

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

Mi Kwon,^{1,2*} Gloria Iacoboni,^{3,4*} Juan Luis Reguera,⁵ Lucía López Corral,⁶ Rafael Hernani Morales,⁷ Valentín Ortiz-Maldonado,⁸ Manuel Guerreiro,⁹ Ana Carolina Caballero,¹⁰ María Luisa Guerra Domínguez,¹¹ Jose Maria Sanchez Pina,¹² Alberto Mussetti,¹³ Juan Manuel Sancho,¹⁴ Mariana Bastos-Oreiro,^{1,2} Eva Catala,^{3,4} Javier Delgado,⁵ Hugo Luzardo Henriquez,¹¹ Jaime Sanz,⁹ María Calbacho,¹² Rebeca Bailén,^{1,2} Cecilia Carpio,^{3,4} Jose Maria Ribera,¹⁴ Anna Sureda,¹³ Javier Briones,¹⁰ Juan Carlos Hernandez-Boluda,⁷ Nuria Martínez Cebrián,⁸ Jose Luis Diez Martin,^{1,2,15} Alejandro Martín⁶ and Pere Barba^{3,4} on behalf of GETH-TC (Spanish Group of Stem Cell Transplantation and Cell Therapy) and GELTAMO (Spanish Group of Lymphoma and Autologous Stem Cell Transplantation)

¹Department of Hematology, Hospital General Universitario Gregorio Marañón, Madrid;

²Instituto de Investigación Sanitaria Gregorio Marañón, Madrid; ³Department of Hematology, Vall d'Hebron University Hospital, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona; ⁴Department of Medicine, Universitat Autònoma de Barcelona, Bellaterra; ⁵Department of Hematology, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla, Sevilla;

⁶Department of Hematology, Hospital Clínico Universitario de Salamanca, IBSAL, Salamanca;

⁷Department of Hematology, Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria INCLIVA, Valencia; ⁸Department of Hematology, Hospital Clínic, Barcelona; ⁹Department of Hematology, Hospital Universitario y Politécnico La Fe, Valencia;

¹⁰Department of Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona; ¹¹Department of Hematology, Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria; ¹²Department of Hematology, Hospital Universitario 12 de Octubre, Madrid;

¹³Department of Hematology, Hospital Duran i Reynals, Instituto Catalán de Oncología, Barcelona; ¹⁴Department of Hematology, Hospital Universitari Germans Trias i Pujol, Instituto Catalán de Oncología, Josep Carreras Research Institute, Badalona and ¹⁵Universidad Complutense de Madrid, Madrid, Spain

*MK and GI contributed equally as co-first authors.

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

Received: February 7, 2022.

Accepted: June 17, 2022.

Prepublished: June 30, 2022.

<https://doi.org/10.3324/haematol.2022.280805>

©2023 Ferrata Storti Foundation

Published under a CC BY-NC license

Supplemental Material

Table S1. Characteristics of infused patients before lymphodepletion

	Total infused n=261	Axi-cel infused n=134	Tisa-cel infused n=127	p
Bridging therapy, n (%)	210 (80)	104 (78)	106 (83)	0.275
1 Line	194 (92)	95 (71)	99 (78)	
2 Lines	16 (8)	9 (7)	7 (5)	
ECOG, n (%)				0.319
0-1	244 (94)	123 (92)	121 (95)	
2-4	17 (6)	11 (8)	6 (5)	
R-IPI prognostic score, n (%)				0.881
0-2	87 (33)	51 (38)	36 (28)	
3-5	95 (36)	57 (43)	38 (30)	
NA	79 (30)	26 (19)	53 (42)	
Bulky disease, n (%)	67 (26)	41 (31)	26 (20)	0.248
Extranodal disease, n (%)				0.051
≥ 2 sites	47 (18)	30 (22)	17 (14)	
Disease status, n (%)				0.625
Progressive disease	149 (57)	81 (60)	68 (54)	
Stable disease	43 (16)	24 (18)	19 (15)	
Partial response	25 (10)	15 (11)	10 (8)	
Complete response	11 (4)	4 (3)	7 (5)	
NA	33 (13)	10 (8)	23 (18)	
LDH >ULN, n (%)	143 (55)	67 (50)	76 (60)	0.440
CRP >ULN, n (%)	154 (59)	71 (53)	83 (65)	0.119
Platelets x10³/uL				0.921
Median (range)	141.5 (119-558)	142 (28-550)	141 (19-558)	

