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Salvage radiotherapy in relapsed/refractory large B-cell lymphoma after failure of CAR T-cell therapy

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Supplementary methods:

For patients who responded to CAR T, the duration of response was defined from the date of CAR T-cell therapy infusion until the date of disease progression or death from any cause. Treatment responses were evaluated using 18F fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) scan per Lugano criteria for systemic disease, while magnetic resonance imaging (MRI) was utilized to assess treatment responses of patients with central nervous system (CNS) lymphoma. CAR T-cell failure at timepoints other than day 30 was evaluated using a combination of imaging, histopathological examination, and/or clinical assessment. In addition, imaging prior to CAR T-cell therapy infusion was compared with imaging at the time of disease progression /relapse to define whether recurrences occurred in previously involved sites, or new sites. When available, CD19 antigen expression at the time of CAR T relapse/progression was evaluated using flow cytometric analysis and/or immunohistochemistry studies. Bulky disease assessment was based on the PET/CT scan as any nodal or extranodal mass of ≥ 5 cm in maximal diameter at the time of receiving salvage therapy.

Categorical variables were analyzed and compared by chi-square or Fisher's exact tests, where relevant. Continuous data were reported as median and range values, then compared using nonparametric independent samples median test. Survival measures were computed using the Kaplan-Meier method, with comparisons via log-rank test. Predictors with a p-value less than or equal to 0.2 in the univariate analysis were included in the multivariable analyses. Multivariate survival analyses were performed using Cox proportional hazards models with Collet's method. Two-sided p- values < 0.05 were considered statistically significant. Statistical analyses were performed using R software for Mac (version 4.1.2).

Supplementary results:

	RT (N=25)	CMT (N=15)	ST (N=80)	Overall (N=120)	P-value
Age (years) §					
Mean (SD)	65.4 (9.56)	61.9 (8.83)	58.6 (15.3)	60.4 (13.8)	0.0881
Median [Min, Max]	63.0 [43.0, 81.0]	62.0 [40.0, 78.0]	62.0 [15.0, 79.0]	62.0 [15.0, 81.0]	
Gender					
Male	19 (76.0%)	8 (53.3%)	47 (58.8%)	74 (61.7%)	0.234
Female	6 (24.0%)	7 (46.7%)	33 (41.3%)	46 (38.3%)	
Age (years)					
≥60	20 (80.0%)	11 (73.3%)	49 (61.3%)	80 (66.7%)	0.187
<60	5 (20.0%)	4 (26.7%)	31 (38.8%)	40 (33.3%)	
Histopathology					
DLBCL	11 (44.0%)	7 (46.7%)	40 (50.0%)	58 (48.3%)	0.461
DLBCL arising from other low-grade lymphoma	2 (8.0%)	0 (0%)	12 (15.0%)	14 (11.7%)	
HGBCL*	2 (8.0%)	1 (6.7%)	4 (5.0%)	7 (5.8%)	
TFL	9 (36.0%)	6 (40.0%)	18 (22.5%)	33 (27.5%)	
PMBCL	0 (0%)	0 (0%)	5 (6.3%)	5 (4.2%)	
B-cell lymphoma unclassifiable†	1 (4.0%)	1 (6.7%)	1 (1.3%)	3 (2.5%)	
Stage at time of diagnosis					
I	2 (8.0%)	1 (6.7%)	6 (7.5%)	9 (7.5%)	0.845

II	3 (12.0%)	4 (26.7%)	8 (10.0%)	15 (12.5%)	
III	4 (16.0%)	3 (20.0%)	20 (25.0%)	27 (22.5%)	
IV	14 (56.0%)	6 (40.0%)	39 (48.8%)	59 (49.2%)	
Missing	2 (8.0%)	1 (6.7%)	7 (8.8%)	10 (8.3%)	
Extranodal disease at time of diagnosis					
Yes	14 (56.0%)	11 (73.3%)	45 (56.3%)	70 (58.3%)	0.48
No	8 (32.0%)	3 (20.0%)	28 (35.0%)	39 (32.5%)	
Missing	3 (12.0%)	1 (6.7%)	7 (8.8%)	11 (9.2%)	
Consolidative RT pre-CAR T					
Yes	1 (4.0%)	1 (6.7%)	8 (10.0%)	10 (8.3%)	0.619
No	24 (96.0%)	14 (93.3%)	72 (90.0%)	110 (91.7%)	
Salvage RT pre-CAR T					
Yes	1 (4.0%)	5 (33.3%)	10 (12.5%)	16 (13.3%)	**0.0284**
No	24 (96.0%)	10 (66.7%)	70 (87.5%)	104 (86.7%)	
Pre-CAR T transplant					
Yes	6 (24.0%)	3 (20.0%)	19 (23.8%)	28 (23.3%)	0.948
No	19 (76.0%)	12 (80.0%)	61 (76.3%)	92 (76.7%)	

