Case Studies in Immune Effector Cell-related Adverse Events

October 13, 2021

5:30 – 6:30 p.m. ET

The Practical Management Pearls and Case Studies Webinars are part of the Cancer Immunotherapy Clinical Practice Guidelines Advanced Webinar Series supported, in part, by grants from Amgen and Merck & Co., Inc. (as of 9/15/2021)

Webinar Agenda

5:30 – 5:35 p.m. ET	Overview: Welcome and Introductions
5:35 – 6:10 p.m. ET	Presentation and Discussion
6:10 – 6:25 p.m. ET	Question and Answer Session
6:25 – 6:30 p.m. ET	Closing Remarks

Webinar faculty

Marcela V. Maus, MD, PhD – *Massachusetts General Hospital*

Shannon L. Maude, MD, PhD – *Children's Hospital of Philadelphia and University of Pennsylvania*

Michael R. Bishop, MD – *The University of Chicago*

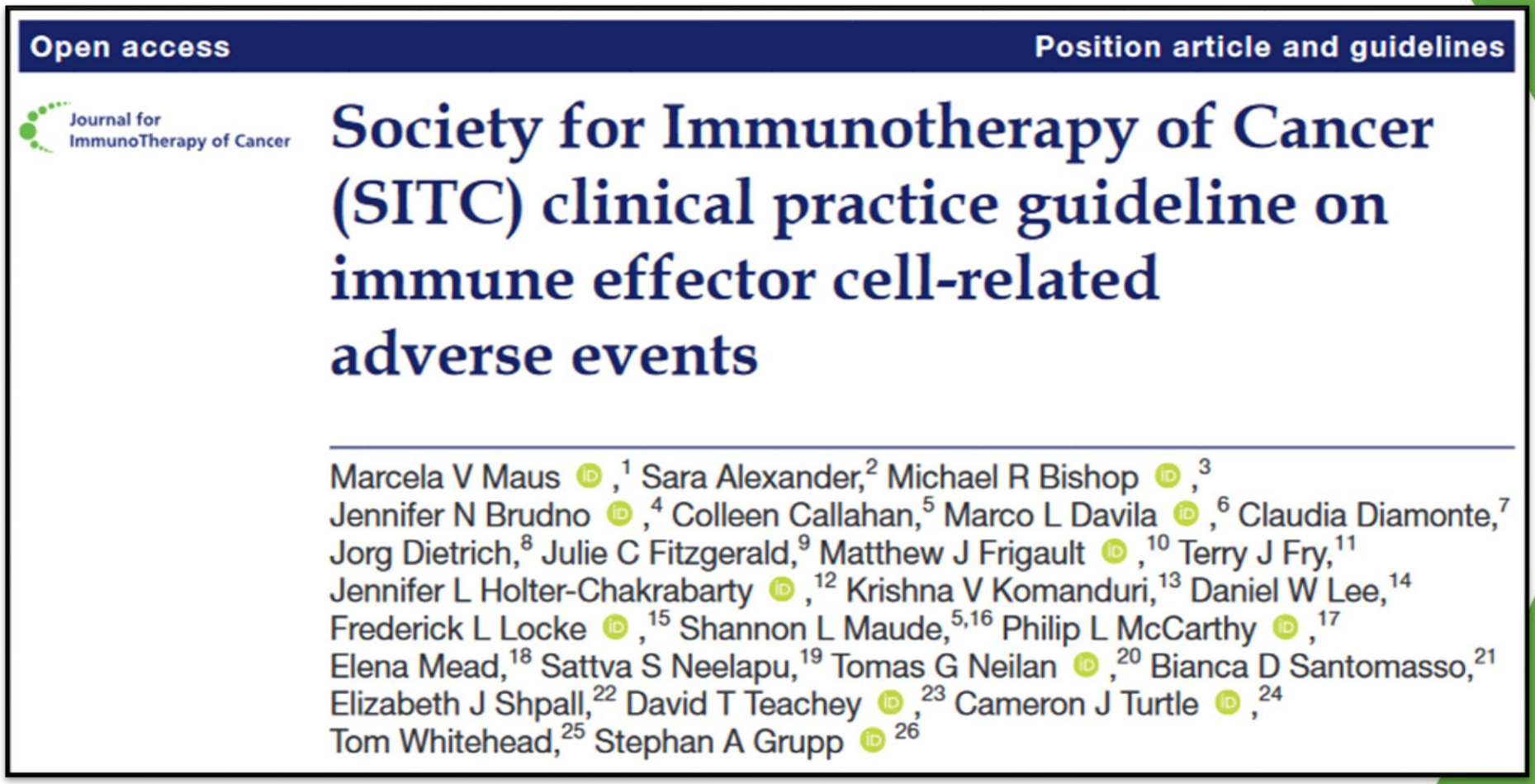
Learning objectives

1. Identify early and late toxicities related to CAR T cell therapy
2. Understand the differences in toxicities between different CAR T cell products
3. Select appropriate treatment strategies related to CAR T cell toxicities
4. Articulate the potential risks and benefits for proceeding with any other possible interventions in the context of immune effector cell treatments

