Increased visceral fat distribution and body composition impact cytokine release syndrome onset and severity after CD19 chimeric antigen receptor T-cell therapy in advanced B-cell malignancies

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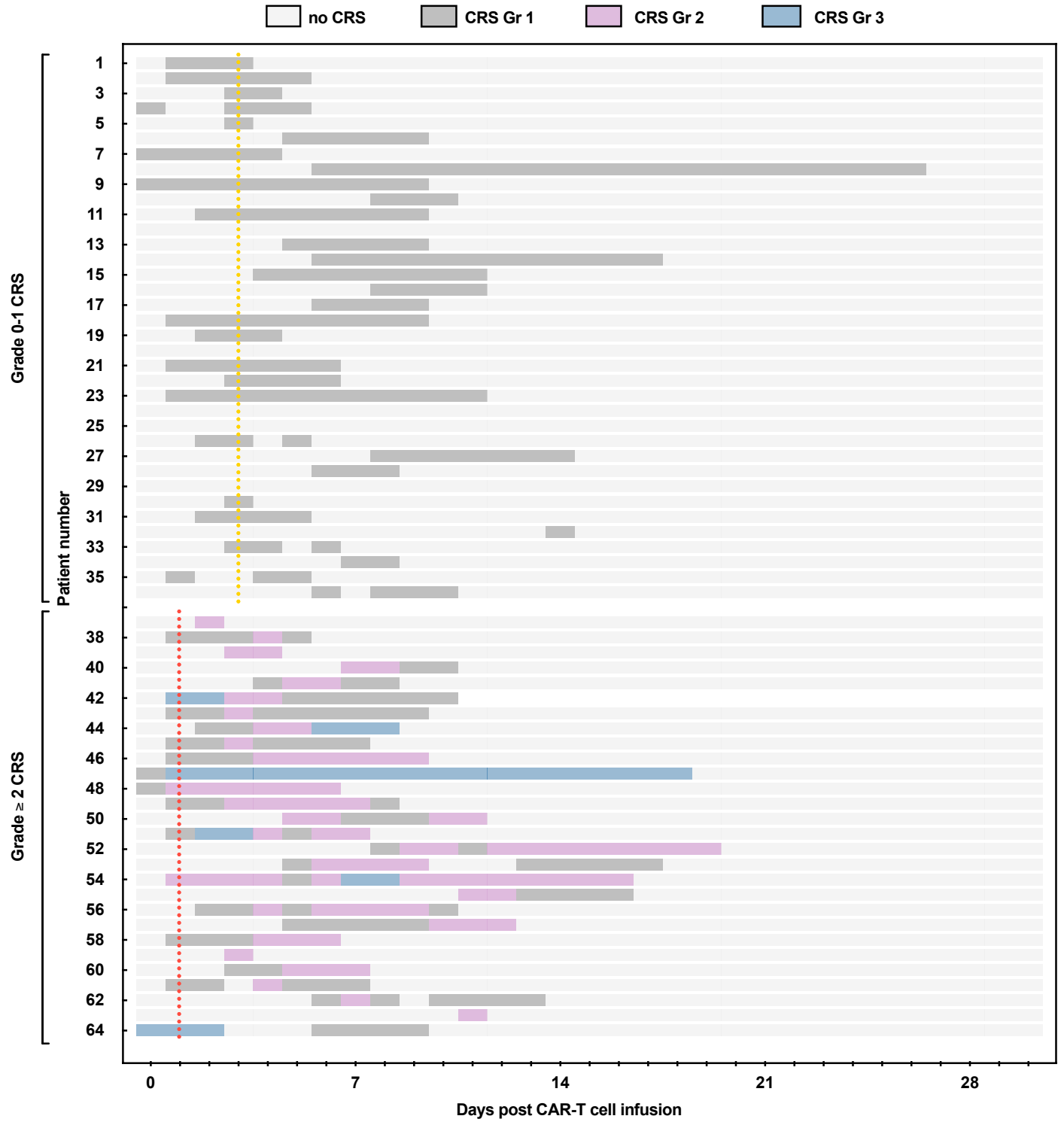

Fig. S1 CRS swimmer plot

Swimmer plot displaying the kinetics of CRS in each patient during the first 30 days after CAR-T (n = 64). Each row represents one patient; the highest grade of CRS recorded each day is color-coded. The median time to first fever ≥38°C for patients with grade 0-1° CRS (yellow dotted line) and grade ≥2° CRS (red dotted line) is indicated.

