



ADVANCED PRACTICE PROVIDER

Let's Take a BiTE Out of CRS and Neurotoxicity

October 18

Bejai Kkrant, MSN, FNP-BC, WHNP-BC

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Start Time

04:00

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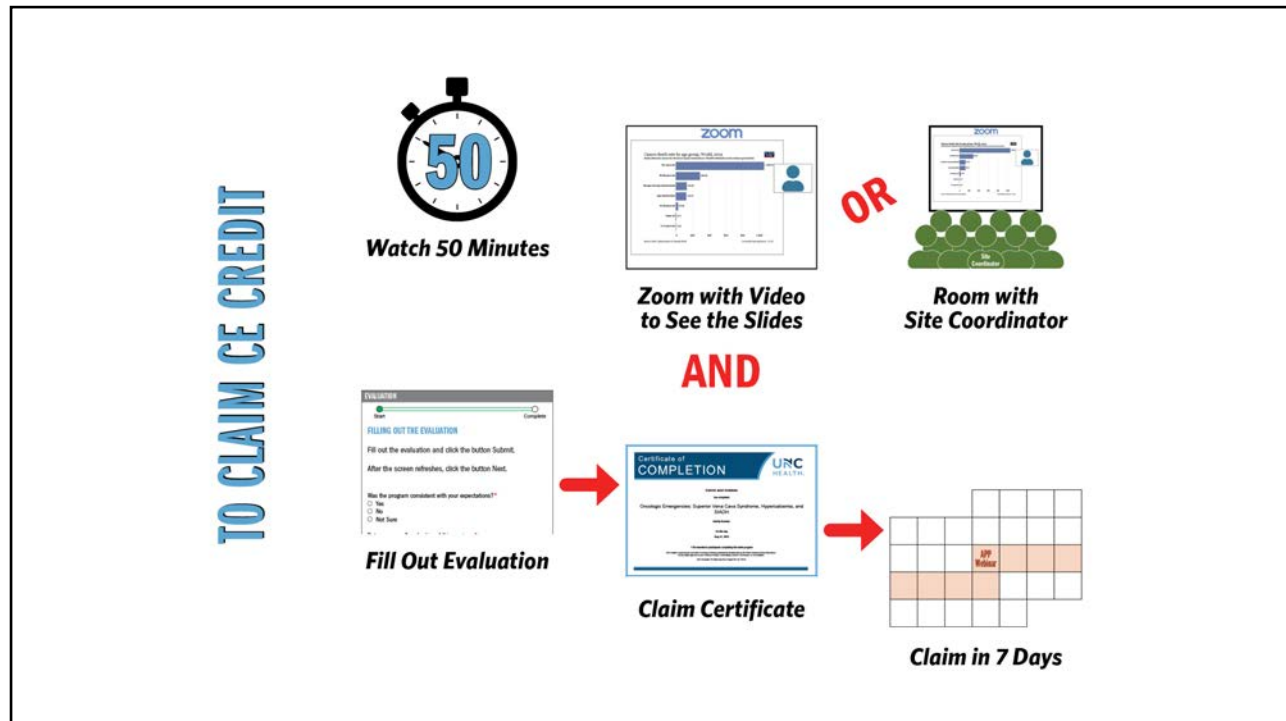
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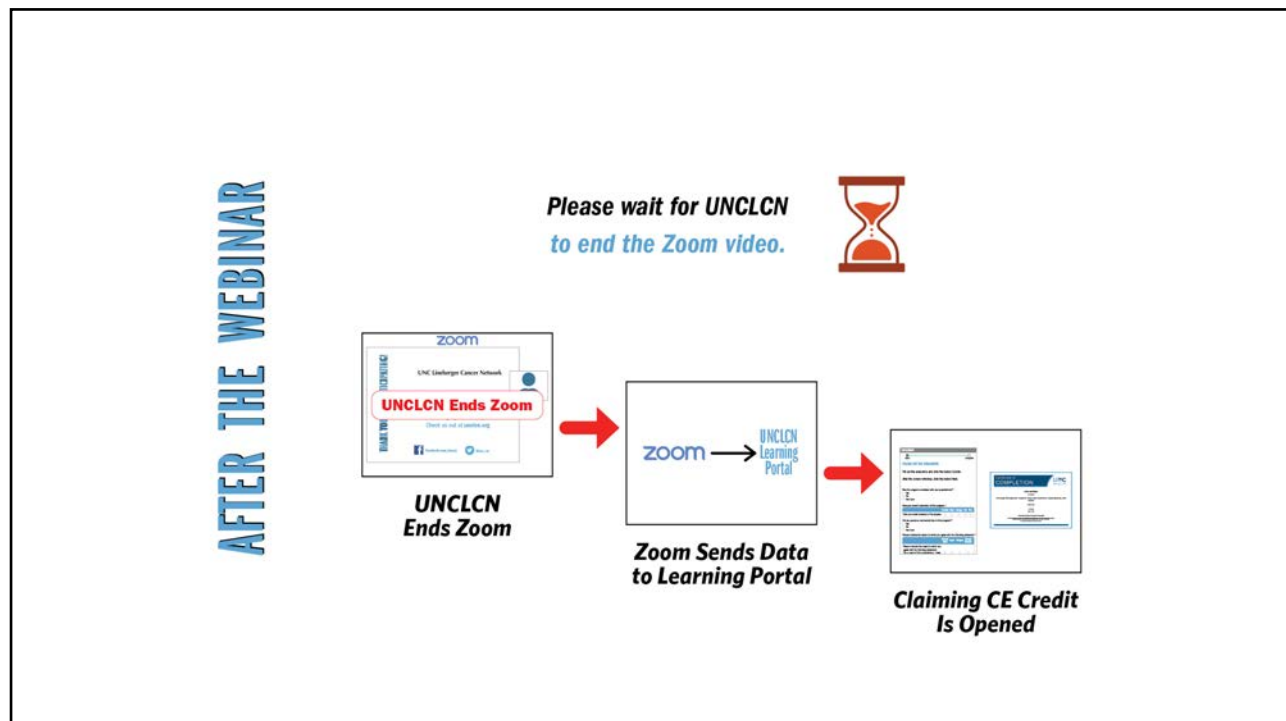


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UNC Lineberger Cancer Network

ADVANCED PRACTICE PROVIDER

Live Webinar

Bejal Kikani, MSN, FNP-BC, WHNP-BC

Let's Take a BiTE Out of CRS and Neurotoxicity

October 18

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OUR PRESENTER



Bejal Kikani,
MSN, FNP-BC, WHNP-BC

Bejal Kikani, MSN, FNP-BC, WHNP-BC, went to ECU for her undergraduate studies and UNC for graduate school.

She has worked at UNC for over 15 years and has been with malignant inpatient hematology for 4 years.

Bejal has developed a true passion for the care of patients with blood cancers and enjoys being able to tie in her interest in infectious diseases.

She is active in helping to roll out inpatient clinical trials and enjoys being a resource for CRS/ICANS management tips.

She is also involved in DEI projects and enjoys teaching.

OUR PRESENTER

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OUR PRESENTER

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4. She has worked at UNC for over 15 years and has been with malignant inpatient hematology for 4 years.
3. She is active in helping to roll out inpatient clinical trials and enjoys being a resource for CRS/ICANS management tips.
2. She is also involved in DEI projects and enjoys teaching.
1. Has three feisty and rambunctious kids: 6-year-old (Avi) and 3-year-old twins (Veda and Meera)

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Q1

Cytokine Release Syndrome (CRS) does not involve the possibility of multiple organ dysfunction that is most often caused by immunotherapy.

