

# **Understanding, Evaluating, and Managing irAEs Associated with CAR T-Cell and BsAb Therapy in Multiple Myeloma:**



**Strategies in Emergency Medicine**

# Faculty

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# Faculty Disclosures

- **Dr. Richter:** Speakers' Bureau—Adaptive Biotechnologies, Bristol Myers Squibb, Janssen, Sanofi; consultant/advisor—AbbVie, Bristol Myers Squibb, Genentech, Janssen, Karyopharm, Pfizer, Sanofi, Takeda
- **Dr. Wattana** has disclosed no relevant financial relationship with any ineligible company (commercial interest)

# Program Information

- This program is provided by HMP Education, an HMP Global company
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# Learning Objectives

- Evaluate recent real-world clinical data of newer and emerging immunotherapeutic options, including CAR T-cell therapy and BsAbs, for the treatment of R/R MM and their potential implications in the development of TRAEs
- Accurately recognize, diagnose, treat, and manage the most common hematological and non-hematological toxicities and TRAEs in patients affected by and treated for MM
- Understand current guidelines and protocols available for TRAEs in MM patients
- Incorporate and implement a multidisciplinary team (MDT) approach to improve MM patient outcomes and quality of life

**irAE = immune-related adverse event; CAR = chimeric antigen receptor; BsAb = bispecific antibody; R/R = relapsed/refractory; TRAE = treatment-related adverse event; MM = multiple myeloma.**

# Pre-Activity Survey

Scan the QR Code below or at your table



We appreciate your participation.

# Question 1

Which of the following targets both CD3 T-cell receptors and the GPRC5D MM receptor and has been associated with CRS and ICANS?

1. Elranatamab
2. Isatuximab
3. Teclistamab
4. Talquetamab
5. Unsure



## Question 2

CRS and ICANS were seen in \_\_\_\_, respectively, of patients treated with cilta-cel in the CARTITUDE-1 trial.

1. ~20% and ~60%
2. ~40% and ~80%
3. ~60% and ~40%
4. ~80% and ~20%
5. Unsure



## Question 3

All of the following may be considered as a therapeutic approach to CAR T- and BsAb-associated CRS except?

1. CD-20 blockade with rituximab
2. IL-6 inhibition with siltuxumab
3. IL-6 inhibition with tocilizumab
4. IL-1 inhibition with anakinra
5. Unsure



## Question 4

How confident are you in your ability to incorporate and implement a multidisciplinary team (MDT) approach to improve MM patient outcomes and quality of life?

1. Very confident
2. Confident
3. Somewhat confident
4. Not very confident
5. Not at all confident



# Understanding, Evaluating, and Managing irAEs Associated with CAR T-Cell and BsAb Therapy in Multiple Myeloma

**Joshua Richter, MD**

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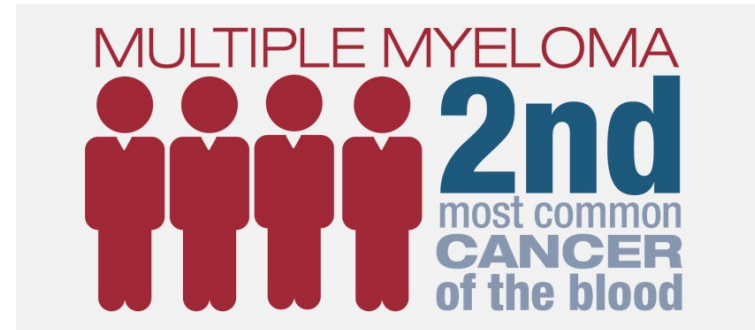
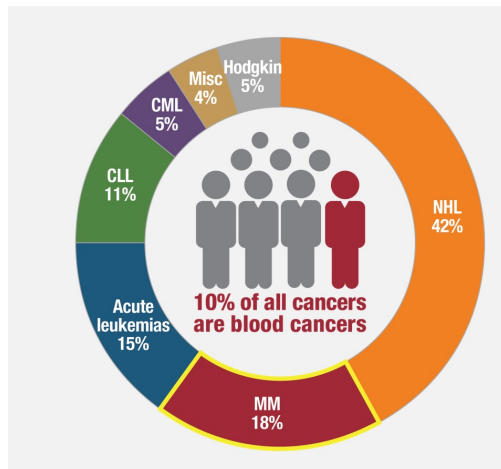
Icahn School of Medicine at Mount Sinai

New York City, New York

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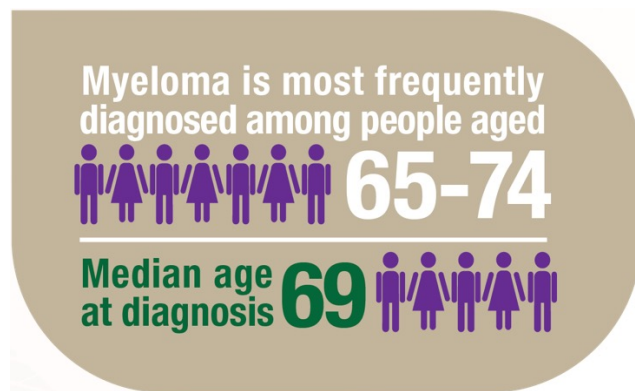
# Overview of Multiple Myeloma

# Pathobiology/Epidemiology

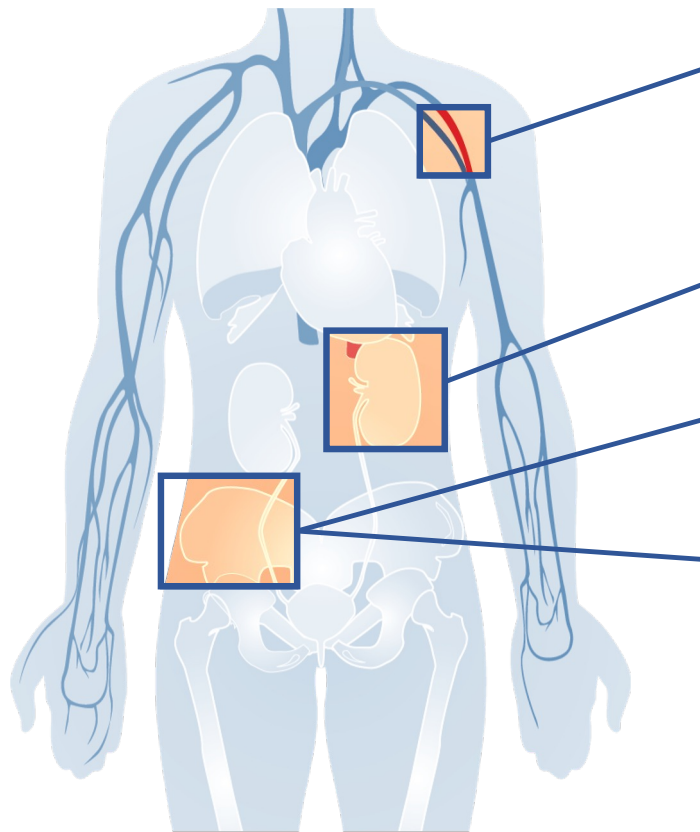


Estimated New Cases in 2023	35,730
% of All New Cancer Cases	1.8%
Estimated Deaths in 2023	12,590
% of All Cancer Deaths	2.1%

5-Year Relative Survival	<b>59.8%</b>
2013–2019	



# Effects of Myeloma and Common Symptoms



## Low blood counts

- Anemia is present in 60% of patients at diagnosis
- May lead to anemia and infection

→ Weakness  
→ Fatigue  
→ Infection

## Decreased kidney function

- Occurs in over half of myeloma patients

→ Weakness

## Bone damage

- Affects 85% of patients
- Common sites include spine, pelvis, and ribs
- Leads to fractures

→ Bone pain

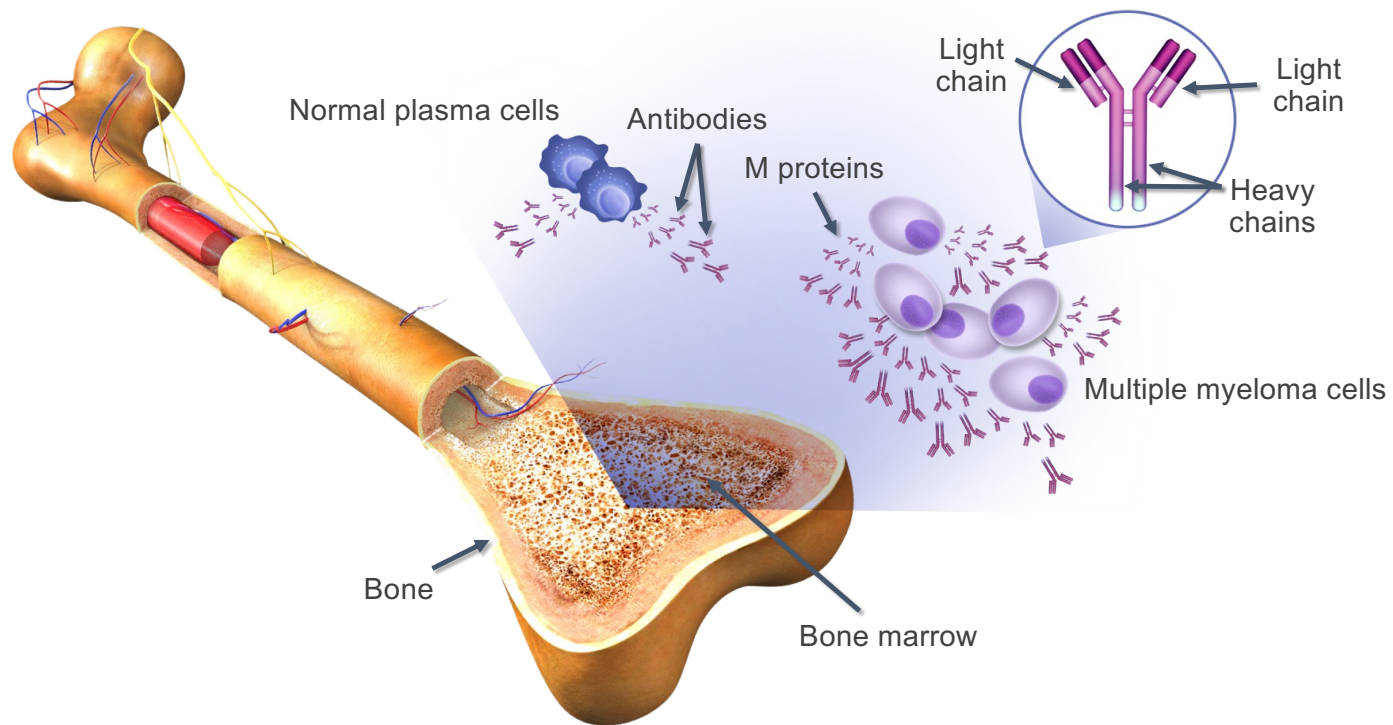
## Bone turnover

- Leads to high levels of calcium in blood (hypercalcemia)

