Outcome of large B-cell lymphoma patients treated with tafasitamab plus lenalidomide either before or after CAR T-cells

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Supplemental data

Supplemental Methods

The French registry DESCART-T

DESCAR-T (NCT04328298) is a real-life multicentric registry set up in French sites qualified for CAR T-cell treatment, sponsored by the Lymphoma Study Association/Lymphoma Academic Research Organization (LYSA/LYSARC) and used in France to collect data from all patients treated with commercial CAR T-cell for all hematologic malignancies outside clinical trials[1]. Patients were included in this registry if they were considered eligible for CAR T-cell by a multidisciplinary committee of an accredited center. All patients received a nonoppositional notice letter before enrollment. Data regarding patient characteristics and medical history, CAR T-cell efficacy and toxicity and subsequent lines of therapy were prospectively collected by local investigators. The protocol was approved by national ethics committees and the data protection agency, and the study was performed in accordance with the Declaration of Helsinki. DESCAR-T is registered under the ClinicalTrials.gov identifier NCT04328298.

Assessment of response and follow-up duration

The best overall response (bORR) was the best response recorded during the patient evaluation period. If a patient received treatment for progression, all responses recorded after the initiation of this new treatment for progression were censored. Assessment of response was based on local investigator assessments using the Lugano classification[2].

Follow-up duration (FUD) was defined as the time between the date of the 1st CAR T-cell infusion and the last contact date for surviving patients in the TL-pre-CAR-T set and TL-post-CAR-T set. Patients who died were censored at the time of death, and the FUD was estimated using the reverse Kaplan–Meier method.

Definition of PFS, OS, PFS2 and OS2

OS was measured from the date of CAR T-cell administration to the date of death from any cause. Patients still alive were censored at their date of last contact. PFS was measured from the date of CAR T-cell administration to the date of progression/relapse by investigator assessment or death from any cause. Patients still alive were censored at their date of last contact. PFS2 was measured from the starting date of the 1st progression treatment to the date of the 2nd progression (as determined by investigator assessments), initiation of a subsequent line of therapy, or death from any cause. Patients who were still alive and without progression were censored at the date of their last contact. If the starting date of the 1st progression treatment was not available, the date of progression was used instead. OS2 was measured from the starting date of the 1st progression treatment to the date of death from any cause. Patients still alive were censored at their date of last contact. For indirect comparisons with control patients, the response rates, PFS2 and OS2 were analyzed from the date of the start of the first progression treatment.

Details of indirect comparison procedures

We conducted an inverse probability weighting (IPW) comparison of TAFA-LEN v. other treatments in the TL-post-CAR-T set. Patients identified as having received anticancer therapy in a clinical trial setting to treat the first progression after CAR T-cell were excluded from IPW comparison. We did not conduct this comparison in the TL-pre-CAR-T set due to the low number of patients treated with TAFA-LEN before CAR-T in the DESCAR-T registry. The IPW was calculated for each patient by using the stabilized weight (SW) method by entering the following covariates (assessed at the time of lymphodepletion for most): age, sex, LDH, ECOG, Ann Arbor stage, number of prior lines, prior allo- or autotransplantation, bulk (≤5; >5 cm), treatment (axi-cel; tisa-cel), response after bridging therapy, time from first progression to first treatment for progression, and histology (LBCL; transformed indolent), as previously described[3].

Sensitivity analysis

A sensitivity analysis using multiple imputation with a chained equation was produced to assess the impact of missing values in weighting variables on the comparison analysis. We performed multiple imputation with the following calibrations (i) 100 imputed datasets were generated, and (ii) 40 iterations of chained equations were performed. Logistic regression was used for binary variables, and polytomous regression was used for other categorical variables. There

were no continuous variables with missing values. The prediction model was composed of all weighting variables. PROC MI and PROC MIANALYSE in SAS 9.4 were used to perform multiple imputation with the following random seed: 16022024. Analyses were then performed on each of the imputed datasets and pooled using Rubin's rule (within method) and adjusted Kaplan–Meier estimates[4].

Supplemental References

1. Broussais, F. *et al.* [DESCAR-T, a nationwide registry for patient treated by CAR-T Cells in France]. *Bull. Cancer (Paris)* **108**, S143–S154 (2021).
2. Cheson, B. D. *et al.* Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J. Clin. Oncol.* **32**, 3059–3067 (2014).
3. Bachy, E. *et al.* A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. *Nat. Med.* **28**, 2145–2154 (2022).
4. Morisot, A. *et al.* Prostate cancer: net survival and cause-specific survival rates after multiple imputation. *BMC Med. Res. Methodol.* **15**, 54 (2015).

Supplemental Table 1: Best response after CAR T-cell infusion in the TL-post-CAR-T set

	N=52	
Best response		
Complete response	18	(34.6%)
Partial response	15	(28.8%)
STable disease	2	(3.8%)
Progressive disease	17	(32.7%)
Best overall Response Rate*		
BORR	33	(63.5%)
95% CI	[49.0% ; 76.4%]	
Time to Best response (months)		
N	33	
Mean (SD)	1.53 (1.348)	
Median	1.05	
Q1; Q3	1.0 ; 1.2	
P1; P99	0.8 ; 6.0	

**Defined as CR+PR*

Supplemental Table 2: Best response rates after TAFA-LEN initiation in the TL-post-CAR-T set

	TL-post-CAR-T set N=52	
Best response		
Complete response	4	(7.7%)
Partial response	3	(5.8%)
STable disease	4	(7.7%)
Progressive disease	29	(55.8%)
Dead	3	(5.8%)
Not reached	5	(9.6%)
Not evaluated	4	(7.7%)
Best overall response rate*		
BORR	7	(13.5%)
95% CI	[5.6% ; 25.8%]	
Best complete response rate		
BCRR	4	(7.7%)
95% CI	[2.1% ; 18.5%]	

* Defined as (CR + PR)

Supplemental Table 3: Description of CD19 (immunohistochemistry) status in the two patient sets according to the timing of the biopsy.

	TL-pre-CAR-T set N=15		TL-post-CAR-T set N=52	
CD19 status before CAR T-cell				
Negative	1	(6.7%)	7	(13.5%)
Positive	3	(20.0%)	12	(23.1%)
Not tested/not done	11	(73.3%)	33	(63.5%)
CD19 status after CAR T-cell				
Negative	2	(13.3%)	0	(0.0%)
Positive	0	(0.0%)	12	(23.1%)
Not tested/not done	13	(86.7%)	39	(75.0%)
Missing	0		1	
CD19 status before Tafasitamab				
Negative	1	(6.7%)	0	(0.0%)
Positive	4	(26.7%)	12	(23.1%)
Not tested/not done	10	(66.7%)	38	(73.1%)
Missing	0		2	
CD19 status after Tafasitamab				
Negative	1	(6.7%)	0	(0.0%)
Positive	3	(20.0%)	1	(1.9%)
Not tested/not done	11	(73.3%)	50	(96.2%)
Missing	0		1	

Supplemental Table 4: Best complete response rate (bCRR) and time to best complete response according to CD19 status before CAR T-cell in the TL-post-CAR-T set

	CD19 status before CAR T-cell						TL-post-CAR-T set	
	Negative		Positive		Not Done			
	N=7		N=12		N=33		N=52	
Best complete response rate								
BCRR	2	(28.6%)	5	(41.7%)	11	(33.3%)	18	(34.6%)
95% CI	[3.7% ; 71.0%]		[15.2% ; 72.3%]		[18.0% ; 51.8%]		[22.0% ; 49.1%]	
Time to best complete response (months)								
N	2		5		11		18	
Mean (SD)	1.03 (0.023)		1.06 (0.094)		2.14 (1.776)		1.72 (1.469)	
Median	1.03		1.05		1.18		1.08	
Q1 ; Q3	1.0 ; 1.1		1.0 ; 1.1		1.0 ; 3.5		1.0 ; 1.3	
P1 ; P99	1.0 ; 1.1		1.0 ; 1.2		0.9 ; 6.0		0.9 ; 6.0	

Supplemental Table 5: Other treatments received for 1st progression/relapse in the control group

