

Acute leucoencephalomyelopathy and quadriplegia after CAR T-cell therapy

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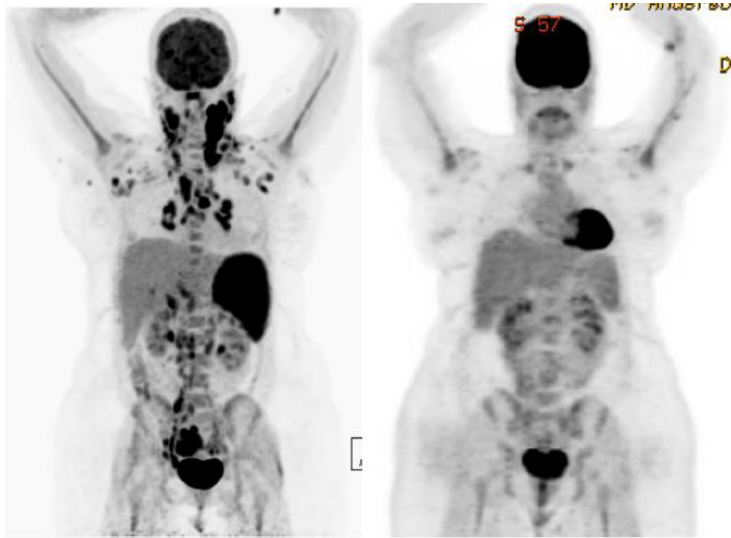
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Supplementary Figures

Supplementary Figure 1. Positron emission tomography scans of patient 1 (A) and 2 (B) before and after axi-cel therapy.

