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Acute leucoencephalomyelopathy and quadriparesis after CAR T-cell therapy

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Chimeric antigen receptor (CAR) T-cell therapy maybe associated with neurologic toxicity, also referred to as immune effector cell-associated neurotoxicity syndrome (ICANS)\(^1,^2\), that typically manifests as encephalopathy. Here, we report two patients, with no known prior neurological disease, treated on ZUMA-1 trial, who developed acute leucoencephalomyelopathy with quadriparesis after treatment with axicabtagene ciloleucel (axi-cel).\(^3^,^4\)

Patient 1 is a 41-year-old female with refractory diffuse large B-cell lymphoma after 4 lines of systemic therapy including high-dose chemotherapy plus autologous stem cell transplantation. She had bulky nodal and splenic disease (Supplementary Figure 1A) prior to treatment with axi-cel.\(^3^,^4\) Her baseline C-reactive protein (CRP) and ferritin were elevated at 136 mg/L and 9,821 ng/mL, respectively (Figures 1A-B). She experienced intermittent grade 1 cytokine release syndrome (CRS) with fever and tachycardia from days 1-6.\(^5\) On day 2, she developed grade 3 ICANS with confusion concurrently with fever, which resolved promptly with tocilizumab and dexamethasone administration along with a dose increase of levetiracetam that was started on day 0 for seizure prophylaxis. On day 4, grade 3 ICANS recurred with aphasia which was non-responsive to a second dose of tocilizumab. On day 5, she developed grade 4 ICANS with clonic seizures evolving to status epilepticus requiring ventilator support, additional anti-epileptic medications, and high-dose methylprednisolone. On days 6 and 7, she had 2 generalized tonic-convulsive seizures with further electrographic seizures (Supplementary Figures 5 and 6). The seizures were eventually controlled with lorazepam, phenytoin, levetiracetam, and phenobarbital. On day 8, as patient mental status improved, she was noted to be weak in the lower extremities with rapid progression to quadriparesis, mute plantar reflexes, and lack of bladder control. Cerebrospinal fluid (CSF) analysis showed increased protein level but no evidence of infection. Magnetic resonance imaging (MRI) of the brain and spine on day 9 showed findings concerning for acute leucoencephalomyelopathy with symmetrical T2 hyperintensity within the centrum semiovale with sparing of the U fibers, the superior cerebellar peduncle and striking diffuse cerebral edema (Figure 2A). Not shown was also involvement of the diffuse periventricular white matter, external capsule, and posterior limb of the internal capsule. MRI of the spine demonstrated centromedullary holocord involvement (Figure 2A). By day 11, upper extremity strength started to improve and she self-extubated. Her cognitive function quickly improved but she experienced retrograde amnesia spanning a time period of about 2 weeks prior to this event. By day 16, the strength in her lower limbs improved to 3/5 and upper limbs to 5/5. Corticosteroids were tapered over 3 weeks. MRI findings of brain and of spine completely normalized by day 27 and 6 months, respectively (Figure 2A). Restaging on day 28 showed complete response (Supplementary Figure 1A), which was ongoing 3 years later. Patient’s lower limb weakness improved with intense rehabilitation and she was able to regain bladder control. She was able to ambulate with a walker by 6 months and eventually using a single-point cane.
Patient 2 is a 30-year-old female who had refractory primary mediastinal B-cell lymphoma after 2 lines of chemoimmunotherapy. She received mediastinal radiotherapy (20Gy) before leukapheresis and bridging therapy consisting of one cycle of rituximab plus bendamustine with 4 days of dexamethasone prior to axi-cel infusion. Baseline cerebral MRI, CSF, CRP, and ferritin were normal (Figures 1D-E, Figure 2B, and Supplementary Table 1). On day 2, the patient developed grade 2 CRS consisting of fever, tachycardia, and hypotension. She improved with intravenous fluids, tocilizumab, and dexamethasone. On day 5, the patient developed grade 3 ICANS with confusion and aphasia while grade 1 CRS was ongoing. The patient developed quadripareisis with complete loss of strength in both legs, near complete paralysis in the upper limbs, urinary incontinence, bilateral extensor plantar responses, brisk deep tendon reflexes in lower limbs, and ankle clonus. Brain and spinal MRI revealed diffuse leptomeningeal enhancement (Figure 2B). CSF revealed increased protein and presence of T-cells (Supplementary Table 1). The patient was treated with high-dose methylprednisolone for 4 days, which was tapered over 2 weeks. Concomitantly, the patient received 4 doses of tocilizumab every 6 hours. Encephalopathy improved quickly within a few hours following methylprednisolone administration. Quadripareisis lasted significantly longer. Motor deficits started to improve in the upper limbs after 2 days and recovered in the lower limbs over several weeks. Patient was able to ambulate with a walker by day 21 and without assistance by day 28. Urinary incontinence resolved but she continued to have decreased bladder sensation and a distal loss of temperature sensation up to T10 dermatome. By day 28, CSF protein was near normal (Supplementary Table 1) and MRI findings were normal (Figure 2B). Restaging showed a partial response at 1 month and a complete response thereafter, which is ongoing at 18 months (Supplementary Figure 1B).

