APPENDIX I. GUIDELINES FOR CYTOKINE RELEASE SYNDROME GRADING AND MANAGEMENT RECOMMENDATIONS

Rescue medication in terms of an antidote to reverse the action of epcoritamab is not available. Potential adverse effects of epcoritamab are to be treated symptomatically.

Cytokine Release Syndrome

Identify cytokine release syndrome (CRS) based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in Table 5. Subjects who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry according to institutional standard-of-care. For patients experiencing severe CRS, an echocardiogram to assess cardiac function should be considered. For severe or life-threatening CRS, consider increasing the level of care to intensive-care supportive therapy.

Consider evaluation for macrophage activation syndrome (MAS)/hemophagocytic lymphohistiocytosis (HLH), as CRS has been reported in some cases to be associated with findings of MAS/HLH, and the physiology of the syndromes may overlap with CRS.

The supportive care may include, but is not limited to:

- Infusion of saline
- Systemic corticosteroids, antihistamines, antipyretic medications
- Support for blood pressure (vasopressin, vasopressors)
- Support for hypoxia with low-flow and high-flow oxygen and positive pressure ventilation
- Monoclonal antibody administration against interleukin (IL)-6R, IL-6 or IL-1, e.g., parenteral administration of tocilizumab, siltuximab and/or anakinra.
- Blood product support, anti-infectives, analgesics, skin and mouth care, etc., should be according to local guidelines and Investigator's discretion.

Table 5. CRS Grading and Recommendations for Management Guidance Based on the American Society for Transplantation and Cellular Therapy Guidelines[a]

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Corticosteroids	Follow up
Grade 1: Fever ≥ 38.0°C No hypotension No hypoxia	Hold epcoritamab until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Evaluate for other causes of fever and initiate broad spectrum antibiotics per local guidelines to continue until fever resolves; in the case of concurrent febrile neutropenia, follow local guidelines until febrile neutropenia resolves. Supportive care per institutional standard of care (antipyretics and IV hydration) Closely monitor neurologic status	Recommended for patients with advanced age, high tumor burden, circulating tumor cells, rapidly progressing disease, history of major organ dysfunction, elevated inflammatory markers (e.g., CRP, ferritin) or fever refractory to antipyretics. Notes: • If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period • If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab • Initiate anticytokine therapy when no improvement within 24 hours (if not already initiated)	Dexamethasone 10 - 20 mg per day (or equivalent) may be initiated. Note: If suspicion of ICANS is concurrent with CRS, initiation of dexamethasone is highly recommended (see Neurotoxicity guidelines in Appendix J).	Not improving after 24 hours: • Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Corticosteroids	Follow up
Grade 2: Fever ≥ 38.0°C With hypotension not requiring vasopressors And/or hypoxia requiring low-flow (≤ 6L/min) Oxygen	Hold epcoritamab until resolution of CRS. In-person evaluation by medical professional, ideally at site or center with experience managing CRS. Evaluate for other causes of fever and initiate broad spectrum antibiotics per local guidelines to continue until fever resolves; in the case of concurrent febrile neutropenia, follow local guidelines until febrile neutropenia resolves. Continuous cardiac telemetry and pulse oximetry as indicated IV fluids bolus for hypotension with 0.5 to 1.0 L isotonic fluids Supplemental oxygen as indicated	Recommended (refer to notes below) Example: Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) Notes: • If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period • If CRS is refractory to 2 doses of tocilizumab, initiate/ increase dose of corticosteroids and consider alternative anticytokine therapy. • If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab	Recommend dexamethasone 10 - 20 mg per day (or equivalent) Note: If suspicion of ICANS is concurrent with CRS, initiation of dexamethasone is highly recommended (see Neurotoxicity guidelines in Appendix J).	<u>Improving</u> • Discontinue anti-cytokine therapy • Taper corticosteroids Manage as above <u>Not improving</u> • Manage as Grade 3 (below)

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Corticosteroids	Follow up

Grade 3:
Symptoms require and respond to aggressive intervention
Fever ≥ 38.0°
With hypotension requiring 1 vasopressor with or without vasopressin[c]
And/or hypoxia requiring high-flow (> 6 L/min) facemask, NC, NRB mask or Venturi mask
	Hold epcoritamab until resolution of CRS.
	In-person evaluation by medical professional, ideally at site or center with experience managing CRS.
	Investigate for infection and rapidly startup broad-spectrum antibiotics. Continuation of antibiotic therapy is recommended until fever and any existing neutropenia resolve. Supportive care per institutional guidelines (antipyretics and IV hydration).
	
