Supplemental Material

Supplemental Methods

Safety Assessment

Serious adverse events (SAEs) were defined as one of the following:

- Fatal or life threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Medically significant (defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above)
- Requires inpatient hospitalization or prolongation of existing hospitalization

Hospitalizations for the following reasons were not reported as SAEs:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or preplanned treatment for a preexisting condition that is unrelated to the indication under study and has not worsened since signing the informed consent/assent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Treatment on an emergency outpatient basis that did not result in hospital admission and involved an event not fulfilling any of the definitions of an SAE given above was not considered an SAE.

CRS was captured as follows: CRS start date was a retrospective assessment for commencement of persistent fevers and/or myalgia consistent with CRS and not explained by other events (eg, sepsis); CRS stop date was defined as the date when the patient had been afebrile and off vasopressors for 24 hours. Medical sequelae may have continued after resolution of CRS as defined above.

Neurologic events were identified as events captured by the standardized MedDRA query for "noninfectious encephalopathy/delirium." Neurologic episodes were defined as concatenation of multiple overlapping or succeeding events of the same risk term "neurologic events" based on predefined search criteria.

Supplemental Table 1. CRS Management Algorithm

Pretreatment
• **Acetaminophen/paracetamol and diphenhydramine/H1 antihistamine** • **Prophylaxis for complications of TLS as appropriate**
Tisagenlecleucel Infusion **Prodromal Syndrome: Low-grade fevers, fatigue, anorexia (hours to days)**
• **Observation, rule out infection (surveillance cultures)** • **Antibiotics per local guidelines (febrile neutropenia)** • **Symptomatic support**
Symptom Progression: High fevers, hypoxia, mild hypotension
First-Line Management: • **Oxygen, fluids, low-dose vasopressor support, antipyretics** • **Monitor/manage complications of TLS**
Further Symptom Progression: • **Hemodynamic instability despite IV fluids and moderate to "high-dose" vasopressor[1] support** **OR** • **Worsening respiratory distress, including pulmonary infiltrates increasing oxygen requirements including high-flow oxygen and/or need for mechanical ventilation** **OR** • **Rapid clinical deterioration**

Second-Line Management:
 	
• **Tocilizumab: IV infusion over 1 hour**
  ○ **Patient weight <30 kg: 12 mg/kg IV**
  ○ **Patient weight ≥30 kg: 8 mg/kg IV (maximum dose, 800 mg)**
 	
• **Hemodynamic and respiratory support**

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Lack of Clinical Improvement While Awaiting Tocilizumab Response
Third-Line Management: • **Consider other diagnosis causing clinical deterioration (ie, sepsis, adrenal insufficiency)** • **If no improvement with first dose of tocilizumab within 12 to 18 hours, consider steroids (plan rapid taper after hemodynamic normalization):**   ○ **2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day. Because steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement** • **If no response to steroids within 24 hours, consider second dose of tocilizumab (dosed as above)** • **Hemodynamic and respiratory support**
Lack of Clinical Improvement While Awaiting Response to Third-Line Management
Fourth-Line Management: • **Consider other diagnosis causing clinical deterioration (ie, sepsis, adrenal insufficiency)** • **If no response to steroids and second dose of tocilizumab within 24 hours or further clinical deterioration, consider siltuximab 11 mg/kg IV over 1 hour** • **Hemodynamic and respiratory support**
Lack of Clinical Improvement While Awaiting Response to Fourth-Line Management
Fifth-Line Management: • **Consider other diagnosis causing clinical deterioration (ie, sepsis, adrenal insufficiency)** • **In ongoing CRS despite prior therapy, consider anti–T-cell therapies such as cyclophosphamide, antithymocyte globulin, or alemtuzumab** • **Hemodynamic and respiratory support**

CRS=cytokine release syndrome; IV=intravenous; TLS=tumor lysis syndrome.

Supplemental Table 2. Common Adverse Events Suspected to Be Related to Tisagenlecleucel

Related AEs, n (%)	All Infused Patients (N=137)		
	All Grades	Grade 3	Grade 4
Any AE	131 (96)	38 (28)	67 (49)
AEs occurring in >20% of patients*			
Cytokine release syndrome†	108 (79)	27 (20)	30 (22)
Hypogammaglobulinemia	52 (38)	7 (5)	0
Febrile neutropenia‡	38 (28)	37 (27)	1 (1)
Pyrexia	36 (26)	9 (7)	3 (2)
White blood cell count decreased	35 (26)	6 (4)	20 (15)
Decreased appetite	34 (25)	16 (12)	1 (1)
Hypotension	33 (24)	12 (9)	14 (10)
Nausea	32 (23)	4 (3)	0
Vomiting	29 (21)	1 (1)	0
Alanine aminotransferase increased	29 (21)	15 (11)	0
Aspartate aminotransferase increased	29 (21)	12 (9)	6 (4)
Anemia	28 (20)	11 (8)	0
Neutrophil count decreased	28 (20)	4 (3)	20 (15)
Headache	28 (20)	3 (2)	0

AE=adverse event.

