Supplementary File

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Wang M, *et al. J Immunother Cancer* 2020; 8:e001114. doi: 10.1136/jitc-2020-001114

Supplementary Methods

Patient Treatment History

The patient's treatment history included a full course of rituximab plus bendamustine (partial remission) with maintenance rituximab (progression), followed by 2 cycles rituximab plus bendamustine (mixed response) with 3 doses maintenance rituximab, approximately 17 cycles of acalabrutinib (complete response followed by progression), and 1 cycle of ibrutinib (progression) which ended 3 weeks prior to leukapheresis.

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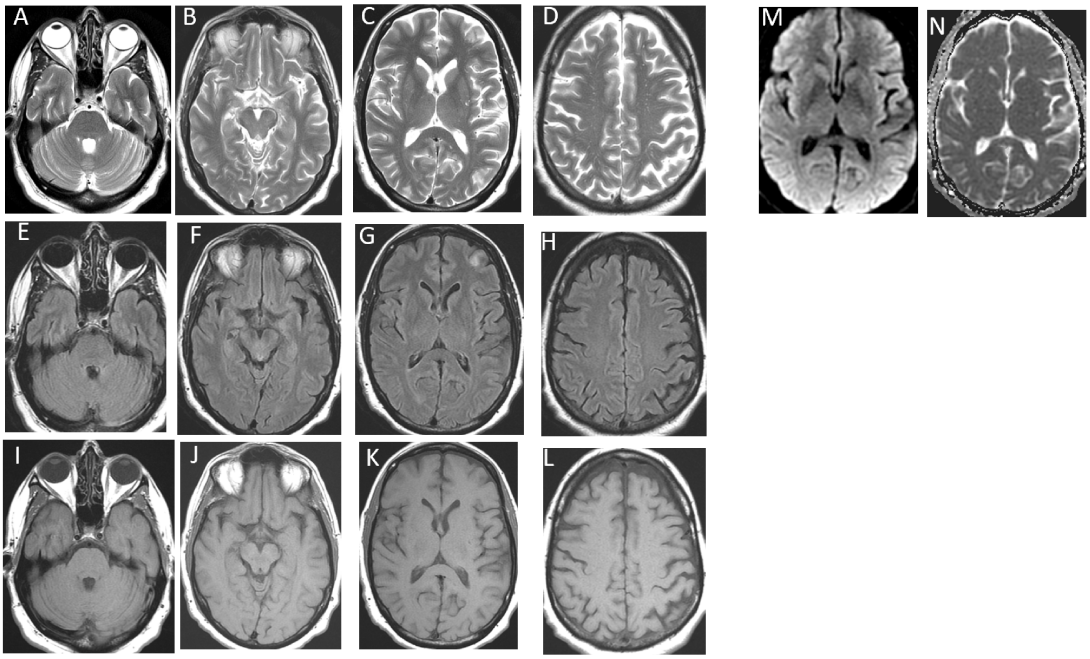
Figure S1. Pretreatment Baseline MRI of the Brain



Axial T2-weighted (Panels A-D), FLAIR (Panels E-H), and T1-weighted pre-contrast (Panels I-L) imaging of the brain 2 days prior to leukapheresis. DWI (Panel M) and ADC (Panel N) map demonstrates no restricted diffusion. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