Supplementary table 1: Characteristics of patients prior to CAR T-cell therapy infusion

Continuous variables reported as median and mean (SD). Categorical variables reported as n (%)
Chi-square test was used to compare categorical variables, and ANOVA test was used to compare the means between three groups.
RT, Radiation therapy; CMT, combined modality therapy; ST, systemic therapy; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma; TFL, transformed follicular lymphoma; HGBCL, high-grade B-cell lymphoma
§ Age at diagnosis for de novo disease patients and age at transformation for patients with transformed disease.
* HGBCL not otherwise specified/HGBCL with rearrangement of MYC with BCL2, or BCL6, or both
† B-cell lymphoma unclassifiable with features intermediate between DLBCL and classic Hodgkin lymphoma

Characteristic	Univariate analysis																	
	All patients			**RT**			**ST**			**CMT**			**ST then RT**			**RT then ST**		
	HR (95% CI)	**Median OS (mo)**	**P-value**	**HR (95 %CI)**	**Median OS (mo)**	**P-value**	**HR (95 %CI)**	**Median OS (mo)**	**P-value**	**HR (95 %CI)**	**Median OS (mo)**	**P-value**	**HR (95 %CI)**	**Median OS (mo)**	**P-value**	**HR (95 %CI)**	**Median OS (mo)**	**P-value**
Gender																		
Male	0.97 (0.58-1.6)	10.5	0.9	1.4 (0.15-12.2)	NR	0.8	0.9 (0.5-1.8)	8.3	0.8	0.5(0.14-2.1)	10.6	0.4	3.3(0.6-16.4)	5.4	0.1	0.9(0.12-4.8)	12.0	0.9
Female		7.3			NR			4.6			7.3			NR			17.1	
Age at time of diagnosis																		
≥60	1.4 (0.8-2.4)	8.3	0.3	2.05 (0.2-18.5)	NR	0.5	1.2 (0.6-2.4)	6.6	0.6	1.2 (0.2-5.6)	7.3	0.8	1.8(0.36-9.0)	6.8	0.5	N/A	15.6	1.0
<60		NR			NR			4.6			10.9			NR			NR	
Pre-CAR T transplant																		
Yes	0.5 (0.28-1.03)	NR	0.06	0.000	NR	0.05	0.6 (0.3-1.2)	NR	0.1	1.6 (0.6-4.4)	10.6	1.0	3.2(0.6-17.8)	4.8	0.2	0.9(0.1-8.1)	18.6	0.9
No		7.3			2.77			4.3			7.3			6.9			13.8	
Bridging therapy																		
Yes	0.74 (0.45-1.2)	10.9	0.2	0.8 (0.13-4.9)	NR	0.8	0.6 (0.3-1.2)	NR	0.2	0.3(0.08-1.4)	10.9	0.1	2.8(0.7-11.5)	4.0	0.1	1.7(0.4-7.9)	10.5	0.5
No		7.3			NR			4.3			5.5			NR			17.1	
CAR T product																		