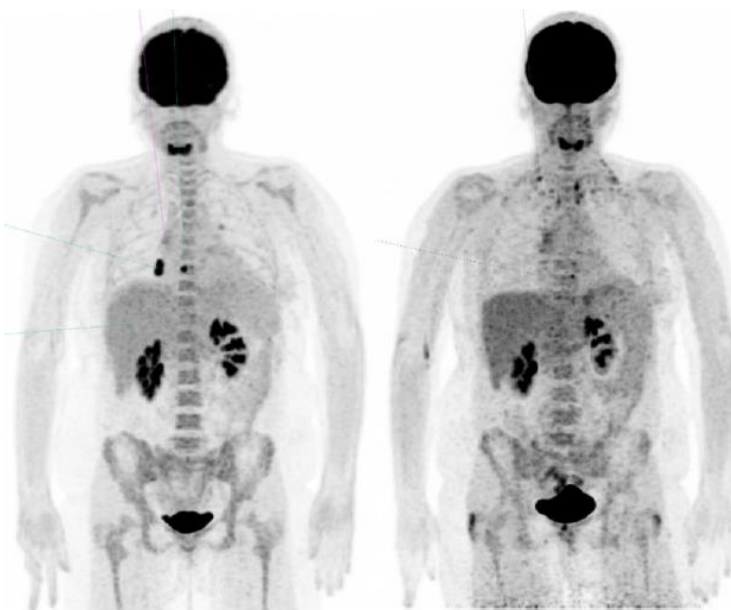
A. Patient 1



Baseline

Day 28

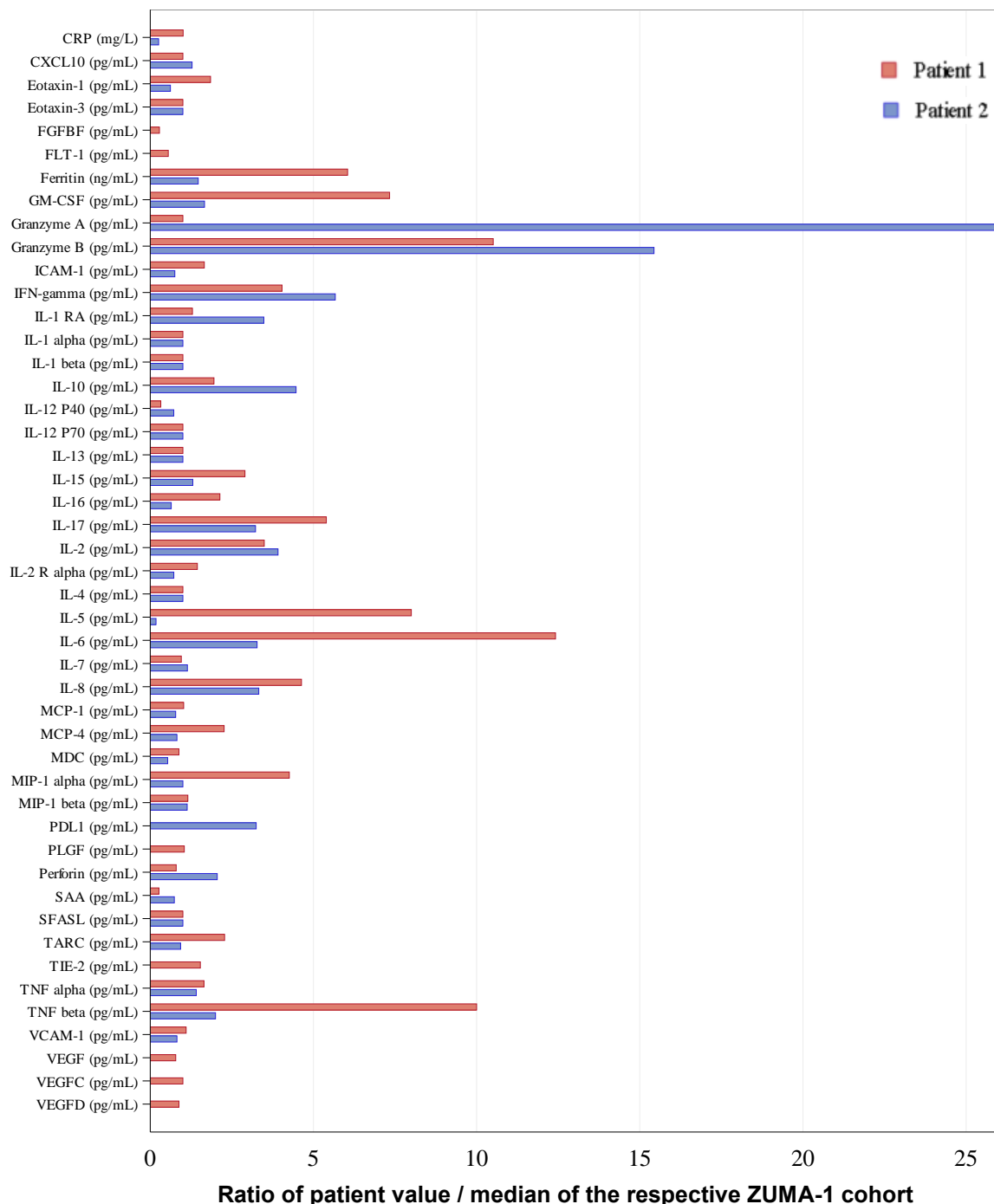
B. Patient 2



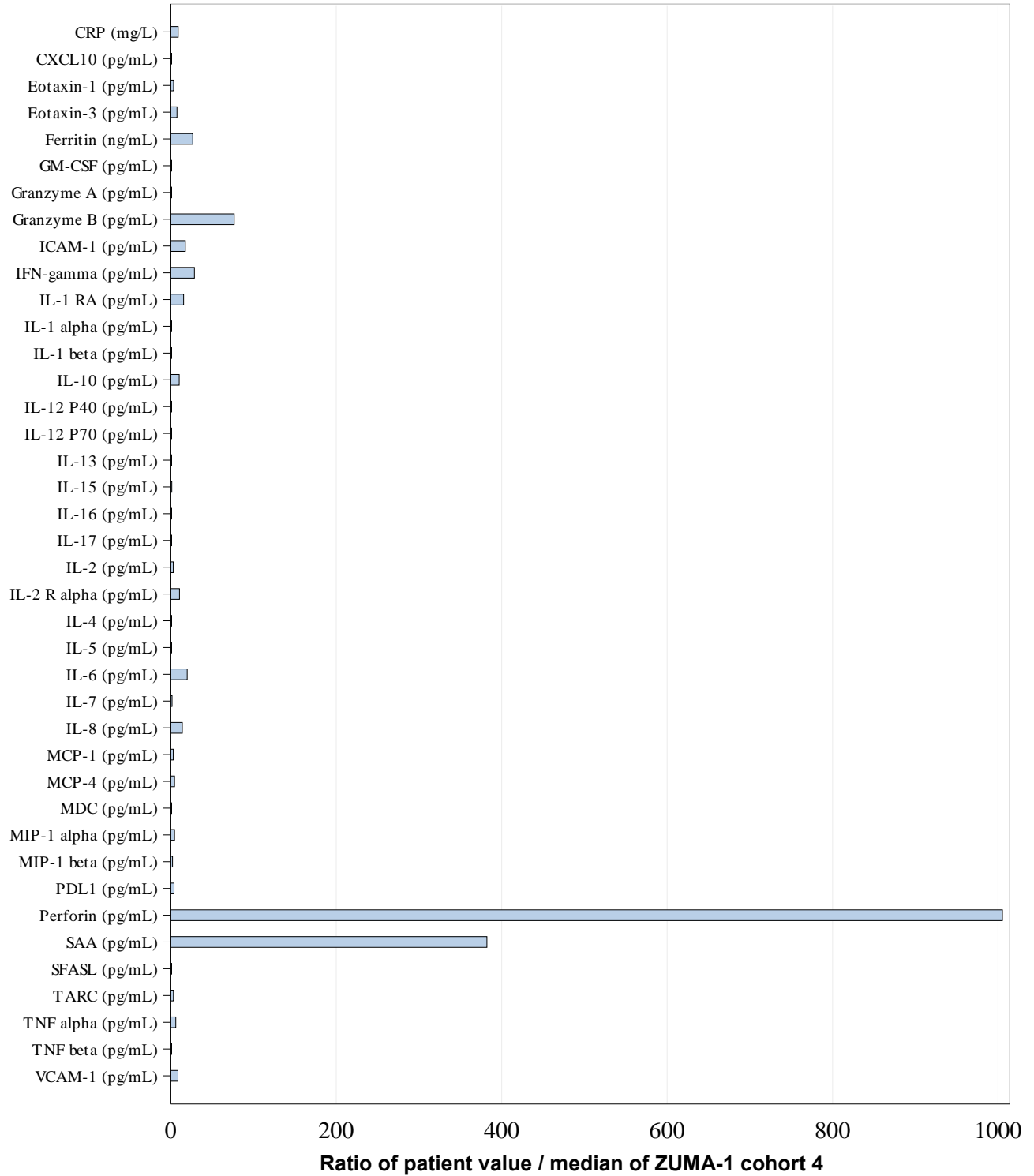
Baseline

At 6 months

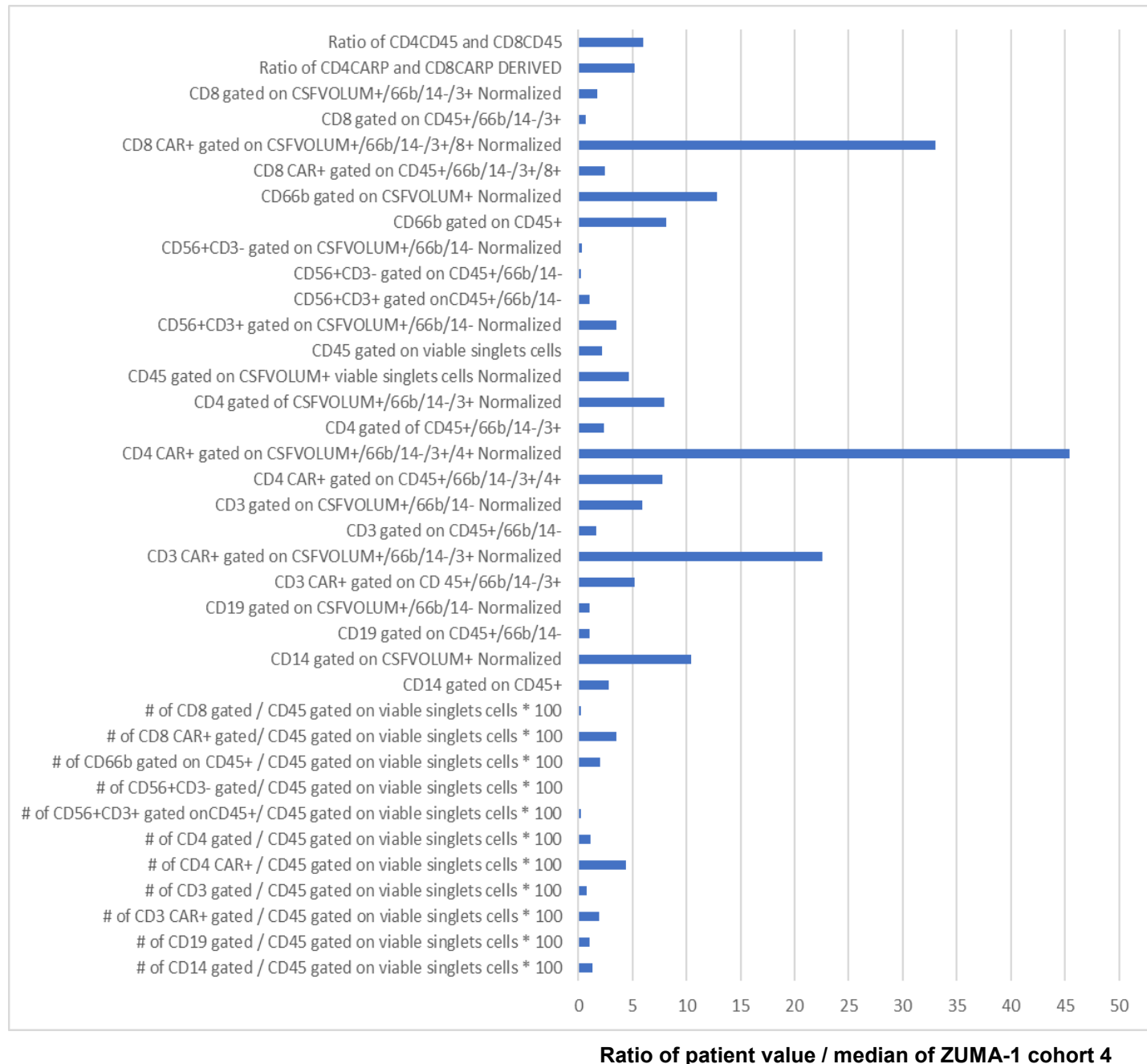
Supplementary Figure 2. Peaks of cytokines in the serum of Patient 1 (cohorts 1 and 2) and 2 (cohort 4) versus their corresponding cohort (ratio of patient value/median of the respective ZUMA-1 cohort). Cohorts 1 and 2 (N=101) were the pivotal cohorts of ZUMA-1 and included patients with diffuse large B-cell lymphoma (Cohort 1) and transformed follicular lymphoma / primary mediastinal B-cell lymphoma (cohort 2). Cohort 4 (N=41) included patients with relapsed/refractory large B-cell lymphoma with similar histologies as in cohorts 1 and 2 but patients received early intervention with corticosteroids to mitigate adverse events. Cytokine evaluations were performed utilizing Meso Scale Discovery (MSD), MILLIPLEX MAP, R&D Systems and Abcam ELISA, and Simple Plex technologies. FGFBF, FLT-1, PLGF, TIE-2, VEGF, VEGFC, and VEGFD were not analyzed in ZUMA-1 Cohort 4. PD-L1 not analyzed in Cohort 1 and 2.



