Supplemental Files

Supplemental Methods

Assessment of immune reconstitution

Blood samples were obtained in the Department of Medicine III as part of pre-planned sample collection and processing, and then routinely analyzed by the accredited Institute of Laboratory Medicine of the LMU University Hospital (LMU Munich). Lymphocyte counts were determined by a Sysmex XN machine (Sysmex, Norderstedt, Germany). T cells were defined as $CD45^+CD3^+$, T helper cells were defined as $CD45^+CD3^+CD4^+CD8^-$, cytotoxic/suppressor T cells were defined as $CD45^+CD3^+CD4^-CD8^+$ and the CD4/CD8 ratio was determined as the ratio of T helper cells to cytotoxic T cells. B cells were defined as $CD45^+CD19^+$ and NK cells were defined as $CD45^+CD16/56^+CD3^-$.

Supplemental Tables

Anti-infective prophylaxis				G-CSF support	IVIG support
Viral	**Bacterial**	**Pneumocystis jirovecii**	**Fungal**	**Trigger**	
Aciclovir for at least 6 months and then until CD4+ T_H cell count >200/µL	None (only in case of neutropenic fever)	Trimethoprim/ Sulfamethoxazole (TMP/SMX) at least for 6 months and then until CD4+ T_H cell count >200/µL	Depending on patient risk factors (prior fungal infection, baseline cytopenia, prolonged corticosteroid application), mainly posaconazole, alternatively micafungin	ANC <500/µL after day 5 post-CAR-T (approximate definition, considerable interpatient variability*)	<4 g/L and severe or recurring infections (more strict indication in case of allergic reaction to IVIG exposure)

Suppl. Table S1. Overview of standard operating procedures concerning anti-infective prophylaxis strategies and regarding the initiation of G-CSF and IVIG support.
*G-CSF support was initially deferred until the 2nd week post CAR-T due to concern of exacerbating immunotoxicity, which was then transitioned to an earlier G-CSF approach. Recently, patients received early G-CSF depending on their risk profile (according to CAR-HEMATOTOX score).

Days post CAR-T	0	7	14	21	30	90	180	360	540	720	900	1080
Cells												
White Blood cells	105	104	102	95	88	66	46	31	24	18	15	8
Platelet Count	105	104	102	95	88	66	46	31	24	18	15	8
Lymphocytes	105	104	102	95	88	66	46	31	24	18	15	8
T cells	105	104	102	95	88	66	46	31	24	18	15	8
CD4+ T helper cells	105	104	102	95	88	66	46	31	24	18	15	8
Cytotoxic CD8+ T cells	105	104	102	95	88	66	46	31	24	18	15	8
B cells	105	104	102	95	88	66	46	31	24	18	15	8
NK cells	105	104	102	95	88	66	46	31	24	18	15	8
Immunoglobulins												
IgG	105	104	102	95	88	66	46	31	24	18	15	8
IgA	105	104	102	95	88	66	46	31	24	18	15	8
IgM	105	104	102	95	88	66	46	31	24	18	15	8

Suppl. Table S2. Number at risk
Patient number at risk at specific timepoints after CAR-T: weekly (first month [M]), monthly (M1-3), twice yearly (after M3).

	Non-responder 3M (n=48)	Responder 3M (n=57)	P value
Baseline characteristics			
Ages, years (range)	60 (19-80)	66 (25-85)	**0.02**
Sex (female), n (% of total)	17 (35.4%)	23 (40.4%)	0.7
Performance status			
Median ECOG at lymphodepletion (range)	1 (1-2)	1 (0-1)	**0.03**
ECOG 0-1, n (%)	33 (68.75%)	50 (87.7%)	**0.03**
ECOG ≥ 2, n (%)	15 (31.25%)	7 (12-3%)	**0.03**
Therapy management			
Prior SCT, n (%)	12 (25%)	16 (28.1%)	0.8
Median lines of therapy before bridging (IQR)	3 (2-5)	3 (2-4)	0.1
Any bendamustine before CAR, n (% of total)	18 (37.5%)	26 (45.6%)	0.4
Bendamustine last 9 months before CAR, n (% of total)	8 (16.7%)	3 (5.2%)	0.1
Bendamustine for bridging or lymphodepletion, n (% of total)	8 (16.7%)	11 (19.3%)	0.8
Holding therapy, n (% of total)	24 (50%)	21 (36.8%)	0.2
Bridging therapy, n (% of total)	37 (77.1%)	38 (66.7%)	0.3
Pola-based bridging, n (% of total)	12 (25%)	15 (26.3%)	>0.999
Immunochemotherapy-based bridging, n (% of total)	35 (72.9%)	33 (57.9%)	0.2
Brain-to-time, days (IQR)	31 (19-48.8)	28 (10-48.5)	0.8
Vein-to-vein time, days (IQR)	40 (32-46)	37 (34-46.5)	0.9
Laboratory parameters parameters at time point pof lymphodepletion (day -5 prior CAR T-cell infusion)			
LDH, U/l (IQR)	382 (237.8-545.5)	216 (179.5-275)	**<0.0001**
GFR, ml/min (IQR)	90 (72.8-103.8)	78 (65.5-92.5)	**0.03**
CRP, mg/dl (IQR)	3.5 (1.2-5.3)	0.3 (0.1-1.03)	**<0.0001**
Ferritin, ng/ml (IQR)	1062 (266.3-2043)	292 (131.5-675)	**0.0008**
ANC, cells/µl (IQR)	1905 (837.5-3503)	2640 (1875-3760)	**0.02**
PLT, G/l (IQR)	152 (66.3-206.8)	175 (125-224)	0.2
Hemoglobin, g/dl (IQR)	8.9 (7.8-10.3)	10.9 (9.5-12.5)	**<0.0001**
CAR-HEMATOTOX Score			
CAR-HEMATOTOX Score Absolute (IQR)	3 (1-4)	1 (0-2)	**<0.0001**
CAR-HEMATOTOX Score Low (0-1), n (% of total)	13 (27.1%)	36 (63.2%)	**0.004**
CAR-HEMATOTOX Score High (>2), n (% of total)	35 (72.9%)	21 (36.8%)	**0.004**
Disease entity, n (% of total)			
Non-transformed lymphoma (DLBCL, PMBCL, THRLBCL)	33 (68.8%)	25 (42.9%)	**0.02**
Transformed lymphoma (trFL, trHL, trMZL, trCLL, trMALT)	11 (22.9%)	21 (36.8%)	0.1
MCL	4 (8.3%)	11 (19.3%)	0.2
Infused CAR T-cell product			
CAR product, n (% of total)			
Axi-cel	26 (54.17%)	24 (42.11%)	0.2
Tisa-cel	17 (35.42%)	16 (28.07%)	0.5
Brexu-cel	3 (6.25%)	11 (19.3%)	0.08
Liso-cel	2 (4.17%)	6 (10.5%)	0.3
Co-stimulatory domain (ICD) of CAR product, n (% of total)			
CD28-based ICD	29 (61.7%)	35 (61.4%)	>0.999
41-BB-based ICD	18 (38.3%)	22 (38.6%)	>0.999
Immunotoxicity			
CRS, n (% of total)			
No CRS	6 (12.5%)	9 (15.8%)	0.8
CRS grade 1-2	37 (77.1%)	43 (75.4%)	>0.999
CRS grade ≥ 3	5 (10.4%)	5 (8.8%)	>0.999
ICANS, n (% of total)			
No ICANS	28 (58.3%)	27 (47.4%)	0.3
ICANS grade 1-2	12 (25)	21 (36.8%)	0.2
ICANS grade ≥ 3	8 (16.7%)	9 (15.8%)	>0.999
Toxicity management, n (% of total)			
Received tocilizumab	40 (83.3%)	37 (64.9%)	**<0.05**
Received dexamethasone	22 (45.8%)	5 (43.9%)	0.9
ICU admission necessary	7 (14.3%)	7 (12.3%)	0.8

Suppl. Table S3. Baseline patient characteristics for patients with response after 3 months
Patient baseline characteristics prior to CAR-T infusion for patients with no response (n=48) and response defined as complete or partial remission (n=57). All laboratory values were determined prior to lymphodepleting chemotherapy with a leniency time period of 3 days. ECOG: Eastern Cooperative Oncology Group. PS: performance status. IQR: interquartile range. LD: lymphodepletion chemotherapy. CI: confidence interval. If a measurement wasn't available for all patients, the denominator is indicated in the table. Statistical significance between groups was explored by Mann-Whitney test for continuous variables and Fisher's exact test for comparison of percentages.

	NR 6M (n=57)*	R 6M (n=44)*	P value
Baseline characteristics			
Ages, years (range)	64 (55.5-68.5)	65 (57-72)	0.2
Sex (female), n (% of total)	18 (31.6%)	19 (43.2%)	0.3
Performance status			
Median ECOG at lymphodepletion (range)	1 (1-2)	1 (0-1)	**0.04**
ECOG 0-1, n (%)	40 (70.2%)	39 (88.6%)	**0.03**
ECOG ≥ 2, n (%)	17 (29.8%)	5 (11.4%)	**0.03**
Therapy management			
Prior SCT, n (%)	14 (75.4%)	14 (31.8%)	0.5
Median lines of therapy before bridging (IQR)	3 (2-4)	2.5 (2-4)	0.25
Any bendamustine before CAR, n (% of total)	20 (35.1%)	23 (52.3%)	0.1
Bendamustine last 9 months before CAR, n (% of total)	9 (15.8%)	2 (4.6%)	0.1
Bendamustine for bridging or lymphodepletion, n (% of total)	9 (15.8%)	9 (20.5%)	0.6
Holding therapy, n (% of total)	43 (75.4%)	16 (36.4%)	**0.0001**
Bridging therapy, n (% of total)	43 (75.4%)	29 (65.9%)	0.4
Pola-based bridging, n (% of total)	14 (24.6%)	12 (27.3%)	0.8
Immunochemotherapy-based bridging, n (% of total)	41 (71.9%)	24 (54.6%)	0.09
Brain-to-vein time, days (IQR)	29 (19.5-49)	28 (20-45.5)	0.4
Vein-to-vein time, days (IQR)	39 (32-44.5)	39.5 (34-49.8)	0.2
Laboratory parameters at time point of lymphodepletion (day -5 prior CAR T-cell infusion)			
LDH, U/l (IQR)	358 (206-533)	214 (183-267.5)	**0.0008**
GFR, ml/min (IQR)	88 (70.5-102)	77.5 (63.3-92.8)	**0.04**
CRP, mg/dl (IQR)	2.4 (0.6-4.9)	0.4 (0.2-1)	**<0.0001**
Ferritin, ng/ml (IQR)	778 (221.5-1996)	300 (118.8-727.8)	**0.006**
ANC, cells/µl (IQR)	1970 (950-3360)	2750 (1965-3850)	**0.006**
PLT, G/l (IQR)	150 (83-204.5)	179.5 (127.8-225.5)	0.1
Hemoglobin, g/dl (IQR)	9.1 (8.1-10.6)	10.9 (9.5-12.4)	**0.0001**
CAR-HEMATOTOX Score			
CAR-HEMATOTOX Score Absolute (IQR)	3 (1-4)	1 (0-2)	**<0.0001**
CAR-HEMATOTOX Score Low (0-1), n (% of total)	17 (29.8%)	30 (68.2%)	**0.0001**
CAR-HEMATOTOX Score High (>2), n (% of total)	40 (70.2%)	14 (31.8%)	**0.0001**
Disease entity, n (% of total)			
Non-transformed lymphoma (DLBCL, PMBCL, THRLBCL)	38 (66.7%)	17 (38.6%)	**0.009**
Transformed lymphoma (trFL, trHL, trMZL, trCLL, trMALT)	13 (22.8%)	18 (40.9%)	0.08
MCL	6 (10.5%)	9 (20.5%)	0.3
Infused CAR T-cell product			
CAR product, n (% of total)			
Axi-cel	31 (54.4%)	15 (34.1%)	**<0.05**
Tisa-cel	18 (31.6%)	15 (34.1%)	0.8
Brexu-cel	5 (8.8%)	9 (20.5%)	0.15
Liso-cel	3 (5.3%)	6 (13.6%)	0.2
Co-stimulatory domain (ICD) of CAR product, n (% of total)			
CD28-based ICD	36 (63.2%)	24 (54.55%)	0.4
41-BB-based ICD	21 (36.8%)	20 (45.45%)	0.4
Immunotoxicity			
CRS, n (% of total)			
No CRS	7 (12.3%)	8 (18.2%)	0.4
CRS grade 1-2	44 (77.2%)	32 (72.7%)	0.65
CRS grade ≥ 3	6 (10.5%)	4 (9.1%)	>0.9999
ICANS, n (% of total)			
No ICANS	33 (57.9%)	21 (47.7%)	0.3
ICANS grade 1-2	15 (26.3%)	16 (36.4%)	0.3
ICANS grade ≥ 3	9 (15.8%)	7 (15.9%)	>0.9999
Toxicity management, n (% of total)			
Received tocilizumab	48 (84.2%)	36 (81.8%)	0.8
Received dexamethasone	25 (43.9%)	18 (40.9%)	0.8
ICU admission necessary	9 (15.8%)	5 (11.4%)	0.6