	In addition:
	• Management in Intensive Care Unit
	• Vasopressor support and/or supplemental oxygen as indicated
	• Consider cardiac echocardiogram
		Recommended (refer to notes)
		Example: Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)
		Notes:
		• If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period
		• If CRS is refractory to 2 doses of tocilizumab, initiate/ increase dose of corticosteroids and consider alternative anticytokine therapy.
		• If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab.
		• If no clinical improvement in signs and symptoms of CRS with tocilizumab:
		  • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only, or
		  • Consider anakinra, 100 mg SC once/day
			Recommend dexamethasone 10 - 20 mg IV every 6 hours (or equivalent).
			Note: If suspicion of ICANS is concurrent with CRS, initiation of dexamethasone is highly recommended (see Neurotoxicity guidelines in Appendix J).
				<u>Improving</u>
				• Discontinue anti-cytokine therapy
				• Taper corticosteroids
				Manage as above
				<u>Not improving</u>
				• Manage as Grade 4 (below)

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Corticosteroids	Follow up

Grade 4:
Life-threatening symptoms
Fever ≥ 38.0°
With hypotension requiring ≥ 2 or high dose vasopressors[c] excluding vasopressin
Requirements for ventilator support and/or continuous renal replacement therapy or other hemodialysis procedures
Consider and assess for development of MAS/HLH[d], including monitoring of fibrinogen and triglyceride levels
	Permanently discontinue epcoritamab for Grade 4 CRS
	In-person evaluation by medical professional, ideally at site or center with experience managing CRS.
	Evaluate for other causes of fever and initiate broad spectrum antibiotics per local guidelines to continue until fever resolves; in the case of concurrent febrile neutropenia, follow local guidelines until febrile neutropenia resolves.
	Manage in Intensive Care Unit with:
	IV fluids as indicated
	Vasopressor support as indicated
	Mechanical ventilation and/or renal replacement therapy may be required
		Recommended (refer to notes)
		Example: Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)
		Notes:
		• If tocilizumab is used, do not exceed more than 2 doses in a 24-hour period
		• If CRS is refractory to 2 doses of tocilizumab, initiate/ increase dose of corticosteroids and consider alternative anticytokine therapy.
		• If suspicion of ICANS is concurrent with CRS, choose alternative to tocilizumab.
		• If no clinical improvement in signs and symptoms of CRS with tocilizumab:
		  • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only, or
		  • Consider anakinra, 100 mg SC once/day
			Recommend high-dose corticosteroids:
			• Dexamethasone 10-20 mg IV every 6 hours or
			• Methylprednisolone 1 mg/kg IV BID
				<u>Improving</u>
				• Discontinue anti-cytokine therapy
				• Taper corticosteroids
				Manage as above
				<u>Not improving</u>
				• Consider alternative immunosuppressants (e.g., siltuximab, anakinra)

CRS Grade[a]	Supportive Care	Anticytokine Therapy[b]	Corticosteroids	Follow up
Macrophage activation syndrome (MAS) / hemophagocytic lymphohistiocytosis (HLH)	For MAS/HLH combined with CRS: permanently discontinue epcoritamab. Intensive supportive care is essential because of frequent life-threatening, severe manifestations at presentation. Appropriate broad-spectrum antiviral, antibacterial, antifungal prophylaxis, and treatment must be initiated. The elimination of triggers (particularly infection) is crucial to remove the stimuli that initiate the abnormal immune system activation.	First line treatment: includes IL-6R-blockade with tocilizumab unless tocilizumab was already administered for the management of CRS. Corticosteroids are also indicated for the initial treatment of MAS/HLH, irrespective of the cause (CRS Grade 4 treatment recommendations should be followed). Second-line treatment: Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids. Anakinra should be given until resolution of CRS with a daily dose of 100 mg SC. In more severe CRS cases, especially if combined with MAS/HLH and/or neurotoxicity, anakinra 100 mg twice daily (every 12 hours) SC should be given until resolution of CRS and other concurrent T-cell toxicities, like neurotoxicity and/or MAS/HLH which could benefit from anakinra treatment. In case of rapidly progressing clinical course with ongoing CRS, anakinra should be administered as first line treatment. In more severe MAS/HLH cases, especially if combined with CRS and/or neurotoxicity, anakinra 100 mg SC twice daily should be given until resolution of MAS/HLH, which could benefit from anakinra treatment. -Anti-IL-6 antibody, siltuximab, might be considered as second line therapy		

