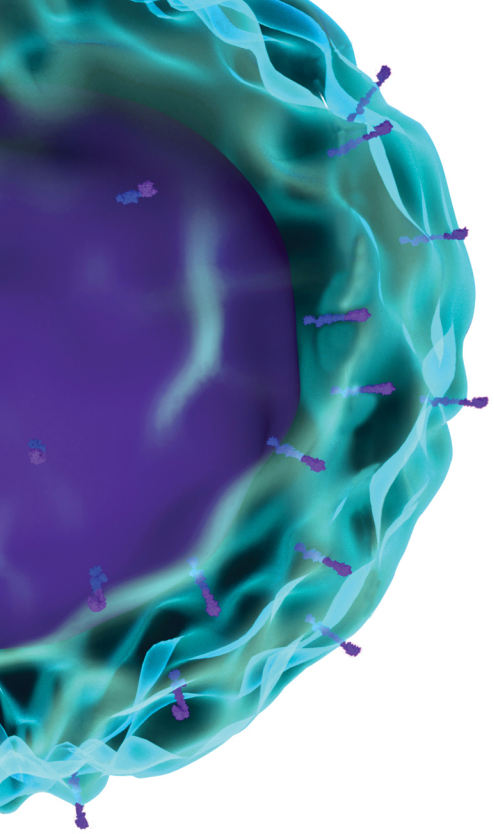


Latest Approaches to
Treating Lymphoma and Myeloma with CAR T-Cell Therapy
Strategies for Integrating Into Practice

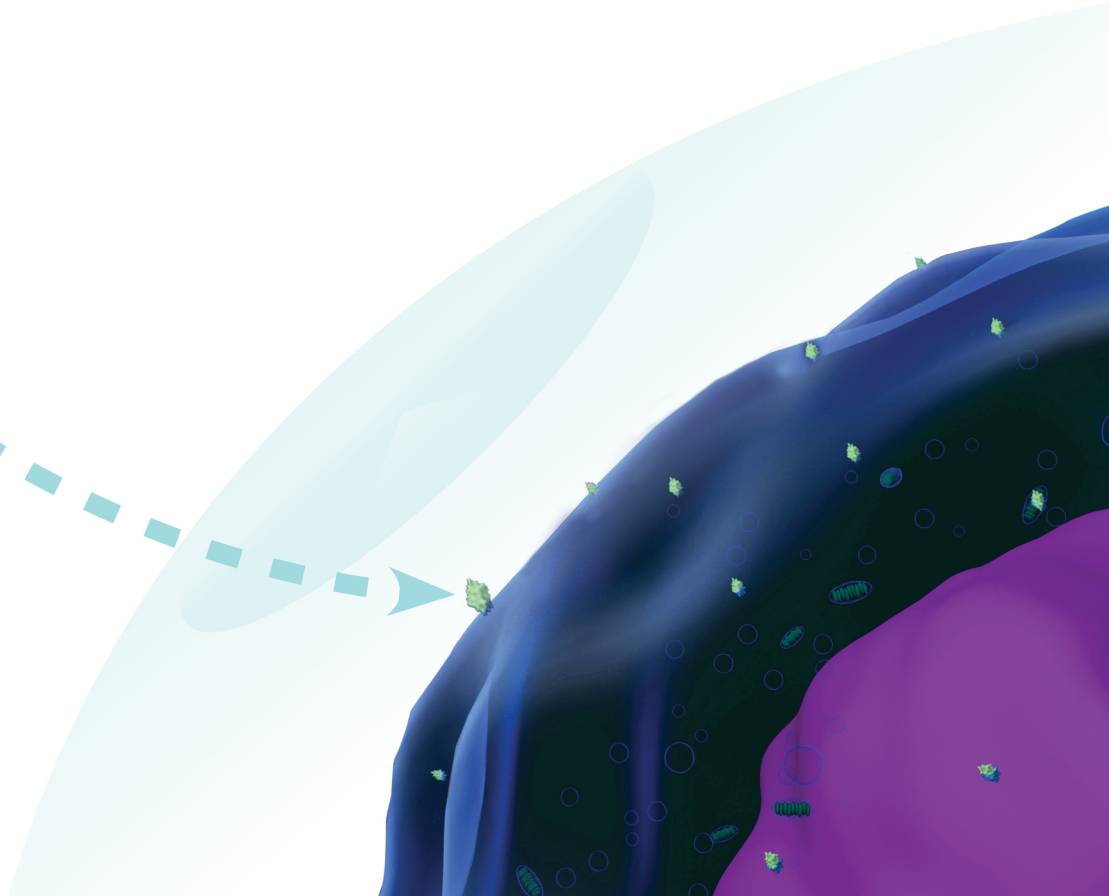
Friday, September 13, 2019

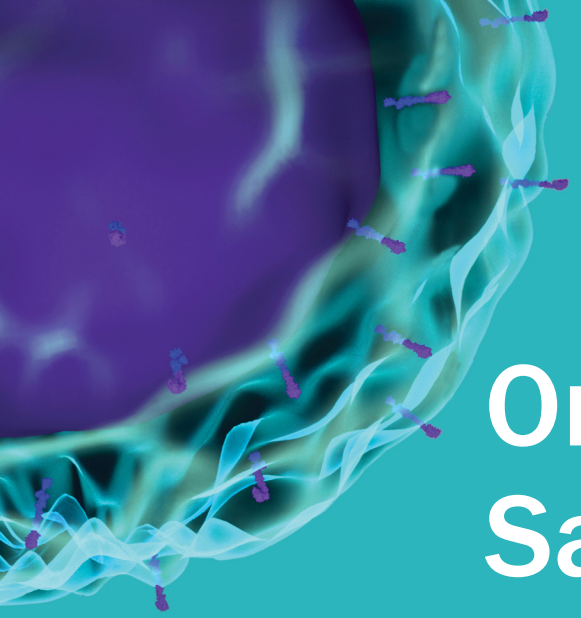
Time: 6:15 AM – 7:45 AM
Grand Ballroom, Level 4, A/B/D/E

This activity is jointly provided by The Postgraduate Institute for Medicine (PIM) and Bio Ascend.