* 4 Patients status pending for 180 days

Suppl. Table S4. Baseline patient characteristics for patients with response after 6 months
Patient baseline characteristics prior to CAR-T infusion for patients with no response (n=57) and response defined as complete or partial remission (n=44) after 6 months. All laboratory values were determined prior to lymphodepleting chemotherapy with a leniency time period of 3 days. ECOG: Eastern Cooperative Oncology Group. PS: performance status. IQR: interquartile range. LD: lymphodepletion chemotherapy. CI: confidence interval. If a measurement wasn't available for all patients, the denominator is indicated in the table. Statistical significance between groups was explored by Mann-Whitney test for continuous variables and Fisher's exact test for comparison of percentages.

	Responder 3M No recovery (n=9)	**Responder 3M Any recovery (n=48)**	**P value**
Baseline characteristics			
Ages, years (range)	64 (36-80)	66 (25-85)	0.7
Sex (female), n (% of total)	2 (22.2%)	21 (43.8%)	0.3
Performance status			
Median ECOG at lymphodepletion (range)	1 (0-1)	1 (0.3-1)	0.7
ECOG 0-1, n (%)	8 (88.9%)	42 (87.5%)	>0.9999
ECOG ≥ 2, n (%)	1 (11.1%)	6 (12.5%)	
Therapy management			
Prior SCT, n (%)	3 (33.3%)	13 (27.1%)	0.7
Median lines of therapy before bridging (IQR)	4 (1.5-4)	2.5 (2-4)	0.45
Any bendamustine before CAR, n (% of total)	4 (44.4%)	22 (45.8%)	>0.9999
Bendamustine last 9 months before CAR, n (% of total)	1 (11.1%)	2 (4.2%)	0.4
Bendamustine for bridging or lymphodepletion, n (% of total)	1 (11.1%)	10 (20.8%)	0.7
Holding therapy, n (% of total)	6 (66.7%)	15 (31.3%)	0.06
Bridging therapy, n (% of total)	8 (88.9%)	30 (62.5%)	0.25
Pola-based bridging, n (% of total)	1 (11.1%)	14 (29.2%)	0.4
Immunochemotherapy-based bridging, n (% of total)	8 (88.9%)	25 (52.1%)	0.065
Brain-to-vein time, days (IQR)	35 (16.5-56)	28 (20-47.8)	0.6
Vein-to-vein time, days (IQR)	35 (28.5-42)	37 (34-47)	0.3
Laboratory parameters parameters at time point of lymphodepletion (day -5 prior CAR T-cell infusion)			
LDH, U/l (IQR)	162 (135-236)	228.5 (192-278)	**0.01**
GFR, ml/min (IQR)	91 (75.5-98)	77 (64.3-91.5)	0.15
CRP, mg/dl (IQR)	0.3 (0.2-3.3)	0.3 (0.1-0.9)	0.6
Ferritin, ng/ml (IQR)	240 (159.5-1569)	300 (118.8-633.8)	0.6
ANC, cells/µl (IQR)	2870 (2420-3660)	2605 (1785-3820)	0.7
PLT, G/l (IQR)	112 (91.5-224.5)	176 (134-225.3)	0.2
Hemoglobin, g/dl (IQR)	10.9 (9.7-12.1)	10.7 (9.4-12.5)	0.9
CAR-HEMATOTOX Score			
CAR-HEMATOTOX Score Absolute (IQR)	1 (0-2.5)	1 (0-2)	0.8
CAR-HEMATOTOX Score Low (0-1), n (% of total)	5 (55.6%)	31 (64.6%)	0.7
CAR-HEMATOTOX Score High (>2), n (% of total)	4 (44.4%)	17 (35.4%)	0.7
Disease entity, n (% of total)			
Non-transformed lymphoma (DLBCL, PMBCL, THRLBCL)	3 (66.7%)	22 (45.8%)	0.7
Transformed lymphoma (trFL, trHL, trMZL, trCLL, trMALT)	3 (66.7%)	18 (37.5%)	>0.9999
MCL	3 (66.7%)	8 (16.7%)	0.4
Infused CAR T-cell product			
CAR product, n (% of total)			
Axi-cel	4 (44.4%)	20 (41.7%)	>0.9999
Tisa-cel	1 (11.1%)	15 (31.3%)	0.4
Brexu-cel	3 (33.3%)	8 (16.7%)	0.4
Liso-cel	1 (11.1%)	5 (10.4%)	>0.9999
Co-stimulatory domain (ICD) of CAR product, n (% of total)			
CD28-based ICD	7 (77.8%)	28 (58.3%)	0.5
41-BB-based ICD	2 (22.2%)	20 (41.7%)	0.5
Immunotoxicity			
CRS, n (% of total)			
No CRS	2 (22.2%)	7 (14.6%)	0.6
CRS grade 1-2	4 (44.4%)	3 (78.2%)	**0.04**
CRS grade ≥ 3	2 (22.2%)	3 (6.3%)	0.2
ICANS, n (% of total)			
No ICANS	3 (33.3%)	24 (50%)	0.5
ICANS grade 1-2	4 (44.4%)	17 (35.4%)	0.7
ICANS grade ≥ 3	2 (22.2%)	7 (14.6%)	0.6
Toxicity management, n (% of total)			
Received tocilizumab	7 (77.8%)	41 (85.4%)	0.6
Received dexamethasone	4 (44.4%)	21 (43.8%)	>0.9999
ICU admission necessary	3 (33.3%)	4 (8.3%)	0.07

Suppl. Table S5. Baseline patient characteristics for 3 months responder with no or any recovery
Patient baseline characteristics prior to CAR-T infusion for responder after 3 months (n=57) with no recovery (n=9) and any recovery (n=48). All laboratory values were determined prior to lymphodepleting chemotherapy with a leniency time period of 3 days. ECOG: Eastern Cooperative Oncology Group. PS: performance status. IQR: interquartile range. LD: lymphodepletion chemotherapy. CI: confidence interval. If a measurement wasn't available for all patients, the denominator is indicated in the table. Statistical significance between groups was explored by Mann-Whitney test for continuous variables and Fisher's exact test for comparison of percentages.

	Responder 3M Poor IR, 0-1 criteria (n=37)	**Responder 3M High IR, 2-3 criteria (n=20)**	**P value**
Baseline characteristics			
Ages, years (range)	66 (25-83)	65.5 (46-85)	0.5
Sex (female), n (% of total)	14 (37.8%)	9 (45%)	0.8
Performance status			
Median ECOG at lymphodepletion (range)	1 (1-1)	1 (0-1.75)	0.9
ECOG 0-1, n (%)	35 (94.6%)	15 (74%)	0.08
ECOG ≥ 2, n (%)	2 (5.4%)	5 (25%)	0.08
Therapy management			
Prior SCT, n (%)	11 (29.7%)	5 (25%)	0.8
Median lines of therapy before bridging (IQR)	3 (2-4)	3 (2-4.75)	0.4
Any bendamustine before CAR, n (% of total)	15 (40.5%)	11 (55%)	0.4
Bendamustine last 9 months before CAR, n (% of total)	3 (8.1%)	0 (0%)	0.5
Bendamustine for bridging or lymphodepletion, n (% of total)	6 (16.2%)	5 (25%)	0.5
Holding therapy, n (% of total)	15 (40.5%)	6 (30%)	0.6
Bridging therapy, n (% of total)	27 (73%)	11 (55%)	0.2
Pola-based bridging, n (% of total)	10 (27%)	5 (25%)	>0.9999
Immunochemotherapy-based bridging, n (% of total)	24 (64.9%)	9 (45%)	0.2
Brain-to-vein time, days (IQR)	28 (20-49)	27.5 (21-39.8)	0.8
Vein-to-vein time, days (IQR)	40 (33.5-46.5)	36 (34-47.3)	0.7
Laboratory parameters parameters at time point of lymphodepletion (day -5 prior CAR T-cell infusion)			
LDH, U/l (IQR)	223 (176.5-277)	214 (183.5-260)	0.9
GFR, ml/min (IQR)	82 (68.5-95.5)	68.5 (63.3-86)	0.09
CRP, mg/dl (IQR)	0.3 (0.15-0.85)	0.5 (0.1-1.18)	0.4
Ferritin, ng/ml (IQR)	292 (138.5-675)	304.5 (118.8-679.3)	0.7
ANC, cells/µl (IQR)	2570 (2085-3675)	2750 (1763-3905)	0.9
PLT, G/l (IQR)	169 (129.5-224.5)	180 (94.3-225.3)	0.98
Hemoglobin, g/dl (IQR)	10.9 (9-12.5)	10.7 (9.6-12.60)	0.7
CAR-HEMATOTOX Score			
CAR-HEMATOTOX Score Absolute (IQR)	1 (0-2)	1 (0-2)	0.7
CAR-HEMATOTOX Score Low (0-1), n (% of total)	23 (62.2%)	13 (65%)	0.8
CAR-HEMATOTOX Score High (>2), n (% of total)	14 (37.8%)	7 (35%)	0.8
Disease entity, n (% of total)			
Non-transformed lymphoma (DLBCL, PMBCL, THRLBCL)	16 (94.1%)	9 (45%)	**0.02**
Transformed lymphoma (trFL, trHL, trMZL, trCLL, trMALT)	13 (27.7%)	8 (40%)	0.4
MCL	8 (21.6%)	3 (15%)	0.7
Infused CAR T-cell product			
CAR product, n (% of total)			
Axi-cel	17 (46%)	7 (35%)	0.6
Tisa-cel	7 (18.9%)	9 (45%)	0.06
Brexu-cel	8 (21.6%)	3 (27.3%)	0.7
Liso-cel	5 (13.5%)	1 (5%)	0.4
Co-stimulatory domain (ICD) of CAR product, n (% of total)			
CD28-based ICD	25 (67.6%)	10 (50%)	0.3
41-BB-based ICD	12 (32.4%)	10 (50%)	0.3
Immunotoxicity			
CRS, n (% of total)			
No CRS	7 (18.9%)	2 (10%)	0.5
CRS grade 1-2	26 (70.3%)	17 (85%)	0.4
CRS grade ≥ 3	4 (10.8%)	1 (5%)	0.7
ICANS, n (% of total)			
No ICANS	20 (54.1%	7 (35%)	0.3
ICANS grade 1-2	11 (29.7%)	10 (50%)	0.2
ICANS grade ≥ 3	6 (16.2%)	3 (15%)	>0.9999
Toxicity management, n (% of total)			
Received tocilizumab	30 (81.1%)	18 (90%)	0.5
Received dexamethasone	17 (46%)	8 (40%)	0.8
ICU admission necessary	6 (16.2%)	1 (5%)	0.4

Suppl. Table S6. Baseline patient characteristics for 3 months responders with poor (0-1 IR criteria) or high (2-3 IR criteria) recovery

Patient baseline characteristics prior to CAR-T infusion for responder after 3 months (n=57) with poor (0-1 IR criteria) (n=37) or high (2-3 IR criteria) (n=20) recovery. All laboratory values were determined prior to lymphodepleting chemotherapy with a leniency time period of 3 days. ECOG: Eastern Cooperative Oncology Group. PS: performance status. IQR: interquartile range. LD: lymphodepletion chemotherapy. CI: confidence interval. If a measurement wasn't available for all patients, the denominator is indicated in the table. Statistical significance between groups was explored by Mann-Whitney test for continuous variables and Fisher's exact test for comparison of percentages.

