CRS vs. ICANS What Does This Mean?

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8/7/2020

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Disclosures

I have nothing to disclose.

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Objectives

- Recognize clinical manifestations of cytokine release syndrome (CRS) and immune effector cell associated neurotoxicity syndrome (ICANS)
- Discuss grading systems for CAR-T cell associated toxicities
- Describe treatment options for patients presenting with CRS and/or ICANS

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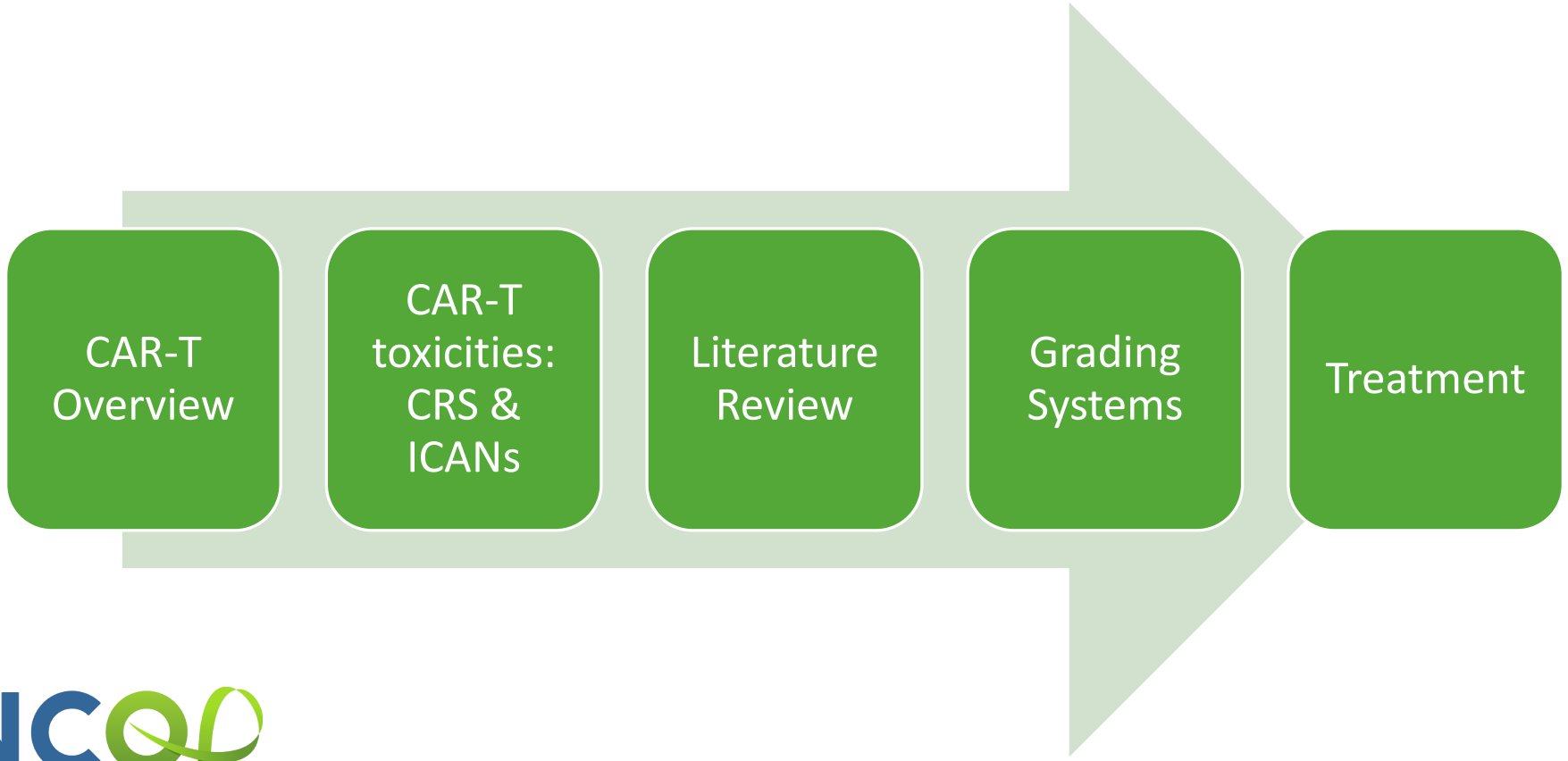
Outline



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CAR-T= Chimeric antigen receptor (CAR) T-cell therapy

CAR-T Overview

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What is CAR-T?

- CAR-T= Chimeric antigen receptor (CAR) T-cell therapy
- Genetically modified autologous T-cell immunotherapy
- Targets CD19 on cancerous cells
- Emerging therapy for hematologic malignancies
  - B-cell lymphoma and B-cell leukemia
- Increases T-cell proliferation and cytokine release leading to immune activation
- Cytokine release allows for unique toxicities including cytokine release syndrome (CRS) and neurotoxicity