Abbreviations: R-IPI, revised international prognostic index; NA, not available; LDH, lactate dehydrogenase, CRP, c-reactive protein; >ULN, upper limit of normal

Tables S2.

A. Bridging therapy regimens used in axicabtagene ciloleucel and tisagenlecleucel–treated patients.

	Total infused n=261	Axi-cel infused n=134	Tisa-cel infused n=127
Bridging therapy, n (%)	210 (80)	104 (78)	106 (83)
Chemotherapy*	127 (48)	64 (48)	63 (49)
Low intensity regimen ^{&}	43 (16)	12 (9)	31 (24)
Radiotherapy	18 (7)	13 (10)	5 (4)
Steroids only	12 (5)	10 (7)	2 (1.5)
Other [§]	4 (1.5)	1 (0.7)	3 (2)
Unknown	6 (2)	4 (3)	2 (2)

*: Gemcitabine based n=67, intensive regimen n=27 (R-ICE n=13, R-ESHAP or DHAP n= 3, R-MINE n=3, reduced R-HyCVAD n=1, reduced BEAM n=1, Burkimab n=1, R-MACOB n=1, other n=4), bendamustine based n=22 (11 combined with polatuzumab), cyclophosphamide based n=11

&: Cyclophosphamide +/- prednisone +/- rituximab n=34, R-lenalidomide n=5, rituximab n=1, polatuzumab + rituximab n=1, ibrutinib n=1, brentuximab n=1

§: pembrolizumab n=1, pixantrona n=3

B. Response rates reported to the different bridging therapies.

	N	Complete Response	Partial Response	Stable Disease	Progressive Disease
Chemotherapy	116	7 (6)	15 (12)	16 (14)	68 (59)
Low intensity regimen	42	1 (2)	3 (7)	4 (10)	22 (52)
Polatuzumab-based					
PBR	11	2 (18)	3 (27)	2 (18)	4 (37)
PR	1	0 (0)	0 (0)	0 (0)	1 (100)
Radiotherapy	18	0 (0)	1 (6)	4 (22)	13 (72)
Steroids	12	0 (0)	0 (0)	1 (8)	11 (92)
Other/unknown	10	0 (0)	0 (0)	0 (0)	7 (70)

PBR: polatuzumab-bendamustine-rituximab; PR: polatuzumab-rituximab

Table S3. A. Univariable analysis for PFS and OS. B. Logistic regression analysis for CRS grade ≥ 3 and ICANS grade ≥ 3 .