	Responder 3M B cell aplasia (n=46)	Responder 3M B cell recovery (n=11)	P value
Baseline characteristics			
Ages, years (range)	65 (57-72)	67 (63-76)	0.2
Sex (female), n (% of total)	20 (43.5%)	2 (20%)	0.3
Performance status			
Median ECOG at lymphodepletion (range)	1 (0.75-1)	1 (0-1)	0.7
ECOG 0-1, n (%)	41 (89.1%)	9 (81.8%)	0.6
ECOG ≥ 2, n (%)	5 (10.9%)	2 (18.2%)	0.6
Therapy management			
Prior SCT, n (%)	14 (30.4%)	2 (18.2%)	0.7
Median lines of therapy before bridging (IQR)	3 (2-4)	2 (2-4)	0.6
Any bendamustine before CAR, n (% of total)	22 (47.8%)	4 (364.4%)	0.7
Bendamustine last 9 months before CAR, n (% of total)	3 (6.5%)	0 (0%)	>0.9999
Bendamustine for bridging or lymphodepletion, n (% of total)	9 (19.6%)	2 (18.2%)	>0.9999
Holding therapy, n (% of total)	18 (39.1%)	3 (27.3%)	0.7
Bridging therapy, n (% of total)	34 (73.9%)	4 (36.4%)	**0.03**
Pola-based bridging, n (% of total)	29 (63%)	1 (9.1%)	**0.002**
Immunochemotherapy-based bridging, n (% of total)	29 (63%)	11 (100%)	**0.02**
Brain-to-vein time, days (IQR)	28 (20-49)	28 (20-36)	0.8
Vein-to-vein time, days (IQR)	37.5 (34-47)	33 (29-40)	0.06
Laboratory parameters at time point of lymphodepletion (day -5 prior CAR T-cell infusion)			
LDH, U/l (IQR)	211.5 (180.5-275)	228 (164-410)	0.9
GFR, ml/min (IQR)	78.5 (63.8-93.3)	74 (67-90)	0.8
CRP, mg/dl (IQR)	0.3 (0.1-0.9)	0.2 (0.2-1.1)	0.4
Ferritin, ng/ml (IQR)	300 (128.5-717.3)	261 (130-387)	0.5
ANC, cells/µl (IQR)	2605 (1958-3663)	2650 (1770-3920)	0.9
PLT, G/l (IQR)	169 (115-227.3)	180 (162-220)	0.5
Hemoglobin, g/dl (IQR)	10.7 (9.3-12.1)	12.3 (10.1-13.5)	0.2
CAR-HEMATOTOX Score			
CAR-HEMATOTOX Score Absolute (IQR)	1 (0-2)	1 (0-2)	0.4
CAR-HEMATOTOX Score Low (0-1), n (% of total)	28 (60.9%)	8 (72.7%)	0.7
CAR-HEMATOTOX Score High (>2), n (% of total)	18 (39.1%)	3 (27.3%)	0.7
Disease entity, n (% of total)			
Non-transformed lymphoma (DLBCL, PMBCL, THRLBCL)	20 (43.5%)	5 (45.5%)	>0.9999
Transformed lymphoma (trFL, trHL, trMZL, trCLL, trMALT)	18 (39.1%)	3 (27.3%)	0.7
MCL	8 (17.4%)	3 (27.3%)	0.4
Infused CAR T-cell product			
CAR product, n (% of total)			
Axi-cel	17 (37%)	7 (63.6%)	0.2
Tisa-cel	16 (34.8%)	0 (0%)	**0.02**
Brexu-cel	8 (17.4%)	3 (27.3%)	0.4
Liso-cel	5 (10.9%)	1 (9.1%)	>0.9999
Co-stimulatory domain (ICD) of CAR product, n (% of total)			
CD28-based ICD	25 (54.45%)	10 (90.9%)	**0.04**
41-BB-based ICD	21 (45.65%)	1 (9.1%)	**0.04**
Immunotoxicity			
CRS, n (% of total)			
No CRS	8 (17.4%)	1 (9.1%)	0.7
CRS grade 1-2	33 (71.7%)	10 (90.9%)	0.3
CRS grade ≥ 3	5 (10.9%)	0 (0%)	0.6
ICANS, n (% of total)			
No ICANS	23 (50%)	3 (27.3%)	0.2
ICANS grade 1-2	16 (34.8%)	4 (36.4%)	>0.9999
ICANS grade ≥ 3	7 (15.2%)	2 (18.2%)	>0.9999
Toxicity management, n (% of total)			
Received tocilizumab	38 (82.6%)	20 (90.9%)	0.7
Received dexamethasone	18 (39.1%)	7 (63.6%)	0.2
ICU admission necessary	6 (13%)	1 (9.1%)	>0.9999

Suppl. Table S7. Baseline patient characteristics for 3 months responders with B-cell aplasia
Patient baseline characteristics prior to CAR-T infusion for responder after 3 months (n=57) with B cell aplasia (n=46) or B cell recovery (n=11). All laboratory values were determined prior to lymphodepleting chemotherapy with a leniency time period of 3 days. ECOG: Eastern Cooperative Oncology Group. PS: performance status. IQR: interquartile range. LD: lymphodepletion chemotherapy. CI: confidence interval. If a measurement wasn't available for all patients, the denominator is indicated in the table. Statistical significance between groups was explored by Mann-Whitney test for continuous variables and Fisher's exact test for comparison of percentages.

	CD28-based ICD (n=44)	41BB-based ICD (n=28)	P value
Laboratory parameters at progression			
Leucocytes, G/l (IQR)	3.3 (1.4-5.8)	3.6 (1.6-6.4)	0.6
Thrombocytes, G/l (IQR)	70 (36-129)	96 (24-183)	0.4
Neutrophiles, G/l (IQR)	1.7 (0.6-3.8)	2.1 (0.7-3.7)	0.6
Hemoglobin, g/dl (IQR)	9.9 (8.1-11.5)	8.6 (7.6-11.2)	0.1
LDH, U/l (IQR)	291 (210-470)	292.5 (246-601.5)	0.4
Lymphocyte subpopulations at progression			
Lymphocytes, cells/µl (IQR)	510 (242-878)	451 (270-1201)	0.9
T cells, cells/µl (IQR)	303 (124-629)	339 (124-607)	0.8
T helper cells, cells/µl (IQR)	85 (46-190)	200 (64-239)	**<0.05**
Cytotoxic T cells, cells/µl (IQR)	133 (51-427)	135 (67-278)	0.95
CD4/CD8 ratio (IQR)	0.7 (0.3-1.2)	1 (0.6-2.1)	**0.03**
B cells, cells/µl (IQR)	0 (0-0)	0 (0-0)	0.7
NK cells, cells/µl (IQR)	117 (57-193)	116 (29-194)	0.8

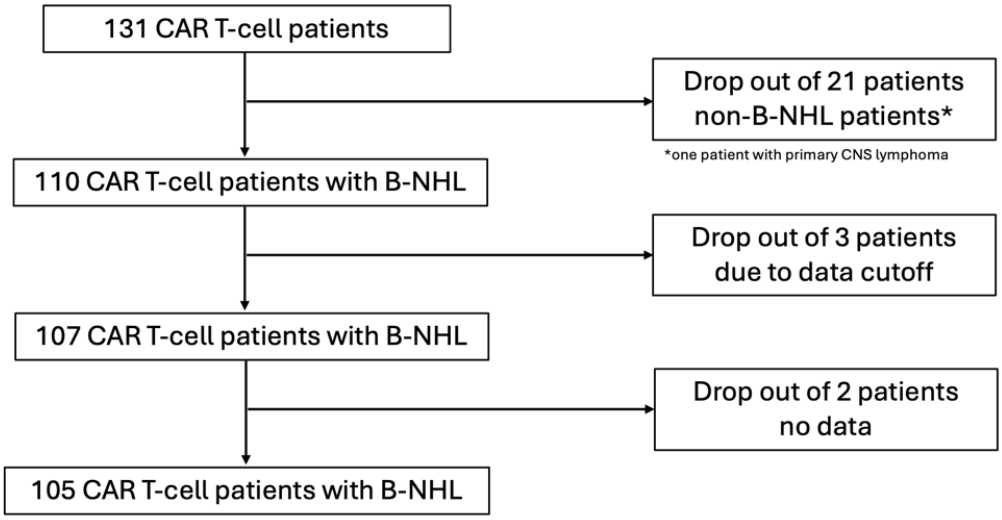
Suppl. Table S8. Laboratory parameters and immune cell counts at time of progression for CD28-based versus 41BB-based CAR T-cell products.
Laboratory parameters and immune cell counts at time point of progression or relapse for patients treated with CD28-based or 41BB-based CAR T-cell products. P-values determined by Mann-Whitney test. P-values determined by Mann-Whitney test.

	Non-transformed lymphoma (n=42)	Transformed lymphoma (n=20)	MCL (n=10)	P value one-way ANOVA
Laboratory parameters at progression				
Leucocytes, G/l (IQR)	3.2 (1.3-5.4)	3.2 (2.1-6.1)	7 (2.5-14)	**0.003**
Thrombocytes, G/l (IQR)	71.5 (17.5-136)	138.5 (41.3-189.8)	51 (23.3-94)	0.07
Neutrophiles, G/l (IQR)	1.5 (0.6-3.6)	1.9 (0.9-3.4)	1.9 (0.2-4.2)	0.99
Hemoglobin, g/dl (IQR)	9.2 (7.8-11.4)	10.8 (9.1-13.1)	8.6 (7.6-10.8)	0.1
LDH, U/l (IQR)	336 (242-613)	279 (220-441.8)	246 (179.8-536.5)	0.4
Lymphocyte subpopulations at progression				
Lymphocytes, cells/µl (IQR)	371 (180-700)	701 (344.5-1352)	2751 (894.5-10324)	**<0.0001**
T cells, cells/µl (IQR)	195 (95-453)	498.5 (252.8-984.3)	697.5 (342.5-817.8)	**0.02**
T helper cells, cells/µl (IQR)	68 (33-200)	147 (88.8-236.5)	172 (96.3-496.5)	**0.03**
Cytotoxic T cells, cells/µl (IQR)	94 (53-287)	251 (57.8-666.3)	349.5 (94.5-557.5)	**0.03**
CD4/CD8 ratio (IQR)	0.9 (0.3-1.5)	0.9 (0.4-2.2)	0.6 (0.2-1.5)	0.99
B cells, cells/µl (IQR)	0 (0-0)	0 (0-23.3)	0 (0-9618)	**<0.0001**
NK cells, cells/µl (IQR)	84 (25-144)	158.5 (75-210)	212 (140.3-329)	**0.04**

Suppl. Table S9. Laboratory parameters and immune cell counts at time of progression across the different B-NHL entities.

