried out propensity score matching to select comparable axi-cel and tisa-cel populations. They included in the final analysis 418 infused patients, 209 with axi-cel and tisa-cel, respectively. In terms of toxicity, patients who received axi-cel presented higher rates of CRS (any grade) and ICANS (any grade and grade ≥3). Hematological toxicity was also increased in the axi-cel cohort, both any grade and grade ≥3. Regarding efficacy, overall and complete response rates were significantly higher in the axi-cel group, as well as progression-free and overall survival.

Table 21. Main CAR-T real-world studies in Europe.

	UK (126)		Germany (75)		France (131)		Italy (132)
	Axi-cel	**Tisa-cel**	**Axi-cel**	**Tisa-cel**	**Axi-cel**	**Tisa-cel**	
Apheresis, n	375		-		809 (before PSM)		208
Infusion, n	224	76	173	183	209	209	191
Turnaround, days	40	50	35	55	-		-
Objective response (%)	77%	57%	74%	53%	80%	66%	76%
Complete response (%)	52%	44%	42%	32%	60%	42%	44%
PFS, median (mo)	5.5	2.9	35% (12-mo)	24% (12-mo)	8.2	3.1	56% (6-mo)
OS, median (mo)	15.6	10.2	55% (12-mo)	53% (12-mo)	NR	11.2	80% (6-mo)
Follow-up, median (mo)	13.9		11				7.7
CRS, any grade (%)	93	74	81%	65%	86%	76%	79%
CRS grade ≥3 (%)	8	8	10%	13%	5%	9%	5%
ICANS, any grade (%)	44	15	44%	22%	49%	22%	24%
ICANS grade ≥3 (%)	20	4	16%	7%	14%	3%	8%
ICU admission (%)	22%	12%	-		-		13%

NOTE: The real-world data from Spain is presented in *Results*.

1.4.3 Clinical trials in earlier treatment lines

1.4.3.1 Second-line treatment

Following the promising results of CAR-T therapy in third or later line of treatment for patients with LBCL, its role in earlier phases of the disease has been explored.

Three phase III trials (ZUMA-7, BELINDA and TRANSFORM, with axi-cel, tisa-cel and liso-cel, respectively) were carried out for transplant-eligible patients who were refractory or relapsed early (<12 months) after a first line of treatment (Table 22). These studies randomized patients to SOC treatment with platinum-based chemotherapy and an auto-HCT consolidation or CAR-T therapy. Primary endpoint in all 3 studies was event-free survival, but the definition of this endpoint was different in each trial. Both the axi-cel and liso-cel trials met their primary endpoint, while tisa-cel did not. Based on these results, the EMA has recently granted approval to axi-cel in second-line for this patient population.

For patients who are not candidates for an auto-HCT because of older age or moderate/severe comorbidities, there are ongoing clinical trials with liso-cel (NCT03483103, NCT03484702), axi-cel (NCT04531046) and tisa-cel (NCT04161118) in second line of treatment. The results of the PILOT study, with liso-cel, have already been published. In this trial, apheresis was performed in 74 patients, of which 61 were infused. Regarding efficacy, ORR was 80% and CMR was achieved in 54% of infused patients. Median PFS was 9 months for all infused patients and 23 months for patients who achieved a CMR. In terms of toxicity, any grade of CRS and ICANS occurred in 38% (grade 3 in 1 patient) and 31% (grade 3 in 3 patients), respectively (133).

Table 22. Phase III randomized trials in second-line treatment for LBCL.

	ZUMA-7 (134)	BELINDA (135)	TRANSFORM (136)
Construct	Axi-cel	Tisa-cel	Liso-cel
Number patients	359 (1:1)	322 (1:1)	184 (1:1)
HGBL	19%	24%	24%
Primary refractory	74%	66%	73%*
Bridging therapy	36% (Steroids)	83% (SOC regimen)	63% (SOC regimen)
Crossover	No	No response after 12 wks	SD/PD >9 wks PD/New therapy
EFS definition	Death PD New therapy SD (+150)	Death SD/PD >wk 12	Death PD New therapy SD/PD >9 weeks
Days to infusion	26	52 (41 US vs 57 EU)	31
Follow-up (mo)	24.9	10.0	6.2
N auto-HCT, %	36	33	46
N crossover, %	56*	51	54
ORR CART (CR), % **ORR auto-HCT (CR), %**	83 (65) 50 (32)	46 (28) 43 (28)	86 (66) 48 (39)
EFS CART (mo) **EFS auto-HCT**	8.3 (HR 0.4) 2.0	3.0 3.0	10.1 (HR 0.35) 2.3
CRS (any/G≥3), %	92/6 Toci 65% Steroids 24%	59/5 Toci 52% Steroids 17%	49/1
ICANS (any/G≥3), %	60/21 Steroids 32%	10/2	12/4
Tocilizumab/steroids	-	-	24/17

1.4.3.2 First-line treatment

Finally, results in first-line with axi-cel have already been published. The ZUMA-12 study evaluated CAR-T therapy in patients with HGBL (double or triple hit) or high-risk DLBCL (IPI ≥3) who did not achieve a complete response (Deauville Score 4 or 5) after 2 cycles

of first-line immunochemotherapy. Of 37 infused and evaluable patients, ORR was 89% and CMR was achieved in 78%. With a median follow-up of 15.9 months, 73% of the patients maintained the response. In terms of toxicity, grade ≥3 CRS and ICANS occurred in 8% and 23%, respectively (137).

1.4.4 Prognostic factors for CAR T-cell treatment

The pivotal trials and real-world studies have tried to identify prognostic factors for efficacy and toxicity with CAR T-cell treatment. Both the patients' performance status and tumor burden at time of infusion have shown to have the most significant impact on outcome. Thus, patients with a high score (≥2) on the ECOG scale have a shorter PFS than patients with an ECOG of 0 or 1 (123, 124, 129). Regarding tumor burden, several studies have shown that patients with DLBCL who have an elevated baseline LDH and/or total metabolic tumor volume have shorter PFS and OS after axi-cel and tisa-cel infusion(123, 127, 130, 138). For this reason, it is essential to prepare patients during the bridging period, while the product is being manufactured. Most patients with DLBCL require treatment after apheresis (84, 127, 129), but strategies in this period are highly variable in scheme and intensity. Apart from chemotherapy, there is published data with novel strategies such as lenalidomide, ibrutinib, polatuzumab (77, 139) and radiotherapy, the latter being a recommended option in chemo-refractory patients with a main accessible lesion (74, 140).

Other relevant prognostic factors are the presence of extranodal sites (130) and the inclusion of fludarabine in the lymphodeplective chemotherapy regimen (78). Age and comorbidities have also been evaluated as potential prognostic factors, although it seems that their role is less significant, at least with regards to efficacy; however, a higher risk of ICANS has been described in elderly patients (141, 142, 143). Of note, efficacy is also lower in patients with primary refractory disease(127). Finally, an increased value of certain biomarkers, such as ferritin and C-reactive protein (CRP), has been associated

with worse efficacy outcomes (122). Other studies have documented that high levels of monocyte chemotactic protein 1 (MCP-1) and a low peak of interleukin-7 (IL-7) on the day of infusion may favor the antitumor effect and increase the CMR rate (78); however, most of these immunological factors are not routinely available in clinical practice.

1.4.5 Future strategies under development

There are multiple ongoing studies with the aim of improving the efficacy and toxicity profile of the available CAR-T products for patients with LBCL.

One approach is to target novel antigens, different to CD19. There are clinical trials with CAR T-cells directed against CD20(144, 145) and CD22 (146). Also, CD37 has been used as a target for CAR-T constructs *in vitro* (147) and is being studied in other trials (NCT04136275). Dual CAR T-cells, constructs with two recognition domains directed against different targets, are also being explored. This strategy aims to avoid treatment resistance if one of the targets has a weak or null expression in the lymphoma; the most frequently used combination is CD19/CD22 (148, 149).

Another approach would be to incorporate an additional intracytoplasmic costimulatory domain (third generation CARs), or to generate constructs which release cytokines upon CAR signaling in the targeted tumor tissue (fourth generation CARs)(150, 151).

A novel strategy are allogeneic CAR T-cells, prepared from healthy donor lymphocytes. Potential advantages of this approach include immediate availability, without the manufacturing delay inherent to autologous products, and better T-cell fitness. However, there is a theoretical risk of graft-versus-host disease (GVHD) and shorter persistence (152). Recently, the results of a clinical trial with CD19-targeted allogeneic CAR-NK lymphocytes were presented for 11 patients with R/R lymphoproliferative diseases (153). No cases of CRS, ICANS or GVHD were reported. Eight (73%) patients responded, with a CMR in 7 patients. Responses were achieved early but duration of response was not

evaluable because most underwent an allo-HCT consolidation or additional anti-lymphoma therapy.

Finally, there is growing interest in combining CAR T-cells with other drugs to increase efficacy outcomes. The best example would be the concomitant use of ibrutinib with anti-CD19 CAR-T therapy in CLL, which has shown to improve safety and efficacy in the context of clinical trials(154). Other combinations are currently underway with checkpoint inhibitors and immunomodulatory drugs (NCT03310619, NCT03630159, NCT02926833, NCT03704298, NCT04002401, NCT03876028).

1.4.6 Relapse after chimeric antigen receptor T-cells

Approximately 60-70% of patients with LBCL will progress after CAR T-cell therapy(155). Resistance to CAR-T can derive from a weak/absent CD19 expression (reported in 30% of patients at time of progression)(165), insufficient CAR-T expansion relative to tumor burden, or an immunosuppressive tumor microenvironment, amongst others(156, 162).

Median overall survival after progression is approximately 5-6 months. Main factors influencing survival after CAR-T progression are:

- Time from infusion to disease progression. Patients with an early progression, in the first month after infusion, have a worse outcome than patients who initially respond to CAR-T and relapse at a later timepoint(161).
- Disease characteristics at baseline and relapse. Tumor burden and LDH levels have an impact on outcome, both at time of CAR-T infusion and at relapse.
- Response to salvage treatment. Patients who are only candidates for supportive care (approximately 25-35% of patients at progression) have a dismal outcome, with a median OS of 1-2 months. If patients are salvage-candidates, response to their next line of treatment will significantly impact their outcome.

There is no consensus on the optimal treatment regimen after CAR-T progression. Even though clinical trials are the first option in many centers, less than 20% of patients will finally meet inclusion criteria, mainly due to prolonged hematologic toxicity(160). Main treatment strategies in this setting include lenalidomide, checkpoint inhibitors(164), chemotherapy, BTK inhibitors, polatuzumab, bispecific antibodies and, in some cases of localized relapses, radiation(159). Overall and complete responses range from 29-47% and 17-25%, respectively. Median PFS in available reports is 2-3 months, with no significant differences between treatment approaches. However, chemotherapy seems to fare worse in most studies when compared to bispecific antibodies, polatuzumab- or lenalidomide-based combinations(157, 163, 167).

If a response to salvage treatment is achieved, consolidation with an allo-HCT is considered for young, fit patients(166). A recent registry study reported the outcome of 88 patients with LBCL who progressed after CAR T-cell treatment, were salvaged with a median of 1 line of therapy and underwent an allo-HCT consolidation. Most patients received a low-intensity conditioning and peripheral blood was the main graft source. Regarding survival outcomes, 1-year PFS, OS and NRM were 45%, 59% and 22%, respectively. Requiring only 1 line of treatment after CAR-T failure and undergoing an allo-HCT in CMR held a positive prognostic impact on survival(158).

2 HYPOTHESIS

The hypothesis on which this Doctoral Thesis stands is:

- Identifying pretreatment factors associated with efficacy and toxicity prior to CAR T-cell infusion could enable a better patient selection, leading to higher overall and complete response rates, together with a tailored approach for safety management.

3 OBJECTIVES

3.1 Main objective

1. To describe the efficacy, safety and potential predictive factors of CAR T-cell outcomes in patients with LBCL treated in the real-world setting.

3.2 Secondary objectives

1. To describe the patient characteristics of CAR T-cell candidates with LBCL.

2. To report efficacy and safety outcomes of commercially-approved CAR T-cell therapies in patients with LBCL treated in the real-world setting.

3. To assess the role of pre- and post-treatment metabolic features on patient outcomes, as a standard approach for tumor burden assessment.

4. To analyze the impact of baseline patient and disease characteristics on CART-related adverse events and treatment efficacy.

4 COMPENDIUM OF PUBLICATIONS

4.1 First publication

Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma. Iacoboni G, Villacampa G, Martinez-Cibrian N, Bailén R, Lopez Corral L, Sanchez JM, Guerreiro M, Caballero AC, Mussetti A, Sancho JM, Hernani R, Abrisqueta P, Solano C, Sureda A, Briones J, Martin Garcia-Sancho A, Kwon M, Reguera-Ortega JL, Barba P on behalf of GETH, GELTAMO Spanish Groups. Cancer Medicine 2021 May;10(10):3214-3223. doi: 10.1002/cam4.3881

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ORIGINAL RESEARCH

Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma

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Abstract

Tisagenlecleucel (tisa-cel) is a second-generation autologous CD19-targeted chimeric antigen receptor (CAR) T-cell therapy approved for relapsed/refractory (R/R) large B-cell lymphoma (LBCL). The approval was based on the results of phase II JULIET trial, with a best overall response rate (ORR) and complete response (CR) rate in infused patients of 52% and 40%, respectively. We report outcomes with tisa-cel in the standard-of-care (SOC) setting for R/R LBCL. Data from all patients with R/R LBCL

who underwent leukapheresis from December 2018 until June 2020 with the intent to receive SOC tisa-cel were retrospectively collected at 10 Spanish institutions. Toxicities were graded according to ASTCT criteria and responses were assessed as per Lugano 2014 classification. Of 91 patients who underwent leukapheresis, 75 (82%) received tisa-cel therapy. Grade 3 or higher cytokine release syndrome and neurotoxicity occurred in 5% and 1%, respectively; non-relapse mortality was 4%. Among the infused patients, best ORR and CR were 60% and 32%, respectively, with a median duration of response of 8.9 months. With a median follow-up of 14.1 months from CAR T-cell infusion, median progression-free survival and overall survival were 3 months and 10.7 months, respectively. At 12 months, patients in CR at first disease evaluation had a PFS of 87% and OS of 93%. Patients with an elevated lactate dehydrogenase showed a shorter PFS and OS on multivariate analysis. Treatment with tisa-cel for patients with relapsed/refractory LBCL in a European SOC setting showed a manageable safety profile and durable complete responses.