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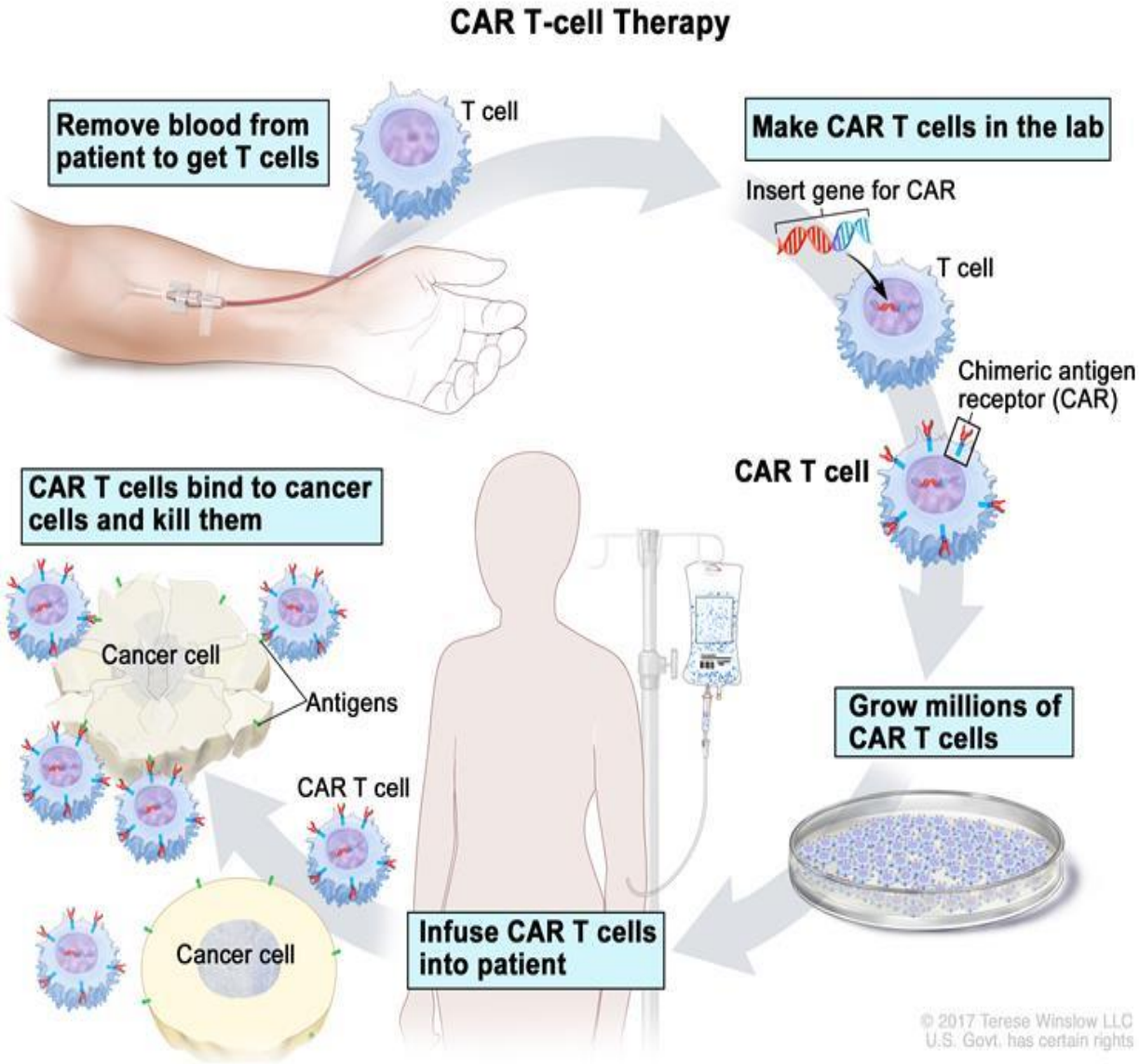
Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. Version 1. 2020.



CAR-T Cell Process

American Society of Clinical Oncology. Weighing the Cost and Value of Car-T cell Therapy. 2018. Available at https://www.ascopost.com/issues/may-25-2018/weighing-the-cost-and-value-of-car-t-cell-therapy/

Available CAR-T Products

Tisagenlecleucel (Kymriah)

- FDA approved for adult patients with relapsed or refractory (r/r) large B-cell lymphoma after 2 or more lines of systemic therapy
- FDA approved for r/r B-cell precursor acute lymphoblastic leukemia (ALL) in 2nd or later relapse in adults up to age 25

Axicabtagene Ciloleucel (Yescarta)

- FDA approved for adult patients with r/r large B-cell lymphoma after 2 or more lines of systemic therapy including DLBCL

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Tisagenlecleucel (Kymriah) [package insert] East Hanover, NJ. Novartis Pharmaceuticals; 2018.
Axicabtagene Ciloleucel (Yescarta) [package insert]. Santa Monica, CA. Kite Pharma, Inc; 2020.

CAR-T Toxicities

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Toxicities of CAR-T

- Cytokine Release Syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Late Complications

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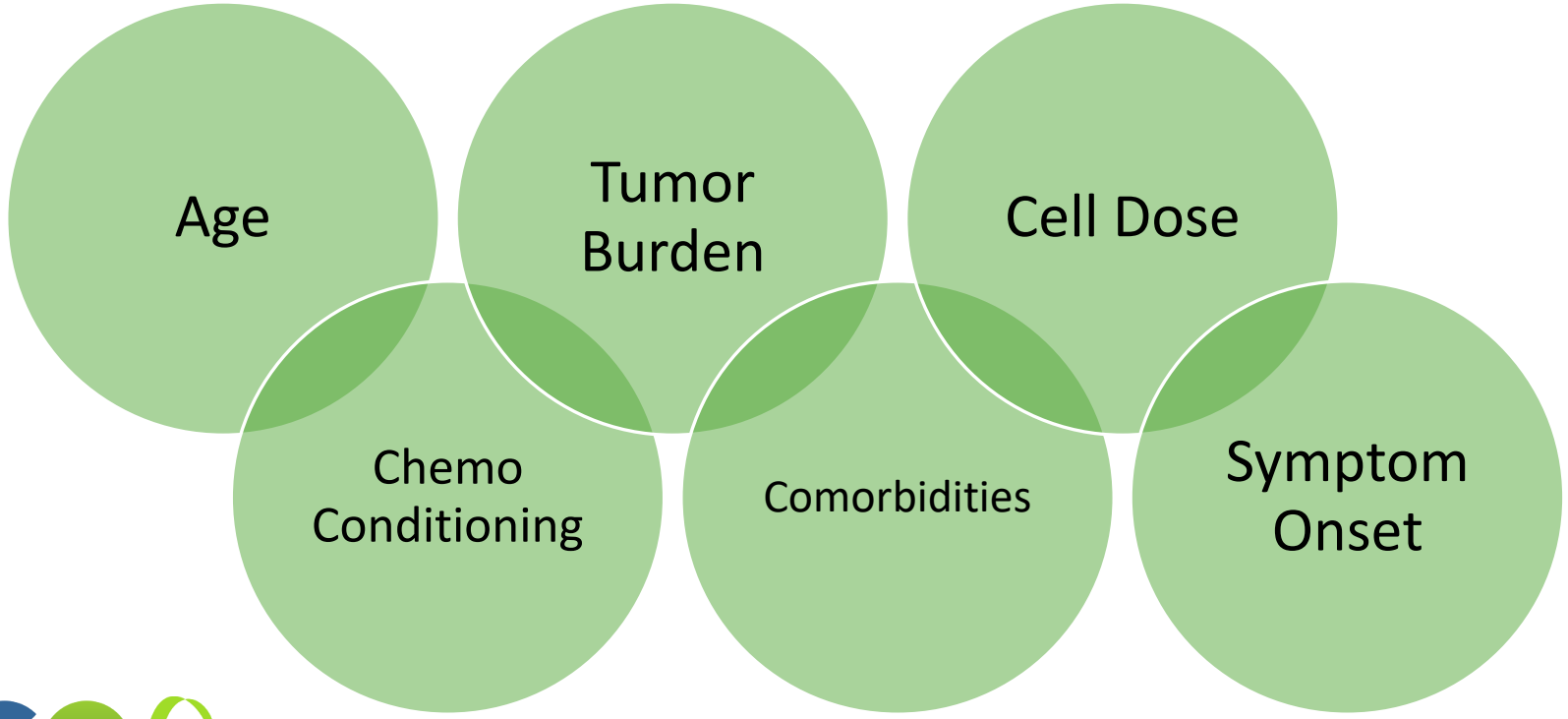
Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. Version 1. 2020.

