



ASTCT Consensus Grading for CRS and ICANS

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- Advisory Board Member / Consultant for Kite/Gilead, Merck, Celgene, Novartis, Unum Therapeutics, Pfizer, Precision Biosciences, CellMedica, Allogene, and Incyte.

Safety in multicenter CD19 CAR T trials in adult NHL

Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥ 3	NT All Grades	NT Grade ≥ 3	Ref
ZUMA1 Kite	CD19/CD3 ζ / CD28	108	92%	11%	67%	32%	Neelapu et al, NEJM 2017
JULIET Novartis	CD19/CD3 ζ / 4-1BB	111	58%	22%	21%	12%	Schuster et al, NEJM 2019
TRANSCEND Juno	CD19/CD3 ζ / 4-1BB	73	37%	1%	25%	15%	Abramson et al, ASCO 2018

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 4 deaths on ZUMA1 due to AEs – 1 cardiac arrest, 1 HLH, 1 pulmonary embolism, 1 intracerebral hemorrhage

CRS Grading Schemes

- CTCAE Versions 4.03 & Version 5.0
- Lee Criteria
- Penn Criteria
- MSKCC Criteria
- CARTOX (Neelapu, et al)

CRS Grading Schemes

- Difficult to compare CRS across studies
- 54 yo with DLBCL who develops hypotension requiring a low dose vasopressor for 2 days after CD19 CAR T-cell therapy
 - Grade 2 on 2014 Lee/CARTOX scale
 - Grade 3 on Penn/MSKCC scale
 - Grade 4 on CTCAE v4.0 scale

Neurotoxicity in multicenter CD19 CAR T trials in adult NHL

Study	Product	NT All Grades	NT Grade ≥ 3	Reference	NT All Grades	NT Grade ≥ 3	Reference
ZUMA-1	CD19/CD3 ζ / CD28	67%	32%	Neelapu et al, <i>NEJM</i> 2017 Locke et al, <i>Lancet Oncol</i> 2019	87%	31%	Axicabtagene ciloleucel US Prescribing Information
JULIET	CD19/CD3 ζ / 4-1BB	21%	12%	Schuster et al, <i>NEJM</i> 2019	58%	18%	Tisagenlecleucel US Prescribing Information

- CTCAE vs 4.03 criteria for neurotoxicity (NT) grading
- Monitoring strategies for neurotoxicity differed between the two studies
- Adverse event terms used also differed between the two studies
- Adverse events included under neurotoxicity differed between investigator reporting and USPI

Neurologic and psychiatric adverse reactions reported with approved CAR T products

Tisagenlecleucel	Axicabtagene ciloleucel
<p>encephalopathy--includes: encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism</p> <p>delirium--includes: delirium, agitation, hallucination, hallucination visual, irritability, restlessness</p> <p>headache--includes headache and migraine</p> <p>anxiety</p> <p>sleep disorder--includes: sleep disorder, insomnia, and nightmare</p>	<p>encephalopathy--includes: encephalopathy, cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor</p> <p>delirium--includes: agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness</p> <p>headache</p> <p>dizziness--includes: dizziness, presyncope, syncope</p> <p>aphasia: includes aphasia, dysphasia</p> <p>motor dysfunction</p> <p>motor dysfunction--includes: muscle spasms, muscular weakness</p> <p>tremor</p> <p>ataxia</p> <p>seizure</p> <p>dyscalculia</p> <p>myoclonus</p>

CTCAE v4.03 grading of neurotoxicity

Symptom/Sign	Grade 1	Grade 2	Grade 3	Grade 4
Level of consciousness	Mild drowsiness / sleepiness	Moderate somnolence, limiting instrumental ADL	Obtundation or stupor	Life-threatening needing urgent intervention/ mechanical ventilation
Orientation / Confusion	Mild disorientation / confusion	Moderate disorientation, limiting instrumental ADL	Severe disorientation, limiting self-care ADL	Life-threatening needing urgent intervention/ mechanical ventilation
Encephalopathy	Mild limiting of ADL	Limiting instrumental ADL	Limiting self-care ADL	Life-threatening needing urgent intervention/ mechanical ventilation
Speech	Dysphasia not impairing ability to communicate	Dysphasia with moderate impairment in ability to communicate spontaneously	Severe receptive or expressive dysphasia, impairing ability to read, write or communicate	-
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures
Tremors	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	-
Motor weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self-care ADL, disabling	-
Bowel or bladder incontinence	-	-	Intervention indicated; limiting self care ADL	-
Cerebral edema	-	-	-	Life-threatening; urgent intervention indicated