(A) Propensity Score set and Unweighted set

	Propensity score set				Unweighted set	
	TL-post-CAR-T set N=43		Control N=354		N=397	
Patients who progressed/relapsed	43	(100.0%)	354	(100.0%)	397	(100.0%)
Treatment of Progression / Relapse						
No	0	(0.0%)	0	(0.0%)	0	(0.0%)
Yes	43	(100.0%)	354	(100.0%)	397	(100.0%)
If yes, type of treatment*						
Monoclonal antibody	43	(100.0%)	170	(48.0%)	213	(53.7%)
Checkpoints inhibitor	0	(0.0%)	25	(7.1%)	25	(6.3%)
Bispecific antibody	0	(0.0%)	35	(9.9%)	35	(8.8%)
Other immunotherapy	0	(0.0%)	1	(0.3%)	1	(0.3%)
Chemotherapy	0	(0.0%)	91	(25.7%)	91	(22.9%)
Radiotherapy	0	(0.0%)	43	(12.1%)	43	(10.8%)
Autologous transplant	0	(0.0%)	2	(0.6%)	2	(0.5%)
Allogenic transplant	1	(2.3%)	4	(1.1%)	5	(1.3%)
IMiD	41	(95.3%)	167	(47.2%)	208	(52.4%)
Epigenetic modifiers agents	0	(0.0%)	0	(0.0%)	0	(0.0%)
Kinase inhibitor	1	(2.3%)	27	(7.6%)	28	(7.1%)
CAR-T cell infusion	0	(0.0%)	0	(0.0%)	0	(0.0%)
Corticosteroids	3	(7.0%)	24	(6.8%)	27	(6.8%)
Other anti-cancer therapy	0	(0.0%)	9	(2.5%)	9	(2.3%)
Missing	0		0		0	

(B) Propensity Score set and Stabilized weight (SW) set

	Propensity score set				Stabilized weight set (SW)	
	TL-post-CAR-T set		Control			
	47.5		350.1		397.6	
Patients who progressed/relapsed	47.5	(100.0%)	350.1	(100.0%)	397.6	(100.0%)
Treatment of Progression / Relapse						
No	0.0	(0.0%)	0.0	(0.0%)	0.0	(0.0%)
Yes	47.5	(100.0%)	350.1	(100.0%)	397.6	(100.0%)
If yes, type of treatment*						
Monoclonal antibody	47.5	(100.0%)	168.9	(48.3%)	216.5	(54.4%)
Checkpoints inhibitor	0.0	(0.0%)	24.6	(7.0%)	24.6	(6.2%)
Bispecific antibody	0.0	(0.0%)	35.6	(10.2%)	35.6	(9.0%)
Other immunotherapy	0.0	(0.0%)	0.9	(0.3%)	0.9	(0.2%)
Chemotherapy	0.0	(0.0%)	90.1	(25.7%)	90.1	(22.7%)
Radiotherapy	0.0	(0.0%)	43.2	(12.3%)	43.2	(10.9%)
Autologous transplant	0.0	(0.0%)	2.0	(0.6%)	2.0	(0.5%)
Allogenic transplant	0.4	(0.8%)	4.1	(1.2%)	4.5	(1.1%)
IMiD	45.1	(94.9%)	164.9	(47.1%)	210.0	(52.8%)
Epigenetic modifiers agents	0.0	(0.0%)	0.0	(0.0%)	0.0	(0.0%)
Kinase inhibitor	0.4	(0.8%)	26.2	(7.5%)	26.6	(6.7%)
CAR-T cell infusion	0.0	(0.0%)	0.0	(0.0%)	0.0	(0.0%)
Corticosteroids	2.2	(4.6%)	23.0	(6.6%)	25.2	(6.3%)
Other anti-cancer therapy	0.0	(0.0%)	8.4	(2.4%)	8.4	(2.1%)
Missing	0.0		0.0		0.0	

Supplemental Table 6: Best response rates after TAFA-LEN vs. other treatments (control group) for first progression after CAR T-cell infusion – stabilized weight (SW)

	SW	
	TL-post-CAR-T set	Control
	47.5	350.1
Best response		
Complete Response	5.5 (11.6%)	48.4 (13.8%)
Partial Response	4.2 (8.9%)	28.8 (8.2%)
Stable Disease	2.4 (5.0%)	13.8 (3.9%)
Progressive Disease	27.6 (58.0%)	209.7 (59.9%)
Dead	1.4 (2.8%)	18.4 (5.3%)
Not reached	5.0 (10.5%)	15.1 (4.3%)
Not Evaluated	1.5 (3.1%)	15.9 (4.5%)
Best overall Response Rate*		
BORR	9.8 (20.6%)	77.2 (22.1%)
95% CI	[4.8% ; 27.8%]	[8.2% ; 30.3%]
Best Complete Response Rate*		
BCRR	5.5 (11.6%)	48.4 (13.8%)
95% CI	[0.3% ; 18.3%]	[5.2% ; 25.5%]

* Defined as (CR + PR)

Best response from all safety follow-ups. The best response is censored in the case of a second treatment for progression.

Supplemental Table 7: Best response rates after TAFA-LEN vs. LEN for first progression after CAR T-cell infusion – stabilized weight (SW)

	Stabilized weight set (SW)				Test
	TAFA-LEN		LEN		
	42.8		50.0		
Best response					
Complete response	2.6	(6.0%)	6.7	(13.4%)	
Partial response	3.4	(7.9%)	1.5	(3.0%)	
STable disease	2.2	(5.1%)	4.1	(8.2%)	
Progressive disease	26.9	(62.9%)	32.6	(65.2%)	
Dead	1.2	(2.9%)	4.1	(8.2%)	
Not reached	5.5	(12.9%)	0.9	(1.9%)	
Not evaluated	1.0	(2.3%)	0.0	(0.0%)	
Best overall response rate*					
BORR	5.9	(13.9%)	8.2	(16.4%)	Weighted Chi2: P=0.7397
95% CI	[2.4% ; 25.3%]		[5.8% ; 27.1%]		
Best complete response rate					
BCRR	2.6	(6.0%)	6.7	(13.4%)	Weighted Chi2: P=0.1944
95% CI	[0.0% ; 12.2%]		[3.7% ; 23.1%]		

* Defined as (CR + PR)

Best response from all safety follow-ups. The best response is censored in the case of a second treatment for progression.

Supplemental Table 8: Description of TAFA-LEN use in the TL-pre-CAR-T set

	TL-pre-CAR-T set	
	N=15	
TAFA-LEN prior CAR-T infusion	15	(100.0%)
If yes,		
TAFA-LEN for prior treatment line*	13	(86.7%)
TAFA-LEN for last line of treatment prior to CAR T-cell administration (excl. bridging)	1	(6.7%)
TAFA-LEN during bridging therapy*	3	(20.0%)
TAFA-LEN for last bridging therapy	2	(13.3%)
TAFA-LEN for last line of treatment prior to CAR T-cell administration (bridging/prior line)	2	(13.3%)

*One patient had TAFA-LEN as both a prior treatment line and bridging therapy.