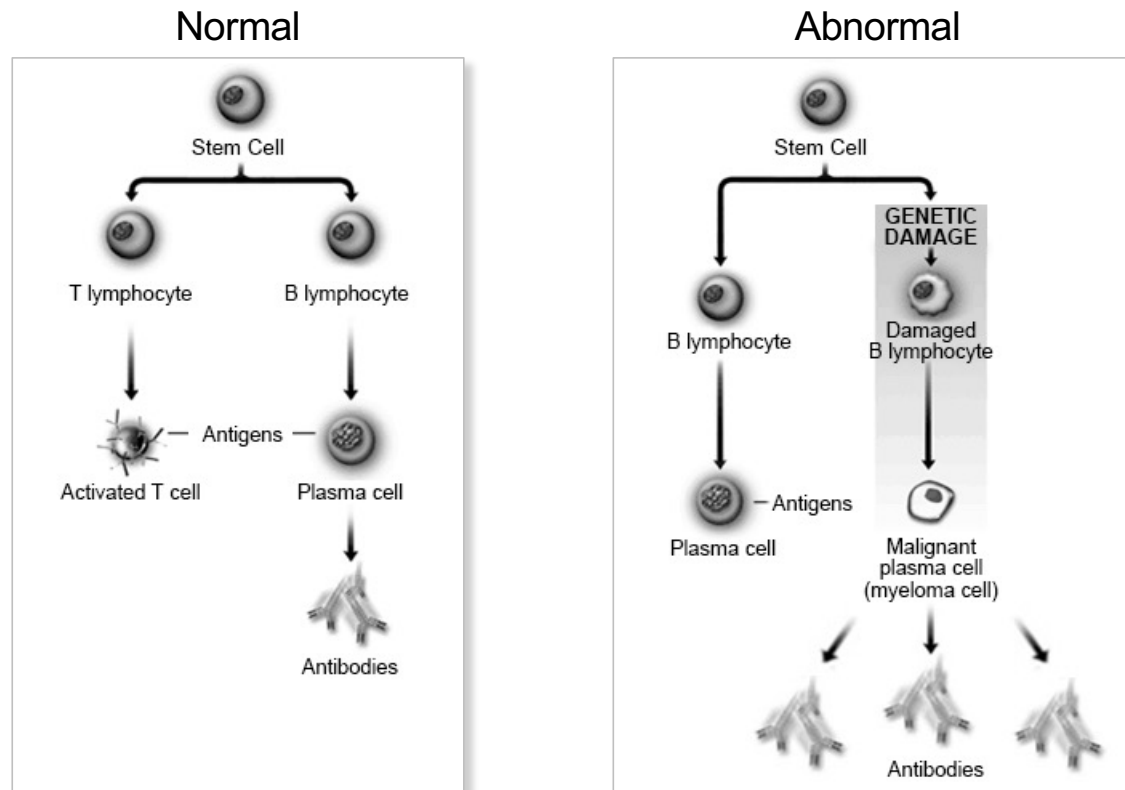
→ Loss of appetite  
→ Weight loss

***About 10% to 20% of patients with newly diagnosed myeloma will not have any symptoms.***

# What Is Multiple Myeloma?

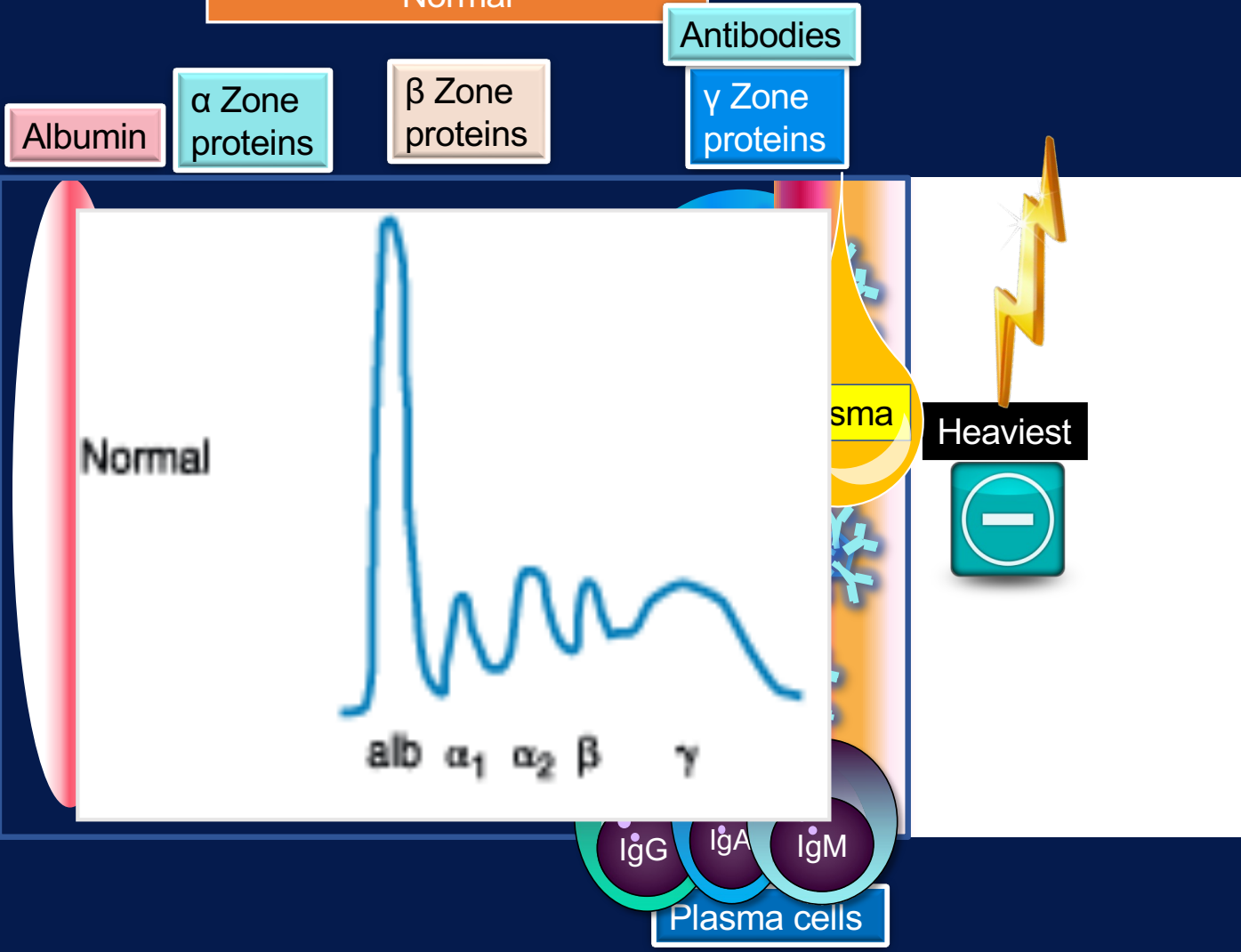


# Normal vs Abnormal Plasma Cells

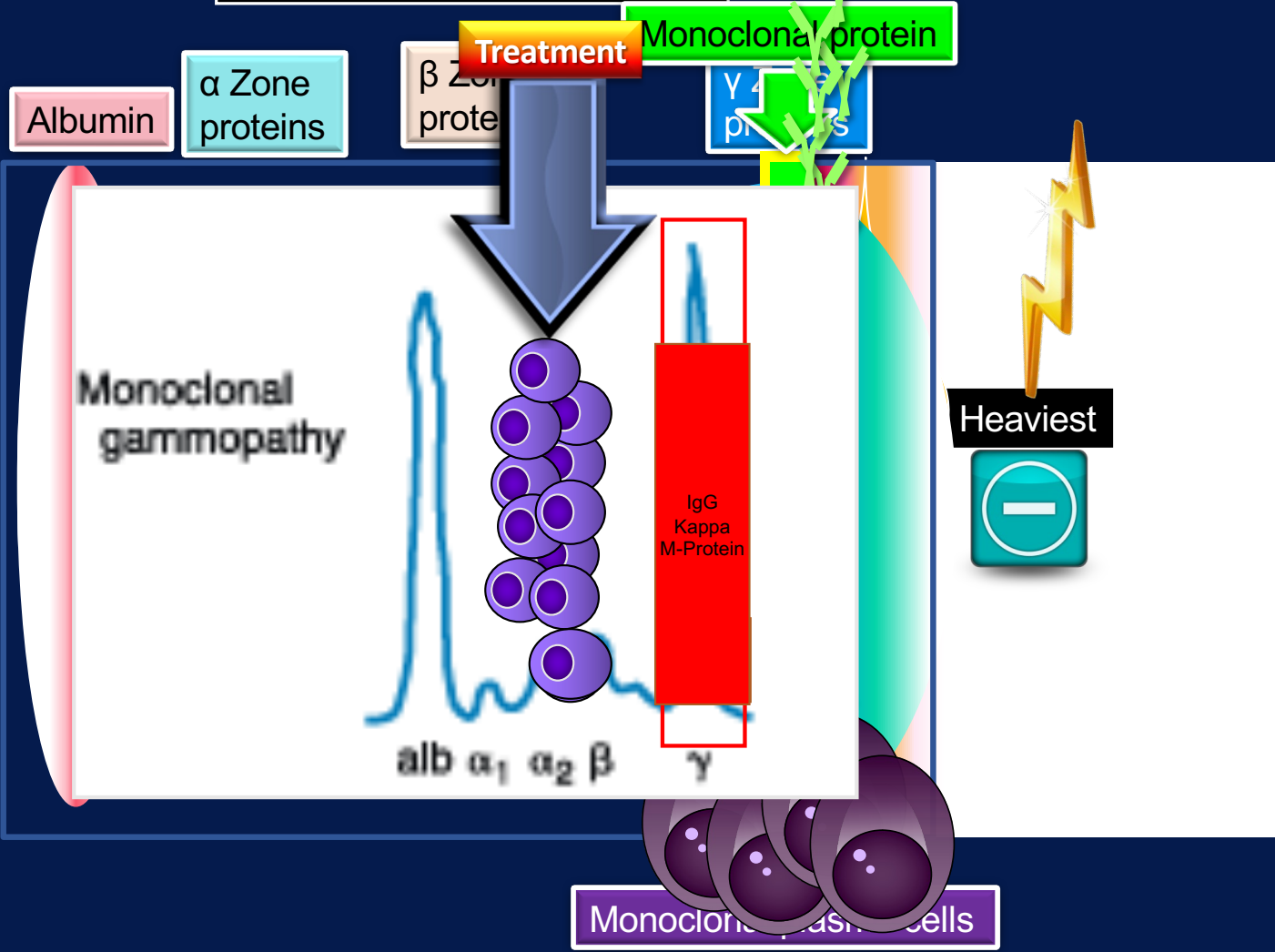


Adapted from Multiple Myeloma Research Foundation.

# Serum Protein Electrophoresis Normal



# Serum Protein Electrophoresis Monoclonal Gammopathy



# Diagnostic Criteria (SLiM-CRAB)

- Clonal bone marrow plasma cells > 10%, bony or extramedullary plasmacytoma with any of the following myeloma-defining events
- End organ damage attributable to myeloma (CRAB)
  - C Hypercalcemia:  $\text{Ca}^{++} > 0.25$  mmol/L above upper limit of normal
  - R Renal insufficiency: creatinine > 2 mg/dL or eGFR < 40 mL/min
  - A Anemia: Hgb > 2 g/dL below the lower limit of normal
  - B Bone lesion: one or more osteolytic bone lesions on X-ray, CT, PET-CT
- Biomarkers of malignancy
  - Clonal bone marrow plasma cells > sixty (60%)
  - Involved:uninvolved serum free light chain ratio > 100:1
  - > 1 focal bone lesion on MRI of at least 5 mm (not same thing as lytic lesion)

Ca = calcium; Hgb = hemoglobin; eGFR = estimated glomerular filtration rate; CT = computed tomography; PET-CT = positron emission tomography-computed tomography; MRI = magnetic resonance imaging. SLiM = S (greater than or equal to sixty percent clonal plasma cells in the bone marrow), Li (involved/uninvolved free light chain ratio of 100 or more with the involved FLC being greater than or equal 100 mg/L), M (MRI with more than one focal marrow lesion).

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# Increasing Awareness of MM TRAEs

# Statistical Analysis of Potentially Preventable Cancer Patient ED Visits

- 35.5 million annual ED visits among patients with cancer
  - 67.1% increase in visits from 2012-2019, compared with an increase of just 7.5% in cancer incidence
- 51.6% of visits were identified as potentially preventable
  - From 2012 to 2019: the absolute number of potentially preventable ED increased from 1.8 million to 3.2 million
  - Potentially preventable ED visits have been associated with poor patient experiences and increasing cancer care costs
  - 30.2% resulted in hospitalization
    - Highest: sepsis (93.3%), pneumonia (76.2%), and anemia (71.7%),
    - Lowest: pain (23.5%), dehydration (28.0%), and nausea (31.8%)

## List of the CMS Potentially Preventable Primary Diagnosis

Anemia

Nausea

Fever

Dehydration

Neutropenia

Diarrhea

Pain

Pneumonia

Sepsis

Emesis

ED = emergency department.

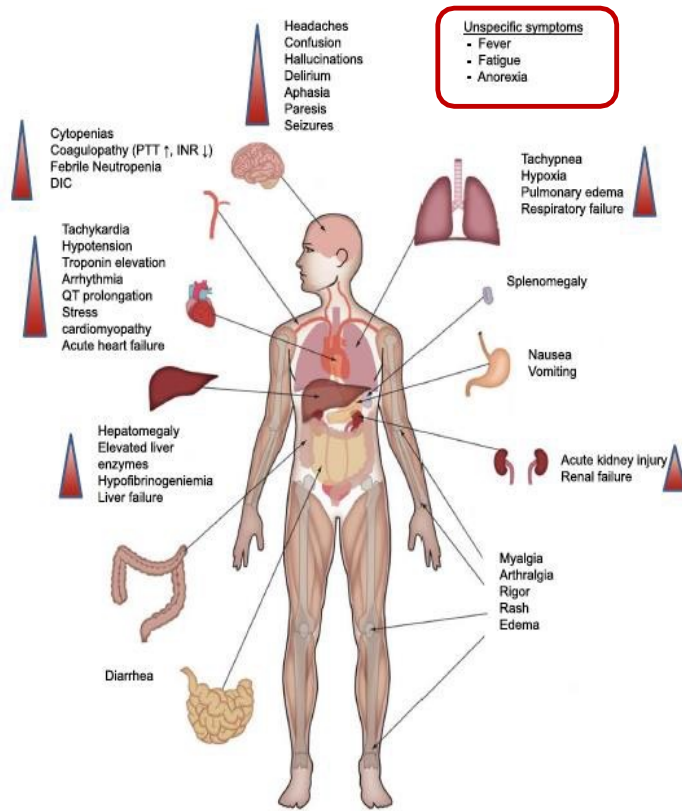
Tabriz AA, et al. *JAMA Netw Open*. 2023;6(1):e2250423.

# NCCN Guidelines: Management of Immunotherapy-Related Toxicities

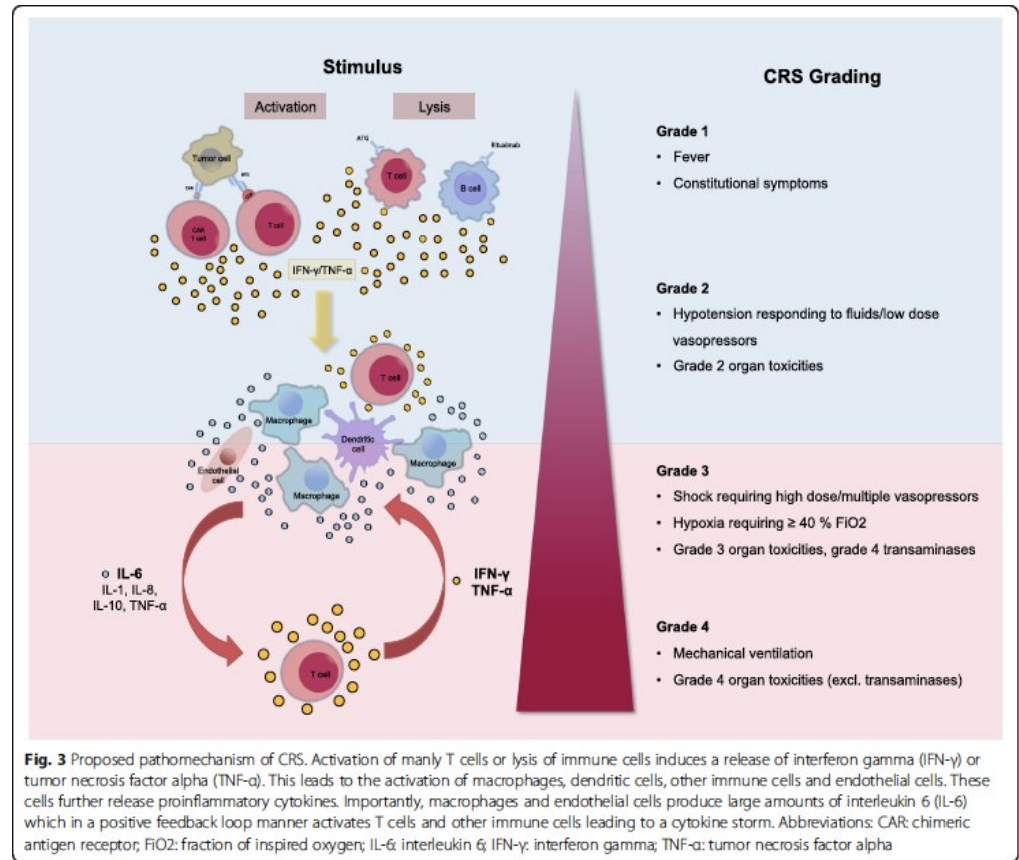
## OVERVIEW OF CAR T-CELL THERAPY-RELATED TOXICITIES

	Axicabtagene Ciloleucel, Brexucabtagene Autoleucel, Idecabtagene Vicleucel, Lisocabtagene Maraleucel, and Tisagenlecleucel <sup>a</sup>
CRS (CART-3)	<ul style="list-style-type: none"> <li>• Typical time to onset: 2–3 days; however, CRS may occur as early as hours after infusion and as late as 10-15 days post-infusion</li> <li>• Typical duration: 7–8 days</li> <li>• Manifestation may include fever, hypotension, tachycardia, hypoxia, and chills. CRS may be associated with cardiac, hepatic, and/or renal dysfunction.</li> <li>• Serious events may include hypotension, hypoxia, atrial fibrillation and ventricular tachycardia, cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).<sup>b</sup></li> </ul>
Neurologic Toxicity (CART-4)	<ul style="list-style-type: none"> <li>• Typical time to onset: 4–10 days</li> <li>• Typical duration: 14–17 days</li> <li>• Transient neurological symptoms can be heterogeneous and include encephalopathy, delirium, aphasia, lethargy, headache, tremor, myoclonus, dizziness, motor dysfunction, ataxia, sleep disorder (eg, insomnia), anxiety, agitation and signs of psychosis.</li> <li>• Serious events including seizures, depressed level of consciousness, as well as fatal and serious cases of cerebral edema, have occurred.</li> </ul>
Hemophagocytic Lymphohistiocytosis/Macrophage-Activation Syndrome (HLH/MAS) (CART-3)	<ul style="list-style-type: none"> <li>• Criteria for considering HLH/MAS:               <ul style="list-style-type: none"> <li>□ Rapidly rising and high ferritin (&gt;5000 ng/mL) with cytopenias in the context of fever, especially if accompanied by <i>any of the following</i>:                   <ul style="list-style-type: none"> <li>◇ Grade ≥ 3 increase in serum bilirubin, AST, ALT</li> <li>◇ Grade ≥ 3 oliguria or increase in serum creatinine</li> <li>◇ Grade ≥ 3 pulmonary edema</li> </ul> </li> <li>□ Presence of hemophagocytosis in bone marrow or organs based on histopathologic assessment of cell morphology and/or CD68 IHC.</li> </ul> </li> </ul>
Miscellaneous	<ul style="list-style-type: none"> <li>• Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T-cell therapy infusion.</li> <li>• Long-term B-cell aplasia and hypogammaglobulinemia can occur in patients with a complete remission after CAR T-cell therapy infusion.               <ul style="list-style-type: none"> <li>□ After anti-CD19 CAR T-cell therapy, consider monthly 400–500 mg/kg IVIG replacement for select patients with hypogammaglobulinemia (those with serum IgG levels &lt;400–600 mg/dL AND serious or recurrent infections [particularly bacterial]). Continue IVIG until serum IgG levels normalize and infections resolve. The optimal IgG threshold to use may depend on patient characteristics and infection frequency/severity.</li> </ul> </li> </ul>

# Cytokine Release Syndrome



**Fig. 1** Clinical presentation of CRS. Beginning with fever and unspecific symptoms CRS might impact most organ systems. Mild cases can present as flu-like illness. Grade III to IV shows signs of life threatening cardiovascular, pulmonary and renal involvement; Neurotoxicity can occur concurrent or with delay. Abbreviations: DIC: disseminated intravascular coagulation; INR: international normalized ratio; PTT: partial thromboplastin time



**Fig. 3** Proposed pathomechanism of CRS. Activation of many T cells or lysis of immune cells induces a release of interferon gamma (IFN- $\gamma$ ) or tumor necrosis factor alpha (TNF- $\alpha$ ). This leads to the activation of macrophages, dendritic cells, other immune cells and endothelial cells. These cells further release proinflammatory cytokines. Importantly, macrophages and endothelial cells produce large amounts of interleukin 6 (IL-6) which in a positive feedback loop manner activates T cells and other immune cells leading to a cytokine storm. Abbreviations: CAR: chimeric antigen receptor; FIO<sub>2</sub>: fraction of inspired oxygen; IL-6: interleukin 6; IFN- $\gamma$ : interferon gamma; TNF- $\alpha$ : tumor necrosis factor alpha

# ASBMT CRS Grading

## ASBMT CRS Consensus Grading<sup>##</sup>

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
<b>Fever††</b>	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
<b>With either:</b>				
<b>Hypotension</b>	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
<b>And/or‡‡</b>				
<b>Hypoxia</b>	None	Requiring low-flow nasal cannula <sup>^</sup> or blow-by	Requiring high-flow nasal cannula <sup>^</sup> , facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg: CPAP, BiPAP, intubation and mechanical ventilation)

ASBMT = American Society for Blood and Marrow Transplantation; CRS = cytokine release syndrome; CPAP = continuous positive airway pressure; BiPAP = bilevel positive airway pressure.

Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.

