Highlights from
IMS 20th meeting 2023

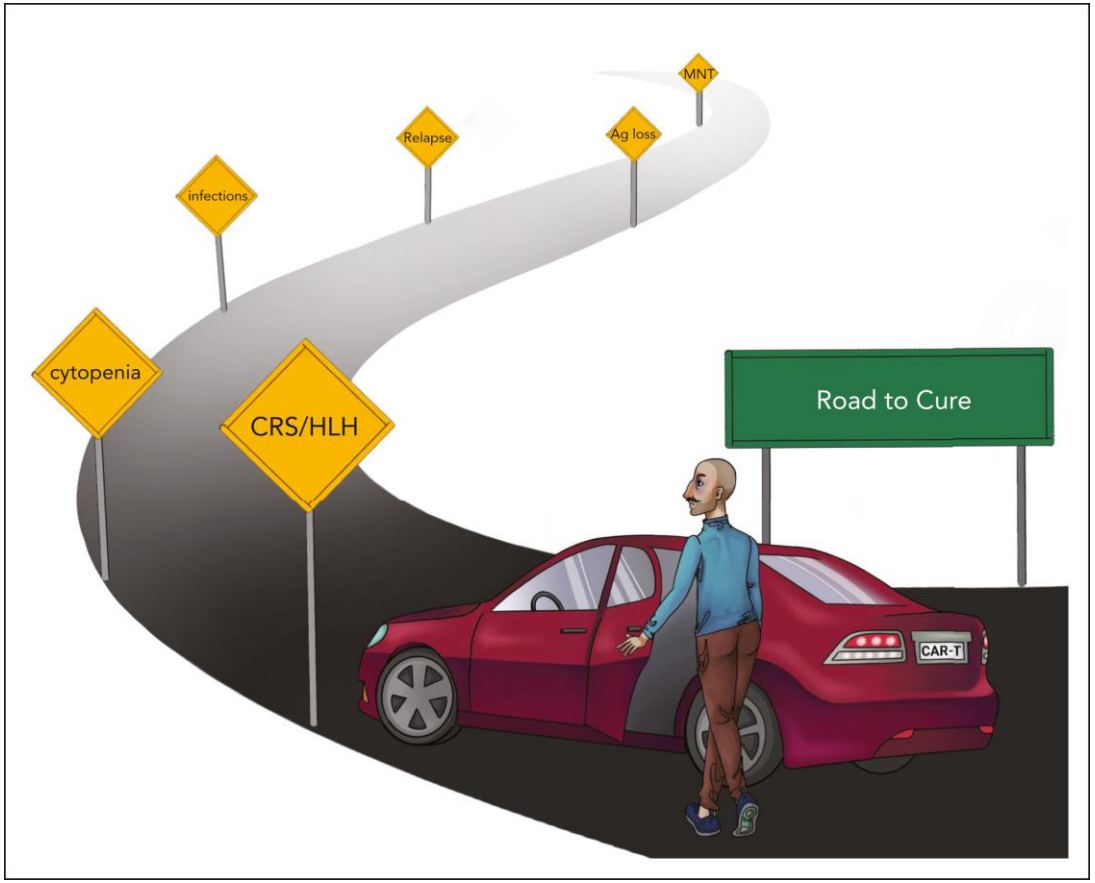
SIMONA SICA

CRS/HLH e ICANS/MNTs: prevenzione e terapia.

30-31 gennaio 2024
BOLOGNA, Royal Hotel Carlton

CONFLITTO DI INTERESSI

- Advisory board and honoraria: Roche, Amgen, Jazz, Pfizer, Sobi, Alexion, Kyte Gilead, Novartis, Astellas



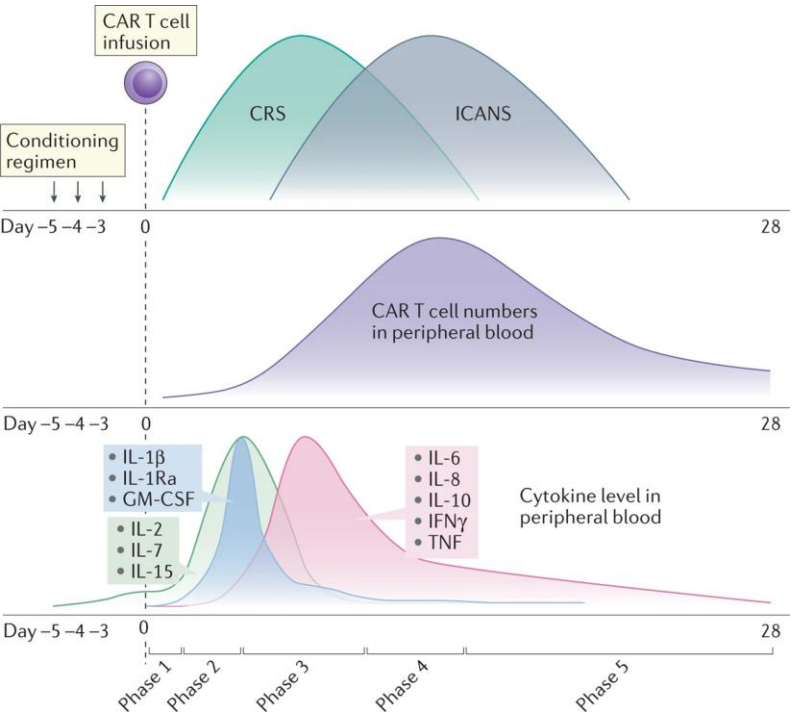
Leo Rasche, Michael Hudecek, Hermann Einsele: Blood 2024

Complications after CART in MM

- CART
  - Hematologic (>95%)
  - CRS (~80-95%)
  - Neurologic (~20%)
    - ICANS
    - Delayed Neurotoxicity (~1-5%)
      - Parkinsonian
      - Cranial neuropathies (Bell's)
  - Infection (~40-50%)
  - HLH/MAS % ?

- BsAb Therapy
  - Infection (75-80%)
    - Viral > Bacterial>fungal
  - CRS (>50-80%): but lower intensity
  - Hematologic (50-80%): shorter duration
  - Neurologic (<5%): reversible
    - HA (5-10%)
    - ICANS (<2%)

Pathophysiology of CRS



- Phase 1 infusion and Ag recognition
- Phase 2 CarT proliferation in tumour site and citokynes production
- Phase 3 increases in cytokines level and Car T expansion
- Phase 4 Diffusion in CSF and CNS with breakdown of the BBB
- Phase 5 activation induced cell death of CarT

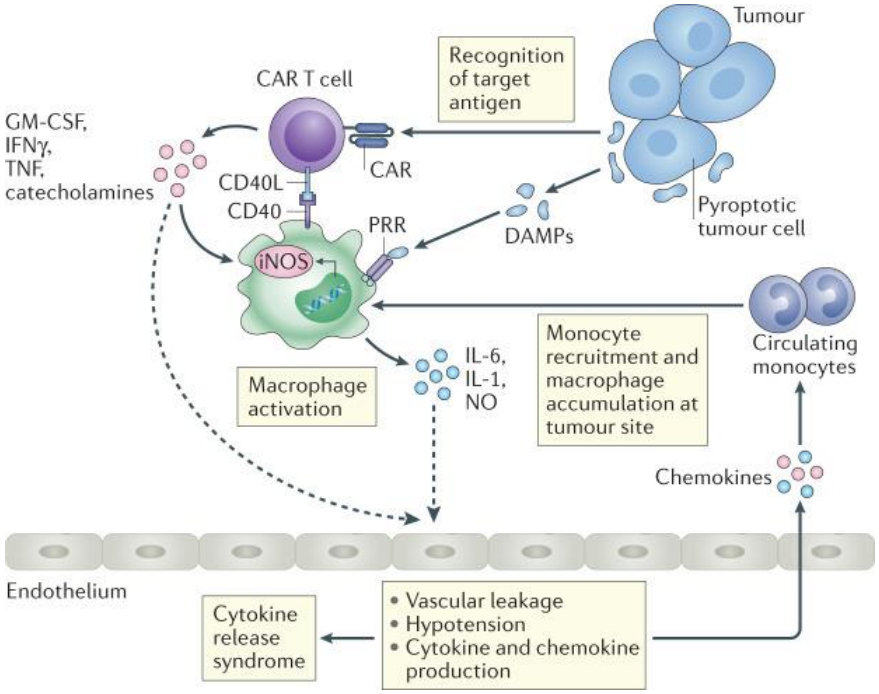
Morris EC, Nat Rev Immun2022

Working model of the pathophysiological mechanisms of CRS.

How does CRS occur?

When a T cell becomes activated following recognition of a tumour cell, there is an initial localised release of **IFN-γ and TNF-α**, activating macrophages and endothelial cells; these then secrete the **pro-inflammatory cytokines IL-6, IL-10 and TNF-α**[1]

IL-6 is a **major contributor** to CRS pathophysiology[1]



Morris EC, Nat Rev Immun2022

CRS may affect most organ systems1

CRS can affect a range of organ systems, including the **GI tract, liver, cardiovascular system, respiratory system, and renal and hepatic dysfunction**[1]

Endothelial cell activation/ dysfunction seems to be a **hallmark of severe CRS**, and may be responsible for certain CRS symptoms including vascular leakage and coagulopathy[1]

Severe CRS may also cause multi-organ system failure or death[1,2]

Factors such as the **type** of therapy, the **underlying disease** and **characteristics** of the patients can influence the risk of CRS[1]

Wider symptoms of CRS[1]

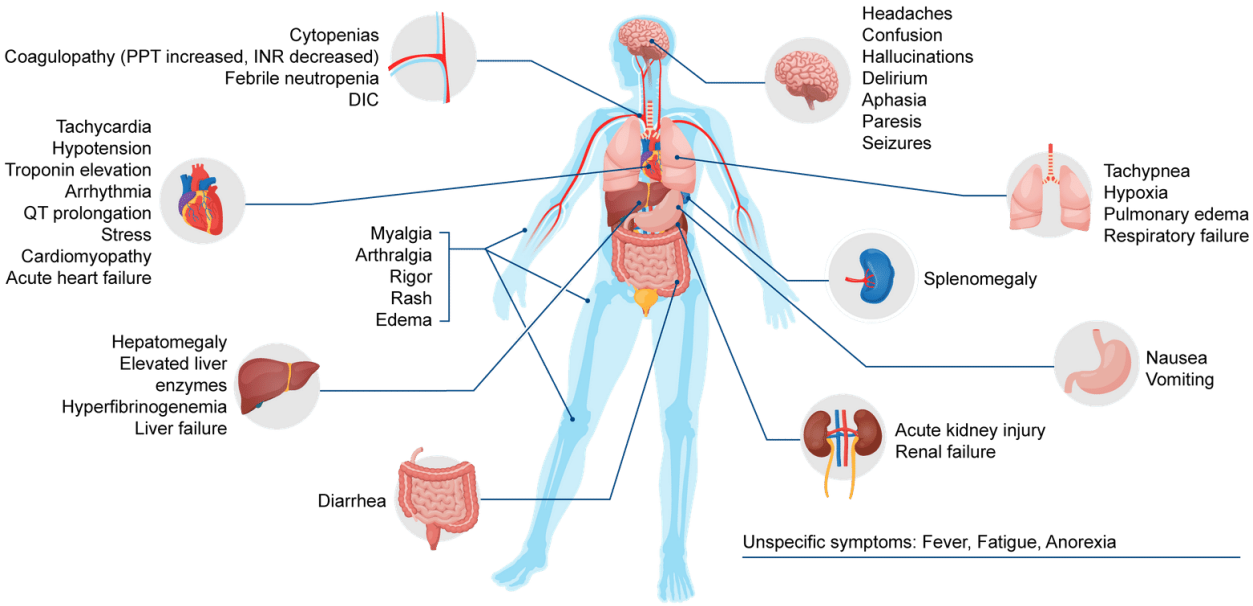


Image adapted from Shimabukuro-Vornhagen A, et al. 2018.
CRS, cytokine release syndrome; DIC, disseminated intravascular coagulation; GI, gastrointestinal; INR, international normalised ratio; PPT, partial thromboplastin time.