KEYWORDS

clinical cancer research, clinical observations, hematological cancer, non-Hodgkin's lymphoma

1 | INTRODUCTION

First-line immunochemotherapy cures around 60% of patients with large B-cell lymphoma (LBCL).[1,2] In the relapse/refractory (R/R) setting, second-line immunochemotherapy, usually including autologous stem cell transplant consolidation, salvages less than half of the patients,[3-6] whereas those in the third-line setting have a dismal prognosis.[7]

Chimeric antigen receptor (CAR) T-cell therapy provides long-term remissions in a proportion of patients with R/R LBCL with significant but manageable toxicity. The results of two pivotal phase 2 clinical trials led to the approval of axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for patients with R/R LBCL after 2 or more lines of systemic therapy. These trials had strict inclusion criteria and infused around 100 patients each, mainly in United States (US).[8-10] Thus, evaluating the feasibility of this therapy outside the US, as well as gaining knowledge on the outcome of patients treated in the commercial setting is mandatory.

Several single-center and registry-based studies have shown that treatment with axi-cel is feasible outside the clinical trial setting with a similar safety and efficacy profile to the pivotal trial.[11-14] However, data regarding the use of tisa-cel in patients with R/R LBCL outside clinical trials are scarce.[13-15]

To provide valuable information on patient outcomes with commercial tisa-cel in LBCL, we performed a national, multicenter, retrospective study evaluating the safety and efficacy of tisa-cel in a European real-life setting.

2 | METHODS

2.1 | Data collection and analysis

Data were collected retrospectively on all consecutive patients with R/R LBCL who underwent leukapheresis with the intent to manufacture commercial tisa-cel at 10 Spanish institutions from December 1st, 2018, until June 1st, 2020.

For the safety analysis, we included all patients who received a tisa-cel infusion and had a minimum follow-up of 1 month. Efficacy-evaluable patients included those who met the prior criteria and had an 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. The study was approved by the ethics committee of the Vall d'Hebron Hospital Board.

2.2 | Patient management

Patients were selected by hematologists around the country when they met technical data sheet criteria. A checklist with the usual screening tests (PET scan, laboratory results, echocardiogram, repeat biopsy if applicable) was forwarded to the Spanish Ministry of Health, who reviewed the proposal. Once it received approval, apheresis was performed. Bridging treatment was usually carried out at the local hospital.

Lymphodepleting (LD) chemotherapy included three consecutive days of fludarabine (25 mg/m^2/day) and

cyclophosphamide (250 mg/m^2/day) in all cases and started once tisa-cel had arrived on site; if the CAR T-cell product did not meet commercial release criteria according to EMA requirements (out-of-specification, OOS) but it was considered acceptable by the physician, patients were offered treatment through an expanded access protocol and their results were included. After 2–4 days of chemotherapy washout, patients received the CAR T-cell infusion in a hospitalization regimen to guarantee a close monitoring of adverse events, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Management of these adverse events was carried out according to the institutional guidelines in each center. Infectious complications were managed homogenously according to the Spanish consensus guidelines.[16]

For the efficacy analysis, 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) at the infusing center. Disease evaluation after CAR T-cell therapy was scheduled at 1, 3, 6, 12, 18, and 24 months after infusion. The imaging reports were based on the Lugano recommendation for response assessment,[17] and PET images were graded according to the 5-point Deauville score.

2.3 | Definitions and endpoints

Disease status at leukapheresis was defined as one of three possibilities: (a) primary refractory if never achieving end-of-treatment CR; (b) refractory to last therapy if not primary refractory but not achieving a complete response to the most recent therapy, (c) or relapsed. Bridging therapy was defined as any lymphoma-specific treatment administered after leukapheresis and before lymphodepleting chemotherapy.

Grading of CRS and ICANS was performed following the American Society for Transplantation and Cellular Therapy (ASTCT) criteria.[18] Patients who were infused before April 2019 were graded according to the Lee criteria[19] and then re-assessed retrospectively to meet the 2019 criteria. Severe CRS and/or ICANS were defined as grade 3 or higher events. For the reporting of other adverse events, Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used.[20] Tumor lysis syndrome was defined according to Cairo-Bishop criteria.[21]

Objective response rate (ORR) was defined as the percentage of patients who achieved a partial remission (PR) or complete remission (CR) after CAR T-cell infusion. 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. The duration of response (DOR) was defined as the time from CR or PR to relapse, progression, or death from any cause, whichever occurred first.

2.4 | Statistical analyses

A descriptive analysis of all included variables in the study was performed. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as absolute values and percentages. Univariate logistic regression model was carried out to estimate the association between ORR and baseline factors. Survival analysis (PFS and OS) was calculated using the Kaplan–Meier method and the log-rank test was used for statistical comparison. Cox proportional hazard models were used to obtain hazard ratios (HRs) with 95% CIs. For variable selection in multivariate analysis, we used the least absolute shrinkage and selection operator (LASSO) method to construct the most parsimonious model.[22] To assess the importance of the type of response at first evaluation, a landmark analysis using the date of first evaluation in non-progressor patients was performed.[23]

The data analyses were carried out using R statistical software version 3.6.2.

3 | RESULTS

3.1 | Patients and product characteristics

Ninety-one patients with R/R LBCL underwent leukapheresis for tisa-cel. Seventy-five (82%) patients received the CAR T-cell infusion, whereas 16 (18%) did not. Reasons to not receive the infusion were: progressive disease (n = 11, 69%), manufacturing failure (n = 4, 25%), and psychiatric disorder (n = 1, 6%). All 75 patients had at least the first disease response evaluation at 1-month post-infusion.

Baseline characteristics of the infused patients are summarized in Table 1. The median age was 60 years (IQR 52–67) and 59% were male patients. Most had an International Prognostic Index score >2 (62%), an advanced stage (92%) and were primary refractory (52%). Sixty-five patients (87%) received bridging therapy before infusion, including chemotherapy in most cases (n = 56, 86%). The median time from apheresis to infusion was 53 days (IQR 49–56). Median infused cell dose was 3.5×10^8 CAR positive viable T-cells (IQR 1.5–4.2). Eight products were considered OOS according to EMA requirements and four could not be manufactured. Reasons for OOS were low cellularity (n = 6, 75%) and low viability (n = 2, 25%). Six of the eight OOS products were infused (Table S1), the other two patients were not infused due

TABLE 1 Baseline characteristics of infused patients

Baseline characteristics of infused patients[a]	N = 75
Median age (IQR) -years	60 (52–67)
Age ≥65 y– n (%)	23 (31)
Gender –n (%)	
Male	44 (59)
Female	31 (41)
ECOG score, median (IQR)	1 (0–1)
0–n (%)	25 (33)
1–n (%)	41 (55)
2–n (%)	5 (7)
Missing data –n (%)	4 (5)
Histology – n (%)	
Diffuse large B-cell lymphoma, NOS	44 (58)
High grade B-cell lymphoma DH/TH	11 (15)
Transformed from follicular lymphoma	17 (23)
Transformed from other indolent histology	3 (4)
Cell of origin – n (%)	
GCB	44 (59)
Non-GCB	24 (32)
Missing data	7 (9)
Disease stage- n (%)	
Stage I-II	6 (8)
Stage III-IV	69 (92)
Extranodal disease (≥1 site)–n (%)	60 (80)
Bulky disease (>7 cm)–n (%)	30 (42)
LDH levels before treatment	
<2xULN	51 (68)
≥2xULN	24 (32)
IPI prognostic score – n (%)	
0–2	25 (33)
3–5	46 (62)
Missing data	4 (5)
Number of previous lines of treatment, median (IQR)	3 (2–4)
2–3	54 (72)
>3	21 (28)
Previous ASCT – n (%)	29 (39)
Response to previous therapy – n (%)	
Primary refractory	39 (52)
Refractory to last therapy	22 (29)
Relapsed	14 (19)
Bridging treatment -n (%)	65 (87)
Cyclophosphamide-Prednisone/CVP[b]	29 (44)
Platinum-based[c]	16 (24)
Bendamustine-based[d]	5 (8)
Rituximab-CHOP[e]	3 (5)
Steroids	2 (3)
Radiotherapy	2 (3)
Rituximab-Lenalidomide	2 (3)
Other chemotherapy[f]	3 (5)
Data not available	3 (5)

Abbreviations: ASCT, Autologous Stem Cell Transplant; DH/TH, Double Hit/Triple Hit; ECOG, Eastern Cooperative Oncology Group; GCB, Germinal Center B-cell; IPI, International Prognostic Index; IQR, Interquartile range; LDH, Lactate Dehydrogenase; NOS, Not Otherwise Specified; ULN, Upper Limit of Normal.

[a]ECOG score was missing in four patients, IPI missing in four patients; Bulky data missing in two patients, extranodal missing in one patient.

[b]CVP, Cyclophosphamide, vincristine, and prednisolone.

[c]Platinum-based strategies included R-GEMOX (12), R-GDP (3) and R-ESHAP (1).

[d]Bendamustine based included Rituximab-Bendamustine with (2) or without (3) Polatuzumab.

[e]CHOP, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone.

[f]Other chemotherapy included MINE (Mesna, Ifosfamide, Mitoxantrone, Etoposide), R-IE (rituximab, ifosfamide, and etoposide) and R-hyperCVAD (Cyclophosphamide, Vincristine, Adriamycin, and Dexamethasone).

to rapid disease progression. Median follow-up from CAR T-cell infusion was 14.1 months (95%CI 13.1–17.4).

3.2 | Safety analysis

Among the infused patients, 53 (71%) developed any grade of CRS; 21 (28%) and four (5%) patients developed grade ≥2 and grade ≥3 CRS, respectively. Eleven (15%) patients developed any grade of ICANS, whereas five (7%) and one (1%) developed grade ≥2 and grade ≥3 ICANS, respectively. The median time from infusion to the onset of symptoms of CRS and ICANS was 2 days (IQR 1–4) and 7 days (IQR 5–9), respectively. Tocilizumab and steroids were administered to 24 (32%) and 16 (21%) patients, respectively. Ten (13%) patients required admission to the Intensive Care Unit. By day 90 post-infusion, three (4%) patients experienced treatment-related mortality: two from bacterial infection, specifically one case of Klebsiella pneumoniae BLEE sepsis and another of multiresistant Pseudomonas aeruginosa soft tissue infection (at 26 and 30 days from infusion, respectively) and one from macrophage activation syndrome (MAS)[24] (at 36 days from infusion), despite treatment with tocilizumab, steroids, anakinra, and siltuximab. There were two other cases of MAS: one resolved with dexamethasone and the other without specific treatment. Other adverse events including infection and tumor lysis syndrome are summarized in Table 2.

The univariate analysis of risk factors for the development of adverse events is summarized in Table S2. The baseline characteristics associated with an increased risk of grade ≥2

TABLE 2 Safety analysis of infused patients

Safety profile of infused patients	N = 75
CRS	
Any grade; n (%)	53 (71)
Grade ≥2; n (%)	21 (28)
Grade ≥3; n (%)	4 (5)
Time from infusion to start of CRS; median days (IQR)	2 (1–4)
Duration CRS; median days (IQR)	4 (4–6)
ICANS	
Any grade; n (%)	11 (15)
Grade ≥2; n (%)	6 (8)
Grade ≥3; n (%)	1 (1)
Time from infusion to start of ICANS; median days (IQR)	7 (5–9)
Duration ICANS; median days (IQR)	9(3–14)
ICU, n (%)	10 (13)
Tocilizumab	
Patients; n (%)	24 (32)
Median number doses tocilizumab (IQR)	1 (1–5)
Corticosteroids	
Patients; n (%)	16 (21)
Duration steroids; median days (IQR)	11 (8–15)
Macrophage activation syndrome, n (%)	3 (4)
Infections in the first month after infusion	
Patients, n (%)	21 (28)
Infectious events	31
Bacterial	19
Viral	8
Fungal	3
Not identified	1
Tumor Lysis Syndrome, n (%)	2 (3)
Treatment-related mortality, n (%)	3 (4)

Abbreviations: Cytokine Release Syndrome (CRS); Immune Effector Associated Neurotoxicity Syndrome (ICANS); Intensive Care Unit (ICU); Interquartile range (IQR).

CRS and/or ICANS were ECOG (≥1 vs. 0), primary refractory disease, lactate dehydrogenase (LDH) levels (>2xULN [(Upper Limit of Normal)] vs. <2xULN), and the infused cell dose per kg of body weight (0.01-units increase).

3.3 | Efficacy analysis

3.3.1 | Disease response

Among the 75 infused patients, the best response achieved was CR in 24 (32%) patients and PR in 21 (28%), with an ORR of 60%. In the ITT analysis, the best response achieved was CR in 26% (24/91) with an ORR of 49% (45/91). Patients who achieved a response (CR or PR) had a median duration of response of 8.9 months (95%CI 2.2–NA). Stable disease and progressive disease were the best response in 6 (8%) and 24 (32%) patients, respectively. Of the six infused OOS products, two patients achieved a CR, one patient achieved a stable disease and eventually progressed, whereas three patients progressed at the first disease assessment (Table S1).

Regarding the patients who achieved an initial PR at the 1-month disease assessment, five (5/25, 20%) converted to CR at 3 (2 patients), 6, 12, and 18 months, respectively; the other patients in PR progressed in the following 3 to 6 months (18/25, 72%), or were in a maintained PR at data cutoff (2/25, 8%). Regarding the nine patients who achieved an initial SD, two patients converted to a CR at 6- and 18-months post-infusion, respectively, and one patient improved to a PR at 3 months post-infusion; one patient remained in SD at 6 months post-infusion and the remaining five patients had progressed at data cutoff.

In the subgroup analysis, ORR was consistent across all baseline characteristics except for the International Prognostic Index (IPI) score (a high IPI [3–5] showed a lower ORR [OR 0.35, $p = 0.05$]) and a history of previous indolent lymphoma (OR 3.59, $p = 0.04$) (Figure 1). In the subgroup analysis for CR, patients with an ECOG of 0, an LDH <2xULN and a low IPI score had a significantly increased probability of achieving a CR (Figure S1). There was no significant difference in any of the efficacy endpoints for patients with high-grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements.