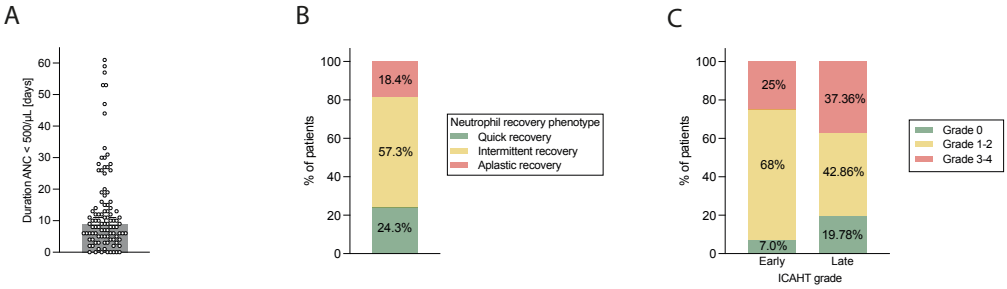
Laboratory parameters and immune cell counts at time of progression or relapse for patients treated with CD19 CAR T-cells with non-transformed lymphoma (DLBCL, PMBCL, THRLBCL), transformed lymphoma (trFL, trHL, trMZL, trCLL, trMALT) or mantle cell lymphoma (MCL). P-values determined by ordinary one-way ANOVA.

Supplemental Figures



Suppl. Figure S1. Consort diagram of patient cohort
CAR-T treatment for a disease entity other than r/r B-NHL (n=21), treatment the <30 days before data cut off (n=3), or insufficient data (n=2) represented the key exclusion criteria, resulting in a final study population of 105 B-NHL patients, including 90 large B-cell lymphoma (LBCL) patients and 15 mantle cell lymphoma (MCL) patients

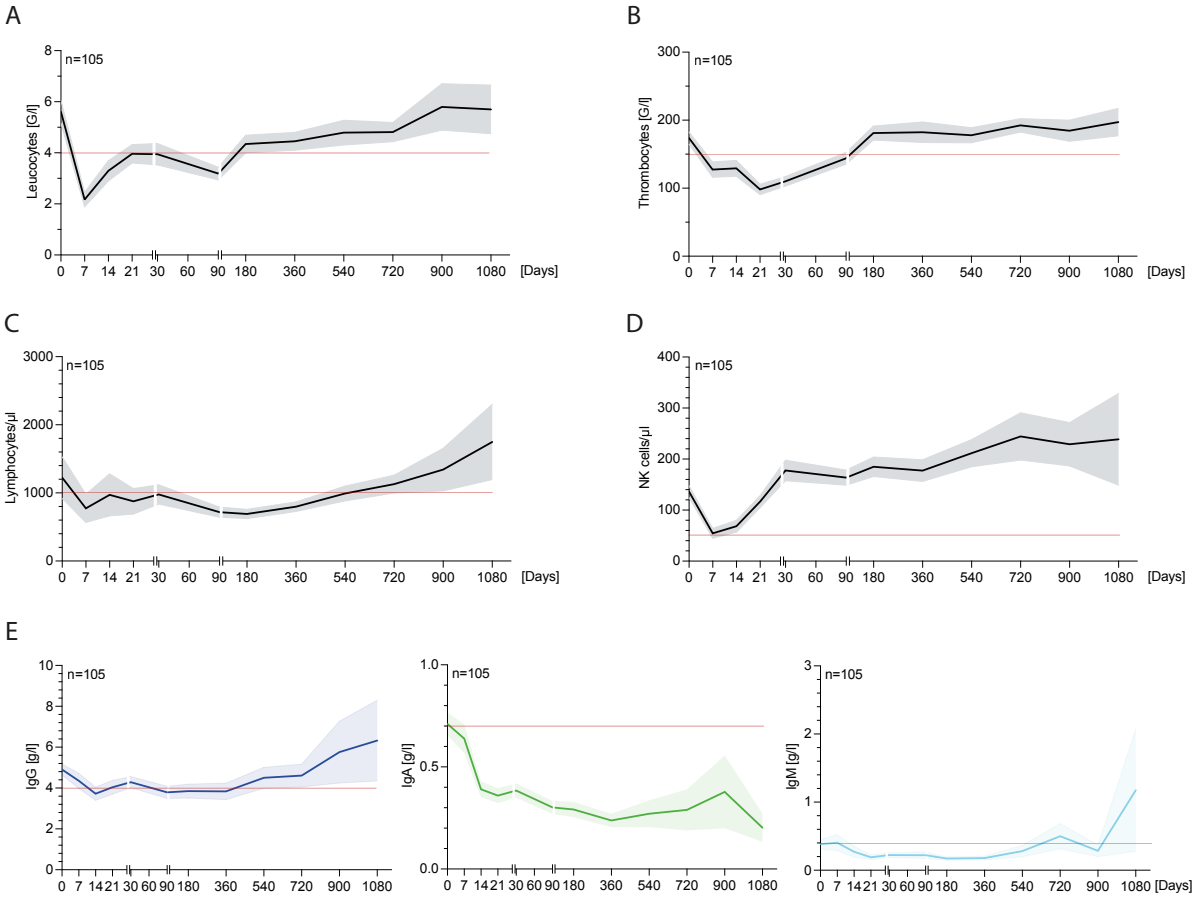
Suppl. Figure S2



Suppl. Figure S2. Neutrophil recovery phenotypes and early/late immune effector cell-associated hematotoxicity severity

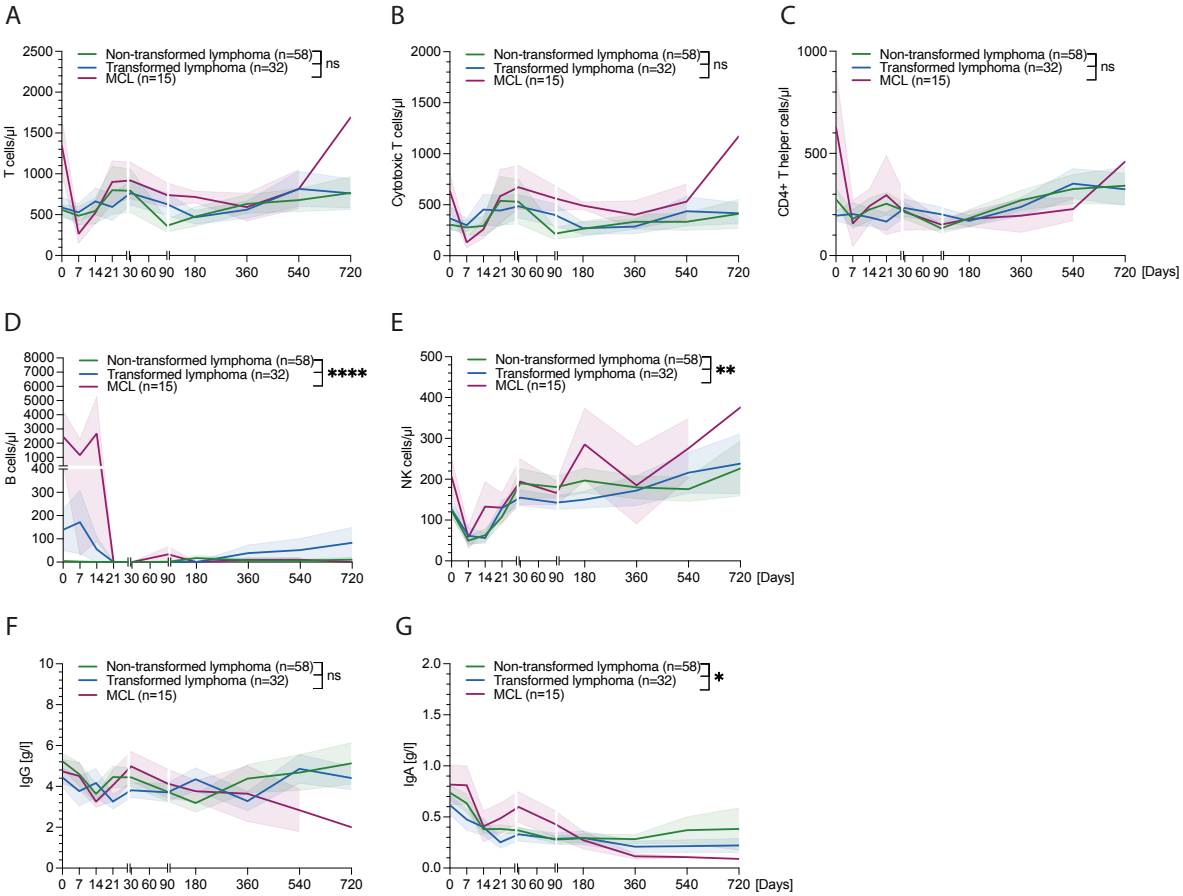
(A) Median duration of ANC < 500/µl in days. Results are presented as median ± 95% CI. (B) Neutrophil recovery phenotype of all patients. (C) early late ICAHT of all patients. ICAHT was graded according to EHA/EBMT consensus guidelines (Rejeski et al, Blood 2023).

Suppl. Figure S3



Suppl. Figure S3. Immune cell counts following CD19 CAR T-cell therapy.
Number of (A) leukocytes, (B) thrombocytes, (C) lymphocytes, (D) NK cells, (E) IgG, IgA and IgM levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion. Results are presented as mean ± standard error of the mean (SEM). The corresponding numbers at risk are provided in supplemental table 1.

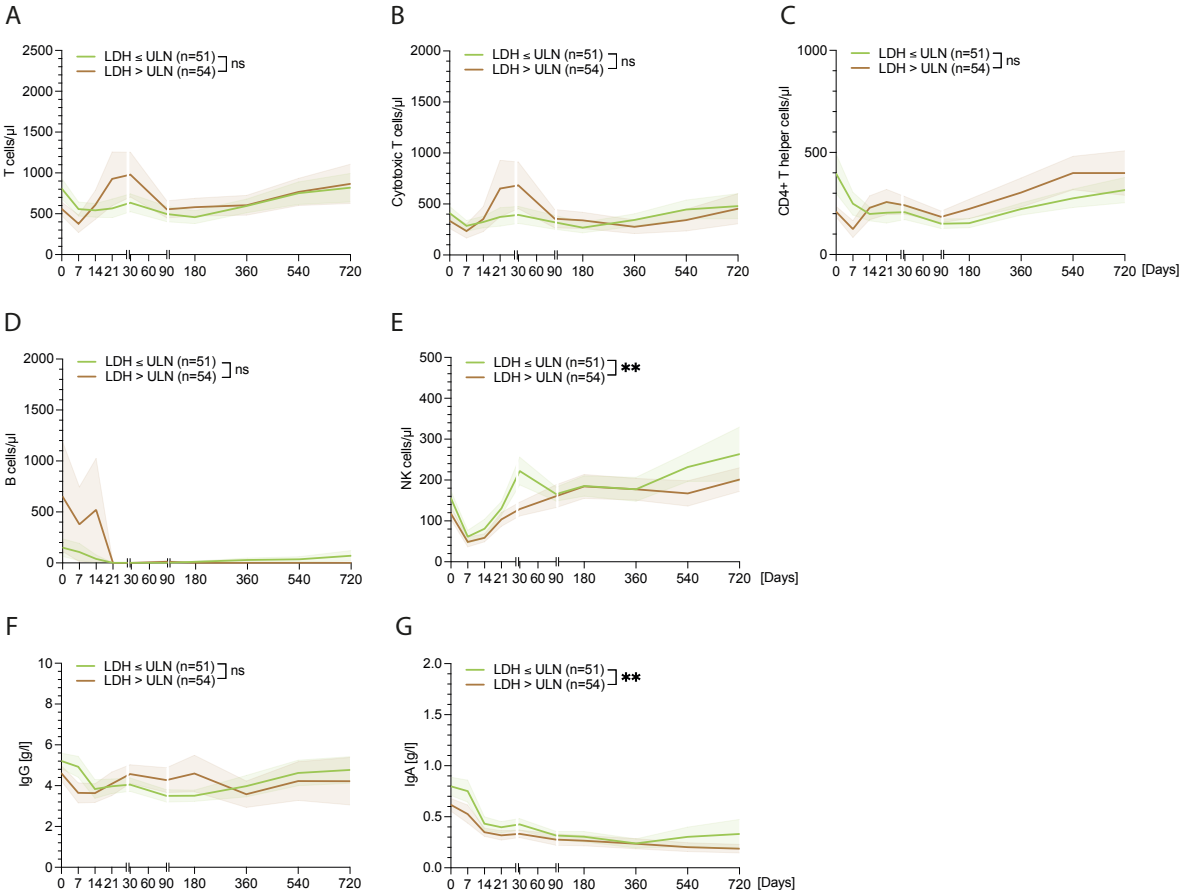
Suppl. Figure S4



Suppl. Figure S4. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by disease entity.