PIM Postgraduate Institute for Medicine

Bio Ascend





Ongoing Efforts to Improve the Safety of CAR T Cell Therapy: Cytokine Release Syndrome and Neurotoxicity

Bianca D. Santomasso MD, PhD

Memorial Sloan Kettering Cancer Center

September 13, 2019

Disclosures

Commercial Interest	Nature of Relationship
Juno Therapeutics/Celgene	Consulting, Advisory Board
Kite Pharma/Gilead	Consulting, Advisory Board
Novartis	Consulting

CAR-T Cell Therapy: Current State of the Art

- ≥ 50% of patients with refractory B cell malignancies show durable complete responses to CD19-CAR T cell therapy
- Promising responses in patients with MM treated with BCMA-CAR T
- Associated with unique and prominent toxicities, boxed warnings on FDA approved products:
  - **Cytokine Release Syndrome**
  - **Neurotoxicity or Immune Cell Associated Neurotoxicity Syndrome** (ICANS)
    - Patients may require ICU management
    - Fatalities have occurred
    - REMS program mandated by FDA for approved products
    - Multi-departmental infrastructure management is critical

Clinical Case

54 year old man with relapsed refractory DLBCL

- Diagnosed with DLBCL of left face/humerus
- DA R-EPOCH x 6 cycles completed 6/2013→PET CR
- Disease relapse 12/2015 s/p DHAX x 3 cycles followed by autologous HSCT
- Recurrence of disease largely in bone

- Fly/Cy conditioning initially delayed due to new PNA treated with antibiotics.
- **Day 1**: Axicabtagene ciloleucel
- **Day 3**: Fevers start, antibiotics started
- **Day 4**: Higher fever 39.5°C and tachycardia to 120s. Received IV fluid bolus for hypotension →increased O2 requirement. Headache. Mild confusion only with fever spikes. Mental status and neurologic exam normal. Grade 2 CRS.
- Tocilizumab administered for Grade 2 CRS →Fever, tachycardia, and hypoxia resolved

Clinical Case

- **Day 6**: Perseverative/stuttering speech, bilateral arm tremor, inattention, slight lethargy with eyes spontaneously closing after several seconds if not stimulated. CRP trending down.

  HCT negative. No seizures on EEG

  Started dexamethasone 10 mg x 1

  Transferred to ICU

- Transient word finding difficulty → nonverbal while awake. Not following commands. Depressed level of consciousness arousable only to persistent tactile stimulus.
- Dexamethasone 20 mg x 1, followed by dexamethasone 10 mg q 6h.
- **Day 7**: More awake, global aphasia and myoclonus. Lumbar puncture: Opening pressure 20 mm Hg, normal cell count, elevated protein
- Hours later mental status markedly improved
- Steroids tapered rapidly over 2 days : 6 mg q 6h, 6 mg q 12h then stopped
- Continued to have mild word finding difficulties and confusion over next 4 days but was ambulatory.
- Returned to neurologic baseline day 12

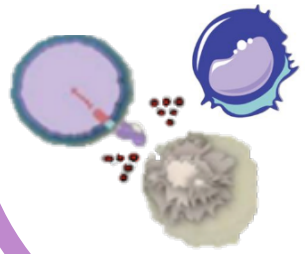
Clinical Case Points

- Tocilizumab +/- corticosteroids can rapidly resolve most cases of CRS
- Neurotoxicity can occur after CRS is completely resolved
- Tocilizumab does not resolve severe neurotoxicity
- Corticosteroids are used for management of severe neurotoxicity although some cases resolve without them
- Other medical issues that may increase risk and/or interfere with assessment and management of CRS and neurotoxicity

CAR-T Toxicities Timeline

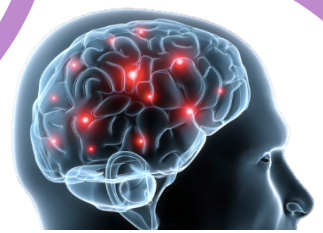
IL6—levels correlate with CRS
IFN-γ
TNF-α
Among others

Cytokine Release Syndrome



Cytokine release

Tumor cell death



Neurological Toxicity

CAR T cell infusion

CRS Typical time to onset: 2-3 days
Neurotoxicity Typical time to onset: 4-10 days

CAR T cell expansion

Days

0 7 14 28

CRS

Neurotoxicity

Adverse Events > Day 30
- **Infections**
- **Cytopenias**
- **B cell aplasia**

Common Toxicities of CAR T cells

Cytokine Release Syndrome

Fever
Hypotension
Capillary leak
Respiratory insufficiency
Coagulopathy/DIC
Hyperferritinemia/MAS
Multi-organ failure

Symptoms rapidly resolve with IL-6R blockade

Neurotoxicity

Global encephalopathy
Aphasia
Tremor
Obtundation
Seizure, seizure-like activity
Hallucinations
(Rapid Onset Cerebral Edema)