Supplemental Table 9: Description of the duration of TAFA-LEN treatment in patients receiving TAFA-LEN as a prior line of therapy in the TL-pre-CAR-T set

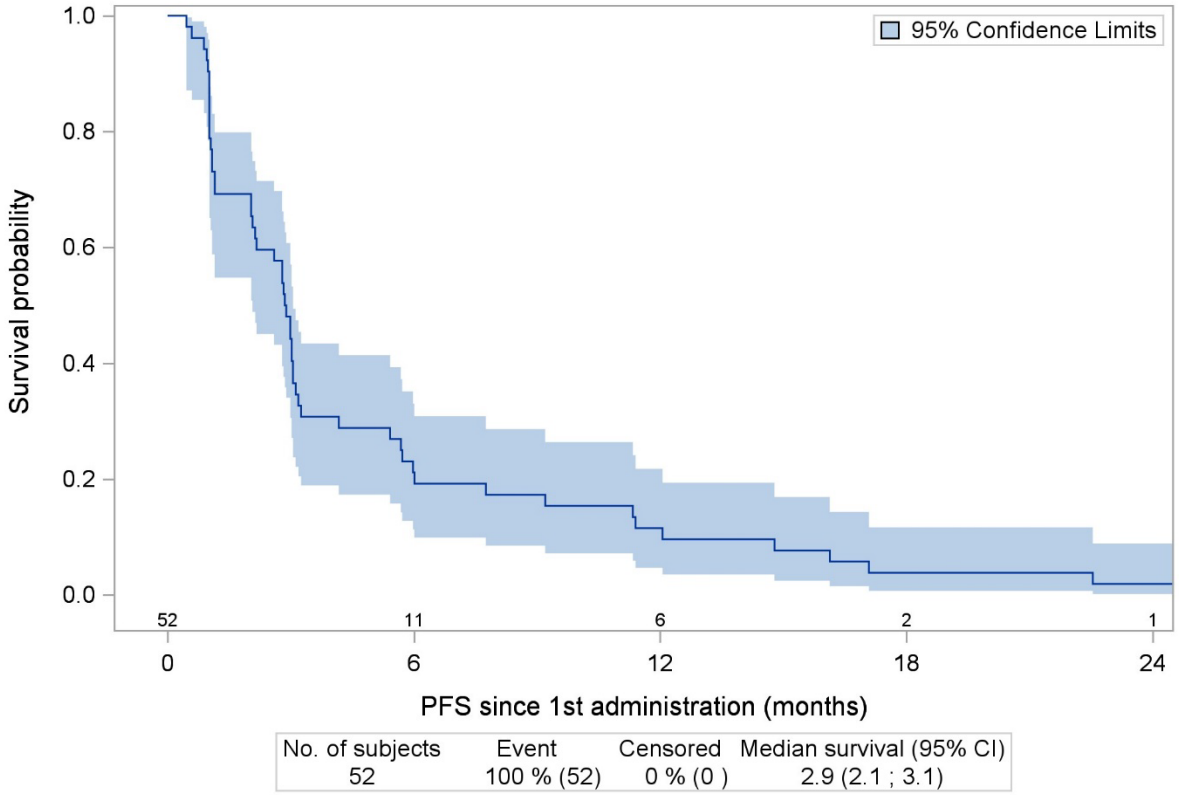
	TAFA-LEN prior CAR T-cell infusion	
	N=15	
TAFA-LEN for prior treatment line	13	(86.7%)
If yes,		
Duration of prior treatment line with TAFA-LEN (months)		
N	13	
Mean (SD)	4.7 (3.53)	
Median	3.7	
Q1 ; Q3	2.0 ; 7.4	
Min ; Max	0.1 ; 12.0	
Time from end of prior TAFA-LEN to 1st CAR T-cell infusion (months)		
N	13	
Mean (SD)	2.8 (1.19)	
Median	2.7	
Q1 ; Q3	2.1 ; 3.4	
Min ; Max	1.3 ; 5.1	

Supplemental Table 10: Description of the duration of TAFA-LEN treatment and response in patients receiving TAFA-LEN as bridging therapy in the TL-pre-CAR-T set

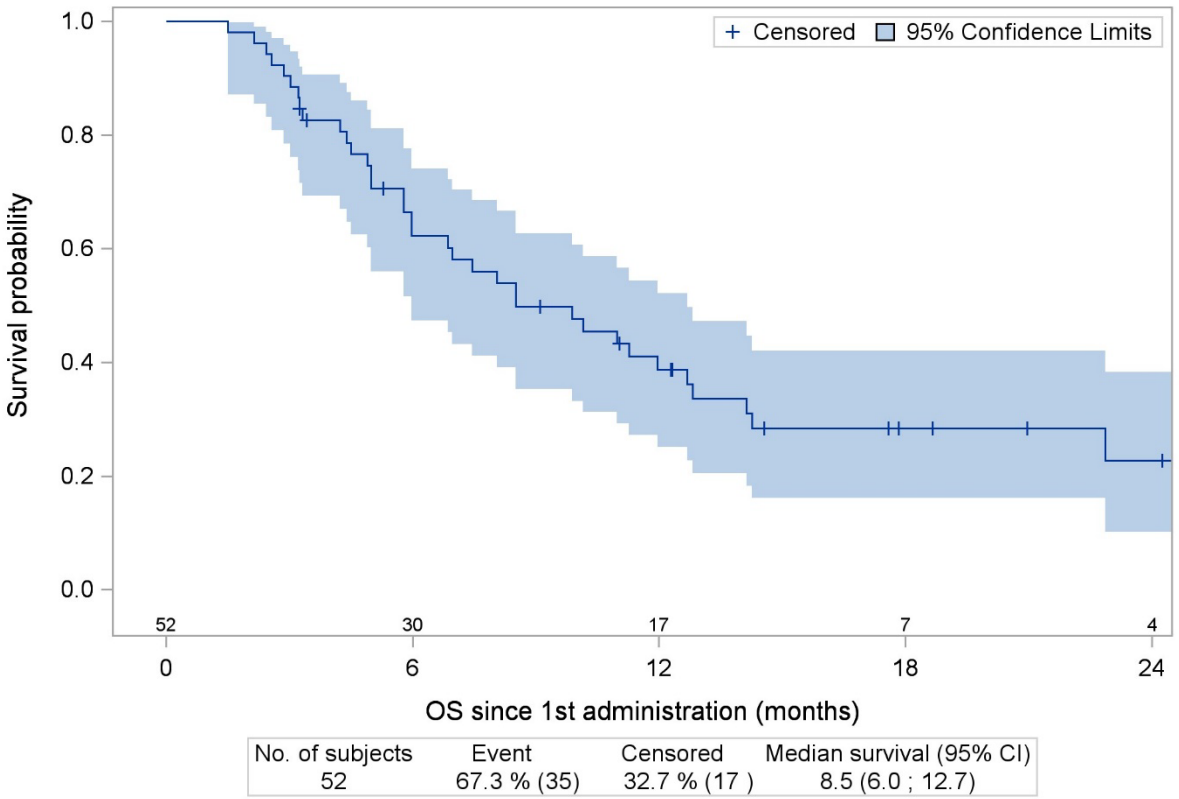
	TAFA-LEN prior to CAR T-cell infusion	
	N=15	
TAFA-LEN during bridging therapy	3	(20.0%)
If yes,		
Duration of bridging line with TAFA-LEN (days)		
N	3	
Mean (SD)	31.7 (23.25)	
Median	23	
Q1 ; Q3	14 ; 58	
Min ; Max	14 ; 58	
Time from end of bridging treatment with TAFA-LEN to 1st CAR T-cell infusion (days)		
N	3	
Mean (SD)	18.0 (14.11)	
Median	20	
Q1 ; Q3	3 ; 31	
Min ; Max	3 ; 31	
Response after bridging treatment with TAFA-LEN		
Partial response	2	(66.7%)
Progressive disease	1	(33.3%)

Supplemental Figure 1: Progression-free survival (PFS) (A) and overall survival (OS) (B) after CAR T-cell infusion in the TL-post-CAR-T set

(A)