*Individual AEs associated with CRS, such as fever, and tachycardia, and coagulopathy, may be under-reported due to collection under the syndrome "CRS" as opposed to being reported separately.

†Graded according to the University of Pennsylvania grading scale.[1,2]

‡Compared with febrile neutropenia reported as an AE, grade 3/4 neutropenia with fever ≥38.3°C occurred in 63% of patients within 8 weeks after infusion.

Supplemental Table 3. Fibrinogen Level During CRS by CRS Grade

	Patients with CRS (N=108)			
	Grade 1/2 (n=51)	**Grade 3 (n=27)**	**Grade 4 (n=30)**	**All grades (N=108)**
Lowest fibrinogen, g/L				
n	44	26	30	100
Mean (SD)	3.7 (1.16)	3.2 (1.63)	1.8 (1.24)	3.0 (1.55)
Median (range)	3.5 (1.4–6.3)	3.1 (0.9–6.8)	1.3 (0.4–5.5)	3.1 (0.4–6.8)
Lowest fibrinogen category, g/L, n (%)				
<1	0	1 (4)	8 (27)	9 (8)
≥1 to <1.5	1 (2)	4 (15)	8 (27)	13 (12)
≥1.5	43 (84)	21 (78)	14 (47)	78 (72)
Lowest fibrinogen level, n (%)				
No grade	41 (80)	21 (78)	10 (33)	72 (67)
Grade 1	2 (4)	1 (4)	5 (17)	8 (7)
Grade 2	1 (2)	3 (11)	9 (30)	13 (12)
Grade 3	0	1 (4)	5 (17)	6 (6)
Grade 4	0	0	1 (3)	1 (1)
Fibrinogen concentrate or cryoprecipitate usage, n (%)	0	4 (15)	19 (63)	23 (21)
Factor I (fibrinogen)	0	1 (4)	5 (17)	6 (6)
Cryoprecipitate	0	3 (11)	14 (47)	17 (16)

CRS=cytokine release syndrome.

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Supplemental Table 4. Neurologic Events Within 8 Weeks After Infusion by Maximum CRS Grade

	Maximum CRS Grade							
	No CRS (n=29)		Grade 1/2 (n=51)		Grade 3 (n=27)		Grade 4 (n=30)	
Neurologic Events, n (%)	**Any Grade**	**Grade 3***	**Any Grade**	**Grade 3***	**Any Grade**	**Grade 3***	**Any Grade**	**Grade 3***
≥1 AE	5 (17)	1 (3)	11 (22)	1 (2)	12 (44)	4 (15)	22 (73)	8 (27)
Muscular weakness	2 (7)	1 (3)	1 (2)	0	0	0	0	0
Delirium	1 (3)	0	0	0	3 (11)	1 (4)	7 (23)	2 (7)
Irritability	1 (3)	0	1 (2)	0	1 (4)	0	2 (7)	0
Tremor	1 (3)	0	1 (2)	0	2 (7)	0	3 (10)	0
Confusion	0	0	4 (8)	0	3 (11)	0	6 (20)	0
Encephalopathy	0	0	2 (4)	1 (2)	6 (22)	2 (7)	4 (13)	3 (10)
Lethargy	0	0	2 (4)	0	1 (4)	0	0	0
Dysarthria	0	0	1 (2)	0	1 (4)	1 (4)	1 (3)	0
Mental status change	0	0	1 (2)	0	1 (4)	0	2 (7)	1 (3)
Seizure	0	0	1 (2)	0	0	0	4 (13)	2 (7)
Somnolence	0	0	1 (2)	0	2 (7)	0	3 (10)	2 (7)
Agitation	0	0	0	0	3 (11)	0	4 (13)	0
Hallucination	0	0	0	0	3 (11)	0	2 (7)	0
Depressed level of consciousness	0	0	0	0	2 (7)	1 (4)	0	0
Affect lability	0	0	0	0	1 (4)	0	0	0
Aphasia	0	0	0	0	1 (4)	0	0	0