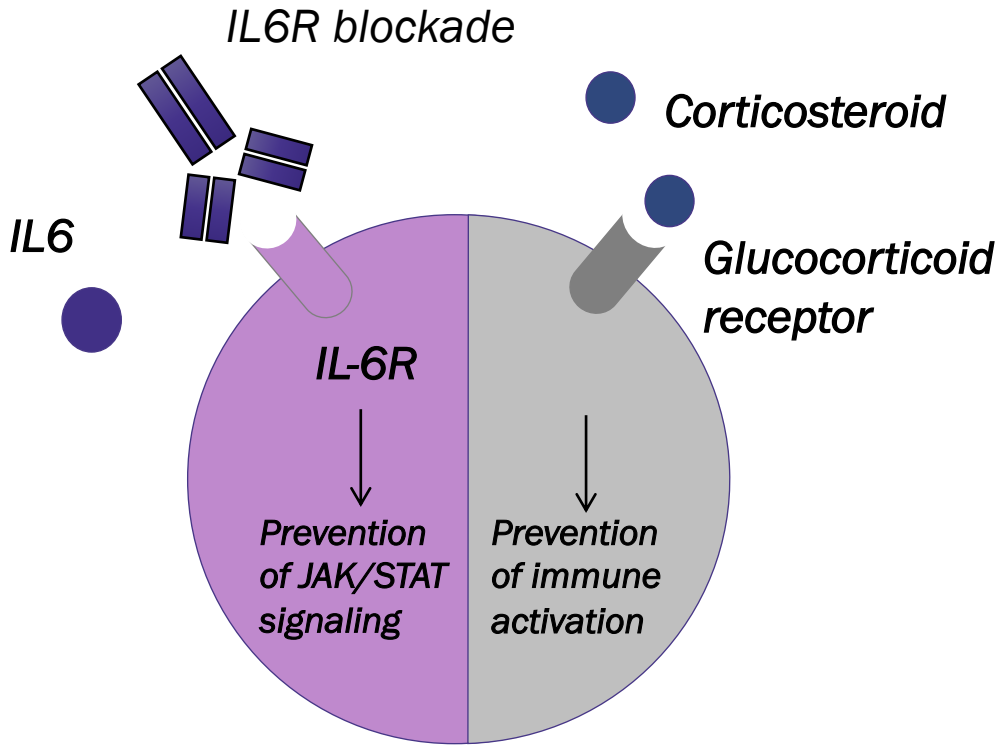
"Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)*"

Severe symptoms do not resolve with IL-6R blockade

*Lee and Santomasso et al. *Biol Blood Marrow Transplant,* Dec 2018

Treatment of CRS

- IL6 Inhibition
  - Tocilizumab (IL6R blockade): Approved for management of CAR T induced CRS in the US and EU
- Corticosteroids
  - Suppress inflammatory immune responses
  - Dexamethasone 10 mg q 6h or methylprednisolone 1 mg/kg q 12h followed by rapid taper



Adapted from:

Maude SL et al. Cancer J **2014** (2): 119-122; Bonifat CL et al. *Oncolytics* 2016

CRS and ICANS in CD19 CAR T cell Trials

CAR Product		N	Gr ≥3 CRS	Gr ≥3 ICANS	Fatal cerebral edema or Gr5 ICANS?
19-28z (MSKCC Phase 1) [1]	Adult B-ALL	53	26%	42%	No
19-41BBz (CTL019-Upenn/CHOP) Peds B-ALL)[2]	Peds B-ALL	75	48%	15%	Yes*
19-41BBz (JCAR017-FHRC)[3]		133	12%	21%	Yes
B-ALL	B-ALL	47		30%	–
NHL	NHL	62		13%	–
CLL	CLL	24		25%	–
19-28z ZUMA-1 Kite Adult NHL[4]	Adult NHL	111	13%	28%	No
SMS cohort 3	Adult NHL	38	3%	41%	Yes
19-28z JCAR15 ROCKET Juno[6]	Adult B-ALL	38	21%	52%	Yes
19-41BB JULIET Novartis[7]	Adult NHL	111	22%	12%	No
19-41BB JCAR17 TRANSCEND Juno[8]	Adult NHL	114	1%	13%	No

Commercial CAR Product	CRS All Gr	Gr≥3 CRS	NTX All Gr	Gr ≥3 NTX
Axicabtagene ciloleucel (Adults)	93%	23%	87%	31%
Tisagenlecleucel (Pediatrics/Young Adults)	77%	22%	58%	18%

[1]Park J, at al. *N Engl J Med*. 2018;378:449-459; [2]Maude SL, et al. *N Engl J Med*. 2018;378:439-448; [3]Turtle C et al. *ASCO Annual Meeting 2017*; [4]Neelapu et al. *N Engl J Med* 2017 **377**(26): 2531-2544; Locke et al. *ASCO 2018;* [6]D'Angelo et al. *SITC Annual Meeting 2017;* [7]Shuster et al. *N Engl J Med* 2019;380:45-56*;* [8]Abramson, et al. ASCO 2018 (abstr 7505) * *Intracerebral hemorrhage*

Anti-BCMA CAR T-Cell Trials

Company/Group	Special Sauce	N	Safety	Response	PFS
bb2121		33	76% CRS (6% G3); 42% neurotoxicity (1pt (3%) G4)	85% ORR	11.8 mo
LEGEND2		57	90% CRS (7% ≥ G3); neurotoxicity 1pt G1	88% ORR	15 mo
Bluebird BB21217	PIK inhibitor co-culture	12	67% CRS (8% G3), 25% neurotox (8% G4)	83% ORR, 25% CR, 4/4 responders MRD neg	NA
JCARH125	Preselecting CD4/ CD8 ratio	44	9% CRS wirh 1 G4, 7% neurotox	82% ORR, 27% CR	NA
Fred Hutch FCARH143	1:1 ratio of CD4+:CD8+ cells	11, incl 8/11 HR, 5/11 with prior allo	10/12 CRS, 0 G3	100% ORR, 4/11 CR	NA
MCARH171		11	55% CRS, no G3, 9% 23 neurotox	64% ORR	NA
LCAR-B38M	Bi-epitope targeting of BCMA, also CD38 targeting	57	90 % CRS (7% G4), 1% neurotox	88% ORR, 74% CR, 68% MRD neg	15 mo (24 for MRD-)
Jiangsu Institute of Hematology, Shanghai Unicar	Tandem CD19 and BCMA CAR infusion	10	100% CRS (0 G3), 0 neurotox	100% ORR, 70% CR, 60% MRD-	NA
Poseida P-BCMA-101	Centyrin (less immunogenic), higher TSCM proportion	23 (15)	10% CRS (0 G3), 5% neurotox (G3)	63% ORR, (100% at highest dose)	NA
Wenzhou Medical University, Wenzhou, China/ CARsgen CT053		14	38% CRS, (7% G3)	100% ORR, 36% CR	NA
HRAIN Biotechnology, Shanghai, China		20	45% CRS, (5% G3), 0 neurotox (?1 G1 seizure)	85% ORR, 45%	15 mo

