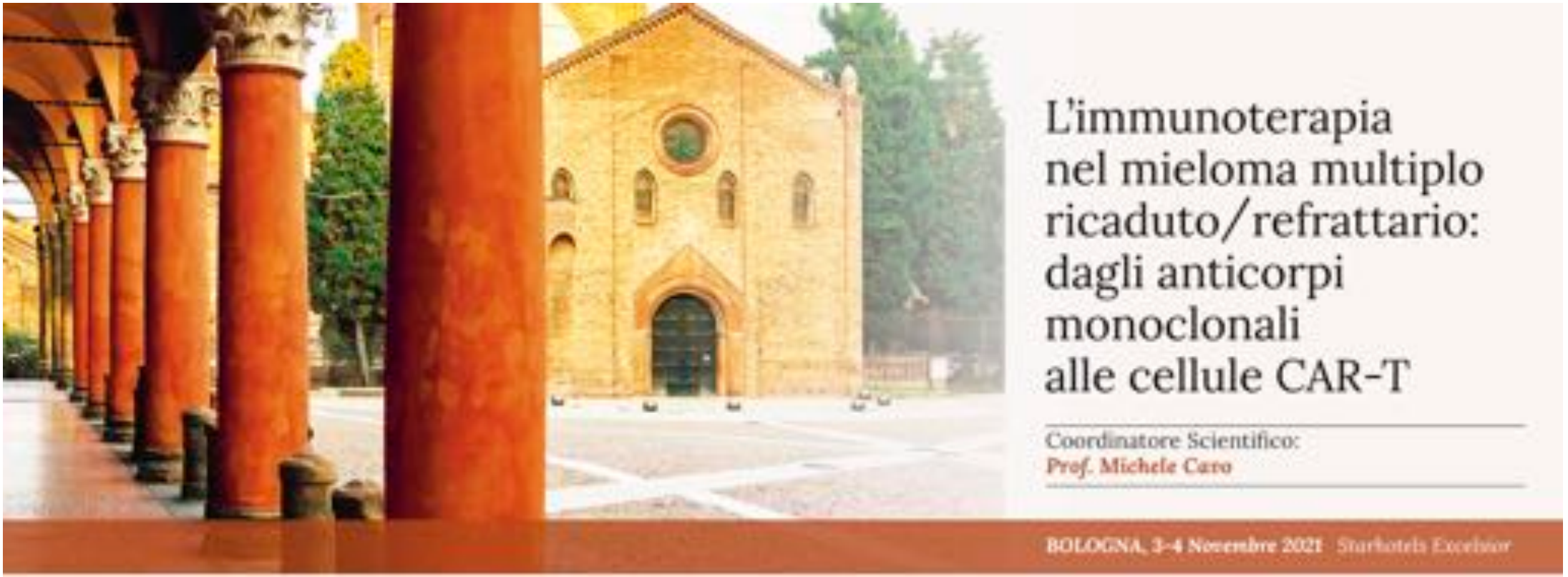

Eventi avvversi dell' immunoterapia con CAR-T e anticorpi bispecifici e loro gestione

Elena Zamagni

Istituto di Ematologia "Seragnoli"

IRCCS, Azienda Ospedaliero-Universitaria S. Orsola-Malpighi di Bologna

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Overview of T- cell re-directed therapies adverse reactions

Serious life-threatening reactions that may lead to death are known to occur with T-cell redirected therapies

Serious AEs include **CRS, NT, HLS/MAS, and cytopenia's**

Other adverse events may be serious or life-threatening and include:

- Hypersensitivity reactions
- Serious infections
- Prolonged cytopenias
- Hypogammaglobulinemia; related to B cell aplasia
- Secondary malignancies

1. Lee DW et al. *Biol Blood Marrow Transplant* 2019;25:625–638. 2. DailyMed - KYMRIAH- tisagenlecleucel injection, suspension. Retrieved from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189. 3. DailyMed - YESCARTA- axicabtagene ciloleucel suspension. Retrieved from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59.

Cytokine release syndrome (CRS)

CRS: *Cytokine release syndrome*

Inflammatory process related to exponential T cell proliferation and activation/expansion

Release of supra-physiological levels of pro-inflammatory cytokines (IL-6, INFγ, TNFα)

IL-6 believed to be central mediator

Onset 1–7 days after treatment, duration 7–8 days

High levels of CRP, ferritin, IL-6, IL-10

Associated with high tumor burden

- Clinical signs and symptoms of CRS:
  - High fever
  - Rigors
  - Hepatorenal toxicities
  - Myalgia
  - Arthralgia
  - Nausea
  - Vomiting
  - Fatigue
  - Anorexia
  - Dyspnea
  - Tachypnea
  - Hypoxia[a]
  - Hypotension[a]
  - Tachycardia

CRS grading criteria: Lee et al. *Blood*. 2014

Grade	Lee et al. 2014 Criteria
1	• Symptoms are not life threatening, require symptomatic treatment (e.g. fever, nausea, fatigue, headache, myalgias, malaise)
2	• Symptoms require and respond to moderate intervention • Oxygen requirement, 40% OR • Hypotension responsive to fluids or low dose of one vasopressor OR • Grade 2 organ toxicity[a]
3	• Symptoms require and respond to aggressive intervention • Oxygen requirement ≥ 40% OR • Hypotension requiring high dose or multiple vasopressors OR • Grade 3 organ toxicity[a] or Grade 4 transaminitis
4	• Life-threatening symptoms • Requirement for ventilator support OR • Grade 4 organ toxicity[a] (excluding transaminitis)
5	• Death

[a]As per CTCAE Version 4.03.

Abbreviations are defined in the Notes Page section.

1. Lee DW et al. *Blood* 2014;124:188-195. 2. Raje N et al. *N Engl J Med* 2019;380:1726-1737.

CRS grading criteria: ASTCT consensus grading[a]

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[b]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
With either:				
Hypotension	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or[c]				
Hypoxia	None	Requiring low-flow nasal cannula[d] or blow-by	Requiring high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

[a]Organ toxicities related to CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

[b]Fever is defined as temperature ≥38°C not due to any other cause. In patients who have CRS then receive antipyretics or anti-cytokine therapy such as tocilizumab or steroids, fever is not required to grade subsequent CRS severity. Here, CRS grading is driven by hypotension and/or hypoxia.

[c]CRS grade is assessed by the more severe event: hypotension or hypoxia not due to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring one vasopressor and hypoxia requiring low-flow nasal cannula is classified as having Grade 3 CRS.