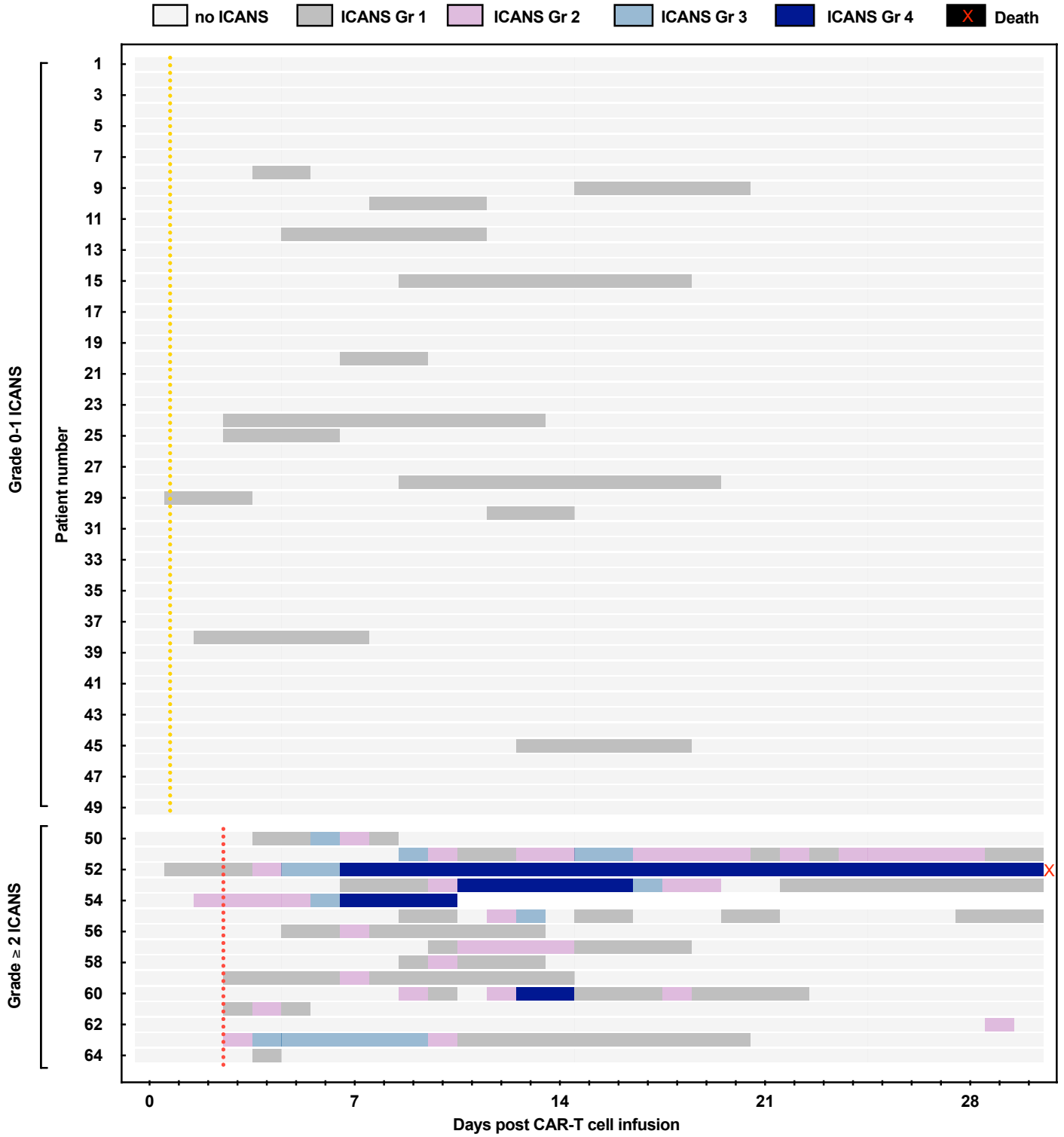

Fig. S2 ICANS swimmer plot
Swimmer plot displaying the kinetics of ICANS in each patient during the first 30 days after CAR-T (n = 64). Each row represents one patient; the highest grade of ICANS recorded each day is color-coded. One patient died of ICANS on day 59 (red "X"). The median time to first fever ≥38°C for patients with grade 0-1° ICANS (yellow dotted line) and grade ≥2° ICANS (red dotted line) is indicated.