Slide c

Factors Associated With Toxicity After CAR T-Cell Therapy

Host/Tumor Factors

- Type of malignancy (ALL > DLBCL>MM)
- Tumor burden
- Baseline inflammatory state
- Thrombocytopenia before lymphodepletion (ALL)

Therapy-Related Factors

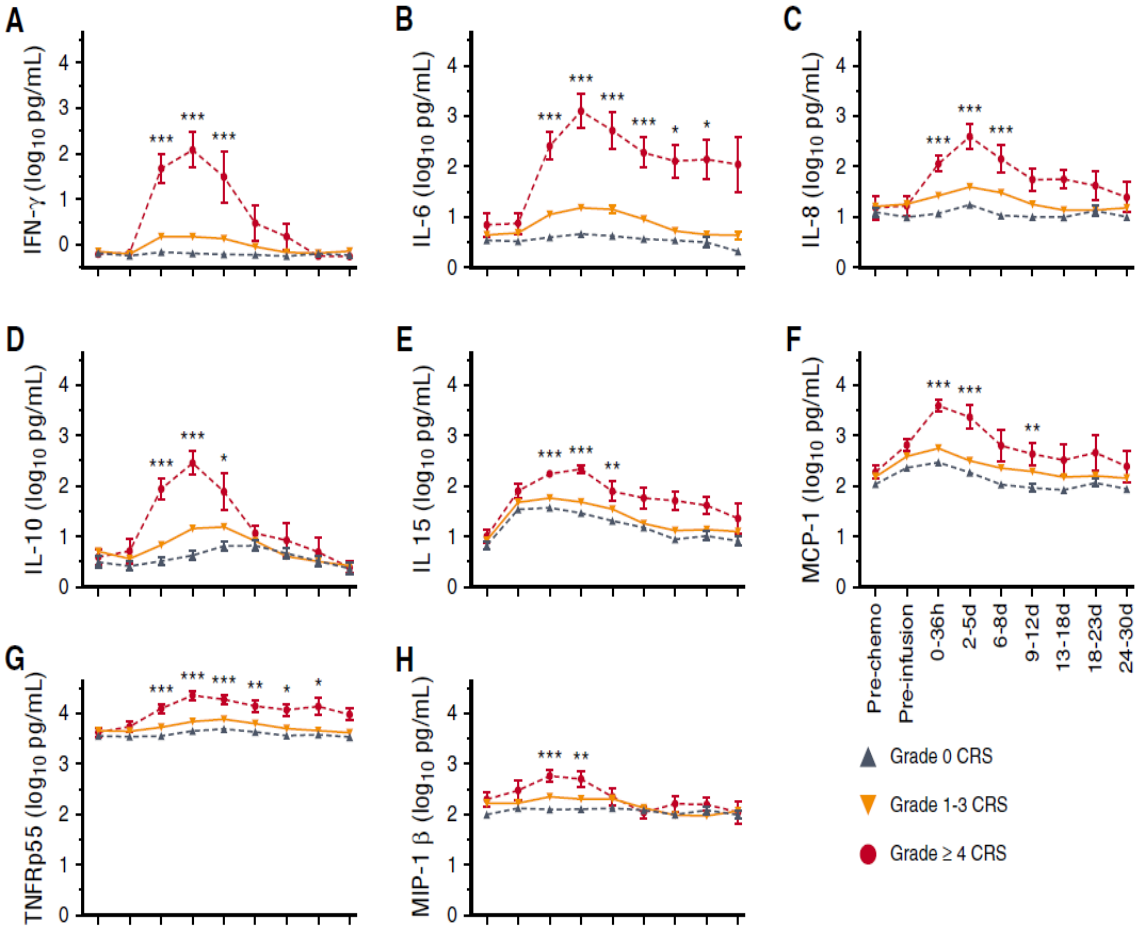
- Lymphodepleting/conditioning therapy
- CAR T-cell dose
- Peak blood CAR T-cell levels
- CAR T-cell design (CD28 > 4-1BB)
- Early and peak levels of certain cytokines
- Endothelial activation
- Prior severe CRS → increased risk of severe ICANs

Maude SL, et al. *N Engl J Med.* 2014; Davila ML, et al. *Sci Transl Med.* 2014; Lee DW, et al. *Lancet.* 2015; Teachey DT, et al. *Cancer Discov.* 2016; Turtle CJ, et al. *J Clin Invest.* 2016; Turtle CJ, et al. *Sci Transl Med.* 2016; Gust J, et al. *Cancer Discov.* 2017;
Hay KA, et al. *Blood.* 2017; Neelapu SS, et al. *N Engl J Med.* 2017; Maude SL, et al. *N Eng J Med.* 2018; Park JH, et al. *N Engl J Med.* 2018; Santomasso BD, et al. *Cancer Discov.* 2018.

