Study Design and Participants

The study was performed according to Declaration of Helsinki and good clinical practice guidelines. Ethical approval was obtained from the institutional ethics committee of each site (INT 180/19, approval number 431/DG, 2019). All patients provided written informed consent and were treated with two different commercial products available in Italy at the time of analyses: axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel).

Definitions and endpoints

The outcomes were evaluated in terms of overall response rate (ORR), complete response rate (CR), OS, PFS, DOR, post-relapse OS, NRM, and the incidence and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

OS was defined as the time from CAR T-cells infusion to death from any cause with censoring at last follow-up for alive patients, and PFS was defined as the time from CAR T-cells infusion to disease progression or death, whichever occurred first with censoring at last follow-up for alive patients without progression. DOR time was calculated for patients who achieved complete response (CR) or partial response (PR) at day 30, starting from the date of response until progression or death, whichever occurred first, with censoring at the last follow-up for alive patients without progression. NRM was defined as death after CAR T-cells therapy without prior lymphoma relapse or progression. Post-relapse OS was defined as the time from CAR T-cells failure to death from any cause and living patients were censored at the date of the last follow-up.

Each center performed a clinical response assessment using the Lugano 2014 criteria[10]. CRS and ICANS were graded according to modified Lee criteria and the American Society for Transplantation and Cellular Therapy (ASCTC) criteria[11].Hematological and non-hematological toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5. (Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute).

Table 1S. Univariate analyses of factors influencing PFS and OS in HGBL

Characteristics	PFS		OS	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**
Sex (M vs F)	1.64 (0.92-2.96)	0.091	1.57 (0.84-2.91)	0.150
Age	0.99 (0.96-1.01)	0.299	1 (0.97-1.02)	0.742
Histology (Others vs DH/TH)	1.16 (0.65-2.09)	0.616	0.88 (0.47-1.67)	0.698
LDH (high vs no)	1.97 (0.99-3.89)	0.062	2.03 (0.99-4.17)	0.063
CRP (high vs no)	1.71 (0.96-3.04)	0.065	1.79 (0.98-3.27)	0.058
ECOG (≥1 vs no)	1.32 (0.74-2.33)	0.349	1.35 (0.74-2.48)	0.336
Refractory vs Relapsed	1.36 (0.66-2.80)	0.396	1.41 (0.62-3.17)	0.392
IPI (> 2 vs 0-2)	1.21 (0.68-2.17)	0.513	2.01 (0.94-4.86)	**0.030**
N°extranodal (2 vs 0-2)	1.57 (0.70-3.55)	0.300	2.14 (0.94-4.86)	0.093
CR to bridge	0.36 (0.13-1.01)	**0.026**	0.45(0.16-1.26)	0.089
Bulky (yes vs no)	2.36 (1.33-4.19)	**0.004**	3.17 (1.71-5.90)	**<0.001**
CAR T-cells product (Tisacel vs Axicel)	1.17 (0.66-2.07)	0.588	0.68 (0.37-1.25)	0.217

HGBL, High-Grade B cell lymphomas; LDH, lactate dehydrogenase; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; CR, Complete Remission; CAR, Chimeric Antigen Receptor.