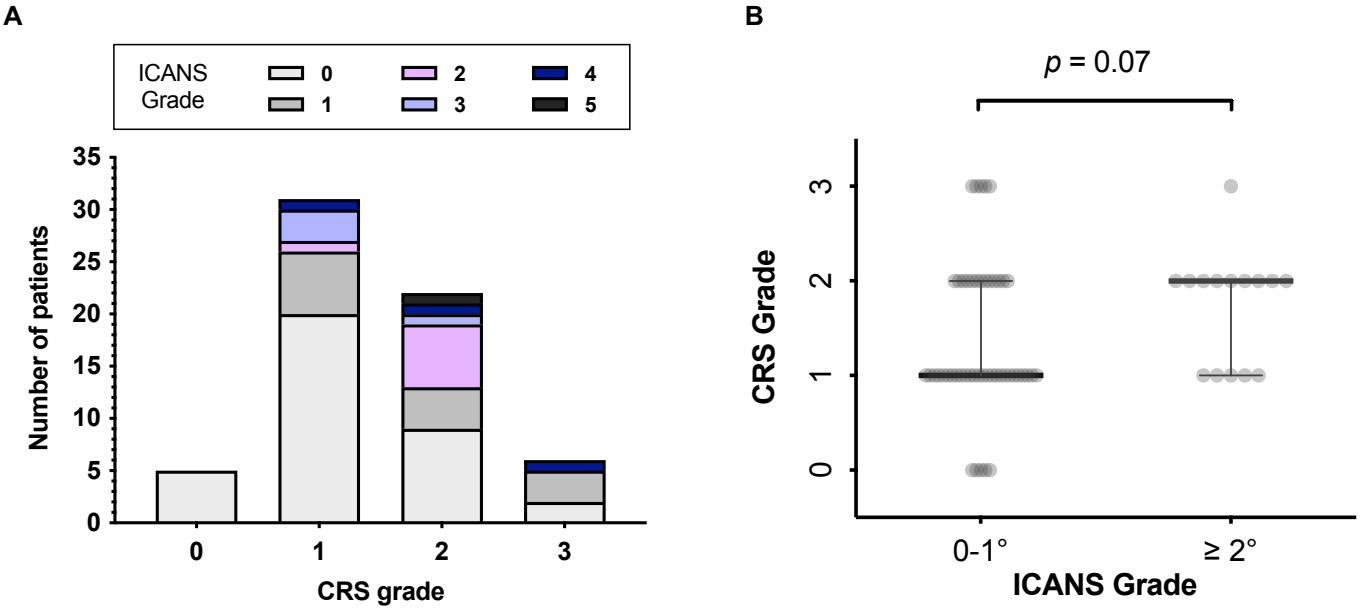

Fig. S3 Correlation of CRS with neurotoxicity

A Number of patients with each grade of CRS with shading indicating concomitant ICANS grade. **B** Maximal CRS grade comparing low (0-1°) vs. high-grade (≥ 2°) neurotoxicity. Box and whiskers indicated the median with the 95% CI, significance values were determined by Mann-Whitney Test.