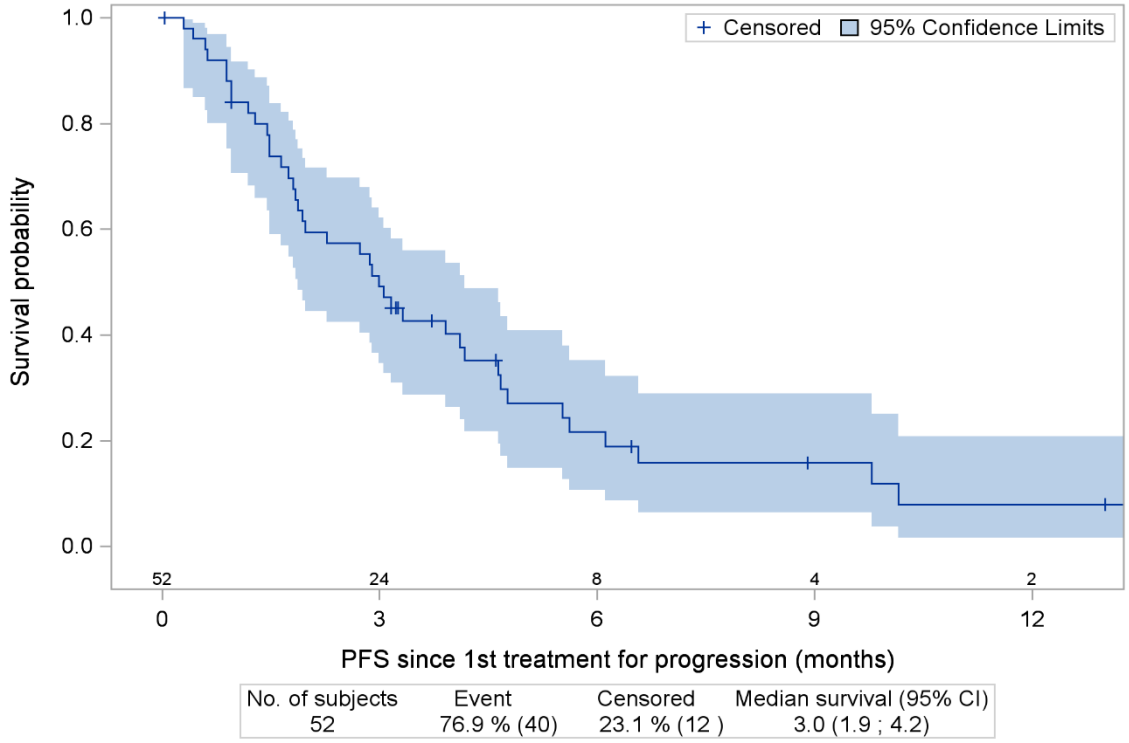


(B)



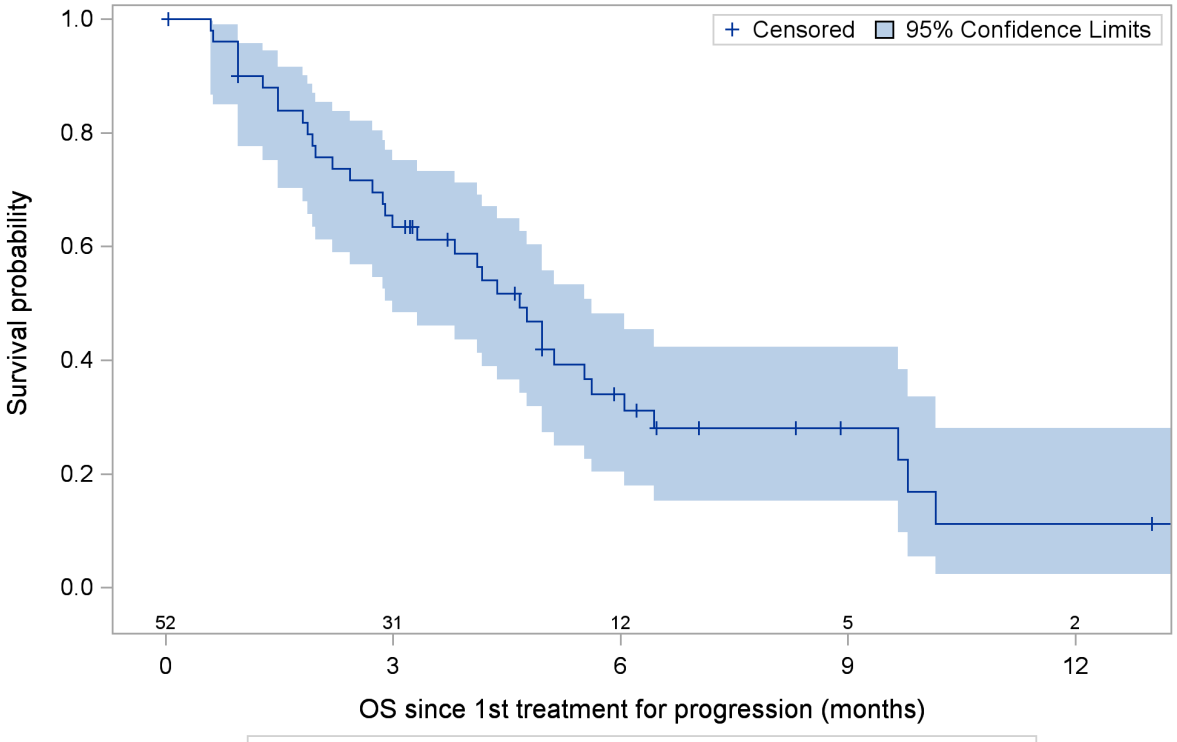
Supplemental Figure 2: Progression-free survival (A), overall survival (B) and duration of response (C) since treatment for the 1st progression (PFS2, OS2 and DOR2, respectively) in the TL-post-CAR-T set.

(A)



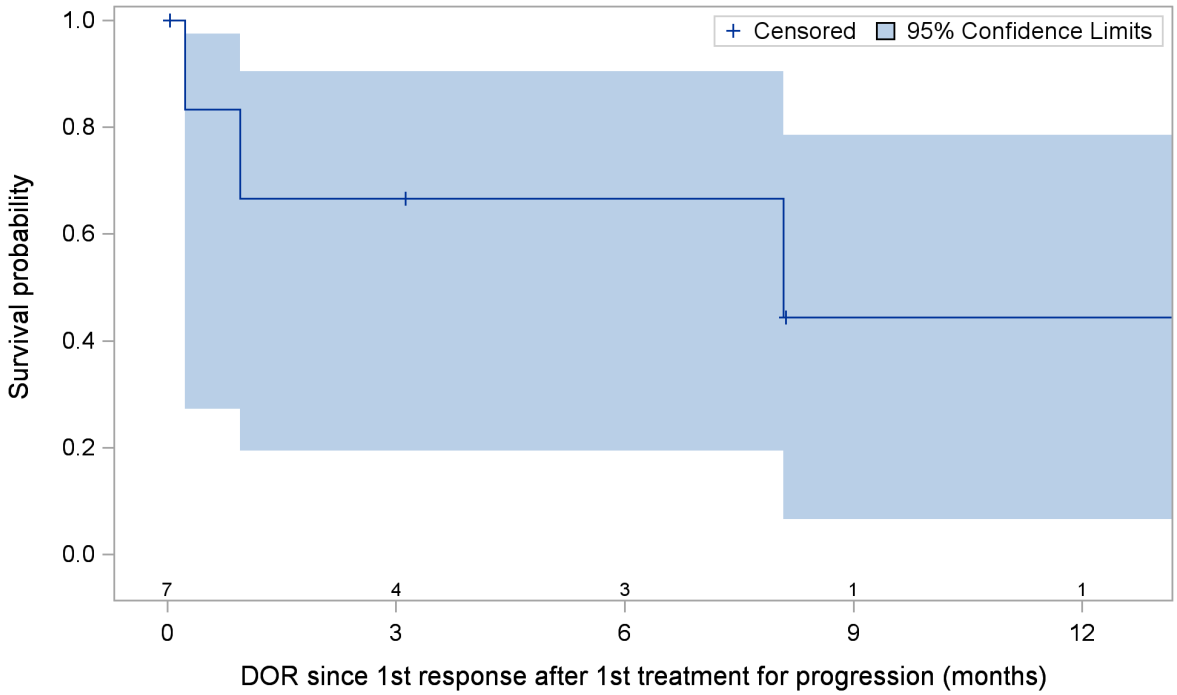
No. of subjects	Event	Censored	Median survival (95% CI)
52	76.9 % (40)	23.1 % (12)	3.0 (1.9 ; 4.2)

(B)



No. of subjects	Event	Censored	Median survival (95% CI)
52	67.3 % (35)	32.7 % (17)	4.7 (3.0 ; 5.6)