CAR-T Toxicity Risk Factors



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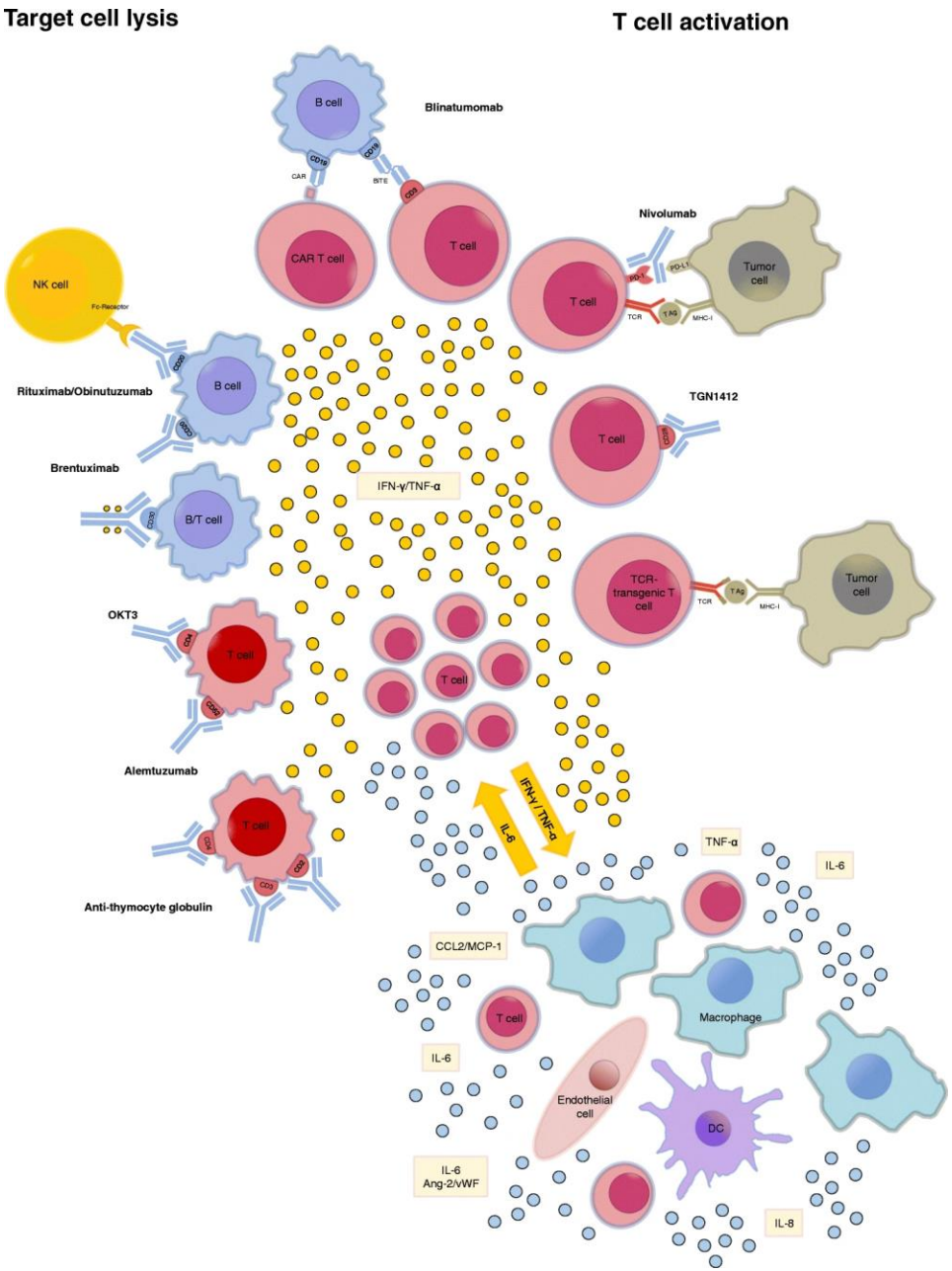

Cytokine Release Syndrome (CRS)

- Inflammatory response
- Greater severity = higher disease burden
- Typical time to onset = 2 to 3 days
- Typical duration = 7 to 8 days
- Fatal complication of CAR-T
- Mostly reversible complication
- Black box warning

National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. Version 1. 2020.
Shimabukuro-Vornhagen A, et al. Journal for ImmunoTherapy of Cancer (2018). 6:56; 1-14.

CRS Clinical Manifestations

- Rarely presents beyond 14 days after initiation of therapy

Fever	Rigors	Hypotension	Hypoxia
Tachycardia	Respiratory Failure	AKI	Coagulopathy
	Capillary Leak	Neurologic Manifestations	

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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. Version 1. 2020.