1. Shimabukuro-Vornhagen A, et al. *J Immunother Cancer* 2018;6:56; 2. Riegler LL, et al. *Ther Clin Risk Manag* 2019;15:323–335.

	ASTCT[1]	Penn Scale[2]	MSKCC Criteria[3]	CARTOX Criteria[4]
Grade 1	• Temperature ≥38°C with or without constitutional symptoms	• Mild reaction: treated with supportive care (antipyretics, anti-emetics)	• Mild symptoms requiring observation or symptomatic care only (eg, antipyretics, anti-emetics, pain medication)	• Temperature ≥38°C • Grade 1 organ toxicity
Grade 2	• Temperature ≥38°C • Hypotension: Does not require vasopressors *and/or* • Hypoxia: Requiring low-flow nasal cannula (oxygen ≤6 L per minute) or blow-by	Moderate reaction • Some signs of organ dysfunction (eg, Grade 2 creatine or Grade 3 LFTs) related to CRS • Hospitalization for CRS-related symptoms including fevers with associated neutropenia • Requires IV therapies (not including fluid resuscitation for hypotension)	Moderate symptoms • Hypotension: Requiring vasopressors <24 h *or* • Hypoxia or dyspnea requiring supplemental oxygen <40%	• Hypotension responds to IV fluids or low-dose vasopressor • Hypoxia requiring fraction of inspired oxygen <40% • Grade 2 organ toxicity
Grade 3	• Temperature ≥38°C • Hypotension: Requires 1 vasopressor with or without vasopressin *and/or* • Hypoxia: Requiring high-flow nasal cannula (oxygen >6 L per minute), facemask, nonrebreather mask, or Venturi mask	More severe reaction requiring hospitalization • Organ dysfunction (Grade 4 LFTs or Grade 3 creatine) related to CRS • Hypotension treated with IV fluids or low-dose vasopressors • Coagulopathy requiring fresh frozen plasma or cryoprecipitate or fibrinogen concentrate • Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high-flow oxygen, CPAP, or BiPAP) • Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS	Severe symptoms • Hypotension requiring any vasopressors ≥24 h *or* • Hypoxia or dyspnea requiring supplemental oxygen ≥40%	• Hypotension needing high-dose or multiple vasopressors • Hypoxia requiring fraction of inspired oxygen ≥40% • Grade 3 organ toxicity or Grade 4 transaminitis
Grade 4	• Temperature ≥38°C • Hypotension: Requires >1 vasopressor (excluding vasopressin) *and/or* • Hypoxia: Requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation)	Life-threatening complications • Hypotension requiring high-dose vasopressors • Hypoxia requiring mechanical ventilation	• Life-threatening symptoms • Hypotension refractory to high-dose vasopressors[a] • Hypoxia or dyspnea requiring mechanical ventilation	• Life-threatening hypotension • Needing ventilator support • Grade 4 organ toxicity except Grade 4 transaminitis

[a]Refractory to vasopressors was defined as failure to reach target blood pressure despite the use of high-dose vasopressors ≥3 hours.

1. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638. 2. Porter D et al. *J Hematol Oncol*. 2018;11(1):35. 3. Park JH et al. *N Engl J Med*. 2018;378(5):449–459 and supplement.
4. Neelapu SS et al. *Nat Rev Clin Oncol*. 2018;15(1):47–62.

Management of CRS: ASCO Guidelines

ASCO | CARTOX | EBMT-EHA

Workup/Evaluation

- CBC, comprehensive metabolic panel, magnesium, phosphorus, C-reactive protein, lactate dehydrogenase, uric acid, fibrinogen, prothrombin time/partial thromboplastin time, and ferritin
- Assess for infection with blood and urine cultures, and a chest radiograph if fever is persistent
- If patient is neutropenic, follow institutional neutropenic fever guidelines
- Patients who experience Grade ≥2 CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygen) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function
- Perform cardiac monitoring in patients who experience Grade ≥2 CRS, clinically significant arrhythmia, and additionally as clinically indicated
- Consider screening for cytomegalovirus and Epstein-Barr virus
- Consider chest or abdominal CT imaging, brain MRI, and/or lumbar puncture

- Santomasso BD et al. *J Clin Oncol*. 2021;39(35):3978–3992.

ASCO Guidelines

ASCO | CARTOX | EBMT-EHA

Management

Grade 1	Grade 2	Grade 3	Grade 4
• Supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms • Neutropenic: May consider empiric brad-spectrum antibiotics. May consider G-CSF in accordance with product guidelines. Note: GM-CSF is not recommended • Persistent (>3 days) or refractory fever (≥38°C): Consider managing as per Grade 2	• Continue supportive care as per Grade 1 and include IV fluid bolus and/or supplemental oxygen as needed • Administer tocilizumab 8 mg/kg IV over 1 h (not to exceed 800 mg/dose). Repeat every 8 h if no improvement; limit to maximum 3 doses in 24 h, with maximum of 4 total doses • Patients with hypotension that persists after 2 fluid boluses and after 1–2 doses of tocilizumab: may consider dexamethasone 10 mg IV (or equivalent) every 12 h for 1–2 doses then reassess • No improvement within 24 h of tocilizumab: Manage per Grade 3	• Continue supportive care as per Grade 2 and include vasopressors as needed • Admit patient to ICU • If not already performed, obtain echocardiogram to assess cardiac function and conduct hemodynamic monitoring • Tocilizumab as per Grade 2 if maximum dose is not reached within 24-hour period plus dexamethasone 10 mg IV every 6 h (or equivalent) and rapidly taper once symptoms improve • If refractory: Manage per Grade 4	• Continue supportive care as per Grade 3 and plus mechanical ventilation as needed • Tocilizumab per Grade 2 if maximum dose not reached within 24 h • Initiate high-dose methylprednisolone (500 mg IV every 12 h for 3 days), then 250 mg IV every 12 h for 2 days, 125 mg IV every 12 h for 2 days, and 60 mg IV every 12 h for 2 days until CRS improvement to Grade 1 • If not improving, consider methylprednisolone 1,000 mg IV twice per day or alternate therapy[a]

[a]Noting limited experience with other agents, alternate options may include anakinra, siltuximab, ruxolitinib, cyclophosphamide, and antithymocyte globulin.

Santomasso BD et al. *J Clin Oncol*. 2021;39(35):3978–3992.

CARTOX Guidelines

ASCO | **CARTOX** | EBMT-EHA

Management

Grade 1

- Fever and Organ Toxicity:
  - Acetaminophen and hypothermia blanket for the treatment of fever; ibuprofen can be used as a second treatment if not contraindicated
  - Assess for infection using blood and urine cultures, and chest radiography
  - Neutropenic: Empiric broad-spectrum antibiotics and filgrastim
  - Maintenance IV fluids for hydration
  - Symptomatic management of constitutional symptoms and organ toxicities
  - Consider tocilizumab 8 mg/kg IVa or siltuximab 11 mg/kg IV for persistent (>3 days) and refractory fever

Grade 2

- Hypotension:
  - Normal saline 500–1,000 mL IV; second IV bolus if systolic blood pressure remains <90 mmHg
  - Hypotension refractory to fluid boluses: Tocilizumab 8 mg/kg IVa or siltuximab 11 mg/kg IV; repeat tocilizumab after 6 h if needed
  - Persistent hypotensionc: Start vasopressors, consider transfer to ICU, obtain echocardiogram, initiate other hemodynamic monitoring methods
  - High-riskb patients or hypotension persists after 1–2 doses of anti–IL-6 therapy: Dexamethasone 10 mg IV every 6 h
  - Fever/constitutional symptoms: As per Grade 1
- Hypoxia[d]: Supplemental oxygen
- Organ toxicities[d]: Symptomatic management

Grade 3

- Hypotension
  - Per Grade 2: IV fluid bolus as needed, tocilizumab and siltuximab if not administered previously
  - Vasopressors as needed
  - Transfer to ICU, obtain echocardiogram, perform hemodynamic monitoring as per Grade 2
  - Dexamethasone 10 mg IV every 6 h
  - Refractory: 20 mg IV every 6 h
  - Fever/constitutional symptoms: As per Grade 1
- Hypoxia[d]: Supplemental oxygen with high-flow O_2 delivery and noninvasive positive pressure ventilation
- Organ toxicities[d]: Symptomatic management

Grade 4

- Hypotension
  - IV fluids, anti–IL-6 therapy, vasopressors, hemodynamic monitoring as per Grade 3
  - Methylprednisolone 1g/day IV
  - Fever/constitutional symptoms as per Grade 1
- Hypoxia[d]: Mechanical ventilation
- Organ toxicities[d]: Symptomatic management

[a]Maximum amount of tocilizumab per dose is 800 mg. [b]High-risk patients include those with bulky disease, those with comorbidities, and those who develop early onset CRS within 3 days of CAR T-cell infusion. [c]After 2 fluid boluses and anti-IL-6 therapy. [d]Tocilizumab or siltuximab +/- corticosteroids and supportive care as indicated and/or recommended for hypotension

Neelapu SS et al. *Nat Rev Clin Oncol*. 2018;15(1):47–62.

EBMT Guidelines

ASCO | CARTOX | EBMT-EHA

Management

Grade 1	Grade 2	Grade 3	Grade 4
• After blood cultures and other infection tests, start preemptive broad-spectrum antibiotics and symptomatic measures (antipyretics, fluids, etc) • In the absence of improvement within 3 days and in the absence of other differential diagnosis: Consider tocilizumab 8 mg/kg IV (maximum 800 mg)[a]	• Antibiotics and symptomatic measures as per Grade 1 • Alert local ICU • Tocilizumab 8 mg/kg IV (maximum 800 mg)[a] to be done in hematology unit before transfer to ICU – Repeat if no improvement after 12 h[a,b] • If persistent symptoms or no improvement: Dexamethasone 10 mg IV every 6 h for 1–3 days	• Antibiotics and symptomatic measures as per Grade 1 • Alert local ICU; transfer to ICU[c] • Tocilizumab 8 mg/kg IV (maximum 800 mg)[a] to be done in hematology unit before transfer to ICU – Repeat if no improvement after 12 h[a,b] • Dexamethasone 10 mg IV every 6 h for 1–3 days • If persistent symptoms or no improvement: Dexamethasone 20 mg IV every 6 h for 1–3 days	• Antibiotics and symptomatic measures as per Grade 1 • Alert local ICU; transfer to ICU[c] • Tocilizumab 8 mg/kg IV (maximum 800 mg)[a] to be done in hematology unit before transfer to ICU – Repeat if no improvement after 12 h[a,b] • Dexamethasone 20 mg IV every 6 h for 3 days, progressive tapering within 3–7 days • If persistent symptoms or no improvement: Switch to methylprednisolone 1,000 mg/day IV for 3 days, then 250 mg BID for 2 days, 125 mg BID for 2 days, 60 mg BID for 2 days; consider repeating tocilizumab (maximum 1 dose) if no ICANS

• [a]In children <30 kg, tocilizumab is given at the dose of 12 mg/kg. [b]In Grade 2 CRS, dexamethasone can be concurrently administered with the second dose of tocilizumab if needed. [c]In centers with little experience, it is recommended to transfer the patients from Grade 2.

Hayden PJ et al. *Ann Oncol*. 2022;33(3):259–275.