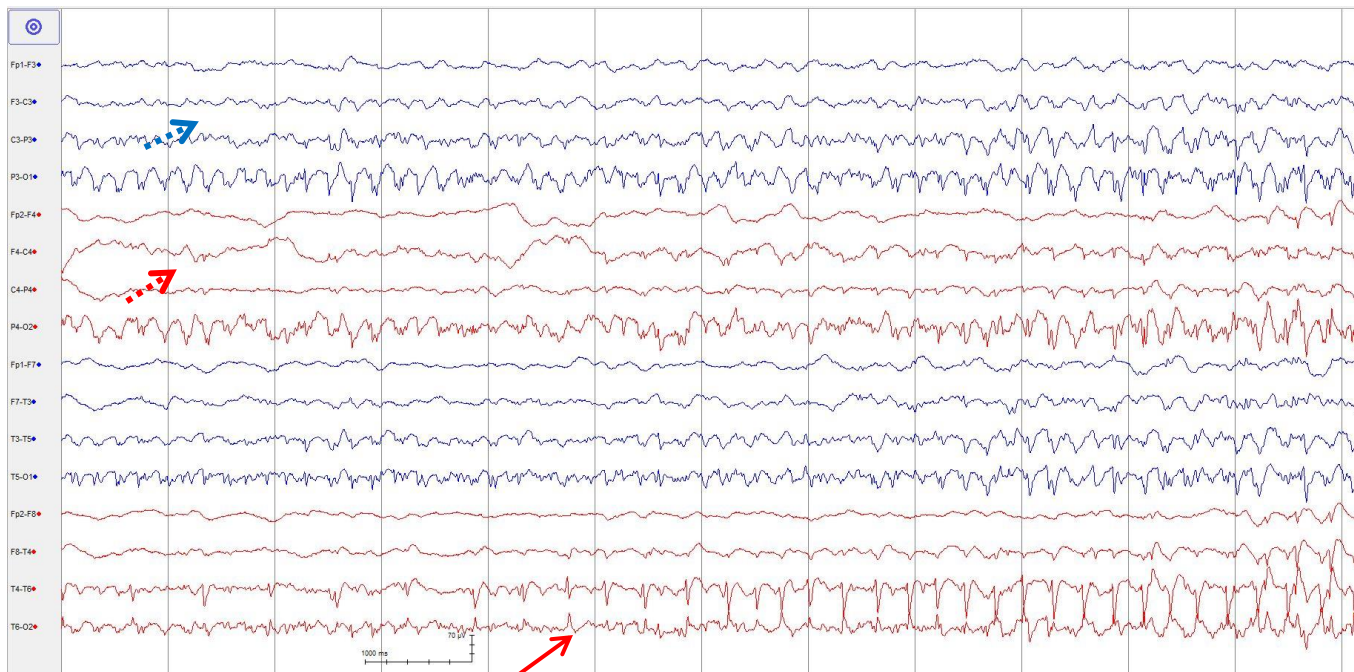
Supplementary Figure 3. CSF cytokines in Patient 2 at day 5 versus its corresponding cohort (ratio of patient value/median of ZUMA-1 cohort 4).



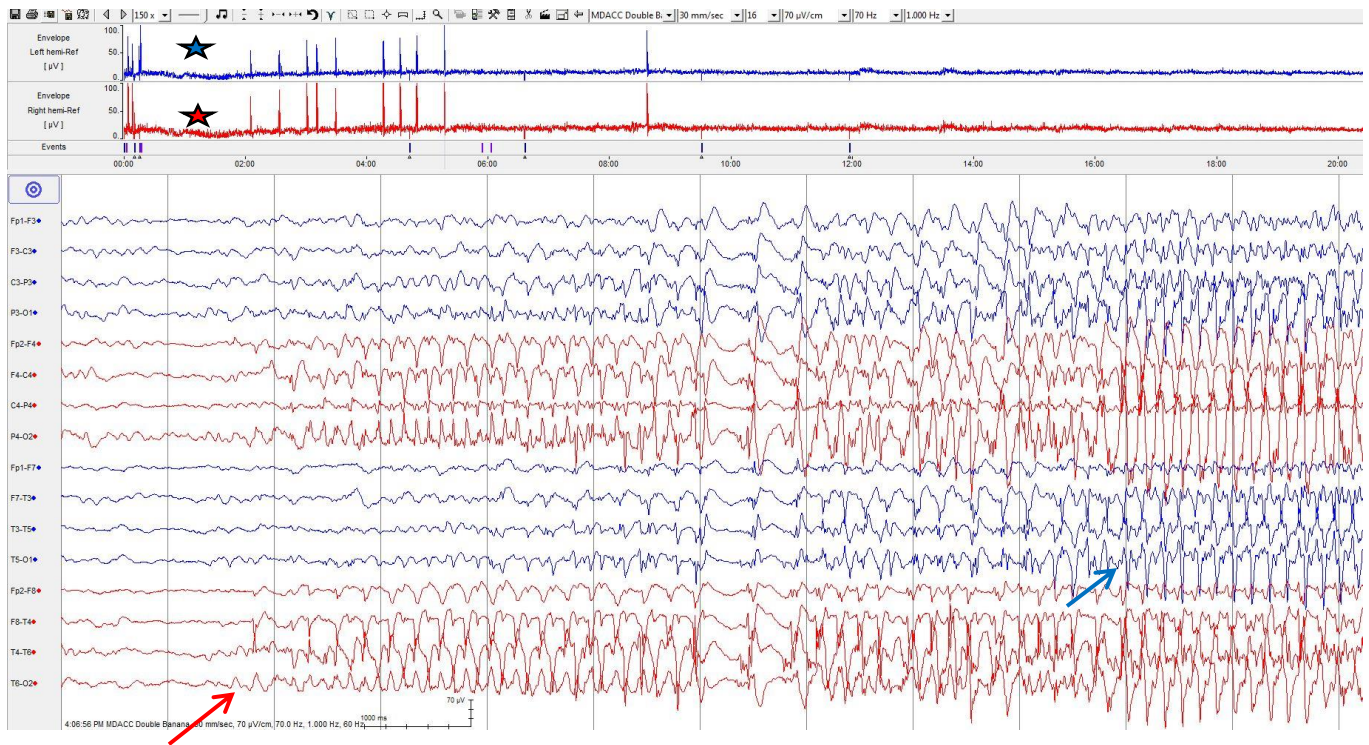
Supplementary Figure 4. Cells in CSF of Patient 2 vs its corresponding cohort (ratio of patient value/median of ZUMA-1 cohort 4)



Supplementary Figure 5. EEG on patient 1 on day 5. Red arrow indicates seizure onset in right posterior region. Dotted arrows indicate ongoing background seizures in both hemispheres. EEG: Bipolar longitudinal double banana montage. Left central, right central, left temporal, right temporal. 7uv/mm,30 mm/sec



Supplementary Figure 6. EEG on patient 1 on day 7. Vertical bars (stars) represent multiple electrographic seizures involving both hemispheres. Red and blue arrows indicate seizure onset and progression in right and left hemispheres, respectively.