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

- Hypotension and hypoxia are the principle determinants of this consensus grading scale
- Grade 5 is defined as death due to CRS where another cause is not the principle factor
- CRS treatment guidelines continue to evolve and may change over time

Abbreviations are defined in the Notes Page section.

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

NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines®) for CRS management: ASTCT consensus grading[a,b]

CRS	Anti-IL-6 Therapy	Corticosteroids[e,f]	Additional Supportive Care
Grade 1 Fever (≥ 38°C)	• For prolonged CRS (> 3 days) in patients with significant symptoms and/or comorbidities, consider tocilizumab per **Grade 2**	• N/A	• Empiric broad-spectrum antibiotics • Consider G-CSF if neutropenic[h] • Maintenance IV fluids for hydration • Organ toxicity management
Grade 2 Fever with hypotension not requiring vasopressors and/or hypoxia[c] requiring low-flow cannula[d] or blow-by	• Tocilizumab 8 mg/kg IV over 1 hour (do not exceed 800 mg/dose)[e] • 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 treatment: Dexamethasone 10 mg IV Q6H or equivalent[g]	• IV fluid boluses PRN • For persistent refractory hypotension after 2 fluid boluses and anti-IL-6: start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring • Manage per **Grade 3** if no improvement within 24 hours after anti-IL-6 treatment initiation • Symptomatic organ toxicity management

[a]For HLH/MAS during CRS, treat as per CRS with addition of steroids. If symptoms do not improve within 48 hours, consider etoposide and intrathecal cytarabine for neurotoxicity. [b]With permission from Elsevier: Lee DW et al. ASTCT Consensus Grading for CRS and NT Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019;25:625-38. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Common Attribution-NonCommercial-No Derivatives License (CC BY NYC ND). [c]CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other causes. [d]Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low flow includes blow-y oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min. [e]After each dose assess need for subsequent dosing. [f]Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity. [g]Alternative steroids at an equivalent dose may be considered. [h]GM-CSF is not recommended in the setting of CAR T-cell therapy.

Abbreviations are defined in the Notes Page section.

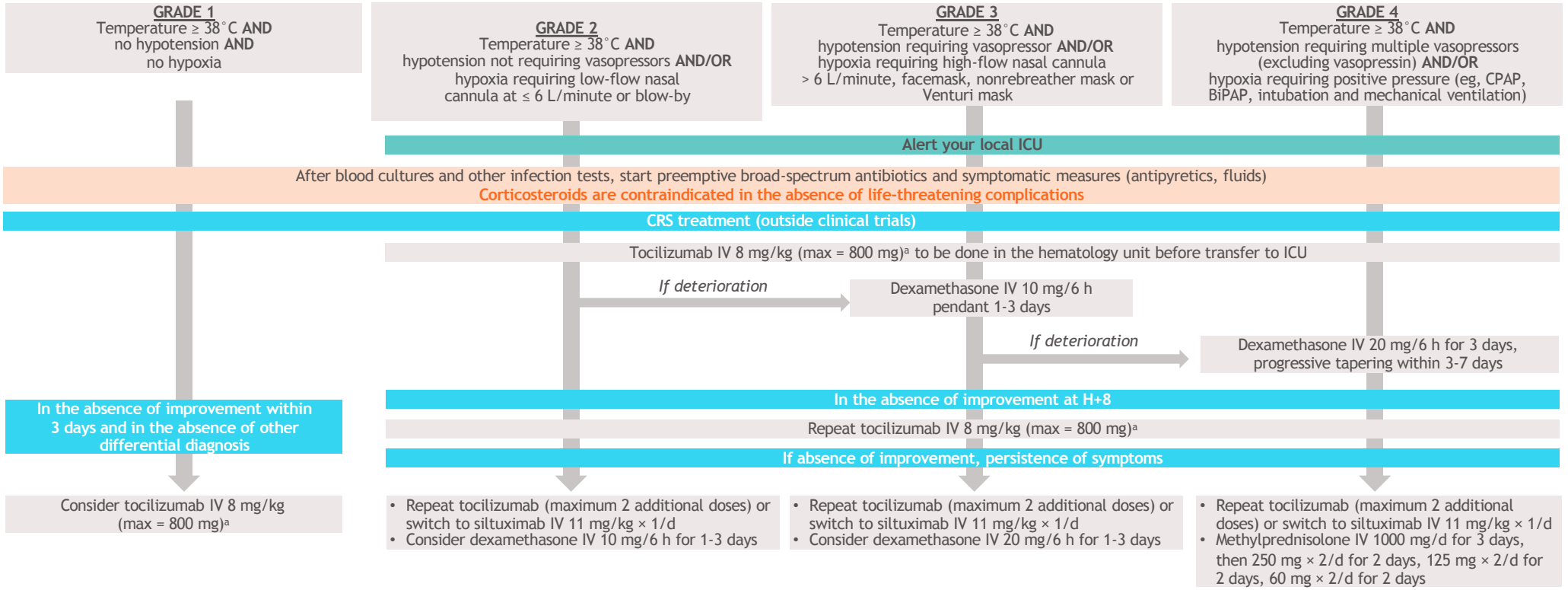
NCCN guidelines® for CRS management – ASTCT consensus grading[a,b]

CRS	Anti-IL-6 Therapy	Corticosteroids[d,e]	Additional Supportive Care
Grade 3 Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula[c], facemask, non-rebreather mask or Venturi mask	• Tocilizumab dosage per **Grade 2**[d] if maximum dose is not reached within the 24-hour period	• Dexamethasone 10 mg IV Q6H or alternative steroids at an equivalent dose[f] • If refractory, manage per **Grade 4**	• Transfer to ICU, obtain ECG, start hemodynamic monitoring • Supplemental oxygen • IV fluid bolus and vasopressors PRN • Organ toxicity management
Grade 4 Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (e.g. CPAP, BiPAP, intubation, mechanical ventilation)	• Tocilizumab dosage per **Grade 2**[d] if maximum dose is not reached within the 24-hour period	• Dexamethasone 10 mg IV Q6H or alternative steroids at an equivalent dose[f] • If refractory, consider methylprednisolone 1 g/day IV[g]	• ICU care and start hemodynamic monitoring • Mechanical ventilation PRN • IV fluid bolus and vasopressors PRN • Organ toxicity management

[a]For HLH/MAS during CRS, treat as per CRS with addition of steroids. If symptoms do not improve within 48 hours, consider etoposide and intrathecal cytarabine for neurotoxicity.
[b]With permission from Elsevier: Lee DW et al. ASTCT Consensus Grading for CRS and NT Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019;25:625-38. DOI: https://doi.org/10.1016/j.bbmt.2018.12.758. This article is published under the terms of the Creative Common Attribution-Non Commercial-No Derivatives License (CC BY NYC ND).
[c]Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/min. Low flow includes blow-y oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min. [d]After each dose assess need for subsequent dosing. [e]Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity. [f]Alternative steroids at an equivalent dose may be considered. [g]For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days

Abbreviations are defined in the Notes Page section.