Webinar outline

- Guideline development
- Background on grading systems and toxicity biology
- Straight-forward management
- Nuanced cases:
  - Low-grade CRS + high-grade neurotoxicity
  - Long-term toxicities (cytopenias)
  - Severe CRS HLH/MAS management

Development of the guideline



Open access Position article and guidelines

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune effector cell-related adverse events

Marcela V Maus [1], Sara Alexander,[2] Michael R Bishop [3], Jennifer N Brudno [4], Colleen Callahan,[5] Marco L Davila [6], Claudia Diamonte,[7] Jorg Dietrich,[8] Julie C Fitzgerald,[9] Matthew J Frigault [10], Terry J Fry,[11] Jennifer L Holter-Chakrabarty [12], Krishna V Komanduri,[13] Daniel W Lee,[14] Frederick L Locke [15], Shannon L Maude,[5,16] Philip L McCarthy [17], Elena Mead,[18] Sattva S Neelapu,[19] Tomas G Neilan [20], Bianca D Santomasso,[21] Elizabeth J Shpall,[22] David T Teachey [23], Cameron J Turtle [24], Tom Whitehead,[25] Stephan A Grupp [26]

Development of the guideline

- Panel included 15 members
- Developed in accordance with The Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines
- Recommendations are based on literature evidence where available and expert consensus where necessary
- Consensus is defined as ≥75% agreement amongst panel members