ASTCT = American Society for Transplantation and Cellular Therapy; BID = twice daily; CRS = cytokine release syndrome; HLH = hemophagocytic lymphohistiocytosis; ICANS = immune effector cell-associated neurotoxicity syndrome; IV = intravenous(ly); MAS = macrophage activation syndrome; NC = nasal cannula; NRB = nonrebreather; SC = subcutaneous(ly); SmPC = summary of product characteristics; USPI = United States prescribing information

a. Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

b. Refer to tocilizumab, siltuximab, or anakinra USPI or SmPC for details.

c. High-dose vasopressors in Table 6.

d. Anakinra should be considered in the event that severe CRS is not responding to tocilizumab and corticosteroids (Lehmberg K, Nichols KE, Henter JI, et al. Consensus recommendations for the diagnosis and management of hemophagocytic lymphohistiocytosis associated with malignancies. Haematologica. 2015;100(8):997-1004.).

Table 6. High-Dose Vasopressors (all Doses are Required for ≥ 3 Hours)[a]

Pressor	Dose-rate
Norepinephrine monotherapy	≥ 20 µ/min
Dopamine monotherapy	≥ 10 µ/kg/min
Phenylephrine monotherapy	≥ 200 µ/min
Epinephrine monotherapy	≥ 10 µ/min
If on vasopressin	Vasopressin 1 norepinephrine equivalent of ≥ 10 µ /min[b]
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 20 µ /min[b]

a. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95.

b. Vasopressor equivalent equation: norepinephrine equivalent dose 5 [norepinephrine (mg/min)] 1 [dopamine (mg/kg/min) 4 2] 1 [epinephrine (mg/min)] 1 [phenylephrine (mg/min) 410].

Table 7. Corticosteroid Dose Equivalents Conversion Table

Corticosteroid	Approximate equivalent dose (mg)
Short-acting	
Cortisone (PO)	500
Hydrocortisone (IV or PO)	400
Intermediate-acting	
Methylprednisolone (IV or PO)	80
Prednisolone (PO)	100
Prednisone (IV or PO)	100
Triamcinolone (IV)	80
Long Acting	
Betamethasone (IV)	15
Dexamethasone (IV or PO)	15

IV = intravenous(ly); PO = oral(ly)

APPENDIX J. RECOMMENDED GUIDELINES FOR IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME (ICANS) GRADING AND MANAGEMENT

Neurotoxicity will be graded according to the ASTCT grading for ICANS, which includes the immune effector cell-associated encephalopathy (ICE) assessment tool.[27] All other neurological toxicities (or non-ICANS events) will be graded per NCI CTCAE version 5.0 criteria.

Monitor patients for signs and symptoms of ICANS/neurotoxicity (Table 8). Rule out other causes of neurologic symptoms. Subjects who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening ICANS/neurotoxicity. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher ICANS. Neurotoxicity management guidelines are found in Table 10.

Table 8. ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ASTCT = American Society for Transplantation and Cellular Therapy; CTCAE = Common Terminology Criteria for Adverse Events; EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = Immune effector cell-associated encephalopathy; ICP = intracranial pressure; N/A = not applicable

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS. Grade 5 is considered to be fatal.

N/A indicates not applicable.

a. A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

b. Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

c. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v 5.0, but they do not influence ICANS grading.

d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v 5.0.

Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

Table 9. Immune Effector Cell-Associated Encephalopathy (ICE) Assessment Tool for Grading of ICANS ICE Tool

ICE Assessment	ICE Scoring:
Orientation: orientation to year, month, city, hospital: 4 points Naming: ability to name 3 objects (e.g., point to clock, pen, button): 3 points Following commands: ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point Writing: ability to write a standard sentence (e.g., "The USA national bird is the bald eagle"): 1 point Attention: ability to count backwards from 100 by 10:1 point	10, no impairment 7-9, Grade 1 ICANS 3-6, Grade 2 ICANS 0-2, Grade 3 ICANS 0 due to patient unarousable and unable to perform ICE assessment, Grade 4 ICANS.

ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell-associated encephalopathy

Source: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.

Table 10. Recommended Management Guidelines for Treatment of Neurotoxicity Associated with Immune Effector Cells

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids	Follow up

Grade 1:
ICE score[a] 7-9 and/or depressed level of consciousness[b] but awakens spontaneously
No seizures, motor weakness, or raised ICP/cerebral edema
Confusion-mild disorientation
Encephalopathy-mild limiting of ADLs
Dysphasia-not impairing ability to communicate
	Hold epcoritamab until resolution of event.
	• Supportive care per institutional standard of care
	• Closely monitor neurologic status
	• Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of event
	  • Aspiration precautions
	  • Recommend brain imaging and EEG per institutional guidelines
		No CRS: not indicated
		Concurrent CRS only:
		Choose alternative to tocilizumab (e.g., siltuximab, anakinra) if possible (refer to CRS guidelines in Table 5)
		• Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. It should be given as a daily dose of 100 mg SC or 200 mg SC (100 mg Q12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment.
			Dexamethasone, 10 mg IV Q12 hours	Not improving
				• Continue supportive care

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids	Follow up

Grade 2:
ICE score[a] 3-6 and/or depressed level of consciousness[b] but awakens to voice
No seizures, motor weakness, or raised ICP/cerebral edema
Somnolence-moderate, limiting instrumental ADLs
Confusion-moderate disorientation
Encephalopathy-limiting instrumental ADLs
Dysphasia-moderate impairing ability to communicate spontaneously
	Hold epcoritamab until resolution of event.
	• Supportive care per institutional standard of care
	• Closely monitor neurologic status
	• Recommend initiating prophylactic non-sedating anti-seizure medication until resolution of event (e.g., levetiracetam)
	  • Aspiration precautions
	• Continuous cardiac telemetry and pulse oximetry as indicated
	• Closely monitor neurologic status with serial neurologic exams to include fundoscopy. Consider neurology consult.
	• Perform brain imaging (e.g., MRI), EEG, and lumbar puncture (with opening pressure) if no contraindications
		No concurrent CRS:
		• Anticytokine therapy not indicated
		Concurrent CRS:
		• Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. It should be given as a daily dose of 100 mg SC or 200 mg SC (100 mg Q12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment.
		  • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.
			Dexamethasone at 10 - 20 mg IV every 12 hours	<u>Improving</u>
				• Discontinue anti-cytokine therapy if started
				• Taper corticosteroids
				<u>Not improving</u>:
				• Manage as Grade 3 (below)

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids	Follow up
Grade 3: ICE score[a] 0-2 and/or depressed level of consciousness[b] but awakens to tactile stimulus And clinical seizure focal or generalized that resolves rapidly, or non-convulsive seizures on EEG that resolve with intervention No motor weakness Focal/local edema on neuroimaging Somnolence-obtundation or stupor Confusion-severe disorientation Encephalopathy-limiting self-care ADLs Dysphasia-severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	**First Episode:** epcoritamab interruption until full resolution. **Second episode:** permanently discontinue epcoritamab at the discretion of the investigator, if clinically indicated.	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated. • Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. It should be given as a daily dose of 100 mg SC or 200 mg SC (100 mg Q12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. • Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	Dexamethasone 10 - 20 mg IV every 6 hours (or its equivalent of methylprednisolone if not available in this circumstance)	<u>Improving</u> • Discontinue anti-cytokine therapy • Taper corticosteroids <u>Not improving:</u> • Manage as Grade 4 (below)

Neurologic Toxicities	Supportive Care	Anticytokine Therapy	Corticosteroids	Follow up
Grade 4: ICE score[a] 0 and patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between Deep focal motor weakness[c] such as hemiparesis or paraparesis Diffuse cerebral edema on neuroimaging[d]; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation	Permanently discontinue epcoritamab for grade 4 event. • Mechanical ventilation may be required • Consider imaging of spine for focal motor weakness • Lower intracranial pressure (ICP) by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema • Aggressive management of ICP with institutional standard of care	No concurrent CRS: Anticytokine therapy not indicated. Concurrent CRS: Anticytokine therapy indicated. Anakinra should be considered in the event of neurotoxicity onset with ongoing CRS as well as neurotoxicity. It should be given as a daily dose of 100 mg SC or 200 mg SC (100 mg every 12 hours) depending on the severity of neurotoxicity and other concurrent toxicities. Anakinra should be given until resolution of neurotoxicity and other concurrent toxicities which could benefit from anakinra treatment. Consider siltuximab, 11 mg/kg IV over 1 hour, one time only.	High-dose cortico-steroids: methylprednisolone 1000 mg/day IV × 3 days (Equivalent dose of dexamethasone is 188 mg/day)	<u>Improving</u> • Taper corticosteroids <u>Not improving:</u> • Consider alternate immune-suppressants (contact Medical Monitor)