EBMT/JACIE recommendations for CRS management



[a]In children weighing less than 30 kg, tocilizumab is given at the dose of 12 mg/kg.
Abbreviations are defined in the Notes Page section.
Algorithm adapted from Yakoub-Agha I, et al. *Haematologica*. 2020;105:297-316.
Yakoub-Agha I et al. *Haematologica* 2020;105:297-316.

Neurotoxicity (ICANS)

ICANS: *Immune effector cell-associated neurotoxicitity syndrome*

Pathophysiology thought to include endothelial activation/dysfunction and microangiopathy

Typical onset 4–5 days, typical duration 14–17 days. May occur together with CRS or independently (after CRS).

Diminished attention, language disturbance, confusion, disorientation, and occasionally seizures/cerebral oedema, delirium (life threatening)

- Clinical signs and symptoms of neurologic events:
  - Altered mental status
  - Aphasia
  - Tremor
  - Ataxia
  - Dysgraphia
  - Headache
  - Altered level of consciousness
  - Impairment of cognitive skills
  - Motor weakness
  - Encephalopathy
  - Seizures or seizure-like activity

1. Brudno JN et al. *Blood* 2016;127:3321-3330. 2. Gust J et al. *Cancer Discov* 2017;7:1404-1141. 3. Hunter BD et al. *J Natl Cancer Inst* 2019;111:646-654. 4. Turtle CJ et al. *J Clin Invest* 2016;126:2123-2138.

Neurotoxicity grading criteria: ASTCT consensus grading

Immune-Effector Cell Associated Encephalopathy (ICE)	Assessment	Score
Orientation	Oriented to date, location	4
Naming	Able to name 3 objects	3
Following commands	Able to follow simple commands	1
Writing	Able to write a standard sentence	1
Attention	Able to count backwards from 100 by 10	1

- This consensus grading scale uses a slightly modified version of the CARTOX-10 screening tool to provide objectivity for the grading of multiple overlapping encephalopathy terms included in the approved CAR T cell products
- The grading of ICANS requires assessment of the 10-point ICE score as well as evaluation of other neurologic domains, which may occur with or without encephalopathy, such as:
  - Level of consciousness
  - Motor symptoms
  - Seizures
  - Signs of elevated ICP/cerebral edema

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

Neurotoxicity grading criteria: ASTCT ICANS consensus grading

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 level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to touch	Patient is unarousable or requires vigorous or repetitive stimulus to arouse
Seizure	N/A	N/A	Any clinical seizure that resolves rapidly or nonconvulsive seizures that resolve with intervention	Life-threatening prolonged seizure (> 5 minutes) or repetitive seizures without intermittent 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

- These consensus guidelines are more aligned with the CTCAE v5.0
- Grade 5 is defined as death due to ICANS, wherein another cause is not the principle factor leading to the outcome

Abbreviations are defined in the Notes Page section.

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

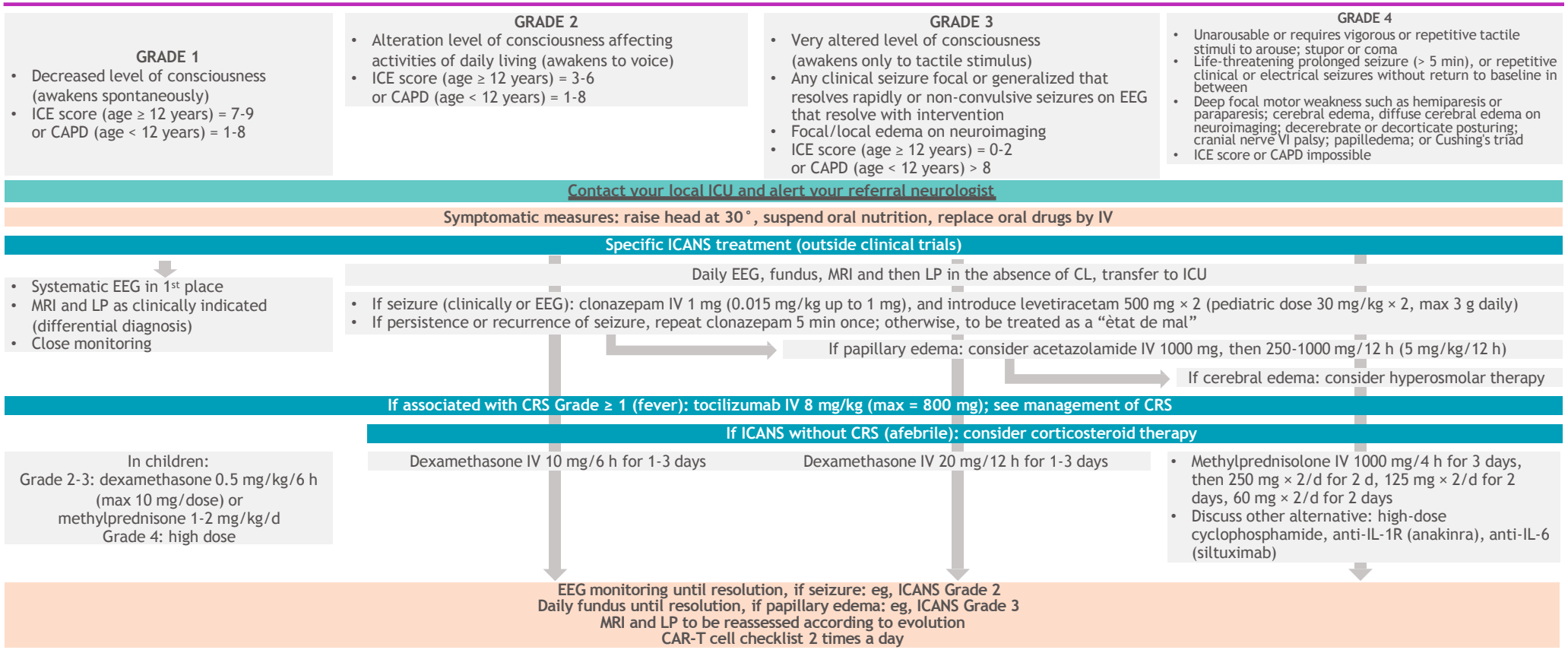
NCCN guidelines for neurotoxicity management