A. Univariable analysis for PFS and OS

	PFS		OS	
	HR (95%CI)	p	HR (95%CI)	p
<i>CART type. axi-cel vs tisa-cel</i>	0.781 (0.586-1.040)	0.090	0.735 (0.527-1.024)	0.069
<i>Sex. male vs female</i>	0.992 (0.737-1.335)	0.958	1.025 (0.731-1.437)	0.885
<i>Age</i>	0.994 (0.982-1.007)	0.385	1.000 (0.984-1.015)	0.946
<i>HCT-CI. 0-2 vs >2</i>	0.930 (0.653-1.323)	0.685	0.944 (0.644-1.385)	0.770
<i>Histology DLBCL vs other</i>	1.222 (0.881-1.694)	0.229	1.067 (0.745-1.528)	0.723
<i>Cell of origin. GCB vs non-GCB</i>	0.780 (0.572-1.063)	0.116	0.754 (0.532-1.067)	0.111
<i>Number prior lines. 2 vs >2</i>	1.088 (0.946-1.251)	0.235	1.134 (0.974-1.321)	0.106
<i>Primary Refractory. yes vs no</i>	1.440 (1.065-1.946)	0.018	1.647 (1.161-2.336)	0.005
<i>Previous ASCT. yes vs no</i>	0.608 (0.438-0.843)	0.003	0.470 (0.310-0.713)	0.000
<i>Disease status. PD vs other</i>	2.179 (1.361-3.490)	0.001	3.803 (1.728-8.372)	0.001
<i>ECOG at apheresis 0-1 vs >1</i>	2.529 (1.336-4.786)	0.004	3.885 (2.034-7.419)	0.000
<i>Disease stage I-II vs III-IV</i>	1.773 (1.26-2.496)	0.001	1.896 (1.226-2.841)	0.002
<i>R-IPI at apheresis</i>	1.291 (1.134-1.470)	0.000	1.535 (1.316-1.791)	0.000
<i>Bulky size at apheresis. yes vs no</i>	1.810 (1.322-2.479)	0.000	1.989 (1.397-2.831)	0.000
<i>LDH at apheresis</i>	2.444 (1.738-3.437)	0.000	3.140 (2.051-4.807)	0.000
<i>CRP at apheresis</i>	2.212 (1.54-3.178)	0.000	2.478 (1.644-3.735)	0.000
<i>Platelets at apheresis</i>	0.998 (0.996-1.000)	0.061	0.996 (0.993-1.000)	0.026
<i>Bridging therapy. yes vs no</i>	1.594 (1.023-2.484)	0.040	2.665 (1.423-4.993)	0.002
<i>Disease status at LD. PD vs other</i>	2.797 (1.891-4.139)	0.000	2.500 (1.508-4.142)	0.000
<i>Bulky size at LD. yes vs no</i>	1.946 (1.386-2.733)	0.000	1.916 (1.264-2.903)	0.002
<i>Extranodal at LD >2 sites. yes vs no</i>	1.450 (1.297-1.622)	0.000	1.441 (1.262-1.646)	0.000
<i>ECOG at LD. 0-1 vs >1</i>	3.056 (1.572-5.944)	0.001	3.072 (1.600-5.897)	0.001
<i>R-IPI at LD</i>	1.301 (1.152-1.470)	0.000	1.343 (1.142-1.580)	0.000
<i>Platelets at LD</i>	0.999 (0.997-1.001)	0.269	0.997 (0.995-1.000)	0.063
<i>LDH at LD</i>	2.233 (1.586-3.144)	0.000	2.598 (1.669-4.043)	0.000
<i>CRP at LD</i>	2.495 (1.644-3.786)	0.000	3.190 (1.877-5.422)	0.000
<i>LDH pre infusion</i>	2.179 (1.463-3.245)	0.000	2.175 (1.324-3.571)	0.002
<i>CRP pre infusion</i>	2.664 (1.570-4.521)	0.000	4.497 (2-128-9.5)	0.000
<i>CRS. yes vs no</i>	0.740 (0.514-1.064)	0.104	1.071 (0.665-1.727)	0.777
<i>CRS 3-4. yes vs no</i>	1.533 (0.752-3.126)	0.239	2.615 (1.250-5.470)	0.011
<i>CRS tocilizumab. yes vs no</i>	0.886 (0.644-1.218)	0.455	1.337 (0.907-1.971)	0.143
<i>CRS steroids. yes vs no</i>	0.895 (0.584-1.372)	0.611	1.219 (0.721-2.062)	0.460
<i>ICANS. yes vs no</i>	0.974 (0.679-1.396)	0.884	1.450 (0.942-2.234)	0.092
<i>ICANS 3-4. yes vs no</i>	1.108 (0.620-1.978)	0.730	1.690 (0.842-3.392)	0.140
<i>ICANS tocilizumab. yes vs no</i>	0.896 (0.579-1.388)	0.623	1.475 (0.884-2.462)	0.137
<i>ICANS steroids. yes vs no</i>	0.990 (0.660-1.483)	0.960	1.396 (0.846-2.301)	0.191