Table 2S. Univariate analyses of factors influencing PFS and OS in DLBCL

Characteristics	PFS		OS	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**
Sex (M vs F)	1.2 (0.90-1.60)	0.210	1.40 (0.97-2.01)	0.063
Age	1.00 (0.99-1.01)	0.644	1.01 (0.99-1.02)	0.363
LDH (high vs no)	2.02 (1.49-2.74)	**<0.001**	3.31(2.28-4.79)	**<0.001**
CRP (high vs no)	2.00 (1.52-2-62)	**< 0.001**	2.77 (1.96-3.92)	**<0.001**
ECOG (≥1 vs no)	1.17 (0.89-1.53)	0.273	1.57 (1.13-2.17)	**0.008**
Refractory vs Relapsed	1.69 (1.24-2.30)	**<0.001**	1.63 (1.11-2.38)	**0.009**
IPI (> 2 vs 0-2)	1.21 (0.92-1.58)	0.172	1.45 (1.05-2.01)	**0.026**
N°extranodal (2 vs 0-2)	1.36 (0.92-2.02)	0.136	1.48 (0.91-2.41)	0.128
CR to bridge	0.37 (0.21-0.64)	**<0.001**	0.24 (0.11-0.55)	**<0.001**
Bulky (yes vs no)	1.56 (1.18-2.07)	**0.002**	1.75 (1.25-2.44)	**0.001**
CAR T-cells product (Tisa vs Axicel)	1.44 (1.10-1.89)	**0.008**	1.27 (0.91-1.76)	0.160

HGBL, High-Grade B cell lymphomas; LDH, lactate dehydrogenase; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group Performance Status; IPI, International Prognostic Index; CR, Complete Remission; CAR, Chimeric Antigen Receptor.

Table 3S. Patients evaluated for CAR T-cells expansion

Variable	HGBL (n=43)	DLBCL (n=50)	p-value
Age (median) <65 years ≥ 65 years	**65 years** 19/43 (44%) 24/43 (56%)	**57 years** 42/50 (84%) 8/50 (16%)	<0,0001
Sex Male Female	 26/43 (61%) 17/43 (39%)	 35/50 (70%) 15/50 (30%)	0.385
IPI n (%) 0-2 >2	 18/43 (42%) 25/43 (58%)	 29/50 (58%) 21/50 (42%)	0.145
LDH n (%) at infusion normal increased missing	 16/43 (37%) 23/43 (54%) 4/43 (9%)	 31/50 (62%) 14/50 (28%) 5/50 (10%)	0.038
CRP n (%) at infusion <10 >=10 Missing	 16/43 (37%) 22/43 (51%) 5/43 (12%)	 28/50 (56%) 22/50 (44%)	0.002
ECOG n (%) 0 >=1	 30/43 (70%) 13/43 (30%)	 42/50 (84%) 8/50 (16%)	0.136
Relapsed/Refractory Relapsed Refractory	 36/43 (84%) 7/43 (16%)	 9/50 (18%) 41/50 (82%)	<0.0001
N° Extranodal Sites n (%) 0-2 >2	 40/43 (93%) 3/43 (7%)	 40/50 (80%) 10/50 (20%)	0.081
ORR to bridge, n (%) No response Response Missing	 31/43 (72%) 7/43 (16%) 5/43 (12%)	 31/50 (62%) 12/50 (24%) 7/50 (14%)	0.576
Bulky disease, n (%) Yes No	 24/43 (56%) 19/43 (44%)	 14/50 (28%) 36/50 (72%)	0.01
CAR T-cells product, n (%) Axi-cel Tisa-cel	 23/43 (54%) 20/43 (46%)	 25/50 (50%) 25/50 (50%)	0.835

HGBL, High-Grade B cell lymphomas; IPI, International Prognostic Index; LDH, lactate dehydrogenase; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; CAR, Chimeric Antigen Receptor.