(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients diagnosed with non-transformed lymphoma [green], transformed lymphoma [blue] or mantle cell lymphoma (MCL) [violet]. Results are presented as mean ± standard error of the mean (SEM). For comparison of three groups a 2-way ANOVA. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

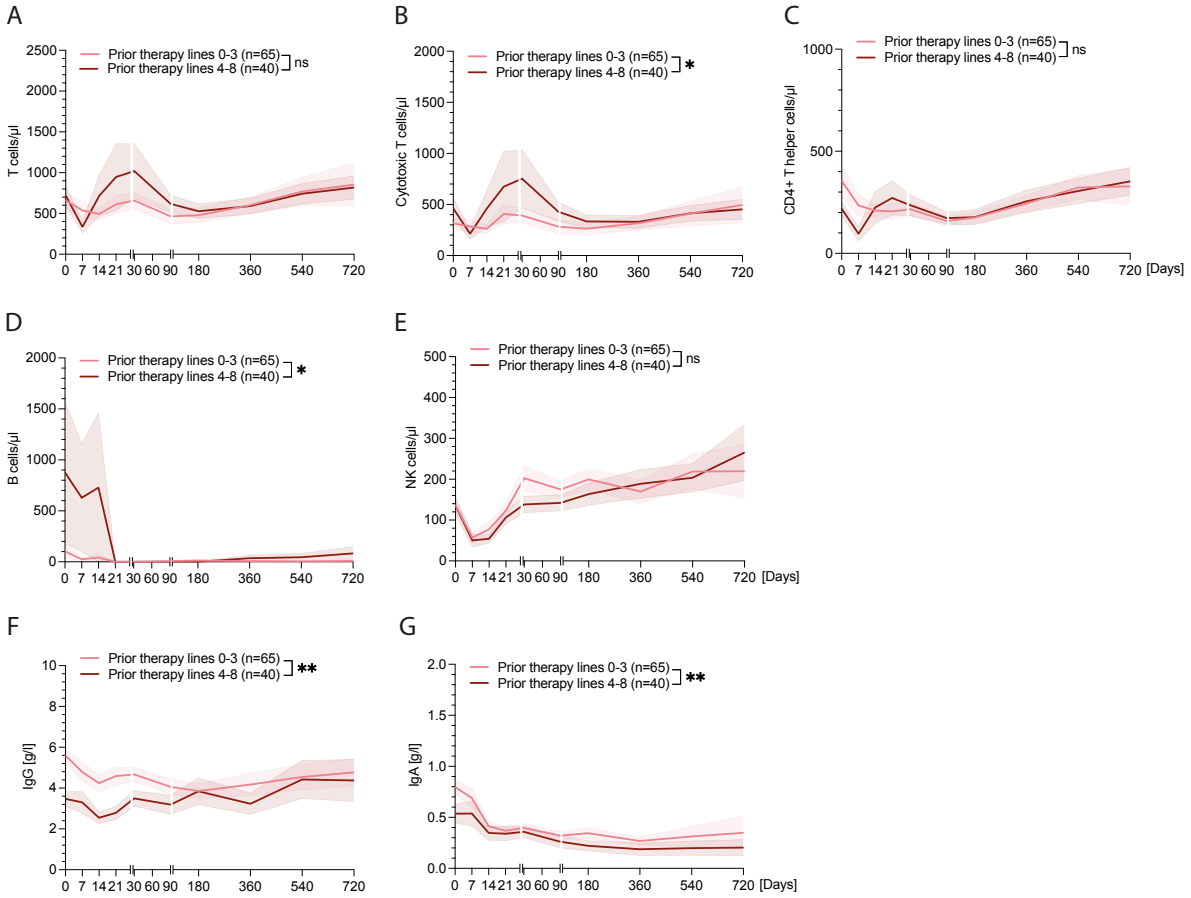
Suppl. Figure S5



Suppl. Figure S5. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by serum LDH levels.

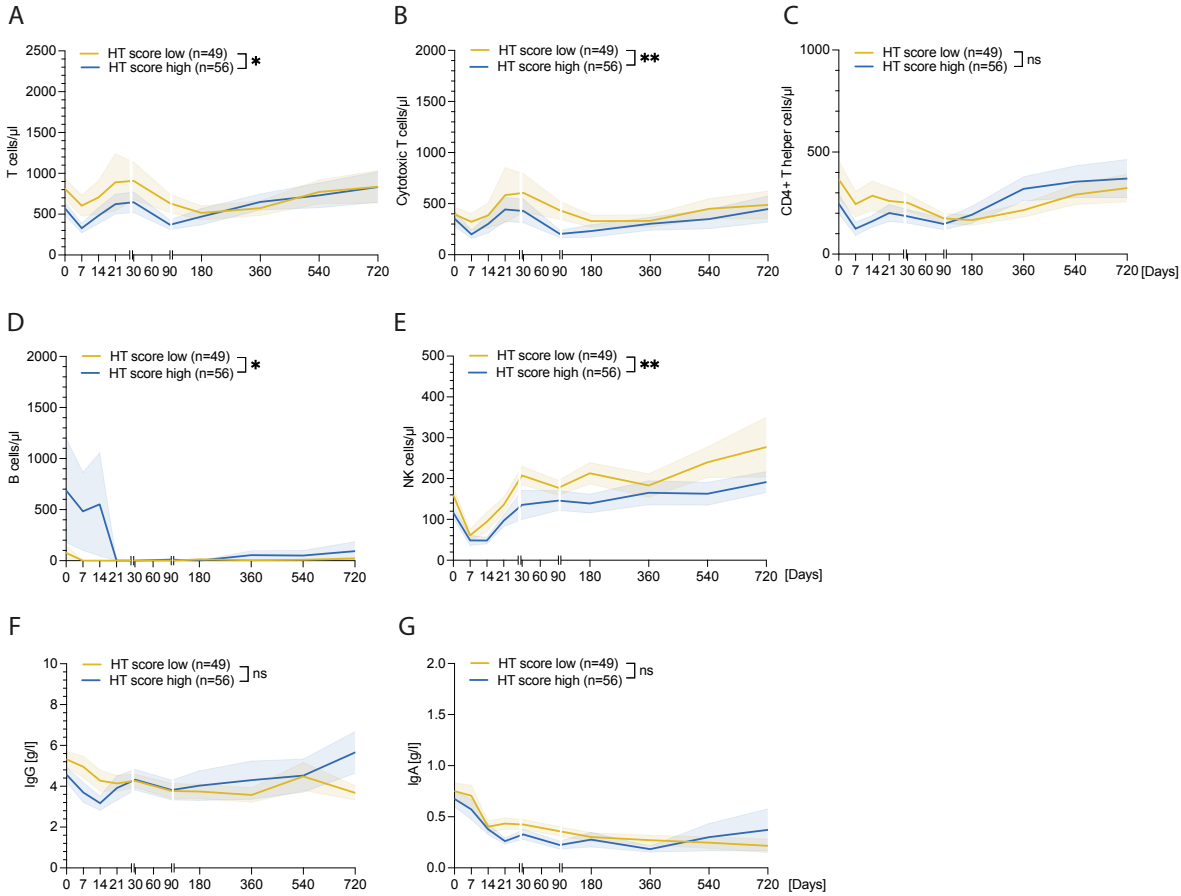
(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients with LDH ≤ upper limit of normal (ULN) [green] or LDH > ULN [brown]. Results are presented as mean ± standard error of the mean (SEM). For comparison of two groups Wilcoxon test was used. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

Suppl. Figure S6



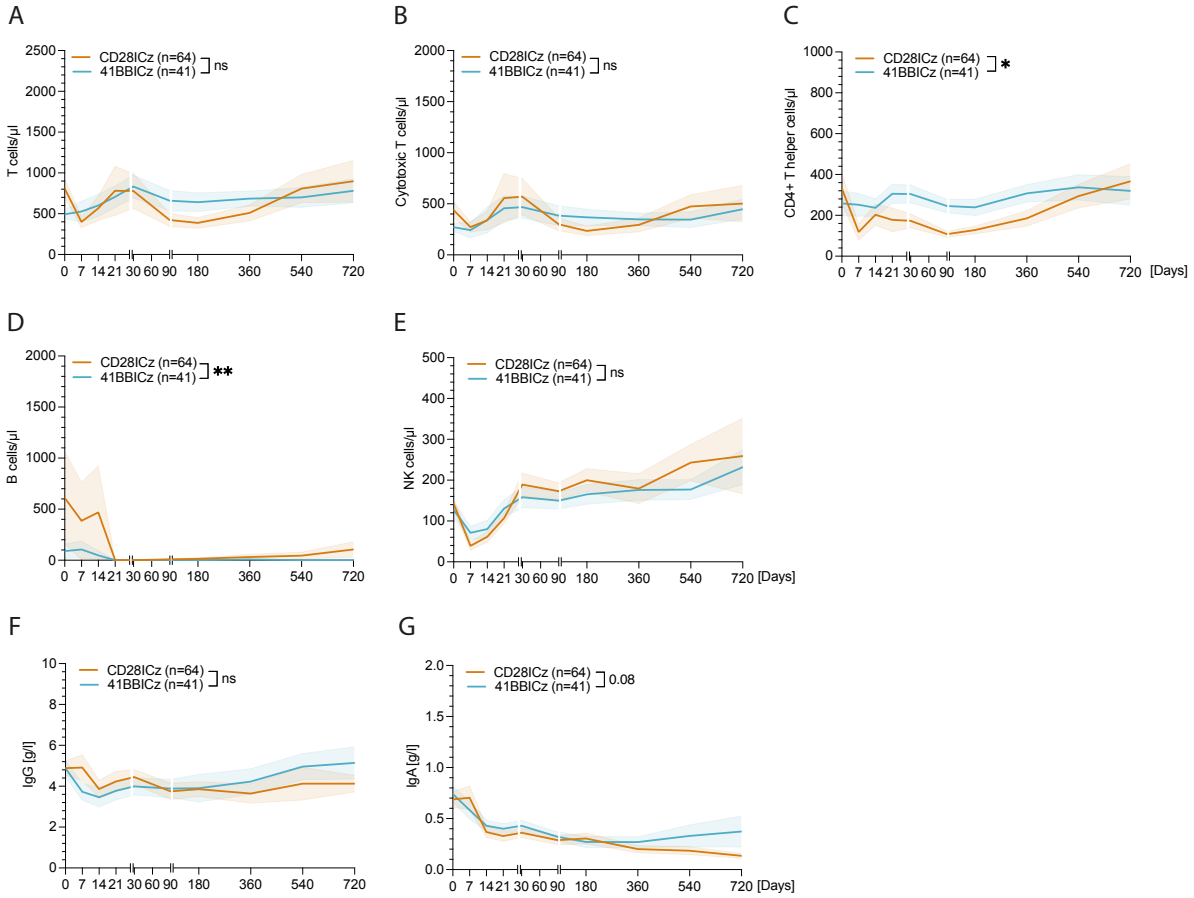
Suppl. Figure S6. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by prior therapy lines.
(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients treated with 0-3 therapy lines prior CAR-T [bright red] or 4-8 therapy lines prior to CAR-T [dark red]. Results are presented as mean ± standard error of the mean (SEM). For comparison of two groups Wilcoxon test was used. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