ADL = activities of daily living; ASBMT = American Society for Bone Marrow Transplant; CRS = cytokine release syndrome; EEG = electroencephalogram; ICANS = immune effector cell-associated neurotoxicity syndrome; ICE = immune effector cell associated encephalopathy; ICP = intracranial pressure; IV = intravenous(ly); Q = every

a. A subject with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a subject with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

b. Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

c. Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

d. Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Note: ICANS grade is determined by the most severe domain event not attributable to any other cause. For example, a subject with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

Sources: Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38.
Neelapu SS. Managing the Toxicities of CAR T-Cell Therapy. Hematol Oncol. 2019;37 (Supp 1):48-52.

APPENDIX K. GUIDELINES FOR CLINICAL TUMOR LYSIS SYNDROME

Subjects who are considered to have an increased risk for clinical tumor lysis syndrome (CTLS) (e.g., due to the type of lymphoma, the tumor burden (bulky disease and/or elevated lactate dehydrogenase [LDH]), renal impairment and/or elevated uric acid should be considered for hydration and prophylactic treatment with a uric acid lowering agent as well as frequent monitoring according to local standards or available guidelines.[28] Close monitoring of laboratory parameters to allow for early diagnosis of possible CTLS is recommended.

If signs of CTLS occur, supportive therapy, including rasburicase, may be used as clinically indicated at the Investigator's discretion and using standard-of-care institutional guidelines.

In laboratory tumor lysis syndrome, 2 or more metabolic abnormalities (i.e., hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterwards. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Table 11. Definitions of Laboratory and Clinical Tumor Lysis Syndrome (Howard Criteria)

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L) in adults	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.45 mmol/L) in adults	
Hyperkalemia	Potassium > 6.0 mmol/L	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 1.12 mg/dL (0.3 mmol/L)[a]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[b]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or a single value > 1.5 × the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 0.5 mL/kg/hr for 6 hrs

a. The corrected calcium level in mg/dL = measured calcium level in mg/dL + 0.8 × (4-albumin in g/dL).

b. Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dL (26.5 µmol/L) or a period of oliguia lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome.

Note: In laboratory tumor lysis syndrome, 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Source: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

Cairo-Bishop Criteria for Clinical Tumor Lysis Syndrome and Grading

Complication	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Creatinine[1]	1.5 × ULN	> 1.5–3.0 × ULN	> 3.0-6.0 × ULN	> 6.0 × ULN	Death
Cardiac arrhythmia	Intervention not indicated	Nonurgent medical intervention needed	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	
Seizure	None	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	

ADL = activities of daily living; CHF = congestive heart failure; ULN = upper limit of normal

Note: If no institutional ULN is specified, ULN is defined as follows: female 105.6 µmol/L, male 114.4 µmol/L.

Source: Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78

APPENDIX L. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE IMBALANCES AND PREVENTION OF CLINICAL TUMOR LYSIS SYNDROME

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise, re-check in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis syndrome. • At the discretion of the investigator, may re-check prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium, and creatinine must be re-checked within 24 hours.
Potassium ≥ ULN and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour and consider repeating every hour STAT. • Perform STAT ECG and consider commence telemetry. • Consider nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Consider administration of Kayexalate up to 60 g per day (in divided doses or Resonium A 60 g). • Consider administration of furosemide 20 mg IV × 1. • Consider administration of insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Consider administration of sodium bicarbonate 1 – 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Consider administration of calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate.

Abnormality	Management Recommendations
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose per institutional guidelines). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 – 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin is low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1-hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium, and creatinine 2 and 4 hours later, if no other evidence of tumor lysis syndrome.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Re-check potassium, phosphorus, uric acid, calcium, and creatinine in 1 – 2 hours STAT.