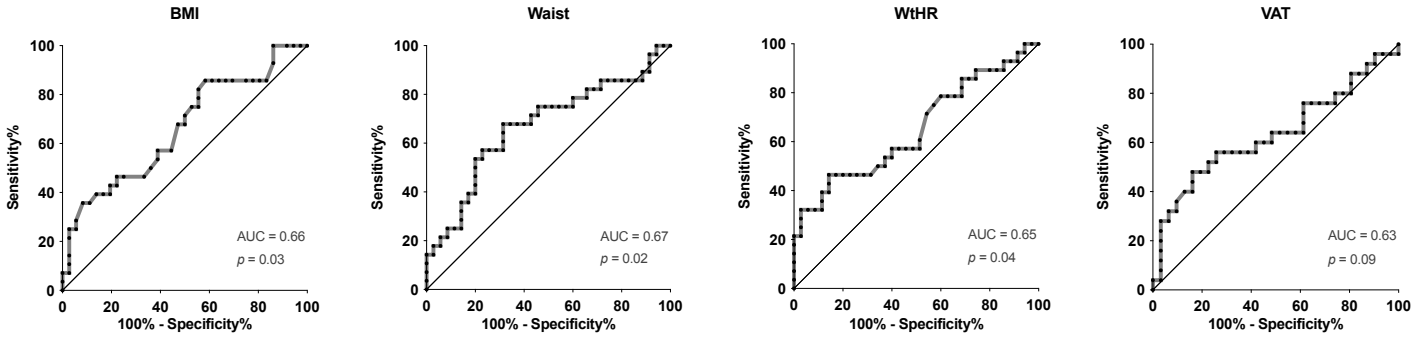

Fig. S4 ROC analyses of CRS severity by body composition
Receiver operating characteristic (ROC) curves studying the influence of BMI, Waist, WtHR, and VAT (from left to right) on the binary outcome CRS 0-1° vs. CRS ≥ 2°. The optimal discriminatory thresholds were determined by optimizing the respective Youden *J* statistic in the ROC analysis.

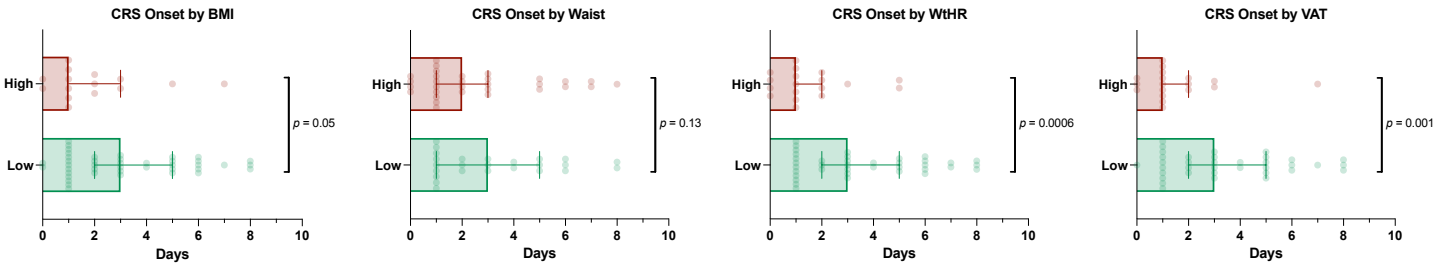

Fig. S5 CRS onset by body composition
Median day of CRS onset by BMI (left), Waist circumference (middle left), Waist-to-Height-Ratio (middle right), and visceral adipose tissue (right). High vs. low groups were defined by ROC analysis. Significance values were determined by Mann-Whitney test.