Patients who developed grade 2 or higher CRS or ICANS had a similar ORR (65% vs. 58%, $p = 0.54$) and OS in comparison to patients who did not develop grade 2 or higher adverse events. There was no significant impact of tocilizumab or steroid use on the ORR (69% and 81%, respectively, p-values >0.1).

3.3.2 | Survival analysis

Median PFS and OS for all infused patients were 3 months (95%CI 2.6–4.7) and 10.7 months (95%CI 7.4–NA), respectively (Figure 2). The overall 6-month and 12-month PFS was 33.3% and 31.7%, respectively. Patients in CR and PR at first disease evaluation had a PFS at 12 months of 87% and 20% ($p < 0.001$) and OS of 93% and 39% ($p < 0.001$), respectively (Figure S2).

In the ITT analysis, median PFS and OS from apheresis were 4.6 months (95%CI 4.1–6.9) and 11.1 months (95%CI 7.9–NA), respectively (Figure S3).

In terms of PFS, patients who were primary refractory, had an ECOG of 1 or higher, a non-GCB cell of origin,

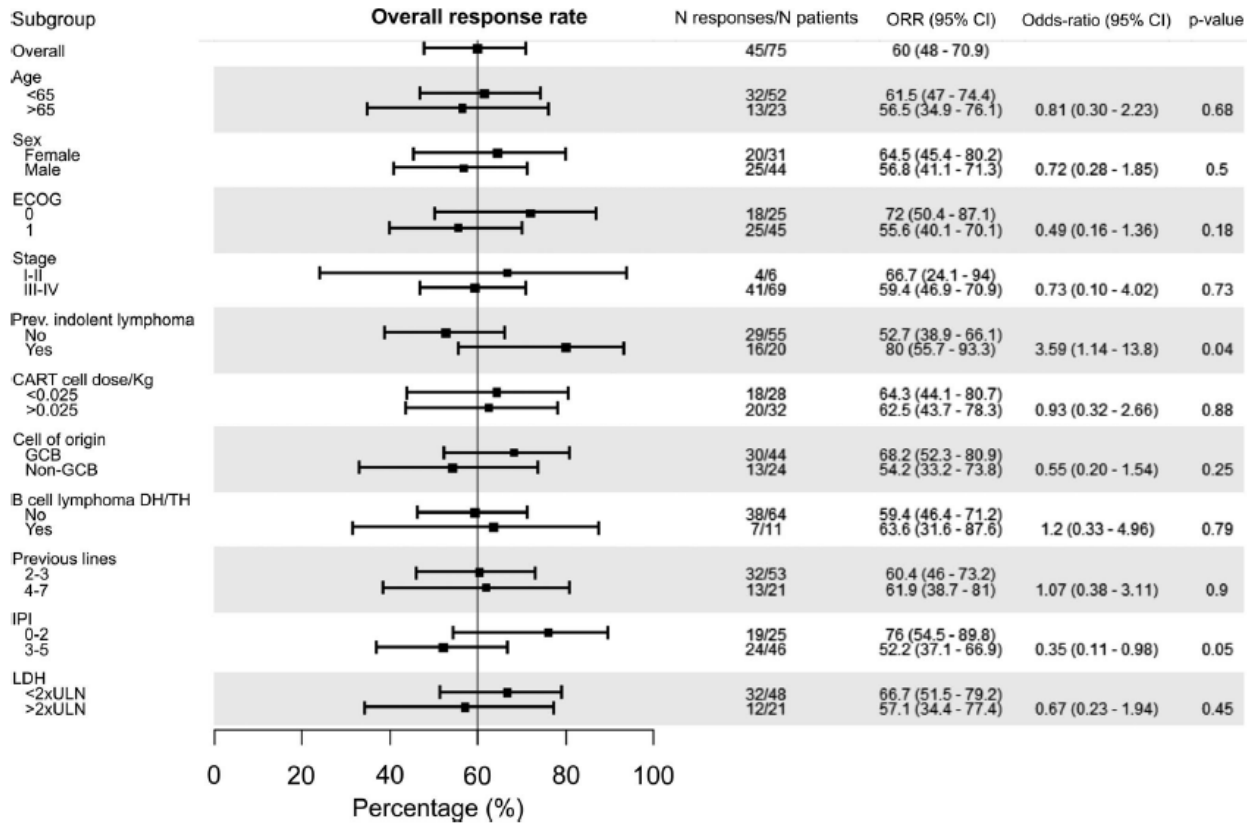

FIGURE 1 Subgroup analysis according to ORR for infused patients. Note: Overall response rate according to baseline patient and disease characteristics

high IPI score and high LDH levels (>2xULN) had a significantly lower PFS in the univariate analysis (Table 3 and Figure 3). Primary refractory disease [HR: 2.24 (95%CI 1.20–4.18), $p = 0.01$] and high LDH levels [HR: 2.18 (95%CI 1.19–3.99), $p = 0.01$] maintained the independent statistical significance in the multivariate model (Table 3).

For OS, patients who were primary refractory, had an ECOG of 1 or higher, high IPI score and high LDH levels were associated with a lower OS in the univariate analysis (Table 3 and Figure 3). In the multivariate analysis, ECOG [HR: 2.80 (95%CI 1.10–7.11), $p = 0.03$] and LDH levels [HR: 2.33 (95%CI 1.14–4.76), $p = 0.02$] remained significantly associated with OS (Table 3).

4 | DISCUSSION

This is the largest study to date focused exclusively on patients with R/R LBCL treated with tisa-cel in the real-world setting. We have shown that CAR T-cell therapy with tisa-cel is feasible outside the US and has a similar safety and efficacy profile to the pivotal clinical trial.[9]

In our study, 91 patients with R/R LBCL underwent leukapheresis for commercial tisa-cel and 75 (82%) patients received an infusion. The median time from apheresis to infusion was similar to the registration trial[9] (54 days vs. 53 days) and in both studies most patients received bridging therapy (92% vs. 87%). This turnaround time is longer than the published real-world data with axi-cel and tisa-cel in the US[11,12,15] but similar to previous tisa-cel reports from European centers.[13,14] Reasons behind this delay would include limited referral experience, reduced number of manufacturing slots, and few European facilities; this could have certainly played a role in the number of patients who dropped out due to disease progression and, even, in the final outcome of the infused patients. This bridging period has gradually improved with the increasing experience of referral sites and a growing number of European manufacturing facilities.

Eight products were considered OOS in our study, mainly due to low cellularity. Low viability, a larger problem in the US, was not as frequent, probably due to the lower EMA limit in comparison with the FDA (70% vs. 80% respectively).[15] In our study, 82% of the patients who underwent apheresis received an infusion; in the pivotal trial[9] only 67% of enrolled patients received an infusion, possibly related to the stricter criteria and the different baseline characteristics, which included a smaller number

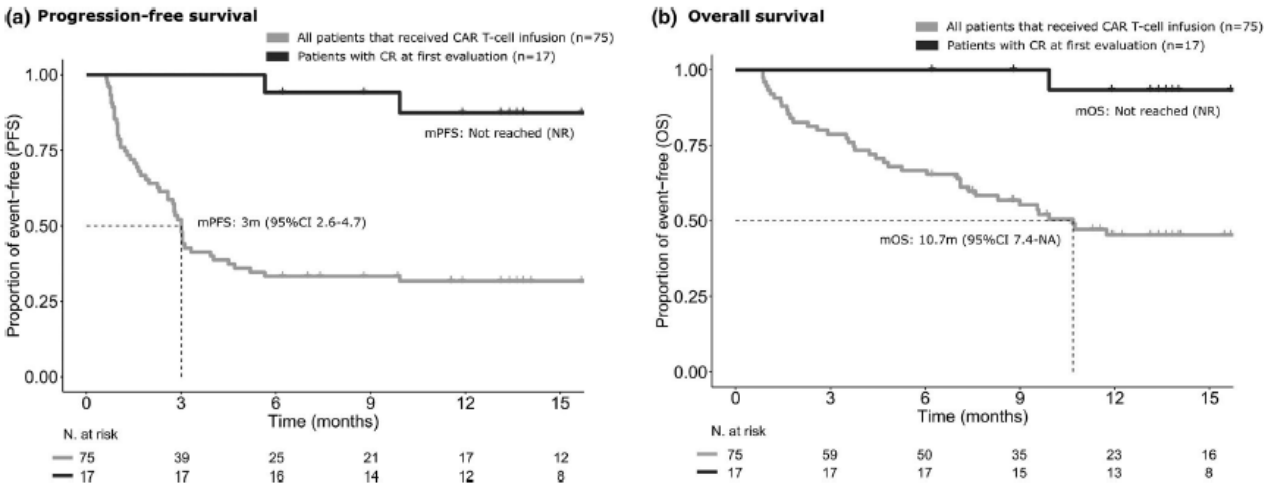

FIGURE 2 PFS (a) and OS (b) for all infused patients and for patients achieving CR at first disease assessment. Note: PFS and OS in infused patients and in patients achieving CR after CAR T-cell infusion

of transformed patients in comparison to our cohort (19% vs. 27%, respectively).

Focusing on the safety analysis, the incidence of severe adverse events, including both CRS (5%) and ICANS (1%), was lower than the JULIET trial (22% and 12%, respectively), taking into account the usual caveats derived from different grading systems.[25,26] Noteworthy, our results were similar to a recent real-world registry-based study including patients with LBCL and acute lymphoblastic leukemia treated with tisa-cel in the US.[15] Reasons behind this trend for a better safety profile in the standard-of-care setting compared with the clinical trial includes an increased use of tocilizumab and steroids[13,15] and more experience in CAR T-cell management.[27] Preliminary data from European centers seem to confirm this lower rate of severe adverse events in the commercial setting.[13,28] The median time to onset of CRS and ICANS was similar between our study and the registration trial (2 vs. 3 days and 7 vs. 6 days, respectively). Patients with primary refractory disease, a higher infused cell dose *per* kg of body weight, an ECOG ≥1 and elevated LDH levels showed an increased risk of developing grade 2 or higher adverse events. In line with the pivotal CAR T-cell trials,[8,9] older age was not associated with an increased risk of grade ≥2 toxicity, suggesting this is a feasible treatment modality for elderly patients with R/R LBCL. There was a 4% of treatment-related mortality in this study; however, all three patients were in progressive disease at the time of these events so this could have played a role in the final outcome.

Efficacy results in our study were similar to the pivotal trial. Interestingly, 12-month PFS for patients who achieved a CR at first disease assessment was 87%, confirming that most patients in this subgroup will maintain their response over time. However, the PR to CR conversion rate was lower in our study than in the pivotal trial[9] (20% vs. 54%). We also observed that patients with a SD or PD as the best response after CAR T-cell therapy represent a high-risk subgroup: the 12-month OS was 14% for patients with PD/SD, in comparison to 28% for patients with PR and 95% for patients with CR. Therefore, patients in CR after tisa-cel therapy seem to have a very good prognosis, with durable remissions in most cases; patients who achieve a PR should be closely monitored during the first 3 months, the highest-risk period, to look out for early signs of progression and start additional therapies as soon as needed.

Patients with high LDH levels had a worse outcome after treatment with tisa-cel. Other studies also identified LDH[11] and high tumor volume, measured on CT[29] or PET scan,[14,30] as clear prognostic factors for disease response after CAR T-cell therapy. Patients with primary refractory disease also had a lower PFS and OS. In line with previous publications, we found no significant efficacy difference for HGBL patients. Taking all this into account, patients progressing after second-line therapy with low tumor burden, a good performance status, and low LDH could potentially benefit most from this treatment.

There are some limitations to this study. The data were collected retrospectively and many of the baseline characteristics were captured before apheresis. Also, disease evaluation was only available previous to lymphodepleting chemotherapy; thus, it was not possible to assess the impact of disease response to bridging treatment as a prognostic factor for the efficacy of CAR T-cell therapy. Longer follow-up is needed to confirm the long-term duration of complete remissions and safety after tisa-cel therapy.

To the best of our knowledge, this is the largest standard-of-care cohort of patients reported to date with tisa-cel for R/R LBCL in a European country. Our results confirm that

TABLE 3 Univariate and multivariate analysis of risk factors for PFS and OS

	Progression-free survival (n = 75, events = 51)				Overall survival (n = 75, events = 39)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (10-years increase)	0.82 (0.65–1.04)	0.10	—	—	0.78 (0.59–1.02)	0.07	—	—
Sex (male vs. female)	1.30 (0.73–2.29)	0.37	—	—	1.37 (0.71–2.64)	0.34	—	—
ECOG (1+ vs. 0)	1.97 (1.06–3.68)	**0.03**	—	—	4.23 (1.75–10.2)	**<0.01**	2.83 (1.12–7.11)	**0.03**
Stage (III-IV vs. I-II)	1.54 (0.55–4.28)	0.41	—	—	2.24 (0.54–9.29)	0.27	—	—
Prev. indolent lymphoma (yes vs. no)	0.89 (0.47–1.67)	0.71	—	—	0.90 (0.44–1.85)	0.78	—	—
Primary refractory (yes vs. no)	2.19 (1.24–3.87)	**<0.01**	1.99 (1.12–3.55)	**0.02**	2.00 (1.04–3.86)	**0.04**	1.79 (0.90–3.56)	0.09
Bulky (>7 cm vs. <7 cm)	1.56 (0.88–2.75)	0.13	—	—	1.86 (0.96–3.58)	0.06	—	—
Cell of origin (Non-GCB vs. GCB)	1.70 (0.93–3.09)	0.08	—	—	1.81 (0.92–3.57)	0.09	—	—
HGBL (yes vs. no)	0.99 (0.45–2.19)	0.98	—	—	1.31 (0.58–2.96)	0.52	—	—
Previous lines	1.05 (0.83–1.33)	0.69	—	—	1.17 (0.88–1.54)	0.28	—	—
IPI score	1.74 (1.30–2.31)	**<0.001**	*	*	1.79 (1.28–2.51)	**<0.001**	*	*
CAR T-cell dose	0.81 (0.58–1.12)	0.21	—	—	0.69 (0.46–1.02)	0.07	—	—
CAR T-cell dose/kg (0.01-units increase)	0.86 (0.68–1.07)	0.18	—	—	0.81 (0.62–1.06)	0.12	—	—
LDH (>2xULN vs. <2xULN)	2.70 (1.53–4.86)	**<0.001**	2.48 (1.40–4.40)	**<0.01**	3.92 (2.08–7.40)	**<0.001**	2.75 (1.38–5.46)	**<0.01**

*IPI score was not included in the multivariate analysis because of the high multicollinearity with other covariates. IPI score and CAR T-cell dose were analyzed as continuous variables.