IL-6–directed Therapies: Tocilizumab and Siltuximab

- Studies suggest inhibitors of IL-6 signaling (i.e., tocilizumab and siltuximab) can induce rapid resolution of CRS symptoms[1]

	Tocilizumab	Siltuximab
Mechanism of Action	• Humanized monoclonal antibody targeted to the IL-6 receptor[1] • Blocks binding of IL-6 to both membrane-bound and soluble IL-6 receptors, inhibiting both classic and trans IL-6 signaling[1]	• Chimeric monoclonal antibody targeted to IL-6[4] • Binds directly to IL-6 and removes it from circulation, inhibiting both classic and trans IL-6 signaling[1] • Siltuximab has higher affinity for IL-6 (K_d~1 pM) than tocilizumab has for the IL-6 receptor (K_d = 2.54 nM), suggesting greater potency than tocilizumab[5]
Evidence for use in CRS	• FDA approval was based on a retrospective analysis of CAR-T data in clinical studies of patients with hematologic malignancies[6]	• Clinical study data in CRS management are limited; however, the available studies suggest rapid resolution of CRS with siltuximab[7]
FDA Approval	• Intravenous infusion for the treatment of severe or life-threatening CAR-T cell-induced CRS[7]	• Intravenous infusion for the treatment of multicentric Castleman's disease[8]
Half-life	11–14 days[8]	~21 days[9]

CAR-T, chimeric antigen receptor; CRS, cytokine release syndrome; FDA, Food and Drug Administration.

1. Si S, Teachey DT. *Ther Clin Risk Manag.* 2020;16:705-714. 2. Le RQ, et al. *Oncologist.* 2018;23(8):943-947. 3. Lipe BC, Renaud T. *Clin Lymph Myeloma Leukemia.* [manuscript under review]. 4. Zhou Z, Price CC. *Expert Opin Investig Drugs.* 2020;29(12):1407-1412. 5. Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1)L47-62. 6. Grupp SA, et al. *N Engl J Med.* 2013;368(16):1509-1518. 7. Shimabukuro-Vornhagen, et al. *J Immunother Cancer.* 2018;6:56. 8. Yildhizan E, et al. *J of Oncological Sciences.* 2018;4:134-141. 9. Riegler LL, et al. *Ther Clin Risk Manag.* 2019;15:323-335.

BCMA, B-cell maturation antigen; BTK, bruton tyrosine kinase; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; FDA, Food and Drug Administration; GM-CSF, granulocyte-macrophage colony-stimulating factor; TNF, tumor necrosis factor.

Additional Therapies Under Investigation for Treatment of CRS

IL-1 Receptor Antagonist (i.e., anakinra)

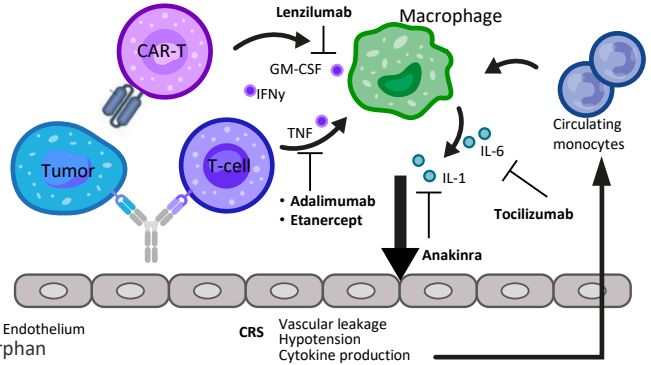
- IL-1 is an inflammatory cytokine produced by myeloid cells that has been linked to CRS and may precede widespread IL-6 increases[1]
  - Anakinra is approved by the FDA for treatment of moderate-to-severe rheumatoid arthritis[2]
- Anakinra has been used to treat CRS in patients receiving BCMA-targeted CAR-T in clinical studies[3-5]

TNFα Inhibitors (e.g., etanercept, adalimumab)

- TNFα is secreted by activated macrophages, monocytes, and lymphocytes, and elevated TNFα has been observed in CRS[6]
  - Etanercept is widely used for the treatment of rheumatoid arthritis[6]
- Case reports have described the use of etanercept in patients with CRS who have high levels of TNFα[6]

Other Investigational Therapies for CRS

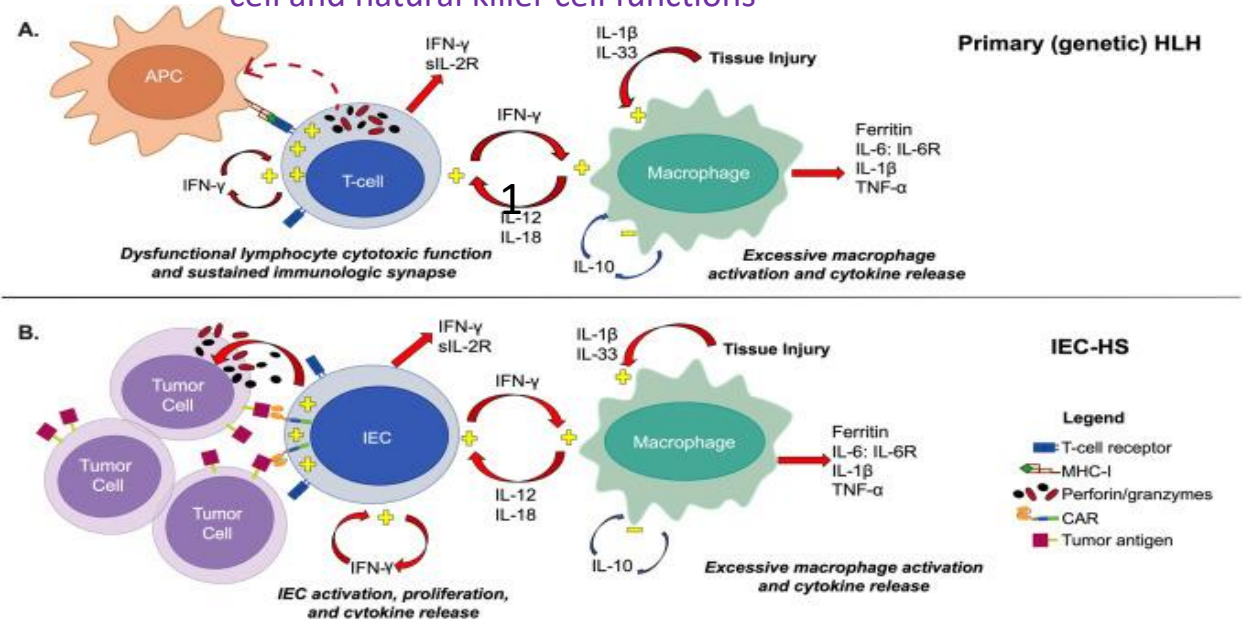
- GM-CSF depletion (e.g., lenzilumab)[1]
  - GM-CSF is implicated in stimulation of myeloid cells in CRS and neurotoxicity[1]
- BTK inhibition (e.g., ibrutinib)[1]
  - BTK plays a key role in B cell receptor signaling
  - Inhibition may decrease T-cell exhaustion markers and enhance Th1 functions in some patients



1. Siegler EL, Kenderian SS. *Front Immunol.* 2020;11:1973. 2. Kineret® [anakinra] full prescribing information. Swedish Orphan Biovitrum AB (publ). Stockholm, Sweden. 3. Berdeja JG, et al. *Lancet*. 2021;398(10297):314-324. 4. Munshi NC, et al. *N Engl J Med*. 2021;384:705-716. 5. Banerjee R, et al. *Transplant Cell Ther.* 2021;27:477e1-e7. 6. Zhang L, et al. *Exp Hematol Oncol.* 2021;10(1):16.

Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)

are clinical syndromes of pathological hyperinflammation and uncontrolled macrophage activation that are usually associated with triggers such as viral infections, rheumatological diseases or inherited defects in T cell and natural killer cell functions



- Hinnes M Transplantation and cellular therapy 2023

HLH/MAS: Symptoms and Diagnosis

Symptoms (ASCO)[1]*

- Fever
- Enlarged spleen
- Enlarged liver
- Swollen lymph nodes
- Skin rash
- Jaundice
- Lung problems (eg, coughing or trouble breathing)
- Digestive problems (eg, stomach ache, vomiting, and diarrhea)
- Nervous system problems (eg, headaches, trouble walking, vision disturbances, and weakness)

Select Diagnostic Criteria[2]*

HLH-2004 (for fHLH)	Molecular diagnosis consistent with HLH or 5/8 of the following: • Fever • Splenomegaly • Bi- or tri-lineage cytopenia • Hypertriglyceridemia ± hypofibrinogenemia • Hemophagocytosis on bone marrow biopsy • No diagnosis of malignancy • Low/absent natural killer cell activity • Raised ferritin • Raised sIL-2R
H-score (for all sHLH/MAS)	Known underlying immunosuppression, fever, organomegaly, mono-, bi-, or tri-lineage cytopenia, ferritin, triglycerides, fibrinogen, AST, hemophagocytosis on bone marrow biopsy • Overall score predicts likelihood of sHLH/MAS
MD Anderson	Ferritin of >10,000 µg/L and 2 of: • Grade >3 increase in serum transaminases or bilirubin • Grade >3 oliguria or increase in serum creatinine • Grade >3 pulmonary edema • Histological evidence of hemophagocytosis in bone marrow or organs

- *This presentation contains a select list of complications, symptoms, and diagnostic criteria of adverse events and toxicities from select clinical practice recommendations, guidelines, and other publications. This is not an exhaustive list.

1. Santomasso BD et al. *J Clin Oncol*. 2021;39(35):3978–3992. 2. Sandler RD et al. *Front Immunol*. 2020;11:524.

Management of HLH/MAS: ASCO

ASCO | CARTOX | EBMT-EHA | SITC

Workup/Evaluation

- CBC with differential and coagulation studies (prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer)
- Liver function tests (ALT, AST, gamma-glutamyl transferase, total bilirubin, albumin, and lactate dehydrogenase)
- Serum triglycerides (fasting) and serum ferritin
- Soluble IL-2 receptor alpha (sCD25 or sIL-2R) and/or CXCL9
- Perform the following based on the signs/symptoms of specific organ involvement and/or degree of suspicion of HLH:
  - Cultures of blood, bone marrow, urine, and CSF, and viral titers and qPCR testing for EBV, CMV, adenovirus, and other suspected viruses. Follow levels of any identified virus during treatment with appropriate antiviral therapy
  - Bone marrow aspirate and biopsy
  - Electrocardiograph, chest radiograph, and echocardiogram
  - Lumbar puncture with CSF analysis
  - Brain MRI scan, with and without contrast. Imaging of CNS may show parameningeal infiltrations, subdural effusions, necrosis, and other abnormalities

Management

All Grades

- Offer supportive care
- Use corticosteroids if the patient is deteriorating or unstable
- Replacement of fibrinogen should be considered in patients with a fibrinogen level <150 mg/dL (data insufficient to recommend a transfusion threshold level)
- Manage Grade ≥3 organ toxicity with IL-6 antagonist plus corticosteroids
- If insufficient response after 48 hours, consider adding anakinra
- Etoposide could be considered in severe, refractory cases, although there is a lack of data in this setting and concern for effect on lymphocytes. Intrathecal cytarabine, with or without hydrocortisone, may also be considered for patients with HLH-associated neurotoxicity

• Santomasso BD et al. *J Clin Oncol*. 2021;39(35):3978–3992.