Treatment by Grade	No Concurrent CRS	Additional Therapy if Concurrent CRS
Grade 1	• Supportive care	• Tocilizumab 8 mg/kg IV over 1 hour (do not exceed 800 mg/dose)[a]
Grade 2[b]	• Supportive care • Dexamethasone 10 mg IV × 1 and reassess. Can repeat every 6–12 hours, if no improvement.	• Anti-IL-6 therapy per **Grade 1**[a] • Consider transferring patient to ICU if neurotoxicity associated with Grade ≥ 2 CRS
Grade 3[b]	• ICU care recommended • Dexamethasone 10 mg IV Q6H or methylprednisolone 1 mg/kg IV Q12H[c,d] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity	• Anti-IL-6 therapy per **Grade 1**[a]
Grade 4[b]	• ICU care, consider mechanical ventilation for airway protection • High-dose corticosteroids[c,e] • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity • Treat convulsive status epilepticus per institutional guidelines	• Anti-IL-6 therapy per **Grade 1**[a]

[a]Repeat every 8 hours as needed if not responsive to IV fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. [b]Diagnostic lumbar puncture for Grade 3-4 neurotoxicity; consider for Grade 2. [c]Antifungal prophylaxis should be strongly considered in patients receiving steroids for the treatment of CRS and/or neurotoxicity. [d]For axicabtagene ciloleucel or brexucabtagene autoleucel, methylprednisolone 1 g daily for 3-5 days may be preferable [e]For example, methylprednisolone IV 1000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 25 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days.

Abbreviations are defined in the Notes Page section.

EBMT/JACIE recommendations for neurotoxicity management



Abbreviations are defined in the Notes Page section.

Yakoub-Agha I et al. *Haematologica* 2020;105:297-316.

Algorithm adapted from Yakoub-Agha I et al. *Haematologica* 2020;105:297-316.

Additional toxicities

Additional toxicities	Management Strategies
Cytopenias	▪ Supportive care
Macrophage activation-like syndrome	▪ Measure ferritin, IL-2R, NK cell activation, coags ▪ Steroids, IV Ig, Anakinra
Immunosuppression	▪ IV Ig ▪ Antimicrobial prophylaxis

ASTCT, American Society for Transplantation and Cellular Therapy; CRP, C-reactive protein; ICU, intensive care unit; Ig , immunoglobulin; IL, interleukin; INF, interferon; IV, intravenous; NK, natural killer; TNF, tumor necrosis factor.

1. Maus MV, et al. *J Immunother Cancer* 2020;8:e001511. **2.** Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25:625. **3.** Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15:47. **4.** Mehta P, at al. *Lancet Rheumatol* 2020;2:358. **5**. Crayne CB, et al. *Front Immunol* 2019;10:119.

KARMMA: Safety results: AEs, CRS, neurotoxic effects, and deaths

Variable	Total (N = 128), n (%)	
	Any grade	Grade 3/4
AEs[a]		
Any	128 (100)	127 (99)
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	35 (27)	34 (27)
Febrile neutropenia	21 (16)	20 (16)
GI		
Diarrhea	45 (35)	2 (2)
Nausea	37 (29)	0
Constipation	20 (16)	0
Other		
Hypokalemia	45 (35)	3 (2)
Fatigue	43 (34)	2 (2)
Other (continued)		
Hypophosphatemia	38 (30)	20 (16)
Hypocalcemia	34 (27)	10 (8)
Pyrexia	32 (25)	3 (2)
Hypomagnesemia	30 (23)	0
Decreased appetite	27 (21)	1 (< 1)
Headache	27 (21)	1 (< 1)
Hypogammaglobulinemia	27 (21)	1 (< 1)
Cough	26 (20)	0
Hyponatremia	24 (19)	7 (5)
Hypoalbuminemia	22 (17)	4 (3)
Aspartate aminotransferase level increased	21 (16)	2 (2)
Hypotension	21 (16)	1 (< 1)
CRS[b]	107 (84)	7 (5)
Neurotoxic effect[c]	23 (18)	4 (3)

Deaths during the study

44 patients (34%) died during the study

- Most deaths (n=27) were attributed by the investigator to complications of myeloma progression
- 3 patients (2%) died within 8 weeks of ide-cel infusion due to ide-cel-related AEs (bronchopulmonary aspergillosis, GI hemorrhage, and CRS)
- A patient (1%) died between 8 weeks and 6 months from an ide-cel–related AE (CMV pneumonia)
- 5 patients (4%) died after 6 months from unrelated AEs
- 8 patients (6%) died after disease progression

- Infections occurred in 69% of patients, and 22% were grade 3/4
- Median time to recovery ≤ grade 2 neutropenia/thrombocytopenia: 2 months

Included with permission Munshi et al, 2021, N Engl Med

[a]AEs that occurred in ≥ 15% of the patients receiving ide-cel. [b]The clustered term includes the preferred term; events were uniformly graded according to Lee DW et al. *Blood* 2014;124:188–195. Included is 1 patient who had progression to a grade 5 event. [c]Investigator-identified neurotoxicity was the preferred term.

Munshi NC et al. N Engl J Med 2021;384:705-16. DOI: 10.1056/NEJMoa2024850

KarMMa study. NCT03361748

Characteristics and management of CRS

Parameter	Ide-cel target dose of CAR+ T cells			Total (N = 128)
	150×10^6 (n = 4)	300×10^6 (n = 70)	450×10^6 (n = 54)	
Patients with a CRS event, n (%)[a]	2 (50)	53 (76)	52 (96)	107 (84)
Grade 1	1 (25)	33 (47)	27 (50)	61 (48)
Grade 2	1 (25)	16 (23)	22 (41)	39 (30)
Grade 3	0	2 (3)	3 (6)	5 (4)
Grade 4	0	1 (1)	0	1 (< 1)
Grade 5	0	1 (1)	0	1 (< 1)
Median (range) time to onset, days	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median (range) duration, days	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab use, n (%)[b]	1 (25)	30 (43)	36 (67)	67 (52)
1 dose	1 (25)	21 (30)	22 (41)	44 (34)
> 1 dose	0	9 (13)	14 (26)	23 (18)
Glucocorticoid use, n (%)	0	7 (10)	12 (22)	19 (15)
Siltuximab use, n (%)	0	1 (1)	0	1 (< 1)
Anakinra use, n (%)	0	1 (1)	1 (2)	2 (2)

Included with permission Munshi et al, 2021, N Engl Med

[a]Uniformly graded per Lee DW et al. *Blood* 2014;124:188–195. [b]The decision to give tocilizumab was at the treating physician's discretion based on protocol-specified toxicity management guidelines.