Abbreviations: CART, Chimeric Antigen Receptor T-cell; ECOG, Eastern Cooperative Oncology Group; GCB, Germinal Center B-cell; HGBL, High-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, Lactate Dehydrogenase; ULN, Upper Limit of Normal.

treatment with tisa-cel in Europe is feasible and has similar results to the pivotal trial.

COMPLIANCE WITH ETHICAL STANDARDS

Ethical approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval was granted by the Vall d'Hebron Hospital Ethical Committee, study identified with code PR(AG)404/2020.

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CONFLICTS OF INTEREST

G.I. declares having received honoraria from BMS/Celgene, Gilead, Novartis, Janssen, and Roche, not related with this article. G.V. reported receiving honoraria for speaker activities from Merck Sharp & Dohme and an advisory role from Astrazeneca. A.M. declares having received Gilead research fundings and honoraria from Novartis and Takeda. JM. S. declares having received honoraria from Roche, Novartis, Gilead, Celgene, Janssen, Takeda, and Incyte; also consulting for Roche, Novartis, Gilead, Celgene, Janssen, Incyte,

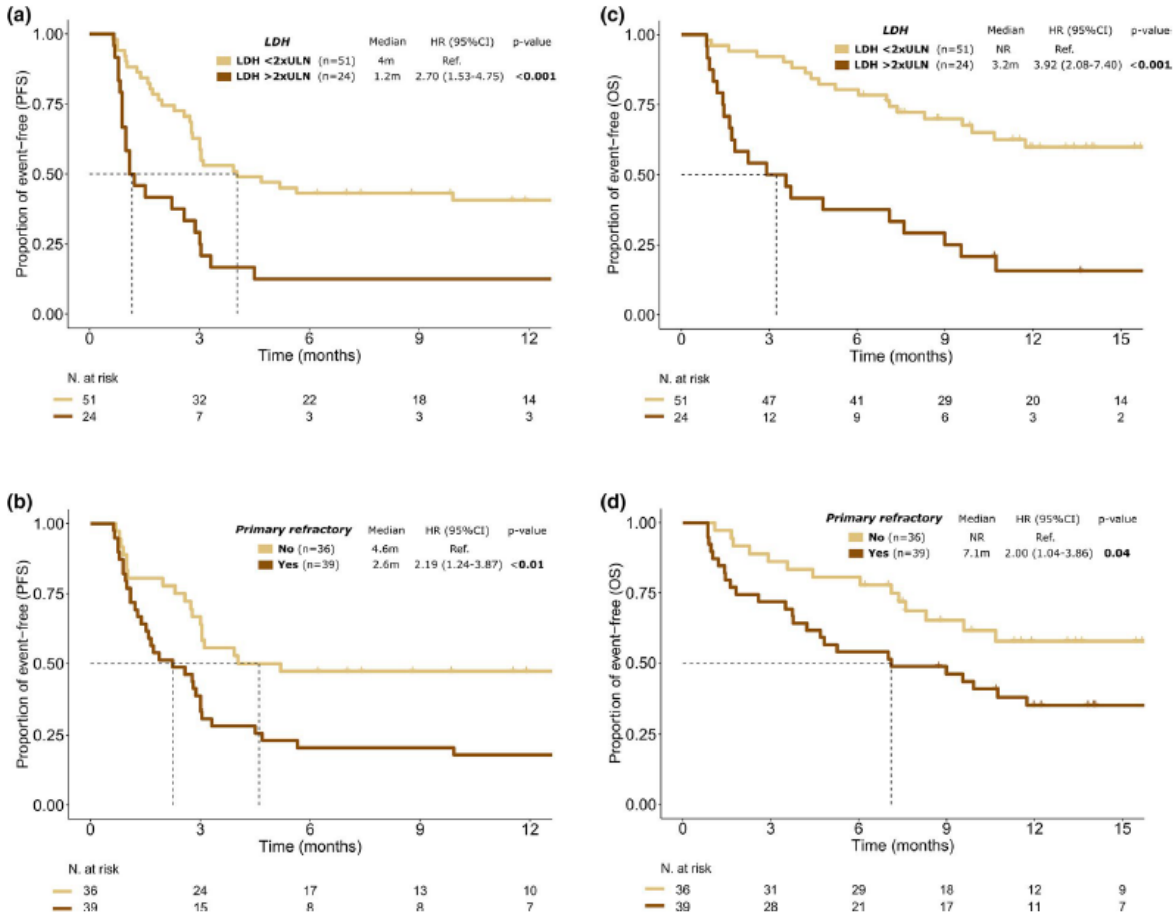

FIGURE 3 Impact of LDH levels and primary refractory disease on PFS and OS of infused patients. Note: Impact of LDH levels on PFS (a) and OS (c); impact of primary refractory disease on PFS (b) and OS (d)

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AUTHORS' CONTRIBUTIONS

Concept and design were undertaken by PB and GI. Data analysis and interpretation were performed by GV, PB, and GI. Collection and assembly of data were performed by all authors. All authors contributed to manuscript writing and final approval of the manuscript, and are accountable for all aspects of the work (ensuring questions related to accuracy or integrity of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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4.2 Second publication

Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of aggressive B-cell lymphoma. Kwon M*, Iacoboni G*, Reguera JL, López Corral L, Hernani Morales R, Ortiz-Maldonado V, Guerreiro M, Caballero AC, Guerra Domínguez ML, Sanchez Pina JM, Mussetti A, Sancho JM, Bastos-Oreiro M, Catala E, Delgado J, Luzardo Henriquez H, Sanz J, Calbacho M, Bailén R, Carpio C, Ribera JM, Sureda A, Briones J, Hernandez-Boluda JC, Martínez Cebrián N, Diez Martin JL, Martín A and Barba P. Haematologica 2022 Jun 30. doi: 10.3324/haematol.2022.280805. Online ahead of print. **co-first authors*

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

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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 $x10^3/\mu L$, median (range)	0.9 (0.1-11)	0.88 (0.1-6.3)	0.9 (0.1-11.0)	0.711
Platelets $x10^3/\mu L$, 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 (%)	211 (81)	118 (88)	93 (73)	**0.003**
CRS grade ≥3, N (%)	19 (7)	11 (8)	8 (6)	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	120 (46)	81 (60)	39 (31)	**<0.001**
Steroids	52 (20)	41 (31)	11 (9)	**<0.001**
ICANS, N (%)	78 (30)	57 (42)	21 (16)	**<0.001**
ICANS grade ≥3, N (%)	30 (11)	24 (18)	6 (5)	**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	2 (1)	2 (1)	0 (0)	**<0.001**
Steroids	65 (25)	48 (36)	17 (13)	**<0.001**
Anakinra	15 (6)	12 (9)	3 (2)	**<0.001**
Siltuximab	14 (5)	11 (8)	3 (2)	**<0.001**
Hospitalization days, median (IQR)	20 (17-27)	22 (20-29)	18 (14-22)	**<0.001**
ICU admission, N (%)	49 (18)	30 (22)	19 (15)	0.154
median stay, days (IQR)	3 (2-7)	4 (2-7)	3 (1-5)	**<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	53 (24)	31 (28)	22 (19)	0.082
Thrombocytopenia grade 3-4	95 (43)	49 (47)	46 (40)	0.278
Persistent cytopenias by day 90, N (%)*				
Neutropenia grade 3-4	12 (10)	6 (10)	6 (10)	1.000
Thrombocytopenia grade 3-4	18 (15)	10 (16)	8 (13)	0.799
Persistent cytopenias by day 180, N (%)*				
Neutropenia grade 3-4	2 (3)	1 (3)	1 (3)	1.000
Thrombocytopenia grade 3-4	4 (6)	3 (8)	1 (3)	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

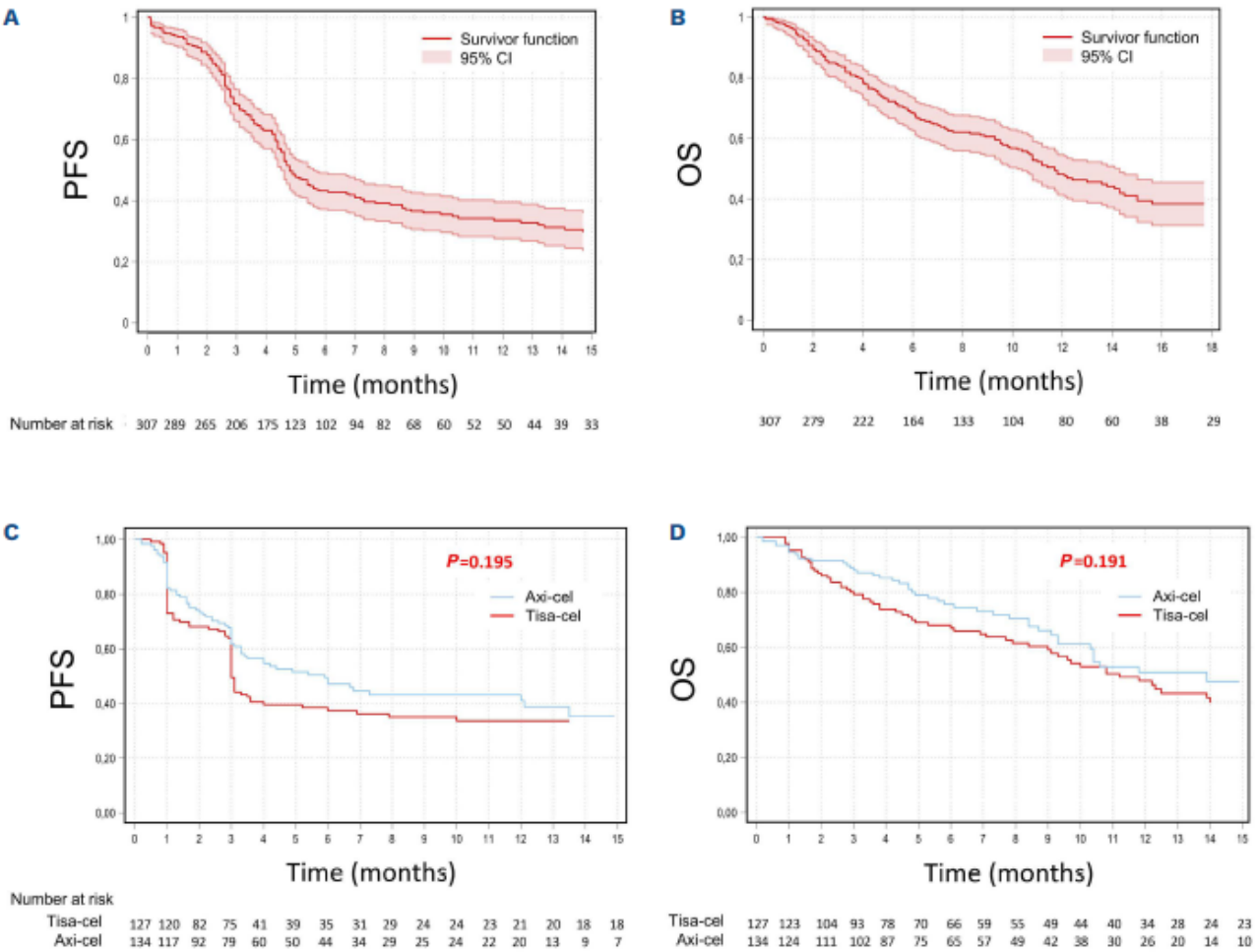

Figure 1. Progression-free survival and overal survival of patients treated with axicabtagene ciloleucel and tisagenlecleucel. (A) Progression-free survival (PFS) from apheresis for the intention-to-treat (ITT) population. (B) Overall survival (OS) from apheresis for the ITT population. (C) PFS from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

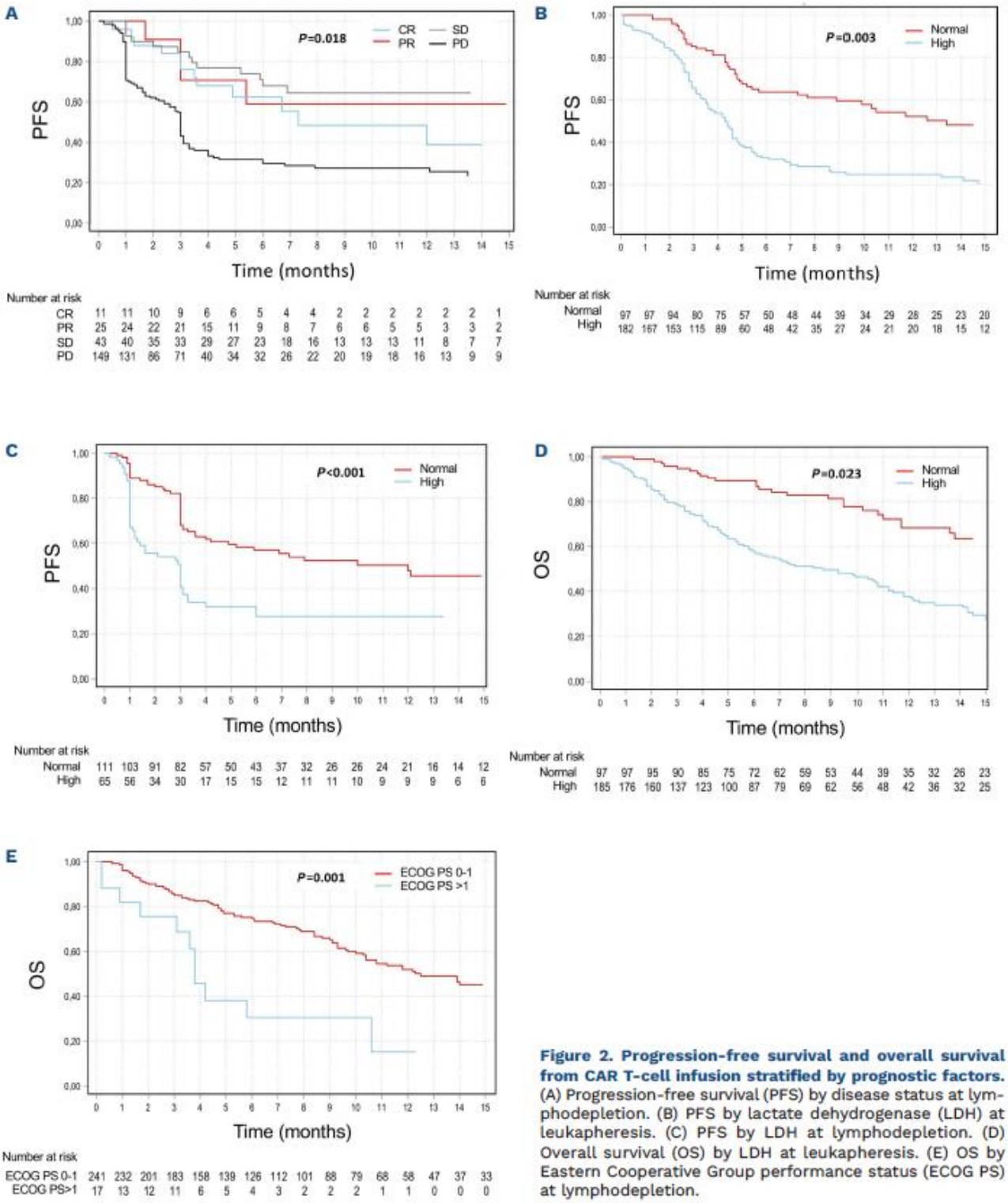

Figure 2. Progression-free survival and overall survival from CAR T-cell infusion stratified by prognostic factors. (A) Progression-free survival (PFS) by disease status at lymphodepletion. (B) PFS by lactate dehydrogenase (LDH) at leukapheresis. (C) PFS by LDH at lymphodepletion. (D) Overall survival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