Supplementary Table 1. Cerebral spinal fluid at baseline (before CAR-T cells infusion), at neurotoxicity onset (day 6 post infusion), and after resolution of neurotoxicity (day 28) in patient 2.

CSF	CSF at baseline (prior to CAR infusion)	CSF at neurotoxicity onset (D6)	CSF after resolution of neurotoxicity (D28)
Macroscopic aspect	Clear fluid	Yellow fluid, xanthochromia	Clear fluid
Red blood cells (/mm³)	150	10	0
Protein (g/L)	0.28	12.50	0.47
Glucose (mmol/L)	3.96	3.59	2.81
Nucleated cells (/mm³)	1	17	2
Polynuclear Neutrophil (absolute count)	25	29	6
Lymphocytes (absolute count)	2	57	29
Other cells (absolute count)	3 monohistiocytes	5 activated lymphocytes 57 monohistiocytes	15 monohistiocytes
Immunophenotype of white blood cells	Not done	30% T-cells /MNC 66% of CD4 T-cells/T cells 17% of CD8 T-cells/T cells 3% NK-cells/MNC 0% B-cells/MNC	48% T-cells/MNC 35% of CD4 T-cells/T cells 11% of CD8 T-cells/T cells 2% NK-cells/MNC 0% B-cells/MNC

MNC = mononuclear cells

Supplementary Table 2. Kinetics of CAR-T cells in patients 1 (A) and 2 (B) versus their respective ZUMA-1 cohort. Q1 and Q3 refer to quartile 1 and quartile 3, respectively.

A. Patient 1 vs Cohort 1 & 2

Parameter	Cohort 1 & 2 excluding patient 1 CAR T Cells in Blood (cells/uL)				Patient 1 CAR T cells in blood (cells/uL)
	Q1	Median	Q3	95 Percentile	
Baseline	0	0	0	0	0
Day 7	11	26.35	62.48	156.12	190.43
Week 2	3.41	13.56	40.58	162.94	2.37
Week 4	0.79	2.09	6.06	76.43	0.2
Month 3	0.05	0.41	1.04	4.69	0.07
Month 6	0.01	0.17	0.97	2.63	0.03
Month 9	0	0.06	0.62	2.45	0
Month 12	0	0.11	0.56	1.87	
Month 15	0.01	0.26	0.64	1.39	0.01
Month 18	0.34	0.93	1.51	1.51	
CAR T Peak	14.68	35.27	81.28	286.04	190.43
CAR T AUC (Day 0-28)	148.73	451.57	917.48	2899.91	1359.29
Time to Peak (days)	8	8	15	28	8

B. Patient 2 vs Cohort 4

Parameter	Cohort 4 excluding patient 2 CAR T Cells in Blood (cells/uL)				Patient 2 CAR T cells in blood (cells/uL)
	Q1	Median	Q3	95 Percentile	
Baseline	0	0	0	0	0
Day 3	0	0.01	0.02	0.92	6.13
Day 7	11.73	38.13	64.39	422.74	165.18
Day 10	27.25	60.51	78.4	320.45	19.18
Week 2	6.34	20.95	33.76	75.86	46.08
Week 3	2.81	8.08	29.35	57.74	10.69
Week 4	0.46	2.36	7.6	19.31	1.51
Month 3	0.04	0.27	0.99	13.55	0.59
Month 6	0	0.09	0.53	0.77	
Month 9	0	0.19	0.59	0.89	
CAR T Peak	29.91	52.91	89.58	422.74	165.18
CAR T AUC(Day 0-28)	182.97	487.95	904.45	3006.56	1000.33
Time to Peak (days)	8	10	13	86	8

Supplementary Table 3. Peaks of cytokines in the serum in Patient 1 (A) and 2 (B) versus their respective ZUMA-1 cohort. Q1 and Q3 refer to quartile 1 and quartile 3, respectively.

A. Patient 1 vs Cohort 1 & 2

Parameter	ZUMA-1 Cohort 1 & 2 excluding Patient 1 Peak of Cytokine in Serum				Patient 1 Peak of Cytokine in Serum
	Q1	Median	Q3	95 Percentile	
CRP (mg/L)	135	214	355.2	496 ^a	215.7
CXCL10 (pg/mL)	1503.7	2000 ^a	2000 ^a	2000 ^a	2000 ^a
Eotaxin-1 (pg/mL)	101.9	141	184.3	354.3	260.5
Eotaxin-3 (pg/mL)	10.2 ^a	10.2 ^a	10.2 ^a	127	10.2 ^a
FGFBF (pg/mL)	11.9	22.7	35.7	71.2	6.4
FLT-1 (pg/mL)	149.5	305.2	922.6	3767.6	168.8
Ferritin (ng/mL)	1322.6	2920	6665.8	25000 ^a	17659.4
GM-CSF (pg/mL)	1.9 ^a	7.1	16	52.4	52
Granzyme A (pg/mL)	20 ^a	20 ^a	20 ^a	1213.9	20 ^a
Granzyme B (pg/mL)	10.4	22.7	55.6	370.5	238.2
ICAM-1 (pg/mL)	829019.4	1239689.1	1749366	3674890.2	2053229.1
IFN-gamma (pg/mL)	185.2	464.7	1095.5	1876 ^a	1876 ^a
IL-1 RA (pg/mL)	1550	2280	4000 ^a	4000 ^a	2949.1
IL-1 alpha (pg/mL)	2.9 ^a	2.9 ^a	2.9 ^a	2.9 ^a	2.9 ^a
IL-1 beta (pg/mL)	2.1 ^a	2.1 ^a	2.1 ^a	3.2	2.1 ^a
IL-10 (pg/mL)	14.7	40.1	98.6	466 ^a	78.3
IL-12 P40 (pg/mL)	188	266.8	393.1	650.9	86.3
IL-12 P70 (pg/mL)	1.2 ^a	1.2 ^a	1.2 ^a	22.6	1.2 ^a
IL-13 (pg/mL)	4.2 ^a	4.2 ^a	4.2 ^a	15.9	4.2 ^a
IL-15 (pg/mL)	34.4	51.6	71.5	184	149.6
IL-16 (pg/mL)	167.3	254.7	413.6	1011	543.6
IL-17 (pg/mL)	9.3 ^a	26.5	59.4	235	143.1
IL-2 (pg/mL)	10.1	20.8	37.5	81	72.6
IL-2 R alpha (pg/mL)	6809.6	11894.2	24459.7	66101.7	17165.9
IL-4 (pg/mL)	0.5 ^a	0.5 ^a	0.5 ^a	5.5	0.5 ^a
IL-5 (pg/mL)	21.1	53.4	169.2	577.1	427.5
IL-6 (pg/mL)	21.3	78.6	338.3	976 ^a	976 ^a