Management of HLH/MAS: CARTOX

ASCO | **CARTOX** | EBMT-EHA | SITC

Workup/Evaluation

Diagnostic criteria[a]

- Peak serum ferritin level >10,000 ng/mL during CRS phase of CAR T-cell therapy (typically the first 5 days after cell infusion) and subsequently developed two of the following:
  - Grade ≥3 increase in serum albumin, AST, ALT levels
  - Grade ≥3 oliguria or increase in serum creatinine levels
  - Grade ≥3 pulmonary edema
  - Presence of hemophagocytosis in bone marrow or organs based on histopathological assessment of cell morphology and/or CD68 immunohistochemistry

Management

General
• Anti–IL-6 therapy and corticosteroids for Grade ≥3 organ toxicities as per the CRS recommendations
• If no improvement clinically or serologically within 48 hours, additional therapy with etoposide (75–100 ng/m^2) should be considered
• Etoposide can be repeated after 4–7 days, as indicated clinically or serologically, to achieve adequate disease control
• Intrathecal cytarabine, with or without hydrocortisone, should be considered for patients with HLH-associated neurotoxicity

- [a] Grading as per Common Terminology Criteria for Adverse Events, version 4.03[2]

1. Neelapu SS et al. *Nat Rev Clin Oncol*. 2018;15(1):47–62.
2. U.S. Department of Health & Human Services. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Management of HLH/MAS:EBMT-EHA

Workup/Evaluation

- Persistent fever despite tocilizumab with organomegaly, cytopenias (± hemophagocytosis in the bone marrow), hyperferritinemia (>10,000 ng/mL), liver dysfunction, coagulopathy (hypofibrinogenemia requiring cryoprecipitate/fibrinogen concentrate), and hypertriglyceridemia favors CRS/MAS overlap syndrome
- Monitor patients twice daily with blood tests (full blood count, liver function, ferritin, C-reactive protein)

Management

General

- Treat with anakinra 100 mg SC or IV × 2–4/day in combination with dexamethasone 10–20 mg IV × 4/day

After Evaluation at 24–48 Hours

- Absence of clinical improvement / increase in serum ferritin level: Switch to methylprednisolone 1,000 mg/day IV for 3 days then 250 mg BID for 2 days, 125 mg BID for 2 days, 60 mg BID for 2 days; anakinra 100 mg IV or SC × 2–4/day
- Deterioration / increase in serum ferritin level: Consider etoposide 75 mg/m^2 IV at Day 1; if needed, repeat at Day 4 and Day 7 if needed

- Hayden PJ et al. *Ann Oncol*. 2022;33(3):259–275.

Management of HLH/MAS: SITC

Workup/Evaluation

- CRS and HLH/MAS substantially overlap
- Late-onset, tocilizumab-refractory HLH/MAS-like symptoms may represent a distinct and separate pathology than conventional CRS[a]
- Delayed coagulopathy may possibly be one hallmark of delayed onset HLH/MAS-like toxicity, typically hypofibrinogenemia disproportionately worse than changes in PT/PTT, which requires close follow-up and replacement cryoprecipitate[a]

Management

General

- Etoposide should only be administered to patients experiencing late-onset, tocilizumab-refractory HLH/MAS-like symptoms after CAR T-cell therapy as a last resort[a]
- For treatment of late-onset, HLH/MAS-like pathology, which may be tocilizumab-refractory, third-line CRS agents such as anakinra and steroids may be considered[a]

- [a]Oxford Level of Evidence 4: Recommendation is based on evidence from case series, case-control, or historically controlled study.
- Maus MV et al. *J Immunother Cancer*. 2020;8(2):e001511.

frontiers in Immunology

ORIGINAL RESEARCH
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Diagnosis and Management of Secondary HLH/MAS Following HSCT and CAR-T Cell Therapy in Adults; A Review of the Literature and a Survey of Practice Within EBMT Centres on Behalf of the Autoimmune Diseases Working Party (ADWP) and Transplant Complications Working Party (TCWP)

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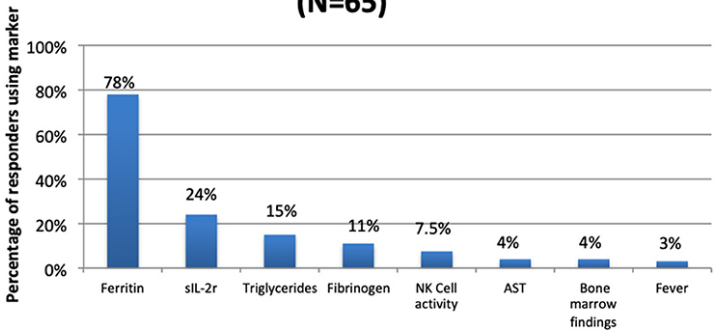
Results: 114/472 centres from 24 different countries responded (24%). We report estimated rates of sHLH/MAS of 1.09% (95% CI = 0.89–1.30) following allogeneic HSCT, 0.15% (95% CI = 0.09–5.89) following autologous HSCT and 3.48% (95% CI = 0.95–6.01) following CAR-T cell therapy. A majority of centres (70%) did not use a

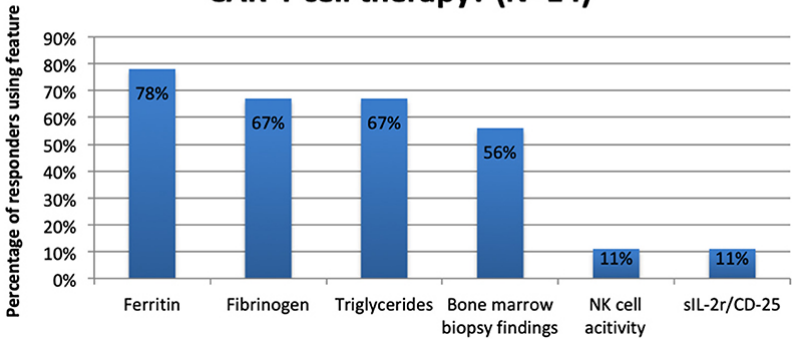
DIFFERENT DIAGNOSTIC CRITERIA

Published criteria	Components of criteria	Centres (%)
HLH-2004 (for fHLH) (24)	Molecular diagnosis consistent with HLH or 5/8 of the following: Fever, splenomegaly, bi or tri-lineage cytopenia, hypertriglyceridaemia ± hypofibrinogenaemia, haemophagocytosis on bone marrow biopsy, no diagnosis of malignancy, low/absent NK cell activity, raised ferritin, raised sIL-2r	43
H-score (for all sHLH/MAS) (25)	Known underlying immunosuppression, fever, organomegaly, mono-, bi-, or tri-lineage cytopenia, ferritin, triglycerides, fibrinogen, AST, haemophagocytosis on bone marrow biopsy. Overall score predicts likelihood of sHLH/MAS	16
Takagi et al. (for SHLH/MAS post-HSCT)	2 major or 1 major and all 4 minor criteria required. Major criteria: (A) engraftment delay, primary or secondary failure or (B) histopathological evidence of haemophagocytosis. Minor criteria: fever, hepatosplenomegaly, elevated ferritin, elevated LDH.	10
PRINTO (for sHLH/MAS in sJIA)	Ferritin > 684 μg/L and 2 of: platelets <181 × 109, AST >48 U/L, triglycerides >256 mg/dL, fibrinogen < 360mg/dL	1
MD Anderson (for sHLH/MAS post-CAR-T cell therapy)	Ferritin of > 10,000 μg/L and 2 of: grade > 3 increase in serum transaminases or bilirubin; grade > 3 oliguria or increase in serum creatinine; grade > 3 pulmonary oedema; or histological evidence of haemophagocytosis in bone marrow or organs	7
Combination of the above		23

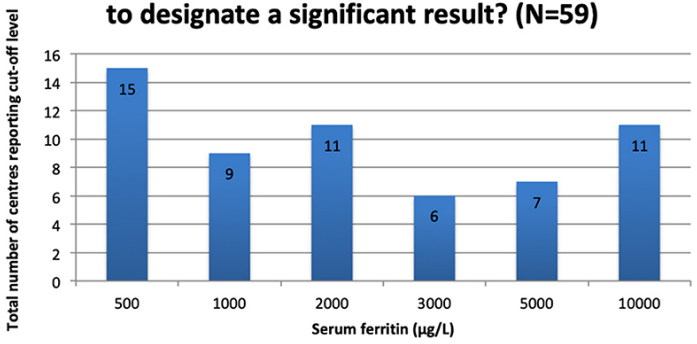
Which markers do you use to screen for sHLH/MAS post-HSCT or CAR-T cell therapy? (N=65)



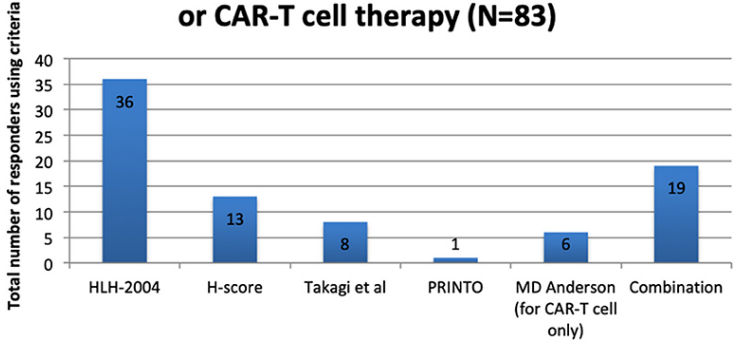
What features do you use to help differentiate sHLH/MAS from CRS following CAR-T cell therapy? (N=14)



What is your cut-off level for serum ferritin to designate a significant result? (N=59)



Which published criteria do you use to help make the diagnosis of sHLH/MAS post-HSCT or CAR-T cell therapy (N=83)



When asked which agents are used to treat sHLH/MAS there were 16 different responses from 97 centres.

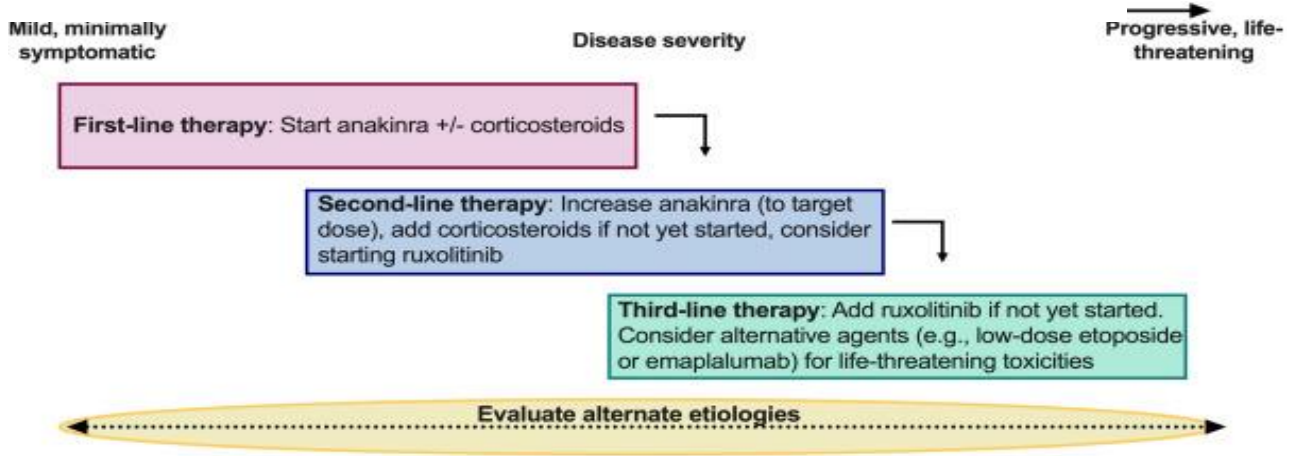
Published protocol	Components of protocol	Centres (*N*)
MD Anderson (post CAR-T cell) (44)	Supportive organ-specific treatment, broad-spectrum antibiotics, IV Tocilizumab or Siltuximab (anti-IL6 agents), IV corticosteroids	4
HLH-2004 (for fHLH) (24)	8 weeks initial therapy with IV dexamethasone and Etoposide. Then ciclosporin is introduced, dexamethasone continues to be pulsed and etoposide continued whilst awaiting a donor for BMT	2
La Rosee et al. (45)	Use of corticosteroids +/- IVIG in most cases with addition of etoposide (if malignancy-triggered), ciclosporin & anakinra (if autoimmune-related) or anti-IL-6 (if CAR-T cell related)	1
HLH-94 (for fHLH)	8 weeks initial therapy with IV dexamethasone and Etoposide before proceeding to definitive treatment with BMT	1

- corticosteroids +chemotherapy (25%),
- corticosteroids + monoclonal antibodies + chemotherapy (15%)
- , corticosteroids + chemotherapy + cytokine blockade (13%),
- corticosteroids + cytokine blockade (12%), and corticosteroids alone (10%).
- specific agents reported as being used in the management of sHLH/MAS: etoposide (*n* = 17), rituximab (*n* = 8), and tocilizumab (*n* = 7)
- Cytosorb®, ruxolitinib, CSA, IVIG, anakinra, ATG, alemtuzumab, methotrexate, vincristine, baricitinib, and siltuximab….