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4.3 Third publication

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ORIGINAL ARTICLE

Prognostic impact of total metabolic tumor volume in large B-cell lymphoma patients receiving CAR T-cell therapy

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy provides long-term remissions in patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL). Total metabolic tumor volume (TMTV) assessed by 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) has a confirmed prognostic value in the setting of chemoimmunotherapy, but its predictive role with CAR T-cell therapy is not fully established. Thirty-five patients with R/R LBCL who received CAR T-cells were included in the study. TMTV and maximum standardized uptake value (SUVmax) were measured at baseline and 1-month after CAR T-cell infusion. Best response included 9 (26%) patients in complete metabolic response (CMR) and 16 (46%) in partial metabolic response (PMR). At a median follow-up of 7.6 months, median PFS and OS were 3.4 and 8.2 months, respectively. A high baseline TMTV (≥ 25 cm^3) was associated with a lower PFS (median PFS, 2.3 vs. 8.9 months; HR = 3.44 [95% CI 1.18–10.1], p = 0.02). High baseline TMTV also showed a trend towards shorter OS (HR = 6.3 [95% CI 0.83–47.9], p = 0.08). Baseline SUVmax did not have a significant impact on efficacy endpoints. TMTV and SUVmax values showed no association with adverse events. Metabolic tumor burden parameters measured by 18FDG-PET before CAR T-cell infusion can identify LBCL patients who benefit most from this therapy.

Keywords CAR T-cells · Positron emission tomography · Total metabolic tumor volume · Maximum standardized uptake value

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Introduction

The advent of chimeric antigen receptor (CAR) T-cell therapy has changed the treatment paradigm of patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL) who fail two or more lines of systemic therapy [1, 2]. This novel strategy achieves 30 to 40% of durable complete remissions with a manageable toxicity profile [3, 4].

The widening use of CAR T-cell therapy prompted to identify which baseline characteristics selected the patients who would benefit most from this innovative approach, both in terms of safety and efficacy [5, 6]. Baseline tumor burden, assessed through imaging procedures, could potentially have predictive value. Of note, albeit tumor volume measured by 18F-fluorodeoxyglucose positron emission tomography (18FDG-PET) has been identified as a prognostic factor in patients with LBCL receiving immunochemotherapy [7], data in the context of CAR T-cell treatment is scarce and controversial [4, 8, 9]. In addition, the optimal time point

for disease evaluation after CAR T-cell infusion remains to be established; pivotal clinical trials reported the 3-month PET as the key evaluation time point to predict a long-term outcome.

In this study, we assessed the impact of baseline tumor burden, measured with semi-quantitative PET parameters, on response and adverse events in a series of R/R LBCL patients who received CD19-targeted second-generation CAR T-cells with a 4-1BB costimulatory domain from a single institution. Additionally, we analyzed the usefulness of the 1-month PET scan evaluation as a predictor of long-term efficacy outcomes.

Methods

Patient management

We conducted a comprehensive retrospective review of all consecutive patients with R/R LBCL (de novo or transformed from an indolent lymphoma) who received a single infusion of CD19-targeted second-generation CAR T-cells carrying a 4-1BB costimulatory domain from July 2018 to January 2020 at Vall d'Hebron University Hospital. Patients received tisagenlecleucel (tisa-cel) or an investigational second-generation CAR-T product; to avoid breaking confidentiality with the investigational drug data we pooled all products together.

Lymphodepleting (LD) chemotherapy included 3 consecutive days of fludarabine (25–30 mg/m^2/day) and cyclophosphamide (250–300 mg/m^2/day) in all cases. After 2–4 days of washout, patients were admitted to the advanced therapies ward prior to CAR T-cell infusion for a close monitoring of adverse events, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Both CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria [10]. The study was approved by the ethics committee of the Vall d'Hebron Hospital Board.

Disease assessment and evaluation

All patients underwent a PET scan after the last bridging regimen, within 7 days of starting LD chemotherapy. Disease evaluation after CAR T-cell therapy was scheduled at 1, 3, 6, 12, 18, and 24 months after infusion. The imaging reports were based on the Lugano recommendation for response assessment, and PET images were graded according to the 5-point Deauville score [11–14]. Patients achieving a complete metabolic response (CMR, Deauville scores 1–3) or partial metabolic response (PMR) were considered as *responders* to CAR T-cell therapy.

Imaging acquisition and metabolic parameters

The PET/CT exam required a minimum of 6-h fast prior to the intravenous administration of 3.7 MBq/Kg (222–370 MBq) of 18-fluorodeoxyglucose (18F-FDG). Glucose values below 140 mg/dL were required in all cases prior to administration of the radiopharmaceutical. Before scanning, the patients were at rest for a minimum of 60 min. Images were obtained using a Siemens Biograph mCT, which combines a spiral CT of 64 slices (210 keV, 120 mAs, care dose) with a dedicated PET, from the skull to the upper third of both femurs. Acquisition of the images was done after 60 min of the administration of the radiopharmaceutical. The images generated were interpreted by Nuclear Medicine specialists in a syngo.via Siemens Healthcare workstation.

All semi-quantitative parameters, such as standardized uptake value (SUV), and volumetric parameters, such as total metabolic tumor volume (TMTV), from all 18F-FDG PET/CT examinations were reported. Volumetric parameters were calculated using a custom semi-automated workflow in the MIM Encore™ software (MIM Software Inc., Cleveland, OH, USA). TMTV was computed with the 41% maximum standardized uptake value threshold method, as recommended by the European Association of Nuclear Medicine. The maximum SUV, or SUVmax, was defined as the highest SUV value within the metabolically active lesions on the PET scan [15].

Definitions and endpoints

The primary endpoint was progression-free survival (PFS), defined in this study as the time from infusion to progression according to Lugano criteria [11] or death from any cause, whichever happened first. Secondary endpoints were overall survival (OS), defined as the time from infusion to death from any cause or last follow-up, and clinically significant adverse events, defined as grade 2 or higher CRS and/or ICANS in this study.

Statistical analyses

A descriptive analysis of all included variables in the study was performed. Continuous variables were expressed as the median and interquartile range (IQR), and categorical variables were expressed as absolute values and percentages. Survival analysis (PFS and OS) was calculated using the Kaplan–Meier method and the log-rank test was used for statistical comparison. To identify the optimal cutoffs for metabolic parameters, we used the maximally selected log-rank statistics in the PFS analysis. In this method, we

looked at all possible cutoff points and selected the cutoff that maximized the log-rank statistic [16]. Furthermore, to analyze the association between continuous TMTV and survival outcomes, we relaxed the linearity assumption using restricted cubic splines by means of *rms* R package [17]. Univariate Cox proportional-hazard models were used to obtain hazard ratios (HR) with 95% CIs. To assess the 1-month evaluation, we performed a landmark analysis using the date of 1-month evaluation in non-progressor patients [18]. Categorical variables were studied using the Fisher exact test. Median follow-up was calculated using the reverse Kaplan–Meier method. No data imputation was performed. The data analyses were carried out using R statistical software version 3.6.2.

Results

Patient characteristics and outcome

Thirty-five consecutive patients with R/R LBCL who received CAR T-cell therapy were included in the study. Patients' baseline characteristics are summarized in Table 1. The median age at treatment was 58 years, and 74% were male. At the time of CAR T-cell therapy, most of them had an advanced stage of disease (74%). The median number of prior lines of therapy was 3 (IQR 2–3), and 11 patients (31%) had undergone a previous autologous stem cell transplant (ASCT). The median time between the last day of bridging therapy and the pre-treatment PET scan was 16 days (IQR 14–28).

Best response after CAR T-cell therapy included 9 (26%) patients in CMR and 16 (46%) in PMR. Ten (28%) patients were in progressive metabolic disease (PMD) at the 1-month disease evaluation. The median follow-up was 7.6 months. Median PFS and OS were 3.4 months (95% CI 2.5–3.7) and 8.2 months (95% CI 6.4–NA), respectively.

Regarding toxicity, eleven (31%) patients developed clinically significant CAR-T-related adverse events, as defined above. Seven (20%) and 6 (17%) patients presented grade ≥ 2 CRS and grade ≥ 2 ICANS, respectively.

Impact of baseline metabolic parameters on CAR T-cell efficacy and toxicity

All patients included in this analysis had measurable disease before lymphodepleting chemotherapy, according to the pre-treatment PET scan. Median baseline TMTV was 119 cm^3 (IQR 32–300) and median SUVmax was 24 (IQR 17–32).

Regarding disease response to CAR T-cell therapy, patients who responded showed a weak trend towards lower median baseline TMTV values compared with non-responders (median of 63 cm^3 vs 160 cm^3, p = 0.17) (Fig. 1). No

Table 1 Baseline patient and disease characteristics

Characteristics	N = 35
Median age, years (IQR)	58 (50–68)
Age, ≥ 65 years, n (%)	13 (37)
Gender, male, n (%)	26 (74)
Disease stage before CAR T-cell therapy	
- Stages I–II, n (%)	9 (26)
- Stages III–IV, n (%)	26 (74)
Previous lines of treatment, > 2, n (%)	22 (63)
Previous ASCT, n (%)	11 (31)
ECOG, median (IQR)	1 (0–1)
Primary refractory, n (%)	21 (60)
Median LDH × ULN (IQR), U/L	1.77 (1.27–3.85)
IPI prognostic score, n (%)#	
- 0–2	14 (40)
- 3–5	20 (57)
Bulky disease (> 7 cm), n (%)	18 (51)
Histology, n (%)	
- Transformed from indolent lymphoma	11 (31)
- DLBCL de novo	18 (51)
- High-grade B-cell lymphoma (DH/TH)	6 (17)
Cell of origin, n (%)	
- GCB	19 (54)
- Non-GCB	12 (34)
- Not available	4 (11)
Bridging therapy, n (%)	30 (86)

Abbreviations: Autologous stem cell transplant (ASCT); International Prognostic Index (IPI); Eastern Cooperative Oncology Group (ECOG); lactate dehydrogenase (LDH); germinal center B-cell (GCB); diffuse large B-cell lymphoma (DLBCL); double hit/triple hit (DH/TH); upper limit of normal (ULN)

#The IPI score was unavailable for one patient

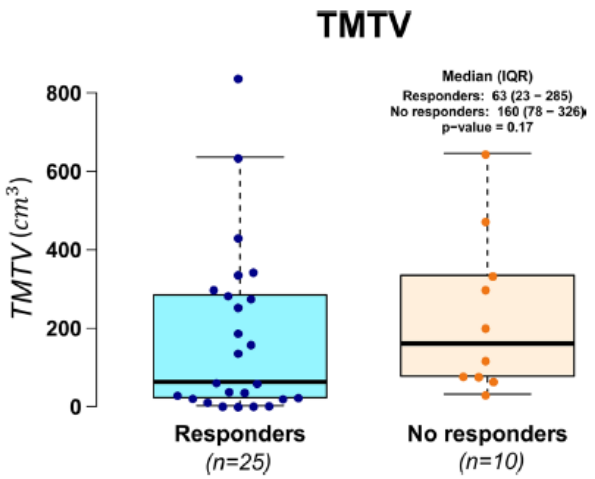


Fig. 1 Impact of baseline total metabolic tumor volume (TMTV) on 1-month treatment response

Table 2 Impact of baseline and 1-month metabolic parameters on patients' outcome

	Progression-free survival (PFS)			Overall survival (OS)		
A	Baseline metabolic parameters to predict patients' outcome (all patients) (n = 35)					
	Median PFS	HR 95% CI	P value	Median OS	HR 95% CI	P value
TMTV						
Low < 25 cm^3 (n = 8)	8.9 m	Ref	-	NR	Ref	-
High ≥ 25 cm^3 (n = 27)	2.3 m	3.44 (1.18–10.10)	0.02	7.2 m	6.3 (0.83–47.90)	0.08
SUVmax						
Low < 20 (n = 12)	3.5 m	Ref	-	8.2 m	Ref	-
High ≥ 20 (n = 23)	3.4 m	1.63 (0.71–3.76)	0.25	8.5 m	1.1 (0.38–3.20)	0.87
B	1-month metabolic parameters to predict patients' outcome (PMR patients) (n = 17)					
	Median PFS[a]	HR 95% CI	P value	Median OS[a]	HR 95% CI	P value
TMTV *(at 1-month)*						
Low < 9 cm^3 (n = 6)	2.3 m	Ref	-	NR	Ref	-
High ≥ 9 cm^3 (n = 11)	1.8 m	3 (0.92–9.80)	0.07	10.7 m	0.91 (0.10–9.10)	0.94
SUVmax *(at 1-month)*						
Low < 9 (n = 8)	2.3 m	Ref	-	NR	Ref	-
High ≥ 9 (n = 9)	1.7 m	4.6 (1.40–15.50)	0.01	5.9 m	4.3 (0.50–37.20)	0.19

[a]In B, median PFS and median OS were calculated from the 1-month evaluation date

Abbreviations: *TMTV* total metabolic tumor volume, *SUVmax* maximum standardized uptake value, *m* months, *NR* not reached

association was found between baseline SUVmax and disease response (25 vs 21, p = 0.21) (Supplementary Fig. 1).