Kinetics and biomarkers of severe toxicity: Cytokine Levels and CAR expansion

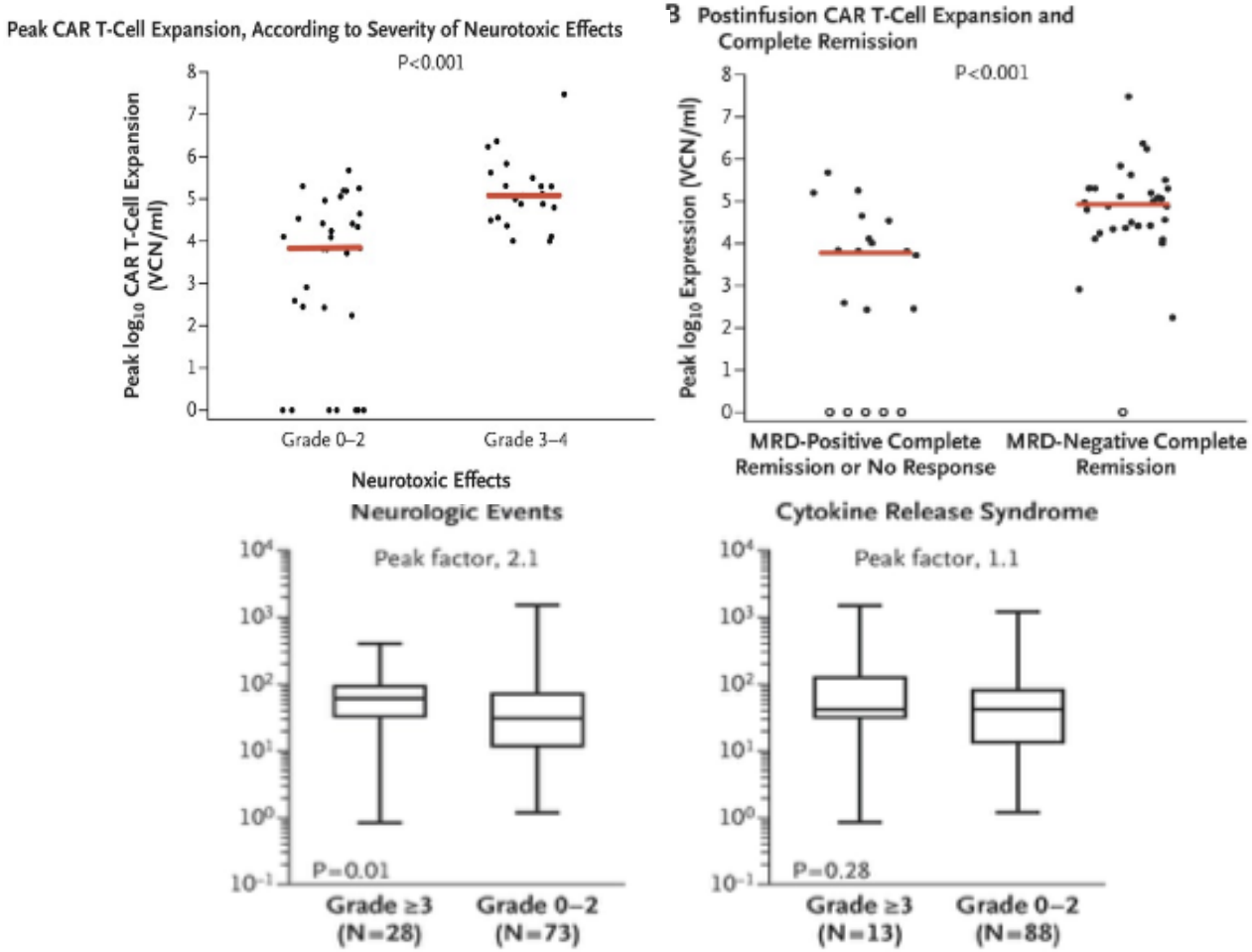
CRS

Multiple cytokines elevations are associated with severe CRS



ICANS

CAR T cell expansion is associated with ORR and severe neurotoxicity, but not severe CRS

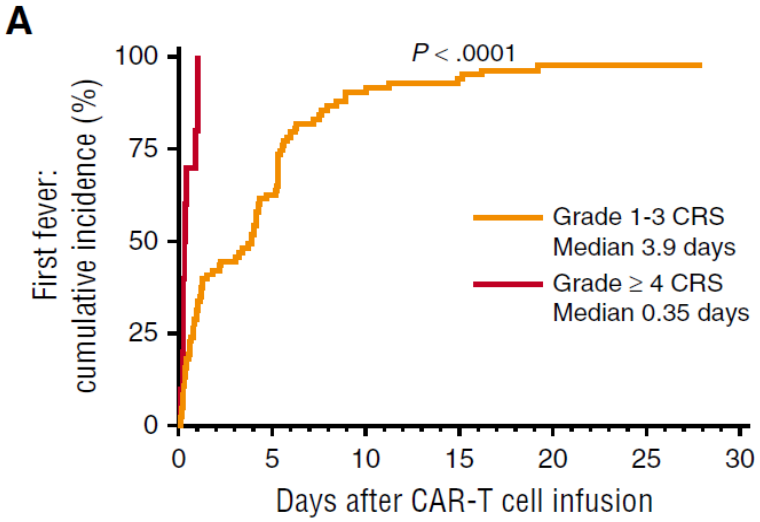


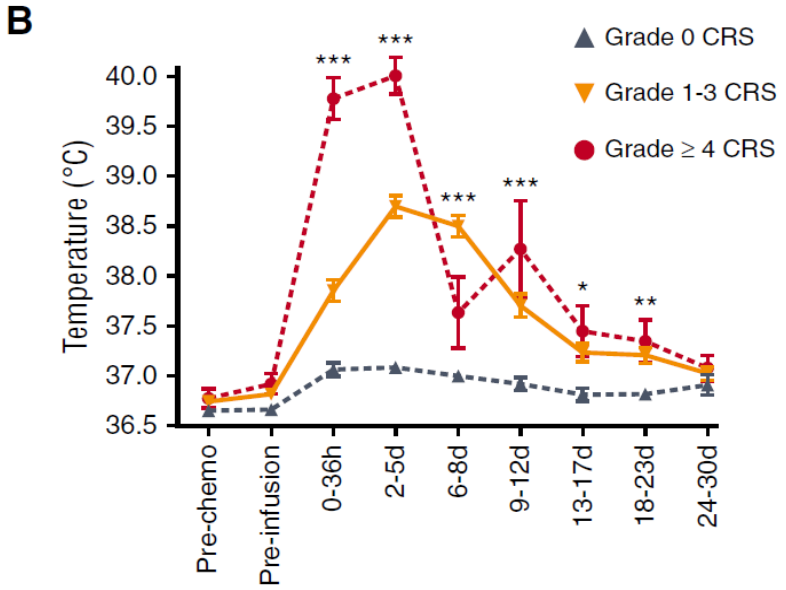
Hay KA, et al. *Blood.* 2017**, 130:2295;** Park JH, et al. *N Engl J Med.* 2018; 378: 449; Neelapu SS, et al. NEJM 2017; 377:2531