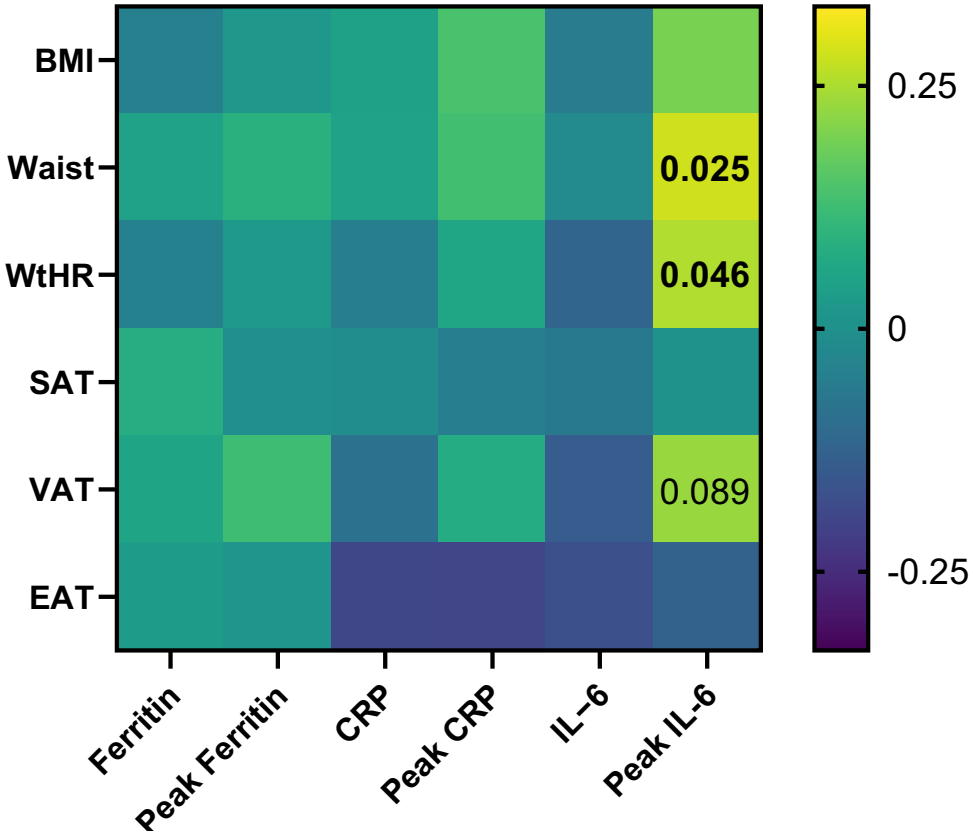

Fig. S6 Adipose tissue correlates with peak IL-6 and IL-6 dynamics
Heatmap: Correlation coefficients determined by univariate analysis comparing anthropometric features and adipose tissue deposits with both baseline and peak cytokine levels (Ferritin, CRP, IL-6). P-Values < 0.1 are annotated.

Suppl. Table 1. Comparison of risk factors between CRS/ICANS 0-1° vs CRS/ICANS 2°.

Patient Characteristics	CRS			ICANS		
	CRS 0-1° (N = 36)	CRS ≥ 2° (N = 28)	P-Value	ICANS 0-1° (N = 49)	ICANS ≥ 2° (N = 15)	P-Value
Age	61 (53-68)	62 (47-69)	0.77	61 (54-69)	59 (44-69)	0.47
Sex						
Female	13	11	0.79	15	8	0.13
Male	24	16		34	7	
Costimulatory Domain						
CD28z (Axi-cel, Brexu-cel)	17	13	0.95	20	10	0.14
41BB (Tisa-cel)	19	15		29	5	
STLV	86.4 (17.1-319.4)	129.6 (38-464.1)	0.28	87.8 (21.9-355.2)	204.9 (36.7-437.7)	0.57
Baseline Laboratory Values						
CRP [mg/dl]	1.2 (0.3-3.8)	0.6 (0.2-3.7)	0.58	0.9 (0.2-2.5)	1.1 (0.3-4.3)	0.51
Ferritin [ng/ml]	1158 (324-2097)	475.5 (203.8-1483)	0.35	772.5 (289-1444)	1434 (236-3195)	0.31
Albumin [g/dl]	3.9 (3.4-4.2)	3.8 (3.5-4.2)	0.9	3.9 (3.5-4.2)	3.8 (3.2-3.9)	0.12
LDH [U/ml]	278 (212-410)	229 (195-591)	0.69	271 (200-418)	297 (184-623)	0.98
Platelets [G/l]	137 (86-188)	158 (68-228)	0.5	139 (90-213)	126 (45-230)	0.66