B. Univariable logistic regression analysis for CRS grade ≥ 3 and ICANS grade ≥ 3

	CRS grade ≥ 3		ICANS grade ≥ 3	
	OR (95%CI)	P	OR (95%CI)	P
<i>CART type. axi-cel vs tisa-cel</i>	1.330 (0.516-3.429)	0.555	4.400 (1.731-11.180)	0.002
<i>Age</i>	1.001 (0.995-1.050)	0.970	1.004 (0.968-1.041)	0.836
<i>HCT-CI. 0-2 vs >2</i>	0.401 (0.090-1.795)	0.232	1.106 (0.447-2.733)	0.828
<i>Histology DLBCL vs other</i>	0.719 (0.395-1.309)	0.281	0.914 (0.609-1.372)	0.665
<i>Cell of origin. GCB vs non-GCB</i>	0.671 (0.239-1.882)	0.448	1.438 (0.572-3.615)	0.440
<i>Number prior lines. 2 vs ></i>	1.067 (0.676-1.684)	0.782	0.534 (0.336-0.848)	0.008
<i>Primary Refractory. yes vs o</i>	1.270 (0.482-3.345)	0.628	1.105 (0.508-2.404)	0.801
<i>LDH at apheresis</i>	2.547 (0.817-7.938)	0.107	0.984 (0.438-2.206)	0.968
<i>CRP at apheresis</i>	1.779 (0.537-5.895)	0.346	0.539 (0.228-1.271)	0.158
<i>Leucocyte count at apheresis</i>	0.898 (0.701-1.150)	0.392	1.040 (0.940-1.151)	0.449
<i>Lymphocyte count at apheresis</i>	0.922 (0.581-1.463)	0.730	1.020 (0.774-1.346)	0.886
<i>Platelet count at apheresis</i>	0.993 (0.984-1.002)	0.121	1.000 (0.997-1.003)	0.927
<i>Bridging therapy. yes vs no</i>	2.158 (0.481-9.683)	0.315	2.361 (0.685-8.131)	0.173
<i>Disease status PD vs other</i>	1.296 (0.439-3.830)	0.639	1.219 (0.504-2.950)	0.660
<i>Bulky at LD. yes vs no</i>	1.985 (0.760-5.185)	0.162	1.250 (0.534-2.925)	0.608
<i>Extranodal at LD. 0-2 vs >2</i>	1.012 (0.7701-331)	0.930	1.225 (0.890-1.686)	0.213
<i>ECOG at LD. 0-1 vs >1</i>	6.756 (2.082-21.920)	0.001	2.658 (0.803-8.800)	0.109
<i>R-IPI at LD. 0-2 vs >2</i>	2.717 (0.829-8.907)	0.099	2.315 (0.901-5.947)	0.081
<i>Platelets at LD</i>	1.001 (0.996-1.006)	0.682	1.002 (0.992-1.006)	0.337
<i>LDH at LD</i>	6.299 (1.411-28.120)	0.016	0.924 (0.426-2.001)	0.840
<i>CRP at LD</i>	2.705 (0.761-9.624)	0.124	1.961 (0.760-5.057)	0.164
<i>LDH at infusion</i>	1.026 (0.236-4.459)	0.973	1.461 (0.569-3.749)	0.430
<i>CRP at infusion</i>	2.162 (0.480-9.740)	0.315	1.591 (0.524-4.832)	0.413

Abbreviations: HCT-CI, Hematopoietic Cell Transplantation-Comorbidity Index; GCB, germinal center B-cell; ASCT, autologous stem cell transplantation; PD, progressive disease; R-IPI, revised international prognostic index; LDH, lactate dehydrogenase; CRP, c-reactive protein; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, lymphodepletion.

Table S4. Infections within the first six months after infusion in axicabtagene ciloleucel and tisagenlecleucel-treated patients.