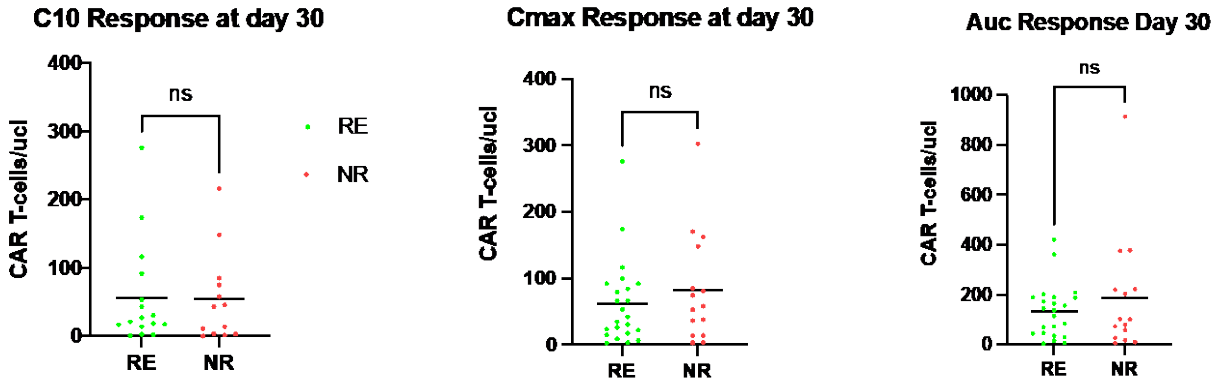

Figure 1S. Expansion CAR T-cells in HGBL

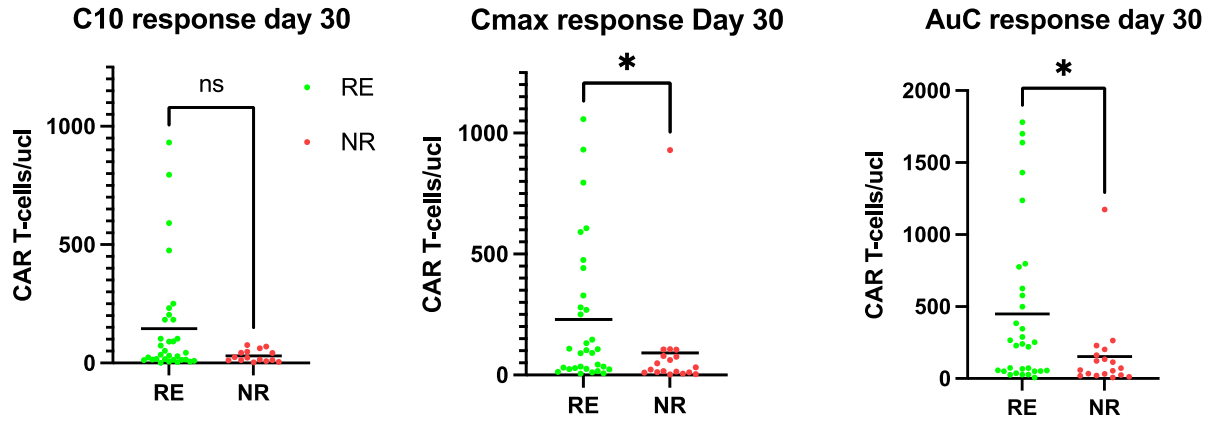

Figure 2S. Expansion CAR T-cells in DLBCL with p-value of 0.014 for CMAX and p-value of 0.016 for AUC 0-30. Expansion was not compared between the HGBL and DLBCL groups, as patients with HGBL were significantly characterized by poor prognostic factors that could influence CAR T-cells expansion (see Table 3S).

Table 4S. Univariable logistic model for CRS any grade

Variable	N	Event	OR	95% CI	p-value
Population	432	361			0.037
HGBL			-	-	
DLBCL			0.45	0.18-0.96	

HGBL, High-Grade B cell lymphomas; DLBCL; Diffuse Large B cell lymphomas; OR, Odds Ratio.

Table 5S. Weighted logistic regression for CRS any grade

Variable	N	Event	OR	95% CI	p-value
Population	155.85				0.139
HGBL			-	-	
DLBCL			0.49	0.17-1.26	

HGBL, High-Grade B cell lymphomas; DLBCL; Diffuse Large B cell lymphomas; OR, Odds Ratio.

Table 6S. Univariable logistic model for ICANS any grade

Variable	N	Event	OR	95% CI	p-value
Population	432	91			0.012
HGBL			-		
DLBCL			0.49	0.28-0.85	

HGBL, High-Grade B cell lymphomas; DLBCL; Diffuse Large B cell lymphomas; OR, Odds Ratio.