Abbreviations: CRP = c-reactive protein, LDH = lactate dehydrogenase, STLV = sum of target lesion volumina.

Suppl. Table 2. Distribution of body composition parameters in CAR T-cell patients with CRS/ICANS 0-1° vs CRS/ICANS ≥ 2°.

Body Composition Parameter	CRS			ICANS		
	CRS 0-1° (N = 36)	CRS ≥ 2° (N = 28)	P-Value	ICANS 0-1° (N = 49)	ICANS ≥ 2° (N = 15)	P-Value
Anthropometry						
BMI [kg/m²]	22.9 (21.3-24.5)	24.3 (22.6-28.5)	**0.01**	23.4 (21.7-26)	24.3 (21.3-28)	0.32
Waist [cm]	95 (85.7-101.5)	104.1 (93.5-107.4)	**0.01**	98.4 (88.7-106.4)	100.7 (95-107.8)	0.36
WtHR [cm/m²]	0.54 (0.51-0.58)	0.56 (0.53-0.64)	**0.02**	0.55 (0.52-0.6)	0.58 (0.5-0.62)	0.54
Adipose Tissues						
SAT [cm²]	140.5 (96.7-185.6)	169.1 (106.8-251.9)	0.054	141 (99.9-189.7)	190.6 (101.9-267.3)	0.22
VAT [cm²]	90.6 (51-121.1)	126.8 (60.5-195.2)	**0.048**	100.8 (52.5-144.4)	104.6 (53.1-214.3)	0.51
EAT [cm²]	6.5 (3.8-17.7)	5.9 (3.9-13.2)	0.83	6.3 (3.8-15.6)	7 (4.6-15.6)	0.69
Muscle Tissues						
Psoas Muscle [cm²]	17.3 (13.3-21.4)	19.8 (13.9-21.6)	0.44	19 (13.8-22.1)	17.5 (12.3-20.7)	0.26
PMI [cm²/m²]	5.6 (4.8-6.2)	6 (4.9-6.9)	0.49	5.8 (4.9-7.1)	6 (4.4-6.5)	0.37
Skeletal Muscle [cm²]	118.6 (103.8-145.1)	133.6 (106.7-164.4)	0.25	129 (111.5-152.6)	115.7 (94.4-162.5)	0.52
SMI [cm²/m²]	41.4 (36.5-44.3)	42.8 (36.1-51)	0.39	41.6 (36.9-47.7)	40.3 (34.9-50.5)	0.70

All values are shown in median (IQR). P-values were calculated either by unpaired t-test or Mann-Whitney test according to normality distribution. Abbreviations: BMI = body mass index, CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome, PMI = psoas muscle index, SMI = skeletal muscle index, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue, WtHR = waist-to-height-ratio.

Suppl. Table 3. Comparison of risk factors patient cohorts based on BC parameter thresholds.