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	Maximum CRS Grade							
	No CRS (n=29)		Grade 1/2 (n=51)		Grade 3 (n=27)		Grade 4 (n=30)	
Neurologic Events, n (%)	**Any Grade**	**Grade 3***	**Any Grade**	**Grade 3***	**Any Grade**	**Grade 3***	**Any Grade**	**Grade 3***
Disturbance in attention	0	0	0	0	1 (4)	0	0	0
Restlessness	0	0	0	0	1 (4)	0	0	0
Sluggishness	0	0	0	0	1 (4)	0	0	0
Social avoidant behavior	0	0	0	0	1 (4)	0	0	0
Cognitive disorder	0	0	0	0	0	0	3 (10)	1 (3)
Dysphagia	0	0	0	0	0	0	2 (7)	2 (7)
Amnesia	0	0	0	0	0	0	1 (3)	0
Asterixis	0	0	0	0	0	0	1 (3)	0
Generalized tonic-clonic seizure	0	0	0	0	0	0	1 (3)	0
Visual hallucination	0	0	0	0	0	0	1 (3)	0
Listless	0	0	0	0	0	0	1 (3)	0

AE=adverse event; CRS=cytokine-release syndrome.

Neurologic events is a group term for events under the standard Medical Dictionary for Regulatory Activities queries for noninfectious encephalopathy and delirium; headache is not included in the definition. A patient with multiple occurrences of an AE is counted only once in the AE category at the maximum toxicity grade. CRS events were graded according to the University of Pennsylvania grading scale.[1,2]

*There were no grade 4 neurologic events.

Supplemental Table 5. Patient-Level Management of Grade ≥3 Neurologic Events Occurring Within 8 Weeks After Infusion

	CRS*		Neurologic Event					
Patient	**Grade**	**Day of Onset – Resolution†**	**Event‡**	**Day of Onset – Resolution† (duration), days**	**Timing Related to CRS**	**Causality Related to Tisagenlecleucel§**	**CRS Management (dosing†)**	**Other Therapy**
Patient 1 Age: 11 y Female	No CRS	N/A	Muscular weakness (lower limb)	4–NR‖	N/A	No	• Tocilizumab (1 dose, day 11) • Methylprednisolone (first dose on day 11)¶	None
Patient 2 Age: 8 y Female	1/2	3–8	Encephalopathy	6–13 (8)	Concurrent	Yes	None	None
Patient 3 Age: 12 y Male	3	1–9	Encephalopathy	29–33 (5)	After CRS#	Yes	• Tocilizumab (2 doses, days 6, 8) • Methylprednisolone (first dose on day 8 [for CRS])	None
Patient 4 Age: 15 y Female	3	2–12	Encephalopathy	7–8 (2)	Concurrent	Yes	• Tocilizumab (1 dose, day 7)	None
Patient 5 Age: 14 y Male	3	9–26	Delirium Dysarthria (hypokinetic type)	21–30 (10) 28–NR‖	Concurrent After CRS	Yes No	• Tocilizumab (1 dose, day 11)	• Diazepam for agitation • Risperidone and haloperidol for delirium • Quetiapine for agitation and delirium
Patient 6 Age: 8 y Male	3	2–13	Depressed level of consciousness	2–4 (3)	Concurrent	Yes	• Tocilizumab (1 dose, day 12)	None
Patient 7 Age: 18 y Male	4	1–19	Delirium Encephalopathy Somnolence	11–33 (23) 9–42 (34) 15–22 (8)	Concurrent Concurrent Concurrent	Yes Yes Yes	• Tocilizumab (1 dose, day 18) • Methylprednisolone (first dose on day 32)	• Olanzapine for agitation
Patient 8 Age: 21 y Female	4	2–18	Delirium	6–17 (12)	Concurrent	Yes	• Tocilizumab (2 doses, days 6, 15) • Hydrocortisone (day 8)** • Methylprednisolone (first dose on day 15)	• Zolpidem for delirium