# NCCN Guidelines: Cytokine Release Syndrome (CRS)

CRS Grade	Anti-IL-6 Therapy	Corticosteroids <sup>j,k,l</sup>	Additional Supportive Care
<b>Grade 1</b> Fever ( $\geq 38^{\circ}\text{C}$ )	For prolonged CRS ( $>3$ days) <sup>h</sup> in patients or those with significant symptoms, comorbidities and/or are elderly, consider 1 dose of tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) <sup>i,t</sup>	For idecabtagene and lisocabtagene, consider dexamethasone 10 mg IV every 24 hours for early-onset CRS ( $<72$ hours after infusion)	<ul style="list-style-type: none"> <li>Sepsis screen and empiric broad-spectrum antibiotics, consider granulocyte colony-stimulating factor (G-CSF) if neutropenic<sup>q</sup></li> <li>Maintenance IV fluids for hydration</li> <li>Symptomatic management of organ toxicities</li> </ul>
<b>Grade 2</b> Fever with hypotension not requiring vasopressors and/or hypoxia <sup>r</sup> requiring low-flow nasal cannula <sup>g</sup> or blow-by	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). <sup>j</sup> Repeat in 8 hours if no improvement; no more than 3 doses in 24 hours, with a maximum of 4 doses total <sup>t</sup>	For persistent refractory hypotension after 1–2 doses of anti-IL-6 therapy: Consider dexamethasone 10 mg IV every 12–24 hours depending on product <sup>m,n</sup>	<ul style="list-style-type: none"> <li>IV fluid bolus as needed</li> <li>For persistent refractory hypotension after two fluid boluses and anti-IL-6 therapy: Start vasopressors, consider transfer to ICU, consider echocardiogram, and initiate other methods of hemodynamic monitoring. Telemetry, EKG, troponin, and BNP if persistent tachycardia</li> <li>Manage per Grade 3 if no improvement within 24 hours after starting anti-IL-6 therapy</li> <li>Symptomatic management of organ toxicities</li> </ul>
<b>Grade 3</b> Fever with hypotension requiring a vasopressor with or without vasopressin and/or hypoxia requiring high-flow cannula, <sup>g</sup> face mask, nonrebreather mask, or Venturi mask.	Anti-IL-6 therapy as per Grade 2 <sup>j</sup> if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours. <sup>m</sup> If refractory, manage as grade 4	<ul style="list-style-type: none"> <li>Transfer to ICU, obtain echocardiogram, and perform hemodynamic monitoring</li> <li>Supplemental oxygen</li> <li>IV fluid bolus and vasopressors as needed</li> <li>Symptomatic management of organ toxicities</li> </ul>
<b>Grade 4</b> Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, mechanical ventilation).	Anti-IL-6 therapy as per Grade 2 <sup>j</sup> if maximum dose not reached within 24-hour period	Dexamethasone 10 mg IV every 6 hours. <sup>m</sup> If refractory, consider 3 doses of methylprednisolone 1000 mg/day IV; if refractory, consider dosing every 12 hours <sup>o,p</sup>	<ul style="list-style-type: none"> <li>ICU care and hemodynamic monitoring</li> <li>Mechanical ventilation as needed</li> <li>IV fluid bolus and vasopressors as needed</li> <li>Symptomatic management of organ toxicities</li> </ul>

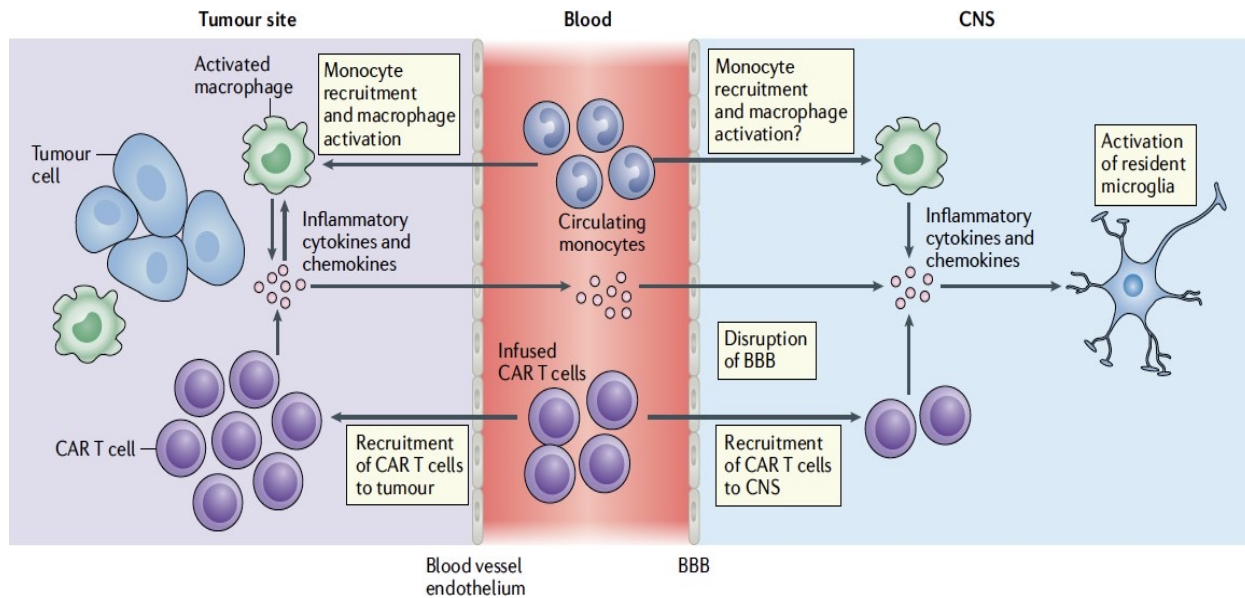
# ASCO Guidelines: Cytokine Release Syndrome

Workup or evaluation and supportive care recommendations (all grades):  
 CBC, CMP, magnesium, phosphorus, CRP, LDH, uric acid, fibrinogen, PT/PTT, and ferritin  
 Assess for infection with blood and urine cultures, and a chest radiograph if fever is present  
 If patient is neutropenic, follow institutional neutropenic fever guidelines  
 Patients who experience grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) 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 at least G2 CRS, clinically significant arrhythmia, and additionally as clinically indicated  
 Consider screening for CMV and EBV  
 Consider chest or abdominal CT imaging, brain MRI, and/or lumbar puncture.

Grading (on the basis of ASTCT consensus grading) <sup>10</sup>	Management
G1: Fever*: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause Hypotension: none Hypoxia: none	Offer supportive care with antipyretics, IV hydration, and symptomatic management of organ toxicities and constitutional symptoms May consider empiric broad-spectrum antibiotics if neutropenic. May consider G-CSF in accordance with product guidelines. Note: GM-CSF is not recommended In patients with persistent (> 3 days) or refractory fever, consider managing as per G2
G2: Fever*: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause <i>plus</i> Hypotension: not requiring vasopressors <i>And/or</i> Hypoxia: requiring low-flow nasal cannula (ie, oxygen delivered at $\leq 6$ L/min) or blowby	Continue supportive care as per G1 and include IV fluid bolus and/or supplemental oxygen as needed Administer tocilizumab <sup>42-44</sup> 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours if no improvement in signs and symptoms of CRS; limit to a maximum of three doses in a 24-hour period, with a maximum of four doses total In patients with hypotension that persists after two fluid boluses and after one to two doses of tocilizumab, may consider dexamethasone 10 mg IV (or equivalent) every 12 hours for one to two doses and then reassess Manage per G3 if no improvement within 24 hours of starting tocilizumab
G3: Fever*: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause <i>plus</i> Hypotension: requiring a vasopressor with or without vasopressin <i>And/or</i> Hypoxia: requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Continue supportive care as per G2 and include vasopressors as needed Admit patient to ICU If echocardiogram was not already performed, obtain ECHO to assess cardiac function and conduct hemodynamic monitoring Tocilizumab as per G2 if maximum dose is not reached within 24-hour period plus dexamethasone 10 mg IV every 6 hours (or equivalent) and rapidly taper once symptoms improve If refractory, manage as per G4
G4: Fever*: temperature $\geq 38^{\circ}\text{C}$ not attributable to any other cause <i>plus</i> Hypotension: requiring multiple vasopressors (excluding vasopressin) <i>And/or</i> Hypoxia: requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)	Continue supportive care as per G3 plus mechanical ventilation as needed Administer tocilizumab as per G2 if maximum is not reached within 24-hour period Initiate high-dose methylprednisolone at a dose of 500 mg IV every 12 hours for 3 days, followed by 250 mg IV every 12 hours for 2 days, 125 mg IV every 12 hours for 2 days, and 60 mg IV every 12 hours until CRS improvement to G1 If not improving, consider methylprednisolone 1,000 mg IV 2 times a day or alternate therapy <sup>6</sup>
Additional considerations: Organ toxicities associated with CRS may be graded according to CTCAE v5.0, but they do not influence CRS grading CRS may be associated with cardiac, hepatic, and/or renal dysfunction Earlier steroid use appears to reduce the rate of CAR T-cell treatment-related CRS and neurologic events and is recommended for some products (axicabtagene ciloleucel or brexucabtagene autoleucel) <sup>45-47</sup> Strongly consider antifungal prophylaxis in patients receiving steroids for the treatment of CRS and/or ICANS	

ASCO = American Society of Clinical Oncology.  
 Santamasso BD, et al. *J Clin Oncol.* 2021;39(35):3978-3992.

# ICANS Pathophysiology



- CAR T-cells have the ability of penetrating into the CNS, crossing the blood-brain barrier
- BsAbs-related ICANS is mediated by the cytokines released by T-lymphocytes, and the T-lymphocyte can potentially penetrate
- This can be related with the fact that after BsAb the incidence and severity are lower

Systemic inflammation and high levels of circulating cytokines → **ENDOTHELIAL CELL ACTIVATION and BLOOD-BRAIN BARRIER DISRUPTION** → **INFLAMMATORY CASCADE WITHIN THE CNS** → cortical and subcortical dysfunction +/- cerebral edema

**CNS = central nervous system; ICANS = immune effector cell-associated neurotoxicity syndrome.**  
**Morris EC, et al. *Nat Rev Immunol.* 2022;22(2):85-96.**

# NCCN Guidelines: CAR T-Cell-Related Neurotoxicity Grading

Neurotoxicity Domain <sup>r</sup>	Grade 1	Grade 2	Grade 3	Grade 4
ICE score <sup>s</sup>	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness <sup>t</sup>	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging <sup>u</sup>	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

# Daily Sentence Is Key to Early Neurotoxicity Detection!!

TO DAY I RECEIVED MY  
T CELL  
10-1-18 CH.

TO DAY I RECEIVED MY T CELL  
10-15-2001

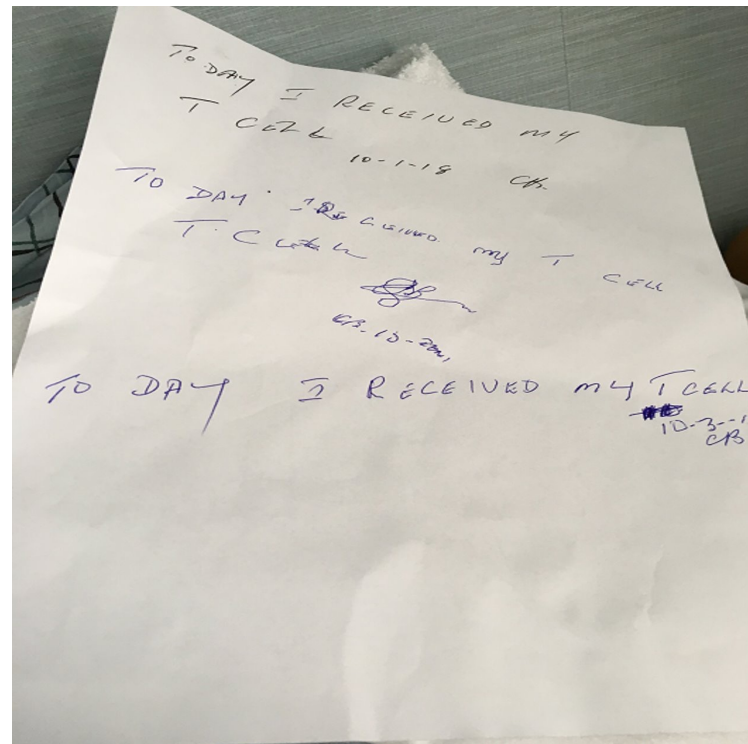
# NCCN Guidelines: CAR T-Cell-Related Neurotoxicity Treatment

Treatment by Grade	No Concurrent CRS <sup>x</sup>	Additional Therapy if Concurrent CRS
Grade 1 <sup>v</sup>	<ul style="list-style-type: none"> <li>Supportive care</li> </ul>	Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose) <sup>aa, †</sup>
Grade 2	<ul style="list-style-type: none"> <li>Supportive care</li> <li>1 dose of dexamethasone 10 mg IV and reassess. Can repeat every 6–12 hours, if no improvement.</li> </ul>	Anti-IL-6 therapy as per Grade 1 <sup>aa</sup> Consider transferring patient to ICU if neurotoxicity associated with grade ≥2 CRS
Grade 3 <sup>w</sup>	<ul style="list-style-type: none"> <li>ICU care is recommended</li> <li>Dexamethasone 10 mg IV every 6 hours or methylprednisolone, 1 mg/kg IV every 12 hours<sup>k,y</sup></li> <li>Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.</li> </ul>	Anti-IL-6 therapy as per Grade 1 <sup>aa</sup>
Grade 4 <sup>w</sup>	<ul style="list-style-type: none"> <li>ICU care, consider mechanical ventilation for airway protection.</li> <li>High-dose corticosteroids<sup>k,z</sup></li> <li>Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent grade ≥3 neurotoxicity.</li> <li>Treat convulsive status epilepticus per institutional guidelines.</li> </ul>	Anti-IL-6 therapy as per Grade 1 <sup>aa</sup>

# ASCO Guidelines: Immune Effector Cell Neurotoxicity Syndrome

<p>Workup or evaluation and supportive care recommendations (all grades):</p> <ul style="list-style-type: none"> <li>Routine neurologic evaluation including the ICE score for cognitive assessment and assessment of motor weakness conducted at least two times a day</li> <li>Continually reassess for improvement or deterioration and escalate or de-escalate treatment and monitoring accordingly</li> <li>Serial monitoring of laboratory tests including CRP, ferritin, CBC, CMP, fibrinogen, and PT/PTT</li> <li>Consider seizure prophylaxis for CAR T-cell products known to be associated with ICANS or in patients at higher risk of seizure, such as those with seizure history, CNS disease, concerning EEG findings, or neoplastic brain lesions<sup>4,46,50</sup></li> <li>Initiate neurology consultation in patients with signs of neurotoxicity</li> <li>Aspiration precautions and elevated head of bed</li> <li>Neuroimaging of the brain (MRI with and without contrast or CT if MRI is not available or feasible) for <math>\geq</math> G2 neurotoxicity. For persistent grade <math>\geq</math> 3 neurotoxicity, consider repeat neuroimaging (MRI or CT) every 2-3 days</li> <li>Lumbar puncture for <math>\geq</math> G3 neurotoxicity and may consider for G2</li> <li>EEG evaluation for unexplained altered mental status to assess seizure activity or for <math>\geq</math> G2 neurotoxicity</li> <li>Monitor and correct severe hyponatremia</li> </ul>	
Grading (on the basis of ASTCT consensus grading) <sup>10,a</sup> Management	
<p>G1: ICE score<sup>b</sup>: 7-9 with no depressed level of consciousness</p>	<p>No concurrent CRS Offer supportive care with IV hydration and aspiration precautions</p> <p>With concurrent CRS Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours as needed. Limit to a maximum of three doses in a 24-hour period; maximum total of four doses. Caution with repeated tocilizumab doses in patients with ICANS. Consider adding corticosteroids to tocilizumab past the first dose</p>
<p>G2: ICE score<sup>b</sup>: 3-6 <i>And/or</i> Mild somnolence awaking to voice</p>	<p>No concurrent CRS Offer supportive care as per G1</p> <p>For high-risk products or patients, consider dexamethasone 10 mg IV <math>\times</math> two doses (or equivalent) and reassess. Repeat every 6-12 hours if no improvement.<sup>c</sup> Rapidly taper steroids as clinically appropriate once symptoms improve to G1<sup>d</sup></p> <p>With concurrent CRS Consider ICU transfer if ICANS associated with <math>\geq</math> G2 CRS Administer tocilizumab as per G1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours<sup>e</sup>) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate<sup>d</sup></p>
<p>G3: ICE score<sup>b</sup>: 0-2 <i>And/or</i> Depressed level of consciousness awakening only to tactile stimulus <i>And/or</i> Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention <i>And/or</i> Focal or local edema on neuroimaging</p>	<p>All G3 patients: Transfer patient to ICU</p> <p>No concurrent CRS Administer dexamethasone (10 mg IV every 6-12 hours<sup>e</sup>) or methylprednisolone equivalent (1 mg/kg IV every 12 hours).</p> <p>With concurrent CRS Administer tocilizumab as per grade 1 If refractory to tocilizumab past the first dose, initiate dexamethasone (10 mg IV every 6-12 hours<sup>e</sup>) or methylprednisolone equivalent (1 mg/kg IV every 12 hours). Continue corticosteroids until improvement to grade 1, and then rapidly taper as clinically appropriate<sup>d</sup></p>
<p>G4: ICE score<sup>b</sup>: 0 (patient is unarousable and unable to perform ICE) <i>And/or</i> Stupor or coma <i>And/or</i> Life-threatening prolonged seizure (&gt; 5 minutes) or repetitive clinical or electrical seizures without return to baseline in between <i>And/or</i> Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing or papilloedema, cranial nerve VI palsy, or Cushing's triad</p>	<p>All G4 patients: Admit patient to ICU if not already receiving ICU care. Consider mechanical ventilation for airway protection</p> <p>No concurrent CRS Administer high-dose methylprednisolone IV 1,000 mg one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone two to three times per day or alternate therapy<sup>f</sup> Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate<sup>d</sup></p> <p>Status epilepticus to be treated as per institutional guidelines</p> <p>With concurrent CRS Administer tocilizumab as per grade 1 in addition to methylprednisolone 1,000 mg IV one to two times per day for 3 days If not improving, consider 1,000 mg of methylprednisolone IV two to three times a day or alternate therapy<sup>f</sup> Continue corticosteroids until improvement to grade 1, and then taper as clinically appropriate<sup>d</sup></p>

# Normalization of the Handwriting



# ASCO Guidelines: Hemophagocytic Lymphohistiocytosis

## Workup or evaluation<sup>55</sup>:

CBC with differential and coagulation studies (PT, aPTT, fibrinogen, and D-dimer)

Liver function tests (ALT, AST, GGT, total bilirubin, albumin, and lactate dehydrogenase)

Serum triglycerides (fasting) and serum ferritin

Soluble IL-2 receptor alpha (sCD25 or sIL-2R) and/or CXCL9

The following testing should be performed in all patients, on the basis of the signs and symptoms of specific organ involvement and/or the degree of suspicion for the presence of HLH<sup>55</sup>:

Cultures of blood, bone marrow, urine, and CSF, and viral titers and quantitative PCR testing for EBV, CMV, adenovirus, and other suspected viruses.