Patient Characteristics	BMI			Waist			WtHR			VAT		
	< 27.05 kg/m²	> 27.05 kg/m²	P-Value	< 99.23 cm	> 99.23 cm	P-Value	< 0.5935	> 0.5935	P-Value	< 144.3 cm²	> 144.3 cm²	P-Value
Age [years]	60 (45-70)	58 (39-67)	0.5	60 (41-70)	65 (57-69)	0.1	60 (48-69)	65 (54-70)	0.5	60 (45-68)	66 (58-71)	0.1
Costimulatory Domain												
CD28z (Axi-cel, Brexu-cel)	27	7	> 0.9	15	18	0.5	22	11	0.4	23	10	0.8
41BB (Tisa-cel)	24	6		17	13		23	7		21	7	
STLV [cm²]	88 (27-384)	165 (10-387)	> 0.9	171 (30-438)	88 (21-225)	0.4	97 (22-365)	74 (25-365)	> 0.9	89 (21-340)	61 (21-438)	0.8
Baseline Laboratory Values												
CRP [mg/dl]	1 (0.3-4.7)	1.1 (0.3-3.7)	0.99	0.8 (0.2-4.3)	1.1 (0.3-2.6)	0.7	0.9 (0.2-4.2)	1 (0.3-3.4)	0.8	1.2 (0.2-4.3)	0.8 (0.3-2.4)	0.6
Ferritin [ng/ml]	1158 (236-2286)	1198 (496-1434)	0.9	812 (288-1818)	509 (239-1629)	0.9	733 (288-1827)	1062 (236-1629)	0.8	843 (239-2132)	1062 (284-1434)	0.8
Albumin [g/dl]	3.8 (3.4-4.2)	3.8 (3.4-4.2)	> 0.9	3.9 (3.6-4.2)	3.8 (3.4-4.2)	0.2	3.9 (3.5-4.2)	3.8 (3.1-4.2)	0.3	3.8 (3.4-4.2)	3.8 (3.5-4.1)	0.6
LDH [U/ml]	269 (196-410)	278 (206-833)	0.4	286 (194-487)	267 (207-459)	0.7	274 (195-442)	264 (210-628)	0.5	273 (201-421)	267 (199-666)	> 0.9
Platelets [G/l]	133 (65-223)	148 (113-234)	0.2	147 (95-207)	139 (65-223)	0.7	132 (71-206)	160 (96-231)	0.3	133 (68-218)	139 (91-232)	0.5

Abbreviations: CRP = c-reactive protein, LDH = lactate dehydrogenase, STLV = sum of target lesion volumina.

Suppl. Table 4. Correlations analyses between body composition parameters and CRS dynamics.

Body Composition Parameter	CRS Duration		CRS Onset	
	Correlation coefficient	P-Value	Correlation coefficient	P-Value
Anthropometry				
BMI [kg/m²]	0.12	0.39	-0.38	**0.003**
Waist [cm]	0.06	0.68	-0.32	**0.02**
WtHR [cm/m²]	0.19	0.17	-0.37	**0.005**
Adipose Tissues				
SAT [cm²]	0.07	0.61	-0.13	0.38
VAT [cm²]	0.11	0.45	-0.37	**0.008**
EAT [cm²]	-0.01	0.97	-0.12	0.39
Muscle Tissues				
Psoas Muscle [cm²]	-0.1	0.47	0.001	0.99
PMI [cm²/m²]	-0.09	0.54	0.007	0.96
Skeletal Muscle [cm²]	-0.04	0.81	-0.11	0.45
SMI [cm²/m²]	-0.05	0.74	-0.16	0.27
STLV	0.17	0.21	0.09	0.54

P-values were calculated either by unpaired t-test or Mann-Whitney test according to normality distribution. Abbreviations: BMI = body mass index, CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome, PMI = psoas muscle index, SMI = skeletal muscle index, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue, STLV = sum of target lesion voluminal, WtHR = waist-to-height-ratio.

Suppl. Table 5. Correlations analyses between body composition parameters and ICANS dynamics.