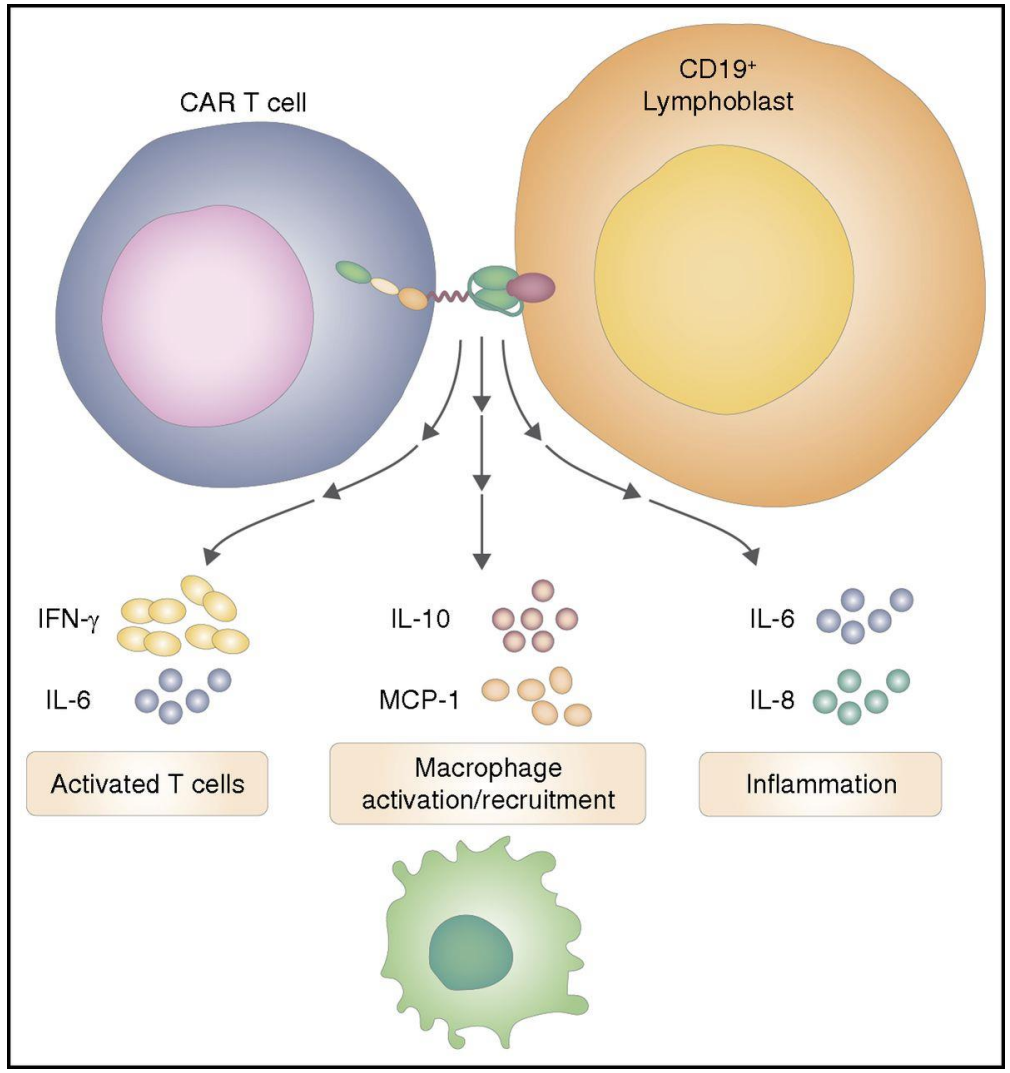
Webinar outline

- Guideline development
- Background on grading systems and toxicity biology
- Straight-forward management
- Nuanced cases

Toxicities of CAR T Cells Targeting CD19

<u>Acute:</u>
CRS
Neurotoxicity
Cytopenias

<u>Chronic:</u>
B cell aplasia
Cytopenias



Maude SL. Blood 2017;130:2238-2240

The need for specialized CRS Grading Scales

Grading Scale	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE v4.0	Mild No infusion interruption No intervention	Infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medications and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support

Can't "interrupt" a CAR T cell therapy

Fever >24h automatically raises grade to 3

Most CRS after CAR T cells would be graded as 3/4; therefore, miss the high degree of variability in CRS

CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; NSAID, nonsteroidal anti-inflammatory drug.

1. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed September 26, 2016.

CAR T cell CRS Grading Scales

- Institutions conducting CAR T cell trials developed CRS grading scales to more accurately capture the severity spectrum

Grading Scale	Grade 1	Grade 2	Grade 3	Grade 4
UPenn/CHOP	Mild reaction treated with supportive care only	Moderate reaction requiring IV therapies or parenteral nutrition. Mild signs of organ dysfunction (creatinine ≤ grade 2 or LFTs ≤ grade3) Hospitalization for CRS or febrile neutropenia	More severe reaction requiring hospitalization. Moderate signs of organ dysfunction (grade 3 creatinine or grade 4 LFTs) related to CRS. Hypotension treated with IV fluids or low-dose pressors Hypoxemia requiring oxygenation, BiPAP, or CPAP	Life-threatening complications including hypotension requiring high-dose vasoactives or hypoxemia requiring mechanical ventilation
2014 NCI Consensus	Symptoms are not life threatening and require symptomatic treatment only; eg, fever, nausea, fatigue, headache, myalgias, malaise	Symptoms require and respond to moderate intervention Oxygen requirement < 40% or hypotension responsive to fluids or low-dose pressors or grade 2 organ toxicity	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% or hypotension requiring high-dose or multiple pressors or grade 3 organ toxicity or grade 4 transaminitis	Life-threatening symptoms Requirement for ventilator support or grade 4 organ toxicity (excluding transaminitis)
CTCAE v4.0 (blinatumomab)	Mild No infusion interruption No intervention	Infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (eg, not rapidly responsive to symptomatic medications and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilator support

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1. Lee D et al., *Blood.* 2014; 124(2):188-195; 2. Fitzgerald JC, et al. *Crit Care Med*. 2016;44(12):2241-2250.
3. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed September 26, 2016.

Comparison of CRS Grading Scales

Hypotension treated with high-dose pressors

Grading Scale	Grade 1	Grade 2	Grade 3	Grade 4
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Penn/CHOP: Grade 4

NCI: Grade 2

NCI: Grade 1

CTCAE: Grade 4

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1. Lee D et al., *Blood.* 2014; 124(2):188-195; 2. Fitzgerald JC, et al. *Crit Care Med*. 2016;44(12):2241-2250.
3. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed September 26, 2016.

Case Study: A Patient With CRS Graded Using 3 Different Scales

Grading Scale	Grade 1	Grade 2	Grade 3	Grade 4
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- Case: 32-year-old with r/r ALL treated with CTL019
- The patient developed hypotension requiring low-dose pressors after therapy
- Question: How would the patient's CRS be graded?