(A) True

0%

(B) False

0%

Instructions

Responses

More

Clear responses

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ACCME DISCLOSURE

This activity has been planned and implemented under the sole supervision of the Course Director, William A. Wood, MD, MPH, in association with the UNC Office of Continuing Professional Development (CPD). The course director and CPD staff have no relevant financial relationships with ineligible companies as defined by the ACCME.

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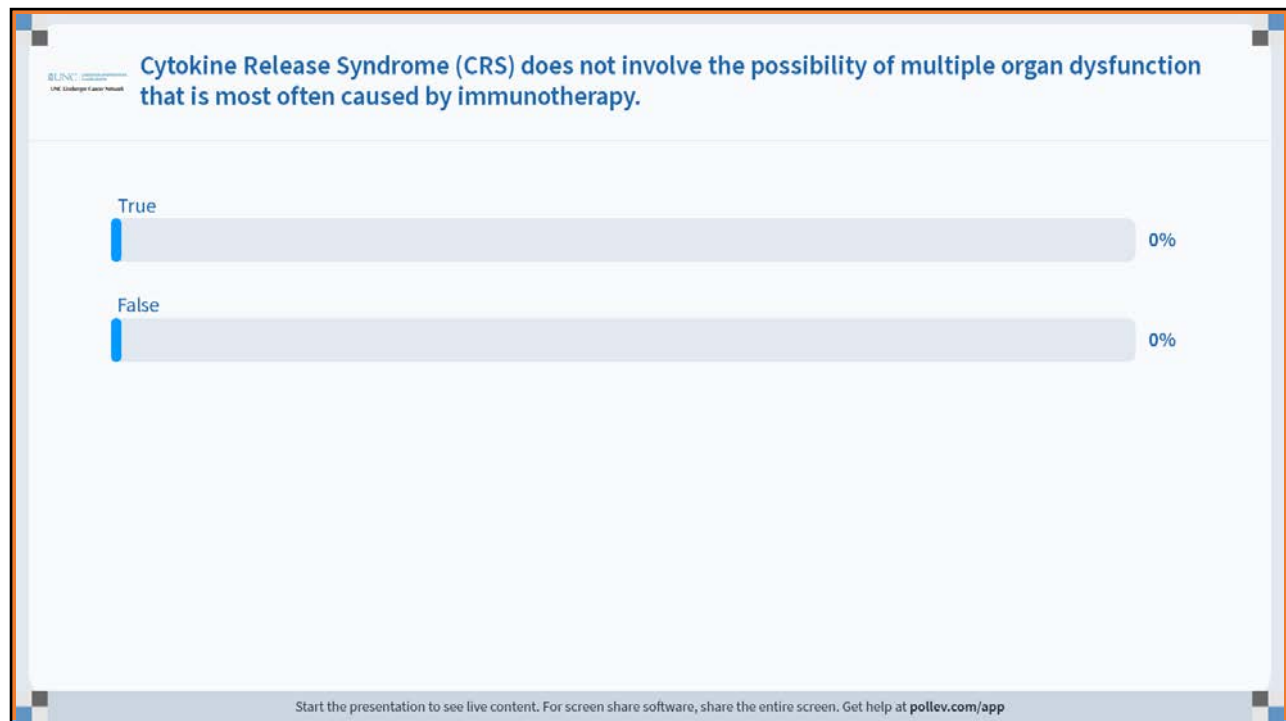
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Let's take a BiTE out of CRS and Neurotoxicity

Bejal Kikani, MSN, FNP-BC, WHNP-BC
Inpatient Malignant Hematology
October 18, 2023



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Disclosures

Co-Investigator. No direct compensation

Janssen

Gilead

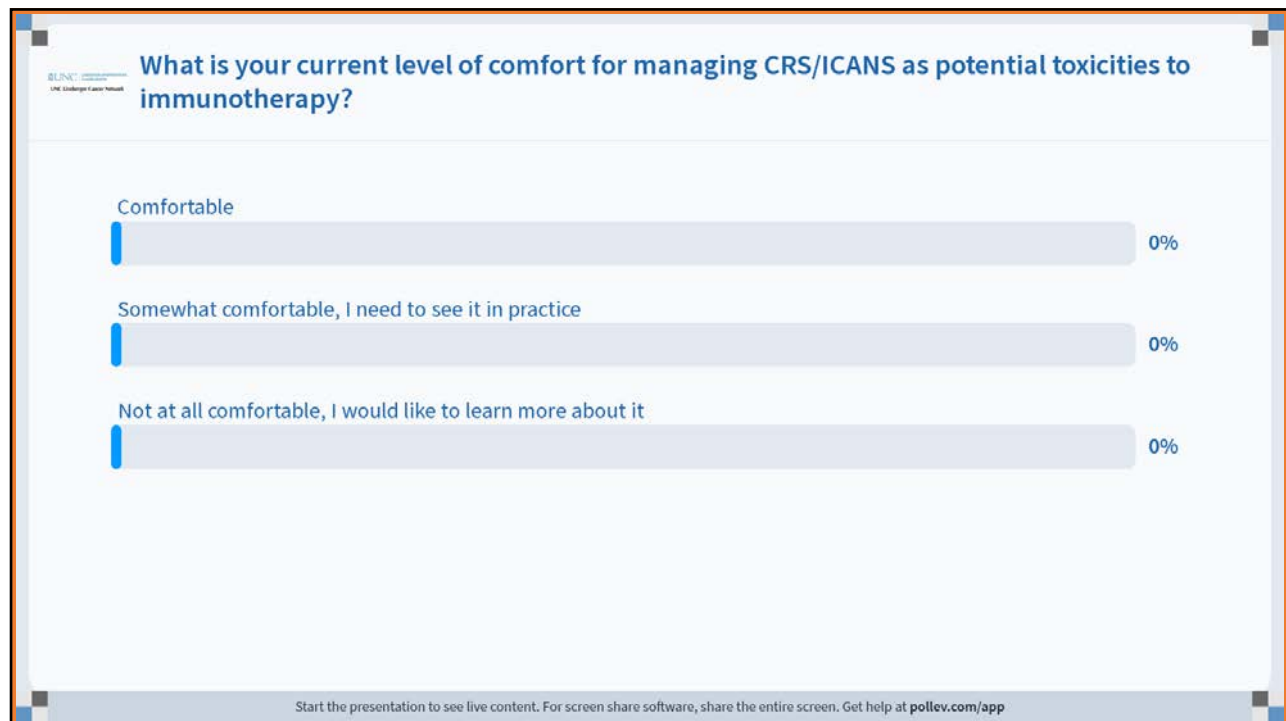
Regeneron

Amgen



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Learning objectives

- Examine the pathophysiology of cytokine release syndrome (CRS) and neurotoxicity caused by T-cell engaging therapies
- Discuss the signs of CRS and neurotoxicity as toxicities of T-cell engaging therapies
- Identify the grade of CRS and neurotoxicity
- Discuss treatment recommendations for CRS and neurotoxicity based on the associated grading



Relevance to practice

Immunotherapy as cancer-directed therapy has evolved, particularly in the field of T cell-engaging therapies