Toxicities of CAR-T

- Cytokine Release Syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Late Complications

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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
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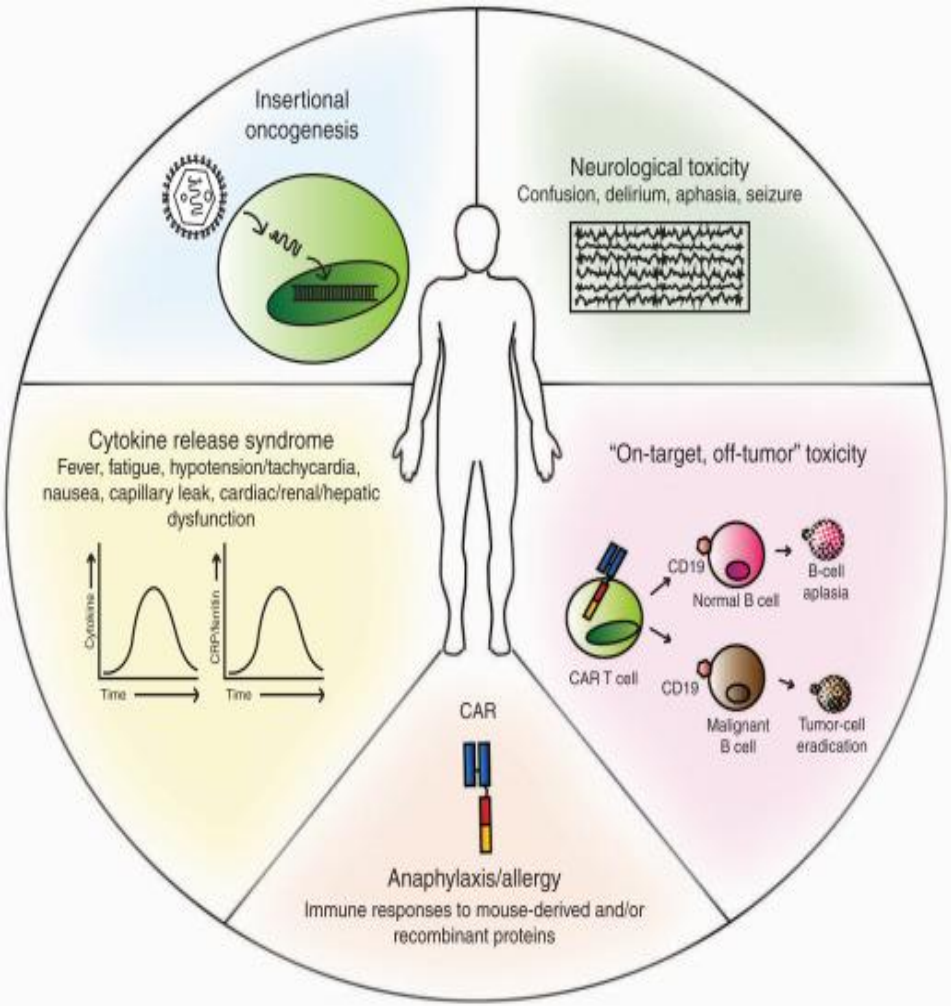

Immune Effector Cell Associated Neurotoxicity (ICANS)

- Endothelial activation and blood-brain barrier disruption
- Proinflammatory cytokines
- Elevated levels of glutamate and quinolinic acid in cerebrospinal fluid
- Typical time to onset = 4 to 10 days
- Typical duration = 14 to 17 days
- Fatal complication
- Reversible??
- Black box warning

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
Bonifant, et al. Molecular Therapy. Oncolytics (2016) 3, 16011. 1-7.
National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. Version 1. 2020.

ICANs Clinical Manifestations

Delirium	Encephalopathy	Aphasia	Lethargy
Seizures	Agitation	Tremor	Difficulty Concentrating
	Cerebral Edema (rare)	Dizziness	

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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
National Comprehensive Cancer Network. Management of Immunotherapy-Related Toxicities. Version 1. 2020.

Audience response

JM is a 65 year old male who recently received tisagenlecleucel for relapsed or refractory DLBCL. Two days after his infusion, he was noted to have a temperature of 101.5^{o} F with chills and rigors. His vitals included a blood pressure of 96/58 mmHg and heart rate of 145. He subsequently required 4L of oxygen via nasal cannula.

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Which of the following is JM likely experiencing?

Immune effector cell-associated neurotoxicity syndrome (ICANS)

Cytokine release syndrome (CRS)

CAR-related encephalopathy syndrome (CRES)

Fever neutropenia

Literature Review

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Landmark Trials

	JULIET Trial (N = 111)	ZUMA-1 Trial (N = 111)
Study Design:	Single-group, open-label, multicenter, international, phase 2	Multicenter, phase 2 study
Objective:	Evaluate safety and efficacy of tisagenlecleucel in adult patients with r/r DLBCL	Evaluate the safety and efficacy of axicabtagene ciloleucel in adult patients with r/r DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma
Lymphodepleting Regimen:	-Fludarabine 25 mg/m2 + cyclophosphamide 250 mg/m2 for 3 days OR -Bendamustine 90 mg/m2 for 2 days	Fludarabine 30 mg/m2 + cyclophosphamide 500 mg/m2 for 3 days (day -5, -4, -3)
Safety Outcomes:	Most common AE were CRS, anemia, pyrexia, cytopenias and diarrhea	Most common AE of any grade were pyrexia, neutropenia, CRS and anemia

Schuster SJ, et al. N Engl J Med. 2019;380:45-56.
Neelapu SS, et al. N Engl J Med. 2017;377:2531-44.

r/r= relapsed or refractory
AE= adverse events
CRS= cytokine release syndrome
DLBCL= Diffuse Large B-cell Lymphoma

Landmark Trials

	TRANSCEND Trial* (N = 268)	ELIANA Trial (N = 75)
Study Design:	Multicenter, pivotal phase 1 study	Single cohort, multicenter, phase 2 study
Objective:	To determine the safety and efficacy of lisocabtagene maraleucel in patients with with r/r large B-cell NHL	To determine the safety and efficacy of tisagenlecleucel in pediatric and young adult patients with CD19+ r/r B-cell ALL
Lymphodepleting Regimen:	Fludarabine 30 mg/m2 + Cyclophosphamide 300 mg/m2 for 3 days	96% of patients received lymphodepleting chemotherapy prior to tisagenlecleucel infusion -unclear of specific regimens received
Safety Outcomes:	Most common AE of any grade were cytopenias (anemia, thrombocytopenia, neutropenia) and CRS	Most common AE of any grade were CRS, pyrexia, decreased appetite, fever neutropenia, and headache

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*Data from DLBCL cohort

Abramson JS, et al. *Blood* (2019) 134 (Supplement_1): 241.
Maude SL, et al. N Engl J Med 2018;378:439-48.