	Total infused (n=261)	Axi-cel infused (n=134)	Tisa-cel infused (n=127)
Infectious episodes, n	91	56	35
Bacterial, n (%)	54 (59)	32 (57)	22 (63)
Mild	3 (3)	1 (2)	2 (6)
Moderate	9 (11)	3 (5)	6 (17)
Severe	37 (41)	25 (45)	12 (34)
Life-threatening	4 (4)	2 (4)	2 (6)
Fatal	1 (1)	1 (2)	0 (0)
Viral, n (%)	31 (34)	22 (36)	9 (26)
Mild	13 (14)	7 (13)	6 (17)
Moderate	6 (7)	4 (7)	2 (6)
Severe	5 (5)	4 (7)	1 (3)
Life-threatening	6 (7)	6 (11)	0 (0)
Fatal	1 (1)	1 (2)	0 (0)
Fungal, n (%)	6 (7)	2 (4)	4 (11)
Mild	1 (1)	0 (0)	1 (3)
Moderate	1 (1)	1 (2)	0 (0)
Severe	2 (2)	0 (0)	2 (6)
Life-threatening	1 (1)	0 (0)	1 (3)
Fatal	1 (1)	1 (2)	0 (0)

Figure S1. Reasons for not undergoing CAR T-cell infusion for patients intended to be treated with axi-cel and tisa-cel

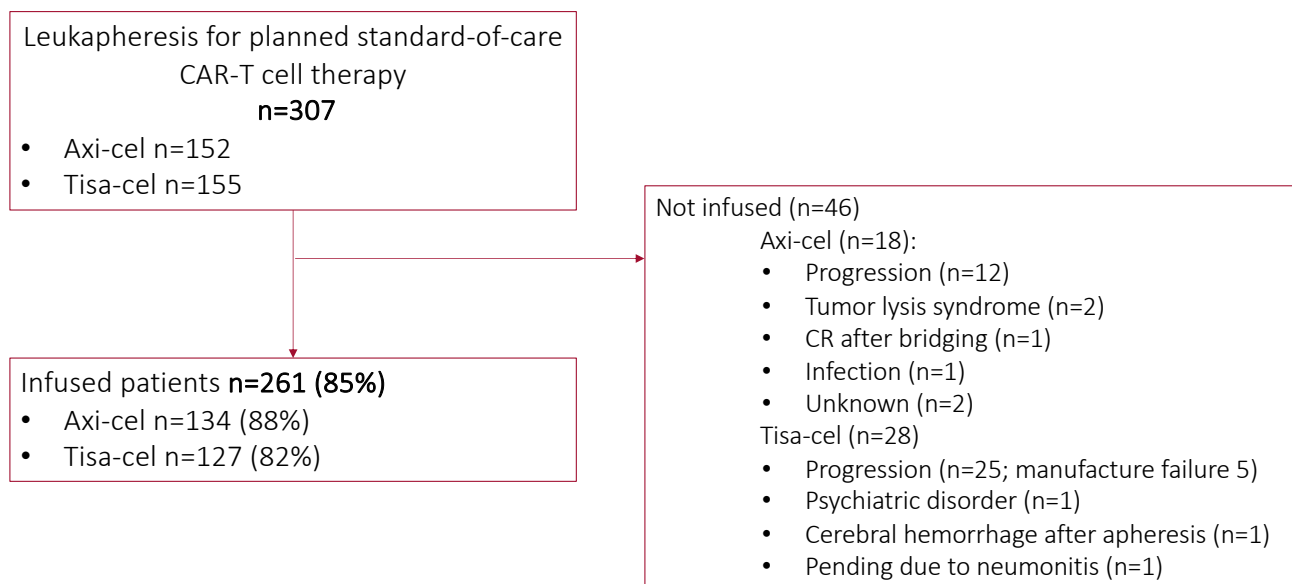
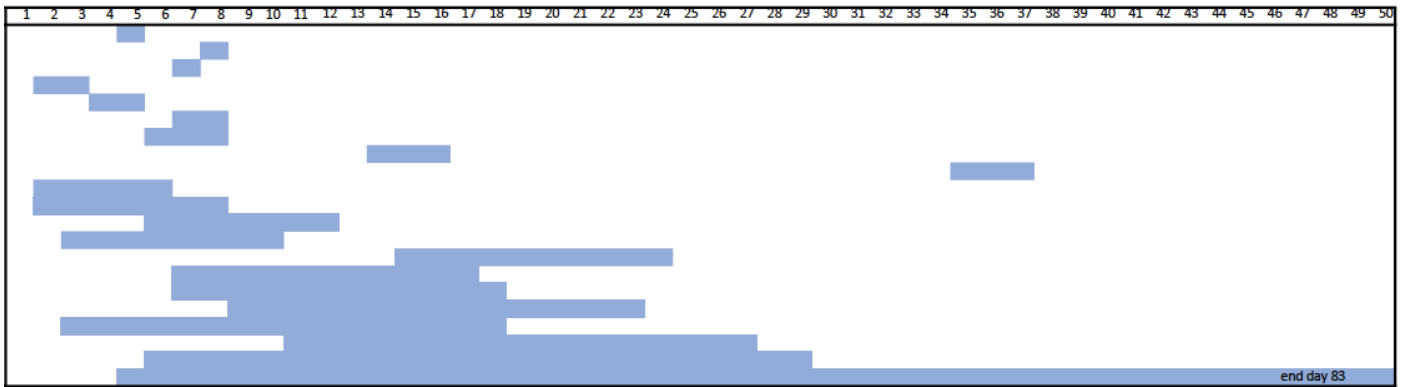