Scale	Grade
UPenn/CHOP[2]	**3**
NCI[1]	**2**
CTCAE v4.0[3]	**4**

Frey, ASH 2016

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1. Lee D et al., *Blood.* 2014; 124(2):188-195; 2. Fitzgerald JC, et al. *Crit Care Med*. 2016;44(12):2241-2250.
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Webinar outline

- Guideline development
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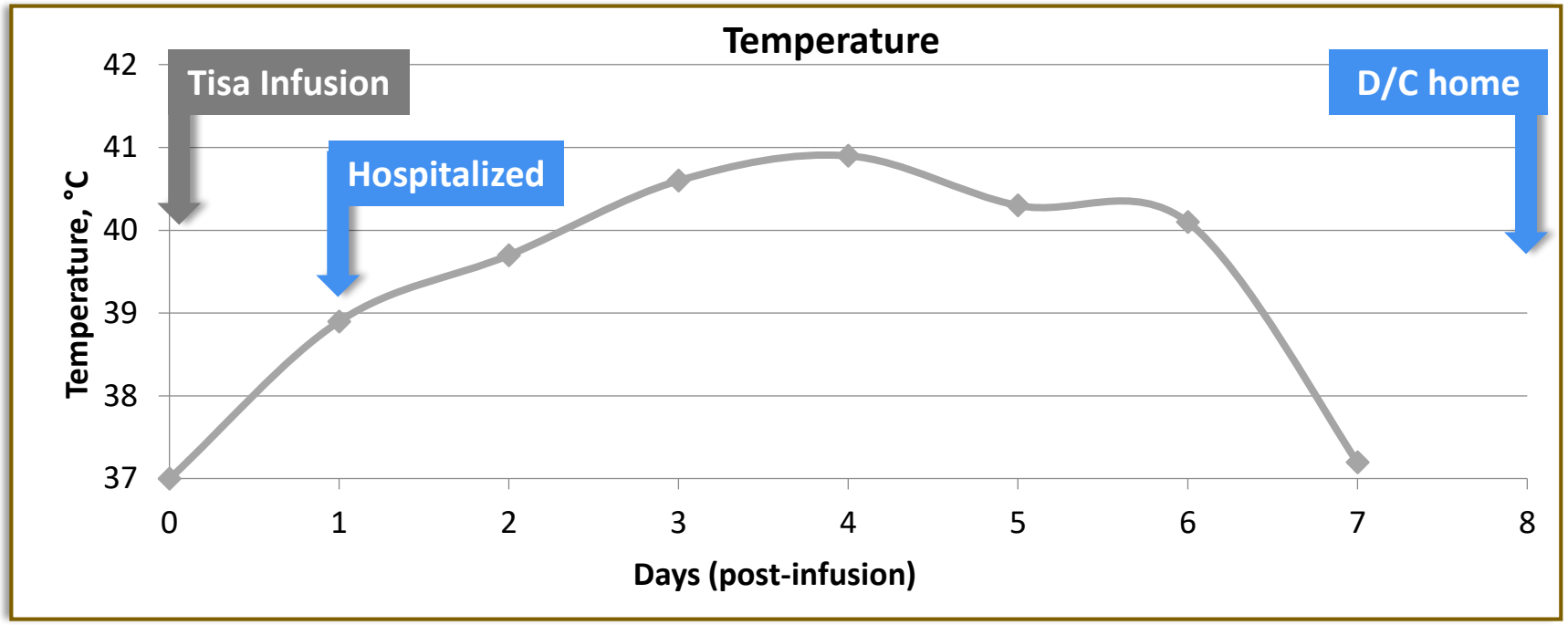
- Straight-forward management
- Nuanced cases

Case: 5-year-old girl with 2nd B-ALL Relapse, BM 5% blasts pre-infusion



Narcotics (days 3-6)

Myalgias (days 2-7)

Antibiotics (days 1-7)

Case Discussion:

- Would your management have changed?
  - If this were a 65-year-old?
  - If the pre-infusion bone marrow had 90% blasts?
  - If this patient were treated with a CD28 product?

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Case: 15-year-old boy with 2nd CNS Relapse of B-ALL

- Prior therapy included cranial radiation, triple intrathecals, and CNS-directed systemic chemotherapy
- Complications: methotrexate neurotoxicity – hemiparesis, fully recovered
- Presented with headaches -> LP showed CSF WBC 330, BM MRD 0.5%
- CSF cleared after 3 weekly triple intrathecals

Case: 15-year-old boy with 2nd CNS Relapse of B-ALL

- Pre-infusion CSF neg, BM MRD neg
- Day 0 – tisagenlecleucel infusion
- Day +4 – hospitalized for fever
- Day +7 – develops confusion and hallucinations; persistent high fevers, hemodynamically stable, no hypoxia or respiratory distress
- Day +8 – progresses to obtundation, EEG reveals subclinical status epilepticus; CRS remains grade 1 on ASTCT scale

Case Discussion:

- What would your management include?
- Would your management have changed?
  - If the pre-infusion bone marrow had 90% blasts and CRS was grade 4?
  - If this patient had already received tocilizumab?
  - If this patient were treated with a CD28 product and symptoms progressed over the first 24 hours after infusion?