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	CRS*		Neurologic Event					
Patient	**Grade**	**Day of Onset – Resolution†**	**Event‡**	**Day of Onset – Resolution† (duration), days**	**Timing Related to CRS**	**Causality Related to Tisagenlecleucel§**	**CRS Management (dosing†)**	**Other Therapy**
Patient 9 Age: 4 y Female	4	2–22	Encephalopathy	23–29 (7)	After CRS	Yes	• Tocilizumab (3 doses, days 3,6,8) • Methylprednisolone (first dose on day 2) • Hydrocortisone (day 6)** • Etanercept (1 dose, day 8) • Siltuximab (1 dose, day 9) • Infliximab (1 dose, day 10)	None
Patient 10 Age: 9 y Female	4	5–12	Seizure	7–10 (4)	Concurrent	Yes	• Tocilizumab (1 dose, 7)	• Levetiracetam for seizure
Patient 11 Age: 7 y Female	4	2–11	Seizure (tonic-clonic)	6 (1)	Concurrent	Yes††	• Tocilizumab (2 doses, days 3, 6) • Dexamethasone (first dose day 7 [for CRS]) • Etanercept (1 dose, days 6, 8)	• Lorazepam, levetiracetam, and diazepam for seizure
Patient 12 Age: 22 y Female	4	3–17	Cognitive disorder	5–8 (4)	Concurrent	Yes	• Tocilizumab (3 doses, days 4,8,9) • Methylprednisolone (day 5) • Hydrocortisone (day 9)** • Siltuximab (1 dose, day 10)	None
Patient 13 Age: 3 y Male	4	2–19	Dysphagia	18–57 (40)	Concurrent ‡‡	Yes	• Tocilizumab (1 dose, day 7)	• Olanzapine for irritability • Speech therapy for dysphagia

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	CRS*		Neurologic Event					
Patient	**Grade**	**Day of Onset – Resolution†**	**Event‡**	**Day of Onset – Resolution† (duration), days**	**Timing Related to CRS**	**Causality Related to Tisagenlecleucel§**	**CRS Management (dosing†)**	**Other Therapy**
Patient 14 Age: 16 y Female	4	2–10	Mental status change	5–41 (37)	Concurrent	Yes	• Tocilizumab (1 dose, day 7)	• Lorazepam and levetiracetam for seizure • Clonidine and olanzapine for agitation and somnolence
			Somnolence	8–20 (13)	Concurrent	Yes		
			Dysphasia	18–28 (11)	After CRS	Yes		
			Encephalopathy	32–37 (6)	After CRS	Yes		

Tocilizumab and/or corticosteroids were administered for CRS management and not specifically for management of neurologic events. Within 8 weeks post-infusion, 29/43 patients (67%) who received tocilizumab had neurologic events versus 21/94 (22%) who did not receive tocilizumab (P<0.001); 10 patients had neurologic events after receiving tocilizumab. Eighteen of 26 patients (69%) who received corticosteroids had neurologic events versus 32/111 (29%) who did not receive corticosteroids (P<0.001). CRS=cytokine-release syndrome; NR=not resolved.

*Graded according to the University of Pennsylvania grading scale.[1,2]

†Day of tisagenlecleucel infusion was considered day 1.

‡All neurologic events were grade 3: encephalopathy, 6 (4%); delirium, 3 (2%); dysphagia, 2 (1%); seizure, 2 (1%); somnolence, 2 (1%); cognitive disorder, 1 (1%); depressed level of consciousness, 1 (1%); dysarthria, 1 (1%); mental status change, 1 (1%); muscular weakness, 1 (1%).

§As reported by the investigator.

‖The event was not resolved at time of death. Patient 1 died due to rapid leukemia progression on day 10. Patient 5 died after treatment discontinuation due to leukemia progression on day 123.

¶Tocilizumab and methylprednisolone were administered for presumed CRS, which was later ruled out.

#Onset of the neurologic event was delayed, compared to the timing of CRS.

**Stress dose.

††Event was considered not related by investigator due to history of pre-existing seizure with exacerbation following tisagenlecleucel infusion.

‡‡Resolution of the neurologic event was delayed, compared to the timing of CRS.

Supplemental Table 6. Select Cardiac Events*

	All Infused Patients (N=137)		
AE, n (%)	**Any Time Post-Infusion (n=137)**	**Within 8 Weeks Post-Infusion (n=137)**	**After 8 Weeks Post-Infusion† (n=116)**
Any select cardiac AE	47 (34)	43 (31)	7 (6)
Arrhythmia	41 (30)	40 (29)	3 (3)
Cardiac dysfunction	11 (8)	8 (6)	3 (3)
Pericardial effusion	3 (2)	3 (2)	0
Valvular dysfunction	1 (1)	1 (1)	1 (1)
Any grade 3/4 select cardiac AE	12 (9)	10 (7)	2 (2)
Arrhythmia	6 (4)	6 (4)	0
Cardiac dysfunction	8 (6)	6 (4)	2 (2)
Any select cardiac AE suspected to be treatment related	39 (28)	39 (28)	0
Arrhythmia	35 (26)	35 (26)	0
Cardiac dysfunction	7 (5)	7 (5)	0
Valvular dysfunction	1 (1)	1 (1)	0

*Select cardiac events include arrhythmia, cardiac dysfunction, valvular dysfunction, and pericardial effusion. The most common events occurring ≤8 weeks post-infusion were arrhythmias (29%), specifically tachycardia (26%). Five patients (4%) developed cardiac dysfunction during CRS (grade 3 dysfunction, n=4; grade 4, n=1), which resolved in all but 2 patients (both with left ventricular dysfunction) who died due to disease progression.