Axi-cel	1.6 (0.9-2.8)	7.0	0.1	0.85 (0.14-5.2)	NR	0.9	1.6 (0.7-3.6)	4.3	0.3	1.8 (0.4-8.9)	5.9	0.4	1.1(0.2-5.5)	6.9	0.9	1.5(0.3-7.6)	13.8	0.7
Tisa-cel		19.1			NR			NR			10.9			4.2			19.1	
CR or PR obtained post-CAR as Best Overall Response																		
Yes	0.7 (0.4-1.2)	10.5	0.3	0.4 (0.06-2.4)	NR	0.3	0.7 (0.4-1.5)	8.3	0.4	1.0 (0.3-4.3)	6.3	0.9	0.6(0.2-2.5)	6.8	0.5	9.1e+08 (0-inf)	13.8	0.1
No		7.0			0.17			3.4			10.6			5.6			NR	
CNS disease																		
Yes	0.8 (0.4-1.6)	10.9	0.5	1.9 (0.31-11.3)	1.47	0.5	0.4 (0.1-1.3)	NR	0.1	0.6(0.07-5.1)	7.3	0.7	3.2(0.6-17.8)	4.8	0.2	7.5(0.5-120)	9.8	0.09
No		8.3			NR			4.3			10.9			7.0			17.1	
Bulky disease*																		
≥ 5 cm	2.1 (1.2-3.7)	4.03	**0.03**	2.9 (0.26-32.4)	2.77	0.4	1.9 (0.9-3.8)	1.5	0.2	1.2 (0.3-5.3)	7.3	0.5	5.2(0.8-32)	4.2	0.05	N/A	NR	1.0
< 5 cm		12.0			NR			8.3			10.6			NR			17.1	
Disease sites																		
≥2	2.2 (1.2-4.0)	6.8	**0.01**	1.87 (0.2-16.8)	NR	0.6	3.6 (1.3-10.4)	3.7	**0.009**	6.0 (0.7-52.5)	6.3	0.07	0.3(0.6-1.7)	7.0	0.2	1.3(0.3-6.6)	15.3	0.7
<2		19.13			NR			NR			10.9			4.8			15.6	
Extranodal disease																		

≥2	1.4 (0.77 -2.5)	7.3	0.3	9.74 e+0 8 (0.0 00- inf)	2.77	0.1	1.3 (0.6- 2.8)	3.7	0.5	0.9 (0.2- 4.4)	10.6	0.9	1.8(0.2- 14.5)	6.2	0.6	1.4(0.3- 7.4)	17.1	0.7
<2		12.0			NR			8.3			5.5			7.0			12.0	
ECOG PS																		
2-4	2.06 (1.2- 3.7)	2.9	**0.01**	8.07 e+0 9 (0.0 00- inf)	0.17	<**0.00 1**	1.8 (0.8- 4.1)	2.9	0.2	1.8 (0.5- 7.0)	6.3	0.4		NR	0.2	0.9(0.1- 8.1)	18.6	0.9
0-1		10.5			NR			8.3			7.3			6.2			13.8	
Stage																		
III-IV	2.4 (1.4- 4.1)	4.3	**0.001**	5.08 e+0 9 (0.0 00- inf)	1.07	**0.001**	1.8 (0.9- 3.8)	3.7	0.1	2.9 (0.6- 14.4)	7.3	0.2	0.8(0.16 -3.9)	6.8	0.8	1.8(0.3- 10.1)	14.2	0.5
I-II		19.13			NR			13.7			NR			7.0			15.6	
Elevated LDH																		
Yes	3.2 (1.8- 5.7)	4.03	<**0.00 1**	1.56 (0.2 6- 9.3)	2.77	0.6	5.06 (1.9- 13.2)	3.2	<**0.00 1**	2.7 (0.5- 13.5)	5.5	0.2	2.0(0.4- 10.0)	6.8	0.4	0.8(0.17 -3.5)	15.3	0.7
No		NR			NR			NR			10.9			NR			15.6	
IPI																		
≥3	2.5 (1.5- 4.1)	4.03	<**0.00 1**	12.2 (1.3	0.67	**0.005**	2.2 (1.1- 4.5)	3.2	**0.02**	3.6 (0.7-	6.3	0.1	3.6(0.7-	6.8		1.8(0.3-	14.2	0.5

				3-111)						10.6)			18.6)			10.1)		
<3		15.6			NR			14.3			10.9			6.3	0.6		15.6	

Supplementary table 2: Univariate analysis for prognostic factors of overall survival from the start date of salvage therapy

HR, hazard ratio; OS, overall survival; RT, Radiation therapy; CMT, combined modality therapy; ST, systemic therapy; CR, complete response; PR, partial response; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; IPI, international prognostic index
*Patients with CNS lymphoma were excluded