Analysis of the blood (Patient 1 and 2) and CSF (Patient 2) samples showed that many parameters were extremely elevated compared to the rest of the ZUMA-1 cohort. In both patients, CAR-T expansion, as measured by peak and area under the curve, appeared significantly higher than the rest of their respective cohort (Figures 1C&F, and Supplementary Table 2). In the serum, many cytokines were significantly elevated compared to the median of the corresponding cohort, although not consistently to the same extent between the two patients (Supplementary Figure 2 and Supplementary Table 3). In the CSF of patient 2 at day 5, several cytokines and chemokines were elevated (Supplementary Figure 3 and Supplementary Table 4). We also found significant increase of CAR-T and myeloid (CD66b+ and CD14+) cells in the CSF (Supplementary Figure 4 and Supplementary Table 5).

The two patients described here had an atypical neurotoxicity of severe leucoencephalomyelopathy associated with quadripareisis after CAR T-cell therapy. Clinically there appears direct anterior horn cell dysfunction in patient 1 with flaccid paralysis compared to patient 2 with upper motor neuron signs. Nei-
ther patient had history of neurological illnesses or lymphoma in the central nervous system. It is possible that the high-tumor burden and high baseline inflammatory markers may have increased the risk of severe toxicity in patient 1 but patient 2 did not have these high-risk features. The mediastinal radiation field of patient 2 did not explain the clinical nor the radiological presentation. In both patients, we found a massive expansion of CAR T-cells in peripheral blood during the first week. There was increased protein level, CAR-T and myeloid cells detected in CSF of patient 2 compared to the rest of the cohort.\cite{9} Molecules implicated in cytotoxicity (perforin, granzyme B), inflammation (SAA, ferritin, CRP), and trafficking (ICAM-1, VCAM-1, eotaxin-3) also appeared to be extremely elevated. These observations suggest mechanisms that contributed to heightened neurotoxicity in our patients including trafficking of CAR T-cells into the central nervous system, passive diffusion of cytokines, endothelial cell activation/dysfunction leading to blood-brain barrier disruption, and activation of myeloid cells, all which have been previously implicated.\cite{6-10} Spine MRI showing reversible predominantly central spinal cord signal abnormalities in both patients seem to be unique and could represent the above described CSF abnormalities.

Prompt initiation of high-dose corticosteroids helped in reversing the acute leucoencephalomyelopathy and quadriplexes in both patients. Despite the use of high-dose corticosteroids, both patients attained a durable complete response, likely because they achieved peak CAR T-cell levels within the first week. This is consistent with the observation on ZUMA-1 trial that the overall response rate, complete response rate, and durability of those responses were comparable between patients who received corticosteroids vs. those who did not and with the concept that high CAR T-cell levels early after infusion is associated with durable response.\cite{3,4} Collectively, these reports suggest that corticosteroids are unlikely to affect CAR T-cell efficacy when used for management of severe toxicities, their prompt initiation should be strongly considered for grade 4 neurotoxicity.

Acknowledgments

We thank the patients who participated in this study and their families, friends, and caregivers, and the study staff and health care providers.