CTCAE v 4.03/5.0 definition of ADLs

- **Instrumental ADL** refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- **Self care ADL** refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Need for better grading system for neurotoxicity

- Objective
- Reproducible
- Easy to use
- Usable by all healthcare providers involved in patient care
- Allow rapid and dynamic assessment
- Practical tool for grade-based management of toxicities

CARTOX Grading

REVIEWS

CONSENSUS
STATEMENT

Adults

Chimeric antigen receptor T-cell therapy — assessment and management of toxicities

Sattva S. Neelapu¹, Sudhakar Tummala², Partow Kebriaei³, William Wierda⁴, Cristina Gutierrez⁵, Frederick L. Locke⁶, Krishna V. Komanduri⁷, Yi Lin⁸, Nitin Jain⁴, Naval Daver⁴, Jason Westin¹, Alison M. Gulbis⁹, Monica E. Loghin², John F. de Groot², Sherry Adkins¹, Suzanne E. Davis¹⁰, Katayoun Rezvani³, Patrick Hwu¹⁰, Elizabeth J. Shpall³

Neelapu et al. *Nat Rev Clin Oncol*, Jan 2018

Children

EXPERT CONSENSUS DOCUMENT

Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy

Kris M. Mahadeo^{1,20}, Sajad J. Khazal¹, Hisham Abdel-Azim², Julie C. Fitzgerald^{5,20}, Agne Taraseviciute⁴, Catherine M. Bollard⁵, Priti Tewari⁶, Christine Duncan^{7,20}, Chani Traube^{8,20}, David McCall¹, Marie E. Steiner^{9,20}, Ira M. Cheifetz^{10,20}, Leslie E. Lehmann^{7,20}, Rodrigo Mejia¹¹, John M. Slopis¹², Rajinder Bajwa^{13,20}, Partow Kebriaei¹⁴, Paul L. Martin^{15,20}, Jerelyn Moffet^{15,20}, Jennifer McArthur^{16,20}, Demetrios Petropoulos¹, Joan O'Hanlon Curry¹, Sarah Featherston¹, Jessica Foglesong¹, Basirat Shoberu¹⁷, Alison Gulbis¹⁸, Maria E. Mireles¹⁸, Lisa Hafemeister¹, Cathy Nguyen¹, Neena Kapoor², Katayoun Rezvani^{14,21}, Sattva S. Neelapu^{19,21} and Elizabeth J. Shpall^{14,21}, the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network*

Mahadeo et al, *Nat Rev Clin Oncol*, Aug 2018



ELSEVIER

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Guideline

ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells



Daniel W. Lee^{1, #}, Bianca D. Santomasso^{2, #}, Frederick L. Locke³, Armin Ghobadi⁴, Cameron J. Turtle⁵, Jennifer N. Brudno⁶, Marcela V. Maus⁷, Jae H. Park⁸, Elena Mead⁹, Steven Pavletic⁶, William Y. Go¹⁰, Lamis Eldjerou¹¹, Rebecca A. Gardner¹², Noelle Frey¹³, Kevin J. Curran¹⁴, Karl Peggs¹⁵, Marcelo Pasquini¹⁶, John F. DiPersio⁴, Marcel R.M. van den Brink⁸, Krishna V. Komanduri¹⁷, Stephan A. Grupp^{18, *}, Sattva S. Neelapu^{19, **}

ASTCT Workshop
June 20-21, 2018
Washington, DC

- **49 participants**
- Broad group of leaders from major academic CAR T centers
- Industry
- ASBMT, CIBMTR, ASH, NCI

ASTCT Definition of CRS

- CRS is “a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset and may include hypotension, capillary leak (hypoxia) and end organ dysfunction.”
- CRS should be applied to any immune effector cell engaging therapy, not just CAR T cells.

ASTCT Consensus Grading of CRS

CRS Parameter*	Grade 1	Grade 2	Grade 3	Grade 4
Fever#†	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
		With		
Hypotension#	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/ or‡		
Hypoxia#	None	Requiring low-flow nasal cannula [^] or blow-by	Requiring high-flow nasal cannula [^] , facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

#Not attributable to any other cause

†In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity

‡CRS grade is determined by the more severe event

[^]Low-flow nasal cannula is ≤ 6 L/min and high-flow nasal cannula is > 6 L/min

*Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

CRS Grading: Specific comments

- Not be attributable to any other cause
- Fever $\geq 38^{\circ}\text{C}$ is required
- After treatment, fever is no longer required and CRS grading is driven by hypotension and/or hypoxia
- CRS grade is determined by the more severe event
- Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading

ASTCT definition of ICANS

(IEC-Associated Neurotoxicity Syndrome)

- ICANS is “a disorder characterized by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema.”
- Similar to CRS, ICANS should be applied to any immune effector cell engaging therapy, not just CAR T cells.