- CRS frequency increased with dose, but was mostly low grade
- The median time to onset of CRS was 1 day (range, 1-12), with a median duration of 5 days (range, 1-63)
- Few grade 1 CRS events progressed to grade ≥ 3

- For the management of CRS, 52% (n=67) of patients received tocilizumab and 15% (n=19) were treated with glucocorticoids
- Most patients (83%) with maximum grade ≥ 2 CRS received at least 1 dose of tocilizumab and approximately one-third (35%) received corticosteroids, compared with 48% and 5%, of patients with maximum grade 1 CRS

KarMMa study. NCT03361748

Characteristics and management of ICANS

Parameter	Ide-cel target dose of CAR+ T cells			Total (N = 128)
	150×10^6 (n = 4)	300×10^6 (n = 70)	450×10^6 (n = 54)	
Patients with a neurotoxicity event, n (%)[a]	0	12 (17)	11 (20)	23 (18)
Grade 1	0	7 (10)	5 (9)	12 (9)
Grade 2	0	4 (6)	3 (6)	7 (5)
Grade 3	0	1 (1)	3 (6)	4 (3)
Median (range) time to onset, days	NA	3 (1–10)	2 (1–5)	2 (1–10)
Median (range) duration, days[b]	NA	3 (2–26)	5 (1–22)	3 (1–26)
Glucocorticoid use, n (%)	0	2 (3)	8 (15)	10 (8)
Tocilizumab use, n (%)	0	0	3 (6)	3 (2)
Anakinra use, n (%)	0	0	1 (2)	1 (< 1)

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[a]Investigator-identified neurotoxicity including the following preferred terms: bradyphrenia, brain edema, confusional state, dizziness, hallucination, insomnia, lethargy, memory impairment, neurotoxicity, nystagmus, somnolence, and tremor. Graded per CTCAE v4.03. [b]Ongoing events excluded from calculation. Overlapping events with different preferred terms were considered different events.

- The median time to any neurotoxic effect was 2 days (range, 1-10), with a median duration of 3 days (range, 1-26)
- For the management of neurotoxic effects, 2% (n=3) of patients received tocilizumab and 8% (n=10) were treated with glucocorticoids

Munshi NC et al. N Engl J Med 2021;384:705-16. DOI: 10.1056/NEJMoa2024850

Abbreviations are defined in the Notes Page section.

Table 3. Signs and symptoms reported in patients experiencing NT

Characteristics	All ide-cel treated (N=128)	
	Any grade	Grade 3 (n = 5)
Confusional state	12 (9.4)	1 (0.8)
Encephalopathy	7 (5.5)	3 (2.3)
Metabolic encephalopathy	1 (0.8)	1 (0.8)
Aphasia	6 (4.7)	1 (0.8)
Hallucination	4 (3.1)	—
Mental status changes	4 (3.1)	1 (0.8)
Delirium	3 (2.3)	—
Lethargy	3 (2.3)	1 (0.8)
Tremor	3 (2.3)	—
Asthenia	2 (1.6)	—
Cognitive disorder	2 (1.6)	—
Dysgraphia	2 (1.6)	—
Hemiparesis	2 (1.6)	1 (0.8)
Somnolence	2 (1.6)	—

[a]Events occurring in ≥ 2 patients or a grade 3 event.
Events occurring in 1 patient were amnesia, ataxia, bradyphrenia, disorientation, disturbance in attention, dysarthria, dyscalculia, eyelid ptosis, gait disturbance, hypotonia, memory impairment, metabolic encephalopathy, motor dysfunction, muscular weakness, toxic encephalopathy, urinary incontinence, and vision blurred.

Manier et al. Poster presented at American Society of Hematology; June 4-8, 2021; Virtual congress

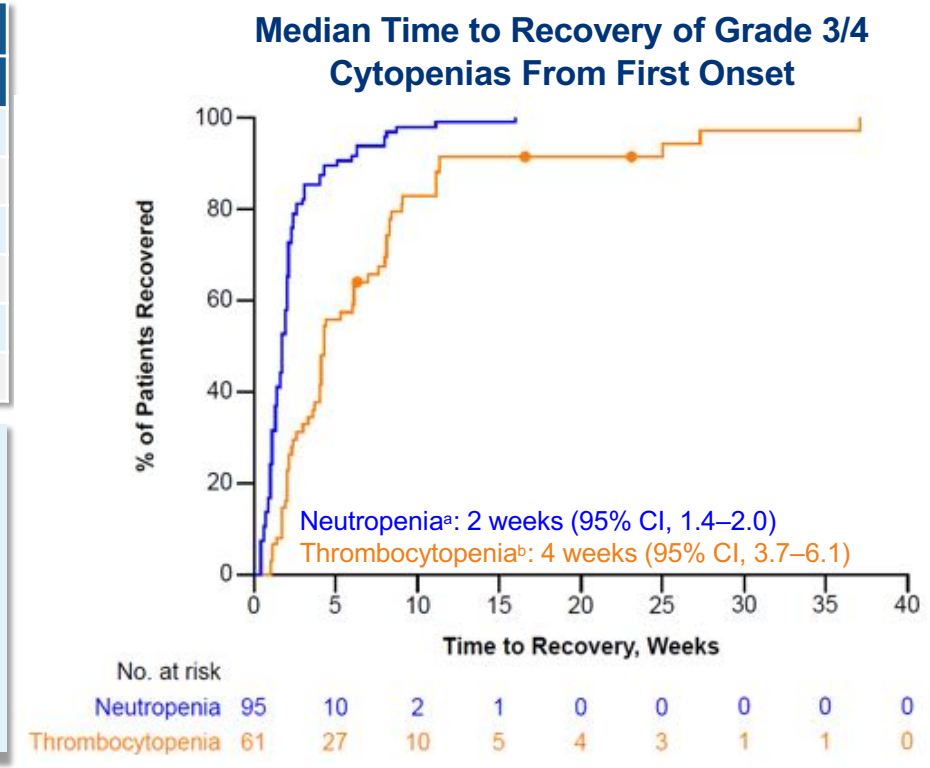
Biomarkers for CRS and ICANS

- Baseline proinflammatory markers (CRP, ferritin, IL-6) levels not associated with CRS/NT, but peak levels correlated with severity of toxicities
- NT events were associated with higher peak inflammatory cytokine production (ferritin, IL-6) and trends in altered baseline and peak angiopoietin-1 (lower) or angiopoietin-2 (higher) levels
- No difference in CRS max grade in different sub-group of patients (by risk, age…) but for patients with high tumor burden defined as ≥ 50% BMPCs and ISS 3

CARTITUDE-1: Hematologic AEs and Infections

AEs ≥20%, n (%)	N=97	
	Any grade	Grade 3/4
Hematologic	97 (100)	96 (99.0)
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)

- Late recovery (>1 month) of grade 3/4 cytopenias from first onset
  - Neutropenia: 10.3%
  - Thrombocytopenia: 25.8%
- Any-grade infections: 57.7%
  - Grade 3/4: 19.6%
    - Pneumonia: 8.2%
    - Sepsis: 4.1%



AE, adverse event.