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- Nuanced cases:
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Case: 21-year-old male with refractory B-ALL

- Early medullary relapse
- Refractory to intensive reinduction – BM 50% blasts with ANC 0
- Refractory to blinatumomab – BM 90% blasts, CD19+ with ANC 50
- Referred for CAR T cell therapy
- Receives HD AraC and develops S mitis bacteremia, cleared but remains on broad-spectrum antibiotics without ANC recovery
- Returns for infusion with ANC 0 (ANC has been 0-50 for >3 months)

Case: 21-year-old male with refractory B-ALL

- Pre-infusion BM 90% blasts
- Day 0 – receives tisagenlecleucel infusion
- Experiences grade 4 CRS
- Receives tocilizumab with improvement
- Day +28 – BM MRD neg, cellularity <5%, ANC 0
- Starts G-CSF
- By month 3, ANC recovers to 500, G-CSF stopped, BM 10% cellularity

Case Discussion:

- What are the risk factors for prolonged cytopenias?
- Would your management have changed?
  - If the ANC remained 0 and cellularity <5% at month 3?
  - If the patient developed persistent bacteremia?
  - If this patient had a prior HSCT? When would you consider stem cell boost?

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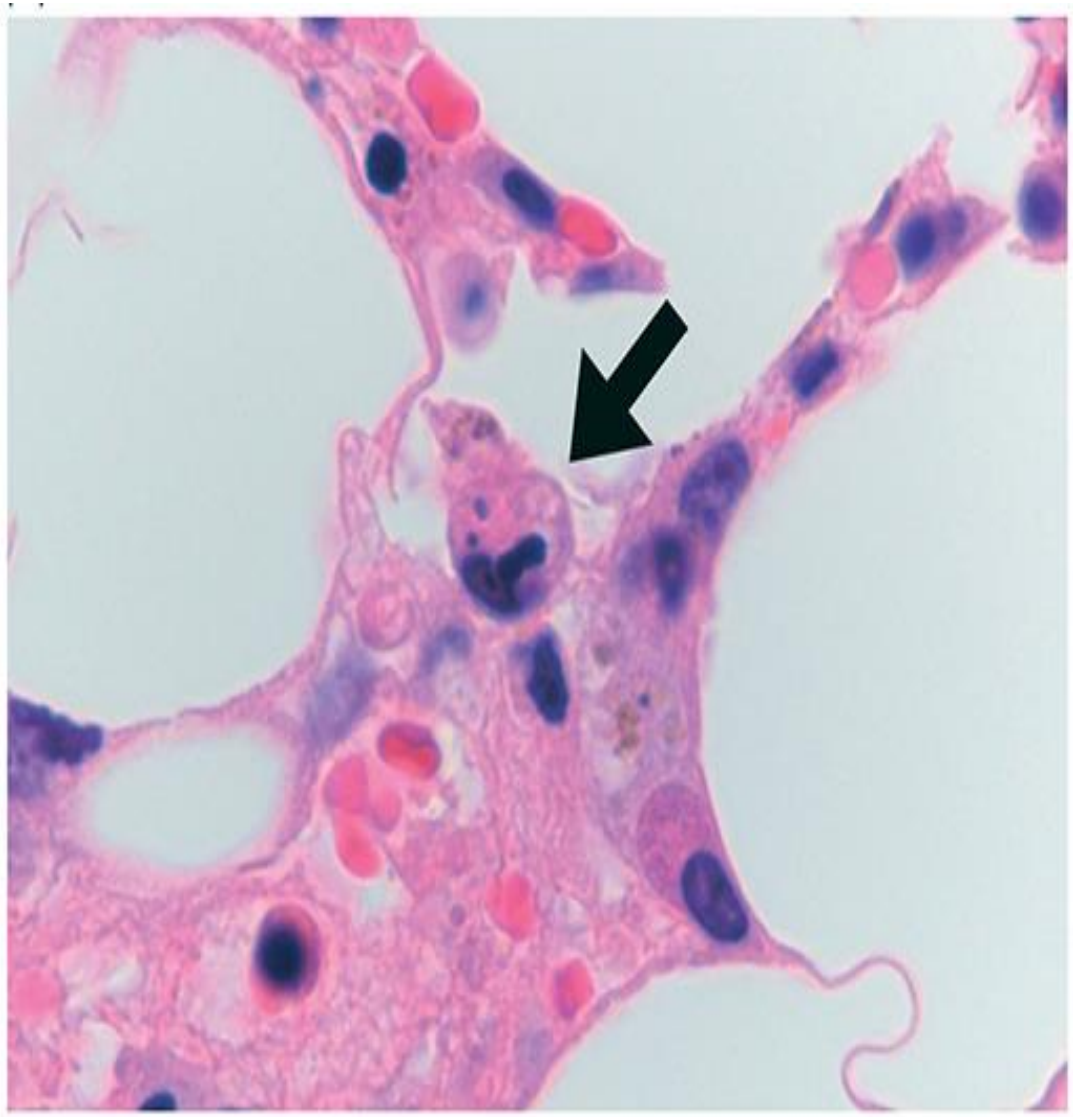
Case Presentation