Parameter	ZUMA-1 Cohort 1 & 2 excluding Patient 1 Peak of Cytokine in Serum				Patient 1 Peak of Cytokine in Serum
	Q1	Median	Q3	95 Percentile	
IL-7 (pg/mL)	31	41.1	53	91.7	39.1
IL-8 (pg/mL)	45.2	93.1	327.7	750 ^a	431.5
MCP-1 (pg/mL)	889.8	1464.7	1500 ^a	1500 ^a	1500 ^a
MCP-4 (pg/mL)	190.7	275.7	376.1	906.7	624.1
MDC (pg/mL)	624.1	947.2	1880.1	10752.1	833.4
MIP-1 alpha (pg/mL)	13.8 ^a	13.8 ^a	61.4	149.9	58.8
MIP-1 beta (pg/mL)	193	267.1	369.1	1075.4	307.8
PLGF (pg/mL)	120.7	160.9	213.2	337.3	167.8
Perforin (pg/mL)	6424.3	10489.8	15968.6	28742.4	8345.1
SAA (pg/mL)	252766608.5	572468320.5	1299562823.7	1380000000 ^a	152934133.3
SFASL (pg/mL)	10 ^a	10 ^a	10 ^a	23.2	10 ^a
TARC (pg/mL)	705.7	1441.2	3855.9	4480 ^a	3283.8
TIE-2 (pg/mL)	3651.1	4567.9	5942.1	8548.8	7016.6
TNF alpha (pg/mL)	5.6	7.8	11.9	36.8	12.8
TNF beta (pg/mL)	1.2 ^a	1.2 ^a	2.7	18.1	12
VCAM-1 (pg/mL)	983599.7	1390967.1	1933236	2735788.2	1529394.6
VEGF (pg/mL)	291.6	491	859.3	2005.6	383.5
VEGFC (pg/mL)	146 ^a	146 ^a	146 ^a	364.8	146 ^a
VEGFD (pg/mL)	1302.2	1596.2	2061.4	3046.4	1404.9

a Reported values represent an assigned numerical value given to results that fell outside the dilution-corrected limit of quantification.

B. Patient 2 vs Cohort 4

Parameter	ZUMA-1 Cohort 4 excluding Patient 2 Peak of Cytokine in Serum				Patient 2 Peak of Cytokine in Serum
	Q1	Median	Q3	95 Percentile	
CRP (mg/L)	63	126.6	277.9	496 ^a	32.6
CXCL10 (pg/mL)	1034.7	1560.7	2000 ^a	2000 ^a	2000 ^a
Eotaxin-1 (pg/mL)	145.6	206.8	317.7	483.3	127.8
Eotaxin-3 (pg/mL)	10.2 ^a	10.2 ^a	10.2 ^a	54.1	10.2 ^a
Ferritin (ng/mL)	471.7	1079.2	2746.3	13870.5	1586.6
GM-CSF (pg/mL)	1.9 ^a	4.2	6.9	37.2	6.9
Granzyme A (pg/mL)	20 ^a	20 ^a	396.5	1621.1	520.3
Granzyme B (pg/mL)	6.2	20.9	37	80.8	322.6
ICAM-1 (pg/mL)	631048.6	1000688.9	1809021.9	3032339.6	753862.7
IFN-gamma (pg/mL)	125.9	324.8	705.7	1876 ^a	1841.4
IL-1 RA (pg/mL)	637.7	1037.9	2435.2	3456.9	3613.2
IL-1 alpha (pg/mL)	2.9 ^a	2.9 ^a	2.9 ^a	2.9 ^a	2.9 ^a
IL-1 beta (pg/mL)	2.1 ^a	2.1 ^a	2.1 ^a	2.1 ^a	2.1 ^a
IL-10 (pg/mL)	8.4	19.5	48.8	460.8	86.9
IL-12 P40 (pg/mL)	122.5	161.5	283.1	502.5	116.4
IL-12 P70 (pg/mL)	1.2 ^a	1.2 ^a	1.2 ^a	3.0	1.2 ^a
IL-13 (pg/mL)	4.2 ^a	4.2 ^a	4.2 ^a	4.2 ^a	4.2 ^a
IL-15 (pg/mL)	31.1	45.6	59.9	123.7	59.5
IL-16 (pg/mL)	149.4	217.6	332.5	2443.9	139.9
IL-17 (pg/mL)	9.3 ^a	9.3 ^a	53.1	120	30
IL-2 (pg/mL)	5.0	10.6	20.5	56.9	41.5
IL-2 R alpha (pg/mL)	6217.7	11654	19217.8	43353.2	8416.4
IL-4 (pg/mL)	0.5 ^a	0.5 ^a	0.5 ^a	3.5	0.5 ^a
IL-5 (pg/mL)	6.3 ^a	35.5	57.1	475.7	6.3 ^a
IL-6 (pg/mL)	13.9	128.9	340.5	976 ^a	421.8
IL-7 (pg/mL)	26.7	33	42.7	62.7	37.6
IL-8 (pg/mL)	28.9	65.7	158.9	750 ^a	218.6
MCP-1 (pg/mL)	728.4	1270.2	1500 ^a	1500 ^a	990.1
MCP-4 (pg/mL)	82.5	131.3	183.5	480.3	107.4