In this study, a high baseline TMTV was defined as ≥ 25 cm^3 (see "Statistical analyses"). In terms of PFS, a high baseline TMTV was associated with a shorter PFS compared to patients with low TMTV values (median PFS, 2.3 months vs. 8.9 months; HR 3.44 [95% CI 1.18–10.1], p = 0.02) (Table 2 and Fig. 2A). No association was found between SUVmax values and PFS (Table 2).

As to OS, patients with high baseline TMTV (≥ 25 cm^3) showed a trend towards shorter OS (HR 6.28 [95% CI (0.83–47.9)], p = 0.08) (Fig. 2B). The shape of the association between TMTV and survival outcomes after relaxing the linearity assumption for continuous variables is showed in Supplementary Fig. 2. Again, no association was found between baseline SUVmax values and OS (Table 2).

Baseline TMTV and SUVmax values were not significantly associated with grade ≥ 2 CRS and ICANS, or clinically significant CAR-T-related toxicity in general (Supplementary Table 2). The proportion of grade ≥ 2 toxicity in patients with high baseline TMTV was 33.3% compared with 12.5% in those with low TMTV (p = 0.39). Regarding

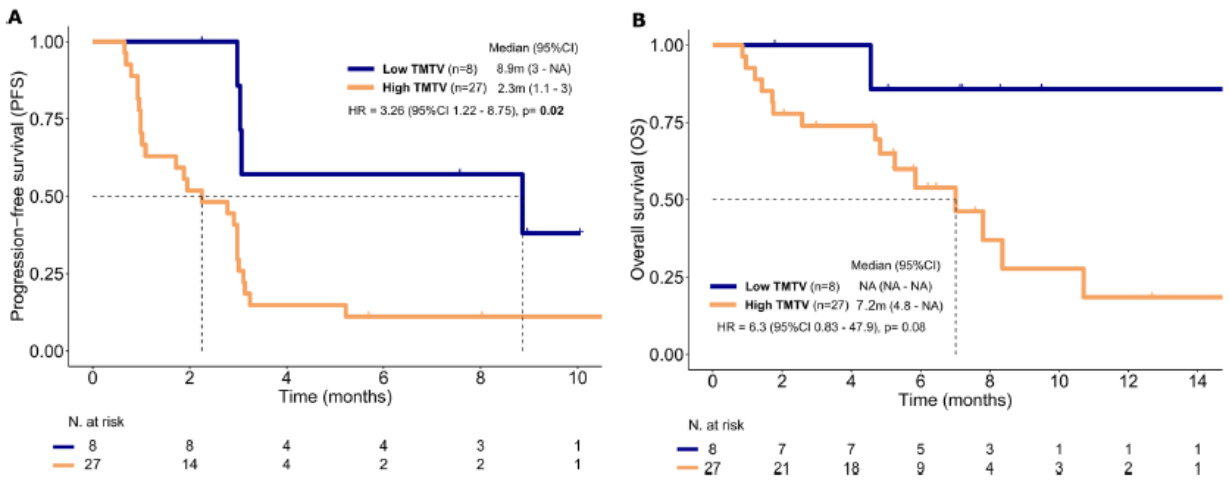


Fig. 2 Impact of baseline metabolic tumor volume (TMTV) on progression-free survival (PFS) and overall survival (OS)

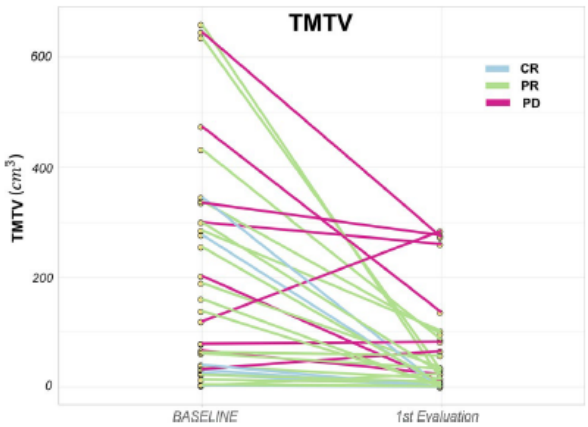


Fig. 3 Individual metabolic tumor volume (TMTV) changes between baseline and the 1-month disease evaluation

SUVmax, the proportion of adverse events in patients with low (< 20) and high (≥ 20) values was 33.3% vs 26.1%, (p = 0.71), respectively.

Impact of 1-month disease evaluation on patient outcomes and on redefinition of partial responses

All patients underwent a 1-month post-infusion PET scan evaluation. Disease response at this time point was as follows: CMR (n = 8, 23%), PMR (n = 17, 49%), and PMD (n = 10, 28%) (Supplementary Table 1). Among the patients in CMR at 1 month, 4 of them eventually relapsed (2 at 3 months, 1 at 5 months, and 1 at 9 months after infusion). One (6%) patient in PMR at 1-month converted to CMR at the 3-month evaluation.

Probability of PFS at 6 months (6 m-PFS) for patients in CMR and PMR at 1-month was 62.5% and 12.7%, respectively, (HR = 3.89, p = 0.02). Changes in TMTV between baseline and the 1-month assessment for each patient can be visualized in Fig. 3.

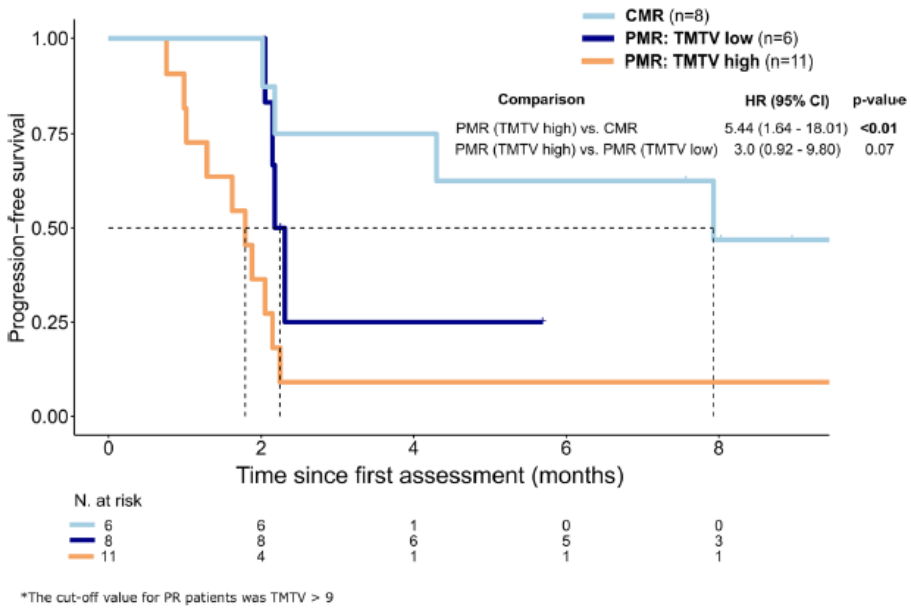
Regarding the patients attaining a PMR at the 1-month evaluation (n = 17), the median TMTV at this time point was 25 cm^3. Patients in PMR with low TMTV (< 9 cm^3) and high TMTV (≥ 9 cm^3) had a 6 m-PFS of 25% and 0%, respectively (HR = 3 [95% CI 0.92–9.8], p = 0.07) (Fig. 4). Importantly, in these PMR patients, the 1-month SUVmax values predicted PFS and a trend towards significance was observed for the TMTV values (Table 2B).

Discussion

The current study evaluated the prognostic impact of pre-treatment PET parameters on the outcome and adverse events of LBCL patients receiving a second-generation CAR-T with a 4-1BB costimulatory domain. Baseline metabolic parameters, especially TMTV, showed a weak correlation with disease response and were predictive of PFS; no association was found with adverse events. Metabolic tumor volume at the 1-month assessment was prognostic in terms of PFS and seemed to contribute to identify patients in PR harboring a better long-term outcome.

Previous studies have shown the prognostic impact of tumor burden, quantified by baseline TMTV, in LBCL patients who receive treatment with chemoimmunotherapy [19–21]. Recently, Vercellino et al. [7] reported that baseline

Fig. 4 Progression-free survival (PFS) according to metabolic tumor volume (TMTV) at 1-month post-infusion in responding patients



*The cut-off value for PR patients was TMTV > 9

TMTV, in LBCL patients who achieved a CMR or PMR after R-CHOP, had a significant prognostic impact in terms of PFS and OS. Similarly, studies including patients with other types of lymphoma also identified the prognostic role of baseline TMTV [22]. More limited data is available on the impact of baseline PET parameters on safety and efficacy after CAR T-cell therapy. Regarding efficacy, patients included in the JULIET trial did not show significant differences in outcome irrespective of baseline TMTV, but another cutoff could have yielded different results. In another study with 19 non-Hodgkin lymphoma patients treated with a 4-1BB second-generation CAR-T, TMTV did not have a significant impact on treatment response or overall survival. Recently, two larger studies analyzed the impact of TMTV in the CAR T-cell setting, one with 96 LBCL patients treated with axicabtagene ciloleucel (axi-cel) and the second with 116 patients who received either axi-cel or tisa-cel; both studies confirmed an impact on PFS and OS [9, 23]. In our study, conducted exclusively with CD19/4-1BB constructs, we observed that patients harboring higher baseline TMTV values (≥ 25 cm^3) had a poorer disease response and a shorter PFS. Even though we identified a trend between TMTV and OS, results were not significant, maybe influenced by the short follow-up. The different results observed in these studies could be related to the intrinsic differences between the costimulatory domains and the number of patients included in each one.

The TMTV cutoffs identified in our study were low, which is not surprising considering most of these patients received bridging therapy prior to the pre-treatment PET scan; nevertheless, the optimal cutoff values remain to be defined in future studies. Despite this low pre-treatment tumor burden, the outcomes of these patients were not as good as expected when compared to real-world data studies [9, 24, 25]. Reasons behind this discrepancy are beyond the scope of this study, but this was the first set of patients who received CAR-T at our center; there was a reduced number of manufacturing slots and most of the patients were heavily pre-treated (63% had more than 2 prior lines of treatment); this could have certainly played a role in the final outcome of the infused patients.

Regarding safety, we did not find any association between any of these PET parameters and the development of CRS or ICANS, as was suggested in previous studies [8, 23]. However, our analysis could have been underpowered due to the limited number of patients included and the low number of grade ≥ 2 adverse events in patients receiving 4-1BB CAR T-cells.

Considering there is no clear consensus on when is the best time to perform disease assessment after CAR-T cell infusion with 4-1BB constructs in patients with lymphoma, we decided to explore the response analysis on the first 1-month post-infusion evaluation and found that it was highly discriminative of patients' outcome. In a previous study with 7 patients who received tisa-cel, metabolic response assessed at 1-month post-infusion was correlated with long-term survival [26]. Of note, registration trials focused on the 3- and 6-month results, although they also included a disease assessment at 1-month post-infusion and described a high PMR to CMR conversion rate from the 1 to the 3-month evaluation. In contrast to what is described in registration trials, we did not identify a significant response improvement over time; only 1 patient converted from PMR to CMR at 3 months; the rest of PMRs progressed except 1 who remained in PMR at data cutoff, at 1-year post-infusion. A higher number of patients and longer follow-up is needed to fully evaluate the high number of initial partial responses in our cohort which eventually progressed. Metabolic parameters such as TMTV could help redefine the 1-month PET response, currently based solely on uptake according to the Deauville score (Lugano criteria). We observed that patients in partial remission with a low TMTV (< 9 cm^3) at the 1-month PET scan had a longer PFS compared to those with high TMTV (≥ 9 cm^3). Despite the limited number of patients, this exploratory analysis could be clinically meaningful to foresee which patients could have an increased risk of progressing and requiring further therapy. This could be improved by combining the PET scan with other parameters to increase the prognostic accuracy. Thus, an original approach would be measuring circulating tumor DNA (ctDNA) after CAR T-cell infusion [27, 28]. Frank et al. [29] reported in a 50-patient cohort that detectable ctDNA 28 days after axi-cel treatment was associated with a poor outcome and was a more specific tool than PET. Nevertheless, in the same study, PET-negative patients demonstrated an improved median PFS and OS; day 28 MRD status proved particularly helpful in identifying high-risk patients who had a 1-month PMR or no metabolic response.

There are some limitations to our study. First, our results can only be applied taking into consideration the TMTV before the start of lymphodepleting chemotherapy and not at the time of apheresis, since the former was the only time point where the disease was assessed in this study. Hence, it was not possible to determine if a more intensive bridging regimen, leading to a lower disease burden at the time of lymphodepleting chemotherapy, would have been an optimal strategy to improve patients' outcome. Other limitations of the study derive from the sample size and its retrospective nature.

In conclusion, baseline TMTV seems to carry a prognostic impact on best response and PFS in patients with LBCL receiving CAR T-cell therapy; we did not identify a significant impact on the development of clinically significant adverse events. The implementation of these metabolic tumor burden parameters in the future could improve patient selection, focusing on patients with low values who have a higher chance of response and could potentially benefit most from this therapy. This could spare the high-burden group of patients from

undergoing a treatment with significant potential toxicity and low expected efficacy, with an additional financial impact. The 1-month TMTV values were also significantly associated with patient outcome and could identify patients in PMR harboring a dismal prognosis who require closer follow-up and early treatment intervention.

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Author contributions Concept and design were undertaken by PB, GI, and MS. Data analysis and interpretation were performed by GV, MS, PB, and GI. Collection and assembly of data were performed by GI, PB, CC, and EC. All authors contributed to manuscript writing and final approval of the manuscript, and are accountable for all aspects of the work (ensuring questions related to accuracy or integrity of the work are appropriately investigated and resolved).