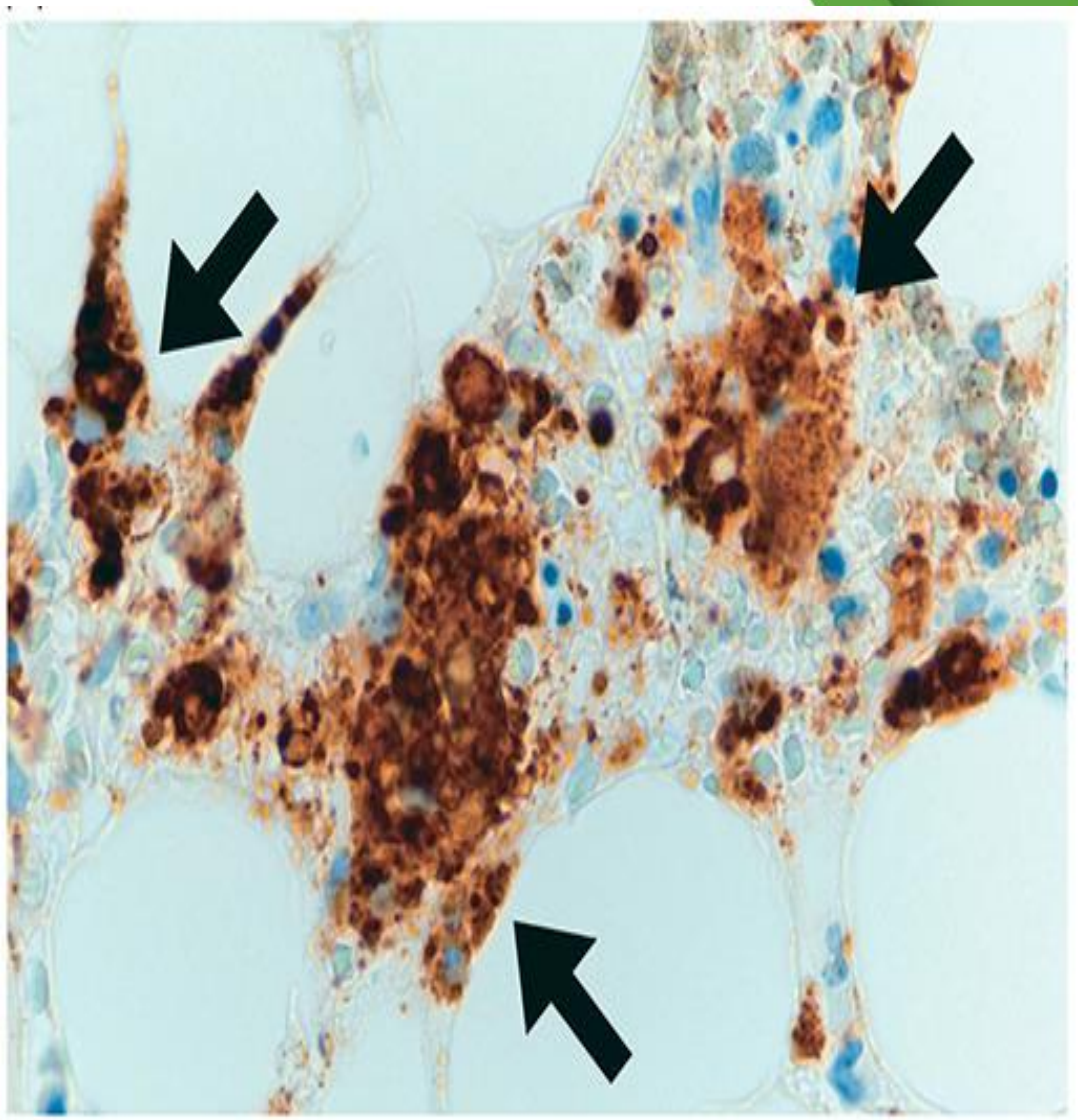
- A 23yo F with r/r Ph(-) B-ALL was admitted for CAR-T therapy with tisagenlecleucel (tisa-cel; Kymriah®) preceded by fludarabine and cyclophosphamide lymphodepletion.
- On admission, the patient was pancytopenic with 50–60% iBM nvolvement by B-ALL.
- At the time of tisa-cel infusion, the patient was afebrile, hemodynamically within normal limits, and had a baseline ferritin of 3200 ng/mL.
- The patient developed Grade 1 CRS on *D*+1 with a fever (39.7 °C) without any hypotension or hypoxia. She received empiric antipyretics and antibiotics for neutropenic fever.
- She continued to have temps >39 °C during *D*+2 and *D*+3 after CAR-T and was given tocilizumab 8 mg/kg IV x 1 and scheduled dexamethasone 10 mg IV daily on *D*+3.