Author Contribution

RH and SSN designed research, analyzed data, and wrote the paper. NR, GD, FL, ALB, LM, JR, MS, AX, AK, NJ, LC, ST performed research, analyzed data, and wrote the paper.
Conflict-of-interest disclosure

LM received honoraria from Merck, Novartis, Roche, Biogen and Teva. JR, MS, AX, and AK are employees and stock holders of Gilead Sciences Inc. SSN reports research support from Kite/Gilead, Merck, Bristol-Myers Squibb, Cellectis, Poseida, Karus, Acerta, and Unum Therapeutics. He also serves as an advisory Board Member / Consultant for Kite/Gilead, Merck, Celgene, Bristol-Myers Squibb, Novartis, Unum Therapeutics, Pfizer, Precision Biosciences, Cell Medica, Allogene, Incyte, and Legend Biotech. RH received honoraria from Bristol-Myers Squibb, MSD, Gilead, Kite, Roche, Novartis, Janssen, and Celgene. NR, GD, FL, ALB, NJ, LC and ST report no conflict of interest.

References


Figure Legends

Figure 1. Clinical and biological parameters, and therapeutic intervention over time in patient 1 (A, B, C) and 2 (D, E, F). Conditioning chemotherapy with fludarabine and cyclophosphamide was given on days -5 to -3, with infusion of axicabtagene ciloleucel CAR T cells on day zero. Tocilizumab was administered intravenously at 8 mg/kg, dexamethasone intravenously at 10 mg every 6 hours, and methylprednisolone intravenously at 1000 mg/day with gradual taper. The CAR T cell levels in the peripheral blood in patients 1 (C) and 2 (F) were compared to the median CAR T cell levels in patients treated on the corresponding cohort of ZUMA-1 study (cohorts 1 and 2 for patient 1 and cohort 4 for patient 2). HR: Heart rate; Tmax: Temperature maximum, CRP: C-reactive protein.

Figure 2. Leucoencephalomyelopathy changes on magnetic resonance imaging in patient 1 (A) and 2 (B).

A. Patient 1. T2-weighted fluid attenuation inversion recovery axial images of the brain (top 2 rows) demonstrate evolution and resolution of symmetrical T2 hyperintensity within the superior cerebellar peduncle, the centrum semiovale white matter with respect of U fibers, from Day 9 to 6 months. T2 fast spin echo (FSE) with fat saturation sagittal imaging of the cervico-thoracic spine (row 3) and representative T2 FSE axial sections of the cervical cord (row 4) illustrate resolution of extensive centromedullary T2 changes over time. By 6 months, MRI changes normalized.

B. Patient 2. Brain and cervical spine MRI performed at neurotoxicity onset on day 5 demonstrating diffuse infratentorial and supratentorial leptomeningeal uptake predominant around the brain stem, cervical spinal cord, and cerebellar and occipital sulci (3D FLAIR with gadolinium). Diffuse leptomeningeal enhancement (3D T1 Black Blood with gadolinium) and T2 hyperintensity extending from C2 to C4 was also noted with a slender swelling of the spinal cord. At day 28 reevaluation, MRI showed almost complete resolution of leptomeningeal uptake with persistence of discreet gadolinium enhancement in the posterior parieto-occipital sulcus (3D T1 VISTA with gadolinium) and complete disappearance of the intramedullary T2 hyperintensity.
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