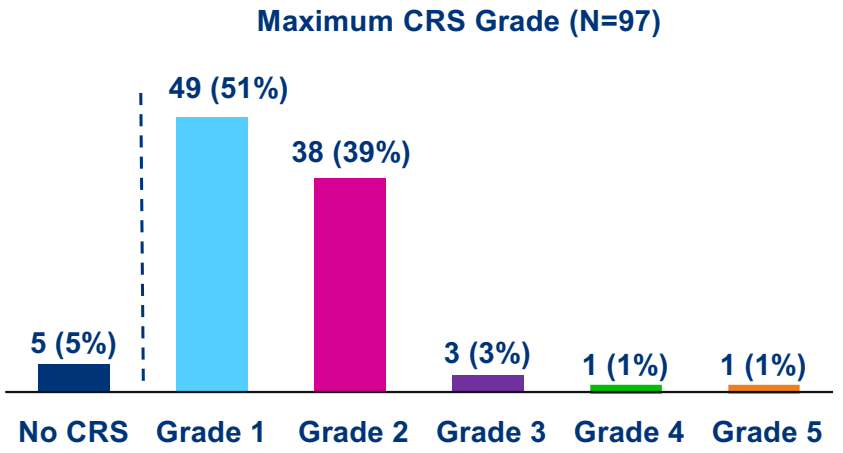
[a]Recovery of grade 3/4 neutropenia defined as the first incidence of absolute neutrophils count ≥1000 cells/μL after the onset; recovery does not take into account treatment for neutropenia.

[b]Recovery of grade 3/4 thrombocytopenia defined as the first incidence of platelets count ≥50,000 cells/μL after the onset; recovery does not take into account treatment for thrombocytopenia.

CARTITUDE-1: CRS

	N=97
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]
Supportive measures, n (%)	88 (90.7)
Tocilizumab	67 (69.1)
Corticosteroids	21 (21.6)
Anakinra	18 (18.6)
Vasopressor used	4 (4.1)
Intubation/mechanical ventilation	1 (1.0)
Other	
Cyclophosphamide	1 (1.0)
Etanercept	1 (1.0)

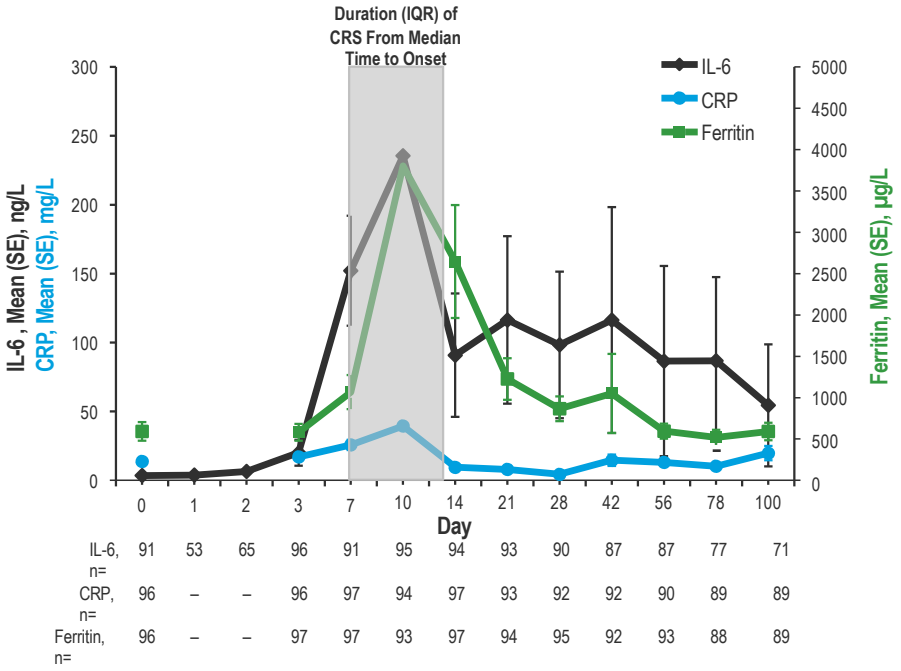
- Cilta-cel CAR+ T cells showed maximum peripheral expansion at a median of 13 days (range, 9–55)

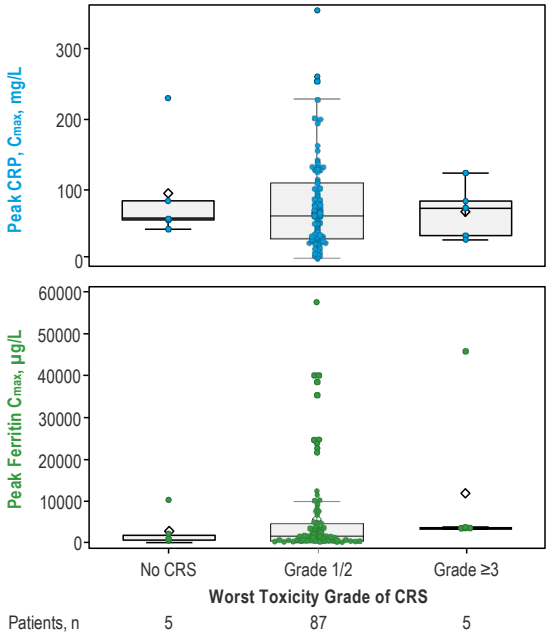


- Of 92 patients with CRS, majority (94.6%) were grades 1/2
- CRS onset
  - Day 4 or later: 89.1% (n=82)
  - Day 6 or later: 73.9% (n=68)
- CRS resolved in 91 (98.9%) patients within 14 days of onset

ASTCT, American Society for Transplantation and Cellular Therapy; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis.
[a]CRS was graded using Lee et al. (*Blood* 2014) in the phase 1b portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase 1b portion. [b]The patient with 97-day duration died due to CRS/HLH.