Follow levels of any identified virus during treatment with the appropriate antiviral therapy

Bone marrow aspirate and biopsy

Electrocardiograph, chest radiography, and echocardiogram

Lumbar puncture with CSF analysis

Brain MRI scan, with and without contrast. Imaging of the CNS may show parameningeal infiltrations, subdural effusions, necrosis, and other abnormalities

## Grading Management<sup>14,56,57</sup>

All grades Offer supportive care

Use corticosteroids if the patient is deteriorating or unstable

Although data are insufficient to recommend a transfusion threshold, replacement of fibrinogen should be considered in patients with a fibrinogen level below 150 mg/dL

Manage  $G \geq 3$  organ toxicity with IL-6 antagonist plus corticosteroids

If insufficient response after 48 hours, consider adding anakinra<sup>11,58,59</sup>

Etoposide could be considered in severe, refractory cases, although there is a lack of data in this setting and concern for effect on lymphocytes.<sup>16,60</sup> Intrathecal cytarabine, with or without hydrocortisone, may also be considered for patients with HLH-associated neurotoxicity

# ASCO Guidelines: Cytopenias and B-Cell Aplasia

Workup or evaluation: CBC with differential, peripheral blood smear, reticulocyte count. If abnormalities are detected and further investigation is necessary for a diagnosis, proceed with bone marrow evaluation	
Grading	Management
G1: anemia: LLN—10.0 g/dL; neutropenia: > 1,500 per mm <sup>3</sup> ; thrombocytopenia: > 75,000 per mm <sup>3</sup>	Offer supportive care
G2: anemia: < 10.0-8.0 g/dL; neutropenia: > 1,000 per mm <sup>3</sup> ; thrombocytopenia: > 50,000 per mm <sup>3</sup>	Offer supportive care and/or consider corticosteroids If improved to ≤ G1, taper steroids over 4-6 weeks
G3: anemia: < 8.0/dL; neutropenia: > 500 per mm <sup>3</sup> ; thrombocytopenia: > 25,000 per mm <sup>3</sup>	Critical care support Use high-dose methylprednisolone
G4: anemia: life-threatening; neutropenia: < 500 per mm <sup>3</sup> ; thrombocytopenia: < 25,000 per mm <sup>3</sup>	Consider growth factor support for neutrophil recovery, per institutional guidelines
Workup or evaluation: Full blood count	
Grading	Management <sup>7,49,61,62</sup>
All grades	Recommend influenza and COVID vaccination for patients and family members Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until the CD4 cell count is > 200 cells/μL Antifungal agents should be considered for high-risk patients including any patient receiving corticosteroids for management of CRS or ICANS
G1: asymptomatic, no intervention needed	Offer supportive care
G2: symptomatic (ie, recurrent infections), nonurgent intervention indicated	Consider treatment with IVIG replacement therapy at IgG levels < 400
G3: urgent intervention indicated	Consider treatment with IVIG replacement therapy at IgG levels < 400
G4: life-threatening	

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

# ASCO Guidelines: Infections and DIC

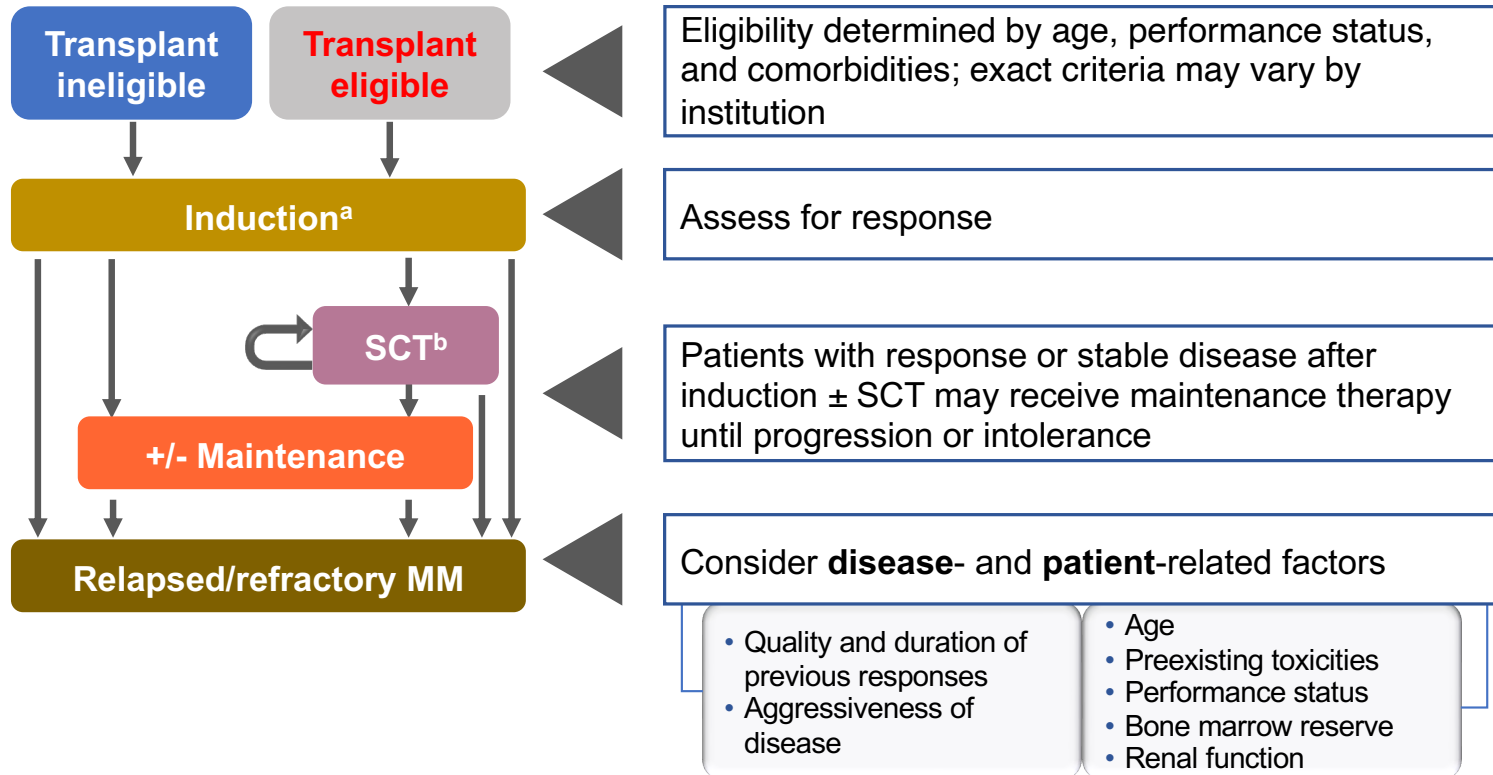
Workup or evaluation: History and physical examination Full blood count Bacterial cultures and evaluation for other infection (fungal and viral)	
Grading	Management <sup>7,49,61,62</sup>
All grades	Antiviral and PJP prophylaxis per institutional standards, for 6-12 months following CAR T-cell infusion and/or until the CD4 cell count is > 200 cells/ $\mu$ L Antifungal agents should be considered for high-risk patients G-CSF should be considered in patients after CRS with > 7 days of neutropenia
G1: mild infection only	Offer supportive care Empiric antimicrobials (antibiotics such as levofloxacin or ciprofloxacin, antifungals such as fluconazole or antivirals such as valacyclovir or acyclovir) should be considered upon onset of fever
G2: mild infection; oral intervention indicated (eg, antibiotic, antifungal, or antiviral)	Start course of oral antimicrobials
G3: severe infection; IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Start IV antimicrobials
G4: life-threatening consequences; urgent intervention indicated	Critical care support
Workup or evaluation: Full blood count to assess platelet number, fibrinogen, PT, PTT, and d-dimer. A test scoring system developed by the ISTH may be used to help determine if DIC is present. <sup>63</sup> The higher the score, the more likely it is that DIC is present	
Grading	Management
G1: —	Offer supportive care
G2: laboratory findings with no bleeding	Use IL-6 antagonist with or without corticosteroids If improved to $\leq$ G1, taper steroids over 4-6 weeks
G3: laboratory findings with bleeding	Critical care support
G4: life-threatening; urgent intervention indicated	Use IL-6 antagonist and methylprednisolone IV 1,000 mg/day for 3 days, followed by rapid taper at 250 mg every 12 hours for 2 days, 125 mg every 12 hours for 2 days, and 60 mg every 12 hours for 2 days Consider replacement of fibrinogen in patients with a fibrinogen level below 150 mg/dL

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

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# MM Treatment Guidelines

# Algorithm for Treatment of MM per NCCN Guidelines and Palumbo, et al.



<sup>a</sup>Consolidation therapy after induction is widely accepted, although no specific guidelines are available. <sup>b</sup>Planned tandem or second SCT in response to progression.

SCT = stem cell transplant.

Palumbo A, et al. *N Engl J Med.* 2011;364(11):1046-1060. National Comprehensive Cancer Network [www.nccn.org]. Last updated April 18, 2023. [https://www.nccn.org/guidelines/category\\_1](https://www.nccn.org/guidelines/category_1). Mohty B, et al. *Leukemia.* 2012;26(1):73-85.

# Current Approvals for Myeloma

IMiDs	Proteasome inhibitors	Anthracyclines	Alkylators	Steroids	Antibodies	SINE	CAR T	Bispecific Ab
Thalidomide	Bortezomib	Doxil	Melphalan	Dexamethasone	Elotuzumab	Selinexor	Ide-cel	Teclistamab
Lenalidomide	Carfilzomib	Doxorubicin	Cytosan	Prednisone	Daratumumab		Cilta-cel	Elranatamab
Pomalidomide	Ixazomib		Bendamustine	Solumedrol	Isatuximab			Talquetamab

IMiD = immunomodulatory drugs; SINE = selective inhibitor of nuclear export.

# NCCN Guidelines: Initial Therapy | Transplant Eligible

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES <sup>a-d</sup>
<p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide/dexamethasone (category 1)</li> <li>• Carfilzomib/lenalidomide/dexamethasone<sup>k</sup></li> </ul>
<p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Daratumumab/lenalidomide/bortezomib/dexamethasone</li> </ul>
<p><b>Useful In Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Bortezomib/cyclophosphamide/dexamethasone<sup>e</sup></li> <li>• Bortezomib/doxorubicin/dexamethasone</li> <li>• Carfilzomib/cyclophosphamide/dexamethasone<sup>e,f,k</sup></li> <li>• Daratumumab/bortezomib/thalidomide/dexamethasone</li> <li>• Daratumumab/bortezomib/cyclophosphamide/dexamethasone</li> <li>• Daratumumab/carfilzomib/lenalidomide/dexamethasone<sup>k</sup></li> <li>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib<sup>g</sup> (VTD-PACE)</li> <li>• Isatuximab-irfc/lenalidomide/bortezomib/dexamethasone</li> </ul>

MAINTENANCE THERAPY
<p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• Lenalidomide<sup>h</sup> (category 1)</li> </ul>
<p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Bortezomib</li> </ul>
<p><b>Useful In Certain Circumstances<sup>z</sup></b></p> <ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide<sup>l</sup></li> <li>• Carfilzomib/lenalidomide<sup>l</sup></li> <li>• Daratumumab ± lenalidomide<sup>l</sup></li> <li>• Ixazomib (category 2B)<sup>i</sup></li> </ul>

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# NCCN Guidelines: Initial Therapy | Transplant Ineligible

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES <sup>a-d</sup>	
<b>Preferred Regimens</b>	
<ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide/dexamethasone (category 1)</li> <li>• Daratumumab/lenalidomide/dexamethasone (category 1)</li> </ul>	
<b>Other Recommended Regimens</b>	
<ul style="list-style-type: none"> <li>• Daratumumab/bortezomib/melphalan/prednisone (category 1)</li> <li>• Carfilzomib/lenalidomide/dexamethasone<sup>k</sup></li> <li>• Daratumumab/cyclophosphamide/bortezomib/dexamethasone</li> </ul>	
<b>Useful In Certain Circumstances</b>	
<ul style="list-style-type: none"> <li>• Lenalidomide/low-dose dexamethasone (category 1)<sup>m</sup></li> <li>• Bortezomib/cyclophosphamide/dexamethasone<sup>e</sup></li> <li>• Bortezomib/dexamethasone</li> </ul>	<ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients</li> <li>• Carfilzomib/cyclophosphamide/dexamethasone<sup>f,k</sup></li> <li>• Lenalidomide/cyclophosphamide/dexamethasone</li> </ul>

MAINTENANCE THERAPY
<b>Preferred Regimens</b>
<ul style="list-style-type: none"> <li>• Lenalidomide (category 1)</li> </ul>
<b>Other Recommended Regimens</b>
<ul style="list-style-type: none"> <li>• Bortezomib</li> </ul>
<b>Useful In Certain Circumstances</b>
<ul style="list-style-type: none"> <li>• Bortezomib/lenalidomide<sup>l</sup></li> <li>• Ixazomib (category 2B)<sup>i</sup></li> </ul>

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# NCCN Guidelines: Early Relapse (1-3 Prior Therapies)

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA <sup>a-d,n-o,q</sup> Relapsed/Refractory Disease After 1–3 Prior Therapies	
Preferred Regimens <i>Order of regimens does not indicate comparative efficacy</i>	
Bortezomib-Refractory <sup>P</sup>	Lenalidomide-Refractory <sup>P</sup>
<ul style="list-style-type: none"> <li>• Carfilzomib/lenalidomide/dexamethasone (category 1)</li> <li>• Daratumumab/carfilzomib/dexamethasone (category 1)</li> <li>• Daratumumab/lenalidomide/dexamethasone (category 1)</li> <li>• Isatuximab-irfc/carfilzomib/dexamethasone (category 1)</li> <li>• Carfilzomib/pomalidomide/dexamethasone</li> </ul> <p><i>After one prior therapy including lenalidomide and a PI</i></p> <ul style="list-style-type: none"> <li>▶ Daratumumab/pomalidomide/dexamethasone (category 1)</li> </ul> <p><i>After two prior therapies including lenalidomide and a PI</i></p> <ul style="list-style-type: none"> <li>▶ Isatuximab-irfc/pomalidomide/dexamethasone (category 1)</li> </ul>	<ul style="list-style-type: none"> <li>• Daratumumab/bortezomib/dexamethasone (category 1)</li> <li>• Daratumumab/carfilzomib/dexamethasone (category 1)</li> <li>• Isatuximab-irfc/carfilzomib/dexamethasone (category 1)</li> <li>• Pomalidomide/bortezomib/dexamethasone (category 1)</li> <li>• Selinexor/bortezomib/dexamethasone (category 1)</li> <li>• Carfilzomib/pomalidomide/dexamethasone</li> <li>• Elotuzumab/pomalidomide/dexamethasone</li> </ul> <p><i>After one prior therapy including lenalidomide and a PI</i></p> <ul style="list-style-type: none"> <li>▶ Daratumumab/pomalidomide/dexamethasone (category 1)</li> </ul> <p><i>After two prior therapies including lenalidomide and a PI</i></p> <ul style="list-style-type: none"> <li>▶ Isatuximab-irfc/pomalidomide/dexamethasone (category 1)</li> </ul> <p><i>After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy</i></p> <ul style="list-style-type: none"> <li>▶ Ixazomib/pomalidomide/dexamethasone</li> </ul>

PI = proteasome inhibitor.