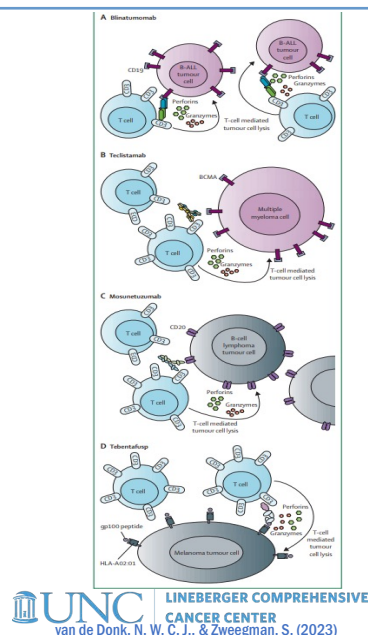
Toxicities: Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Role of the APP



On the market

Drug	Disease	Pharmacological Category
Blinatumomab	ALL	Anti-CD19/CD3
Teclistamab	MM	Anti-BCMA/AntiCD3
Talquetamab	MM	Anti-GPRC5D/AntiCD3
Mosunetuzumab	FL	Anti-CD20/CD3
CAR-T	ALL, MM, Lymphoma	Anti-BCMA/Anti-CD19
Tebentafusp	Uveal melanoma	Anti-CD3



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CRS PATHOPHYSIOLOGY

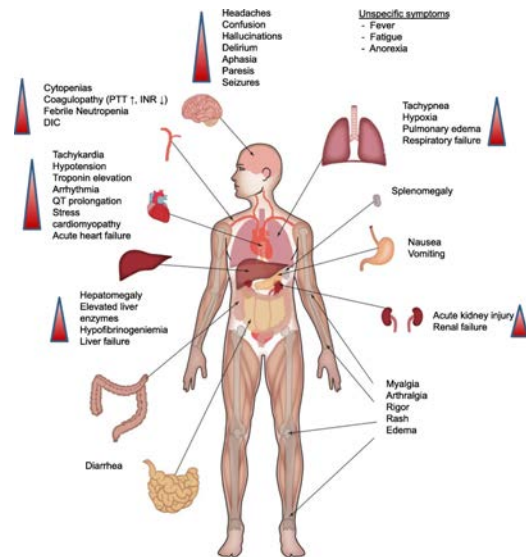
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Cytokine Release Syndrome

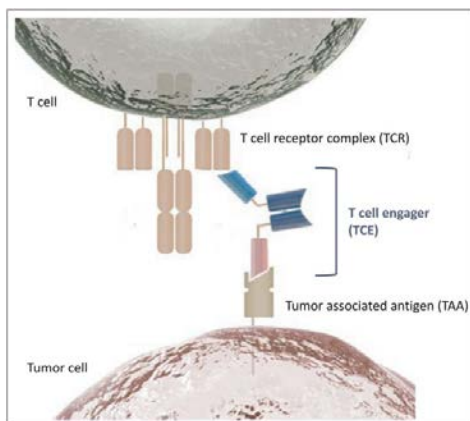
Cytokine Release Syndrome (CRS) is an acute systemic inflammatory syndrome characterized by **fever** and multiple organ dysfunction that is most often caused by immunotherapy.



Shimabukuro-Vornhagen, et al. 2018 *J. Immunotherapy Cancer*
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Mechanism of action



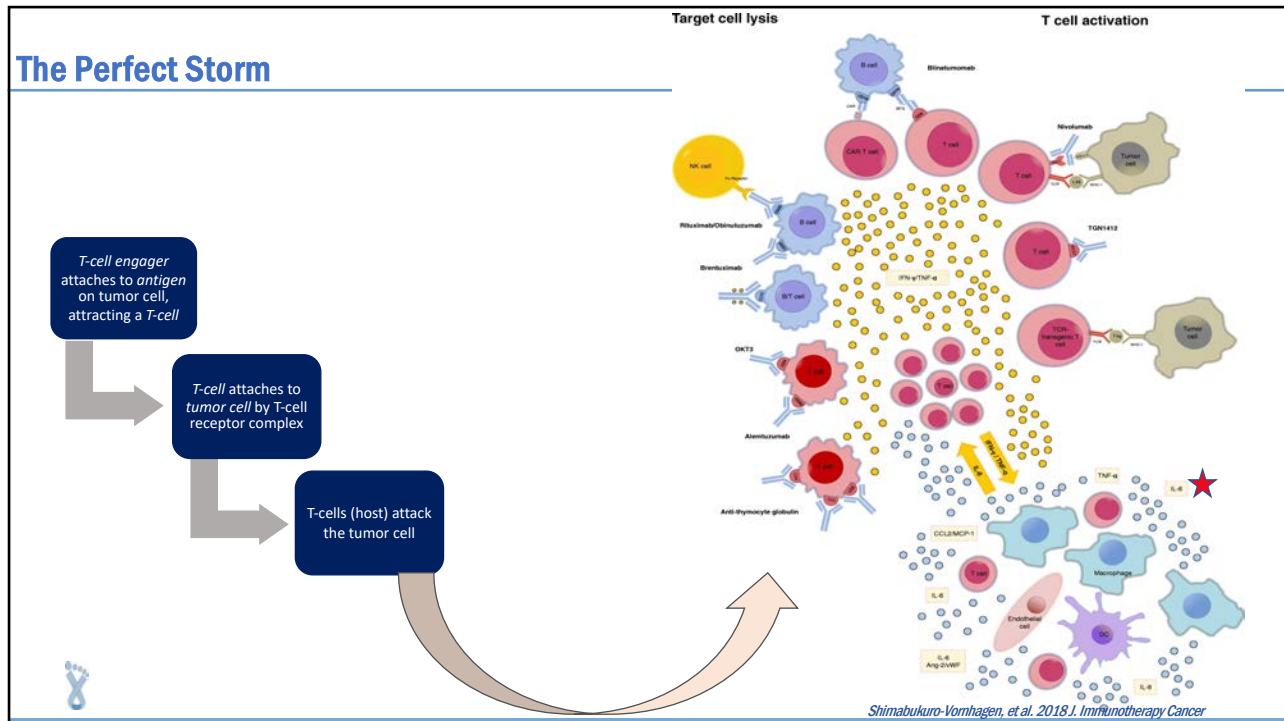
*T-cell engager
attaches to antigen
on tumor cell,
attracting a T-cell*

*T-cell attaches to
tumor cell by T-cell
receptor complex*

*T-cells (host) attack
the tumor cell*

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 Baeuerle, P. A., & Wesche, H. (2022)

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Step-up Dosing

The “first-dose effect”

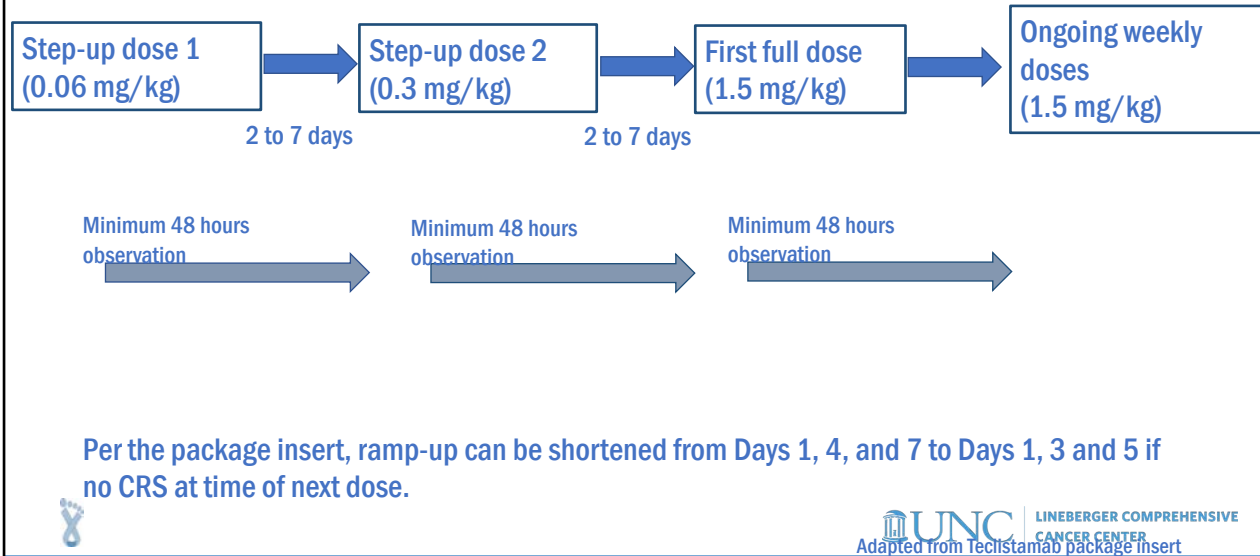
Priming with incremental dose increase to reduce risk of CRS/ICANS