B. Patient 2
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)

<table>
<thead>
<tr>
<th>Ratio of CD4CD45 and CD8CD45</th>
<th>Ratio of CD4CARP and CD8CARP DERIVED</th>
<th>CD8 gated on CSFVOLUM+66b/14/-3+ Normalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8 gated on CD45+/66b/14/-3+ Normalized</td>
<td>CD8 gated on CD45+/66b/14/-3+ Normalized</td>
<td>CD8 CAR+ gated on CSFVOLUM+/66b/14/3+/8+ Normalized</td>
</tr>
<tr>
<td>CD6b gated on CD45+</td>
<td>CD6b gated on CD45+</td>
<td>CD6b gated on CSFVOLUM+ Normalized</td>
</tr>
<tr>
<td>CD6b gated on CD45+</td>
<td>CD6b gated on CD45+</td>
<td>CD6b gated on CD45+</td>
</tr>
<tr>
<td>CD56+CD3- gated on CSFVOLUM+/66b/14- Normalized</td>
<td>CD56+CD3- gated on CD45+/66b/14-</td>
<td>CD56+CD3- gated on CD45+/66b/14-</td>
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<td>CD56+CD3- gated on CD45+/66b/14-</td>
<td>CD56+CD3+ gated on CSFVOLUM+/66b/14- Normalized</td>
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<td>CD45 gated on viable singlets cells</td>
<td>CD45 gated on viable singlets cells</td>
<td>CD45 gated on viable singlets cells</td>
</tr>
<tr>
<td>CD4 gated of CSFVOLUM+/66b/14/-3+ Normalized</td>
<td>CD4 gated of CD45+/66b/14/-3+ Normalized</td>
<td>CD4 CAR+ gated on CSFVOLUM+/66b/14/-3/+4 Normalized</td>
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<tr>
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<td>CD4 CAR+ gated on CSFVOLUM+/66b/14/-3/+4+ Normalized</td>
</tr>
<tr>
<td>CD3 gated on CSFVOLUM+/66b/14- Normalized</td>
<td>CD3 gated on CSFVOLUM+/66b/14- Normalized</td>
<td>CD3 CAR+ gated on CD45+/66b/14/-3+</td>
</tr>
<tr>
<td>CD3 CAR+ gated on CD45+/66b/14/-3+</td>
<td>CD3 CAR+ gated on CD45+/66b/14/-3+</td>
<td>CD3 CAR+ gated on CD45+/66b/14/-3+</td>
</tr>
<tr>
<td>CD19 gated on CSFVOLUM+/66b/14- Normalized</td>
<td>CD19 gated on CSFVOLUM+/66b/14- Normalized</td>
<td>CD14 gated on CSFVOLUM+ Normalized</td>
</tr>
<tr>
<td>CD14 gated on CSFVOLUM+</td>
<td>CD14 gated on CD45+</td>
<td></td>
</tr>
</tbody>
</table>

Ratio of patient value / median of ZUMA-1 cohort 4

# of CD8 gated / CD45 gated on viable singlets cells * 100
# of CD8 CAR+ gated / CD45 gated on viable singlets cells * 100
# of CD66b gated on CD45+ / CD45 gated on viable singlets cells * 100
# of CD56+CD3- gated / CD45 gated on viable singlets cells * 100
# of CD56+CD3+ gated onCD45+/CD45 gated on viable singlets cells * 100
# of CD4 gated / CD45 gated on viable singlets cells * 100
# of CD4 CAR+ / CD45 gated on viable singlets cells * 100
# of CD3 gated / CD45 gated on viable singlets cells * 100
# of CD3 CAR+ gated / CD45 gated on viable singlets cells * 100
# of CD19 gated / CD45 gated on viable singlets cells * 100
# of CD14 gated / CD45 gated on viable singlets cells * 100
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. 7μV/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.

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort 1 &amp; 2 excluding patient 1</th>
<th>Patient 1</th>
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<tbody>
<tr>
<td>CAR T Cells in Blood (cells/uL)</td>
<td>Q1</td>
<td>Median</td>
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<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Day 7</td>
<td>11</td>
<td>26.35</td>
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<tr>
<td>Week 2</td>
<td>3.41</td>
<td>13.56</td>
</tr>
<tr>
<td>Week 4</td>
<td>0.79</td>
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<tr>
<td>Month 3</td>
<td>0.05</td>
<td>0.41</td>
</tr>
<tr>
<td>Month 6</td>
<td>0.01</td>
<td>0.17</td>
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<tr>
<td>Month 9</td>
<td>0</td>
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<tr>
<td>Month 12</td>
<td>0</td>
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<td>Month 15</td>
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<tr>
<td>Month 18</td>
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<tr>
<td>CAR T Peak</td>
<td>14.68</td>
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<tr>
<td>CAR T AUC (Day 0-28)</td>
<td>148.73</td>
<td>451.57</td>
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<td>Time to Peak (days)</td>
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### B. Patient 2 vs Cohort 4