Literature Comparison: CRS

	JULIET N = 111	ZUMA-1 N = 101	TRANSCEND* N = 268	ELIANA N = 75
CRS- any grade; (%)	64 (58)	94 (93)	113 (42)	58 (77)
CRS- grade ≥ 3; (%)	24 (22)	13 (13)	6 (2)	35 (47)
Median time from infusion to onset	3 days	2 days	5 days	3 days
Median duration of CRS	7 days	8 days	-	8 days
Tocilizumab use; (%)	15 (14)	48 (43)	(19)	28 (37)
Tocilizumab + glucocorticoid use; (%)	11 (10)	30 (27)	(21)	-
Grading System	University of Penn	Lee	Lee	Univ of Penn

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*Data from DLBCL cohort

Schuster SJ, et al. N Engl J Med. 2019;380:45-56.
Neelapu SS, et al. N Engl J Med. 2017;377:2531-44.
Maude SL, et al. N Engl J Med 2018;378:439-48.
Abramson JS, et al. *Blood* (2019) 134 (Supplement_1): 241.

Literature Comparison: Neurotoxicity

	JULIET N = 111	ZUMA-1 N = 101	TRANSCEND* N = 268	ELIANA N = 75
Neurotoxicity- any grade; (%)	23 (21)	65 (64)	80 (30)	30 (40)
Neurotoxicity- grade ≥ 3; (%)	13 (12)	28 (28)	27 (10)	10 (13)
Median time from infusion to onset	6 days	5 days	9 days	-
Median duration of neurotoxicity	14 days	17 days	-	10 days
Concurrent CRS + neurotoxicity	9 (8)	-	-	26 (35)
Grading System	CTCAE v4.03	CTCAE v4.03	CTCAE v4.03	CTCAE v4.03

*Data from DLBCL cohort

Schuster SJ, et al. N Engl J Med. 2019;380:45-56.
Neelapu SS, et al. N Engl J Med. 2017;377:2531-44.

Grading Systems

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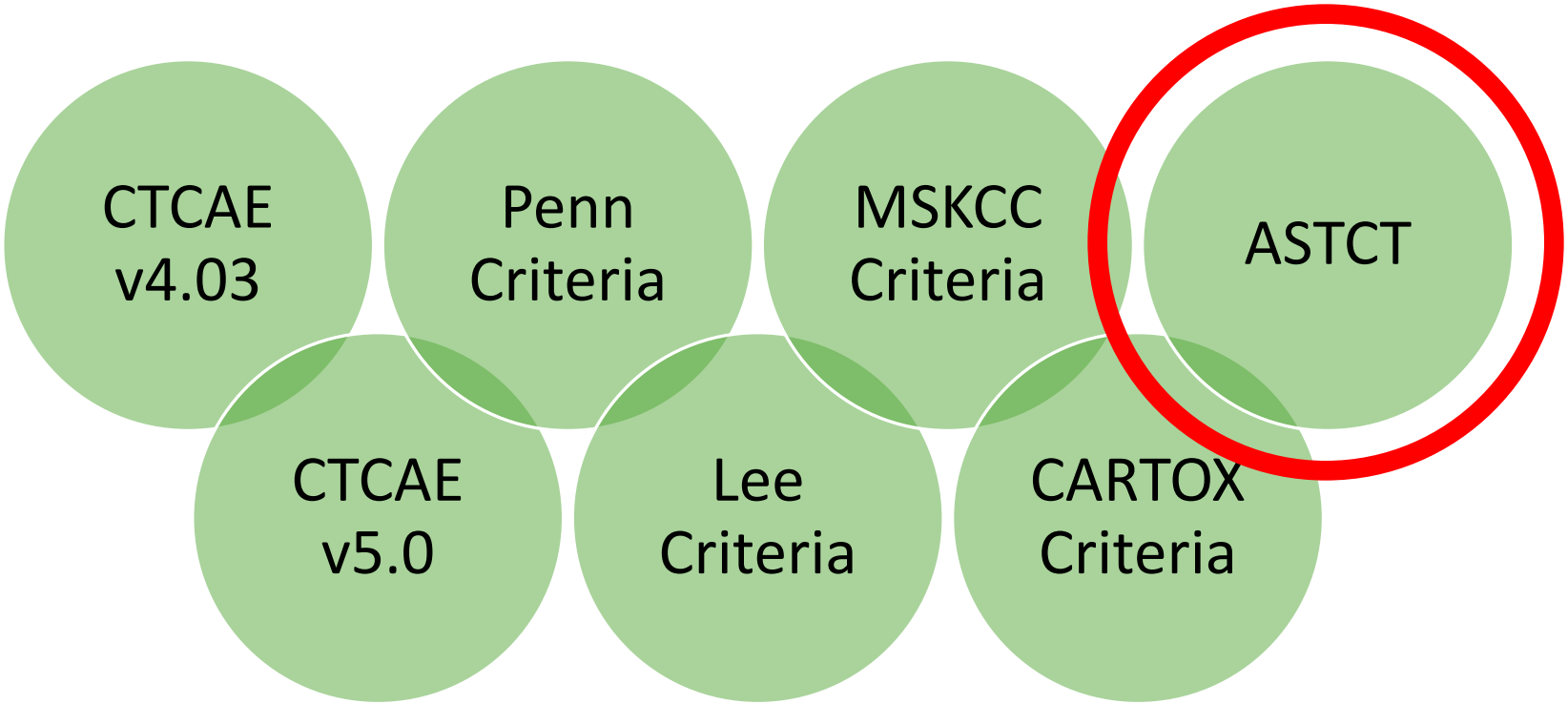
Grading Systems Available



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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

CRS Grading System

	CTCAE v4.03	CTCAE v5.0
Grade 1	-Mild reaction -Infusion interruption not indicated -**Intervention not indicated**	-**Fever** with or without symptoms
Grade 2	-Therapy interruption indicated but **responds to symptomatic treatment** -Prophylactic medications indicated for ≤ 24 hours	-**Hypotension** responding to fluids -**Hypoxia** responding to **< 40%** FiO2
Grade 3	-Prolonged recurrence of symptoms following initial improvement -**Hospitalization indicated**	-Hypotension managed with **1 pressor** -Hypoxia requiring **≥ 40%** FiO2
Grade 4	-Life-threatening consequences -**Pressor or ventilatory support indicated**	-Life-threatening consequences -Urgent intervention needed

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03.
National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v5.0.