Declarations

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

Conflict of interest G.I. declares having received honoraria from Celgene, Gilead, Novartis, and Roche, not related with the present article. G.V. reported receiving honoraria for speaker activities from Merck Sharp & Dohme and advisory role from Astrazeneca. E.C. declares having no conflict of interest. C.C. declares having received honoraria from Takeda and Regeneron, not related with the present article. C. D-L declares having received honoraria from Celgene and Novartis, not related with the present article. A.V.J. received funding from Fondo de Investigaciones Sanitarias and Instituto de Salud Carlos III (FIS PI17/02162); and has engaged in consulting and/or participated as speaker in events organized by Novartis, Roche, Teva, Mylan, Biogen, Merck, and Sanofi. A.P. declares having no conflict of interest. M.J. declares having no conflict of interest. P.A. declares having received honoraria from Celgene, Gilead, Janssen, Abbvie, and Roche, not related with the present article. F.B. declares having received honoraria from Celgene, Gilead, Novartis, Pfizer, and Roche, not related with the present article. P.B. declares having received honoraria from Amgen, Celgene, Gilead, Incyte, Jazz Pharmaceuticals, MSD, Novartis, Pfizer, and Roche, not related with the present article. P.B. received funding from the Carlos III FIS16/01433 Health Institute, Asociación Española contra el Cáncer (Ideas Semilla 2019) and a PERIS 2018–2020 grant from the Generalitat de Catalunya (BDNS357800).

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5 OVERALL SUMMARY OF RESULTS

Since the approval of axi-cel and tisa-cel in the third-line setting for R/R LBCL patients, the prognosis of this population has significantly improved. However, only 40% of infused patients will have a durable remission. The registration trials ZUMA-1 and JULIET included a limited number of patients and had substantial differences in trial design, precluding the possibility of a direct comparison and identification of predictive factors for treatment safety and efficacy.

In the first manuscript presented in this Doctoral Thesis, *Real-world evidence of tisagenlecleucel for the treatment of relapsed or refractory large B-cell lymphoma,* we collected retrospective data on all patients who carried out an apheresis with intent to manufacture tisa-cel from December 2018 until June 2020. We included 91 patients from 10 Spanish sites, of whom 75 (82%) received the CAR T-cell infusion. Main reason for drop out was disease progression (69%). Regarding baseline characteristics, a large proportion of infused patients had an advanced stage of disease (92%), a high risk IPI score (62%) and were primary refractory to previous lines of treatment (52%). Also, most of the patients required bridging therapy (87%).

In terms of toxicity, 71% and 15% developed any grade of CRS and ICANS, respectively. Grade ≥3 adverse events, according to ASTCT grading criteria, occurred in 4 (5%) patients and 1 (1%) patient, respectively. Thirty-two percent of patients required tocilizumab and 21% steroids to manage these adverse events. Thirteen percent of infused patients were admitted to the intensive care unit. Treatment-related mortality was 4% (n=3), with 2 cases of infection and 1 of macrophage activation syndrome. Given the small number of severe adverse events, a univariate analysis was carried out to determine risk factors for CRS and/or ICANS grade 2 or higher: an ECOG ≥1, primary refractory disease, LDH levels >2xULN and a higher infused cell dose per kg of body weight were identified as risk factors.

Regarding efficacy in infused patients, the overall and complete response rate was 60% and 32%, respectively. Patients who received an out-of-specification product, mainly due

to low cellularity (75%), presented similar outcomes to the rest of the cohort. Median duration for responding patients, including CMR and PMR, was 8.9 months. Concerning patients in PMR, 20% converted to a CMR with extended follow-up. Patients with a high IPI score (>2) presented a lower chance of responding to therapy. On the other hand, patients with a previous history of indolent lymphoma had an increased overall response rate. Other baseline characteristics associated with higher CMR rates were a good performance status and low LDH values (<2xULN). Harboring a HGBL histology, presence of adverse events grade 2 or higher, use of tocilizumab and/or steroids did not impact the ORR rate. Progression-free survival at 12 months was 32% for the full cohort and 87% for patients in CMR at first disease assessment, 1 month after cell infusion. Regarding multivariate analysis for survival outcomes, primary refractory disease and increased LDH levels showed a significant negative impact on PFS, whereas ECOG ≥1 and higher LDH levels had a significant impact on OS.

In the second manuscript included in this Doctoral Thesis, *Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of aggressive B-cell lymphoma,* we attempted to further analyze commercially-approved CAR T-cell outcomes in a larger cohort including both available constructs, axi-cel and tisa-cel. All patients with relapsed/refractory DLBCL (*de novo* or transformed from an indolent histology) and HGBL who underwent apheresis from November 2018 to August 2021 at 12 Spanish centers were included.

Of the 152 and 155 patients who underwent lymphocyte apheresis for axi-cel and tisa-cel, respectively, 134 (88%) and 127 (82%) received the CAR T-cell infusion in each case; main reason for drop out was disease progression. Median time from apheresis to infusion was 41 days for axi-cel and 52 days for tisa-cel (p=0.006). Of the infused patients, 80% received bridging therapy (BT), chemotherapy-based in most patients (60%). Only a minority of patients (14%) achieved a complete or partial response to BT.

Baseline characteristics for both cohorts did not present significant differences. Regarding all patients who underwent apheresis, a large proportion of patients had an advanced stage of disease (76%), a high-risk IPI score (>2, 49%), were primary refractory to chemotherapy (58%) and had increased LDH (60%) and C-reactive protein (50%) values at time of treatment.

In terms of toxicity, any grade of CRS and ICANS occurred in 81% and 30% patients, respectively. Median time to onset was 2 days for CRS and 7 days for ICANS. Severe adverse events, defined as grade ≥3 CRS and ICANS, occurred in 7% and 11%, respectively. Persistent grade ≥3 cytopenias, at 3 months post-infusion, included neutropenia in 10% and thrombocytopenia in 15% of patients. Treatment-related mortality was 5%, mainly driven by infections.

In terms of significant differences between the axi-cel and tisa-cel safety profile, patients who received the former presented higher rates of CRS, any grade (p=0.003), and ICANS, any grade (p<0.001) and grade ≥3 (p=0.001). Use of anti-cytokine drugs and steroids for adverse event management was more frequent in the axi-cel group as well. This translated into a longer hospital stay (p<0.001) and a higher rate of infections during the first 6 months (p=0.033) for patients who received axi-cel. In the multivariate analysis, patients with a pretreatment ECOG ≥2 had an increased risk of severe CRS (p=0.046), while receiving axi-cel (p=0.027) and having received more previous lines of treatment (p=0.015) increased the risk of severe ICANS.

Concerning efficacy outcomes for the full infused cohort, 38% and 19% achieved a CMR and PMR, respectively. Median duration of response was 14.1 months for responding patients and not reached for patients who achieved a CMR, without significant differences between axi-cel and tisa-cel (p=0.494). In the modified intention-to-treat analysis, the estimated 12-month PFS and OS was 41% and 51% for axi-cel, 33% and 47% for tisa-cel, respectively (p=NS). In the multivariate analysis, patients with an

increased LDH, an ECOG ≥2 and progressive disease as best response to BT presented a significantly shorter PFS. Regarding OS, an increased LDH, an ECOG ≥2 and refractory disease at time of apheresis had a negative prognostic impact.

In the third manuscript included in this Doctoral Thesis, *Prognostic impact of total metabolic tumor volume in large B-cell lymphoma patients receiving CAR T-cell therapy,* we collected retrospective data on 35 patients with relapsed/refractory large B-cell lymphoma who received a 4-1BB CAR-T at Vall d'Hebron Hospital from July 2018 to January 2020 and had measurable disease in the pretreatment PET scan. In terms of baseline characteristics, most patients had an advanced stage of disease (74%), more than 2 previous lines of treatment (63%), primary refractory disease (60%), increased LDH levels (median 1.77 x ULN), high-risk IPI score (>2, 57%) and bulky disease (> 7cm, 51%). Bridging therapy was necessary in 86% of infused patients.

Seven (20%) and 6 (17%) patients developed grade ≥2 CRS and ICANS, respectively. Regarding efficacy, 9 (26%) patients achieved a CMR and 16 (46%) a PMR as best response after infusion. With a median follow-up of 7.6 months, median PFS and OS were 3.4 months (95% CI 2.5–3.7) and 8.2 months (95% CI 6.4–NA), respectively.

We analyzed the impact of baseline metabolic parameters on efficacy and toxicity outcomes. Median baseline total metabolic tumor volume (TMTV) of the full cohort was 119 cm^3 (IQR 32–300) and median standardized uptake value (SUVmax) was 24 (IQR 17–32). Patients who responded to CAR T-cell therapy (CMR or PMR) showed a trend for lower median pretreatment TMTV values (63 cm^3 vs 160 cm^3, p = 0.17), without significant differences in SUVmax (p = 0.21). Regarding survival outcomes, patients with a high baseline TMTV (≥25 cm^3) presented a shorter PFS (HR 3.44 [95% CI 1.18–10.1], p= 0.02) and a trend for a shorter OS (HR 6.28 [95% CI 0.83–47.9], p= 0.08) than patients with lower pretreatment values. The baseline value of SUVmax showed no impact on

survival outcomes. In terms of grade ≥2 adverse events, there were no significant differences regardless of baseline TMTV (p=0.39) or SUVmax (p=0.71).

Finally, we analyzed the impact of the metabolic parameters at the first disease assessment, carried out 1 month after CAR T-cell infusion. Patients who achieved a CMR (23%) or PMR (49%) at this time point had a 6-month PFS of 62.5% and 12.7% (p=0.02), respectively. Focusing on the PMR patients, PFS was significantly shorter for patients with high 1-month SUVmax values (≥9, p=0.01) and a trend was observed for patients with high TMTV (≥ 9 cm^3, p=0.07). Neither of these parameters had a significant association with OS.

6 OVERALL SUMMARY OF THE DISCUSSION

Patients with relapsed/refractory large B-cell lymphoma had a dismal prognosis before the advent of CAR T-cell therapy(49). The registration trials for axi-cel and tisa-cel included a limited number of patients, mainly in the US, and patient selection was based on strict inclusion and exclusion criteria(83, 84). Results outside the context of clinical trials, in a broader range of countries and hospital settings, are mandatory to confirm the real potential of these novel therapies. With this objective we conducted the 3 studies included in this Doctoral Thesis.

In the first paper, we analyzed the outcomes of all patients who underwent apheresis with intent to manufacture commercial tisa-cel at 10 centers, from its first availability in Spain in December 2018, until data cutoff in June 2020. We included 91 patients, of whom 75 finally received the cell infusion. The 18% drop out rate, mainly driven by lymphoma progression, was lower compared with the pivotal trial (33%), taking into account that the time from apheresis to infusion was similar (53 vs 54 days) (84, 120). Other real-world European studies, published after this one, observed a similar median turnaround for tisa-cel (75, 126) albeit US data showed a significant shorter turnaround (124). The lack of experience in patient selection and low number of European manufacturing facilities could have contributed to these observations and even played a role in the final outcomes of infused patients. As could be expected with a high-risk patient population and long manufacturing period, most patients required bridging therapy (BT). Unfortunately, the impact of BT response on CAR T-cell outcomes was not available.

Regarding the toxicity profile, rates of grade ≥3 adverse events in our series were lower than the JULIET data but the different grading scales used in each study precludes making a direct comparison (121, 168). In fact, our safety results are similar to real-world US and European tisa-cel data(75, 124, 126, 131). This improvement is probably related to an earlier use of tocilizumab and steroids, together with increased experience in patient selection and adverse event management. Noteworthy, the favorable safety

profile makes this product a candidate for outpatient management and, in fact, this is standard practice at some centers(125, 169). The lower hospital resource utilization and associated costs with tisa-cel, in comparison to other commercial products such as axi-cel, should be taken into account when planning for this therapy(170).

We analyzed the pretreatment patient and disease-related factors with a potential impact on development of grade ≥2 CRS and/or ICANS. We identified a higher CAR T-cell dose, chemotherapy-refractory disease, a PS ≥1 and increased LDH levels as risk factors for clinically significant adverse events; age did not increase this risk, making this therapeutic option an attractive alternative for elderly patient who are not candidates for an auto-HCT or other intensive treatment regimens.

Regarding efficacy outcomes, patients who achieved an early CMR had a high-rate of durable remissions at 1-year post-infusion, supporting the curative potential of this treatment. However, only 20% of patients in PMR at the first disease evaluation eventually converted to CMR at a later timepoint. This is significantly lower than the 54% conversion rate reported in the JULIET trial(84). This difference could be related to the fact that the registration trial used a CT scan evaluation at 1-month and PET scan at the 3-month assessment, so many patients labeled as PR in the first evaluation because of residual morphologic lesions could have already been in CMR, had a metabolic assessment been available. In any case, most of the patients in PMR at 1-month post-infusion will progress early, in the first 3-6 months, and should therefore be monitored closely to plan for salvage treatment as soon as progression is suspected.

In terms of prognostic factors for response, chemo-refractory disease, a PS ≥1 and increased LDH levels had a significant negative impact on survival outcomes. Noteworthy, many of these factors overlap with those impacting safety and can help us identify the subgroup of patients with a highest chance of benefitting long-term from tisa-cel therapy.

There are several limitations to the study, beyond its retrospective nature and limited follow-up. One of the main issues is the lack of data on bridging outcomes and how this impacted CAR T-cell responses. It has to be taken into consideration that most patients were referred from non-infusing sites, so the pre-apheresis PET scan was carried out at the referral site and the pre-LD scan at the infusing site, precluding a direct comparison. Data on pretreatment tumor burden, such as the total metabolic tumor volume (TMTV) was not assessed; presence of bulky disease (>7 cm) at the pretreatment PET/CT scan was the only available information, together with LDH as a surrogate marker. Therefore, more precise data on tumor burden are warranted.

In the second study of this Doctoral Thesis, we analyzed all patients with R/R LBCL who received a commercial CAR T-cell product in Spain since its first availability in November 2018 until August 2021, including 307 patients who underwent apheresis for either axi-cel or tisa-cel. In comparison with the first manuscript of this Doctoral Thesis, we included higher numbers and longer follow-up, allowing a more mature analysis of patient outcomes. In fact, this is one of the largest European real-world cohorts published to date, alongside the UK, German and French data(75, 126, 131).