Suppl. Figure S7



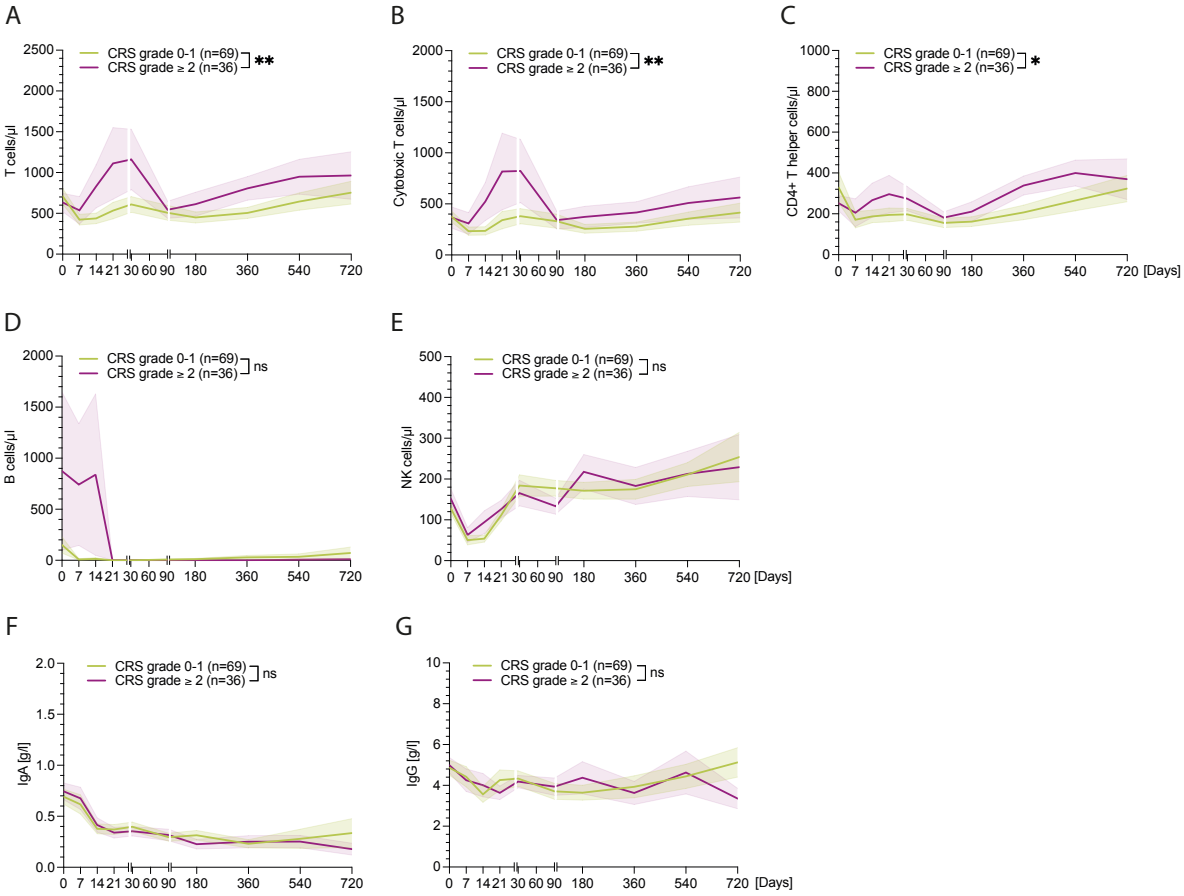
Suppl. Figure S7. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by CAR-HEMATOTOX (HT) score.
(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients showing a low HT score [yellow] or a high HT scope [dark blue]. Results are presented as mean ± standard error of the mean (SEM). For comparison of two groups Wilcoxon test was used. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

Suppl. Figure S8



Suppl. Figure S8. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by the co-stimulatory domain of the applied CAR T-cell product.
(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients having been treated with a CD28ICz-based CAR T-cell product [orange] or a 41BBICz-based CAR T-cell product [turquoise]. Results are presented as mean ± standard error of the mean (SEM). For comparison of two groups Wilcoxon test was used. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

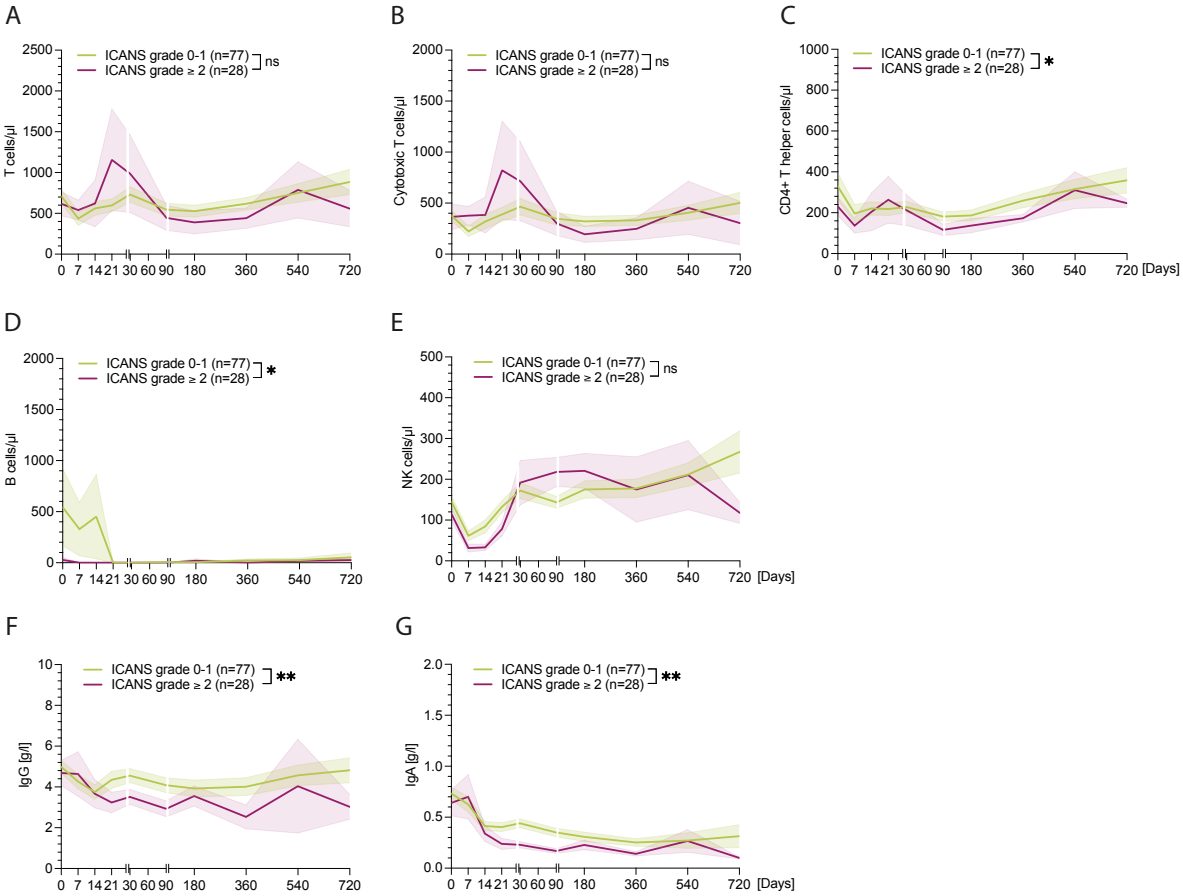
Suppl. Figure S9



Suppl. Figure S9. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by CRS severity.

(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients having CRS grade 0-1 [bright green] or ICANS grade ≥ 2 [violet]. Results are presented as mean ± standard error of the mean (SEM). For comparison of two groups Wilcoxon test was used. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

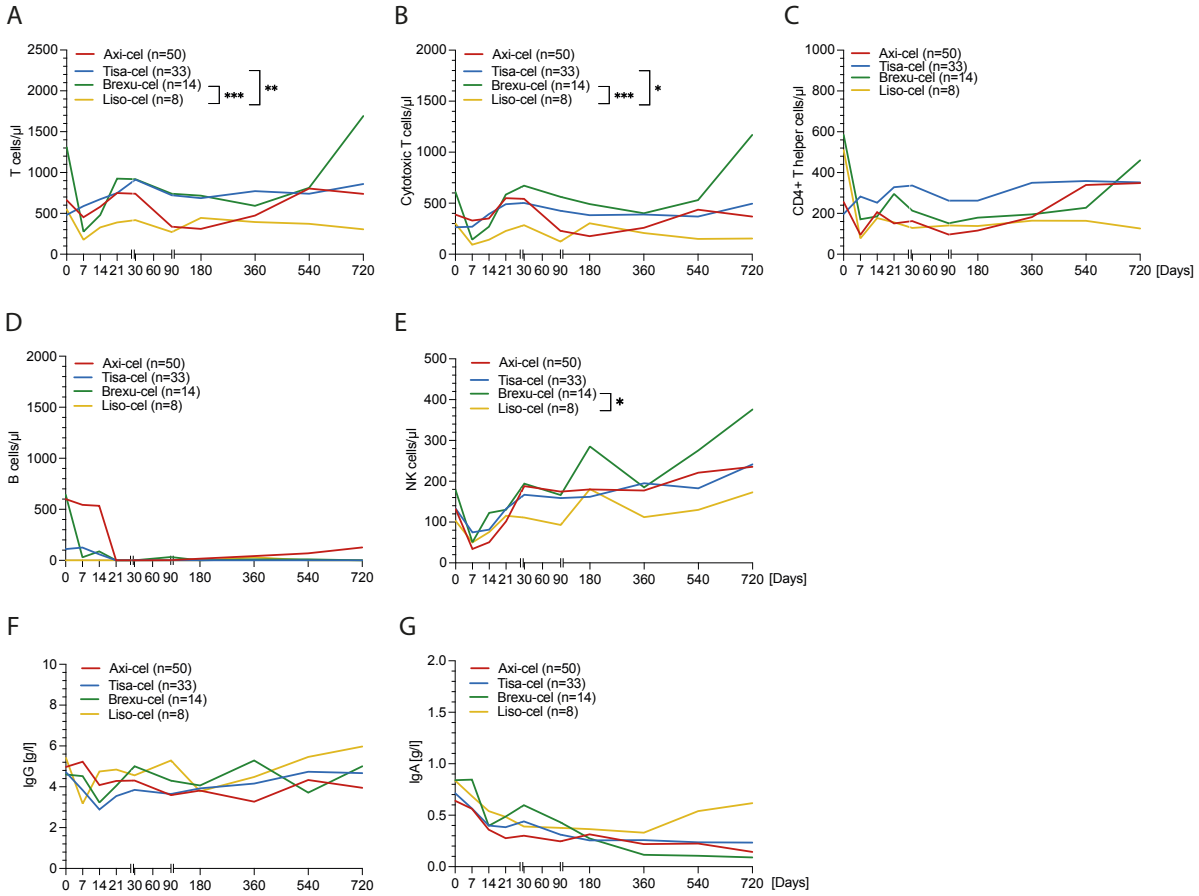
Suppl. Figure S10



Suppl. Figure S10. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by ICANS severity.

(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients having ICANS grade 0-1 [bright green] or ICANS grade ≥ 2 [violet]. Results are presented as mean ± standard error of the mean (SEM). For comparison of two groups Wilcoxon test was used. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

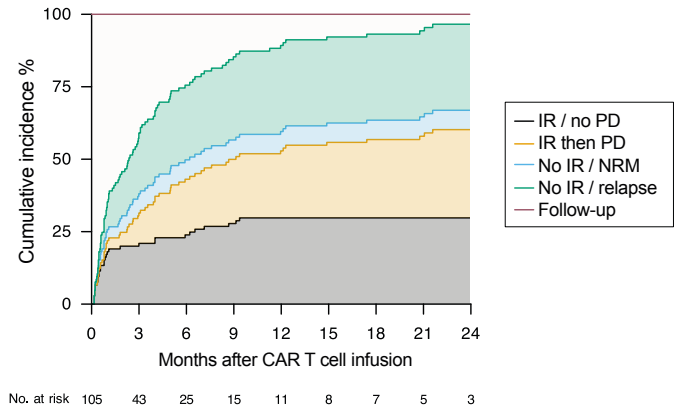
Suppl. Figure S11



Suppl. Figure S11. Lymphocyte and immunoglobulin recovery following CD19 CAR T-cell therapy analyzed by CAR T-cell product.