Case Presentation

- Fevers persisted to 40.1 °C on *D*+4 through *D*+6, and she received tocilizumab 8 mg/kg on *D*+5 and again on *D*+6.
- She did not defervesce despite toci x 3 and daily dexamethasone, but only met criteria for Grade 1 CRS and without evidence of ICANS.
- Her ferritin had increased to 37,437 mg/mL by *D*+6. She the received siltuximab 11 mg/kg IV once and anakinra 100 mg subcutaneously once on *D*+6 and dexamethasone was increased to 10 mg IV every 6h.
- On *D*+7, the patient continued to be febrile with ferritin increasing to 55,909 mg/mL. dexamethasone was increased to 20 mg IV every 6 h.

Case Presentation





ZUMA-3: CRS and Neurologic Events

Parameter	N=55
CRS	
Any grade CRS, n (%)[a,b]	49 (89)
Grade ≥3	13 (24)
Most common any grade symptoms, n (%)[c]	
Pyrexia	46 (94)
Hypotension	33 (67)
Median time to onset (range), days	5
Median duration of events, days	7.5
Neurologic Events	
Any grade neurologic event, n (%)[b]	33 (60)
Grade ≥3	14 (25)
Most common any grade symptoms, n (%)	
Tremor	15 (27)
Confusional state	14 (25)
Median time to onset (range), days	9
Median duration of events, days	7

[a] CRS was graded per Lee DW, et al. *Blood*. 2014;124:188–195. [b] Individual symptoms of CRS and neurologic events were graded per National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03. [c] Percentages for individual CRS symptoms were calculated out of the 49 patients who experienced CRS. CRS, cytokine release syndrome.

- No Grade 5 CRS occurred
- One patient had Grade 5 brain herniation related to KTE-X19
- Tocilizumab, steroids, and vasopressors were given to 80%, 75%, and 40% of patients, respectively

Shah et al. ASCO 2021

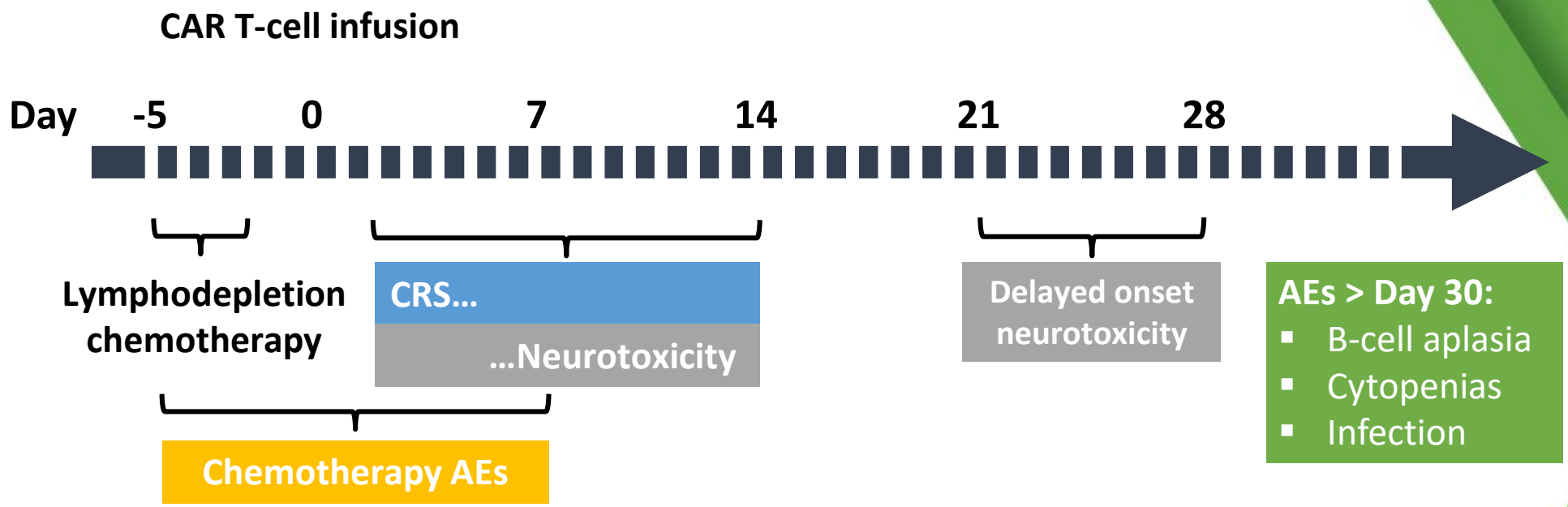
Class Effects of the Cell-Mediated Immune Response: CRS and Neurotoxicity