Figure S2. Timeline of neurotoxicity (ICANS) after infusion of tisagenlecleucel (A) and axicabtagene ciloleucel (B).

A



B

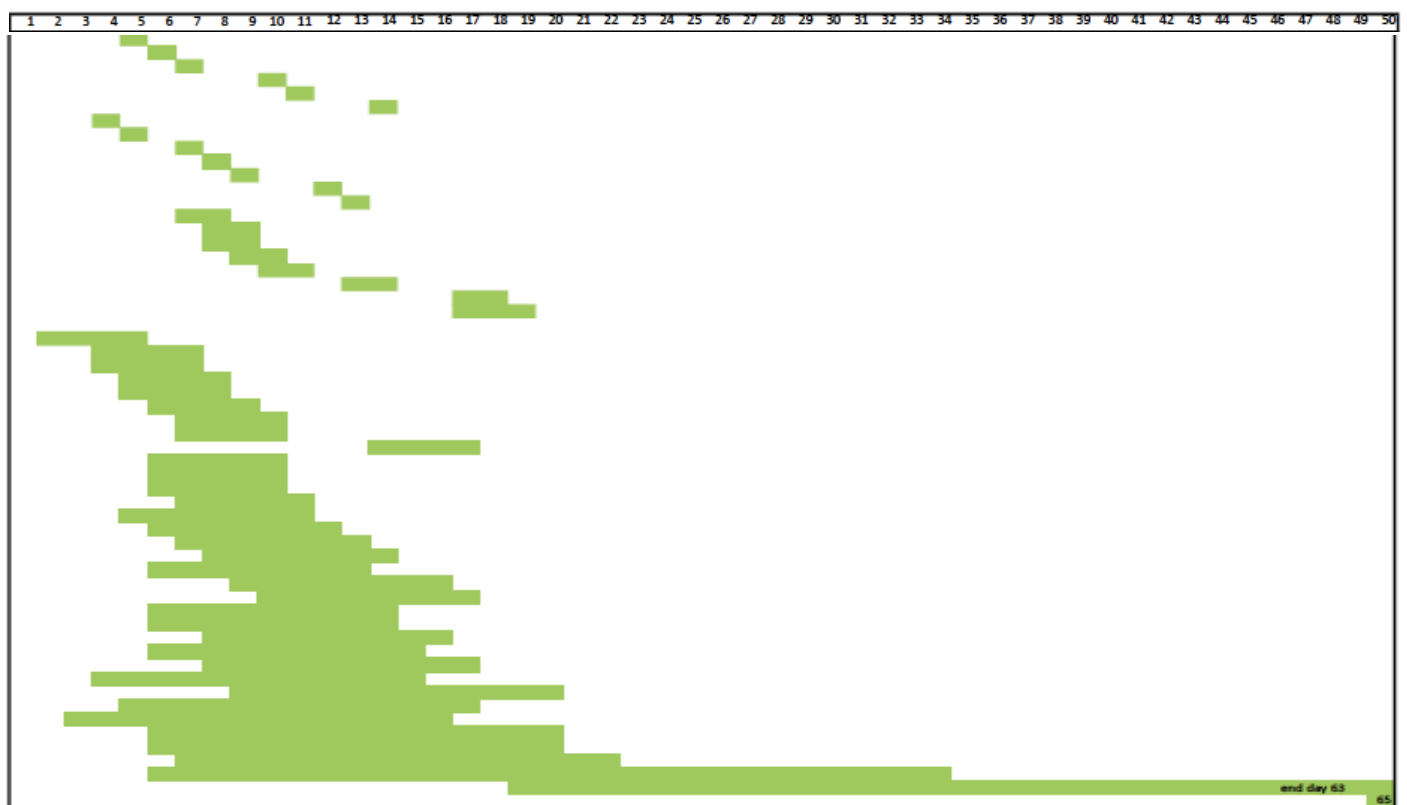