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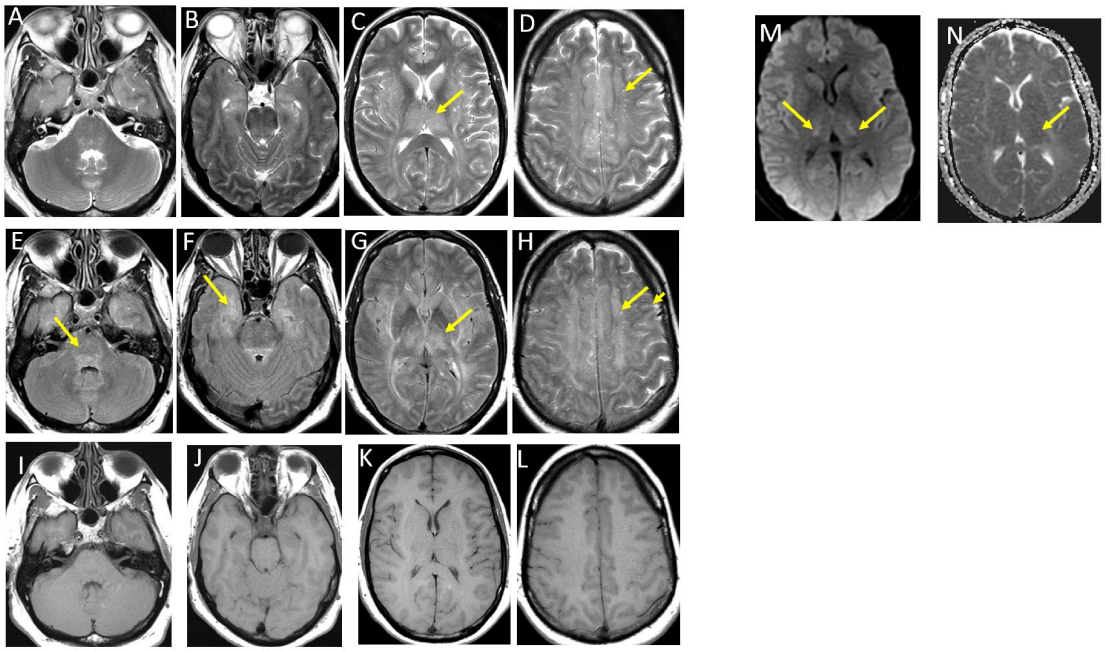
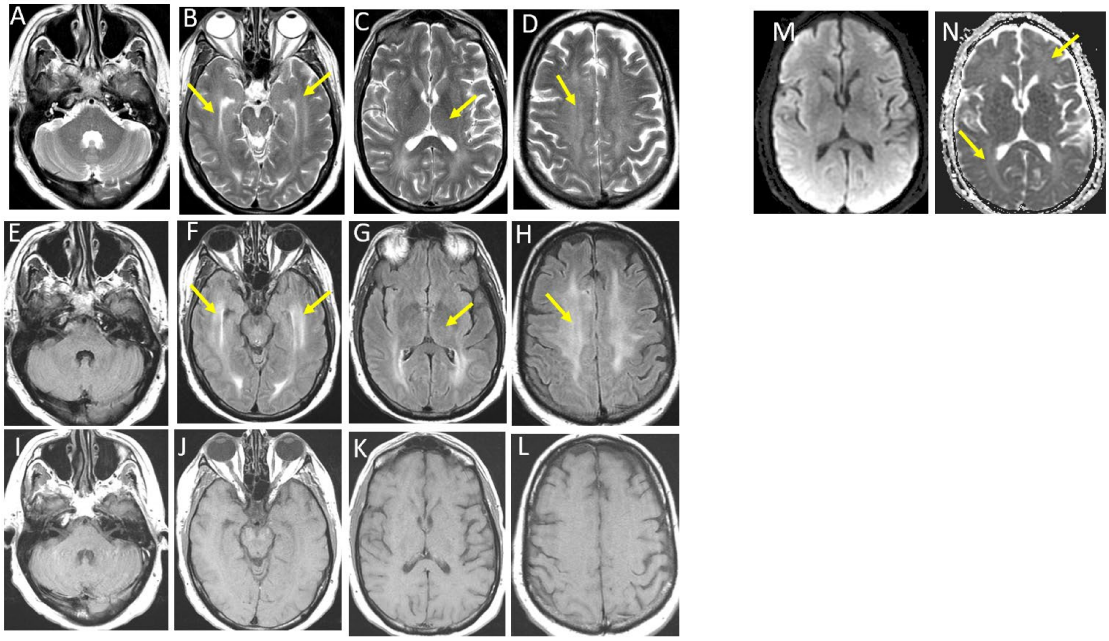
Figure S2. Day 6 After Infusion of KTE-X19 and Prior to ATG Infusion