Table 2
IEC-HS Grading

Adverse Event	Grade				
	1	2	3	4	5
IEC-HS*	Asymptomatic or mild symptoms; requires observation and/or clinical and diagnostic evaluation. Intervention not indicated.	Mild to moderate symptoms, with intervention indicated (eg, immunosuppressive agents directed at IEC-HS, transfusions for asymptomatic hypofibrinogenemia)	Severe or medically significant but not immediately life- threatening (eg, coagulopathy with bleeding requiring transfusion support, or hospitalization required for new-onset acute kidney injury, hypotension, or respiratory distress)	Life-threatening consequences: urgent intervention indicated (eg, life-threatening bleeding or hypotension, respiratory distress requiring intubation, dialysis indicated for acute kidney injury)	Death

* Not attributable to other causes; defined by the development of pathological and biochemical features of macrophage activation/HLH that is attributable to IEC therapy and associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia and hepatic transaminitis (>5 × ULN)). While HLH-like manifestations are frequently seen in in patients with severe CRS (as defined by ASTCT), IEC-HS is often delayed in onset and manifests as CRS is resolved/resolving.



- Hinnes M Transplantation and cellular therapy 2023

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TABLE 2. Definition, Workup, and Management of CAR-T–Associated Toxicities

Toxicity	Definition	Baseline Workup	Management[a]
CRS	Grade 1: fever Grade 2-4: fever, hypotension, and hypoxemia	Monitor CRP and ferritin Consider chemokine panel (IL-6, IL1-receptor alpha, and IFN-gamma) Consider viral PCRs Order blood and urine culture Order chest XR/imaging Consider infectious disease consult	Grade 1: acetaminophen, cooling blankets Grade 2-4 tocilizumab (or, if not available, siltuximab), corticosteroids
ICANS	Grade 1: mild confusion Grade 2-4: severe confusion, seizure, motor deficit, and cerebral edema	Monitor CRP and ferritin Consider chemokine panel (IL-6, IL1-receptor alpha, and IFN-gamma) Consider viral PCRs Order EEG Order MRI/CT brain Consider neurology and ophthalmology consult	Corticosteroids (high dose in case of cerebral edema), anakinra
HLH	Elevated ferritin during CRS with organ damage (liver, kidney, and/or lung)	Order complete blood count, coagulation markers, complete metabolic panel, and lipid panel Consider chemokine panel (soluble IL-2 receptor alpha, IL-18, and CXCL9) Consider bone marrow aspirate and biopsy	Corticosteroids, siltuximab, tocilizumab, and anakinra; consider etoposide and intrathecal cytarabine
Cytopenia	Grade 3-4: neutropenia, anemia, and/or thrombocytopenia	Monitor complete blood count Consider viral PCR Order bone marrow aspirate and biopsy Review concomitant medications	Neutropenia: debated use of growth factor within first 21 days; antibiotic and antifungal prophylaxis Anemia: transfusions; debated use of erythropoietin Thrombocytopenia: transfusions; debated use of TPO mimetics Pancytopenia: debated use of immunosuppressive therapy and/or stem-cell transplant
Lymphopenia	CD4 < 200 IgG < 400 mg/dL	Monitor serum IgG and CD4 count	Monthly intravenous immunoglobulins Antiviral and anti-PJP prophylaxis

Abbreviations: CAR-T, chimeric antigen receptor T cell; CRP, C-reactive protein; CRS, cytokine release syndrome; CT, computed tomography; CXCL9, chemokine ligand; IL1, interleukin 1; IL-6, interleukin-6; IL-18, interleukin-18; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell–associated neurotoxicity syndrome; IgG, immunoglobulin G; MRI, magnetic resonance imaging; PCRs, polymerase chain reactions; PJP, pneumocystis jirovecii; TPO, thrombopoietin; XR, X-ray.
[a]Intensification of treatment for G2-3 CRS and ICANS can vary according to disease and product type.

TABLE 1. Efficacy and Safety of FDA-Approved CAR-T Products for Hematologic Malignancies

Disease (CART Product)	B-ALL (tisa-cel)	B-ALL (brexu-cel)	LBCL (axi-cel)	LBCL (tisa-cel)	LBCL (liso-cel)	MCL (brexu-cel)	FL (axi-cel)	FL (tisa-cel)	MM (ide-cel)	MM (cilta-cel)
Year of approval	2017	2021	2017	2018	2021	2020	2021	2022	2021	2022
FDA label (line)	Refractory or second or greater relapse	R/R	Greater than or equal to second line	Greater than second line	Greater than second line	Greater than second line	Greater than second line	Greater than second line	Greater than fourth line	Greater than fourth line
Registration study	ELIANA	ZUMA-3	ZUMA-1[a]	JULIET	TRANSCEND[a]	ZUMA-2	ZUMA-5	ELARA	KARMMA-1	CARTITUTDE-1
Sample size, No.	79	55	111	92	269	68	148	97	128	97
CRS, any grade	77%	89%	93%	58%	42%	91%	82%	49%	84%	95%
CRS, grade 3-5	49%	24%	13%	22%	2%	15%	7%	0%	5%	5%
ICANS, any grade	39%	60%	64%	21%	30%	63%	59%	37%	18%	17%
ICANS, grade 3-5	13%	25%	28%	12%	10%	31%	19%	3%	3%	2%
Day-30 grade 3-5 cytopenia	NR	36%	34%	32%	37%	35%	34%	32%	41% (ANC); 48% (plt)	10% (ANC); 25% (plt)
CR rate (best response)	82%	71%	54%	52%	53%	67%	74%	69%	39%	82.5%
1-year PFS rate	5-year RFS 44%	Median RFS 11.9 months	45%	40%	44%	61%	72%	67%	Median PFS at target dose 11.3 months	77%
1-year OS rate	5-year OS 55%	71%	65%	49%	58%	83%	95%	96%	78%	89%
Median follow-up, months	60.1	26.8	15.4	28.6	18.8	12.3	17.5	17	13.3	12.4

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; CAR-T, chimeric antigen receptor T cell; CR, complete remission; CRS, cytokine release syndrome; FDA, Food and Drug Administration; FL, follicular lymphoma; ICANS, immune effector cell–associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; R/R, relapsed and/or refractory.
[a]Data from ZUMA-7 and TRANSFORM (second-line trials) are not reported in the table.

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CAR-T cells in RRMM

	Approved CAR-T cells			Academic	Alternative manufacturing	Novel Synthetic	Allo-CAR	GPRC5D	
	US. Ide-cel KarMMa[1] (n = 128)	US. Cilta-cel CARTITUDE-1 (n = 97) [2,3]	China CT103A[7] (n= 79)	ARI0002h[4] (n = 60)	P-BCMA-101 PRIME[5,6] (n = 53)	ddBCMA[7] (n= 40)	ALLO-715 UNIVERSAL[8] (n = 43)	CC-95266[9] (n= 70)	OriCAR -017[90] (n= 13)
Phase	II	Ib/II	I/II	I/II	I/II	I	I	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	**GPRC5D**	**GPRC5D**
scFv	**Chimeric mouse**	**Chimeric Llama**	Human	**Humanized**	**Chimeric mouse**	Synthetic	Human	Human	**Humanized Bi-epitopic**
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Specificity	Auto	Auto	Auto	Auto	Auto-**piggyBac**	Auto	**Allo CD52 & TCR KO**	Auto	Auto
Age, (range)	61 (33-78)	61 (56-68)	57 (39-70)	61 (36-74)	60 (42-74)	66 (44-76)	64 (46-77)	60 (38-76)	64 (58-68)
# of lines	6	6	5	3	8	4	5	NR	5.5
HR cytog, %	35	24	34	28	NA	29	37	46	60
EMD, %	39	13	13	18	NA	34	21	43	40
Triple-R, %	84	88	17	67(?)	60	100/68(pent)	91	34(penta)	15
ORR, %	81	98	95	95	67	100	71	86	100
CR/sCR, %	39	82	68	58	NA	76	25	38	60
PFS	12.2 m	34.9 m	NR	15.8 m	NR	67%, 18m	NR	NR	NR

*There, are no head-to-head comparisons of these data and naïve comparison should be conducted with caution
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; HR cytog, high-risk cytogenetics; NA, not available; NR, not reached/not reported; ScFv, single-chain variable fragment; TCR, T-cell receptor; triple-R, triple-class refractory

1. Anderson L et al. ASCO 2021;abstract;8016 (poster presentation); 2. Berdeja J et al. Lancet 2021;398;314-24; 3. Lin Y et al. EHA 2022;abstract P961 (poster presentation); 4. Fernández de Larrea C, et al. EHA 2022;abstract S103 (oral presentation); 5. Costello C, et al. ASH 2020;abstract 134; 6. Mohyuddin GR et al. Blood Adv 2021;5(4):1097-1101; 7. Li C et al. EHA 2022;abstract S187 (oral presentation); 7. Li C, et al. ASH 2021;abstract 143; 8. Mailankody S, et al. ASH 2021;abstract 651; 9. Mailankody S, et al NEJM 2022. 10. Zhang et al Lancet Hematology 2023

Caldes AO, et al. ASH 2023
Frigault, M, et al. ASH2023.
Bal S et al. ASH 23

Du J, et al ASH 2023: Abstract 1022: FasT

Table 1
Results of the KarMMa and CARTITUDE-1 Trials

Characteristic	KarMMa [1,8,10]	CARTITUDE-1 [2,11,13]
Study design		
CAR-T therapy given	Ide-cel	Cilta-cel
CAR-T dose	150-450 × 10^6 cells	.75 × 10^6 cells/kg
Baseline characteristics		
No of patients infused	128	97
Prior lines, median (range)	6 (3-16)	6 (3-18)
R-ISS III, n (%)	21 (16)	14 (14)
R-ISS II-III, n (%)	111 (86)	73 (75)
High-risk FISH (non-1q), n (%)	45 (35)	23 (24)
Add 1q, n (%)	45 (35)	NR
Extramedullary disease, n (%)	50 (39)	13 (13)
African American/black, n (%)	6/100 (6)	17 (17.5)
Triple class refractory, n (%)	108 (84)	85 (88)
Penta-refractory, n (%)	33 (26)	41 (42)
Efficacy		
ORR, n (%)	94 (73)	94 (97.9)
ORR at 450 × 10^6 cell dose, n (%)	44 (81)	N/A
≥ CR, n (%)	42 (33)	80 (83)
≥ VGPR, n (%)	68 (53)	92 (95)
Median PFS, mo	8.8	34.9
Median PFS for 450 × 10^6 cell dose, mo	12.1	N/A
Median OS, mo	24.8	Not reached; 70% at 27 mo
Safety		
CRS any grade, n (%)	107 (84)	92 (95)
CRS grade ≥3, n (%)	7 (5)	4 (4)
Day of CRS onset, median (range)	1 (1-12)	7 (5-8)
Neurotoxicity any grade, n (%)	23 (18)	21 (21)
ICANS grade ≥3, n (%)	5 (4)	10 (10)
Non-ICANS neurotoxicity, n (%)	0 (0)	12 (12.4)

Parameter	KarMMa-3 [7]		CARTITUDE-4 [6,83]	
	Ide-Cel	SOC	Cilta-Cel	SOC
ORR for infused patients, n (%)	NR	NR	175/176 (99.4)	N/A
Progressive disease as best response, n (%)	24 (9)	10 (8)	17 (8)	6 (3)
DOR, mo, median	14.8	9.7	Not reached; 85% at 12 mo	Not reached; 63% at 12 mo
PFS, mo, median	13.3	4.4	Not reached; 76% at 12 mo	11.8 49% at 12 mo
OS, mo, median	NR	NR	Not reached; 84% at 12 mo	Not reached; 84% at 12 mo
Safety (for treated patient only)	N = 225	N = 126	N = 176	N = 176
Infections any grade, n (%)	146 (58)	68 (54)	129/208 (62)	148/208 (71)
Infections grade 3-5, n (%)	72 (28)	26 (20)	56/208 (27)	51/208 (25)
CRS any grade, n (%)	197 (88)	N/A	134/176 (76)	N/A
CRS grade ≥3, n (%)	11 (5)	N/A	2 (1)	N/A
Days to CRS, median (range)	1 (1-14)	N/A	8 (1-23)	N/A
Neurotoxicity any grade, n (%)	34 (15)	N/A	(4.5)	N/A
ICANS grade ≥3, n (%)	7 (3)	N/A	0 (0)	N/A
Non-ICANS neurotoxicity, n (%)	0 (0)	N/A	30 (17); 1 Parkinson, 18 CN palsy, 5 PN	N/A