†There were no select cardiac events >1 year post-infusion.

‡Select cardiac events resolved in all but 11/47 (23%) patients with an event at any time point, including 5/34 (15%) who experienced them during CRS. 10 of these 11 patients died (due to leukemia progression, n=9; embolic stroke, n=1) before the events resolved.

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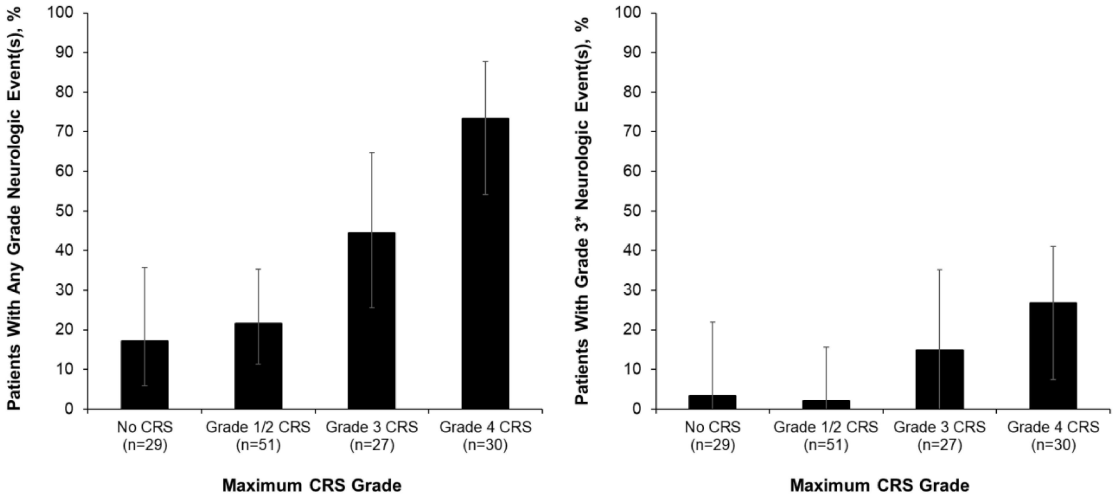
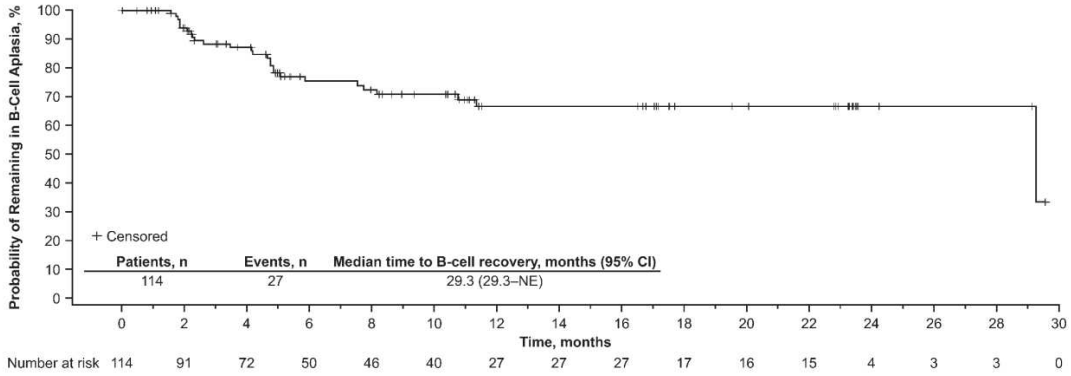
Supplemental Figure 1. Percentage of patients with any grade and grade 3* neurologic events by maximum CRS grade.

CRS graded according to the University of Pennsylvania grading scale.[1,2] CRS=cytokine-release syndrome. *There were no grade 4 neurologic events.



Supplemental Figure 2. Kaplan-Meier Analysis of Time to B-Cell Recovery.

Time to B-cell recovery was defined as the time from onset of remission to the earliest time when the percentage of CD19-positive B cells was ≥1% among viable white blood cells in peripheral blood or ≥3% among lymphocytes. Patients who achieved CR/CRi are included. Kaplan-Meier estimate of continued B-cell aplasia at 12 months is 66% (95% CI, 54%–76%). CI=confidence interval; CR=complete remission; CRi=complete remission with incomplete hematologic recovery; NE=not estimable.



References

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2. Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. *J Hematol Oncol*. 2018;11(1):35.