Figure S3. Non-relapse mortality causes in axicabtagene ciloleucel and tisagenlecleucel–treated patients

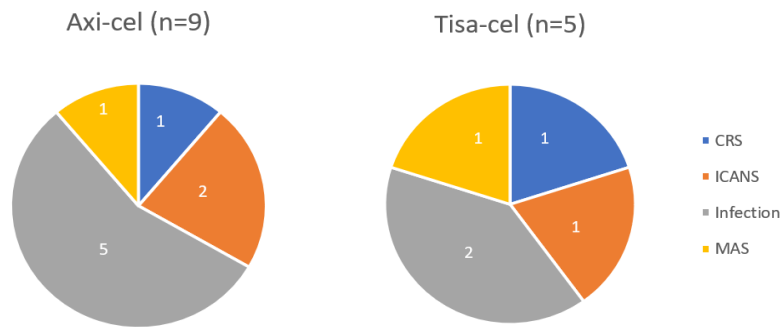
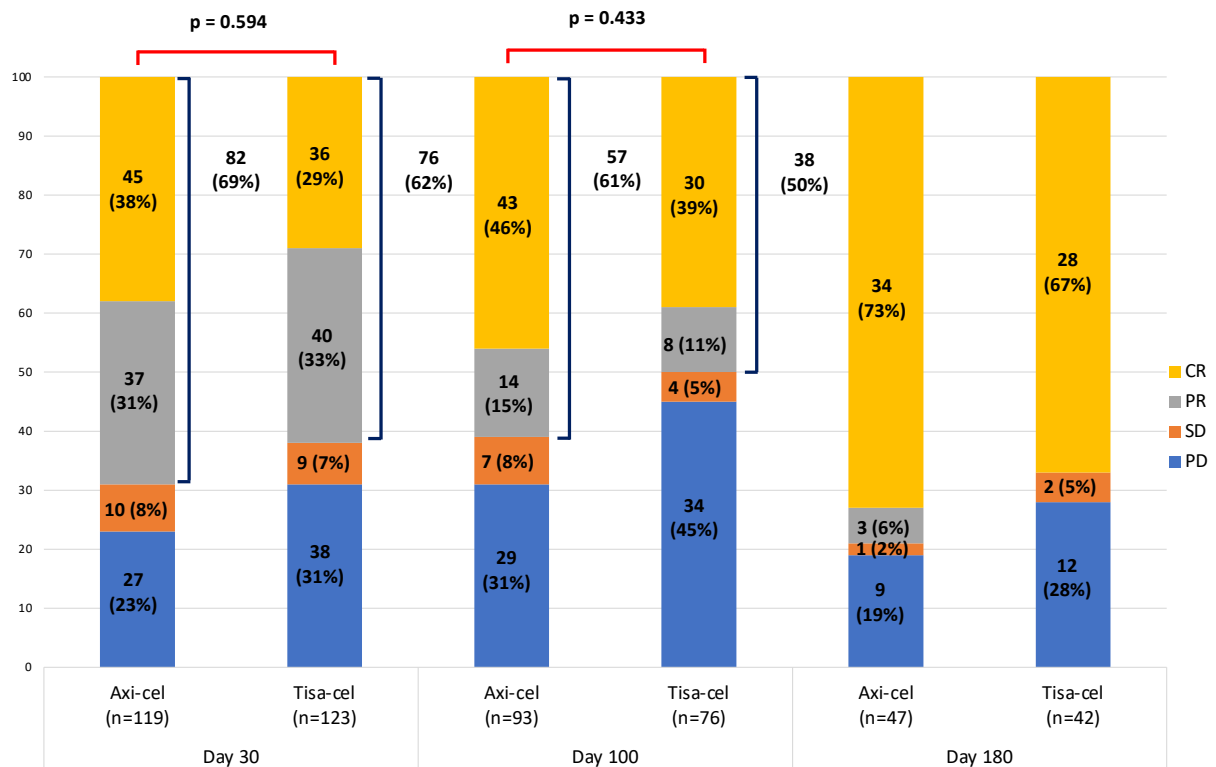