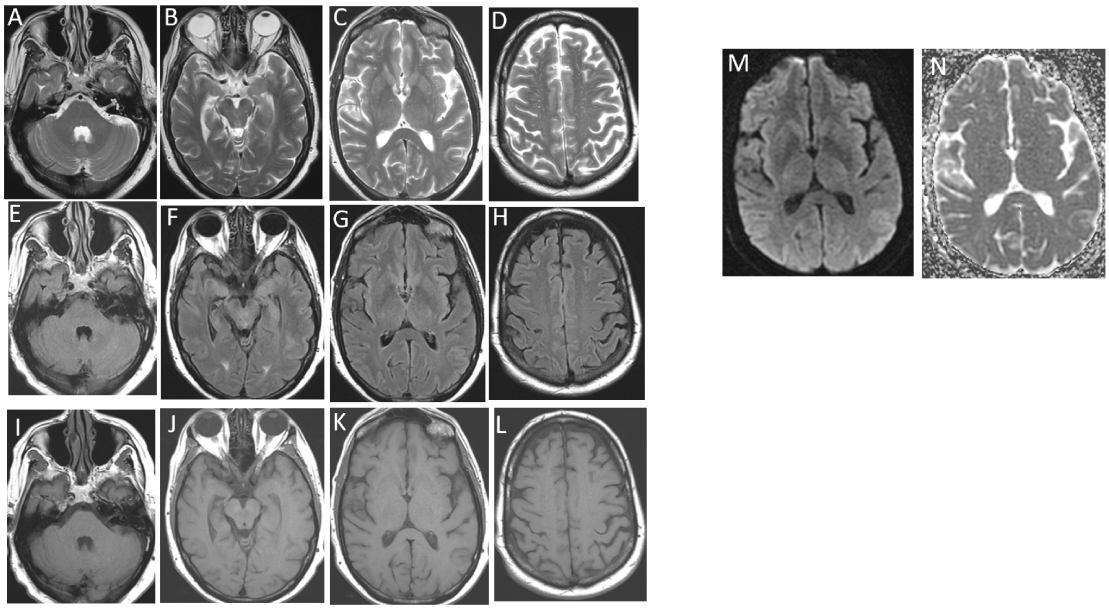
Arrows in panels indicate site of pathologic signal alteration consistent with edema. Axials T2 – weighted (Panels A-D), FLAIR (Panels E-H), and T1-weighted (Panels I-L) images demonstrate new T2 hyperintensity (edema) within the pons (Panel E), the periventricular white matter of the temporal lobes (Panel B and F), caudate, putamen, and thalamus (Panels C and G). Edema is also observed within the white matter at the level of the centrum semiovale and within the left parietal sulci (Panels D and H). The T1-weighted imaging demonstrates accentuated grey-white differentiation secondary to cortical swelling. DWI (Panel M) demonstrates hyperintensity within the thalamus associated with restricted diffusion on ADC map (Panel N). ADC, apparent diffusion coefficient; ATG, anti-thymocyte globulin; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

Figure S3. Improved Cerebral Edema on Day 20



Axial T2-weighted (Panels A-D) and FLAIR (Panels E-F) images demonstrate decreased extent of cerebral edema as compared with that shown in Figure S2. The T2 hyperintensity within the thalami (Panels D and D, arrow) has mostly resolved. Confluent, near symmetrical T2 hyperintensity persists within the periventricular white matter of the temporal lobes (Panels B and F, arrows) and centrum semiovale (Panels D and E, arrow). In comparison with Figure S2, there is no evidence of cortical edema on T1-weighted images (Panels I-L). There is less difference in T1 signal between the cortical grey and subcortical white matter. Panels M and N are the DWI and ADC maps showing near resolution with residual T2 hyperintensity within the frontal lobes and the periventricular white matter of the parieto-occipital region (Panel N, arrows) without restricted diffusion. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

Figure S4. MRI Findings 2-Months After KTE-X19 Infusion



T2-weighted (Panels A-D), FLAIR (Panels E-H) and T1-weighted pre-contrast (Panels I-L) axial imaging of the brain obtained 2 months after KTE-X19 infusion demonstrate resolution of edema within the brainstem (Panels A, E, I), hippocampus (Panels B, F, and J), thalami (Panels C, G, and I), and centrum semiovale (Panels D, H, and L). There is no evidence of abnormal T2 signal within the periventricular white matter and there are no areas of restricted diffusion on DWI (Panel M) and ADC map (Panel N). ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

Table S1. Clinical Evidence Behind Interventions Used to Treat CAR T-Cell–Related Neurotoxicity

Intervention	Symptoms/Clinical Events	Clnical Evidence and Guidelines Used
Tocilizumab[a]	CRS, cerebral edema in the context of CRS	• Lee DW, et al. *Blood* 2014;124(2):188-95[1] • Locke FL, et al. *Blood* 2017;130(Suppl 1):1547[2] • Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15(1):47-62[3] • Rabinstein AA. *The neurologist* 2006;12:59-73[4]
Siltuximab[a,b]	CRS	• Deisseroth A, et al. *Clin Cancer Res* 2015;21(5):950-4[5] • Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15(1):47-62[3]
Methylprednisolone	Severe neurologic symptoms, including cerebral edema	• Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15(1):47-62[3] • Rabinstein AA. *The neurologist* 2006;12:59-73[4] • Wijdicks EF, et al. *Stroke* 2014;45(4):1222-38[6]
Intensive care and intubation	Worsening neurologic syptoms, cerebral edema, airway protection	• Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15(1):47-62[3] • Rabinstein AA. *The neurologist* 2006;12:59-73[4] • Wijdicks EF, et al. *Stroke* 2014;45(4):1222-38[6]
Mannitol	Encephalopathy, cerebral edema	• Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15(1):47-62[3] • Rabinstein AA. *The neurologist* 2006;12:59-73[4] • Wijdicks EF, et al. *Stroke* 2014;45(4):1222-38[6]
Intrathecal hydrocortisone and ara-C	Worsening of severe neurologic symptoms	• Karschnia P, et al. *Blood* 2019;133(20):2212-21[7] • Shah NN, et al. *Blood Adv* 2020;4(10):2119-22[8]
External ventricular drain	Cerebral edema	• Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15(1):47-62[3] • Rabinstein AA. *The neurologist* 2006;12:59-73[4]
Rabbit ATG (Thymoglobulin®)	Cerebral edema	• IEC Therapy Toxicity Assessment and Management (CARTOX) Guidelines[9]

[a] Tocilizumab and siltuximab were administered to prevent exposure of IL-6 to the CNS. Although these agents to not appear to penetrate the blood-brain-barrier and may have a limited role in preventing neurotoxicity, they have been shown to be helpful for neurotoxicity in the presence of CRS.[3]

[b] Siltuximab was not protocol-specified for CRS management.