CRS Grading System

	MSKCC Criteria	CARTOX Criteria
Grade 1	-Mild symptoms requiring observation or supportive care only	-**Temperature** > 38°C -**Grade 1 organ toxicity**
Grade 2	-**Hypotension** + vasopressors **< 24 hours** -**Hypoxia** + supplemental oxygen **< 40%**	-**Hypotension** responding to IV fluids or **low dose vasopressor** -**Hypoxia** requiring FiO2 < 40% **-Grade 2 organ toxicity**
Grade 3	-Hypotension + vasopressors **≥ 24 hours** -Hypoxia + supplemental oxygen **≥ 40%**	-Hypotension + **multiple** vasopressors -Hypoxia requiring FiO2 **≥ 40%** **-Grade 3 organ toxicity or grade 4 transaminitis**
Grade 4	-Life-threatening symptoms -Hypotension refractory to high dose vasopressors -Hypoxia requiring **mechanical ventilation**	-Life-threatening hypotension -Requires ventilator support **-Grade 4 organ toxicity except for grade 4 transaminitis**

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
Park JH, et al. N Engl J Med. 2018;378:449-459.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018;15:47-62.

CRS Grading System

	Penn Criteria
Grade 1	-Mild reaction treated with **supportive care** including antipyretics or antiemetics
Grade 2	-Moderate reaction including some **signs of organ dysfunction** related to CRS -**Hospitalization** for management of CRS related symptoms
Grade 3	-More severe reaction where **hospitalization is required** -Hypotension treated with **multiple fluid boluses or low dose vasopressors** -**Coagulopathy** requiring FFP, cryoprecipitate or fibrinogen concentrate -Hypoxia requiring supplemental oxygen
Grade 4	-Life-threatening complications including hypotension **requiring high dose vasopressors** -Hypoxia requiring **mechanical ventilation**

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
Porter D, et al. J Hematol Oncol. 2018;11:35.

CRS Grading System

	Lee Criteria
Grade 1	-Symptoms are not life threatening and require **symptomatic treatment only**
Grade 2	-Symptoms require and respond to **moderate intervention** (Oxygen requirement < 40% FiO2, or hypotension responsive to IV fluids or a low dose vasopressor, or grade 2 organ toxicity
Grade 3	-Symptoms require and respond to **aggressive intervention** (oxygen requirement $\geq$ 40% FiO2, or hypotension require high dose or multiple vasopressors, or grade 3 organ toxicity or grade 4 transaminitis)
Grade 4	-**Life-threatening symptoms** (requirement of ventilator support or grade 4 organ toxicity excluding transaminitis)

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
Lee DW, et al. Blood. 2014;124:188-195.

Neurotoxicity Grading Systems

- CTCAE v5.0: Grades neurotoxicity domains from 1 to 4 for the following adverse event terms:
  - Encephalopathy, seizure, dysphasia, tremor, headache, confusion, depressed level of consciousness, and cerebral edema
  - Progress from mild→ moderate→ severe→ life-threatening symptoms
  - Encompasses self-care activities of daily living (ADL) and instrumental ADL
- CARTOX Criteria:

CARTOX Criteria

Adverse Event Term	Grade 1	Grade 2	Grade 3	Grade 4
Neurologic Assessment Score (CARTOX-10)	7 to 9 (mild impairment)	3 to 6 (moderate impairment)	0 to 2 (severe impairment)	Patient in critical condition and or obtunded and cannot perform assessment of tasks
Elevated ICP	N/A	N/A	Stage 1 to 2 papilledema or CSF opening pressure < 20 mmHg	Stage 3 to 5 papilledema or CSF opening pressure ≥ 20 mmHg or cerebral edema
Seizures or motor weakness	N/A	N/A	Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine	Generalized seizures or convulsive or non-convulsive status epilepticus or new motor weakness

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018;15:47-62.
National Cancer Institute. CTCAE v5.0

New Standard Grading System

- Numerous grading systems available with overlapping assessments
  - Varies widely across institutions
- Toxicity comparisons between products and trials are difficult
- Lack of objectivity in grading systems
- ASTCT recognized the need for clear and accurate consensus guidelines
  - Experts met June 20-21, 2018 to discuss harmonization of guidelines
  - Agreed CRS is the most appropriate term for symptoms occurring after CAR-T
  - Redefined neurotoxicity complication following CAR-T with term ICANS

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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

New Standard Definitions: ASTCT

- **CRS:**
  - "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"

- **ICANS:**
  - "A disorder characterized by a pathologic process involving the CNS 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"

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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

CRS Grading System: New Standard

	ASTCT Criteria
Grade 1	**-Fever (≥ 38°C)** with or without constitutional symptoms (ie. Myalgia, arthralgia and malaise) -No hypoxia or hypotension present
Grade 2	-Fever (≥ 38°C) with **hypotension** not requiring vasopressors -**Hypoxia** requiring the use of oxygen via low flow nasal canula **(≤ 6 L/min)**
Grade 3	-Fever (≥ 38°C) with **hypotension requiring 1 vasopressor** with or without vasopressin **-Hypoxia requiring high flow nasal cannula (> 6 L/min),** facemask, nonrebreather mask or venturi mask not attributable to any other cause
Grade 4	-Fever (≥ 38°C) with hypotension + **multiple vasopressors** (excluding vasopressin) **-Hypoxia requiring positive pressure** (ie. CPAP, BiPAP, mechanical ventilation and intubation)

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

ICANS Encephalopathy Assessment Tools

	CARTOX-10	ICE
Orientation	Orientation to year, month, city, hospital, president - 5 points	Orientation to year, month, city, hospital - 4 points
Naming	Ability to name 3 objects - 3 points	Ability to name 3 objects - 3 points
Following Commands	N/A	Ability to follow simple commands - 1 point
Writing	Ability to write a standard sentence - 1 point	Ability to write a standard sentence - 1 point
Attention	Ability to count backwards from 100 by 10 - 1 point	Ability to count backwards from 100 by 10 - 1 point
Scoring	7 - 9 = Grade 1 ICANS 3 - 6 = Grade 2 ICANS	0 - 2 = Grade 3 ICANS 0 = Grade 4 ICANS

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.
Neelapu SS, et al. Nat Rev Clin Oncol. 2018;15:47-62.