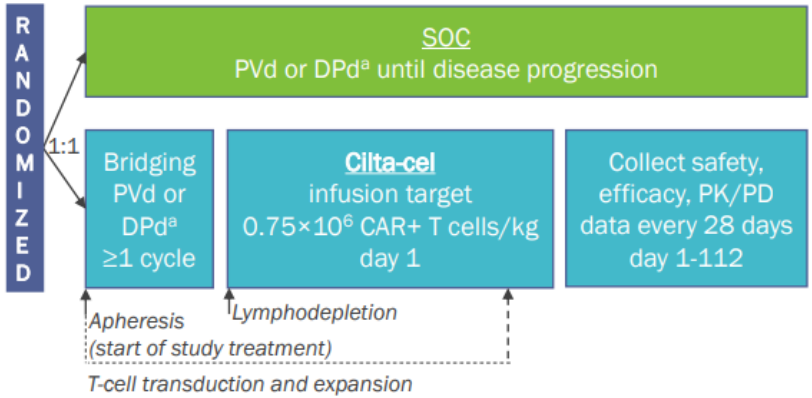
The US Multiple Myeloma CAR-T consortium also recently presented the first real-world safety and efficacy analysis of cilta-cel . Of 153 patients who underwent apheresis, 143 received cilta-cel. In this cohort, 57% of the patients would have been ineligible for the CARTITUDE-1 trial. Despite this, safety and efficacy results were comparable to those for the clinical trial cohort. Among infused patients, the ORR was 89%, and the CR rate was 56%. The incidence and severity of CRS (80%, including grade 3 in 5%) and ICANS (18%, including grade 3 in 6%) were similar to the values for the trial cohort. Delayed neurotoxicity was seen in 12% of the patients, most commonly CN VII palsy (6%). Parkinsonism-like MNTs were seen in 1% of the patients.

Hansen DK et al J Clin Oncol, 41 (16_suppl) (2023)

First Results From the CARTITUDE-4 Patients With Len-Refractory MM: St

Key Eligibility Criteria

- RRMM with 1-3 prior LOT (including PI + IMiD)
- Len refractory
- No prior CAR T-cell therapy or BCMA-targeting therapy
- ECOG PS ≤1



Primary endpoint: PFS
Secondary endpoints: ≥CR, ORR, MRD negativity, OS, safety, PROs

AEs (As-Treated Population; n=176)	Any Grade, n (%)	Grade 3/4, n (%)	Median Time to Onset, d	Median Duration, d	Resolved, n
CRS	134 (76.1)	2 (1.1)	8	3	134
Neurotoxicity[a]	36 (20.5)	5 (2.8)			
ICANS	8 (4.5)	0[b]	10	2	8
Other	30 (17.0)	4 (2.3)			
Cranial nerve palsy[c]	16 (9.1)	2 (1.1)	21	77	14
PN	5 (2.8)	1 (0.6)	63	201	3
MNT	1 (0.6)	0	85	-	0

Table 1. Movement and neurocognitive treatment-emergent adverse events in CARTITUDE-1.

Category	Preferred term
Movement disorder	Ataxia, Balance disorder, Bradykinesia, Cogwheel rigidity, Dysgraphia, Dyskinesia, Dysmetria, Essential tremor, Gait disturbance, Hand-eye coordination impaired, Micrographia, Motor dysfunction, Myoclonus, Parkinsonism, Posture abnormal, Resting tremor, Stereotypy, Tremor
Cognitive impairment	Amnesia, Apraxia, Bradyphrenia, Cognitive disorder, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Incoherent, Leukoencephalopathy, Loss of consciousness, Memory impairment, Mental impairment, Mental status changes, Non-infective encephalitis, Psychomotor retardation
Personality changes	Flat affect, Personality change, Reduced facial expression

In CARTITUDE-1, 6% of patients exhibited signs and symptoms of movement and neurocognitive TEAEs/parkinsonism, but strategies to manage these TEAEs were implemented in CARTITUDE-2 and across the rest of the clinical development program, including more effective bridging therapy, early and aggressive treatment of CRS and ICANS, handwriting assessment, and extensive monitoring. Apart from ICANS, no other neurotoxicities were observed in cohort C (prior exposure to BCMA targeting agents).

A.D. Cohen et al. Blood Canc J 2022

Although some symptoms overlap with ICANS symptomatology (i.e., altered mental status, somnolence), MNT symptoms occur after a period of recovery from CRS and/or ICANS and may present in a unique pattern, including insidious onset; these symptoms are also generally non-responsive to steroids, often progressive and have longer duration than ICANS. Of note, patients also had normal to near normal ICE scores at the time of MNT presentation, which is inconsistent with the current literature definition of ICANS

Patients were considered to have MNTs if they met all three of the following criteria: (i) must have reported at least one or more of the preferred terms in at least two of the above categories; (ii) these reported preferred terms must have occurred following the recovery of CRS and/or ICANS; and (iii) symptoms must have been assessed by the investigator as CAR T-cell–related neurotoxicity (but not recognized as ICANS)

A.D. Cohen et al. Blood Canc J 2022

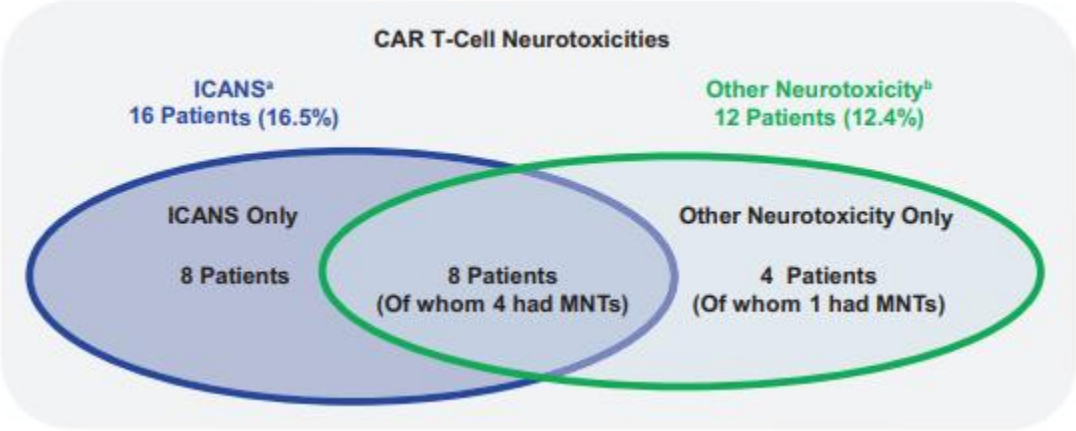


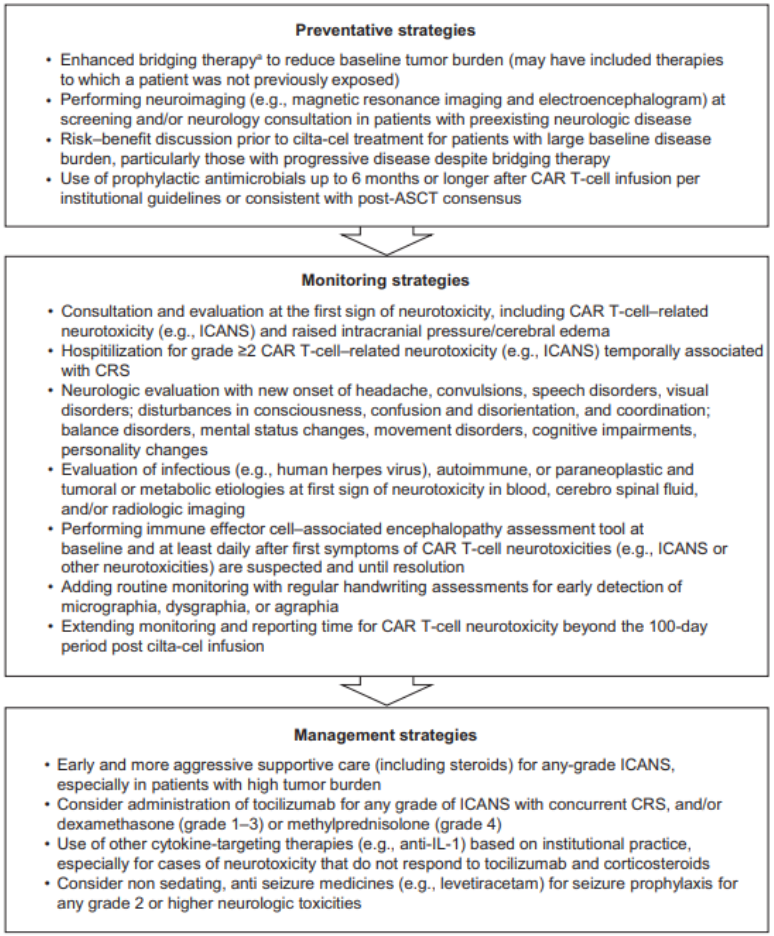
Table 2. Characteristics of MNTs in CARTITUDE-1.

Characteristic	*N* = 97
Patients with MNT[a], *n* (%)	5 (5.2)
Maximum toxicity grade, *n (%)*	
Grade 1	0
Grade 2	1 (1.0)
Grade 3	3 (3.1)
Grade 4	0
Grade 5	1 (1.0)
Median time to onset, days (range)	27.0 (14–108)
Outcome of neurotoxic event, n (%)	
Recovered or resolved	0
Not recovered or not resolved	3 (3.1)[b]
Recovering or resolving	1 (1.0)
Fatal	1 (1.0)

ICANS immune effector cell-associated neurotoxicity syndrome, *MNTs* movement and neurocognitive treatment-emergent adverse events.
[a]Events not reported as ICANS (i.e., onset after a period of recovery from cytokine release syndrome and ICANS).
[b]Not recovered or not resolved at the time of data cutoff; two of these patients died due to other causes (one due to septic shock and one due to lung abscess).