IL-6, CRP, and Ferritin Levels in Patients Treated With Cilta-cel



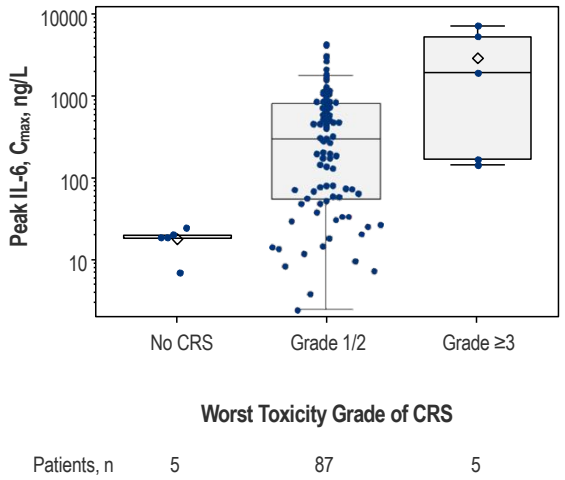


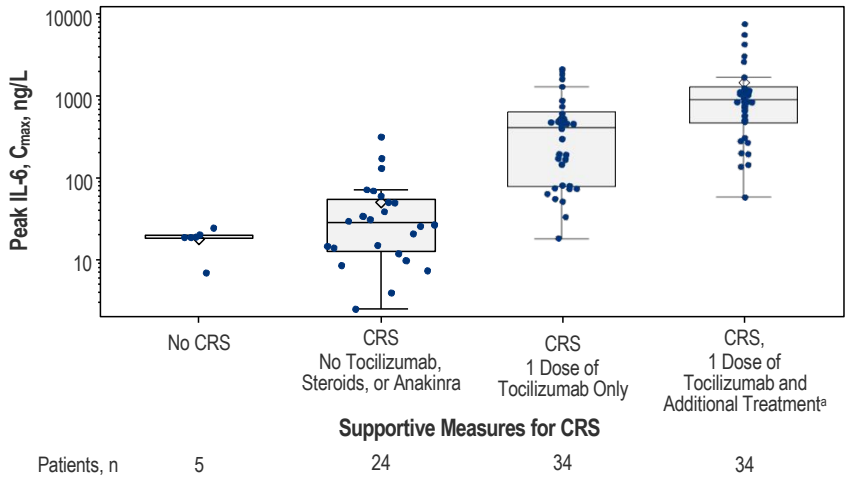
- Across all patients, IL-6 levels peaked at Days 7–14 post–cilta-cel infusion, as did IL-10 and IFN-γ levels
- CRP and ferritin trends follow cytokine levels and can be useful in monitoring CRS
- No association was observed between CRS severity and baseline[a] or peak levels of CRP or ferritin

[a]Data not shown.

BL, baseline; C_{max}, maximum concentration; CRP, C-reactive protein; CRS, cytokine release syndrome; IL, interleukin; IQR, interquartile range; SE, standard error.

Peak IL-6 Levels by CRS Severity and Supportive Measures





CRS severity and supportive measures were associated with peak IL-6 levels, as well as peak levels of IL-10 and IFN-γ[b]

[a]Additional dose of tocilizumab, steroids, and/or anakinra; [b]Data not shown
C_{max}, maximum concentration; CRS, cytokine release syndrome; IL, interleukin.

Delayed Neurotoxicity with Cilta-cel[1,2]

- All grade: 12%, grade 3: 9%
- Median onset: 27 days (range: 11-108)
    1. Movement/Neurocognitive Changes: 5
    2. Nerve palsy, peripheral motor neuropathy: 7
- Mechanism of delayed neurotoxicity: unclear
- Risk Factors: high-tumor burden, CRS/ICANS, high CAR expansion.
- No further events after mitigation strategies
- No delayed neurotoxicity reported in ide-cel KarMMa-1 trial, package insert of ide-cel notes incidence of grade 3 parkinsonism and grade 3 myelitis in another trial
- Poster 8028: Neurotoxicity with cilta-cel in CARTITUDE-2; Poster 8036: Neurotoxicity with ide-cel

1. Madduri et al ASH 2020 abstract 177. 2. Usmani et al ASCO 2021 abstract 8005

Presented By: Surbhi Sidana, MD
Twitter @SurbhiSidanaMD

CARTITUDE-1: Safety

No new incidence of neurotoxicity
No additional movement and neurocognitive TEAEs[a]

Movement and Neurocognitive TEAEs

Occurred in 5 of 97 patients

Risk factors (2 or more)

- High tumor burden[b]
- Grade ≥2 CRS
- ICANS
- High CAR T-cell expansion and persistence

Patient Management Strategies[c]

- Enhanced bridging therapy to reduce tumor burden
- Early and aggressive treatment of CRS and ICANS
- Handwriting assessments and extended monitoring

CARTITUDE Program Level
Over 100 Additional Patients[d] Have Been Dosed

- Patient management strategies to prevent or reduce these AEs have been successfully implemented in new and ongoing cilta-cel studies
- This is reliant on effective implementation of these patient management strategies

AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; TEAE, treatment-emergent AE.
[a]Two patients with ongoing symptoms continued to improve at the time of data cutoff. Patient management strategies were implemented, including enhanced bridging therapy to reduce baseline tumor burden, early aggressive treatment of CRS and ICANS, handwriting assessments for early detection of neurotoxicity symptoms, and extended monitoring and reporting time for neurotoxicity beyond the first 100 days post-cilta-cel infusion. [b]Defined as having high tumor burden when any of the following parameters were met: bone marrow plasma cell ≥80%, serum kappa chain ≥1000 mg/L. [c]Additional details will be presented at the 2021 Annual ASCO meeting (abstract 8526 available by scanning the QR code on the slide). [d]Included patients treated in earlier and later line settings across the CARTITUDE program.