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# NCCN Guidelines: Early Relapse (1-3 Prior Therapies)

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA <sup>a-d,n-r</sup> Relapsed/Refractory Disease After 1–3 Prior Therapies	
<b>Other Recommended Regimens</b>	
<ul style="list-style-type: none"> <li>• Carfilzomib (twice weekly)/dexamethasone (category 1)</li> <li>• Elotuzumab/lenalidomide/dexamethasone (category 1)</li> <li>• Ixazomib/lenalidomide/dexamethasone (category 1)</li> <li>• Bortezomib/cyclophosphamide/dexamethasone</li> <li>• Bortezomib/lenalidomide/dexamethasone</li> <li>• Carfilzomib/cyclophosphamide/dexamethasone</li> <li>• Daratumumab/cyclophosphamide/bortezomib/dexamethasone</li> <li>• Elotuzumab/bortezomib/dexamethasone</li> <li>• Ixazomib/cyclophosphamide/dexamethasone</li> <li>• Lenalidomide/cyclophosphamide/dexamethasone</li> </ul>	<p><i>After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy</i></p> <ul style="list-style-type: none"> <li>▶ Pomalidomide/cyclophosphamide/dexamethasone</li> </ul>
<b>Useful in Certain Circumstances</b>	
<ul style="list-style-type: none"> <li>• Bortezomib/dexamethasone (category 1)</li> <li>• Bortezomib/liposomal doxorubicin/dexamethasone (category 1)</li> <li>• Lenalidomide/dexamethasone (category 1)</li> <li>• Carfilzomib/cyclophosphamide/thalidomide/dexamethasone</li> <li>• Carfilzomib (weekly)/dexamethasone</li> <li>• Selinexor/carfilzomib/dexamethasone</li> <li>• Selinexor/daratumumab/dexamethasone</li> <li>• Venetoclax/dexamethasone ± daratumumab or PI only for t(11;14) patients</li> </ul>	<p><i>After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy</i></p> <ul style="list-style-type: none"> <li>▶ Pomalidomide/dexamethasone (category 1)</li> <li>▶ Ixazomib/pomalidomide/dexamethasone</li> <li>▶ Selinexor/pomalidomide/dexamethasone</li> </ul> <p><i>For treatment of aggressive MM</i></p> <ul style="list-style-type: none"> <li>▶ Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</li> <li>▶ Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)</li> </ul> <p><i>After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD</i></p> <ul style="list-style-type: none"> <li>▶ Daratumumab</li> </ul>

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# NCCN Guidelines: Late Relapse (> 3 Prior Therapies)

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA <sup>a-d,n-o</sup> Relapsed/Refractory Disease After 3 Prior Therapies
<b>Preferred Regimens</b>
<p><i>After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD<sup>s</sup></i></p> <ul style="list-style-type: none"> <li>▶ <i>CAR T-cell Therapy:</i> <ul style="list-style-type: none"> <li>◇ Ciltacabtagene autoleucel</li> <li>◇ Idecabtagene vicleucel</li> </ul> </li> <li>▶ <i>Bispecific Antibodies</i> <ul style="list-style-type: none"> <li>◇ Elranatamab-bcmm</li> <li>◇ Talquetamab-tgvs</li> <li>◇ Teclistamab-cqyv</li> </ul> </li> </ul>
<b>Other Recommended Regimens</b>
<ul style="list-style-type: none"> <li>• Bendamustine<sup>t</sup></li> <li>• Bendamustine/bortezomib/dexamethasone<sup>t</sup></li> <li>• Bendamustine/carfilzomib/dexamethasone<sup>t</sup></li> <li>• Bendamustine/lenalidomide/dexamethasone<sup>t</sup></li> <li>• High-dose or fractionated cyclophosphamide</li> </ul> <p><i>After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody</i></p> <ul style="list-style-type: none"> <li>• Selinexor/dexamethasone</li> </ul>
<b>Useful in Certain Circumstances</b>
<p><i>After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD</i></p> <ul style="list-style-type: none"> <li>• Belantamab mafodotin-blmf (if available through compassionate use program)</li> </ul>

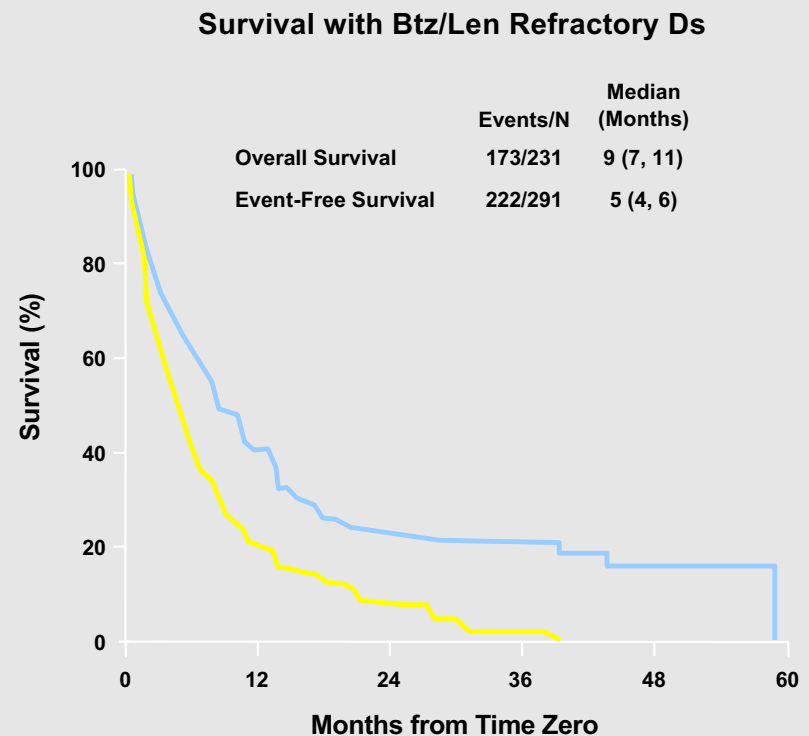
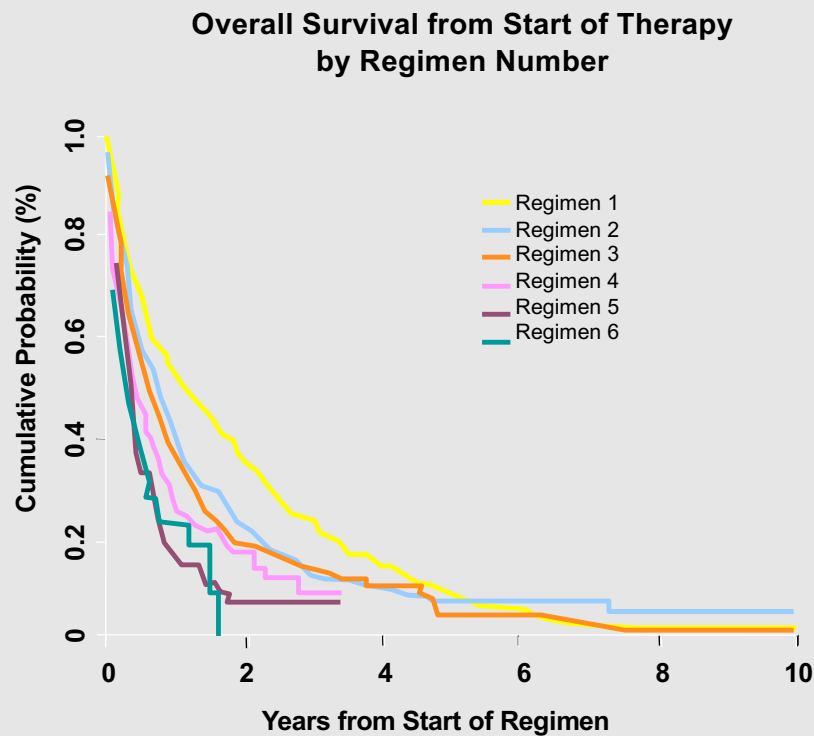
CD = cluster of differentiation.

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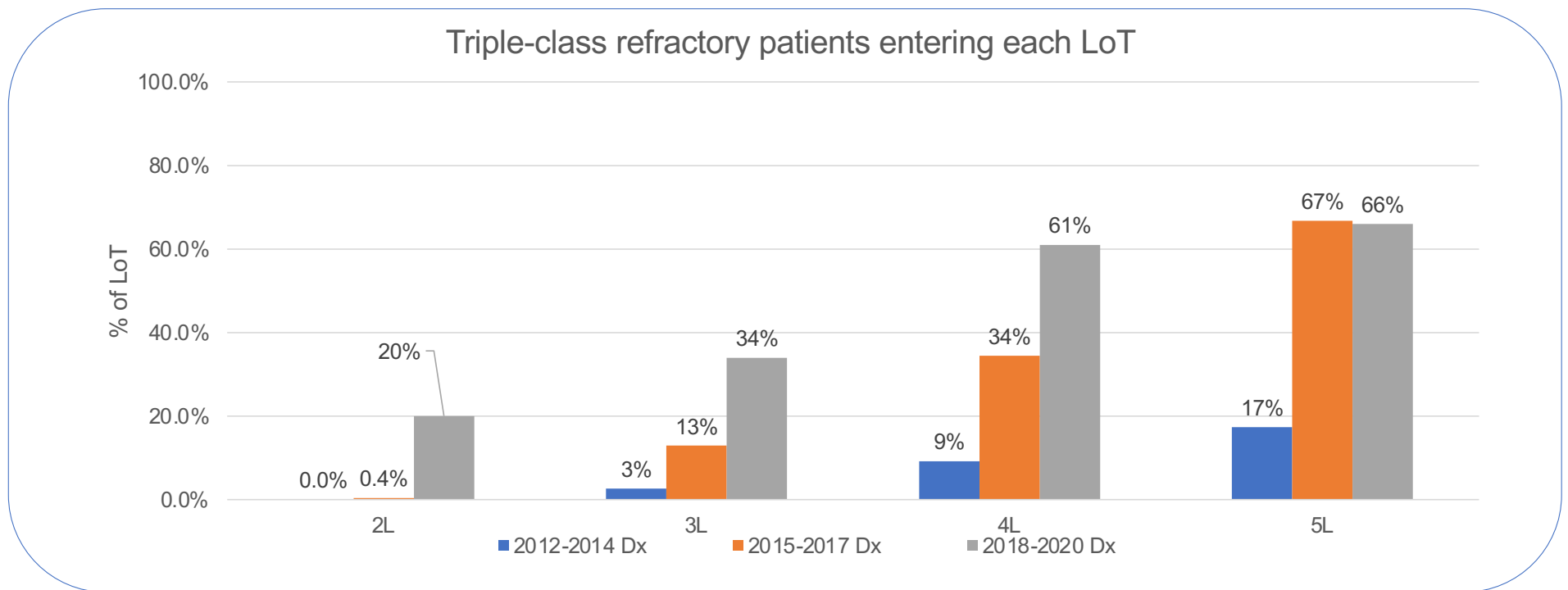


# R/R MM Treatment: Overcoming Resistance Barriers

# Once Treatment Fails, Trouble Begins



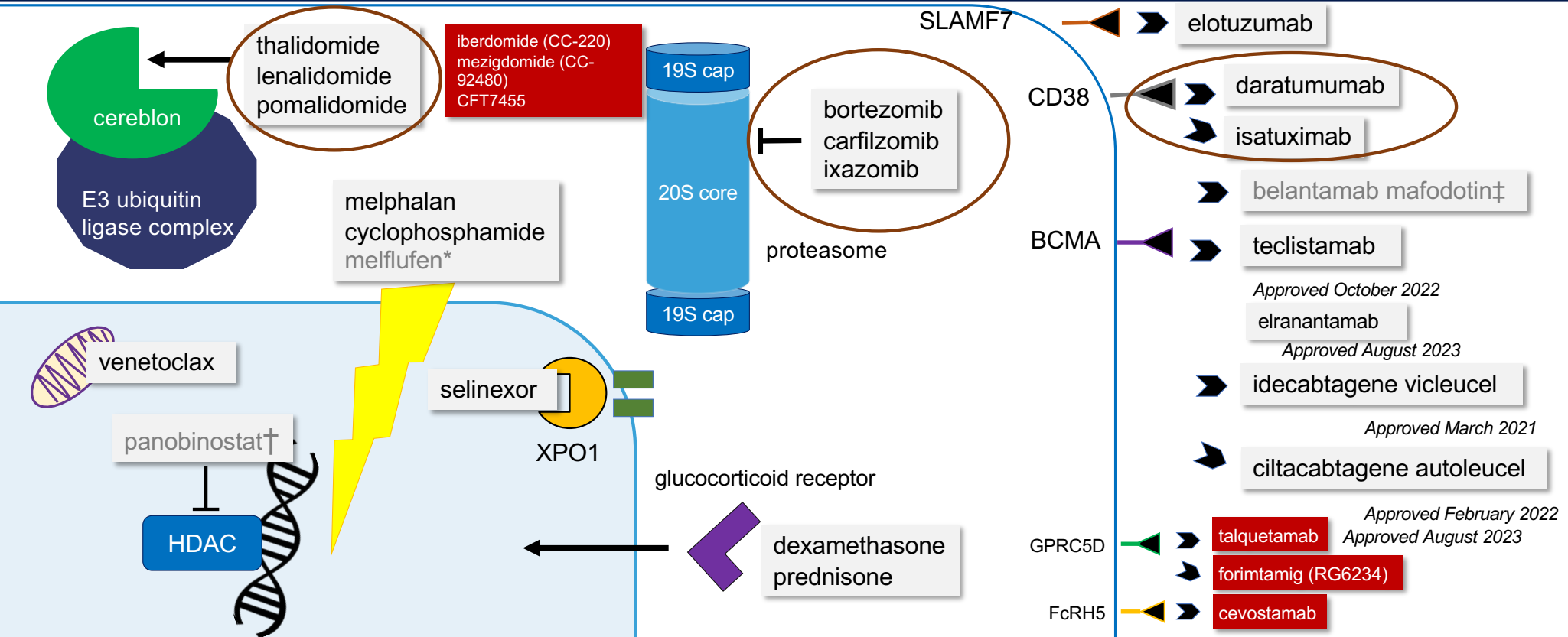
# Triple-Class Refractory Patients Are Growing Quickly and Occurring Earlier in RRMM



LoT = lines of therapy; Dx = diagnosis.

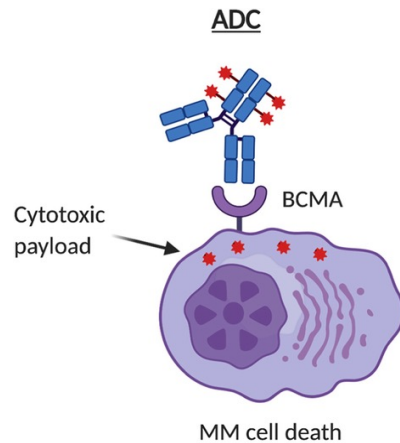
Company market research and analysis, Q2 2020. IQVIA patient data, 2015-2018.

# Moving beyond the 3 Core Drug Classes in Multiple Myeloma



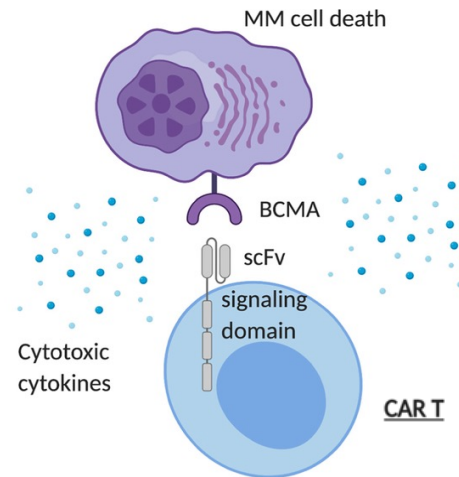
\*Withdrawal from US market October 2021 withdrawn January 2022. †Withdrawn from US market November 2021. ‡Withdrawn from US market November 2022. HDAC = histone deacetylase; XPO = exportin; SLAMF = self-ligand receptor of the signaling lymphocytic activation molecule family; BCMA = B-cell maturation antigen; GPRC5D = G-protein coupled receptor family C group 5 member D; FcRH = Fc receptor-homolog. International Myeloma Foundation [www.myeloma.org]. Last updated October 22, 2021. <https://www.myeloma.org/multiple-myeloma-drugs>.

# BCMA-Targeted Therapies for Multiple Myeloma



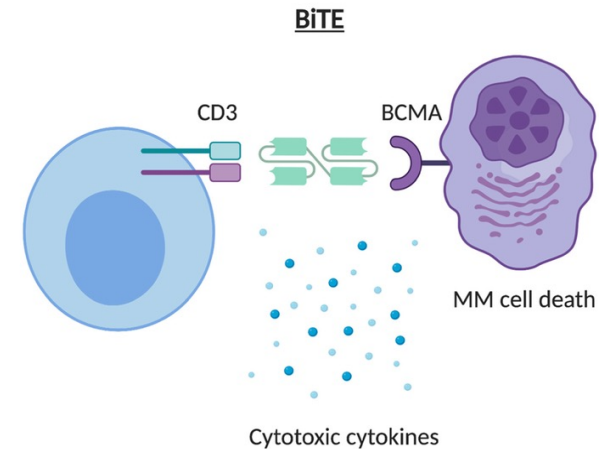
## **Antibody-Drug Conjugates (ADCs)**

*Belantamab mafodotin*  
CC-99712



## **CAR T-Cell Therapies**

*Idecabtagene vicleucel*  
*Ciltacabtagene autoleucel*  
*Orvacabtagene autoleucel*  
*P-BCMA-101*  
*bb21217*  
*ALLO-715*



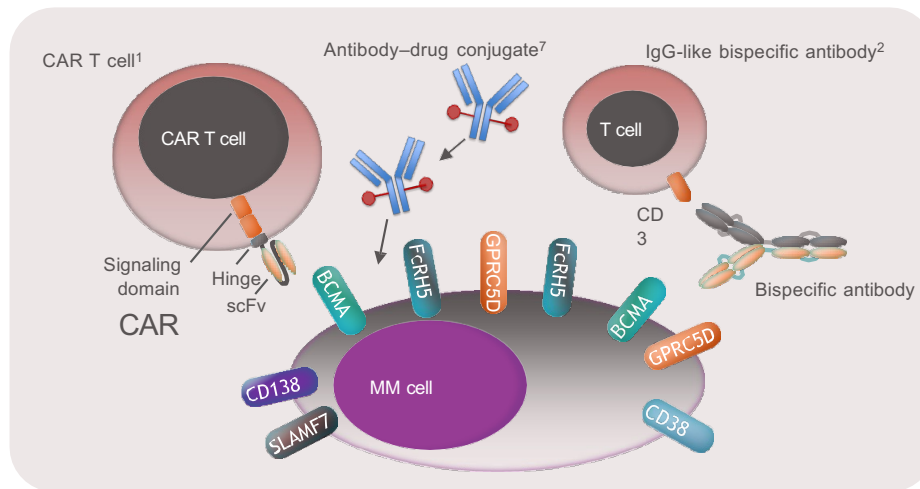
## **Bispecific T-Cell Engagers (BiTEs)**

*CC-93269*  
*REGN5458*  
*JNJ-64007957*  
*PF-06863135*

scFv = single-chain variable fragment.

Yu B, et al. *J Hematol Oncol.* 2020;13(1):125.