ATG, anti-thymocyte globulin; CRS, cytokine release syndrome.

Table S2. Additional Biomarker Levels

	Pre-conditioning chemotherapy	**Post-conditioning chemotherapy/ pre-KTE-X19**	**Post-KTE-X19/ Pre-ATG**	**Post-ATG**			
	Baseline (Day -5) ***Serum***	**Day 0** ***Serum***	**Day 3** ***Serum***	**Day 7** ***Serum***	**Day 8** ***CSF***	**Day 14** ***Serum***	**Day 28** ***Serum***
IL-1 RA, pg/mL	511.3	2286.4	2115.6	1018.9	218.2	449.2	585.6
IL-2 Rα, pg/mL	78	78	3975.9	18680.3	379.5	3965.8	1798.8
IL-6, pg/mL	1.6	1.6	159.5	976	N/A	976	976
TNFα, pg/mL	1.8	1.9	10.4	5.7	N/A	0.7	2.8
IL-8, pg/mL	6.6	1.1	17.1	40.9	64.7	16.6	27.6
ICAM-1, pg/mL	341995.2	384342.2	558924.5	1077257	9040.1	467634.1	355554.8
MDC, pg/mL	824.2	465.4	1094.2	88.3	88.3	88.3	88.3
VCAM-1, ng/mL	427.2	527.5	795.8	1659.7	10.7	833.6	797.1

ATG, anti-thymocyte globulin; CAR, chimeric antigen receptor; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; N/A, not available; Rα, receptor alpha; RA, receptor antagonist; TNFα, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion protein 1.

Table S3. Cerebral Edema Management Guidelines

Supportive Therapy	Tocilizumab	Corticosteroids	Follow-up
• Management in monitored care or intensive care unit • Mechanical ventilation, may be required • Intensive care unit supportive therapy • Optimal head position with elevation of head of bed and straight neck positioning • Administration of diuretics and osmotherapy (eg, mannitol, hypertonic saline) • If cerebral edema documented or strongly suspected, recommend neurosurgical consult • Early tracheal intubation with controlled mechanical mild hyperventilation and good oxygenation • Maintain cerebral perfusion pressure with mild hypervolemia • Avoid hypertension with use of anti-hypertensives (labetalol, nicardipine) • Avoid potent vasodilators • Pharmacological cerebral metabolic suppression (barbiturates, sedation, analgesia, and neuromuscular paralysis, as indicated) • Maintain rigorous glycemic control	• <u>No concurrent CRS:</u> o Tocilizumab not indicated • <u>Concurrent CRS:</u> o Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) o Repeat tocilizumab every 4 to 6 hours as needed if not responsive to IV fluids or increasing supplemental oxygen; maximum of 3 doses in a 24-hour period	• High-dose corticosteroids: methylprednisolone 1000 mg/day (adult patients) or 10 mg/kg/dose (maximum dose 500 mg) twice daily (pediatric patients) x 3 days	<u>Improving</u>: • Very slow steroid taper recommended • Repeat neuroimaging as indicated • Serial neurologic exams as indicated • Consider early neuro-rehabilitation • Discontinue tocilizumab if started <u>Not improving</u>: • Consider alternate immunosuppressants • Consult medical monitor

CRS, cytokine release syndrome; IV, intravenous. Information based on a review of treatment for cerebral edema.[4]

References

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124:188-95.
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4. Rabinstein AA. Treatment of cerebral edema. The neurologist 2006;12:59-73.
5. Deisseroth A, Ko CW, Nie L, et al. FDA approval: siltuximab for the treatment of patients with multicentric Castleman disease. Clin Cancer Res 2015;21:950-4.
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8. Shah NN, Johnson BD, Fenske TS, Raj RV, Hari P. Intrathecal chemotherapy for management of steroid-refractory CAR T-cell-associated neurotoxicity syndrome. Blood Adv 2020;4:2119-22.
9. MD Anderson Cancer Center IEC Therapy Toxicity Assessment and Management (CARTOX) Guidelines; 2019. https://www.mdanderson.org/documents/for-physicians/algorithms/clinical-management/clin-management-cytokine-release-web-algorithm.pdf.