	B-ALL		DLBCL		
	ELIANA[1]	ZUMA-3[2]	JULIET[3]	ZUMA-1[4]	TRANSCEND[5]
CAR T-cell agent	Tisagenlecleucel	KTE-X19	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel
N treated	75	45	111	101	269
CRS, %	77*	93†	58*	93†	42†
Grade ≥ 3 CRS, %	46*	29†	22*	13†	2†
NT, %	40	78	21	64	30
Grade ≥ 3 NT, %	13	38	12	28	10

*Per Penn scale. †Per Lee Scale.

1. Maude. NEJM. 2018;378:439. 2. Shah. ASCO 2019. Abstr 7006. 3. Schuster. NEJM. 2019;380:45. 4. Neelapu. NEJM. 2017;377:2531. 5. Abramson. ASH 2019. Abstr 241. 6. Wang. NEJM. 2020;382:1331. 7. Raje. NEJM. 2019;380:1726.

CAR T-Cell Toxicities Timeline



Number of Days (Range)	CRS		Neurologic AEs	
	Median Time to Onset	Median Duration	Median Time to Onset	Median Duration
Axicabtagene ciloleucel[1]	2 (1-12)	7 (2-58)	4 (1-43)	17
Tisagenlecleucel[2]	3 (1-51)	8 (1-36)	6 (1-359)	ALL: 6; DLBCL: 14

1. Axicabtagene ciloleucel PI. 2. Tisagenlecleucel PI.
Lee. Blood. 2014;124:188. Brudno. Blood. 2016;127:3321. Neelapu. Nat Rev Clin Oncol. 2018;15:47.

Incidence and Monitoring Long-term CAR T Toxicities

B-cell Aplasia/ Hypogammaglobulinemia

- ~ 15% of adults with R/R LBCL or MCL treated with axicabtagene ciloleucel, brexucabtagene autoleucel, or tisagenlecleucel in pivotal trials
- 43% of pediatric/young adult R/R B-cell ALL treated with tisagenlecleucel in pivotal trials
- Immunoglobulin levels should be monitored following therapy

Cytopenias

- Grade ≥ 3 cytopenias unresolved by Day 30 post treatment occur in a significant proportion of patients
- Blood counts should be monitored following therapy

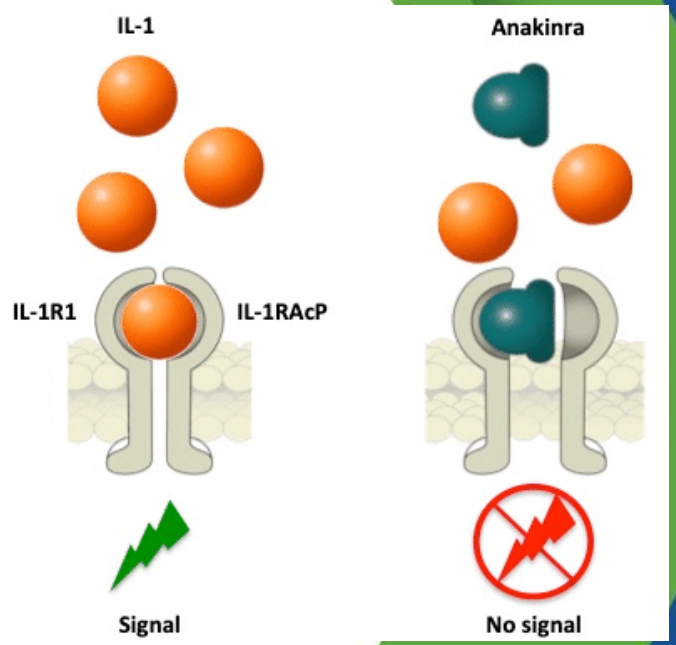
Infections

- Occurred in 38% to 56% of patients treated with approved agents in pivotal trials

Axicabtagene ciloleucel PI. Brexucabtagene autoleucel PI. Tisagenlecleucel PI.

Late CAR T-Cell Toxicities

Toxicity	Management Strategies
Cytopenias	▪ Cytokines ▪ Transfusions
Macrophage activation-like syndrome	▪ Measure ferritin, IL-2R, NK cell activation, coags ▪ Anakinra
B-cell lymphopenia/aplasia	▪ IVIg ▪ Antimicrobial prophylaxis
Late CNS toxicities	▪ Steroids ▪ Supportive care



Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Neelapu. Hematol Oncol. 2019;37(suppl 1):48. Mehta. Lancet Rheumatol. 2020;2:358.

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Questions or comments: connectED@sitcancer.org

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