# BsAbs → New-Generation Immunotherapies in MM



- **ADC:**  
Belantamab  
MEDI2228

- **Bispecifics:**  
AMG701  
Teclistamab,  
talquetamab  
Elranatamab  
REGN5458

- TNB-  
383B CC-  
93269  
Cevostamab

- **CAR T:**  
Ide-cel  
Cilta-cel p-  
BCMA- 101  
CT053  
ALLO-715

## BCMA:

- Selectively overexpressed in plasma cells
- Promotes proliferation and survival of MM cells

## GPRC5D:

- Highly and selectively expressed in MM
- Distribution is similar to but independent of BCMA

## FcRH5:

- High levels of expression on MM cells
- Normally expressed in plasma cells only

Cilta-cel = ciltacabtagene autoleucel; FcRH5 = Fc receptor-like 5; ide-cel = idecabtagene vicleucel; Ig = immunoglobulin.

Rodríguez-Lobato LG, et al. *Front Oncol.* 2020;10:1243. Pillarisetti K, et al. *Blood Adv.* 2020;4(18):4538-4549. Yu B, et al. *J Hematol Oncol.* 2020;13(1):125. Verkleij CPM, et al. *Blood Adv.* 2020;5(8):2196-2215. Smith EL, et al. *Sci Transl Med.* 2019;11(485):eaau7746. Li J, et al. *Cancer Cell.* 2017;31(3):383-395. Bruins WSC, et al. *Front Immunol.* 2020;11:1155. Images adapted from Verkleij CPM, et al. *Curr Opin Oncol.* 2020;32(6):664-671. Bruins WSC, et al. *Front Immunol.* 2020;11:1155.

Bispecific Antibody	Alnuctamab (CC-93269)	Erlantamab	Linvoseltamab	Teclistamab	TNB-383B
Treatment	SC D1,4,8,15,22 C1, QW C2-3, Q2W C4-6, Q4W C7- beyond.	Weekly SC	Weekly IV	Weekly SC	IV q3w
Patients	n=47	n=55	n=252 (Ph1 = 73; Ph2 = 179)	n=165	n= 60 (≥ 40 mg)
Median prior lines	4	5	5	5	5
Triple-class refractory	62%	91%; 24% prior BCMA-directed	81%	78%	65%
ORR @ therapeutic dose	10/13 (77%) ≥ 30 mg SC	64% 215-1000 µg/kg SC	64% 200 mg cohort (n=58)	63% 1.5 mg/kg SC	79% (n=24 mature) ≥ 40 mg
Duration of response	NR	17.1 m	NR	18.4 months	
<b>AEs, (All %/Gr 3+%)</b>					
CRS	89% (62%) 53% (0%)	67% (0%)	95% (66%) 37% (1%)	100% (95%) 72% (1%)	77% (32%) 52% (3%)
Infections				76% (45%)	28%
Neutropenia	34% (30%)			71% (64%)	17%
Anemia	34% (17%)		28% (24%)	52% (37%)	
Thrombocytopenia				40% (21%)	
Deaths (n/%)					Deaths 5 (5%)
Other		ICANS 0% (0%)	ICANS 2% (2%)	Neurotox 15% (1%) ICANS 3 (0%)	

Anti-GPRC5d Talquetamab	Anti-FcRH5 Cevostamab
SC	IV q3w
n=143 (0.4m/kg qwk), n=145 (0.8 mg/kg q2wk)	n=160
6/5	6
74%/69%	85%
74%/73%	55% (160 mg) 37% (90mg)
	15.6 months
79%/75%	99% (59%)
58%/65%	80% (1.3%)
	43% (19%)
ICANS 11%-11%	18% (16%)
Skin-related AEs 56%-71%	32% (22%)
Nail-related AEs 54%-53%	Deaths 1pt (0.6%)
Dysgeusia 50%-48%	Neurological/ Psychiatric 41% (4%)

SC = subcutaneous; IV = intravenous; q = every; w = week(s); ORR = overall response rate.

Wong SW, et al. *Blood*. 2022;140(Suppl 1):400-402. Raje N, et al. Presented at the 64<sup>th</sup> American Society of Hematology (ASH) Annual Meeting; December 10, 2022; New Orleans, Louisiana. Lee HC, et al. *J Clin Oncol*. 2023;41(16\_suppl):8006. Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505. Kumar S, et al. *Blood*. 2021;138(Suppl 1):900. Schinke CD, et al. *J Clin Oncol*. 2023;41(16\_suppl):8036. Trudel S, et al. *Blood*. 2021;138(Suppl 1):157.

# BCMA-Bispecific mAbs: Safety profile

	AMG-701 <sup>1</sup>	CC-93269 <sup>2</sup>	Teclistamab <sup>3</sup>	Elranatamab <sup>4</sup>	REGN5458 <sup>5</sup>	TN3383B <sup>6</sup>
CRS (G 3-4)	64% (9%)	76.7% (3.3%)	71.5% (0.6%)	60.6% (0%)	38% (0%)	69% (4%)
Median onset	-	1 (1-9)	2(1-6)	3	10.1(6-47) hours	1(1-2)
Duration	-	2 (1-6)	2(1-9)	4(1-10)	14 (0-96) hours	1(1-8)
Tocilizumab	29%	43%	36.4%	50%	43%	
NTS			15%	6.4%		
Grade 3-4			0.6%	1.1%	0%	0%
ICANs			3%	0%	4% (g2)	
Median onset	Not reported	Not reported	2.5( 1-7)	NR		
Duration			3(1-37)	NR		
Treatment required			7.3%	NR		
Cytopenias						
Grade 3-4						
Neutropenia	25%	37%	57%	67.3%	22%	24%
Anemia	42%	43%	34,5%	47.3%	23%	15%
Thrombopenia	21%	17%	21.2%	27.3%	13%	9%
Infections			63%		5 exitus infecc	
Grade 3-4	17%	30%	35%			28%
Hypogammaglobulinemia as AEs observed in most patients treated with BCMA-CD3 mAbs along the therapy.						

NTS = neurotoxic syndrome; mAb = monoclonal antibody.

Harrison SJ, et al. Presented at the 62nd ASH Annual Meeting; December 5-8, 2020. Abstract 181. Costa LJ, et al. Presented at the European Hematology Association (EHA) 2020 Congress; June 11-21, 2020; virtual. Abstract S205. Moreau P, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 896. Sebag M, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 895. Zonder JA, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 160. Kumar SK, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 900.

# Anti-GPRC5D Bispecific Antibodies

## Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Phase 1/2 Results From MonumentAL-1

Ajai Chari<sup>1</sup>, Cyrille Touzeau<sup>2</sup>, Carolina Schinke<sup>3</sup>, Monique C Minnema<sup>4</sup>, Jesus G Berdeja<sup>5</sup>, Albert Oriol<sup>6</sup>, Niels WCJ van de Donk<sup>7</sup>, Paula Rodriguez-Otero<sup>8</sup>, Elham Askari<sup>9</sup>, Maria-Victoria Mateos<sup>10</sup>, Luciano J Costa<sup>11</sup>, Jo Caers<sup>12</sup>, Leo Rasche<sup>13</sup>, Amrita Krishnan<sup>14</sup>, Deeksha Vishwamitra<sup>15</sup>, Xuewen Ma<sup>16</sup>, Xiang Qin<sup>17</sup>, Katharine S Gries<sup>18</sup>, Michela Campagna<sup>19</sup>, Tara Masterson<sup>20</sup>, Brandi Hilder<sup>21</sup>, Jaszianna Tolbert<sup>22</sup>, Thomas Renaud<sup>23</sup>, Jenna D Goldberg<sup>24</sup>, Christoph Heuck<sup>25</sup>, Jesús San-Miguel<sup>26</sup>, Philippe Moreau<sup>27</sup>

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Presented at the 64th American Society of Hematology (ASH) Annual Meeting; December 10-13, 2022; New Orleans, LA, USA.

## Forimtamig (RG6234), a GPRC5DxCD3 T-cell-engaging bispecific antibody, is highly active in patients with relapsed/refractory multiple myeloma: updated intravenous and first subcutaneous results from a Phase I dose-escalation study

Carmelo Carlo-Stella,<sup>1</sup> Rita Mazza,<sup>2</sup> Salomon Manier,<sup>2</sup> Thierry Facon,<sup>2</sup> Sung-Soo Yoon,<sup>3,4</sup> Youngil Koh,<sup>5</sup> Simon J Harrison,<sup>6,8</sup> Jeremy Eir,<sup>7</sup> Antonio Pinto,<sup>8</sup> Francesco Volzone,<sup>8</sup> Giulia Perrone,<sup>8</sup> Paolo Corradini,<sup>9</sup> Titouan Cazaubiel,<sup>10</sup> Cynille Hulin,<sup>10</sup> Cynille Touzeau,<sup>11</sup> Philippe Moreau,<sup>12</sup> Enrique M Ocio,<sup>13</sup> Carmen Montes Garcia,<sup>13</sup> Rakesh Popat,<sup>13</sup> Sarah Leong,<sup>13</sup> Fritz Offer,<sup>14</sup> Paula Rodriguez Otero,<sup>15</sup> Ana Alfonso-Pierola,<sup>16</sup> Ann-Marie E Broske,<sup>16</sup> Iryna Dekhtiarenko,<sup>17</sup> Hans-Joachim Helms,<sup>18</sup> Sara Belli,<sup>18</sup> Eva Rossmann,<sup>18</sup> Tanja Fauti,<sup>17</sup> Jan Eckmann,<sup>19</sup> Tom Moore,<sup>19</sup> Meike Schneider,<sup>19</sup> Wolfgang Jacob,<sup>19</sup> Martin Weisser,<sup>19</sup> Martin Hutchings,<sup>19</sup> Caroline Hasselbalch Riley<sup>19</sup>

<sup>1</sup>Humanitas University and IRCCS Humanitas Research Hospital, Milan, Italy; <sup>2</sup>CHU de Lille, Lille, France; <sup>3</sup>Seoul National University College of Medicine, Seoul, South Korea; <sup>4</sup>Seoul National University Hospital, Seoul, South Korea; <sup>5</sup>Peter MacCallum Cancer Center and Royal Melbourne Hospital, Melbourne, VIC, Australia; <sup>6</sup>Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia; <sup>7</sup>The Walter and Eliza Hall Institute of Medical Research and Department of Medical Biology, University of Melbourne, Melbourne, VIC, Australia; <sup>8</sup>Istituto Nazionale dei Tumori "Fondazione G Pascale" IRCCS, Napoli, Italy; <sup>9</sup>IRCCS Istituto Nazionale dei Tumori, University of Milano, Milan, Italy; <sup>10</sup>CHU de Bordeaux, Bordeaux, France; <sup>11</sup>CHU de Nantes, Nantes, France; <sup>12</sup>Hospital Universitario Marques de Valdecilla (IDIVAL), Universidad de Cantabria, Santander, Spain; <sup>13</sup>University College London Hospitals NHS Foundation Trust, London, United Kingdom; <sup>14</sup>Universität Zuercher Genet, Genet, Belgium; <sup>15</sup>Clinica Universidad de Navarra, Navarra, Spain; <sup>16</sup>Roche Pharma Research and Early Development, Roche Innovation Center Munich, Penzberg, Germany; <sup>17</sup>Roche Pharma Research and Early Development, Roche Innovation Center Zurich, Zurich, Switzerland; <sup>18</sup>Roche Pharma Research and Early Development, Roche Innovation Center Basel, Switzerland; <sup>19</sup>Rigshospitalet, Copenhagen, Denmark

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## GPRC5D

G protein-coupled receptor class C group 5 member D

Orphan receptor of unknown function

High expression in myeloma cells; some expression in normal plasma cells; expression independent of BCMA

Limited expression in normal tissues; **but expression in hair follicles, central region of tongue**

Not shed (unlike soluble BCMA), reduced risk for sink effect

Not in memory B cells or progenitor cells

	N	Prior BCMA	ORR   ≥VGPR	PFS	CRS (all   ≥3)	Tociliz.	Schedule	Comments
<b>Talquetamab</b> Chari A et al., ASH 2022	145†	11% (bela)	73.1%   57.2%	11.9 months	72.4%   0.7%	36.6%	sc q2 weeks	0.8 mg/kg sc q2 weeks Grade 3-4 infections, 11.7% <b>Any grade skin 67.6%; nail 43.4%; dysgeusia 46.2%</b>
<b>Forimtamig*</b> (RG6234) Carlo-Stella C et al. ASH 2022	57*	21.1%	63.6%   52.8%		78.%   1.8%	25.9%	sc q2 weeks	1200-7200 µg q2 weeks Grade 3-4 infections, 26.4% Any grade skin 86%, nail 28.1%

**\*91.2% triple class exposed. †Separate cohort (weekly N=43; q2 week N=8) with ORR 72.2% with prior CAR T-cell therapy (out of N=36) and 44.4% prior bispecific antibody (out of N=18).**

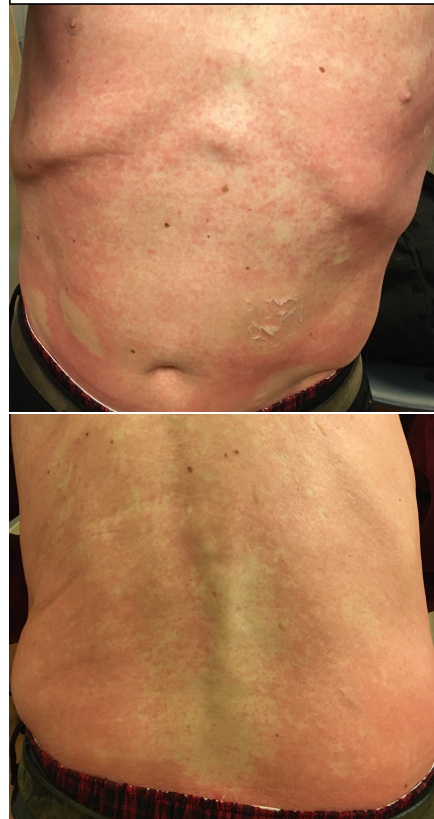
**Chari A, et al. Presented at the 64<sup>th</sup> ASH Annual Meeting; December 10-13, 2022; New Orleans, Louisiana. Carmelo CS, et al. Presented at the 64<sup>th</sup> ASH Annual Meeting; December 10-13, 2022; New Orleans, Louisiana.**

# Non-Hematologic Toxicities of Talquetamab

Palmar/Plantar Desquamation



Body Rash



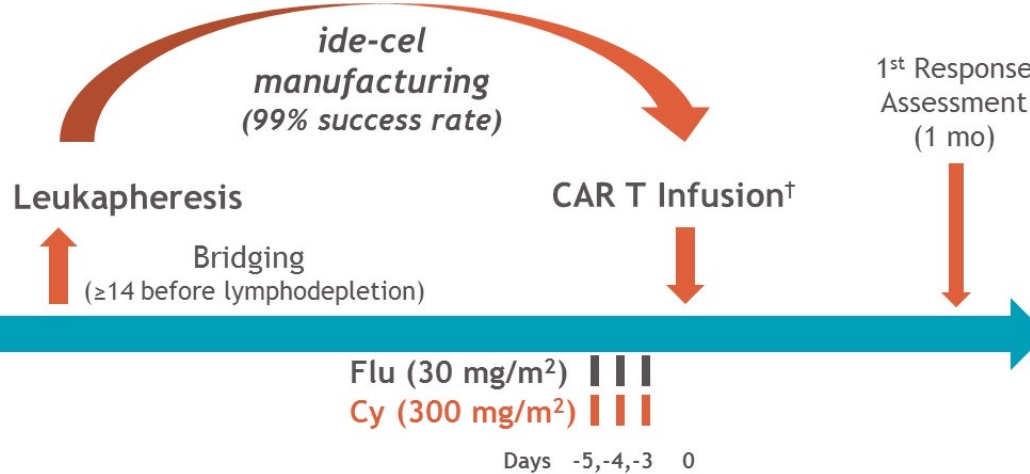
Injection Site Reactions/  
Nail Changes



Ray, et al. Presented at the 20th International Myeloma Society Annual Meeting; September 27-30, 2023; Athens, Greece.