Earlier fever onset with higher temperature and longer duration is associated with severe CRS and ICANS

CRS

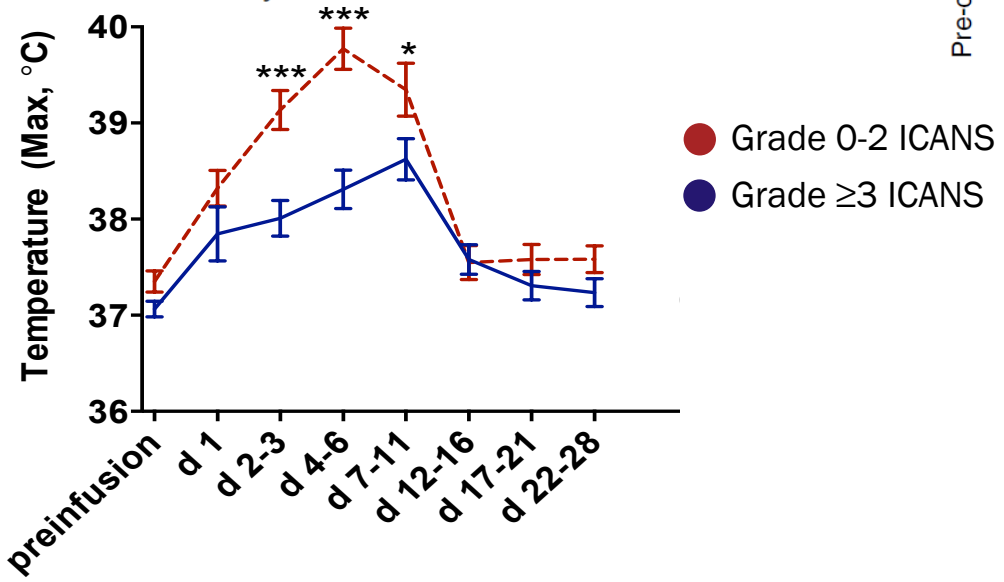
Hay et al., Blood 2017



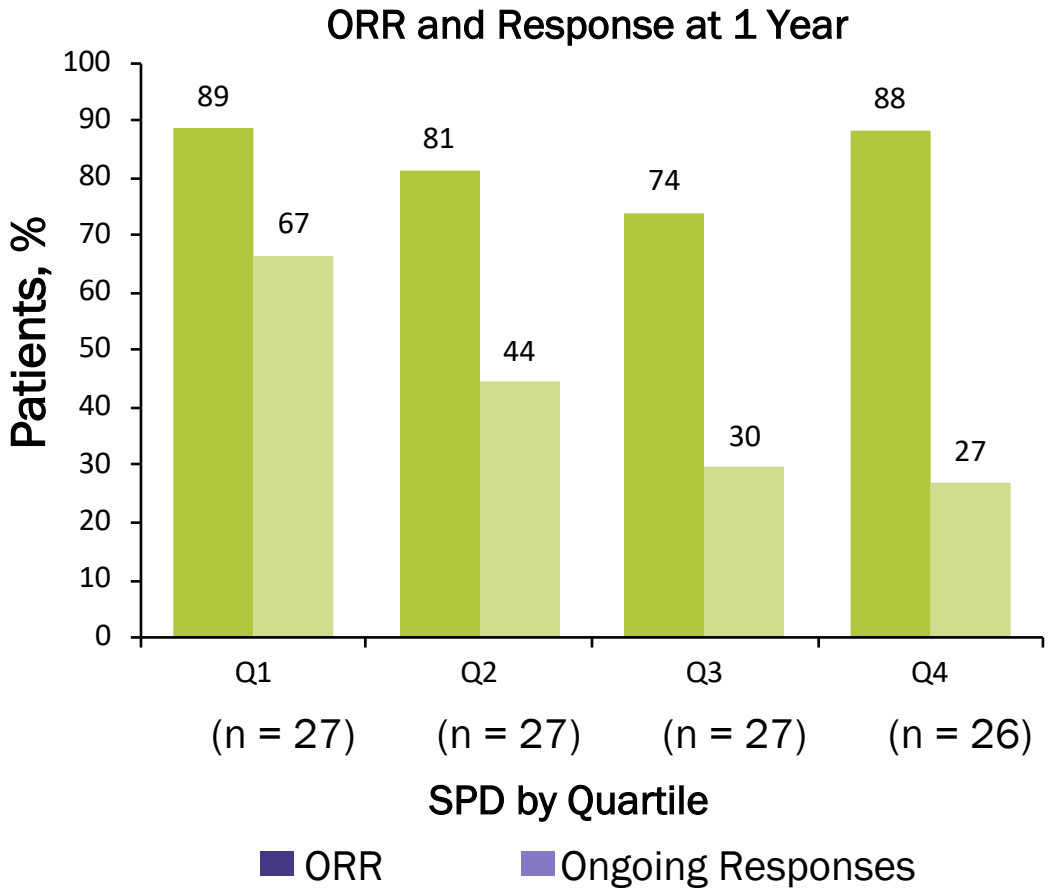


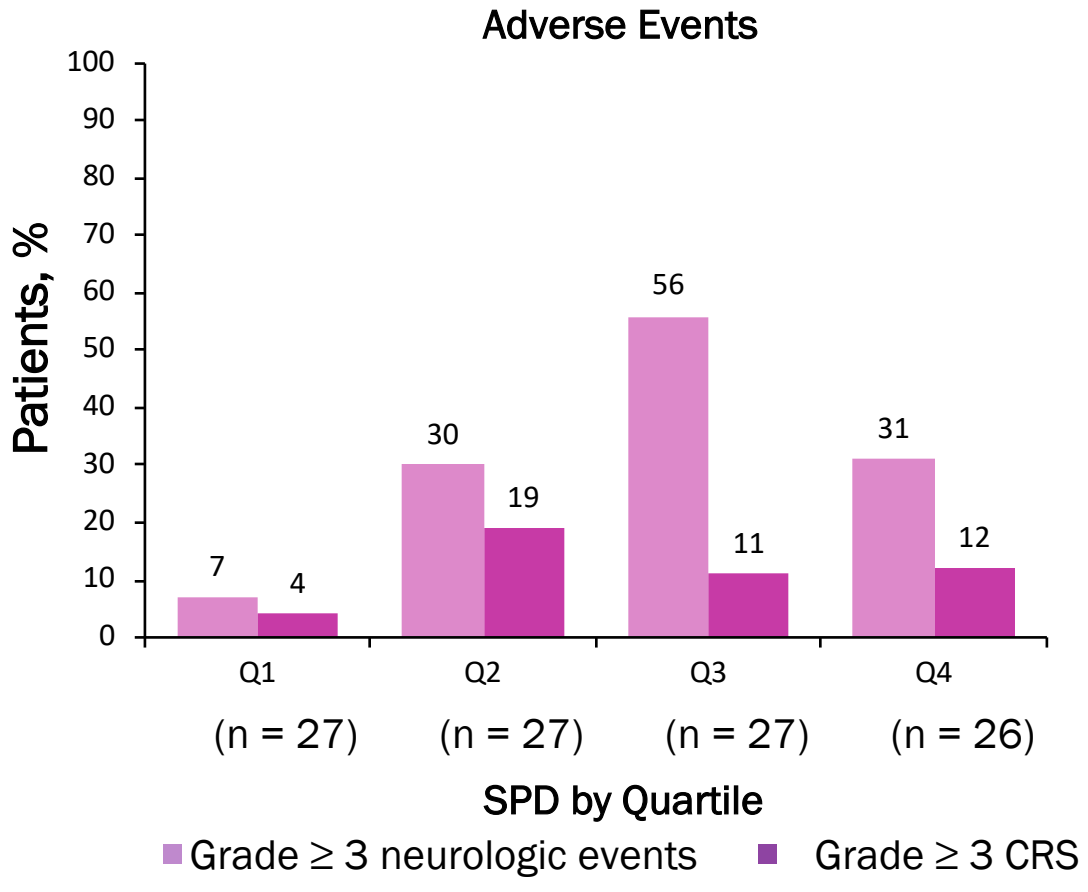
ICANS

Santomasso et al.
Cancer Discovery 2018



ZUMA-1 Predictors: Baseline Tumor Burden
Efficacy and Safety



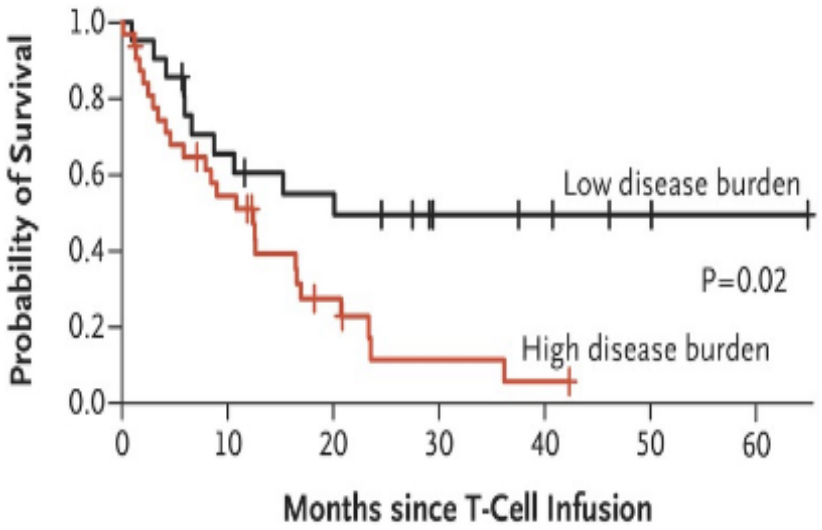


CRS, cytokine release syndrome; Q, quartile; SPD, sum of product diameters.

Locke FL, et al. *J Clin Oncol*. 2018;36(suppl, abstr):3039.

MSK Phase 1 19-28z CAR for R/R B-ALL
Efficacy and Safety

B Overall Survival, According to Disease Burden *



No. at Risk							
Low burden	21	13	10	5	4	2	1
High burden	32	16	6	2	1	0	0

A Subgroup Analysis of Severe Cytokine Release Syndrome

Subgroup	Severe Cytokine Release Syndrome (95% CI)	P Value
Overall	26	
Disease burden		0.004
Low	5 (17 to 55)	
High	41	

B Subgroup Analysis of Severe Neurotoxic Effects

Subgroup	Severe Neurotoxic Effects (95% CI)	P Value
Overall	42	
Disease burden		0.002
Low	14 (22 to 68)	
High	59	

*Disease burden determined bone marrow biopsy prior to lymphodepletion and CAR; Low disease ≤ 5% bone marrow blasts

Park JH, et al. *N Engl J Med.* 2018 **378**(5): 449-459

Need for Harmonization of CRS & Neurotoxicity Grading

- Variation in grading and assessment of CAR T toxicities across clinical trials and different institutions: Leads to difficulties in safety comparisons of different products
  - Hinders the ability to develop optimal strategies for management
  - Examples of different grading systems used: CTCAE, Lee criteria, UPenn criteria, MSKCC grading, CARTOX

- Goals:
  - New definitions that are objective, easy to use, reproducible, and accurate for immune effector cell (IEC) therapy
  - Easy to use by all healthcare providers involved in patient care
  - Allow rapid and dynamic assessment
  - Building block for developing management strategies
  - To be used for CAR T cells and all other IEC across clinical trials and after approval in the clinical setting

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

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. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