ASTCT Consensus Encephalopathy Assessment Tool

CARTOX Tool	Immune-Effector Cell-Associated Encephalopathy (ICE) Tool
<ul style="list-style-type: none">• Orientation: Orientation to year, month, city, hospital, President: 5 points• Naming: Name 3 objects (e.g., point to clock, pen, button): 3 points • Writing: Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point• Attention: Count backwards from 100 by ten: 1 point	<ul style="list-style-type: none">• Orientation: Orientation to year, month, city, hospital: 4 points• Naming: Name 3 objects (e.g., point to clock, pen, button): 3 points• Following 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., Our national bird is the bald eagle): 1 point• Attention: Count backwards from 100 by ten: 1 point

ASTCT Consensus Grading of ICANS for Adults

(IEC-Associated Neurotoxicity Syndrome)

Neurotoxicity Domain [‡]	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly ; or Non-convulsive 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	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging [#]	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

[‡]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

ICANS Grading: Specific comments

- Not be attributable to any other cause
 - ✓ Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)
- ICANS grade is determined by the more severe event
- Tremors and myoclonus may be graded according to CTCAE v5.0 but they do not influence ICANS grading
- 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.

Encephalopathy Assessment: CAPD Score for Children <12 years (Cornell Assessment of Pediatric Delirium)

Answer the following based on interactions with the child over the course of the shift					
	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0
1. Does the child make eye contact with the caregiver?					
2. Are the child's actions purposeful?					
3. Is the child aware of his/her surroundings?					
4. Does the child communicate needs and wants?					
	Never 0	Rarely 1	Sometimes 2	Often 3	Always 4
5. Is the child restless?					
6. Is the child inconsolable?					
7. Is the child underactive – very little movement while awake?					
8. Does it take the child a long time to respond to interactions?					

Encephalopathy Assessment: CAPD Score for Children Age 1-2 years (Cornell Assessment of Pediatric Delirium)

For patients age 1-2 years, the following serve as guidelines to the corresponding questions:

1. Holds gaze. Prefers primary parent. Looks at speaker.
2. Reaches and manipulates objects, tries to change position, if mobile may try to get up
3. Prefers primary parent, upset when separated from preferred caregivers. Comforted by familiar objects (i.e., blanket or stuffed animal)
4. Uses single words or signs
5. No sustained calm state
6. Not soothed by usual comforting actions, for example, singing, holding, talking, and reading
7. Little if any paly, efforts to sit up, pull up, and if mobile crawl or walk around
8. Not following simple directions. If verbal, not engaging in simple dialogue with words or jargon

ASTCT Consensus Grading of ICANS for Children

(IEC-Associated Neurotoxicity Syndrome)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score for children ≥ 12 years [^]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
CAPD score for children < 12 years	1-8	1-8	≥ 9	Unable to perform CAPD
Depressed level of consciousness \diamond	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 (any age)	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive 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 weakness (any age) \S	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP / Cerebral Edema (any age)			Focal/local edema on neuroimaging $\#$	Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad; or Signs of diffuse cerebral edema on neuroimaging

CTCAE vs. ASTCT grading of ICANS

CTCAE Grading	ASTCT Grading
Multiple AE terms used	Composite grade Five neurotoxicity domains – ICE score, level of consciousness, seizures, motor weakness, signs of raised ICP/cerebral edema
Grade based on subjective terms or assessment of ADLs (instrumental or self-care)	ADLs not taken into account
Grading subjective (mild, moderate, severe)	Grading objective based on ICE score and other objective criteria
Seizures can be grade 1-4	Seizures are either grades 3 or 4
Electrical seizures are not considered	Electrical seizures are considered
Motor weakness can be grades 1-3	Motor weakness is grade 4

Toxicities not addressed by ASTCT Grading

- Prolonged cytopenias
- Hemophagocytic lymphohistiocytosis / Macrophage activation syndrome
- On-target off-tumor effects
 - ✓ B-cell aplasia and hypogammaglobulinemia
- Graft-versus-host disease

Summary: ASTCT Consensus Grading

- Consensus grading for CRS and ICANS
- Objective and easy to use at the bedside (available on ASTCT App)
- Grading could be incorporated and automated in EMRs
- Easily verifiable in chart review
- Goal is to apply across all trials and standard of care setting including reporting to CIBMTR for commercial products

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