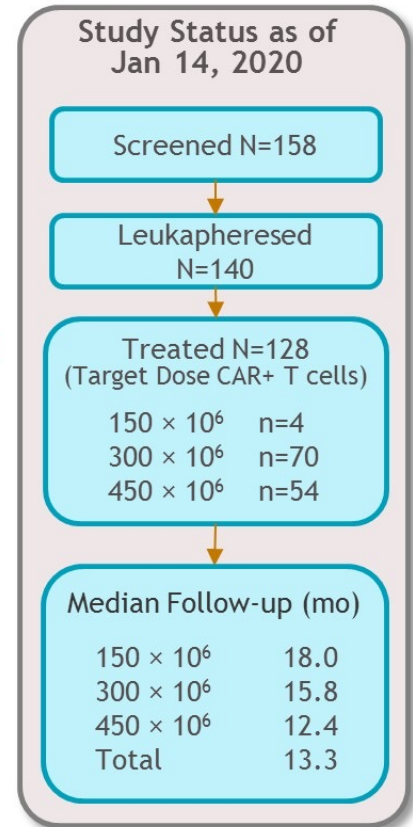
# Phase II Pivotal KarMMa Study

- RRMM
- $\geq 3$  prior regimens with  $\geq 2$  consecutive cycles each (or best response of PD)
- Previously exposed to:
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG\*



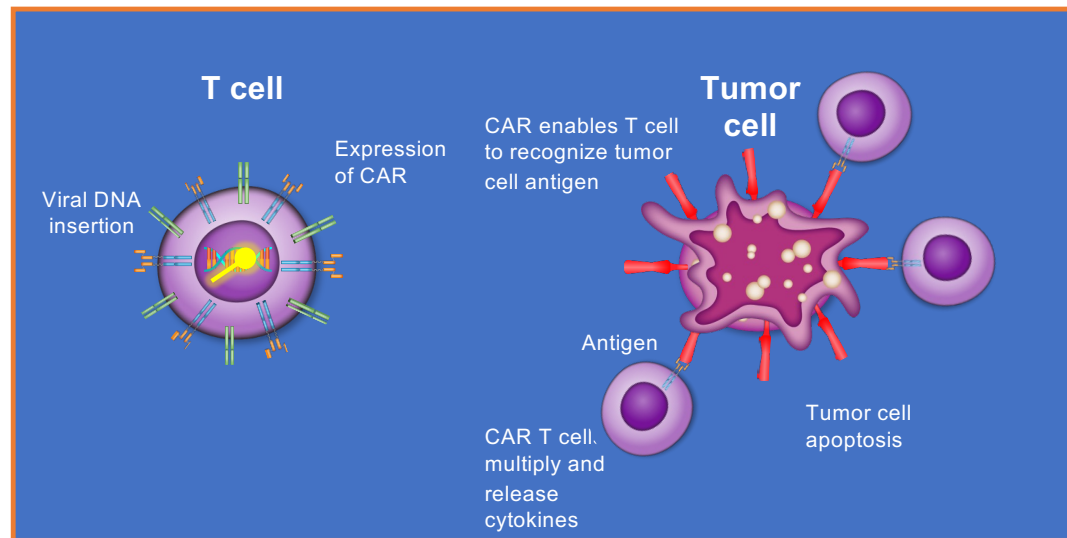
## Endpoints

- **Primary:** ORR (null hypothesis  $\leq 50\%$ )
- **Secondary:** CRR (key secondary; null hypothesis  $\leq 10\%$ ), Safety, DOR, PFS, OS, PK, MRD<sup>‡</sup>, QOL, HEOR
- **Exploratory:** Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM



CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.  
 \*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. <sup>†</sup>Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. <sup>‡</sup>By next-generation sequencing.

# How CAR T-Cell Therapy Works



DNA = deoxyribonucleic acid.

# CAR T-Cells in Myeloma

## Approved CAR T-cells

## Academic

## Alternative manufacturing

## Human scFv

## Allo-CAR

## GPRC5D

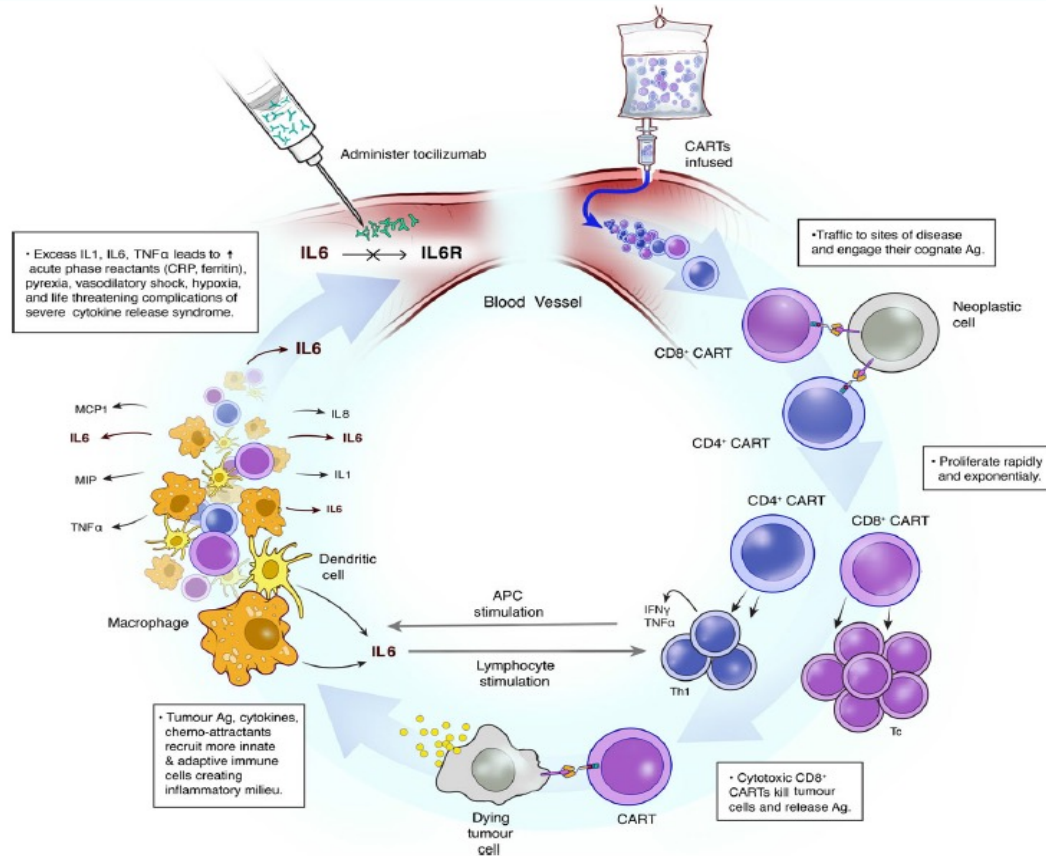
	Ide-cel KarMMa (n=128)	Cilta-cel CARTITUDE-1 (n=97)	ARI0002h (n=30)	P-BCMA-101 PRIME (n=53)	CT053 LUMMICAR (n=24)	CT103A (n=79)	ALLO-715 UNIVERSAL (n=43)	MCARH10 (n=17)
Phase	II	Ib/II	I/II	I/II	I	I/II	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D
scFv	Chimeric mouse	Chimeric llama	Humanized	Chimeric mouse	Human	Human	Human	Human
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous - piggyBac	Autologous	Autologous	Allogenic CD52 & TCR KO	Autologous
Age, (range)	61 (33-78)	61 (56-68)	61 (36-74)	60 (42-74)	62 (33-76)	57 (39-70)	64 (46-77)	60 (38-76)
# of lines	6	6	4	8	NA	5	5	6
HR cytog, %	35	24	33	NA	NA	34	37	77
EMD, %	39	13	20	NA	NA	13	21	41
Triple-R, %	84	88	67	60	NA	17	91	94
ORR, %	81	98	100	67	87	95	71	69
CR/sCR, %	39	82	63	NA	NA	68	25	25
PFS	12.2 m	55%@27 m	53%@18 m	NR	NR	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; 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; PFS = progression-free survival.

Anderson L, et al. Presented at ASCO Annual Meeting; June 4-8, 2021; Chicago, Illinois. Abstract 8016. Berdeja J, et al. *Lancet*. 2021;398(10297):314-324. Lin Y, et al. Presented at the EHA2022 Congress; June 9-17, 2022; Vienna, Austria. Abstract P961. Fernández de Larrea C, et al. Presented at the EHA2022 Congress; June 9-17, 2022; Vienna, Austria. Abstract S103. Costello C, et al. Presented at 62nd ASH Annual Meeting; December 5-8, 2020; virtual. Abstract 134. Mohyuddin GR, et al. *Blood Adv*. 2021;5(4):1097-1101. Li C, et al. Presented at the EHA2022 Congress; June 9-17, 2022; Vienna, Austria. Abstract S187. Li C, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 143. Mailankody S, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 651. Mailankody S, et al. Presented at the 63rd ASH Annual Meeting; December 11-14, 2021; Atlanta, Georgia. Abstract 827.

# Biological Consequences Following Car T-Cell Infusion



IL = interleukin; TNF = tumor necrosis factor; CRP = C-reactive protein; Ag = antigen; MIP = macrophage inflammatory protein; APC = antigen-presenting cells.

Orlowski RJ, et al. *Br J Haematol.* 2017;177(1):13-26.

# Infection and Death in Patients Refractory to Lenalidomide

Rates of infection, grade 3 or higher infection, and deaths from infection across selected relapsed/refractory multiple myeloma trials enrolling patients refractory to lenalidomide

Regimen	Timing of last enrolled patient	Median lines of prior therapy (range)	Overall infection rate (%)	Grade ≥ 3 infection rate (%)	Grade ≥ 3 COVID-19 rate (%)	Deaths from infections /COVID (%)	Median follow-up (months)	Median duration of therapy (months)
Dara-Pd [7]	Pre-COVID	1 (1–5)	71	30	N/A	5	16.9	11.5
Dara-Kd [8]	Pre-COVID*	1 (1–2)	NR	47	< 1	5	27.8	18.3
Teclistamab [2]	COVID era	5 (2–14)	76	45	12.1	12/7	14.1	8.5
Talquetamab [1]^	COVID era	6 (2–17)	47	7	3	0/0	11.7	NR
ABBV-383 [9]	COVID era	5 (3–15)	41	25	6	36/2.5	10.8	NR
Idecabtagene vicleucel [5]	Pre-COVID* and COVID era	3 (2–4)	58–70	26–28	NR	3–5/0.8	13.3–18.6	N/A
Ciltacabtagene autoleucel [10]	Pre-COVID*	6 (4–8)	59	28	N/A	5/0	28	N/A

Abbreviations: N/A = not applicable; NR = not reported; COVID: Coronavirus Disease.

\*Follow-up included time during COVID era (March 2020 onwards).

^Sufficient follow-up only reported at 405 µg dose.

The background of the slide is a solid light blue color. Overlaid on this are several large, curved, semi-transparent shapes in a darker shade of blue. These shapes are arranged in a way that they appear to be overlapping and flowing across the frame, creating a sense of movement and depth. The overall aesthetic is clean, modern, and professional.

# Clinical Case

# Admission at the Hospital the Same Day of the Lockdown in Spain by COVID-19: April 12, 2020

Levels	13-04-2020	14-04-2020	15-04-2020	16-04-2020	17-04-2020	20-04-2020
CRP	0.25 mg/dL					
Ferritin	Normal					
D-dimer	0.4 mcg/mL					
pro-BNP	Normal					
Troponin	ND					
Leucocytes	$7.54 \times 10^9/L$					
Lymphocytes	$2.16 \times 10^9/L$					



Tec 1st step-up dose with premed  
At 12.20 pm-13.35

**BNP = brain natriuretic peptide; ND = not detected.**

# Admission at the Hospital the Same Day of the Lockdown in Spain by COVID-19: April 12, 2020

Levels	13-04-2020	13/14-04-2020	15-04-2020	16-04-2020	17-04-2020	20-04-2020
CRP	0.25 mg/dL	9.68 mg/dL				
Ferritin	Normal	941 ng/mL				
D-dimer	0.4 mcg/mL	7.8 mcg/mL				
pro-BNP	Normal	352.50 pg/mL				
Troponin	ND	Normal				
Leucocytes	7.54 x 10 <sup>9</sup> /L	3.50 x 10 <sup>9</sup> /L				
Lymphocytes	2.16 x 10 <sup>9</sup> /L	0.47 x 10 <sup>9</sup> /L				

Tec 1st step-up dose with premed

Fever 38.2°C at 16:34  
with hypotension at 18:57 and  
O2 sat 88% at 17:59  
Thoracic pain

Cultures of blood, urine, feces, sputum

X-ray

Broad-spectrum Abs → piperaciline-tazobactam

G2 CRS: Tocilizumab on 13-04 20

Cardiological evaluation: Normal

O2 sat = oxygen saturation.

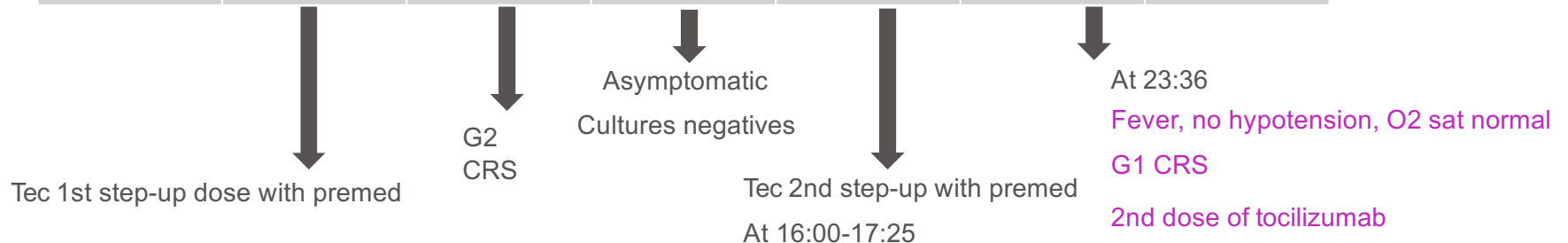
# Admission at the Hospital the Same Day of the Lockdown in Spain by COVID-19: April 12, 2020

Levels	13-04-2020	13-04-2020	15-04-2020	16-04-2020	17-04-2020	18 and 19
CRP	0.25 mg/dL	9.68 mg/dL	7.76 mg/dL			observation
Ferritin	Normal	941 ng/mL	732 ng/mL			
D-dimer	0.4 mcg/mL	7.8 mcg/mL	19.1 mcg/mL			
pro-BNP	Normal	352.50 pg/mL	-			
Troponin	ND	Normal	-			
Leucocytes	7.54 x 10 <sup>9</sup> /L	3.50 x 10 <sup>9</sup> /L	7.54 x 10 <sup>9</sup> /L			
Lymphocytes	2.16 x 10 <sup>9</sup> /L	0.47 x 10 <sup>9</sup> /L	0.75 x 10 <sup>9</sup> /L			



# Admission at the Hospital the Same Day of the Lockdown in Spain by COVID-19: April 12, 2020

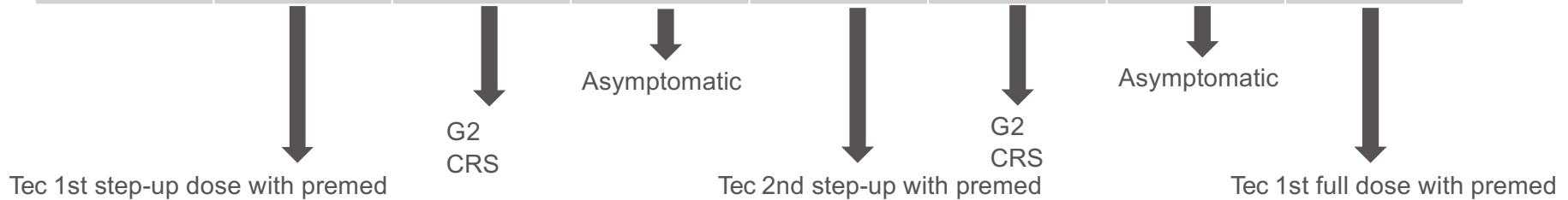
Levels	13-04-2020	14-04-2020	15-04-2020	16-04-2020	17-04-2020	18 and 19
CRP	0.25 mg/dL	9.68 mg/dL	7.76 mg/dL	2.92 mg/dL	2.12 mg/dL	observation
Ferritin	Normal	941 ng/mL	732 ng/mL	ND	698 ng/mL	
D-dimer	0.4 mcg/mL	7.8 mcg/mL	19.1 mcg/mL	2.2 mcg/mL	15.1 mcg/mL	
pro-BNP	Normal	352.50 pg/mL	-	-	-	
Troponin	ND	Normal	-	-	-	
Leucocytes	7.54 x 10 <sup>9</sup> /L	3.50 x 10 <sup>9</sup> /L	7.54 x 10 <sup>9</sup> /L	4.21 x 10 <sup>9</sup> /L	10.4 x 10 <sup>9</sup> /L	
Lymphocytes	2.16 x 10 <sup>9</sup> /L	0.47 x 10 <sup>9</sup> /L	0.75 x 10 <sup>9</sup> /L	1.14 x 10 <sup>9</sup> /L	0.4 x 10 <sup>9</sup> /L	



# Admission at the Hospital the Same Day of the Lockdown in Spain by COVID-19: April 12, 2020

Levels	13-04-2020	14-04-2020	15-04-2020	16-04-2020	17-04-2020	18 and 19	20-04-2020
CRP	0.25 mg/dL	9.68 mg/dL	7.76 mg/dL	2.92 mg/dL	2.12 mg/dL	observation	0.49 mg/dL
Ferritin	Normal	941 ng/mL	732 ng/mL	ND	698 ng/mL		
D-dimer	0.4 mcg/mL	7.8 mcg/mL	19.1 mcg/mL	2.2 mcg/mL	15.1 mcg/mL		0.4 mcg/ml
pro-BNP	Normal	352.50 pg/mL	-	-	-		
Troponin	ND	Normal	-	-	-		
Leucocytes	7.54 x 10 <sup>9</sup> /L	3.50 x 10 <sup>9</sup> /L	7.54 x 10 <sup>9</sup> /L	4.21 x 10 <sup>9</sup> /L	10.4 x 10 <sup>9</sup> /L		5.5 x 10 <sup>9</sup> /L
Lymphocytes	2.16 x 10 <sup>9</sup> /L	0.47 x 10 <sup>9</sup> /L	0.75 x 10 <sup>9</sup> /L	1.14 x 10 <sup>9</sup> /L	0.4 x 10 <sup>9</sup> /L		1.44 x 10 <sup>9</sup> /L

- Asymptomatic
- No more CRS
- Patient is discharged after 48 hours in observation



# Immunotherapy and TRAEs in MM

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# Statistical Analysis of Potentially Preventable Cancer Patient ED Visits