ICANs Grading System: ASTCT

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (patient unarousable)
CAPD score for children age < 12	1-8	1-8	≥ 9	Unable to perform CAPD
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous tactile stimuli to arouse
Seizure	N/A	N/A	Any clinical seizure (focal, generalized, or nonconvulsive) that resolves with intervention	Life-threatening prolonged seizure (> 5 min) or repetitive seizures without return to baseline
Motor findings	N/A	N/A	N/A	Deep focal motor weakness
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

Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

CAPD= Cornell Assessment of Pediatric Delirium

Audience response

Which of the following grading systems were developed in 2018 with the goal of harmonization and standardization in identification of toxicities related to immune effector cell therapies?

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Which of the following grading systems were developed in 2018 with the goal of harmonization and standardization in identification of toxicities related to immune effector cell therapies?

Lee Guidelines

University of Pennsylvania Guidelines

ASTCT Guidelines

CTCAE Guidelines

CRS & ICANs Management

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ASTCT CRS Management

Grade 1

- Antipyretics and IV hydration
- Diagnostic work-up to rule out infection
- Consider growth factors and antibiotics if neutropenic

Grade 2

- Antipyretics and IV hydration
- Supplemental O2
- Tocilizumab +/- dexamethasone or its equivalent methylprednisolone

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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

ASTCT CRS Management

Grade 3

- Antipyretics and IV hydration
- Consider ICU monitoring
- Vasopressor support and/or supplemental O2
- Tocilizumab + dexamethasone 10-20 mg IV q6h or its equivalent methylprednisolone

Grade 4

- Antipyretics and IV hydration
- ICU monitoring
- Vasopressor support and/or supplemental O2 via positive pressure ventilation (CPAP, BiPAP, intubation or mechanical ventilation)
- Tocilizumab + methylprednisolone 1000 mg/day

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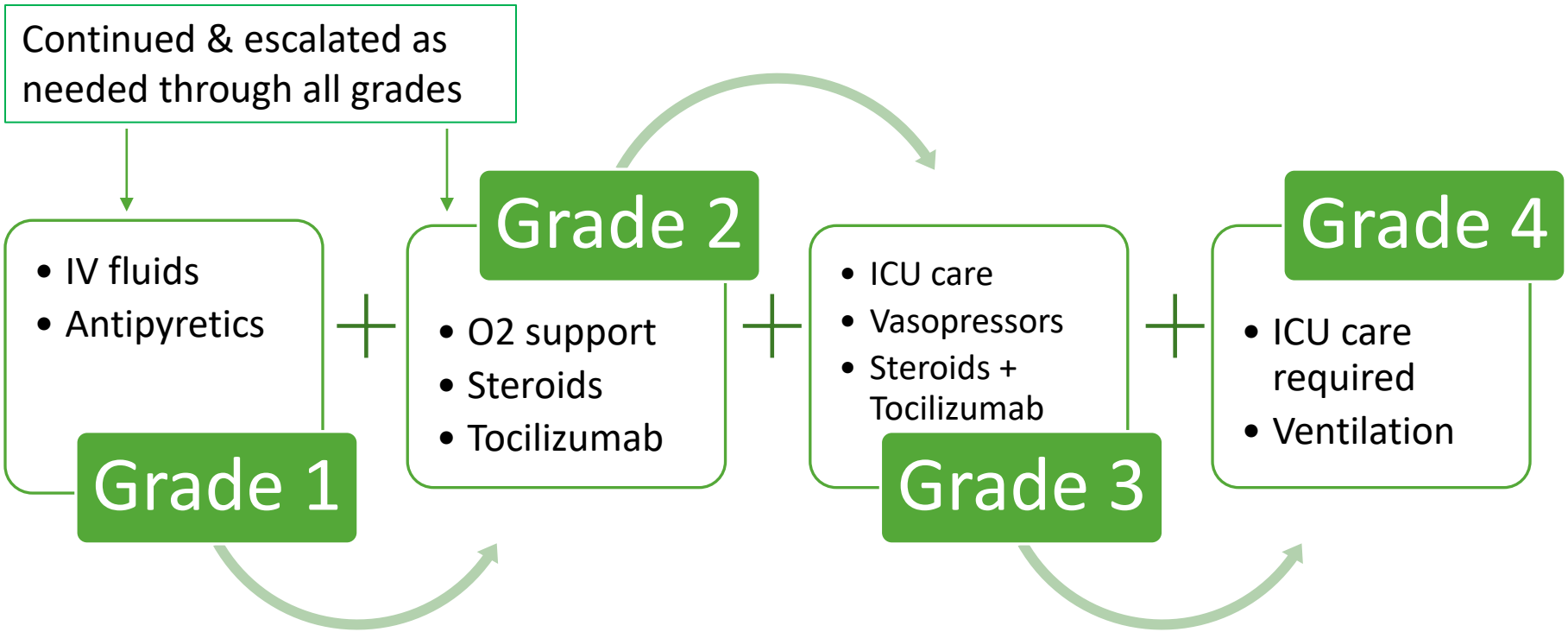
ASTCT Treatment Stepwise Approach: CRS



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ASTCT ICANS Management

Grade 1

- Aspiration precautions and IV hydration
- Seizure prophylaxis with levetiracetam
- EEG monitoring, brain imaging
- Consider tocilizumab if concurrent CRS

Grade 2

- Supportive care from grade 1
- Consider steroids (dexamethasone or methylprednisolone)

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ASTCT ICANS Management

Grade 3

- Supportive care from grade 1
- Dexamethasone 10-20 mg IV q6h
- Seizure management with benzodiazepines for short-term control, levetiracetam +/- phenobarbital and/or lacosamide
- Methylprednisolone 1000 mg/day for local edema