Characteristic	Univariate analysis											
	All patients			**RT**			**ST**			**CMT**		
	HR (95%CI)	**Median EFS (mo)**	**P-value**	**HR (95%CI)**	**Median EFS (mo)**	**P-value**	**HR (95%CI)**	**Median EFS (mo)**	**P-value**	**HR (95%CI)**	**Median EFS (mo)**	**P-value**
Gender												
Male	1.04 (0.68-1.6)	2.6	0.9	1.8 (0.58-5.4)	3.5	0.3	1.01 (0.6-1.7)	1.7	1.0	0.6 (0.2-1.85)	4.9	0.4
Female		2.7			7.6			2.7			1.6	
Age at time of diagnosis												
≥60	0.9 (0.6-1.5)	3.2	0.8	2.65 (0.60-11.5)	3.5	0.2	0.9 (0.5-1.5)	2.7	0.6	0.5 (0.14-1.6)	4.4	0.2
<60		1.7			NR			1.6			1.0	
Pre-CAR T transplant												
Yes	0.66 (0.39-1.1)	3.2	0.1	0.3 (0.08-1.1)	9.7	0.06	0.8 (0.4-1.5)	2.2	0.5	0.8 (0.2-3.2)	5.5	0.8
No		1.9			3.5			1.7			1.9	
Bridging therapy												
Yes	1.01 (0.67-1.5)	1.9	0.9	1.7 (0.68-4.3)	2.5	0.2	0.9 (0.5-1.5)	1.9	0.6	1.1 (0.37-3.3)	2.6	0.8
No		2.7			5.6			2.1			5.5	
CAR T product												
Axi-cel	1.2 (0.77-1.9)	2.6	0.4	1.5 (0.6-4.0)	4.1	0.4	1.3 (0.7-2.4)	1.7	0.3	0.4 (0.13-1.4)	4.4	0.2
Tisa-cel		2.7			3.5			2.7			1.6	
CR or PR obtained post-												

CAR as Best Overall Response												
Yes	0.8 (0.5-1.3)	2.8	0.4	0.95 (0.31-2.9)	3.5	0.9	0.8 (0.5-1.4)	2.2	0.5	0.7 (0.2-2.4)	3.4	0.6
No		1.4			5.6			1.4			3.5	
CNS disease												
Yes	0.8 (0.4-1.5)	1.4	0.6	0.75 (0.22-2.6)	3.5	0.7	0.7 (0.3-1.6)	4.03	0.4	8.5 (1.2-61.5)	1.0	**0.01**
No		2.7			4.1			1.9			4.4	
Bulky disease*												
≥ 5 cm	1.3 (0.8-2.2)	1.7	0.4	2.2 (0.7-7.5)	1.7	0.2	1.4 (0.7-2.5)	1.2	0.4	0.7 (0.2-2.7)	5.6	0.6
< 5 cm		3.2			5.5			2.6			4.4	
Disease sites												
≥2	1.7 (1.02-2.8)	1.9	**0.04**	1.46 (0.57-3.7)	3.2	0.4	1.6 (0.8-3.1)	1.8	0.2	2.3 (0.6-8.5)	2.6	0.2
<2		5.5			6.2			2.9			5.5	
Extranodal disease												
≥2	1.7 (1.01 - 2.85)	1.8	**0.04**	1.5 (0.55-4.3)	2.0	0.4	1.6 (0.8-3.1)	1.7	0.1	1.9 (0.4-8.7)	2.6	0.4
<2		5.1			5.6			3.5			5.5	
ECOG PS												
2-4	1.86 (1.1-3.1)	1.25	**0.02**	2.6 (0.86-8.1)	0.65	0.08	1.6 (0.8-3.1)	1.4	0.2	1.9 (0.6-6.7)	1.5	0.3
0-1		3.2			4.77			2.6			4.4	
Stage												
III-IV	2.4 (1.5-3.8)	1.7	**<0.001**	3.75 (1.47-9.5)	1.1	**0.003**	2.06 (1.1-3.8)	1.7	**0.02**	3.6 (0.9-13.5)	1.9	0.05
I-II		5.6			6.2			3.2			6.9	

Elevated LDH												
Yes	1.9 (1.2-2.9)	1.6	**0.005**	0.93 (0.36-2.4)	5.2	0.9	2.5 (1.4-4.4)	1.35	**0.002**	1.2 (0.3-4.6)	1.9	0.7
No		4.4			3.2			5.7			3.8	
IPI												
≥3	2.0 (1.3-3.1)	1.7	**0.001**	3.2 (1.2-8.06)	1.4	**0.01**	1.7 (0.9-2.9)	1.7	0.06	2.4 (0.7-8.3)	2.6	0.1
<3		5.4			5.6			2.8			5.5	

Supplementary table 3: Univariate analysis for prognostic factors of event-free survival from the start date of the first salvage therapy following CAR T-cell therapy failure.

HR, hazard ratio; EFS, event-free survival; RT, Radiation therapy; CMT, combined modality therapy; ST, systemic therapy; CR, complete response; PR, partial response; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; IPI, international prognostic index
*Patients with CNS lymphoma were excluded