Baseline patient and disease characteristics of the axi-cel and tisa-cel cohorts did not present significant differences, allowing an indirect comparison of outcomes. Product selection was mainly driven by slot availability, center preference and expected turnaround. Regarding the latter, it was a significantly longer for tisa-cel, same as in all real-world European reports(75, 126). The increase in local manufacturing facilities improved the turnaround time and number of slots for both products. However, the required time period for manufacturing was one of the main reasons why 15-20% of patients progressed and dropped out before receiving their CAR T-cell infusion(171). Ongoing efforts for more rapid manufacturing (172) or off-the-shelf allogeneic CAR-T and NK cells are trying to address this important issue(153, 173, 174). Readily available

agents, such as polatuzumab-based regimens (56) and bispecific antibodies(175, 176), carry the significant advantage of avoiding this manufacturing delay and become an attractive alternative for rapidly progressing, chemo-refractory LBCL patients.

In terms of the toxicity profile, axi-cel had increased rates of CRS (any grade) and ICANS (any grade and severe events), requiring a longer median hospitalization than tisa-cel. These results overlap with the other European and US real-world cohorts, all of which also included both axi-cel and tisa-cel data in the same publication(75, 126, 131, 177). These severe adverse event rates with axi-cel are also similar to the US data, supporting our own results(111). Of note, the percentage of severe adverse events was lower in comparison with the pivotal clinical trial ZUMA-1, possibly signaling for a more experienced toxicity management at US and European sites together with an earlier use of immunosuppressive agents(83). The latter is due to the increasing body of evidence which rules out a negative impact of tocilizumab and/or steroids to treat established CRS and/or ICANS after CAR T-cell infusion or even as a prophylactic approach(178, 179). This data includes the subgroup analysis from the registration trials ZUMA-1 and JULIET(83, 84), and the similar efficacy outcomes published with Cohort 4 and 6 of the ZUMA-1 trial which used early (grade 1) or prophylactic steroids, respectively(94, 95). However, these secondary cohorts from ZUMA-1 included a small number of patients with different baseline characteristics from the pivotal cohorts and had limited follow-up. Also, there are contradicting data indicating that early and prolonged high-dose corticosteroids could have a negative impact on CAR T-cell expansion and survival outcomes(180, 181, 182), and prophylactic tocilizumab could potentially increase the risk of ICANS(183). Based on this, prophylactic strategies have not been widely adopted in clinical practice but an earlier use of these agents for grade 2 or persistent grade 1 events is recommended(184).

We also identified a significant higher rate of infections during the first six months after axi-cel infusion, in comparison with tisa-cel. Taking into account that prolonged grade ≥3

neutropenia was similar in both cohorts, this difference was probably driven by the increased rate of adverse events and use of immunosuppressive agents in the axi-cel group. However, non-relapse mortality was not significantly different between axi-cel and tisa-cel. Future efforts to reduce this morbidity burden include a better patient selection, taking into account identified prognostic factors, prediction models which are applicable in the clinic(185) and mitigation strategies with preemptive approaches which do not abrogate the anti-tumor effect of infused CAR T-cells.

Regarding efficacy, the complete response rate was higher among axi-cel infused patients and the intention-to-treat (ITT, since apheresis) survival analysis had a positive trend for axi-cel patients as well, in comparison with tisa-cel recipients. This tendency for a better response after axi-cel infusion has been reproduced in other European and US real-world studies(75, 126, 177). The most robust example would be the recently published French data(131) which carried out a propensity score matching analysis of 418 patients infused with either axi-cel or tisa-cel (1:1) and confirmed a significantly improved PFS and OS for the axi-cel cohort. A matched indirect comparison of the registration trials for both products hinted in the same direction after adjusting for differences in patient characteristics (186). Also, the recently published randomized phase III trial with axi-cel in the second-line setting, ZUMA-7, met its primary endpoint of EFS over the SOC arm, while the BELINDA trial with tisa-cel did not, with the caveat of key differences in trial design. However, the lack of a randomized head-to-head comparison precludes confirming a survival advantage with axi-cel. In fact, some studies have observed similar long-term outcomes (125) and the German data showed an improved PFS with axi-cel which did not translate into an improved OS due to the increased NRM with this construct. Therefore, the increased toxicity, quality of life and hospital resource utilization (cost-effectiveness) has to be considered when analyzing this data(187). Patient selection and logistical aspects could have also played a role in

these results. Finally, longer follow-up is warranted to confirm the rate of durable responses.

We identified LDH and ECOG to be prognostic factors with an impact on efficacy results, as shown in previous real-world publications, including the first paper of this Doctoral Thesis(123, 126, 127, 177). Interestingly, response to BT played an important role in CAR-T outcomes as well; patients who received bridging (usually systemic) and progressed, had significantly worse results. This is in line with the real-world German data (75) and with previous findings signaling for a shorter progression-free and overall survival in chemo-refractory patients (127), probably associated to an inadequate debulking with the lymphodepleting chemotherapy in this patient population. Novel agents which the patients have not previously received, or radiotherapy, should be further explored as BT strategies, aiming to reduce tumor burden and improve patient fitness before CAR T-cell therapy(74, 139). Even in the presence of adverse prognostic factors, CAR T-cell therapy still seems to be the best possible therapeutic option in the relapsed/refractory setting, as underlined by the numerous studies comparing CAR-T with other SOC options(117, 118, 128, 188). Additional data with underrepresented subgroups, such as elderly patients or those with moderate to severe comorbidity, are warranted to provide a clearer understanding of how these factors impact the toxicity and efficacy outcomes.

In conclusion, patients who received axi-cel had higher rates of overall toxicity in comparison to tisa-cel recipients. Survival outcomes for infused patients were not significantly different between both products but a trend for longer PFS and OS in the axi-cel cohort was observed in the ITT analysis. Main prognostic factors influencing efficacy were LDH levels, ECOG and response to BT.

To further address the concept of pretreatment tumor burden in this setting, we conducted the third study of this Doctoral Thesis. We carried out a single-center analysis of the impact of pretreatment metabolic parameters on CAR T-cell outcomes. In general, CAR-T studies in lymphoma included tumor burden in their analysis with the heterogeneous “bulky disease” concept, defined as the presence of a large lesion (5, 7, 7.5 or 10 cm, depending on the study) in the pretreatment PET/CT scan(123, 126, 127, 131), or through sum of product of diameters (SPD) taking into account the sum of lesions on CT scan without considering their metabolic activity(162). In this study, we aimed to assess total metabolic tumor volume (TMTV), computed with the 41% maximum standardized uptake value threshold method(189), capturing all metabolically active areas across the body PET scan. The patient population included 35 consecutive patients who received a 4-1BB second-generation CAR T-cell product at Vall d’Hebron Hospital.

First, we looked at general outcome data from this cohort, including response rates, survival and adverse events. Both were in line with previous clinical trial and real-world publications, including our own results from the first study of this Doctoral Thesis(75, 84, 85, 124, 126, 127).

Next, we analyzed baseline metabolic parameters, focusing on TMTV and SUVmax values. It’s widely accepted that baseline TMTV of newly diagnosed lymphoma patients has an impact on long-term outcomes in the chemotherapy setting(190, 191, 192, 193). In fact, a prognostic index incorporating this parameter to age and stage, the so-called IMPI score, was recently developed and seemed to stratify patients better than the previous IPI score(194). However, until recently, there was scarce data in the context of CAR T-cell recipients. Some of the first data came from the pivotal JULIET trial, where they divided patients in 2 groups according to baseline TMTV values; patients with more or less than 100 mL did not show significant differences regarding overall response rate. However, another cutoff could have yielded different results(84). Outside the context of

a clinical trial, Wang et al analyzed baseline TMTV for 19 patients with NHL who received a 4-1BB CAR-T and did find a significant association with response rate or survival outcomes(195). In our study, patients with lower pretreatment TMTV (<25 cm^3) had an improved PFS and showed a positive trend for OS and overall response rate. This is in line with other published data including both axi-cel and tisa-cel (130, 162, 196), albeit our selected TMTV cutoff was lower than previous reports(130); this could be related to the low median TMTV in our cohort after extensive BT. Noteworthy, a high tumor burden could potentially be offset to some extent with a higher peak of CAR T-cell expansion, as shown by Locke et al in the axi-cel data from the ZUMA-1 trial(162). Therefore, patients with lower burden have more favorable outcomes and those with higher bulk will rely on CAR expansion, amongst other factors, for better results. As an extreme of this "debulking" approach, data has been published with patients who were in CR after bridging therapy (BT) and received their CAR T-cell infusion without measurable disease. Noteworthy, these patients had similar outcomes to reported real-world data and, when available, CAR T-cell expansion appeared in line with expected values (135, 197, 198, 199). Therefore, a more intensive BT could be a potential strategy to improve long-term outcomes in this setting.

We did not identify any association between these metabolic parameters and adverse event incidence, albeit the low number of grade ≥2 CRS and/or ICANS in this cohort could have hampered this analysis. Available publications have very heterogeneous data; in some cases, high tumor burden was associated with a higher risk of developing severe (grade ≥3) CRS (195, 196, 200) and in others with severe ICANS (162). Possibly, the number of patients and severe events, which depend largely on the construct, influenced these results.

Finally, we analyzed the impact of the metabolic parameters at the 1-month disease evaluation. As already mentioned in the first paper, patients in early CMR had excellent long-term outcomes. However, there was a wide variety of results for patients who

achieved an initial PMR; therefore, we focused on this subgroup. We confirmed that patients in PMR with higher TMTV (≥9 cm^3) and SUVmax (≥9) values at 1-month post-infusion had a significantly lower chance of a durable response. Interestingly, the need for an early 1-month disease assessment in patients who received a 4-1BB CAR-T has been questioned and not always conducted in clinical practice. However, many publications with both axi-cel and tisa-cel have confirmed the same results we observed(201). Patients in PMR and a Deauville score of 5 (202), or with high SUVmax values (>10) at 1-month (203, 204), had a significantly lower chance of converting to a CMR over time and most patients progressed, requiring further therapy. Noteworthy, patients with a DS of 4 who had received radiotherapy as BT to a single localized lesion presented similar outcomes to patients who attained a CMR with DS 1-2; residual inflammatory uptake from the previous RT was probably driving the increased SUVmax still present in the 1-month PET assessment. This underlines the importance of maintaining an adequate washout between last BT and the pretreatment PET scan; our study had a median of 16 days (IQR 14-28) and most patients had received chemotherapy as bridging.

The conversion rate from PMR to CMR, which was initially described as 54% in the JULIET study, seems closer to the 20% described in the first paper of this Doctoral Thesis when a PET scan is carried out at the 1-month assessment, and is limited to the subgroup with DS of 4 and/or SUVmax <10 (203). Taking all of this information into consideration could be key to plan for short term follow-up in these patients. Patients in PMR with a DS of 5 or SUVmax >10 could be preemptively considered for clinical trials to avoid waiting for an overt clinical or radiological relapse, where the chances of responding to salvage therapy are significantly lower.

Limitations of this study include the small sample size and limited follow-up. The low TMTV cutoffs at baseline and 1-month assessment are probably in the context of a high use of BT, but more data is needed to define the ideal values with a prognostic impact.

Additional information on response to BT is warranted to inform on the potential of intensifying this treatment for all CAR-T candidates.

The conclusions of this third study are that baseline TMTV has prognostic value but the ideal cut-off is not yet defined. The 1-month PET assessment is useful but additional parameters are needed to better predict long-term outcomes, such as CAR-T peak expansion(162), additional imagining parameters (205, 206) and biological parameters (such as circulating tumor DNA, ctDNA) (207), to add sensitivity and predictive capacity. Collaborative efforts towards standardization of these metabolic variables are warranted to allow a generalized use in clinical practice.

7 CONCLUSIONS

The conclusions of this Doctoral Thesis are:

1. The toxicity profile of commercial CAR T-cells is comparable with the one observed in pivotal trials. Of note, an earlier use of tocilizumab and steroids has led to a lower incidence of severe CRS and ICANS in the real-world setting.

2. Patients who receive axi-cel have higher rates of CRS and ICANS than tisa-cel recipients, leading to an increased use of immunosuppressive agents, hospital stay and infections.

3. Response rate and long-term remissions of axi-cel and tisa-cel in the real-world setting are similar to the pivotal trials. No significant differences in survival outcomes were observed between both products in our retrospective study.

4. Pretreatment high LDH levels, TMTV values and a poor PS are associated with a worse progression-free survival. Response to bridging therapy can be predictive of CAR T-cell outcomes.

5. Patients with increased LDH values, more than 2 previous lines of treatment and patients harboring a poor PS have an increased risk of severe CRS and/or ICANS.

6. The 1-month PET assessment is informative of long-term outcomes and can predict patients in PMR at high risk of disease progression.

8 FUTURE LINES OF RESEARCH

The use of CAR T-cells is expanding into the therapeutic landscape of other hematologic diseases and solid tumors. With the available CAR-T products, less than half of infused patients will benefit long-term, with a considerable toxicity and financial burden. Gaining knowledge on the prognostic factors underlying both safety and efficacy is key to provide insight into the best candidates' profile.

Based on the results reported in the manuscripts included in this Doctoral Thesis, our group is developing new projects to identify prognostic factors for CAR T-cell outcomes. In line with the third publication, we are working on the development of a PET-based radiomics signature to predict durable responses to CAR T-cell therapy in patients with relapsed/refractory LBCL, potentially outperforming conventional PET parameters. Also, we are analyzing fludarabine levels and assessing the impact of residual pre-infusion fludarabine on CAR T-cell expansion and efficacy outcomes.

On the other hand, we are evaluating previous treatment lines which could play a role in the quantity and quality of T-cells at time of apheresis. Bispecific antibodies, mainly anti-CD20/CD3, are frequently used in the context of clinical trials for chemo-refractory LBCL patients. The risk of T-cell exhaustion after this therapy could have a negative impact on CAR T-cell outcomes if a leukapheresis for CAR-T manufacturing is performed soon after the last cycle of bispecific antibody treatment. Another drug with a potential deleterious impact before apheresis is bendamustine. It's prolonged lymphotoxic activity could have a negative effect on T-cell fitness. Preliminary data in this direction was reported in the ZUMA-2 trial for MCL patients, but data in the DLBCL setting is scarce.

Finally, our group is analyzing patient outcomes after CAR T-cell progression. The expected survival rates are dismal, especially when conventional chemotherapy-based strategies are employed. Novel agents, such as polatuzumab and bispecific antibodies, have shown encouraging results but longer follow-up is warranted to confirm if the responses are durable without an allo-HCT consolidation.

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