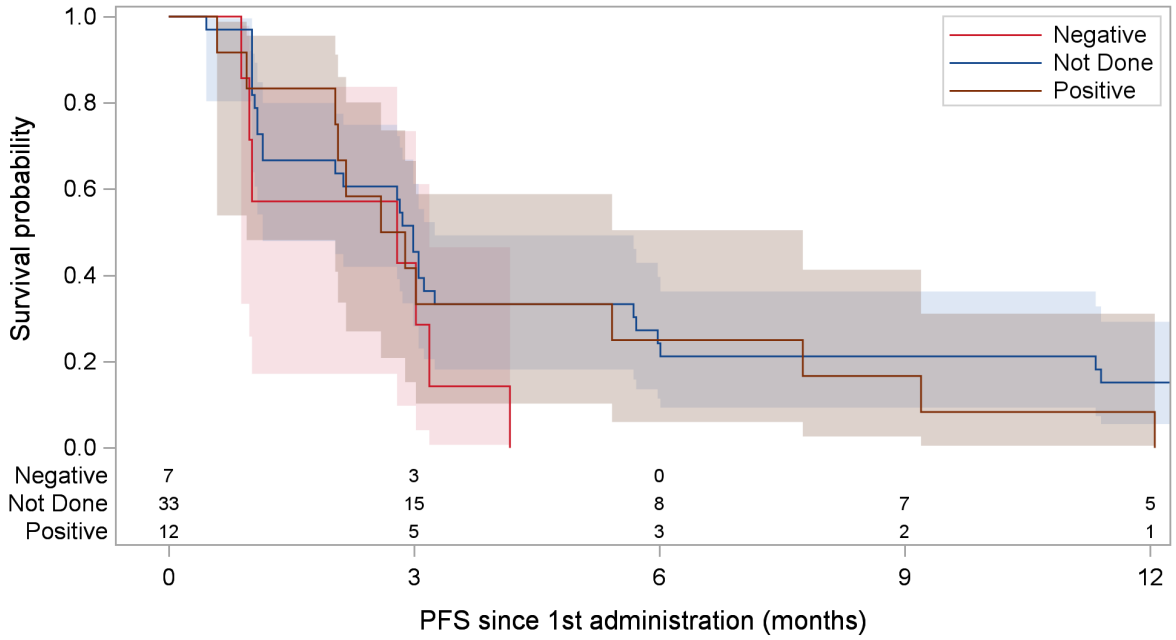
(C)



No. of subjects	Event	Censored	Median survival (95% CI)
7	42.9 % (3)	57.1 % (4)	8.1 (0.2 ; NA)

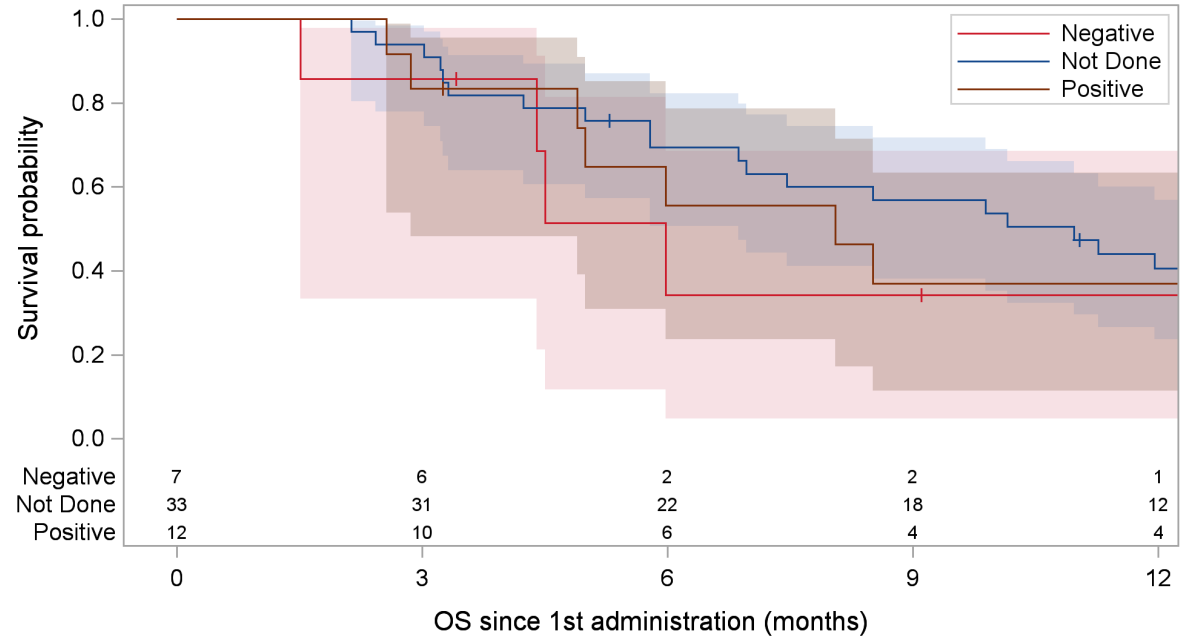
Supplemental Figure 3: Progression-free survival (A) and overall survival (B) after CAR T-cell according to CD19 status before CAR T-cell in the TL-post-CAR-T set

(A)



	No. of subjects	Event	Censored	Median survival (95% CI)
Negative	7	100 % (7)	0 % (0)	2.8 (0.9 ; 3.2)
Not Done	33	100 % (33)	0 % (0)	3.0 (1.1 ; 3.3)
Positive	12	100 % (12)	0 % (0)	2.7 (1.0 ; 7.8)

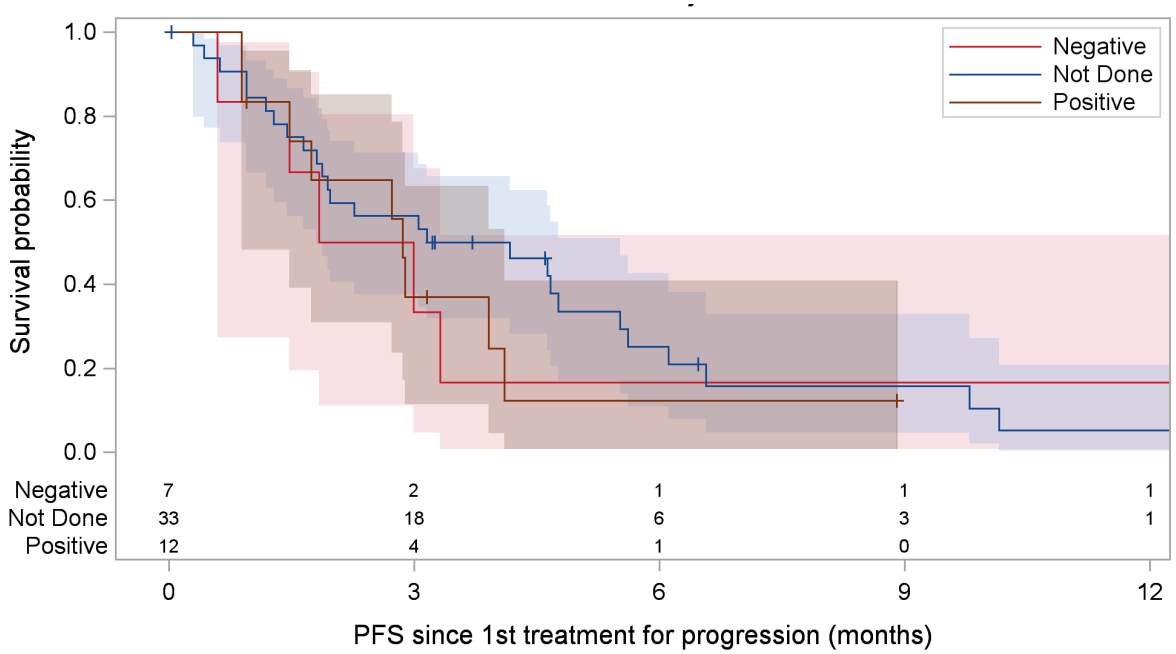
(B)