Table 7S. Weighted logistic regression for ICANS any grade

Variable	N	Event	OR	95% CI	p-value
Population	155.82				0.109
HGBL			-		
DLBCL			0.56	0.26-1.14	

HGBL, High-Grade B cell lymphomas; DLBCL; Diffuse Large B cell lymphomas; OR, Odds Ratio.

Table 8S. Logistic regression for any grade CRS in HGBL

Variable	N	OR	95% CI	p-value
CRS in HGBL	71			0.044
Axicel		-		
Tisacel		0.15	0.01-0.96	

CRS, cytokine release syndrome; HGBL, High-Grade B cell lymphomas; OR, Odds Ratio.

Table 9S. Logistic regression for any grade CRS in DLBCL

Variable	N	OR	95% CI	p-value
CRS in DLBCL	290			0.005
Axicel		-		
Tisacel		0.45	0.25-0.79	

CRS, cytokine release syndrome; DLBCL, Diffuse Large B cell lymphomas; OR, Odds Ratio.

Table 10S. Logistic regression for any grade ICANS in HGBL

Variable	N	OR	95% CI	p-value
ICANS in HGBL	25			<0.001
Axicel		-		
Tisacel		0.06	0.01-0.20	

ICANS, immune effector cell associated neurotoxicity Syndrome; HGBL, High-Grade B cell lymphomas; OR, Odds Ratio.

Table 11S. Logistic regression for any grade ICANS in DLBCL

Variable	N	OR	95% CI	p-value
ICANS DLBCL	66			<0.001
Axicel		-		
Tisacel		0.28	0.15-0.50	

ICANS, immune effector cell associated neurotoxicity Syndrome; DLBCL, Diffuse Large B cell lymphomas; OR, Odds Ratio.

Table 12S. Patient characteristics at relapse

	HGBL (n=40) *	DLBCL (n=167) *	*p-value*
Previous response to CART, n (%)			0.481
No response (PD/SD)	21 (52.5%)	75 (44.9%)	
Response (CR/PR)	19 (47.5%)	92 (55.1%)	
Time from CART infusion to progression, n (%)			**0.020**
<=3 months	30 (75%)	91 (54.5%)	
>3 months	10 (25%)	76 (45.5%)	
Age at relapse, median (range)	62.5 (55-66.3)	60 (51.5-66)	0.389
Ann arbor stage at relapse, n (%)			>0.999
I-II	6 (15%)	25 (15%)	
III-IV	34 (85%)	142 (85%)	
Bulky disease at relapse, n (%)			0.073
Yes	22 (55%)	64 (38.3%)	
No	18 (45%)	103 (61.7%)	
Increased LDH at relapse, n (%)			0.061
Yes	32 (80%)	106 (63.5%)	
No	8 (20%)	61 (36.5%)	
Increased CRP at relapse, n (%)			0.725
Yes	23 (57.5%)	89 (53.3%)	
No	17 (42.5%)	78 (46.7%)	
CNS involvement at relapse, n (%)			>0.999
Yes	2 (5%)	9 (5.4%)	
No	38 (95%)	158 (94.6%)	
Extranodal disease at relapse, n (%)			0.128
Yes	32 (80%)	112 (67.1%)	
No	8 (20%)	55 (32.9%)	

HGBL, High-Grade B cell lymphomas; LDH, lactate dehydrogenase; CRP, C-reactive protein; CART, Chimeric Antigen Receptor T-cells.

**Note: Four HGBL and thirty-five DLBCL patients who relapsed following CAR T-cell therapy were excluded from the analysis due to incomplete data on disease characteristics at relapse, precluding their inclusion in multivariate models.*

Table 13S. Multivariable analysis of patient characteristics at relapse influencing outcome after CAR T failure