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<td>Baseline</td>
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<tr>
<td>Day 3</td>
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<tr>
<td>Day 7</td>
<td>11.73</td>
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<td>Day 10</td>
<td>27.25</td>
<td>60.51</td>
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<tr>
<td>Week 2</td>
<td>6.34</td>
<td>20.95</td>
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<td>Week 3</td>
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<td>Week 4</td>
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<td>Month 3</td>
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<td>Month 6</td>
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<tr>
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<tr>
<td>Time to Peak (days)</td>
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<td>10</td>
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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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ZUMA-1 Cohort 1 &amp; 2 excluding Patient 1 Peak of Cytokine in Serum</th>
<th>Patient 1 Peak of Cytokine in Serum</th>
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<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Median</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>135</td>
<td>214</td>
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<tr>
<td>CXCL10 (pg/mL)</td>
<td>1503.7</td>
<td>2000\textsuperscript{a}</td>
</tr>
<tr>
<td>Eotaxin-1 (pg/mL)</td>
<td>101.9</td>
<td>141</td>
</tr>
<tr>
<td>Eotaxin-3 (pg/mL)</td>
<td>10.2\textsuperscript{a}</td>
<td>10.2\textsuperscript{a}</td>
</tr>
<tr>
<td>FGFBF (pg/mL)</td>
<td>11.9</td>
<td>22.7</td>
</tr>
<tr>
<td>FLT-1 (pg/mL)</td>
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<td>Ferritin (ng/mL)</td>
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<tr>
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<td>Granzyme A (pg/mL)</td>
<td>20\textsuperscript{a}</td>
<td>20\textsuperscript{a}</td>
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<tr>
<td>Granzyme B (pg/mL)</td>
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<td>22.7</td>
</tr>
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<td>ICAM-1 (pg/mL)</td>
<td>829019.4</td>
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<tr>
<td>IFN-gamma (pg/mL)</td>
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<td>464.7</td>
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<td>IL-1 RA (pg/mL)</td>
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<td>2.9\textsuperscript{a}</td>
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<td>2.1\textsuperscript{a}</td>
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<td>IL-10 (pg/mL)</td>
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<td>IL-12 P70 (pg/mL)</td>
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<td>1.2\textsuperscript{a}</td>
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<td>4.2\textsuperscript{a}</td>
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<td>IL-17 (pg/mL)</td>
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<td>26.5</td>
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<td>IL-2 (pg/mL)</td>
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<td>20.8</td>
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<td>0.5\textsuperscript{a}</td>
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<td>Parameter</td>
<td>ZUMA-1 Cohort 1 &amp; 2 excluding Patient 1</td>
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<td>Peak of Cytokine in Serum</td>
<td>Peak of Cytokine in Serum</td>
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<tr>
<td></td>
<td>Q1</td>
<td>Median</td>
</tr>
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<td>IL-7 (pg/mL)</td>
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<td>MDC (pg/mL)</td>
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<td>MIP-1 alpha (pg/mL)</td>
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<td>13.8&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>MIP-1 beta (pg/mL)</td>
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<td>Perforin (pg/mL)</td>
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<td>10489.8</td>
</tr>
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<td>SAA (pg/mL)</td>
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<td>572468320.5</td>
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<tr>
<td>SFASL (pg/mL)</td>
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<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>TARC (pg/mL)</td>
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<td>TIE-2 (pg/mL)</td>
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<td>TNF beta (pg/mL)</td>
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<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>VEGF (pg/mL)</td>
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<tr>
<td>VEGFC (pg/mL)</td>
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<td>VEGFD (pg/mL)</td>
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<sup>a</sup> 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