	No. of subjects	Event	Censored	Median survival (95% CI)
Negative	7	57.1 % (4)	42.9 % (3)	6.0 (1.5 ; NA)
Not Done	33	69.7 % (23)	30.3 % (10)	11.0 (6.9 ; 12.8)
Positive	12	66.7 % (8)	33.3 % (4)	8.0 (2.9 ; NA)

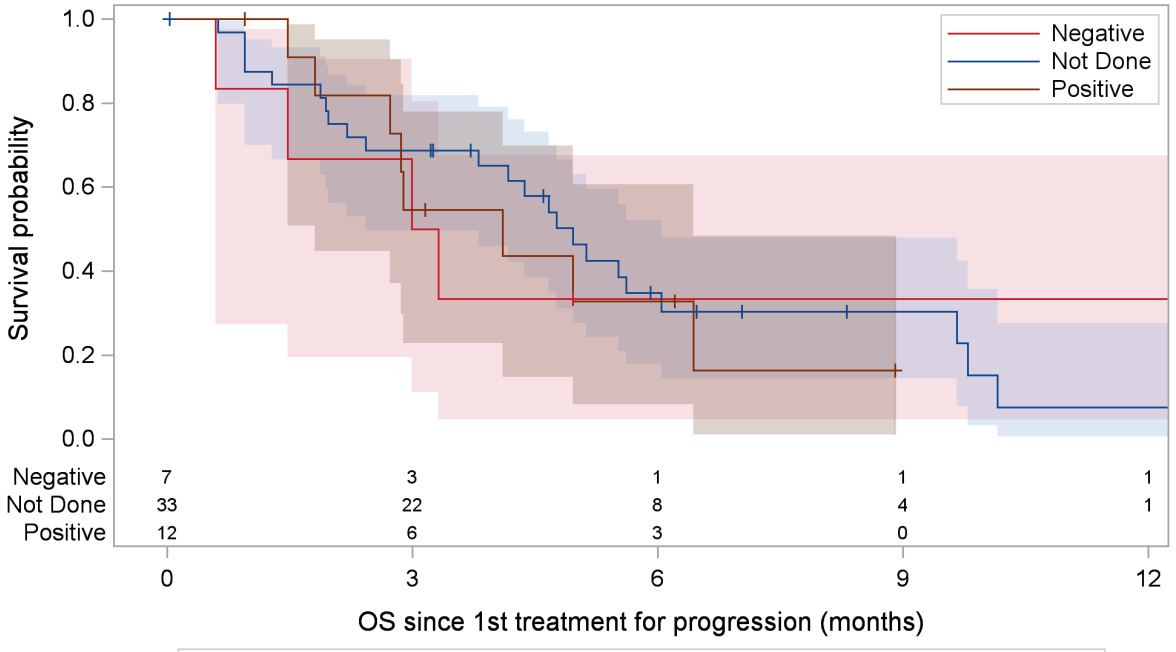
Supplemental Figure 4: PFS2 (A) and OS2 (B) according to CD19 status before CAR T-cell in the TL-post-CAR-T set

(A)



	No. of subjects	Event	Censored	Median survival (95% CI)
Negative	7	71.4 % (5)	28.6 % (2)	2.4 (0.6 ; NA)
Not Done	33	78.8 % (26)	21.2 % (7)	3.7 (1.8 ; 5.5)
Positive	12	75 % (9)	25 % (3)	2.9 (0.9 ; 4.1)

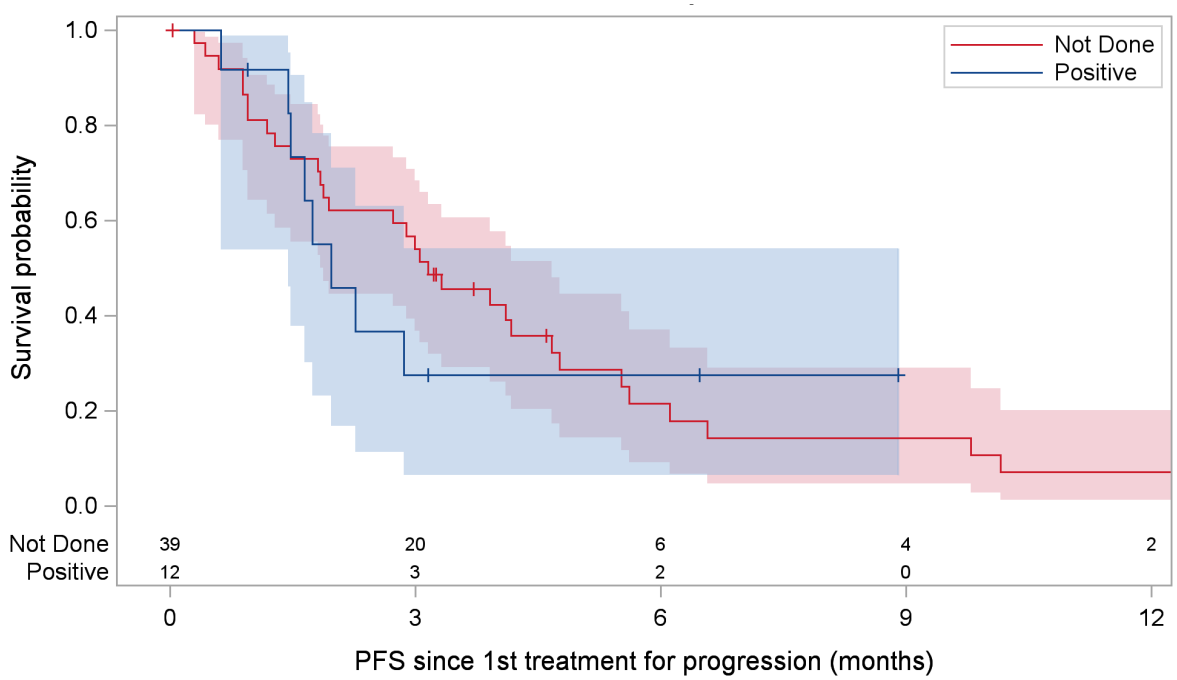
(B)



	No. of subjects	Event	Censored	Median survival (95% CI)
Negative	7	57.1 % (4)	42.9 % (3)	3.2 (0.6 ; NA)
Not Done	33	69.7 % (23)	30.3 % (10)	5.0 (2.4 ; 6.0)
Positive	12	66.7 % (8)	33.3 % (4)	4.1 (1.8 ; 6.4)

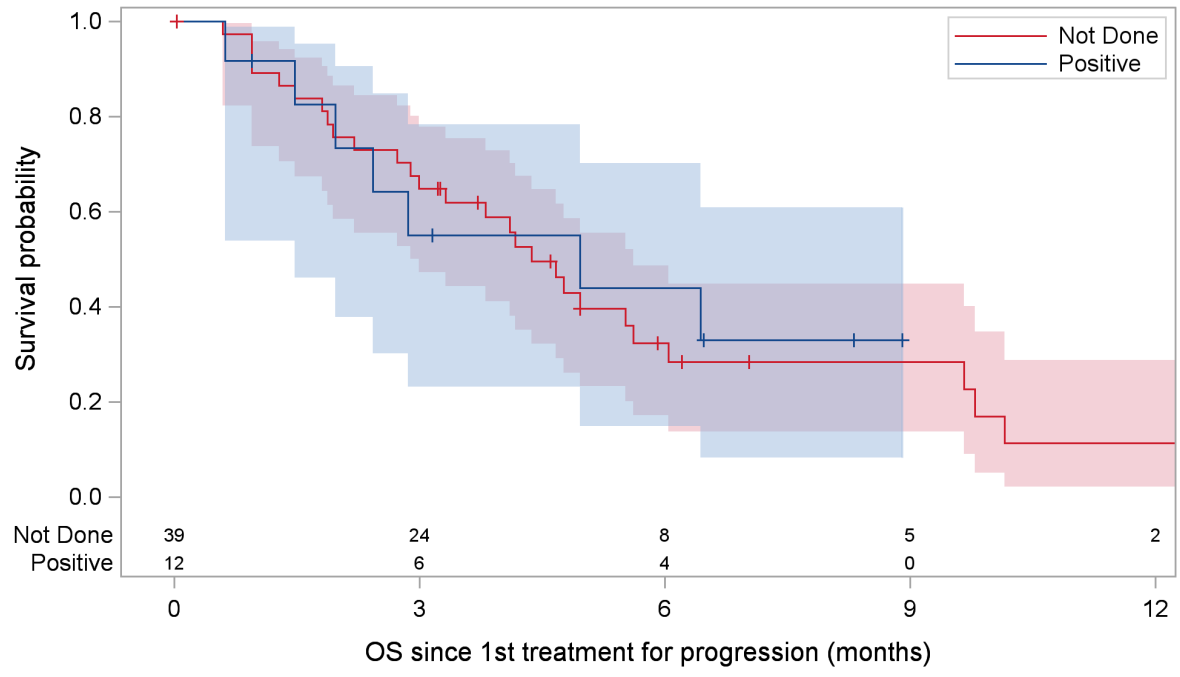
Supplemental Figure 5: PFS2 (A) and OS2 (B) according to CD19 status after CAR T-cell in the TL-post-CAR-T set