(A-C) Number of T cells, (D) number of B cells, (E) number of NK cells, (F) IgG and (G) IgA levels were determined before conditioning chemotherapy and at the indicated time points after CD19 CAR T-cell infusion and analyzed for patients treated with different CAR T-cell products: Axi-cel [red], Tisa-cel [blue], Brexu-cel [green] and Liso-cel [yellow]. Results are presented as mean ± standard error of the mean (SEM). For comparison of the different groups a 1-way ANOVA was used. P-values are shows as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.

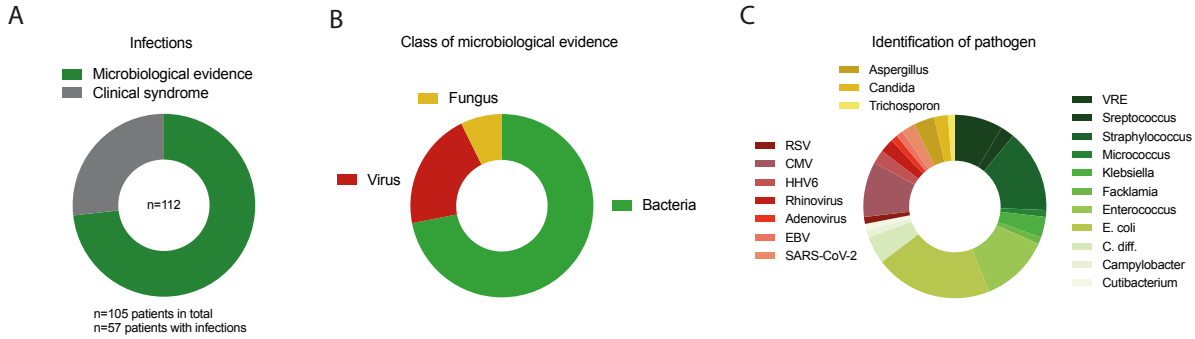
Suppl. Figure S12



Suppl. Figure S12. Competing risk of disease relapse and NRM in the context of immune reconstitution

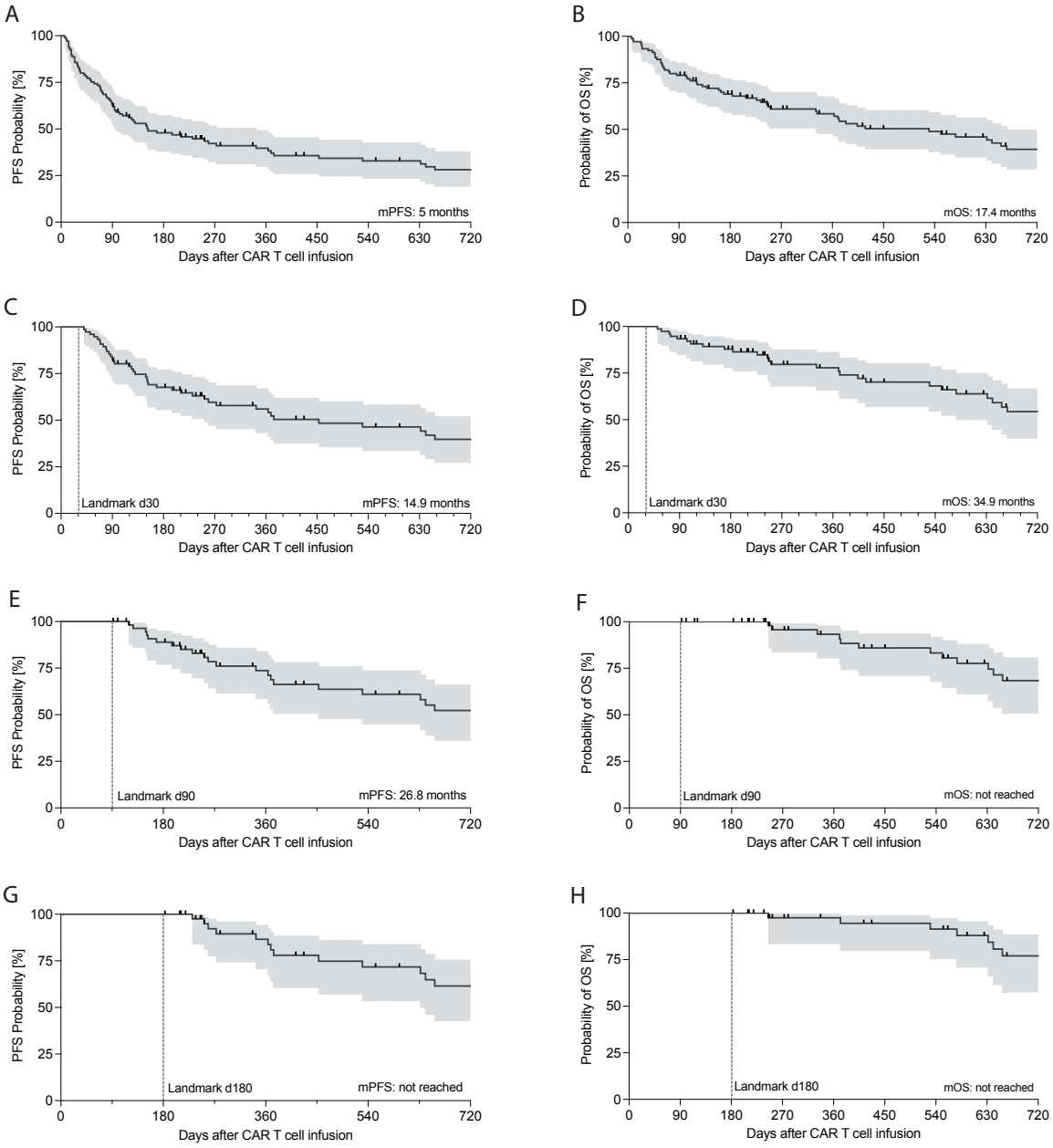
Cumulative incidence of immune reconstitution (IR) in the context of the competing risks of relapse and non-relapse mortality (NRM). The IR group was subdivided into patients without progressive disease (black) and patients with subsequent progression (yellow). The “no IR” group could be further divided into patients having a non-relapse mortality (blue) or relapse (green) events. Because patients were censored for these events in the primary analysis, they occurred before IR by definition. The remaining patients were in active follow-up without IR (purple).

Suppl. Figure S13



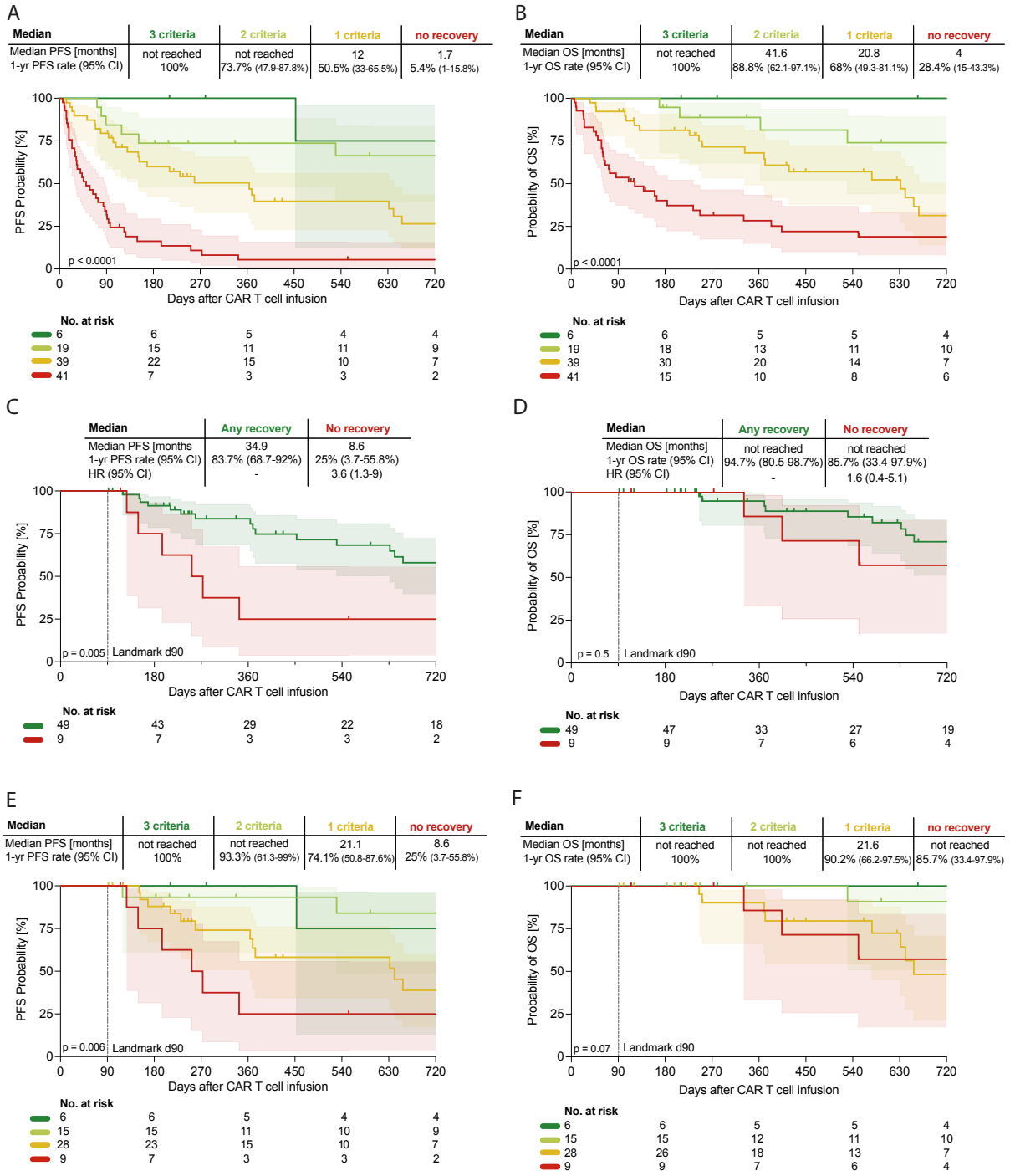
Suppl. Figure S13. Infectious events.
(A) Infections were defined on the basis of microbiologic/histopathologic data (dark green) or as a clinical syndrome of infection on the basis of radiologic evidence or clinical signs (grey). (B) For the microbiologically defined infection, the infection class was further subdivided into bacterial (green), viral (red), or fungal (yellow). (C) Breakdown of the specifically identified pathogen for the bacterial (green), viral (red) and fungal (yellow) infection categories.