Patient characteristic at relapse (n=203) *	HR	95% CI	*p-value*
Salvage treatment			**<0.001**
No treatment	-	-	
Bispecific antibody	0.08	0.04-0.14	
Other treatment	0.18	0.11-0.31	
Histology			**0.006**
HGBL	-	-	
DLBCL *de novo*	0.51	0.33-0.77	
DLBCL *transformed*	0.43	0.22-0.85	
Age at relapse	1.01	1.00-1.03	0.095
Time from CART infusion to progression			**0.010**
<=3 months	-	-	
>3 months	0.52	0.32-0.85	
Previous response to CART			**0.046**
No response (PD/SD)	-	-	
Response (CR/PR)	0.64	0.41-1.00	
Ann arbor stage at relapse			**0.041**
I-II	-	-	
III-IV	1.81	1.00-3.29	
Bulky disease at relapse			0.361
No	-	-	
Yes	1.2	0.81-1.79	
Increased LDH at relapse			<0.001
No	-	-	
Yes	2.16	1.4-3.34	
Extranodal disease at relapse			0.575
No	-	-	
Yes	1.13	0.73-1.75	

HGBL, High-Grade B cell lymphomas; LDH, lactate dehydrogenase; CRP, C-reactive protein; CART, Chimeric Antigen Receptor T-cells; HR, Hazard Ratio; CI, Confidence Interval.

Note: Four HGBL and thirty-five DLBCL patients who relapsed following CAR T-cell therapy were excluded from the analysis due to incomplete data on disease characteristics at relapse, precluding their inclusion in multivariate models.* ***For four of the evaluable patients, post-relapse OS could not be assessed as death occurred on the same day as disease progression.*

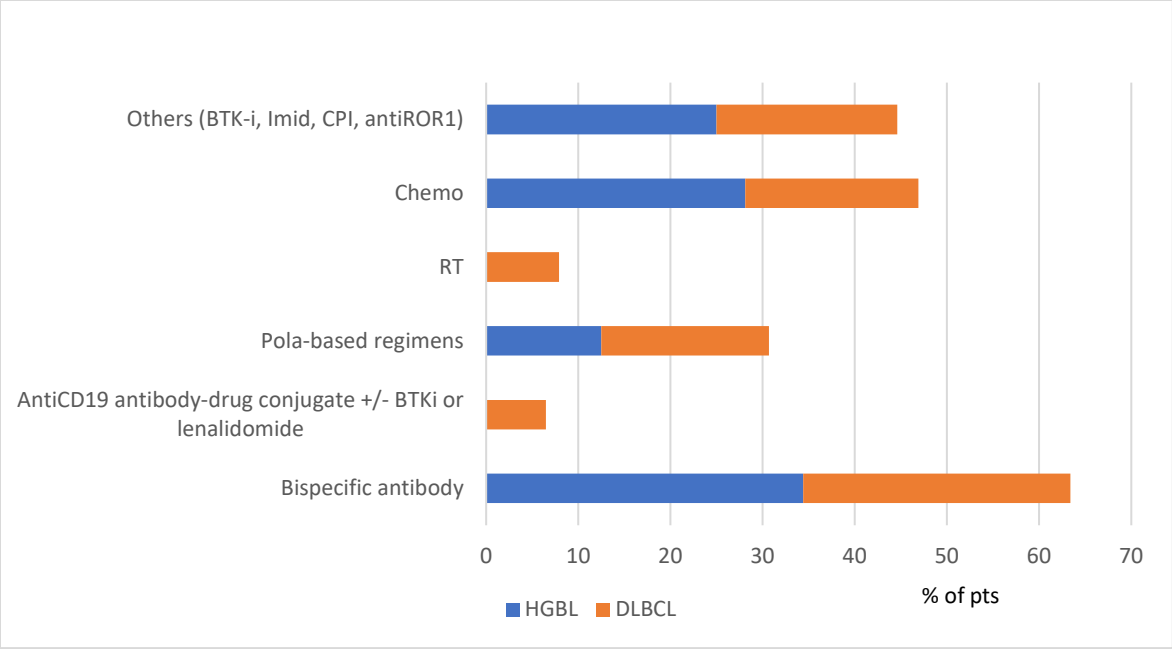

Figure 3S. First salvage therapy following CAR T-cells failure.