(A)



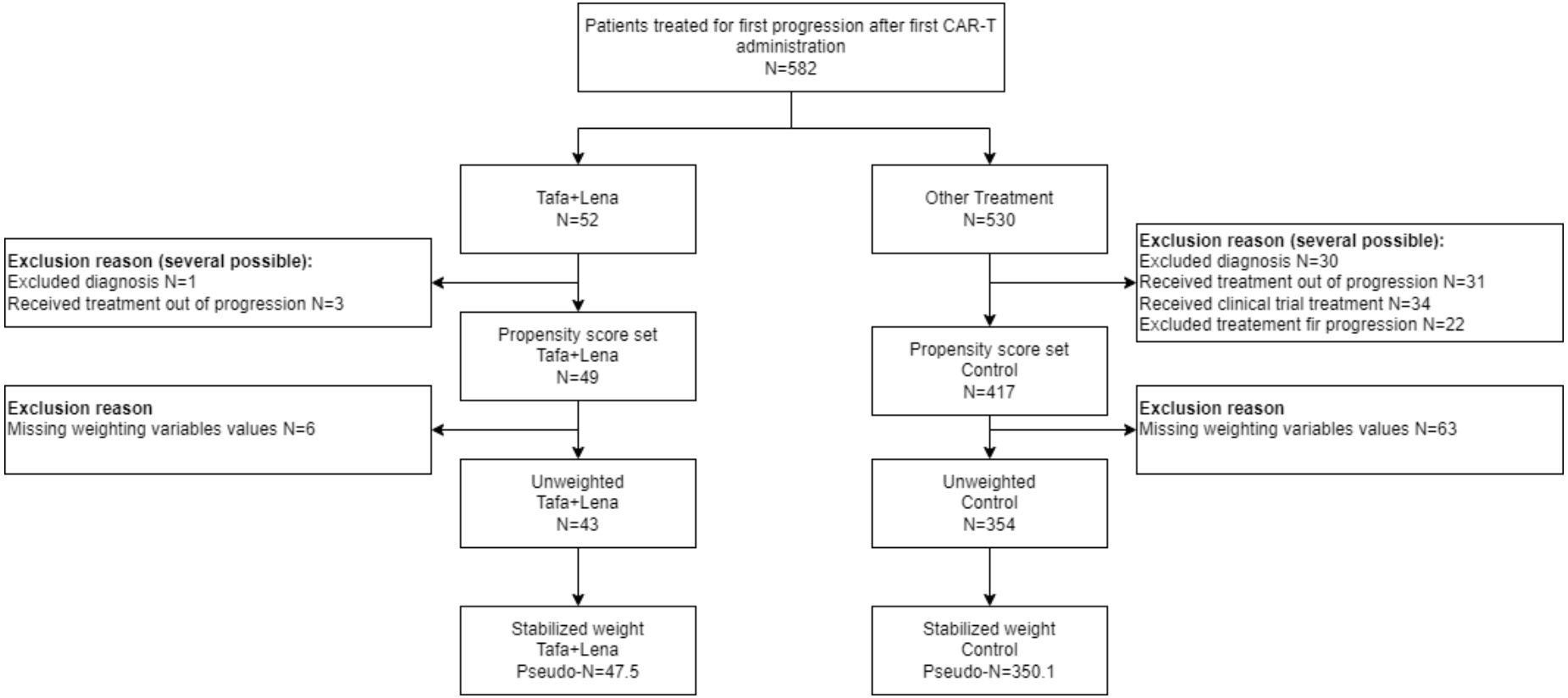
	No. of subjects	Event	Censored	Median survival (95% CI)
Not Done	39	79.5 % (31)	20.5 % (8)	3.2 (1.9 ; 4.7)
Positive	12	66.7 % (8)	33.3 % (4)	2.0 (1.4 ; NA)

(B)

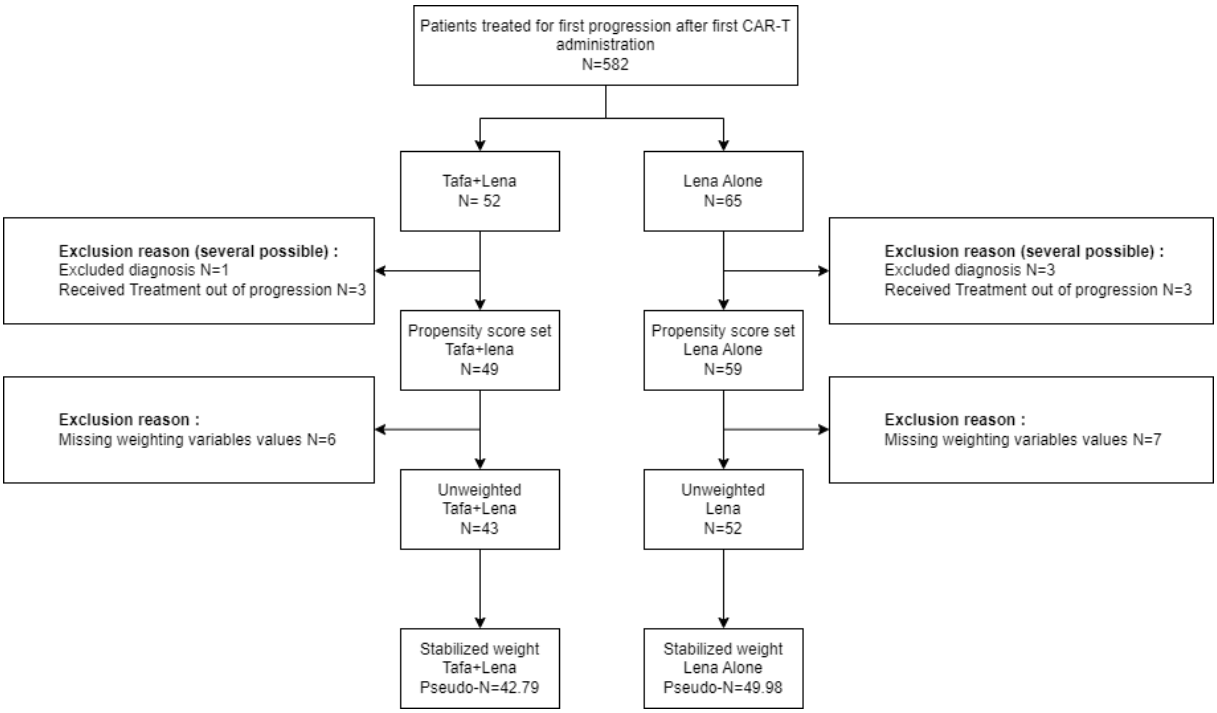


	No. of subjects	Event	Censored	Median survival (95% CI)
Not Done	39	69.2 % (27)	30.8 % (12)	4.4 (3.0 ; 5.6)
Positive	12	58.3 % (7)	41.7 % (5)	5.0 (1.5 ; NA)

Supplemental Figure 6: Diagram of the efficacy comparison between TAFA-LEN and other treatments for first progression