Formulations:

- Continuous IV infusion
- SQ injections
- 2-4 hour IV infusions

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Example of step-up dosing: Teclistamab Initiation



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What vital sign abnormality must be present in order to meet the definition of CRS?

Hypotension	0%
Hypoxia	0%
Fever	0%
All of the above	0%

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CRS GRADING & MANAGEMENT

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CRS Grading Guidelines

- ASTCT 2018
- NCCN 2022
- ASCO 2021



Biology of Blood and
Marrow Transplantation
journal homepage: www.sciencedirect.com



Guideline

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

Daniel W. Lee^{1,2*}, Bianca D. Santomasso^{3,4}, Frederick L. Locke⁵, Armin Ghobadi⁶, Cameron J. Turtle⁷,
Jennifer N. Brudno⁸, Marcela V. Maus⁹, Jae-H. Park¹⁰, Elena Mead¹¹, Steven Pavletic¹², William Y. Go¹³,
Lamis Eldjermi¹⁴, Rebecca A. Gardner¹⁵, Noelle Frey¹⁶, Kevin J. Curran¹⁷, Karl Preiss¹⁸,
Marcelo Pasquini¹⁹, John F. DiPersio²⁰, Marcel R.M. van den Brink²¹, Kreshna V. Komanduri²²,
Stephan A. Grupp²³, Satish S. Neelapu^{24,25}



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

**Management of
Immunotherapy-Related
Toxicities**

**Management of Immune-Related Adverse
Events in Patients Treated With Chimeric Antigen
Receptor T-Cell Therapy: ASCO Guideline**

Bianca D. Santomasso, MD, PhD¹, Loretta J. Nastoupil, MD², Sherry Adkins, RN, MS³, Christina Lacchetti, MHS⁴,
Bryan J. Schneider, MD⁵, Milan Anandhat, MD⁶, Michael B. Atkins, MD⁷, Kelly J. Brissell, PhD, RN⁸, Jeffrey M. Caterino, MD, MPH⁹,
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Ismael Jayarami, DO, MS¹⁵, Jennifer S. Mammen, MD, PhD¹⁶, Januska Naidoo, MD¹⁷, Aung Naing, MD¹⁸, Tanyaika Phillips, MD¹⁹,
Laura D. Porter, MD²⁰, Gilda A. Richner, MD²¹, Guido Siqueira, MBA²², Jung-Min Sung, MD, RN, CNS²³, Alexander Soria, MD, PhD²⁴,
Maria Suarez-Almazor, MD²⁵, Umang Swani, MD²⁶, John A. Thompson, MD²⁷, Pooventh Vikas, MD²⁸, Yinghong Wang, MD²⁹,
Jeffrey S. Weber, MD, PhD³⁰, Kathryn Bolin, MD³¹, and Monalisa Ghosh, MD³²



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Protocol

CRS Grading	CRS Management
Grade 1: Fever $\geq 38^{\circ}\text{C}$, not attributable to any other cause Hypotension: none Hypoxia: none	Supportive care (ie, antipyretics, IV hydration) - Vital signs every 30 minutes for 2 hours after symptoms onset, pulse oximetry, twice daily CMPs - For Initial Fever: Follow Fever SOP. Use clinical judgment for subsequent fevers
Grade 2: Fever $\geq 38^{\circ}\text{C}$, not attributable to any other cause plus Hypotension: not requiring vasopressors And/or Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at $\leq 6\text{ L/min}$) or blow-by *Hypotension: SBP $< 90\text{ mm Hg}$ or if symptomatic	Notify Attending Physician - IV fluid bolus and/or oxygen as needed - Cardiac tele, vital signs every 30 minutes for 2 hours after symptoms onset, pulse oximetry, twice daily CMPs - Tocilizumab 8 mg/kg IV over 1 hour (max dose 800 mg/dose). Repeat every 8 hours if no improvement. Limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total - Hypotension after 2L boluses (consider LR) and after 1-2 doses of tocilizumab, consider dexamethasone 10 mg IV every 12 hours for 1-2 doses - Manage per Grade 3 if no improvement within 24 hours of starting tocilizumab
Grade 3: Fever $\geq 38^{\circ}\text{C}$, not attributable to any other cause plus Hypotension: requiring a vasopressor with or without vasopressin And/or Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask *Hypotension: SBP $< 90\text{ mm Hg}$ or if symptomatic	Notify Attending Physician - Grade 2 Supportive care and include vasopressors as needed - Consider FCHO to assess cardiac function and conduct hemodynamic monitoring - Tocilizumab as per Grade 2 if max dose is not reached within 24-hour period - PLUS dexamethasone 10 mg IV every 6 hours (or equivalent) and taper once symptoms improve - If refractory despite max dose tocilizumab and dexamethasone, manage as per Grade 4
Grade 4: Life threatening Fever $\geq 38^{\circ}\text{C}$, not attributable to any other cause plus Hypotension: requiring multiple vasopressors (exceeding reached within 24-hour period) And/or Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) SBP $< 90\text{ mm Hg}$ or if symptomatic	Notify Attending Physician - Continue supportive care as per Grade 3 plus mechanical ventilation as needed - Administer tocilizumab as per Grade 2 if maximum is not reached within 24-hour period - Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to Grade 1 - If not improving, consider methylprednisolone 10 mg IV 2 times a day