Risk factors for MNTs were similar to those for CRS, including high tumor burden, grade 2+ CRS, any-grade ICANS, or high CAR-T cell expansion/persistence

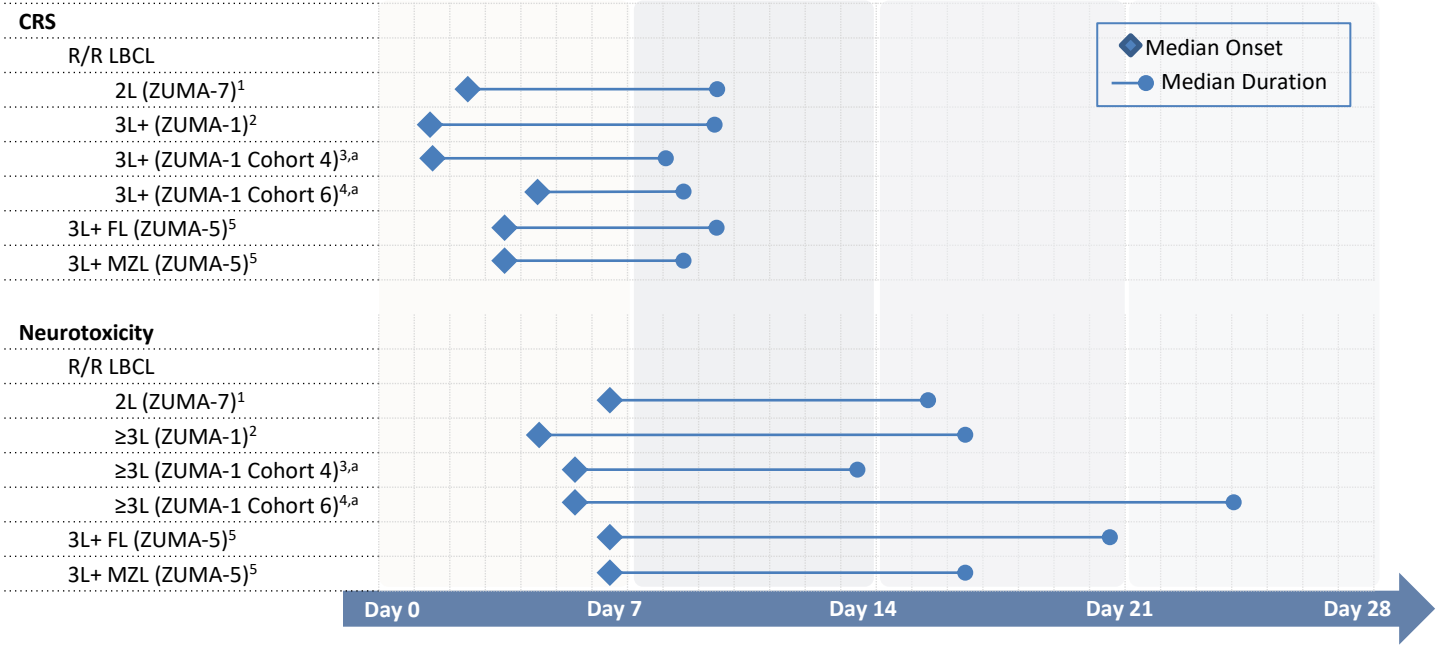
Reduced rates of neurocognitive MNTs to ≤1% with these precautions in the CARTITUDE-2 and CARTITUDE-4 studies, although facial nerve palsy was still seen in 1 patient in CARTITUDE-2 and in 16 patients (9.1%) in CARTITUDE-4



GRAZIE PER L’ATTENZIONE

Timing of CRS after Axi-cel Therapy

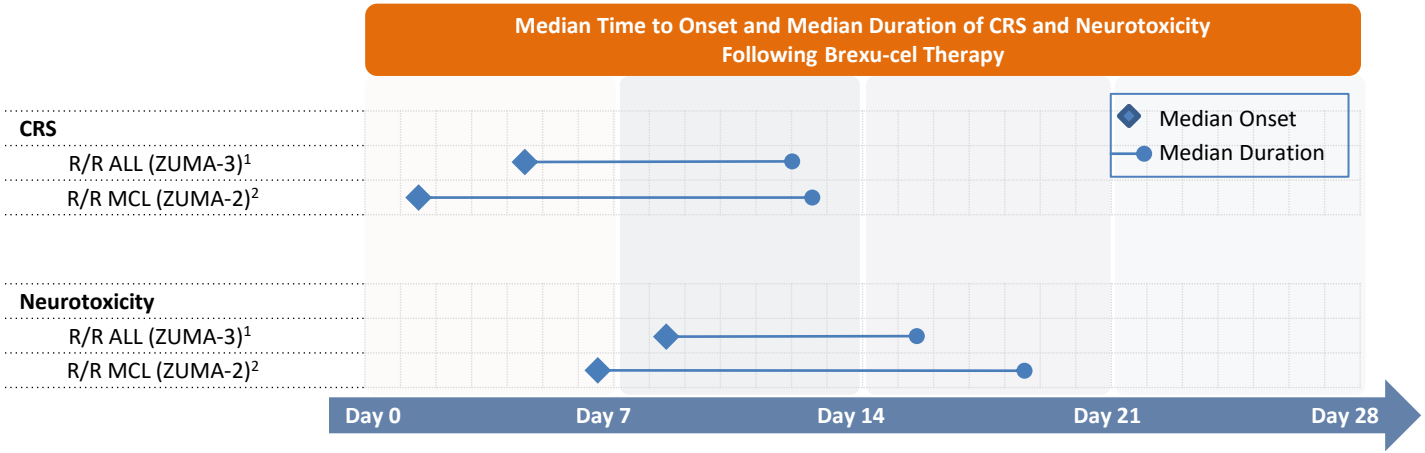
Median Time to Onset and Median Duration of CRS and Neurotoxicity Following Axi-cel Therapy



- [a]Exploratory safety management cohort added to phase 2 of ZUMA-1

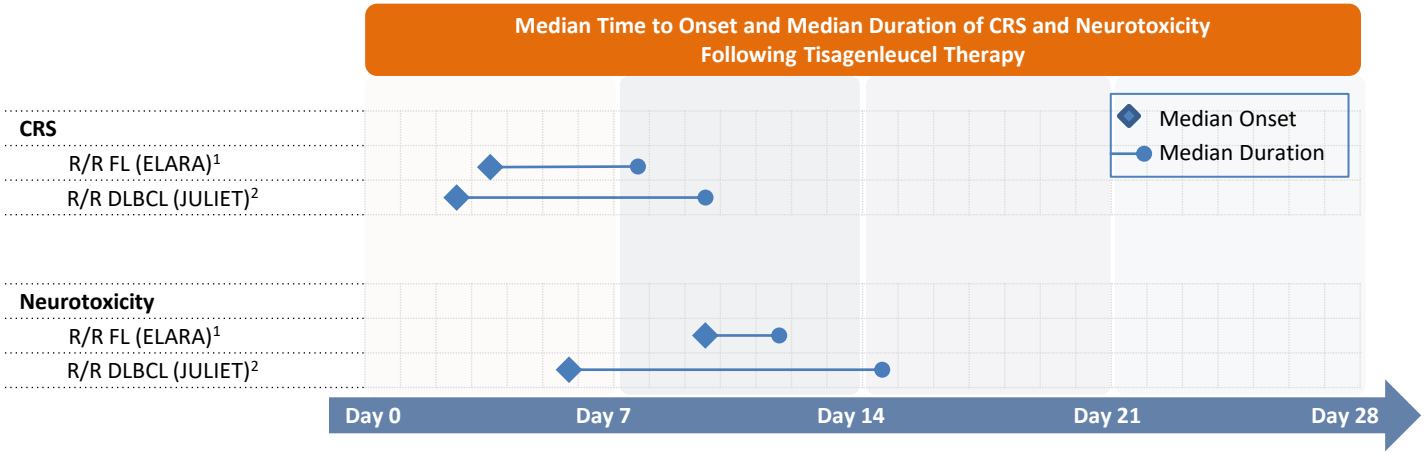
- 1. Locke FL et al. *N Engl J Med*. 2022;386(7):640–654. 2. Neelapu SS et al. *N Engl J Med*. 2017;377(26):2531–2544. 3. Topp MS et al. *Br J Haematol*. 2021;195(3):388–398.
4. Oluwole OO et al. *Br J Haematol*. 2021;194(4):690–700. 5. Jacobson CA et al. *Lancet Oncol*. 2022;23(1):91–103.

Timing of CRS after Brexu-cel Therapy



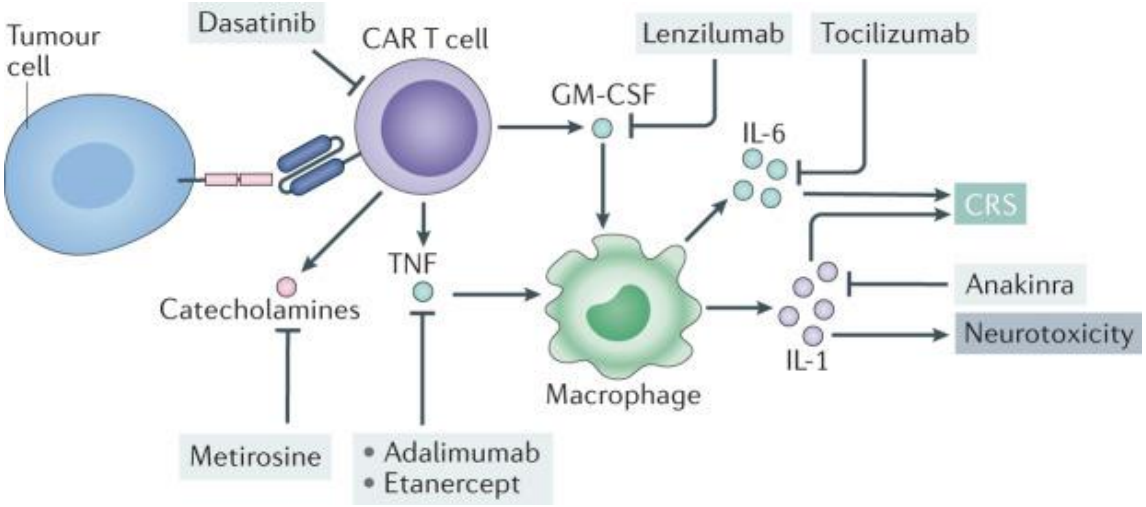
- 1. Shah BD et al. *Lancet*. 2021;398(10299):491–502. 2. Wang M et al. *N Engl J Med*. 2020;382(14):1331–1342.

Timing of CRS after Tisagenleucel Therapy



- 1. Fowler NH, et al. Nat Med. 2022;28(2):325-332.
- 2. Schuster SJ, Tam CS, Borchmann P, et al. Lancet Oncol. 2021; 22 (10):1403-1415.

Schematic representation of current and potential therapeutic interventions for CRS.



Morris EC, Nat Rev Immun2022

CRS in Axi-cel Clinical Trials

Incidence, Time to Onset, and Duration of CRS

Patient Population	Clinical Trial	N	Median Follow-up, Months	Incidence, n (%)		Median Time to Onset, Days (Range)	Median Duration, Days (Range)	Resolution at Data Cutoff, n (%)
				All Grades	Grade ≥3			
2L LBCL	ZUMA-7[1,a]	170	24.9	157 (92)	11 (6)	3 (1–10)	7 (2–43)	157/157 (100)
3L+ LBCL	ZUMA-1 Phases 1 & 2[2]	108[b]	27.1[c]	100 (93)	12 (11)	--	--	--
3L+ LBCL	ZUMA-1 Cohorts 1 & 2[3]	101	8.7	94 (93)	13 (13)	2 (1–12)	8 (--)	93/94 (99)[d]
3L+ LBCL	ZUMA-1 Cohort 4[4,e]	41	14.8	38 (93)	1 (2)	2 (1–8)	6.5 (2–16)	38/38 (100)
3L+ LBCL	ZUMA-1 Cohort 6[5,e]	40	8.9	32 (80)	0	5 (1–15)	4 (1–11)	32/32 (100)
	ZUMA-1 Cohort 6[6,e]	40	14.9	No new cases[f]	No new cases[f]	5 (1–15)[g]	4 (1–11)[g]	NA
3L+ iNHL	ZUMA-5							
	All Patients[7]	148	23.3	121 (82)	10 (7)	--	--	120/121 (99)[i]
	All Patients[8]	149	--	2(1) New cases[h]	No new cases[h]	--	--	--
	FL[7]	124	24.4	97 (78)	8 (6)	4 (IQR, 2–6)	6 (IQR, 4–8)	96/97 (99)[i]
	FL[8]	124	30.9	No new cases[h]	No new cases[h]	--	--	NA
	MZL[7]	24	17.3	24 (100)	2 (8)	4 (IQR, 2–7)	5 (IQR, 3–9)	24/24 (100)
	MZL[8]	25	23.8	2(8) New cases[h]	No new cases[h]	--	--	--

[a]Management guidelines for CAR T-cell related adverse events in ZUMA-7 followed that used in ZUMA-1 Cohorts 1 & 2. [b]Includes 7 patients in Phase 1 and 101 patients in Phase 2 cohorts 1 & 2. [c]For the 101 patients in Phase 2 cohorts 1 & 2. [d]All the events associated with CRS resolved except for one event of grade 5 hemophagocytic lymphohistiocytosis. [e]Exploratory safety management cohort added to phase 2 of ZUMA-1. [f]Includes AEs that occurred after the previous report. [g]Median time for all 40 patients. [h]Includes AEs that occurred after the primary analysis data cutoff date (March 12, 2020), including AEs for 3 additional patients with MZL that were treated after the primary analysis data cutoff. [i]All events in the setting of CRS resolved except one event of multisystem organ failure leading to death on day 7 in a patient with FL who had bulky disease at baseline per GELF criteria

1. Locke FL et al. *N Engl J Med.* 2022;386(7):640–654. 2. Locke FL et al. *Lancet Oncol.* 2019;20(1):31–42 and supplement. 3. Neelapu SS et al. *N Engl J Med.* 2017;377(26):2531–2544. 4. Topp MS et al. *Br J Haematol.* 2021;195(3):388–398. 5. Oluwole OO et al. *Br J Haematol.* 2021;194(4):690–700. 6. Oluwole OO et al. Presented at ASH 2021; poster 2832. 7. Jacobson CA et al. *Lancet Oncol.* 2022;23(1):91–103. 8. Neelapu SS et al. Presented at ASH 2021; abstract 93.