Suppl. Figure S14



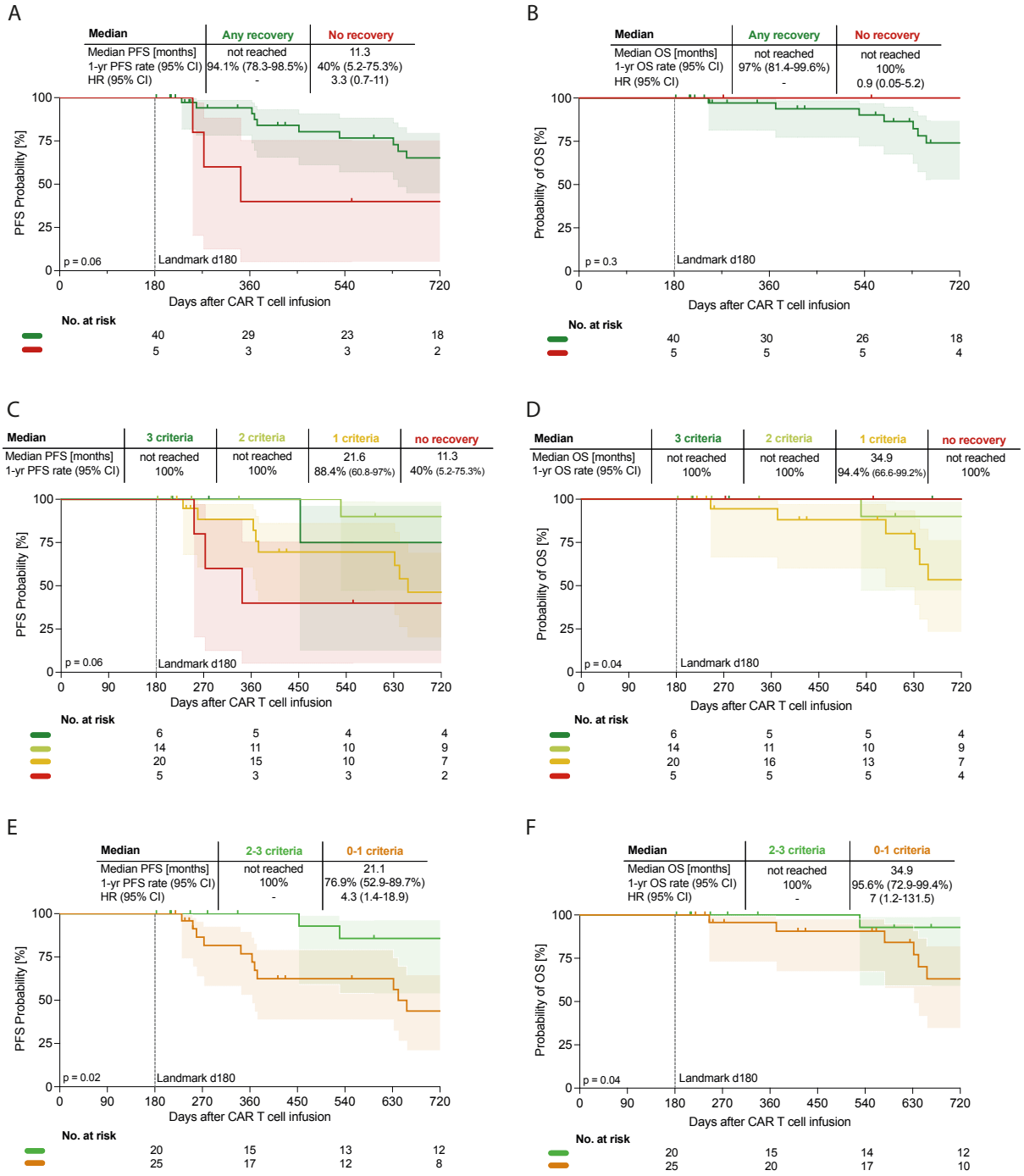
Suppl. Figure S14. Progression-free and overall survival across all patients
(A) Progression free survival (PFS) and (B) overall survival of all B-cell Non-Hodgkin's Lymphoma (B-NHL) patients and according to landmark analyses at (C+D) 30 days, (E+F) 90 days and (G+H) 180 days after CAR T-cell infusion.

Suppl. Figure S15



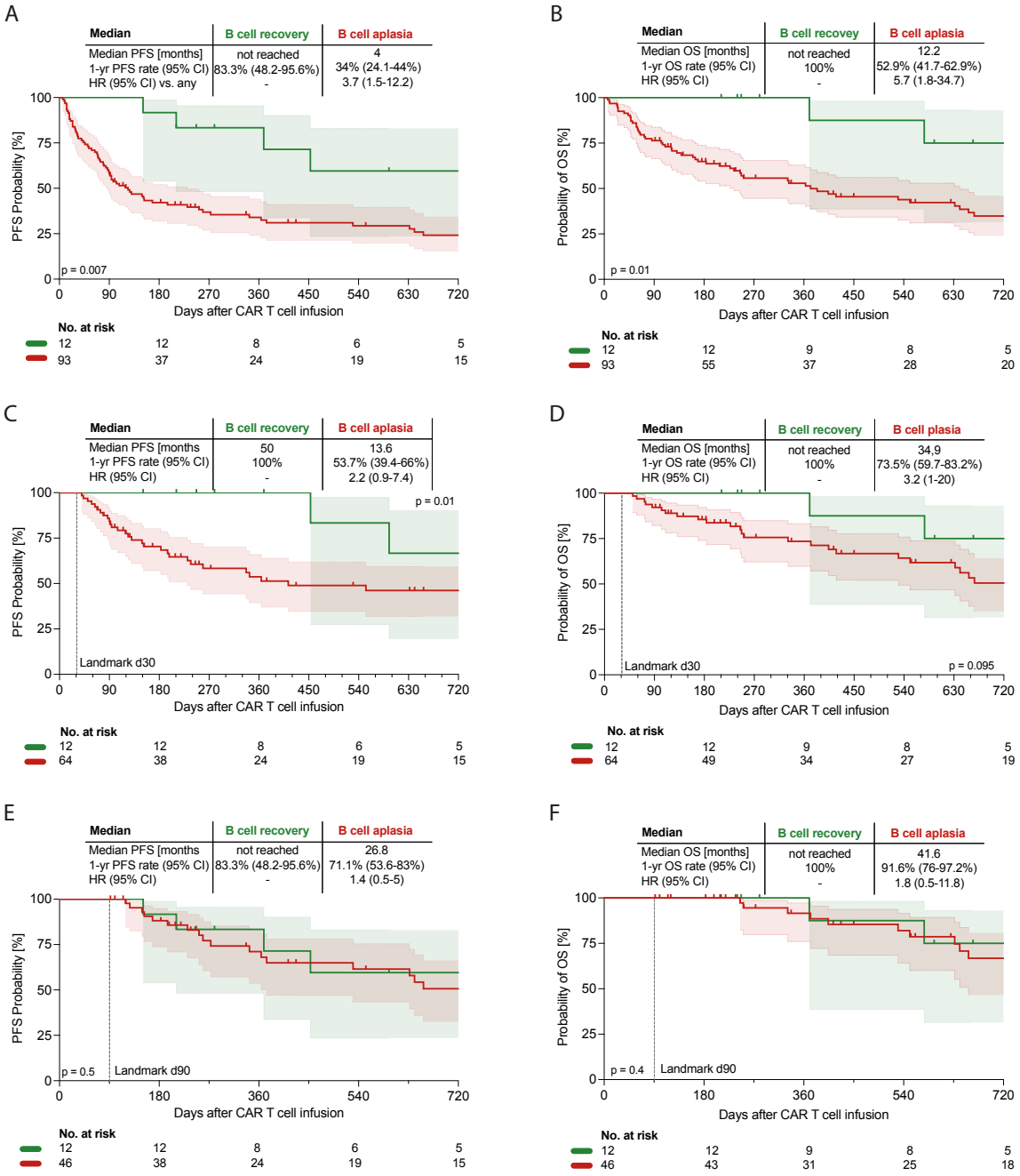
Suppl. Figure S15. IR and clinical response following CD19 CAR T-cell therapy
(A) Progression free survival (PFS) and (B) overall survival were compared for patients with recovery of 3,2,1, or 0 IR criteria. (C+E) Progression free survival (PFS) and (D+F) overall survival of all B-cell Non-Hodgkin's Lymphoma (B-NHL) patients by landmark analysis at 90 days after CAR T-cell infusion. Patients with recovery of 3,2,1, or 0 IR criteria (C+D) and with poor recovery (0-1 criteria) or high recovery (2-3 criteria) (E+F) were compared. P-values determined by log rank method; hazard ratios (HR) determined using a univariate Cox proportional hazards model.

Suppl. Figure S16



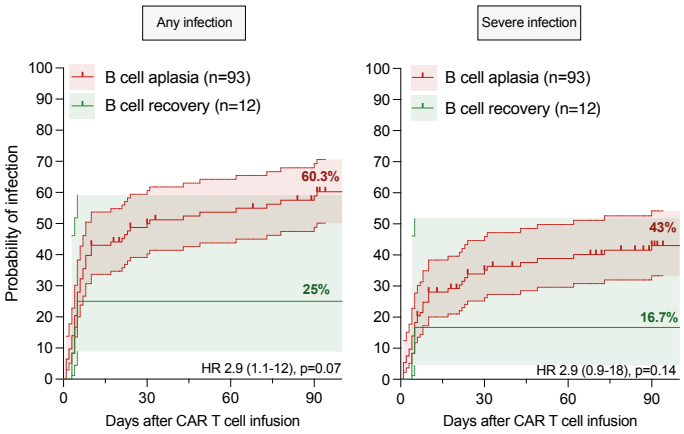
Suppl. Figure S16. Landmark analysis at 180 days post CAR-T for IR and clinical response. (A+C+E) Progression free survival (PFS) and (B+D+F) overall survival of all B-cell Non-Hodgkin's Lymphoma (B-NHL) patients by landmark analysis at 180 days after CAR T-cell infusion. Patients with any IR recovery or no recovery (A+B), with recovery of 3,2,1, or 0 IR criteria (C+D) and with poor recovery (0-1 criteria) or high recovery (2-3 criteria) (E+F) were compared. P-values determined by log rank method; hazard ratios (HR) determined using a univariate Cox proportional hazards model.

Suppl. Figure S17



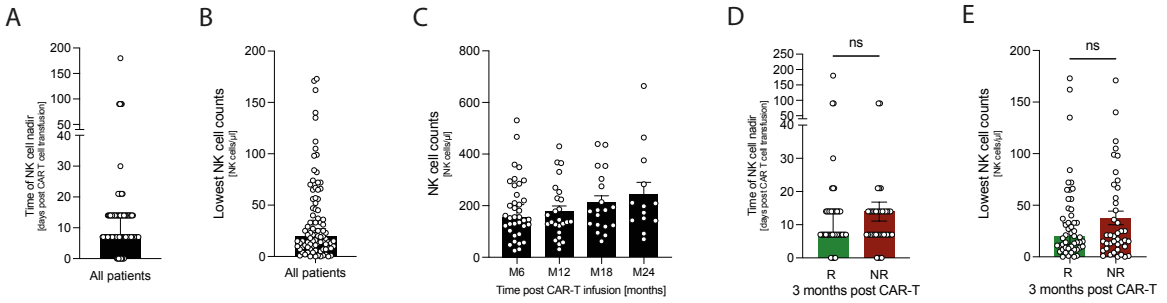
Suppl. Figure S17. B-cell aplasia and clinical response following CD19 CAR T-cell therapy. (A+C+E) Progression free survival (PFS) and (B+D+F) overall survival of all B-cell Non-Hodgkin's Lymphoma (B-NHL) patients for all patients (A-B), by landmark analysis at 30 days (C-D) and by landmark analysis at 180 days (E-F) after CAR T-cell infusion. Patients with B-cell recovery (any detectable B-cell counts) versus B-cell aplasia were compared. P-values determined by log rank method; hazard ratios (HR) determined using a univariate Cox proportional hazards model.

Suppl. Figure S18



Suppl. Figure S18. Relationship between B-cell recovery and the cumulative probability of early infectious complications.
Relative distribution of infection grades for all infection subtypes (left) and severe infections (right) comparing patients with B cell aplasia versus B cell recovery (e.g., any detectable B-cell counts). Hazard ratios (HR) and p-values were determined using a univariate Cox proportional hazards model.

Suppl. Figure S19



Suppl. Figure S19. NK cell counts after CAR T-cell therapy.
(A) Time of NK cell nadir for all patients, (B) lowest NK cell counts and (C) NK cells 6 months (6M), 12 months (12M), 18 months (18M) and 24 months (24M) after CAR T-cell therapy of all patients. (D) Time of NK cell nadir, (E) lowest NK cell counts and (C) NK cells at 6 months (6M) post CAR-T compared for patients with response (R) and no response (NR) 3 months after CAR-T. Mann-Whitney test was used to compare between two groups. P-values are shown as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ or **** $p < 0.0001$.