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CRS Grading	CRS Management
Grade 1: Fever $\geq 38^{\circ}\text{C}$, not attributable to any other cause Hypotension: none Hypoxia: none	- Supportive care (ie, antipyretics, IV hydration) - Vital signs every 30 minutes for 2 hours after symptoms onset, pulse oximetry, twice daily CMPs - For Initial Fever: Follow Fever SOP. Use clinical judgment for subsequent fevers
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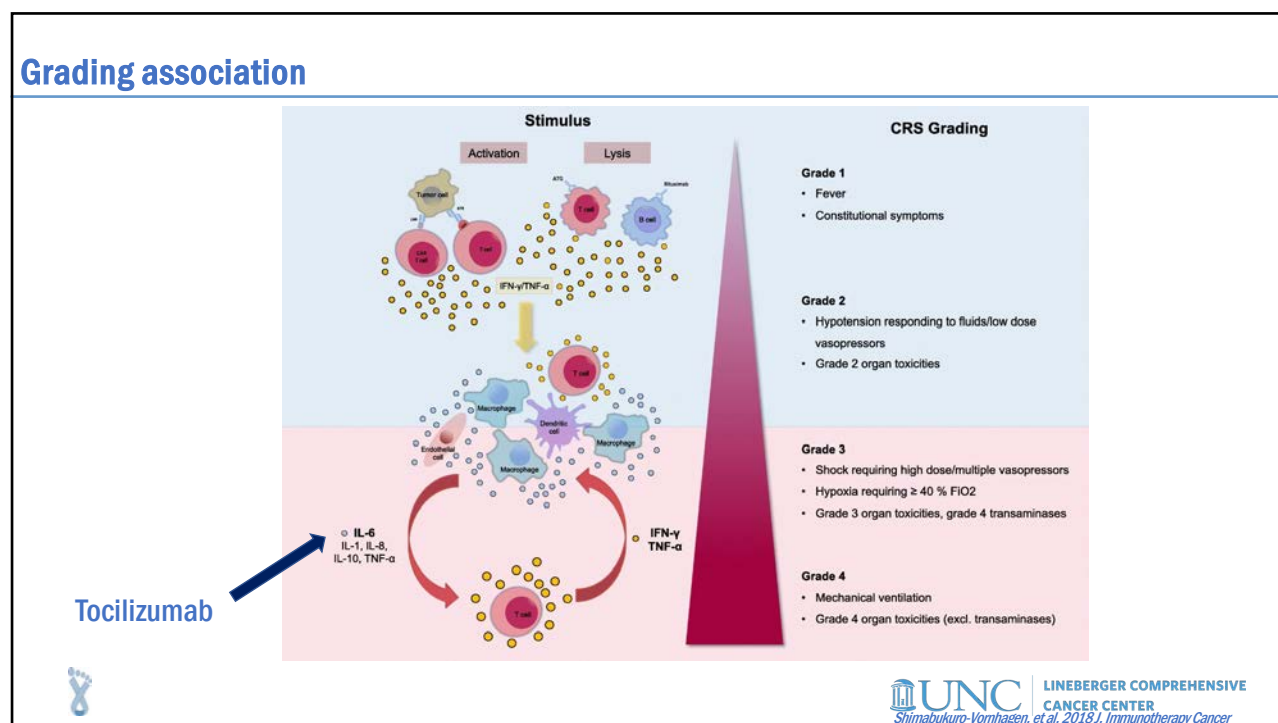


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CRS Grading	CRS Management
Grade 3: Fever $\geq 38^{\circ}\text{C}$, not attributable to any other cause <u>plus</u> Hypotension: requiring a vasopressor with or without vasopressin And/or Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask *Hypotension: SBP < 90 mm Hg or if symptomatic	<ul style="list-style-type: none"> - Notify Attending Physician - Grade 2 Supportive care and include vasopressors as needed - Consider ECHO to assess cardiac function and conduct hemodynamic monitoring - Tocilizumab as per Grade 2 if max dose is not reached within 24-hour period - <u>PLUS</u> dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve - If refractory despite max dose tocilizumab and dexamethasone, manage as per Grade 4 - If on Monumen-TAL, contact MD prior to dexamethasone
Grade 4: Life threatening Fever $\geq 38^{\circ}\text{C}$, not attributable to any other cause - <u>plus</u> Hypotension: requiring multiple vasopressors (excluding vasopressin) -And/or Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) SBP < 90 mm Hg or if symptomatic	<ul style="list-style-type: none"> - Notify Attending Physician - Continue supportive care as per Grade 3 plus mechanical ventilation as needed - Administer tocilizumab as per Grade 2 if maximum is not reached within 24-hour period - Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to Grade 1 - If not improving, consider methylprednisolone 1G IV 2 times a day - If on Monumen-TAL, contact MD prior to dexamethasone

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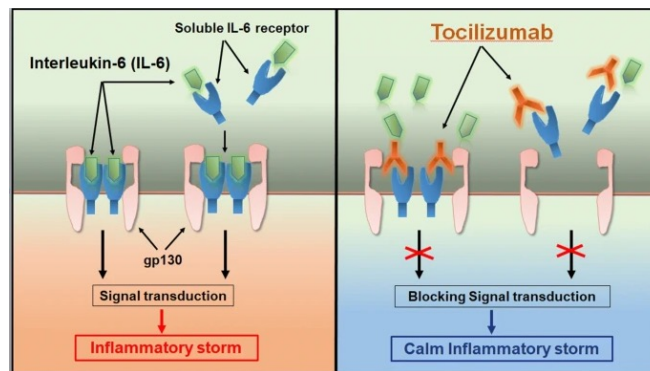
Tocilizumab

FDA approved in 2017 for use in CRS

anti-IL-6 receptor antagonist (inhibits IL-6 by blocking IL-6 receptors)

Prevents proinflammatory effects

Does not cross the BBB



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Fu, B., et al, 2020

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Case study

68yoM with R/R IgG Kappa MM presented for Teclistamab initiation. On D3 (48h after first step-up dose), developed acute L sided mid-sternal and back pain. Improved with IV toradol and protonix. Few hours later, found to be febrile.

Objective:

48h after 1st dose/D3=
Afebrile, normotensive, on RA.
Few hours later, *febrile to 39.2*, remained
normotensive and on RA. ICE score
10/10. Exam benign.

Differential Dx:

CRS
Infectious
MI
Aortic dissection
GERD

Orders:

BCx, EKG, CBC, CMP,
Troponin, CRP

*Per the package insert, ramp-up can be shortened from Days 1, 4, and 7 to
Days 1, 3 and 5 if no CRS at time of next dose.



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Case study

CRS Grading	CRS Management
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CRS Grade 1

Tx:
BCx
APAP

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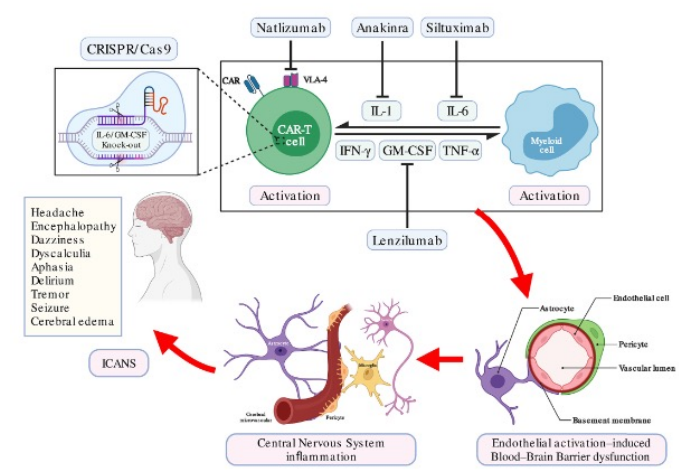
ICANS PATHOPHYSIOLOGY

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What is ICANS?