CRS in Brexu-cel Clinical Trials

Incidence, Time to Onset, and Duration of CRS

Patient Population	Clinical Trial	N	Median Follow-up, Months	Incidence, n (%)		Median Time to Onset, Days (Range)	Median Duration, Days (Range)	Resolution at Data Cutoff, n (%)
				All Grades	Grade ≥3			
R/R MCL	ZUMA-2[1,2]	68	12.3[1] 35.6[2]	62 (91) No new cases[a]	10 (15) No new cases[a]	2 (1–13) --	11 --	62/62 (100%) NA[a]
R/R ALL	ZUMA-3 (Phase 1)[3]	45	22.1	42 (93)	14 (31)	2 (IQR, 1–5)	9 (7–14)	40/42 (95.2%)[b]
R/R ALL	ZUMA-3 (Phase 2)[4,5]	55	16.4[4] 26.8[5]	49 (89) No new cases[a]	13 (24) No new cases[a]	5 (IQR, 3–7) --	7.5 (5–18) --	46/49 (93.9%)[c] NA[a]

- [a] AEs occurring after the previous report.
- [b] Two patients experienced grade 5 KTE-X19-related AEs. One patient treated with 2 x 10^6 CAR T cells per kg had multiorgan failure secondary to CRS (day 6). One patient treated with 0.5 x 10^6 cells per kg developed cerebrovascular accident (stroke) in the context of grade 2 CRS and grade 4 NEs (day 7). These observations prompted the study of lower doses and the revision of AE management.
- [c] 3 patients had ongoing CRS at the time of death; these deaths were due to brain herniation (day 8; considered related to KTE-X19), pneumonia (day 15), or progressive disease (day 21).

- 1. Wang M et al. *N Engl J Med*. 2020;382(14):1331–1342. 2. Wang M et al. *J Clin Oncol*. 2022;JCO2102370 and supplement. 3. Shah BD et al. *Blood*. 2021;138(1):11–22.
4. Shah BD et al. *Lancet*. 2021;398(10299):491–502. 5. Shah BD et al. Presented at ASCO 2022; abstract 7010.

CRS in Tisagenleucel Clinical Trials

Incidence, Time to Onset, and Duration of CRS

Patient Population	Clinical Trial	N	Median Follow-up, Months	Incidence, n (%)		Median Time to Onset, Days (Range)	Median Duration, Days (Range)	Resolution at Data Cutoff, n (%)
				All Grades	Grade ≥3			
R/R FL	ELARA[1,]	97	29	48 (50)	0 (0)	4 (IQR, 2–7)	7 days (5–9)	97/97 (100%)
R/R DLBCL	JULIET[2]	115	40.3	66 (57)	26 (23)	3 (IQR, 2-8)	7 (2–30)	112/115 (97)

1. Fowler NH, et al. Nat Med. 2022;28(2):325-332.
2. Schuster SJ, Tam CS, Borchmann P, et al. Lancet Oncol. 2021; 22 (10):1403-1415.

Incidence of CRS

Cell product	Malignancy	Cell doses	ORR and CR rate (%) Deaths (absolute number)*	CRS (%)	Neurotoxicity (%)
Tisagenlecleucel					
Maude et al. [12], *n* = 75	Pediatric ALL	0.2×10^6 to 5.4×10^6 CAR+ cells /kg	MRD neg CR: 81 Deaths: 0	All[F]: 77 Grade 3–4: 46	All: 40 Grade 3–4: 13
Schuster et al. [28], *n* = 99	DLBCL	$0.1–6 \times 10^8$ CAR+ cells	ORR 53 CR 40 Deaths: 0	All[F]: 58 Grade 3–4: 23	All: NR Grade 3–4: 12
Schuster et al. [26], *n* = 28	NHL	$1.79–5 \times 10^8$ CAR+ cells	DLBCL: ORR 50 CR 43 FL: ORR 79 CR 71 Deaths: 1	All[F]: 57 Grade 3–4: 18	All: 39 Serious: 11[**]
Fraietta et al. [17]; *n* = 41 (reports antimalignancy responses)	CLL	1.5×10^7-5×10^9 total nucleated cells	ORR 39 CR 20	All[F]: 64 Grade 3–4: 43	All: 36 Grade 3–4: 7
Porter et al. [14], *n* = 14 (reports toxicity)			Deaths: 0		
Axicabtagene ciloleucel					
Lee et al. [8], *n* = 21	Pediatric ALL	$0.03–3 \times 10^6$ CAR+ cells /kg	CR 70 MRD neg CR 60 Deaths: 0	All[L]: 76 Grade 3–4: 29	All: 29 Grades 3–4: 5
Kochenderfer et al. [18] Kochenderfer et al. [19] Kochenderfer et al. [21] *n* = 45	NHL and CLL	$1–30 \times 10^6$ CAR+ cells/kg	ORR 81 CR 50 Deaths: 2	All: NR Grade 3–4: NR	All: NR Grade 3–4: 44
Locke et al. [22] Neelapu et al. [25]	Aggressive NHL	2×10^6 CAR+ cells /kg	ORR 80 CR 55	All[L]: 93	All: 67

Brudno JN Blood Rev. 2019

Cell product	Malignancy	Cell doses	ORR and CR rate (%) Deaths (absolute number)[*]	CRS (%)	Neurotoxicity (%)
lisocabtagene maraleucel; JCAR017					
Abramson et al. [27], *n* = 91	Aggressive NHL	≤1 × 10^8 CAR+ T cells	ORR 74 CR 52 Deaths: 0	All[L]: 35 Grade 3–4: 1	All: 19 Grade 3–4: 12
Fred Hutchinson Cancer Center CAR T-cell product					
Turtle et al. [9], *n* = 30	Adult ALL	2 × 10^5-2 × 10^7 CAR+ T cells /kg	MRD neg CR 86 Deaths: 2	All: 83 Serious: 23[^]	All: 50 Grade 3–4: 47
Turtle et al. [20], *n* = 32.	NHL	2 × 10^5-2 × 10^7 CAR+ T cells /kg	All patients: ORR 63 CR 33 Flu/Cy conditioning: ORR 72 CR 50 Deaths: 2	All[L]: 63 Grade 3–4: 22	All: 25 Grade 3–4: 22
Turtle et al. [15], *n* = 24	CLL	2 × 10^5-2 × 10^7 CAR+ T cells /kg	ORR 74 CR 21 Deaths: 1	All[L]: 83 Grade 3–4: 4	All: 33 Grade 3–4: 21
1928z CAR T					
Park et al. [13], *n* = 53	Adult ALL	1– 3 × 10^6 CAR+ T cells/kg	CR 83 MRD neg CR 67 Deaths: 1	All[MSK]: 85 Grade 3–4: 25	All: NR Grade 3–4: 42

Brudno JN Blood Rev. 2019

HLH/MAS in Axi-cel Clinical Trials

Incidence, Time to Onset, and Duration of HLH/MAS

Patient Population	Clinical Trial	N	Median Follow-up, Months	All Grade, n	Grade ≥3, n
2L LBCL	ZUMA-7[1]	170	24.9	--	--
3L+ LBCL	ZUMA-1 Phases 1 & 2[2]	108[a]	27.1[b]	1[c]	--
3L+ LBCL	ZUMA-1 Cohorts 1 & 2[3]	101[b]	8.7	--	1[c]
3L+ LBCL	ZUMA-1 Cohort 4[4,d]	41	14.8	--	--
3L+ LBCL	ZUMA-1 Cohort 6[5,d] ZUMA-1 Cohort 6[6,d]	40 40	8.9 14.9	--	--
3L+ iNHL	ZUMA-5 All Patients[7] All Patients[8] FL[7] FL[8] MZL[7] MZL[8]	 148 149 124 124 24 25	 23.3 -- 24.4 30.9 17.3 23.8	--	--

- [a]Includes 7 patients in Phase 1 and 101 patients in Phase 2 cohorts 1 & 2. [b]For the 101 patients in Phase 2 cohorts 1 & 2. [c]Grade 5 HLH in the context of CRS. [d]Exploratory safety management cohort added to phase 2 of ZUMA-1
- 1. Locke FL et al. *N Engl J Med.* 2022;386(7):640–654. 2. Locke FL et al. *Lancet Oncol*. 2019;20(1):31–42 and supplement. 3. Neelapu SS et al. *N Engl J Med*. 2017;377(26):2531–2544. 4. Topp MS et al. *Br J Haematol*. 2021;195(3):388–398. 5. Oluwole OO et al. *Br J Haematol*. 2021;194(4):690–700. 6. Oluwole OO et al. Presented at ASH 2021; poster 2832. 7. Jacobson CA et al. *Lancet Oncol*. 2022;23(1):91–103. 8. Neelapu SS et al. Presented at ASH 2021; abstract 93

HLH/MAS in Brexu-cel Clinical Trials

Brexu-cel TOC

Incidence of HLH/MAS

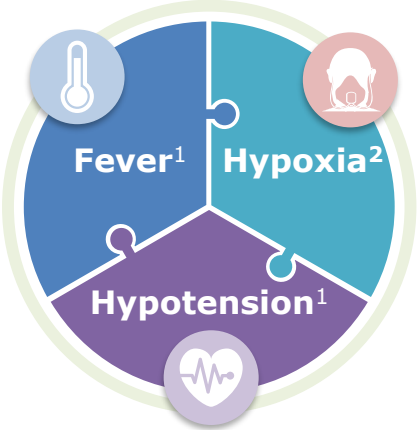
Patient Population	Clinical Trial	N	Median Follow-up, Months	Any, n
R/R MCL	ZUMA-2[1]	68	12.3	0
R/R ALL	ZUMA-3 (Phase 1)[2]	45	22.1	--
R/R ALL	ZUMA-3 (Phase 2)[3]	55	16.4	--

1. Wang M et al. *N Engl J Med*. 2020;382(14):1331–1342. 2. Shah BD et al. *Blood*. 2021;138(1):11–22. 3. Shah BD et al. *Lancet*. 2021;398(10299):491–502.

CRS is a widespread inflammatory response

Defining clinical symptoms of CRS

Patient body temperature is ≥38°C[3]



Generally defined as SaO_2 <88–94% or an individual requiring supplemental oxygen to correct an oxygen deficiency[3]*

Generally defined as SBP <90 mmHg in adults[3]*

*Should be determined on a case-by-case basis.[3]
CRS, cytokine release syndrome; IFN, interferon; IL, interleukin; SaO2, arterial oxygen saturation; SBP, systolic blood pressure; TNF, tumour necrotic factor.

1. Shimabukuro-Vornhagen A, et al. *J Immunother Cancer* 2018;6:56; 2. Riegler LL, et al. *Ther Clin Risk Manag* 2019;15:323–335;
3. Lee D, et al. *Biol Blood Marrow Transplant* 2019;25:625–638.