Abstract 8526

Teclistamab toxicities

- **2 DLTs across all doses; no DLT at RP2D**
  - Gr 4 delirium (20 µg/kg IV step-up dose)
  - Gr 4 thrombocytopenia (180 µg/kg IV)
- **Maximum tolerated dose not reached**
- **Infections in 52% of patients; 27% at RP2D**
  - 15% had Gr ≥3 infections across all doses
  - 6% had Gr ≥3 infections at RP2D
- **Neurotoxicity in 7 patients (5%); 1 (3%) at RP2D**
  - 2 Gr ≥3 events with IV dosing; none with SC
- **Injection-site reactions in 32% of patients; 36% at RP2D (all Gr 1–2)**
- **1 TRAE leading to death; none at RP2D**
  - Gr 5 pneumonia at 80 µg/kg IV

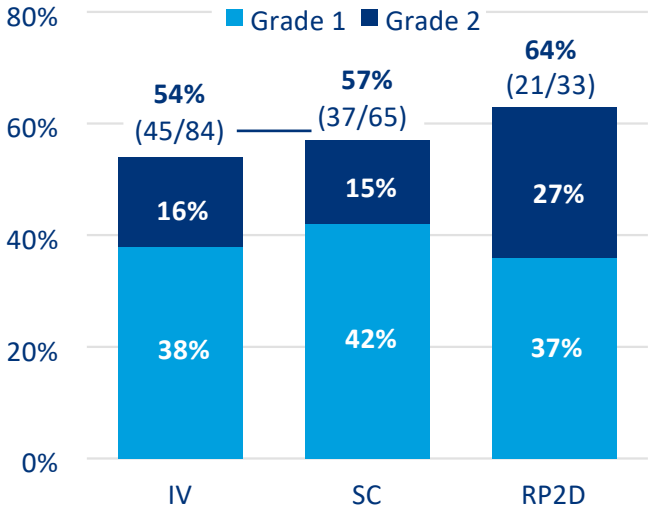
Late immunesuppression!

Teclistamab: Cytokine Release Syndrome

Parameter, n (%)	Total (N=149)	IV	SC
Patients with CRS	82 (55)	45 (54)	37 (57)
Median time to CRS onset[a] (range), days	2 (1–5)	1 (1–3)	2 (1–5)
Median duration of CRS (range), days	2 (1–8)	1 (1–7)	2 (1–8)
Patients with supportive measures to treat CRS[b]	76 (51)	43 (51)	33 (51)
Tocilizumab	35 (23)	22 (26)	13 (20)
Steroids	19 (13)	15 (18)	4 (6)
Low flow oxygen	9 (6)	6 (7)	3 (5)
Single low-dose vasopressor	1 (1)	1 (1)	0

- No treatment discontinuations due to CRS
- CRS was generally confined to step-up and first full doses

Maximum CRS Grade by Dose Groups[c]



- Step-up dosing to mitigate risk of severe CRS
- No grade ≥3 CRS events

[a]Day 1 was day of most recent dose. [b]A patient could receive >1 supportive therapies. [c]Graded according to Lee et al. *Blood* 2014;124:188.

Talquetamab: Safety Profile

- **3 DLTs across all doses; no DLT at RP2D**
  - Gr 4 increased lipase (7.5 µg/kg IV)
  - Gr 3 maculopapular rash (n=2; 135 and 800 µg/kg SC)
- **Dose reductions at the RP2D were less frequent and occurred later compared with the 800 µg/kg dose**
- **Infections in 38% of patients; 16% at RP2D**
  - 8% had Gr ≥3 infections across all doses
  - No Gr ≥3 infections at RP2D
- **Neurotoxicity in 9 patients (6%); 1 (5%) at RP2D**
  - 6 (6%) with IV and 3 (6%) with SC dosing
  - 3 Gr ≥3 events with IV dosing; none with SC
  - Gr 2 encephalopathy at RP2D (resolved)
- **Injection-site reactions in 18% of patients; 21% at RP2D (all events were Gr 1–2)**
- **Skin/mucosal-related AEs in 45%; 58% at RP2D (majority Gr 1–2)**
- **Nail disorders[a] in 17% of patients; 21% at RP2D**
- **No Gr 5 AEs across all doses**

Late immunesuppression!

[a]Includes nail disorders, onychomadesis and nail dystrophy. AEs, adverse events, CRS, cytokine release syndrome; DLT; dose-limiting toxicity; Gr, grade; mF/U, median follow-up; NA, not applicable

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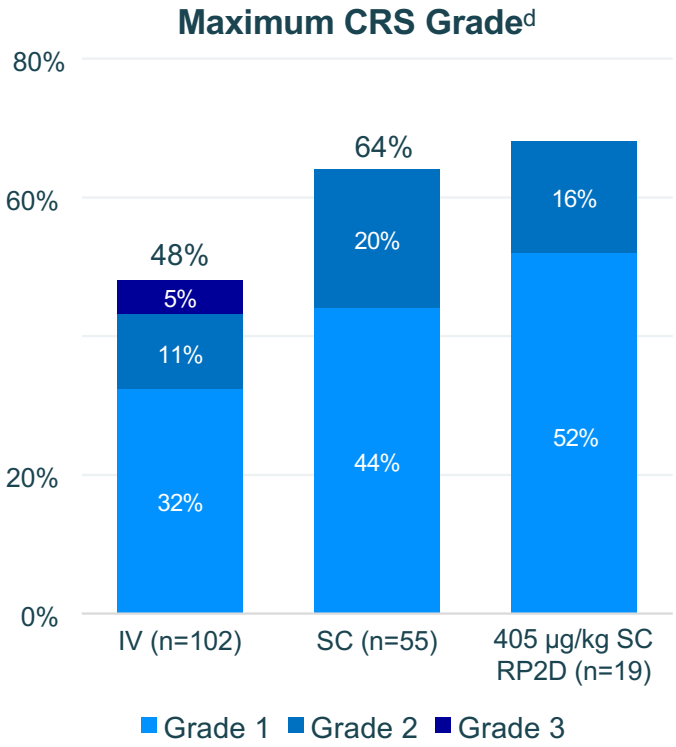
Talquetamab: Cytokine Release Syndrome

Parameter, n (%)	57 pts	IV	SC
Patients with CRS	84 (54)	49 (48)	35 (64)
Median time to CRS onset[a]			
Median duration of CRS	2 (1–9)	2 (1–9)	2 (1–7)
supportive treatments[b]	81 (52)	47 (46)	34 (62)
Tocilizumab	63 (40)	38 (37)	25 (46)
Steroids	13 (8)	11 (11)	2 (4)
Oxygen	12 (8)	8 (8)	4 (7)
Single low-dose vasopressor	3 (2)	2 (2)	1 (2)
Anakinra	2 (1)	1 (1)	1 (2)
Other[c]	68 (43)	44 (43)	24 (44)



[a]Day 1 was day of most recent dose. [b]Patients could receive more than 1 supportive therapy. [c]Includes fever-reducing medications, IV fluids, and other supportive care.
[d]Graded according to Lee 2014 *Blood* 124(2):188

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