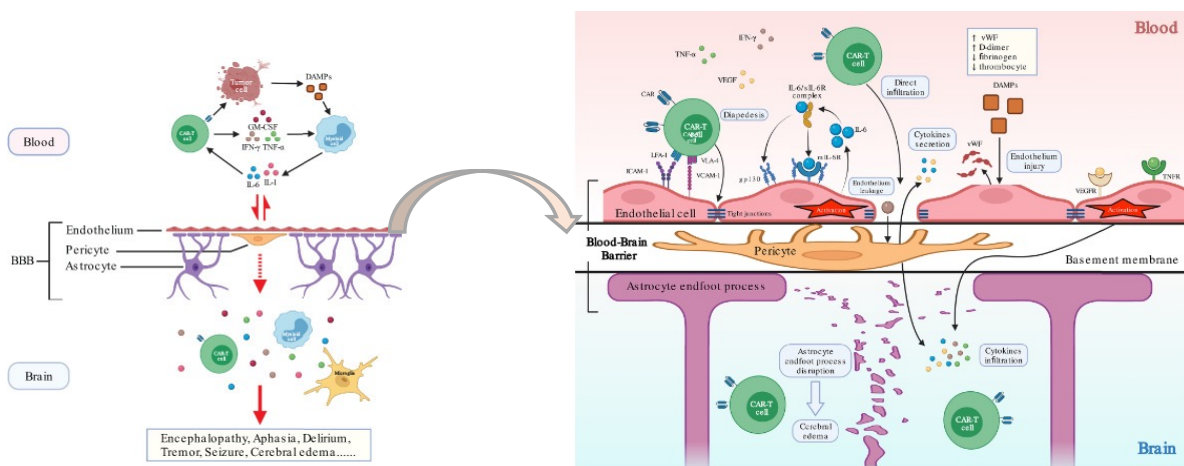
Immune effector cell-associated neurotoxicity syndrome (ICANS), also called cytokine release encephalopathy syndrome (CRES), is a neuropsychiatric syndrome that occurs in patients treated with immunotherapy.



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Pathophysiology

Peripheral immune over activation → Endothelial activation-induced BBB dysfunction → CNS inflammation



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ICANS GRADING & MANAGEMENT

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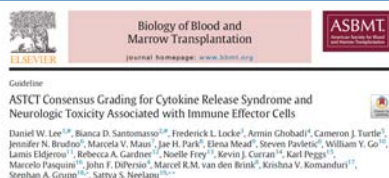


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ICANS Grading Guidelines

- ASTCT 2018
- NCCN 2022
- ASCO 2021



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-Cell Therapy: ASCO Guideline

Bianca D. Santomasso, MD, PhD¹; Loretta J. Nastoupil, MD¹; Sherry Adkins, RN, MS¹; Christina Lacchetti, MHS¹; Bryan J. Schneider, MD²; Milan Anandkumar, MD³; Michael B. Atkins, MD⁴; Kelly J. Brissell, PhD, RN⁵; Jeffrey M. Caterino, MD, MPH⁶; Ian Chao, MD⁷; Marianne J. Davies, DNP⁸; Marc S. Ernstoff, MD⁹; Leslie Fisher, MD¹⁰; Pauline Funchain, MD¹¹; Ishmael Jayesomi, DO, MS¹²; Jennifer S. Mannen, MD, PhD¹³; Januska Naidoo, MD¹⁴; Aung Naing, MD¹⁵; Tanyanka Phillips, MD¹⁶; Laura D. Porter, MD¹⁷; Cristina A. Ritchey, MD¹⁸; Guido Siqueira, MBA¹⁹; Jung-Min Sung, MD, RN, CNS²⁰; Alexander Soria, MD, PhD²¹; Maria Suarez-Almazor, MD²²; Umang Swani, MD²³; John A. Thompson, MD²⁴; Pooventh Vikas, MD²⁵; Yinghong Wang, MD²⁶; Jeffrey S. Weber, MD, PhD²⁷; Kathryn Bolin, MD²⁸; and Monalisa Ghosh, MD²⁹



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ICE ICE Baby...let's talk about the ICE Score

..... Neurotoxicity Grading and Management

Use ICE (Immune Effector Cell-Associated Encephalopathy) score and ICANS (Immune Effector Cell-Associated Neurotoxicity Syndrome) grading in combination when determining management of neurotoxicity

Immune Effector Cell-Associated Encephalopathy (ICE) Score

Orientation	Year, Month, City, Hospital	4 Points
Naming	Ability to name 3 objects (eg point to clock, pen, button)	3 Points
Follow Commands	Ability to follow simple commands (eg "Show me 2 fingers," "Close your eyes and stick out your tongue.")	1 Point
Writing	Ability to write a standard sentence (eg "Our national bird is the bald eagle")	1 Point
Attention	Ability to count backwards from 100 to 0 by 10	1 Point
		Total: 10 points



Tammy's ICE Score

ICE score		
Orientation (4pts)	Year, Month, City, Hospital	4
Naming (3pts)	Ability to name 3 objects	
Follow Commands (1pt)	Ability to follow simple commands	
Writing (1pt)	Ability to write a standard sentence	
Attention (1pt)	Ability to count backwards from 100 by 10	
		Total:



Tammy's ICE Score

ICE score		
Orientation (4pts)	Year, Month, City, Hospital	4
Naming (3pts)	Ability to name 3 objects	3
Follow Commands (1pt)	Ability to follow simple commands	
Writing (1pt)	Ability to write a standard sentence	
Attention (1pt)	Ability to count backwards from 100 by 10	
		Total:

47



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Tammy's ICE Score

ICE score		
Orientation (4pts)	Year, Month, City, Hospital	4
Naming (3pts)	Ability to name 3 objects	3
Follow Commands (1pt)	Ability to follow simple commands	1
Writing (1pt)	Ability to write a standard sentence	
Attention (1pt)	Ability to count backwards from 100 by 10	
		Total:

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Tammy's ICE Score

ICE score		
Orientation (4pts)	Year, Month, City, Hospital	4
Naming (3pts)	Ability to name 3 objects	3
Follow Commands (1pt)	Ability to follow simple commands	1
Writing (1pt)	Ability to write a standard sentence	1
Attention (1pt)	Ability to count backwards from 100 by 10	
Total:		

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Tammy's ICE Score

ICE score		
Orientation (4pts)	Year, Month, City, Hospital	4
Naming (3pts)	Ability to name 3 objects	3
Follow Commands (1pt)	Ability to follow simple commands	1
Writing (1pt)	Ability to write a standard sentence	1
Attention (1pt)	Ability to count backwards from 100 by 10	0
Total: 9 out of 10		

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ICANS Grading

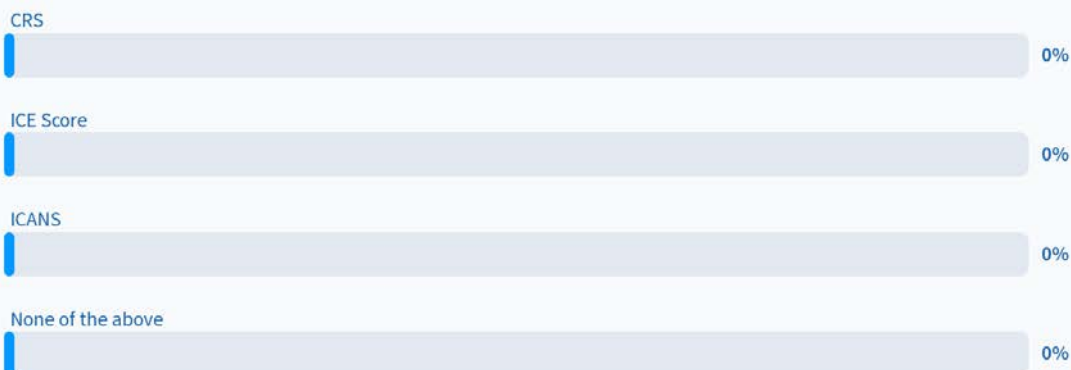
ICANS Grading System: ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unarousable and unable to perform ICE)
Depressed LOC	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires continuous vigorous or repetitive 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
Increased ICP/Cerebral Palsy	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



51

28yoF with R/R ALL with severe acute onset headache within 10 minutes of initiation of blinatumomab infusion. VSS, afebrile. What is an assessment tool you would use to evaluate her neurological status?