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<th>Parameter</th>
<th>ZUMA-1 Cohort 4 excluding Patient 2 Peak of Cytokine in Serum</th>
<th>Patient 2 Peak of Cytokine in Serum</th>
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<td>Median</td>
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<td>CRP (mg/L)</td>
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<td>206.8</td>
</tr>
<tr>
<td>Eotaxin-3 (pg/mL)</td>
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<td>10.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>Ferritin (ng/mL)</td>
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<td>1079.2</td>
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<td>GM-CSF (pg/mL)</td>
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<tr>
<td>Granzyme A (pg/mL)</td>
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<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>Granzyme B (pg/mL)</td>
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<td>ICAM-1 (pg/mL)</td>
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<td>1000688.9</td>
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<tr>
<td>IFN-gamma (pg/mL)</td>
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<td>IL-1 RA (pg/mL)</td>
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<td>2.9&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2.1&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>IL-10 (pg/mL)</td>
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<td>IL-12 P40 (pg/mL)</td>
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<td>161.5</td>
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<td>IL-12 P70 (pg/mL)</td>
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<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>4.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>IL-15 (pg/mL)</td>
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<td>45.6</td>
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<tr>
<td>IL-16 (pg/mL)</td>
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<td>217.6</td>
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<td>IL-17 (pg/mL)</td>
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<td>9.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>IL-4 (pg/mL)</td>
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<td>MCP-1 (pg/mL)</td>
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<td>Patient 2 Peak of Cytokine in Serum</td>
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<td>MDC (pg/mL)</td>
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<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup> 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ZUMA-1 Cohort 4 excluding Patient 2</th>
<th>Maximum level CSF Cytokine at day 5 visit window</th>
<th>Patient 2 Observed value at day 5</th>
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<td>Median</td>
<td>Q3</td>
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<td>12.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Eotaxin-3 (pg/mL)</td>
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<td>10.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>GM-CSF (pg/mL)</td>
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<td>1.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.9&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>479</td>
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<td>2.9&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>2.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.1&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>5.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.7&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>19.1&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>9.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>6.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Patient 2 Observed value at day 5</td>
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<tr>
<td>----------------------</td>
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<td>Maximum level CSF Cytokine at day 5 visit window</td>
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</tr>
<tr>
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<td>Q1</td>
<td>Median</td>
<td>Q3</td>
</tr>
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<td>MCP-1 (pg/mL)</td>
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<td>442.1</td>
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<td>MDC (pg/mL)</td>
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<td>88.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>13.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.8&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>26.2</td>
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<td>PDL1 (pg/mL)</td>
<td>31.5</td>
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<td>65.3</td>
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<td>SFASL (pg/mL)</td>
<td>5.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.0&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>TARC (pg/mL)</td>
<td>8.9</td>
<td>20.3</td>
<td>35.1</td>
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<tr>
<td>TNF alpha (pg/mL)</td>
<td>0.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.7&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>TNF beta (pg/mL)</td>
<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>VCAM-1 (pg/mL)</td>
<td>6433</td>
<td>9450.7</td>
<td>15918.8</td>
</tr>
</tbody>
</table>

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

<sup>b</sup> Day 5 visit window is from day 0 to day 14.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Zuma 1 Cohort 4 excluding Patient 2</th>
<th>Patient 2 Observed value at day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td># of CD14 gated / CD45 gated on viable singlets cells * 100</td>
<td>33.2</td>
<td>64.3</td>
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<tr>
<td># of CD19 gated / CD45 gated on viable singlets cells * 100</td>
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</tr>
<tr>
<td># of CD3 CAR+ gated / CD45 gated on viable singlets cells * 100</td>
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<td># of CD3 gated / CD45 gated on viable singlets cells * 100</td>
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<td># of CD45+CD3+ gated onCD45+/ CD45 gated on viable singlets cells * 100</td>
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<td># of CD56+CD3- gated/ CD45 gated on viable singlets cells * 100</td>
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<td># of CD66b gated on CD45+ / CD45 gated on viable singlets cells * 100</td>
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<td>10.3</td>
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<tr>
<td># of CD8 CAR+ gated/ CD45 gated on viable singlets cells * 100</td>
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<td>CD3 CAR+ gated on CSFVOLUM+/66b/14/-3+ Normalized</td>
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<td>CD56+CD3- gated on CSFVOLUM+/66b/14- Normalized</td>
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<td>CD66b gated on CD45+</td>
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<td>CD66b gated on CSFVOLUM+ Normalized</td>
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<td>Parameter</td>
<td>Zuma 1 Cohort 4 excluding Patient 2</td>
<td>Patient 2 Observed value at day 5</td>
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<tr>
<td>CD8 gated on CSFVOLUM+/66b/14-/3+ Normalized</td>
<td>Q1 0.7</td>
<td>Median 3.1</td>
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<tr>
<td>CSF Volume</td>
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<td>Ratio of CD4CARP and CD8CARP DERIVED</td>
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<td>4.2</td>
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<td>9090</td>
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<td>Viability-Viable cells gated on singlets</td>
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