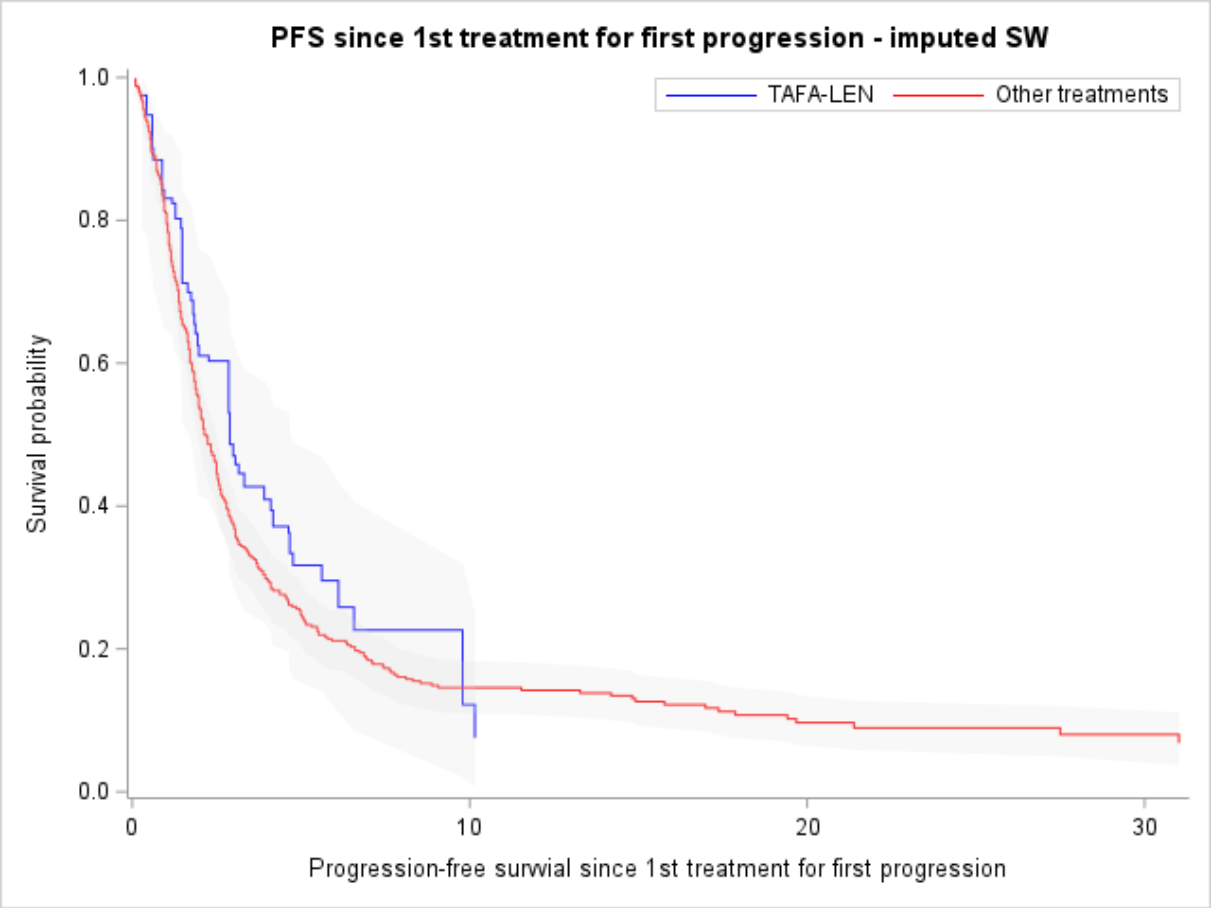


Supplemental Figure 7: Diagram of the efficacy comparison of TAFA-LEN and LEN as treatments for first progression

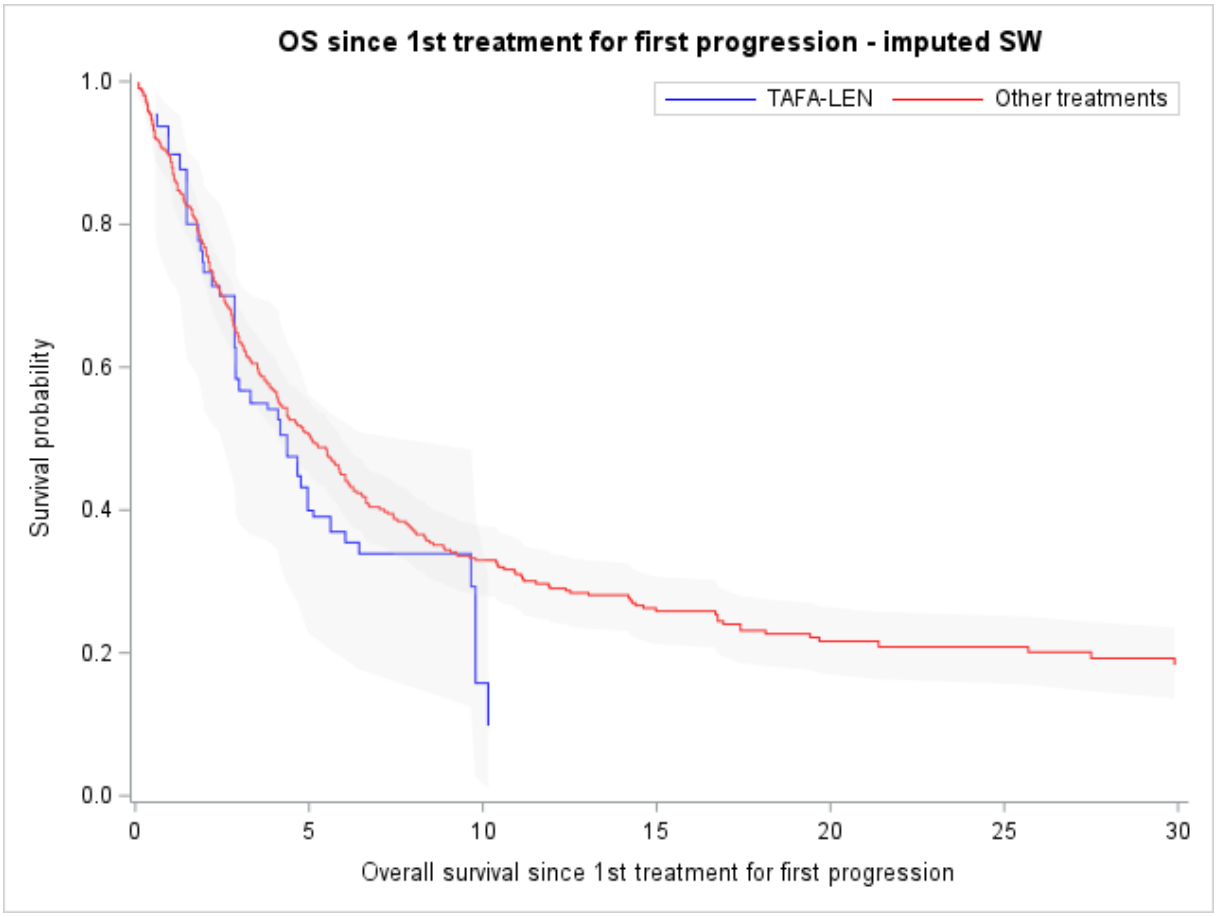


Supplemental Figure 8: Sensitivity analysis by using multiple imputation with chained equation: progression-free survival (PFS) (A) and overall survival (OS) in months (B) since the first treatment for progression after CAR T-cell according to imputed SW between tafasitamab plus lenalidomide (TAFA-LEN) and other treatments.

(A)



(B)


OS since 1st treatment for first progression - imputed SW
TAFA-LEN
Other treatments
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Overall survival since 1st treatment for first progression

Supplemental Figure 9: Figure 4: Swimmer plot of patient response to CAR T-cell over time and CAR T-cell-therapy related adverse events in the TL-pre-CAR-T set, with the duration of treatment with TAFA-LEN as a prior line of therapy. *This Figure does not include any treatment administered in the event of progression after CAR T-cell infusion.*