Body Composition Parameter	ICANS Duration		ICANS Onset	
	Correlation coefficient	P-Value	Correlation coefficient	P-Value
Anthropometry				
BMI [kg/m²]	0.0005	0.99	-0.07	0.73
Waist [cm]	-0.002	0.99	0.08	0.67
WtHR [cm/m²]	-0.21	0.29	-0.04	0.83
Adipose Tissues				
SAT [cm²]	0.04	0.85	0.33	0.11
VAT [cm²]	-0.005	0.98	0.17	0.42
EAT [cm²]	-0.18	0.39	0.13	0.55
Muscle Tissues				
Psoas Muscle [cm²]	0.22	0.31	0.31	0.14
PMI [cm²/m²]	0.03	0.88	0.2	0.36
Skeletal Muscle [cm²]	0.25	0.24	0.18	0.41
SMI [cm²/m²]	0.07	0.74	0.02	0.92
STLV	-0.14	0.5	0.24	0.24

P-values were calculated either by unpaired t-test or Mann-Whitney test according to normality distribution. Abbreviations: BMI = body mass index, CRS = cytokine release syndrome, ICANS = immune effector cell-associated neurotoxicity syndrome, PMI = psoas muscle index, SMI = skeletal muscle index, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue, STLV = sum of target lesion voluminal, WtHR = waist-to-height-ratio.

Suppl. Table 6. Odds ratios and 95% confidence intervals of body composition parameters and previously described risk factors from a multivariate logistic regression for development of CRS ≥ 2°.

	Model BMI					Model Waist			
	OR	Lower 95% CI	Upper 95% CI	P-Value		OR	Lower 95% CI	Upper 95% CI	P-Value
Ferritin	1.000	0.999	1.001	0.74	**Ferritin**	1.000	0.999	1.001	0.86
CRP	0.497	0.239	1.035	0.06	**CRP**	0.543	0.250	1.178	0.12
Albumin	0.281	0.027	2.942	0.29	**Albumin**	0.369	0.027	5.107	0.46
IL-6	1.008	0.922	1.102	0.86	**IL-6**	0.981	0.887	1.085	0.70
STLV	1.004	1.000	1.008	0.06	**STLV**	1.004	0.999	1.009	0.08
LDH	0.998	0.994	1.002	0.38	**LDH**	1.000	0.995	1.004	0.85
Platelets	0.997	0.983	1.011	0.71	**Platelets**	1.000	0.986	1.015	0.95
Age	1.016	0.942	1.096	0.68	**Age**	0.975	0.897	1.060	0.55
Costim. Domain	0.540	0.104	2.797	0.46	**Costim. Domain**	0.387	0.062	2.418	0.31
BMI	1.366	1.022	1.827	**0.04**	**Waist**	1.159	1.038	1.294	**0.009**

	Model WtHR					Model VAT			
	OR	Lower 95% CI	Upper 95% CI	P-Value		OR	Lower 95% CI	Upper 95% CI	P-Value
Ferritin	1.000	0.999	1.001	0.93	**Ferritin**	1.000	0.999	1.001	0.95
CRP	0.522	0.243	1.122	0.096	**CRP**	0.575	0.296	1.115	0.10
Albumin	0.322	0.030	3.441	0.35	**Albumin**	0.323	0.032	3.263	0.34
IL-6	1.010	0.917	1.112	0.84	**IL-6**	0.999	0.912	1.094	0.98
STLV	1.004	1.000	1.008	0.08	**STLV**	1.004	1.000	1.008	0.08
LDH	0.998	0.993	1.003	0.36	**LDH**	0.999	0.994	1.003	0.50
Platelets	0.998	0.984	1.013	0.83	**Platelets**	1.004	0.992	1.017	0.52
Age	0.984	0.907	1.068	0.71	**Age**	0.991	0.916	1.072	0.82
Costim. Domain	0.584	0.107	3.193	0.54	**Costim. Domain**	0.865	0.173	4.318	0.86
WtHR	1.245	1.050	1.477	**0.01**	**VAT**	1.155	1.026	1.301	**0.02**

Abbreviations: BMI = body mass index. Costim. = costimulatory. CRP = c-reactive protein. IL-6 = interleukin-6. LDH = lactate dehydrogenase. STLV = sum of target lesion volumina. VAT = visceral adipose tissue. WtHR = waist-to-height-ratio