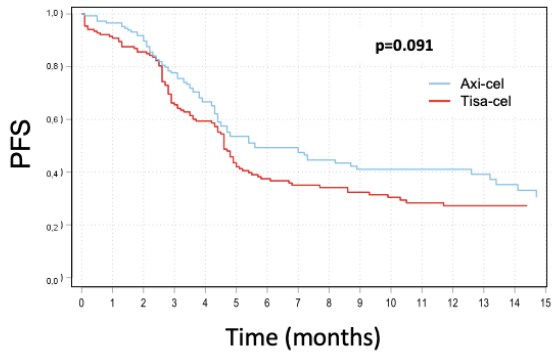
Figure S4. Response assessment in axicabtagene ciloleucel and tisagenlecleucel–treated patients at days 30, 100 and 180 after infusion.



Abbreviations: CR, complete response; PR, partial response; SD: stable disease; PD: progressive disease

Figure S5. Progression free survival (PFS) and Overall survival (OS) from apheresis of patients intended to be treated with axicabtagene ciloleucel and tisagenlecleucel.

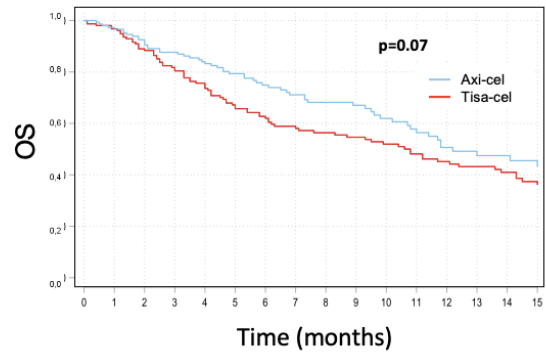
A



Number at risk

Tisa-cel	155	142	130	98	85	58	48	41	38	35	30	26	25	24	23	21
Axi-cel	152	147	133	108	90	65	54	53	44	33	30	26	25	20	16	12

B



Tisa-cel	155	150	137	121	109	91	83	71	66	62	56	50	46	41	36	30
Axi-cel	152	148	135	108	113	94	81	75	67	58	48	41	34	29	24	19