Parameter	ZUMA-1 Cohort 4 excluding Patient 2 Peak of Cytokine in Serum				Patient 2 Peak of Cytokine in Serum
	Q1	Median	Q3	95 Percentile	
MDC (pg/mL)	606.4	902.8	1721.8	13282	482.9
MIP-1 alpha (pg/mL)	13.8 ^a	13.8 ^a	34.9	106.2	13.8 ^a
MIP-1 beta (pg/mL)	173.7	234.9	284.6	449.5	265.9
PDL1 (pg/mL)	102.4	155	291.9	959.1	503
Perforin (pg/mL)	12600.8	16965.7	26200.2	36774.1	34825.3
SAA (pg/mL)	164789962.9	422623900	902594386.3	1380000000 ^a	312092780.2
SFASL (pg/mL)	10 ^a	10 ^a	10 ^a	232.1	10 ^a
TARC (pg/mL)	365.7	923.9	3667.3	4480 ^a	860.3
TNF alpha (pg/mL)	4.0	5.6	8.5	19.9	7.9
TNF beta (pg/mL)	1.2 ^a	1.2 ^a	1.2 ^a	4.9	2.4
VCAM-1 (pg/mL)	1023608.7	1274805.3	1803411.5	3520230.6	1043877.1

a Reported values represent an assigned numerical value given to results that fell outside the dilution-corrected limit of quantification.

Supplementary Table 4. CSF cytokines at day 5 in Patient 2 versus ZUMA-1 Cohort 4. Q1 and Q3 refer to quartile 1 and quartile 3, respectively.

Parameter	ZUMA-1 Cohort 4 excluding Patient 2 Maximum level CSF Cytokine at day 5 visit window				Patient 2 Observed value at day 5
	Q1	Median	Q3	95 Percentile	
CRP (mg/L)	0.1	0.2	0.5	1.1	2.0
CXCL10 (pg/mL)	1353.3	2000 ^a	2000 ^a	2000 ^a	2000 ^a
Eotaxin-1 (pg/mL)	12.3 ^a	12.3 ^a	61.5	88.3	41.9
Eotaxin-3 (pg/mL)	10.2 ^a	10.2 ^a	10.2 ^a	10.2 ^a	76.1
Ferritin (ng/mL)	7.3	10.7	16.9	60.1	283.8
GM-CSF (pg/mL)	1.9 ^a	1.9 ^a	1.9 ^a	1.9 ^a	1.9 ^a
Granzyme A (pg/mL)	10 ^a	10 ^a	10 ^a	491.2	10 ^a
Granzyme B (pg/mL)	0.5 ^a	4.4	23.6	84.4	337.1
ICAM-1 (pg/mL)	4676.6	6405.4	9975.2	27703.4	112229
IFN-gamma (pg/mL)	7.5 ^a	23.4	71.5	401.9	667.4
IL-1 RA (pg/mL)	39.8	109	479	1321	1685
IL-1 alpha (pg/mL)	2.9 ^a	2.9 ^a	2.9 ^a	2.9 ^a	2.9 ^a
IL-1 beta (pg/mL)	2.1 ^a	2.1 ^a	2.1 ^a	2.1 ^a	2.1 ^a
IL-10 (pg/mL)	1.1	3.1	8.7	43.2	31
IL-12 P40 (pg/mL)	5.7 ^a	5.7 ^a	5.7 ^a	15.8	5.7 ^a
IL-12 P70 (pg/mL)	1.2 ^a	1.2 ^a	1.2 ^a	1.2 ^a	1.2 ^a
IL-13 (pg/mL)	4.2 ^a	4.2 ^a	4.2 ^a	4.2 ^a	4.2 ^a
IL-15 (pg/mL)	4.8	8.5	11.9	16.3	10.1
IL-16 (pg/mL)	19.1 ^a	19.1 ^a	19.1 ^a	19.1 ^a	19.1 ^a
IL-17 (pg/mL)	9.3 ^a	9.3 ^a	9.3 ^a	23.7	9.3 ^a
IL-2 (pg/mL)	0.9 ^a	0.9 ^a	0.9 ^a	0.9 ^a	2.7
IL-2 R alpha (pg/mL)	61.8	170	424	1251	1782
IL-4 (pg/mL)	0.5 ^a	0.5 ^a	0.5 ^a	1.0	0.5 ^a
IL-5 (pg/mL)	6.3 ^a	6.3 ^a	6.3 ^a	21.5	6.3 ^a
IL-6 (pg/mL)	7.1	21.3	87.2	584.3	421.4
IL-7 (pg/mL)	1.4 ^a	1.4 ^a	3.3	4.9	2.1
IL-8 (pg/mL)	36	54.1	98.2	750 ^a	750 ^a