Grade 4

- Supportive care from grade 1
- Methylprednisolone 1000 mg/day
- Seizure management with benzodiazepines for short-term control, levetiracetam +/- phenobarbital and/or lacosamide
- Lower ICP by hyperventilation, hyperosmolar therapy with mannitol, hypertonic saline

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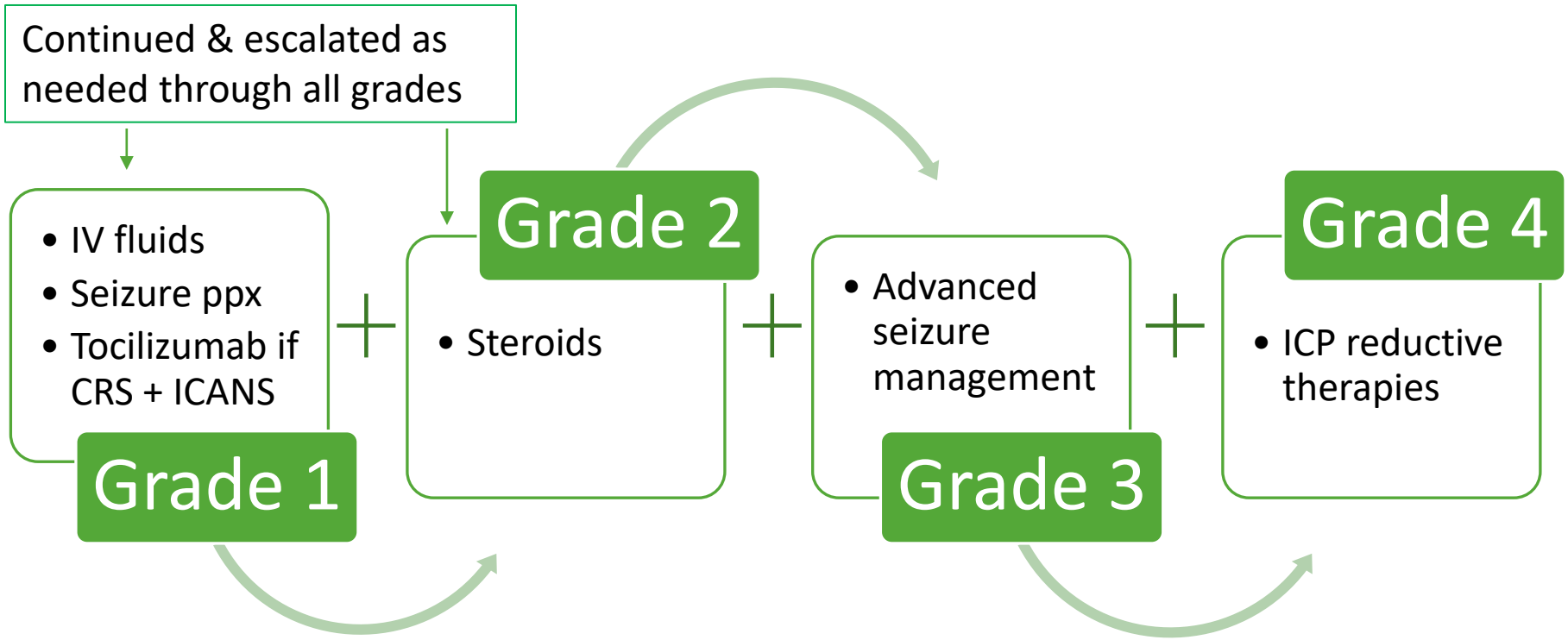
ASTCT Treatment Stepwise Approach: ICANS



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ppx= prophylaxis

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Role of Anti IL-6 Therapy

Tocilizumab

- FDA approved for cytokine release syndrome
- Dosing based on weight
  - < 30 kg = 12 mg/kg
  - ≥ 30 kg = 8 mg/kg
  - Max dose = 800 mg IV over 60 minutes
- If no clinical improvement, may give 3 additional doses at least 8 hours apart

Siltuximab

- Not FDA approved for CRS or ICANs
- Dosing: 11 mg/kg IV over 60 minutes

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Tocilizumab (Actemra) [package insert] San Francisco, CA. Genentech Inc; 2020.
Siltuximab (Sylvant) [package insert]. Hemel Hempstead, Hertfordshire, UK. Eusa Pharma, Inc; 2020.

Resolution of CRS and ICANS

- Once patients meet criteria for CRS and/or ICANs, patients are said to have CRS and/or ICANs until all signs and symptoms leading to diagnosis of CRS and/or ICANs have resolved
- CRS and ICANs can be downgraded in patients as symptoms improve
- Goal = patient returns to baseline or grade 1 toxicity
- Individualized approach given various patient situations

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Lee DW, et al. Biol Blood Marrow Transplant 25 (2019) 625-638.

Audience response

SD is a 71 year old female with history of r/r DLBCL. She recently underwent CAR-T cell infusion with axicabtagene ciloleucel 8 days ago. Overnight, patient had a generalized seizure, and it was determined that she is experiencing an ICANS grade 3 toxicity. SD already has levetiracetam prophylaxis on board as part of the standard protocol for CAR-T patients at your institution.

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Which of the following would be the most appropriate option for further management of her grade 3 ICANS toxicity?

Tocilizumab 8 mg/kg

Advanced seizure management with benzodiazepines for short-term control, increased levetiracetam +/- phenobarbital and/or lacosamide

Dexamethasone 10 mg q6h

IV hydration

Future Considerations

Ongoing Studies

- Over 500 CAR-T cell therapies are under development
- ZUMA-3
- ZUMA-7

Future Indications

- Solid tumors
- Multiple Myeloma
- Allogeneic chimeric antigen receptors
- New antigen targets

Education

- Multidisciplinary education
  - Providers, nursing, pharmacy
- Protocol development

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Summary

- CRS and ICANs are serious complications of CAR-T cell therapy
- Prompt identification and management is essential
- New standard of care grading system available
- Management of CRS and ICANs is a stepwise approach

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Thank You!

Acknowledgements:

- LeAnne Kennedy
- Sally Barbour
- Erin Kennedy
- Entire Duke University Hospital Team!

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CRS vs. ICANS What Does This Mean?

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8/7/2020

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