52

ICANS Management

Neurotoxicity Management:

Grading	Management (neurotoxicity only)
Grade 1:	<ul style="list-style-type: none"> Notify covering provider Daily neuro exam
Grade 2:	<ul style="list-style-type: none"> Notify Attending Physician Notify covering provider 1 dose of dexamethasone 10 mg IV and reassess. Can repeat every 6–12 hours, if no improvement. Daily neuro exam
Grade 3:	<ul style="list-style-type: none"> Notify Attending Physician ICU level of care recommended START Dexamethasone 10 mg IV Q6H or methylprednisolone, 1 mg/kg IV Q12H Anti-epileptic if concern for seizures (ie keppra)
Grade 4:	<ul style="list-style-type: none"> Notify Attending Physician ICU level of care recommended START methylprednisolone IV 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days Treat convulsive status epilepticus

Reference: NCCN Guidelines Version 1.2022 https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf



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Wait...why not tocilizumab?

Tocilizumab does not cross the BBB

Tocilizumab has the *opposite* effect on ICANS. Peripheral IL-6 no longer binding, excess IL-6 crosses into BBB.

Administer for concurrent ICANS and CRS



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Case study

76yoF with R/R kappa MM presented for teclistamab initiation. Step-up dose 1 tolerated well. The day after step-up dose 2, RRT for confusion, inability to track, walk or follow commands and generalized weakness. VSS, Temp > 38.0, SBP 140-150s, mildly tachycardia.

CRS Grading	CRS Management
Grade 1: Fever ≥ 38°C, not attributable to any other cause Hypotension: none Hypoxia: none	Supportive care (ie, antipyretics, IV hydration) - Vital signs every 30 minutes for 2 hours after symptoms onset, pulse oximetry, twice daily CMPs - For Initial Fever: Follow Fever SOP. Use clinical judgment for subsequent fevers.
Grade 2: Fever ≥ 38°C, not attributable to any other cause plus Hypotension: not requiring vasopressors And/or Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at ≤ 6 L/min) or blow-by	Notify Attending Physician - IV fluid bolus and/or oxygen as needed - Cardiac: take vital signs every 30 minutes for 2 hours after symptoms onset, pulse oximetry, twice daily CMPs - Tocilizumab 3 mg/kg IV over 1 hour (max dose 800 mg/dose). Repeat every 8 hours if no improvement. Limit to a maximum of three doses in a 24 hour period, with a maximum of four doses total - Hypotension after 2L boluses (consider LR) and after 1-2 doses of tocilizumab, consider dexamethasone 10 mg IV every 12 hours for 1-2 doses. - Manage per Grade 3 if no improvement within 24 hours of starting tocilizumab
Grade 3: Fever ≥ 38°C, not attributable to any other cause plus Hypotension: requiring a vasopressor with or without vasopressin And/or Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Notify Attending Physician - Grade 2 Supportive care and include vasopressors as needed - Consider ECHO to assess cardiac function and conduct hemodynamic monitoring - Tocilizumab as per Grade 2 if max dose is not reached within 24-hour period - PLUS dexamethasone 10 mg IV every 6 hours (or equivalent) and notify higher nurse symptoms improve - Refractory despite max dose tocilizumab and dexamethasone, manage as per Grade 4

CRS Grade 1



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Let's break it down

RRT for confusion, inability to track, walk or follow commands and generalized weakness. ICE 0/10

ICE score		
Orientation (4pts)	Year, Month, City, Hospital	0
Naming (3pts)	Ability to name 3 objects	0
Follow Commands (1pt)	Ability to follow simple commands	0
Writing (1pt)	Ability to write a standard sentence	0
Attention (1pt)	Ability to count backwards from 100 by 10	0
		Total: 0



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ICANS Grade and Management

ICE score = 0

ICANS Grading System: 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

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unarousable and unable to perform ICE)
Depressed LOC	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable or requires continuous vigorous or repetitive 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
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Tx:

*Dexamethasone 10mg IV for ICANS
Tocilizumab at 8 mg/kg for CRS
(concurrent)*

ICANS= Grade 3

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Case study

73yoF with refractory MM admitted for teclistamab initiation. The day following first step-up dose, APP called to bedside for mild rigors/chills. Endorses a mild headache. Temp 37.2, SBP 130-140's, HR 90's, SP02 upper 90's on RA, RR18. ICE score 10/10. Demerol given, APAP deferred to avoid fever masking.

One hour later, patient febrile to 38.1 with rigors and hypotensive 89/41.

CRS Grading	CRS Management
Grade 1: Fever ≥ 38°C, not attributable to any other cause Hypotension: none Hypoxia: none	Supportive care (ie, antipyretics, IV hydration) - Vital signs every 30 minutes for 2 hours after symptoms onset, pulse oximetry, twice daily CMPs - For mild fever: Follow Fever SOP. Use clinical judgment for subsequent fevers
Grade 2: Fever ≥ 38°C, not attributable to any other cause plus Hypotension: not requiring vasopressors And/or Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at ≤ 6 L/min) or below	Notify Attending Physician - IV fluid bolus and/or oxygen as needed - Cardiac tele: vital signs every 30 minutes for 2 hours after symptoms onset, pulse oximetry, twice daily CMPs - Tocilizumab 8 mg/kg IV over 1 hour (max dose 800 mg/dose). Repeat every 8 hours if no improvement. Limit to a maximum of three doses in a 24 hour period, with a maximum of four doses total - Hypotension after 2L boluses (consider LR) and after 1-2 doses of tocilizumab, consider dexamethasone 10 mg IV every 12 hours for 1-2 doses - Manage per Grade 3 if no improvement within 24 hours of starting tocilizumab
Grade 3: Fever ≥ 38°C, not attributable to any other cause plus Hypotension: requiring a vasopressor with or without vasopressin And/or Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Notify Attending Physician - Grade 2 Supportive care and include vasopressors as needed - Consider FCHO to assess cardiac function and conduct hemodynamic monitoring - Tocilizumab as per Grade 2 if max dose is not reached within 24-hour period - PLUS dexamethasone 10 mg IV every 6 hours (or equivalent) and repeat taper once symptoms improve - If refractory despite max dose tocilizumab and dexamethasone, manage as per Grade 4

CRS Grade 2

Tx: IVF bolus with good response, acetaminophen, demerol, and Tocilizumab. BCx collected



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Patient then received home regimen of methadone, trazodone, gabapentin, and lorazepam. RRT activated for AMS, awakens to voice.

ICE score		
Orientation (4pts)	Year, Month, City, Hospital	1
Naming (3pts)	Ability to name 3 objects	1
Follow Commands (1pt)	Ability to follow simple commands	1
Writing (1pt)	Ability to write a standard sentence	0
Attention (1pt)	Ability to count backwards by 10 from 100	0
		Total: 3

ICANS Grading System: 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

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
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ICANS Grade 2

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ICANS Grading and Management

Neurotoxicity Management:



Grading	Management (neurotoxicity only)
Grade 1:	<ul style="list-style-type: none"> Notify covering provider Daily neuro exam
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Grade 4:	<ul style="list-style-type: none"> Notify Attending Physician ICU level of care recommended START methylprednisolone IV 1000 mg/day (may consider twice a day) for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days Treat convulsive status epilepticus

Reference: NCCN Guidelines Version 1.2022 https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

DDx:
CRS
ICANS with seizure
Sepsis
Over sedation

Tx:
ICU
Narcan gtt
IV Dexamethasone

Follow-up:
1 of 2 (peripheral) BCx + for strep mutans

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64yoM with MM receives first dose of talquetamab. 28 hours after dose, patient develops AMS with Grade 3 ICANS without CRS. Which intervention would not be warranted for this patient?