Parameter	ZUMA-1 Cohort 4 excluding Patient 2 Maximum level CSF Cytokine at day 5 visit window				Patient 2 Observed value at day 5
	Q1	Median	Q3	95 Percentile	
MCP-1 (pg/mL)	276.9	442.1	938.5	1500 ^a	1321.7
MCP-4 (pg/mL)	5.1 ^a	5.1 ^a	25	41.4	23
MDC (pg/mL)	88.3 ^a	88.3 ^a	88.3 ^a	88.3 ^a	88.3 ^a
MIP-1 alpha (pg/mL)	13.8 ^a	13.8 ^a	13.8 ^a	68.2	62
MIP-1 beta (pg/mL)	9.8	16.3	26.2	43.2	33.8
PDL1 (pg/mL)	31.5	43.4	65.3	167	169
Perforin (pg/mL)	5.0 ^a	5.0 ^a	5.0 ^a	314.9	5026.5
SAA (pg/mL)	54	36113.7	145489.9	563590.1	13800000 ^a
SFASL (pg/mL)	5.0 ^a	5.0 ^a	5.0 ^a	5.0 ^a	5.0 ^a
TARC (pg/mL)	8.9	20.3	35.1	64.8	64.7
TNF alpha (pg/mL)	0.7 ^a	0.7 ^a	0.7 ^a	2.3	4.2
TNF beta (pg/mL)	1.2 ^a	1.2 ^a	1.2 ^a	1.2 ^a	1.2 ^a
VCAM-1 (pg/mL)	6433	9450.7	15918.8	28989.5	81673.4

- a Reported values represent an assigned numerical value given to results that fell outside the dilution-corrected limit of quantification.
- b Day 5 visit window is from day 0 to day 14.

Supplementary Table 5. Flow cytometry in CSF at day 5 in Patient 2 versus ZUMA-1 Cohort 4. Q1 and Q3 refer to quartile 1 and quartile 3, respectively.

Parameter	Zuma 1 Cohort 4 excluding Patient 2				Patient 2 Observed value at day 5
	Q1	Median	Q3	95 Percentile	
# of CD14 gated / CD45 gated on viable singlets cells * 100	33.2	48.8	60.5	80.5	64.3
# of CD19 gated / CD45 gated on viable singlets cells * 100	0	0	0.2	4.2	0
# of CD3 CAR+ gated / CD45 gated on viable singlets cells * 100	0.8	8.3	16.2	31.5	16.2
# of CD3 gated / CD45 gated on viable singlets cells * 100	12.2	23	41.4	76.6	17.1
# of CD4 CAR+ / CD45 gated on viable singlets cells * 100	0.3	3.5	13.2	30.1	15.4
# of CD4 gated / CD45 gated on viable singlets cells * 100	4.9	13.6	29.1	53.5	15.7
# of CD56+CD3+ gated on CD45+ / CD45 gated on viable singlets cells * 100	0	0.4	1.3	11	0.1
# of CD56+CD3- gated / CD45 gated on viable singlets cells * 100	0.7	3.9	8.3	22.1	0.1
# of CD66b gated on CD45+ / CD45 gated on viable singlets cells * 100	1.6	5.1	13	33.3	10.3
# of CD8 CAR+ gated / CD45 gated on viable singlets cells * 100	0	0.2	1.8	12	0.7
# of CD8 gated / CD45 gated on viable singlets cells * 100	2.2	5.3	9.7	35.7	1.1
CD14 gated on CD45+	17	164	804	1843	456
CD14 gated on CSFVOLUM+ Normalized	12.4	29.2	104.7	245.7	304
CD19 gated on CD45+/66b/14-	0	0	1	5	0
CD19 gated on CSFVOLUM+/66b/14- Normalized	0	0	0.2	2	0
CD3 CAR+ gated on CD 45+/66b/14-/3+	2	22	101	2694	115
CD3 CAR+ gated on CSFVOLUM+/66b/14-/3+ Normalized	0.4	3.4	15.1	83.6	76.7
CD3 gated on CD45+/66b/14-	9	73	314	5644	121
CD3 gated on CSFVOLUM+/66b/14- Normalized	5.5	13.6	37.8	219.3	80.7
CD4 CAR+ gated on CD45+/66b/14-/3+/4+	1	14	77	1386	109
CD4 CAR+ gated on CSFVOLUM+/66b/14-/3+/4+ Normalized	0	1.6	11.7	76.3	72.7
CD4 gated of CD45+/66b/14-/3+	3	46	288	4620	111
CD4 gated of CSFVOLUM+/66b/14-/3+ Normalized	1.8	9.3	25.1	166	74
CD45 gated on CSFVOLUM+ viable singlets cells Normalized	45.8	102	234	545.6	472.7
CD45 gated on viable singlets cells	54	326	1572	8597	709
CD56+CD3+ gated on CSFVOLUM+/66b/14- Normalized	0	0.2	1.4	21.6	0.7
CD56+CD3+ gated on CD45+/66b/14-	0	1	8	91	1
CD56+CD3- gated on CD45+/66b/14-	2	4	47	663	1
CD56+CD3- gated on CSFVOLUM+/66b/14- Normalized	0.3	2.4	9	72.8	0.7
CD66b gated on CD45+	6	9	15	53	73
CD66b gated on CSFVOLUM+ Normalized	1.4	3.8	7.8	20	48.7
CD8 CAR+ gated on CD45+/66b/14-/3+/8+	0	2	7	272	5
CD8 CAR+ gated on CSFVOLUM+/66b/14-/3+/8+ Normalized	0	0.1	1.8	27.2	3.3
CD8 gated on CD45+/66b/14-/3+	2	12	83	809	8

	Zuma 1 Cohort 4 excluding Patient 2				Patient 2 Observed value at day 5
Parameter	Q1	Median	Q3	95 Percentile	
CD8 gated on CSFVOLUM+/66b/14-/3+ Normalized	0.7	3.1	12.3	80.9	5.3
CSF Volume	1.6	3	7.3	11	1.5
Ratio of CD4CARP and CD8CARP DERIVED	1.2	4.2	12.2	98.8	21.8
Ratio of CD4CD45 and CD8CD45	1.1	2.3	6.7	22	13.9
Viability-Total cells gated on singlets	3146	9090	17132	318058	3347
Viability-Viable cells gated on singlets	813	2337	3805	315929	1155