ASTCT Workshop
June 20-21, 2018
Washington, DC

ASTCT: American Society for Transplantation and Cellular Therapy

ASTCT Consensus Grading for Cytokine Release Syndrome Associated With Immune Effector Cells

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a 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, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

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

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

ASTCT: American Society for Transplantation and Cellular Therapy

Lee DW and Santomasso BD, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Neurologic and psychiatric adverse reactions reported with FDA-approved CAR T products

Tisagenlecleucel

Headache: incl. migraine

Encephalopathy: incl. cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, lethargy, mental status changes, somnolence, and automatism

Delirium: incl. agitation, hallucination, hallucination visual, irritability, restlessness

Anxiety

Sleep disorder: incl. insomnia, and nightmare

Axicabtagene ciloleucel

Encephalopathy: incl. cognitive disorder, confusional state, depressed level of consciousness, disturbance in attention, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor

Headache

Tremor

Dizziness: incl. dizziness, presyncope, syncope

Aphasia: incl. aphasia, dysphasia

Delirium: incl. agitation, delirium, delusion, disorientation, hallucination, hyperactivity, irritability, restlessness

Motor dysfunction: incl. muscle spasms, Muscular weakness

Ataxia

Seizure

Dyscalculia

Myoclonus

CTCAE v4.03 Grading of Neurotoxicity terms
Many terms and grading subjective and relying on ADL

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

ASTCT Consensus Encephalopathy Assessment Tool

Immune-Effector Cell-Associated Encephalopathy (ICE) Tool
• **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 Score 10: No impairment

First symptoms: verbal perseveration, expressive aphasia, especially difficulty naming, stuttering speech, headache

Expressive aphasia is the most characteristic feature of sNTX 21/22 patients
First severe symptom in 19/22 patients

Santomasso et al.
Cancer Discovery 2018

Encephalopathy assessment for children <12 is performed using CAPD Pediatric delirium scale

Lee et al. *Biol Blood Marrow Transplant,* Dec 2018

ASTCT Consensus Grading for Neurologic Toxicity Associated With Immune Effector Cells

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. 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‡	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§	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; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

* 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.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies 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.

Lee DW and Santomasso BD, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Early toxicity grading systems vs. ASTCT grading

CTCAE Grading	CARTOX [1]	ASTCT Grading[2]
Multiple AE terms used	CARTOX 10 (ASTCT ICE score builds on this)	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)	Relies on LP opening pressure and papilledema for grading. May be unreliable	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

[1]Neelapu SS et al. *Nat Rev Clin Oncol* 2018 **15**(1): 47-62; Lee DW and Santomasso BD et al. *Biol Blood Marrow Transplant* 2018

Management of CRS—NCCN Guidelines
NCCN: National Comprehensive Cancer Network

CRS Grade	Anti-IL-6 Therapy	Corticosteroids[h,i]	Additional Supportive Care
Grade 1 Fever (≥ 38°C)	For prolonged CRS (>3 days) in patients with significant symptoms and/or comorbidities, consider tocilizumab as per Grade 2	N/A	• Empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic • Maintenance IV fluids for hydration • Symptomatic management of organ toxicities
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[f] requiring low-flow nasal cannula[g] or blow-by	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose)[h]. Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Dexamethasone 10 mg IV every 6 hours (or equivalent)[j]	• IV fluid bolus as needed • For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to intensive care unit (ICU), consider echocardiogram, and initiate other methods of hemodynamic monitoring • Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy • Symptomatic management of organ toxicities
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula[g], face mask, nonrebreather mask, or Venturi mask.	Anti-IL-6 therapy as per Grade 2[h] if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours (or equivalent)[j]. If refractory, manage as grade 4	• Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors as needed. • Symptomatic management of organ toxicities
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation).	Anti-IL-6 therapy as per Grade 2[h] if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours (or equivalent)[j]. If refractory, consider methylprednisolone 1000 mg/day IV[k]	• ICU care and hemodynamic monitoring • Mechanical ventilation as needed • IV fluid bolus and vasopressors as needed • Symptomatic management of organ toxicities

Management of ICANS—NCCN Guidelines

- Baseline exam, CAR “team” follows, neurologic assessment to include ICE and motor exam q shift
- MRI brain (or brain CT if MRI not feasible) for ≥ grade 2 ICANS
- Neurologic consultation at first sign of ICANS
- EEG for ≥ grade 2 ICANS to evaluate for seizures
- Consider LP for ≥ grade 2 ICANS
- Aspiration precautions, IV medications
- Caution when prescribing medications that can cause central nervous system (CNS) depression (aside from those needed for seizure prophylaxis/treatment)

Treatment by Grade	No Concurrent CRS
Grade 1	• Supportive care
Grade 2	• Supportive care • Dexamethasone 10 mg IV x 1. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 h if symptoms worsen.
Grade 3	• ICU care is recommended. • Dexamethasone 10 mg IV every 6 h or methylprednisolone, 1 mg/kg IV every 12 h[i] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.
Grade 4	• ICU care, consider mechanical ventilation for airway protection. • High-dose corticosteroids[i,k] • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

Management of CRS and ICANS

- Baseline exam, CAR “team” follows, encephalopathy (ICE) screening q shift
- General Principal: Tocilizumab for CRS, corticosteroids for ICANS
- Cytokine Intervention trials: IL1RA (Anakinra), direct IL6 blockade (Siltuximab), GM-CSF neutralization
- Prophylactic anti-seizure medication for CAR T known to be associated with associated with ICANS
- Try to avoid medications with toxic central effects in the setting of blood-CSF barrier dysfunction

Conclusions

- CAR T therapy is associated with unique acute toxicities that require vigilant monitoring, aggressive supportive care, and specialized management.
- Know your product and patient.
- New consensus guidelines for grading will facilitate the safe administration of CAR T cells by providing a framework for developing best management strategies including prophylactic/early intervention.
- CRS and ICANS can be ameliorated by prompt and correct use of anti-IL6 and steroid therapy and supportive care
- Further refinements on management should be guided by insights into the pathophysiology of these toxicities.