Dexamethasone 0%

Tocilizumab 0%

Keppra 0%

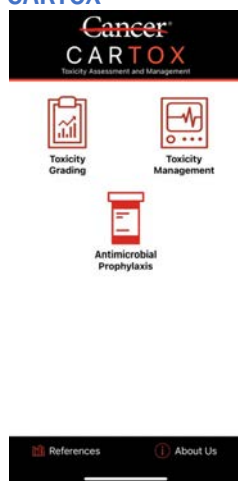
None of the above 0%

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There's an app for that

"CARTOX"



Created by CAR-T team at MD Anderson

CRS Grading

Has the patient recently received antipyretics, anti-cytokine therapy or steroids? ☐ Yes ☒ No

Does the patient have any of the following related to cell therapy?

Fever
temperature $\geq 38.0^{\circ}\text{C}$ ☐ Yes ☒ No

Hypotension
not attributable to any other cause ☐ Yes ☒ No

Select one of the following:

Requiring IV fluids but not requiring vasopressors ☒

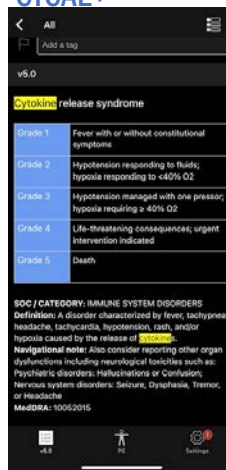
Requires one vasopressor (with or without vasopressin) ☐

Requires multiple vasopressors (excluding vasopressin) ☐

Hypoxia
not attributable to any other cause ☐ Yes ☒ No

Grade

"CTCAE+"



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There's a dot phrase for that

Search for user: "Bejal Kikani"

- .crsneurotoxmanagement
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Name	Description	Editors	ID	Matched On
CHEMOCALTARLATAMABPART1	Tarlatamab Chemo Calendar	KIKANI, BEJAL J and 6 more	1362134	Name
CHEMOCALTARLATAMABPART8	Clinical Trial Amgen 757, Tarlatamab, Part 8, maintenance therapy Cycles 1 and 2	KIKANI, BEJAL J and 9 more	1463015	Name
CRSNEUROTOXMANAGEMENT	CRS AND NEUROTOXICITY MANAGEMENT Not to be used for Blinatumomab NOR Tarlatamab	KIKANI, BEJAL J and 8 more	1269760	Description
TARCRSNEUROTOX	CRS and Neurotox for Tarlatamab (AMG 757) Lung Cancer Trial	KIKANI, BEJAL J and 2 more	1421005	Description

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Future directions

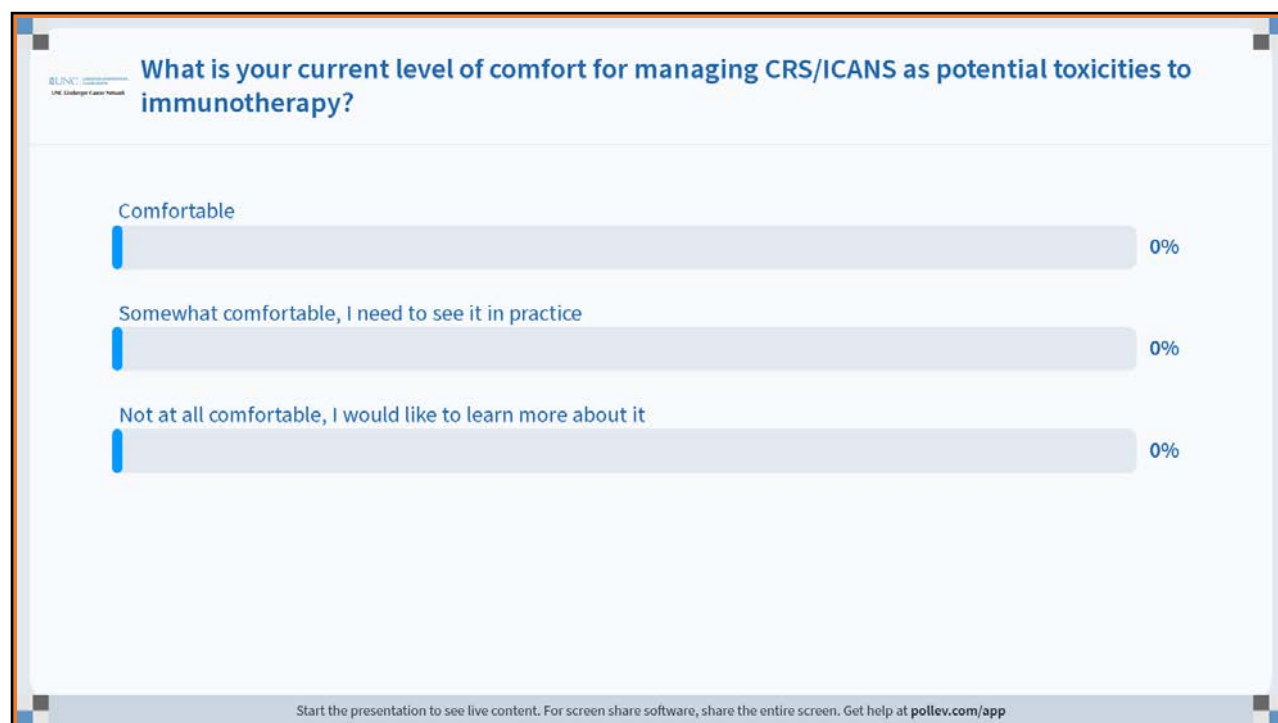
Prophylaxis for CRS/ICANS? Reduce efficacy of treatment?

Role of siltuximab, ruxolitinib, anakinra, dasatinib, and cyclophosphamide

Improve the safety of T cell-engaging immunotherapy



64



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Thank you

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UPCOMING LIVE WEBINARS



RESEARCH
TO PRACTICE

October 25

12:00 PM

Genitourinary Cancer Management in North Carolina:
Updates for 2023

Hung-Jui (Ray) Tan, MD, MSHPM



SOUTHEASTERN AMERICAN
INDIAN CANCER HEALTH
EQUITY PARTNERSHIP

November 1

4:00 PM

Catawba Indian Nation & Lung Cancer Institute:
Partners in Healing

Daniel R Carrizosa, MD, MS

Kia Dungan, PA-C

Darcy Doege, BSN, RN

Mellisa Wheeler, BSW, MHA



PATIENT
CENTERED CARE

November 8

12:00 PM

Next Generation Cancer Care Navigation

William Wood, MD, MPH

Complete details on upcoming Live Webinars: learn.unclcn.org/live-webinars

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SELF-PACED, ONLINE COURSES



ADVANCED PRACTICE PROVIDER
Self-Paced, Online Course
Developing Comprehensive Exercise Programming for People Affected by Cancer
Carly Bailey, MA



RESEARCH TO PRACTICE
Self-Paced, Online Course
Lymphoma Management in North Carolina: Updates for 2023
Natalie Grover, MD



PATIENT CENTERED CARE
Self-Paced, Online Course
Psychotherapy for Cancer-Related Distress
Melissa Holt, DNP, PMHNP-BC, MSW
Lisa Stewart, PsyD

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