- 35.5 million annual ED visits among patients with cancer
  - 67.1% increase in visits from 2012-2019, compared with an increase of just 7.5% in cancer incidence
- 51.6% of visits were identified as potentially preventable
  - From 2012 to 2019: the absolute number of potentially preventable ED increased from 1.8 million to 3.2 million
  - Potentially preventable ED visits have been associated with poor patient experiences and increasing cancer care costs
  - 30.2% resulted in hospitalization
    - Highest: Sepsis (93.3%) ,pneumonia (76.2%) , and anemia (71.7%),
    - Lowest: Pain (23.5%), dehydration (28.0%), and nausea (31.8%)

## List of the CMS Potentially Preventable Primary Diagnosis

Anemia

Nausea

Fever

Dehydration

Neutropenia

Diarrhea

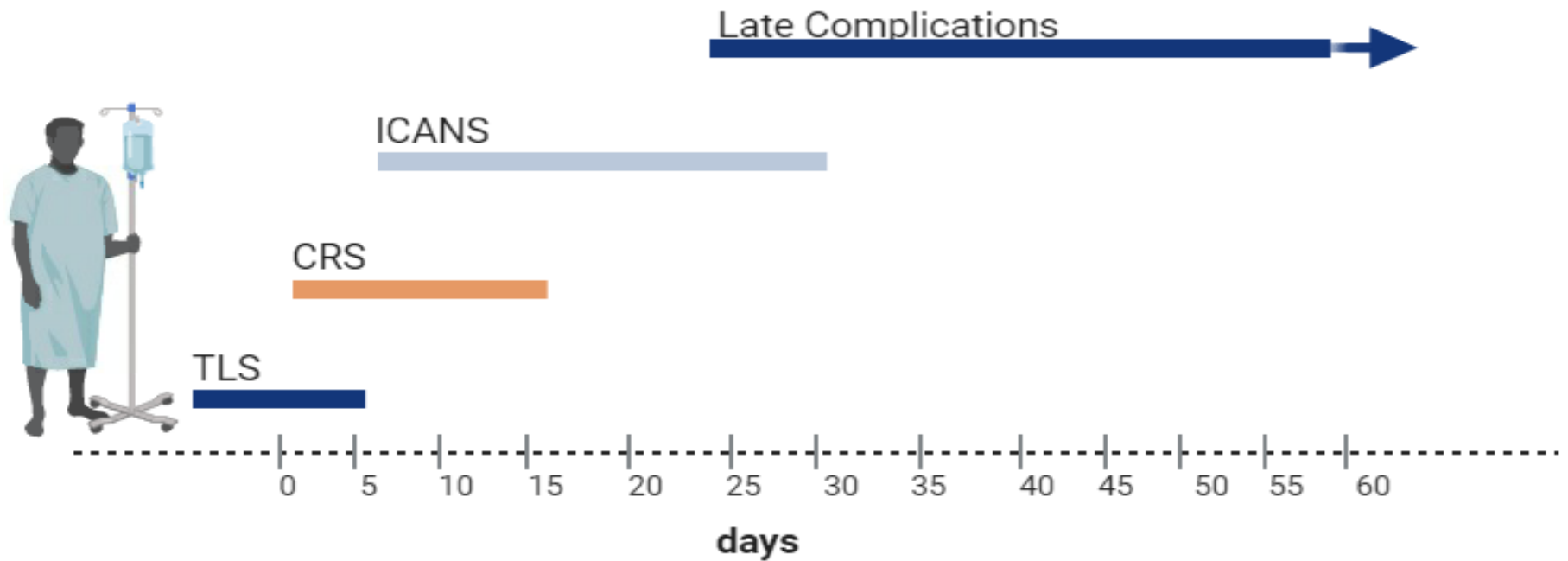
Pain

Pneumonia

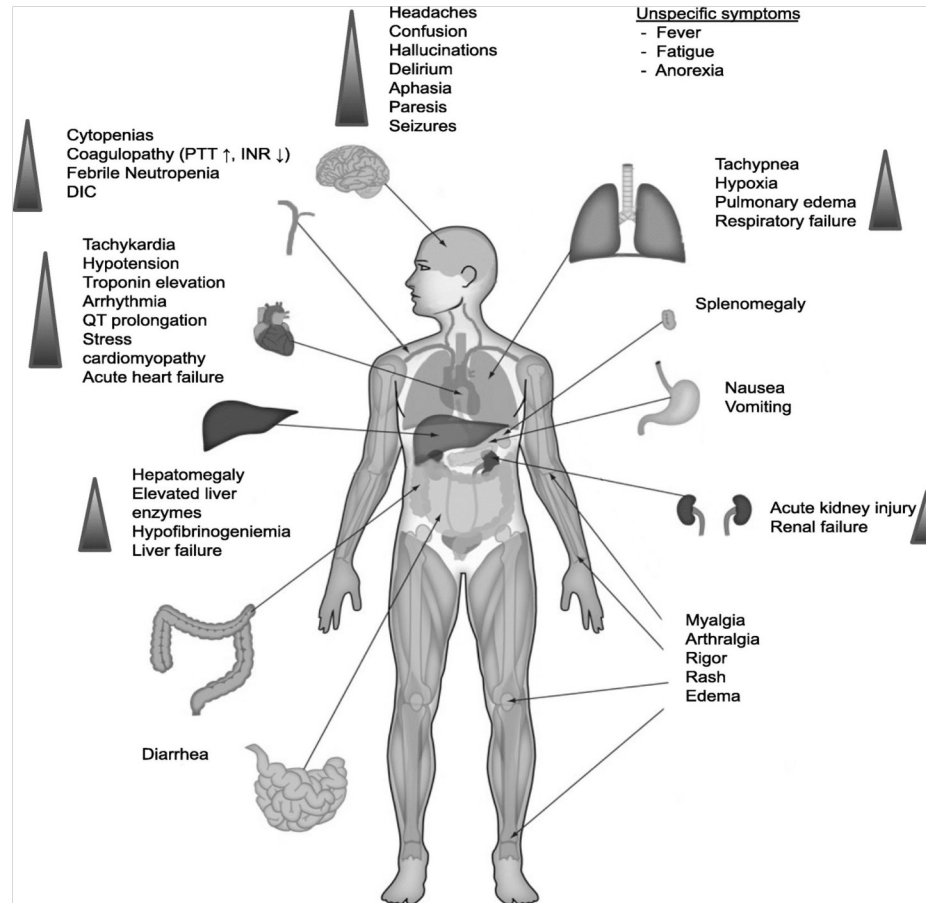
Sepsis

Emesis

# Onset of Complications



# Cytokine Release Syndrome



# CLINICAL CASE - CRS IN THE ED

Levels	13-04-2020	13/14-04-2020	15-04-2020	16-04-2020	17-04-2020	20-04-2020
CRP	0.25 mg/dL	9.68 mg/dL				
Ferritin	Normal	941 ng/mL				
D-dimer	0.4 mcg/mL	7.8 mcg/mL				
pro-BNP	Normal	352.50 pg/mL				
Troponin	ND	Normal				
Leucocytes	7.54 x 10 <sup>9</sup> /L	3.50 x 10 <sup>9</sup> /L				
Lymphocytes	2.16 x 10 <sup>9</sup> /L	0.47 x 10 <sup>9</sup> /L				

Tec 1st step-up dose with premed

Fever 38.2°C at 16:34  
with hypotension at 18:57 and  
O2 sat 88% at 17:59  
Thoracic pain

Cultures of blood, urine, feces, sputum

X-ray

Broad-spectrum Abs → piperaciline-tazobactam

G2 CRS: Tocilizumab on 13-04 20

Cardiological evaluation: Normal

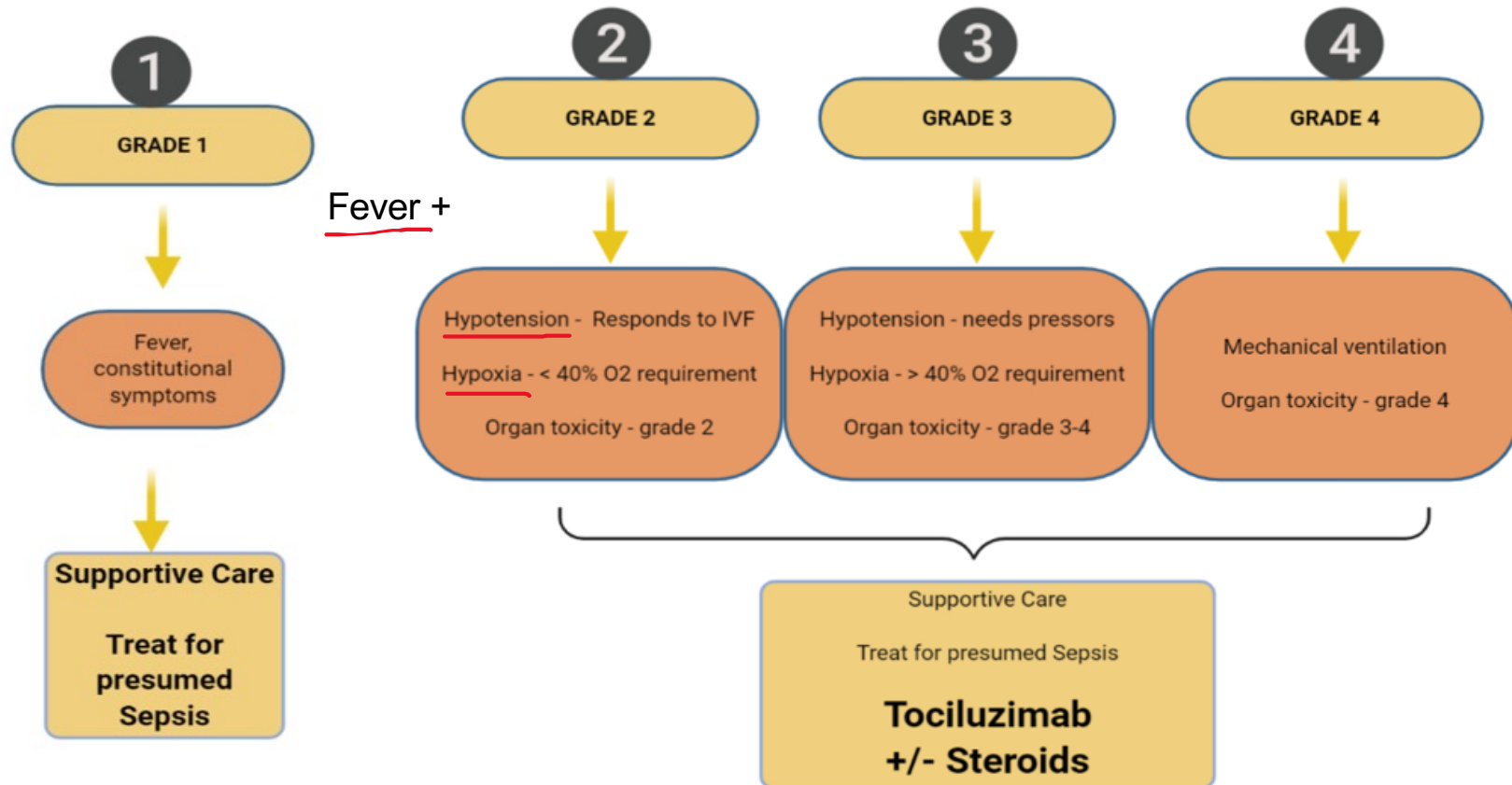
O2 sat = oxygen saturation.

22 y.o.	Shortness of Breath; Cou...		01:56	A... WATTANA...	
54 y.o.	Abdominal Pain, Cough		02:46	C... WATTANA...	
45 y.o.	Abdominal Pain		04:28	R... ALTAY, H	
56 y.o.	Chest Pain		04:52	I... GOMEZ, ...	
69 y.o.	Fall		06:15	S... HITA, A	
o. f) o.	Transfer	✓	06:50	N... LUDWIG, J	
61 y.o.	Neck Pain		09:11	R... KHEDER, E	
59 y.o.	Fever	✓	09:23	A... SENECHA...	✓
37 y.o.	Headache; Diarrhea		09:35	M... WATTANA...	✓
70 y.o.	Drain Complication		09:47	N... HITA, A	✓
86 y.o.	Fever, Fatigue	✓	10:46	A... HAHN, A	✓
60 y.o.	Pain With Breathing; Shortne...		11:48	M... HITA, A	✓
52 y.o.	Fatigue; Altered Mental Status	✓	11:51		✓

Pt put in resuscitation room 1:  
 HR 126    Temp: 38.2  
 BP: 82/55    RR 26    SpO2: 80%RA



# CRS Grading System

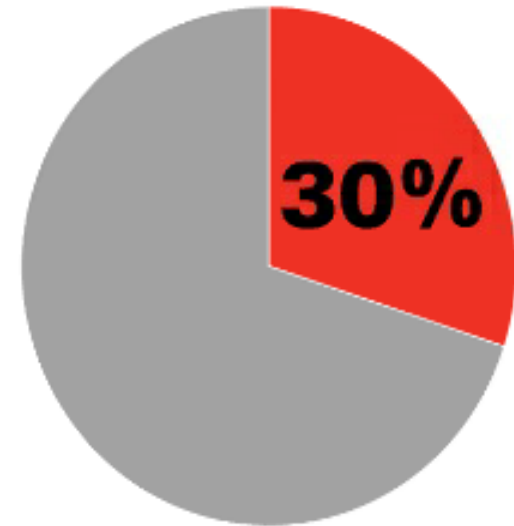




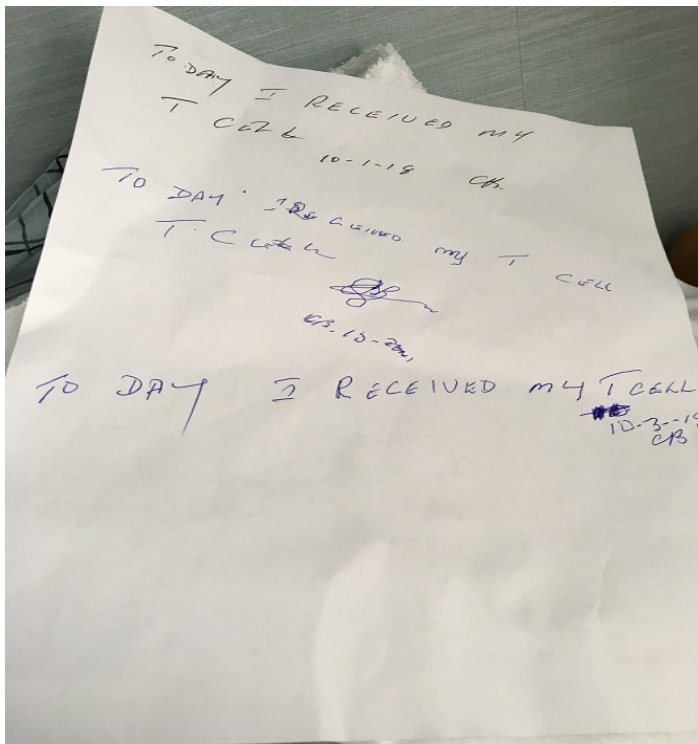
**Cancer Patients**  
**10x**  
**More likely to**  
**develop SEPSIS**



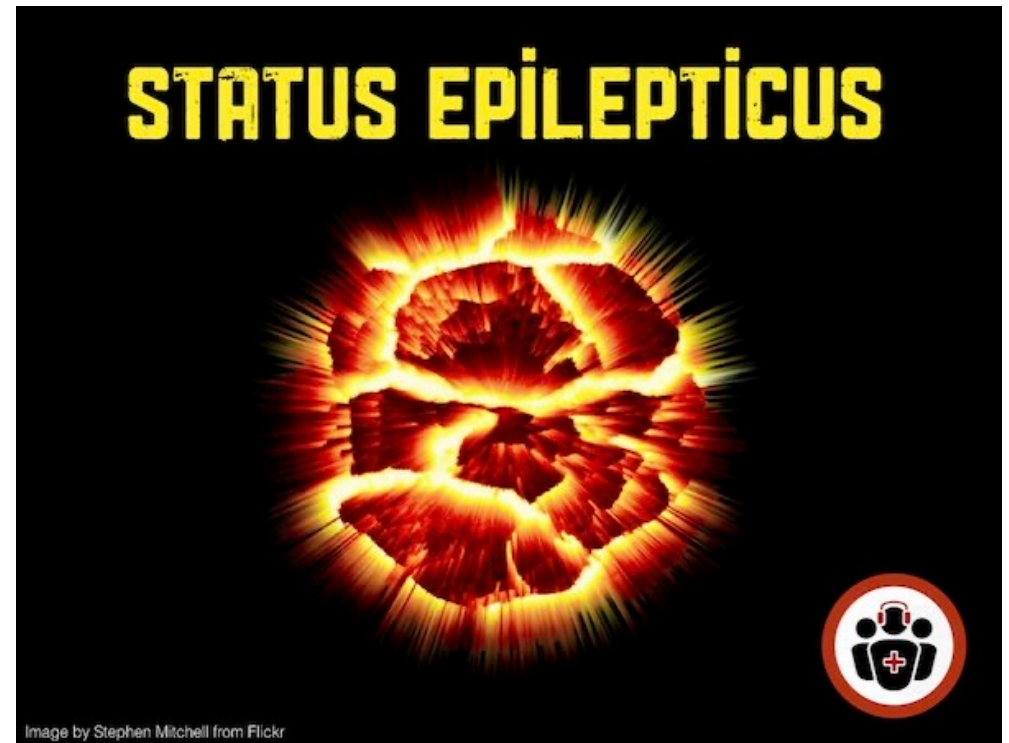
**Cancer Patient**  
**Deaths due to SEPSIS**



# CLINICAL CASE ICANS IN THE ED

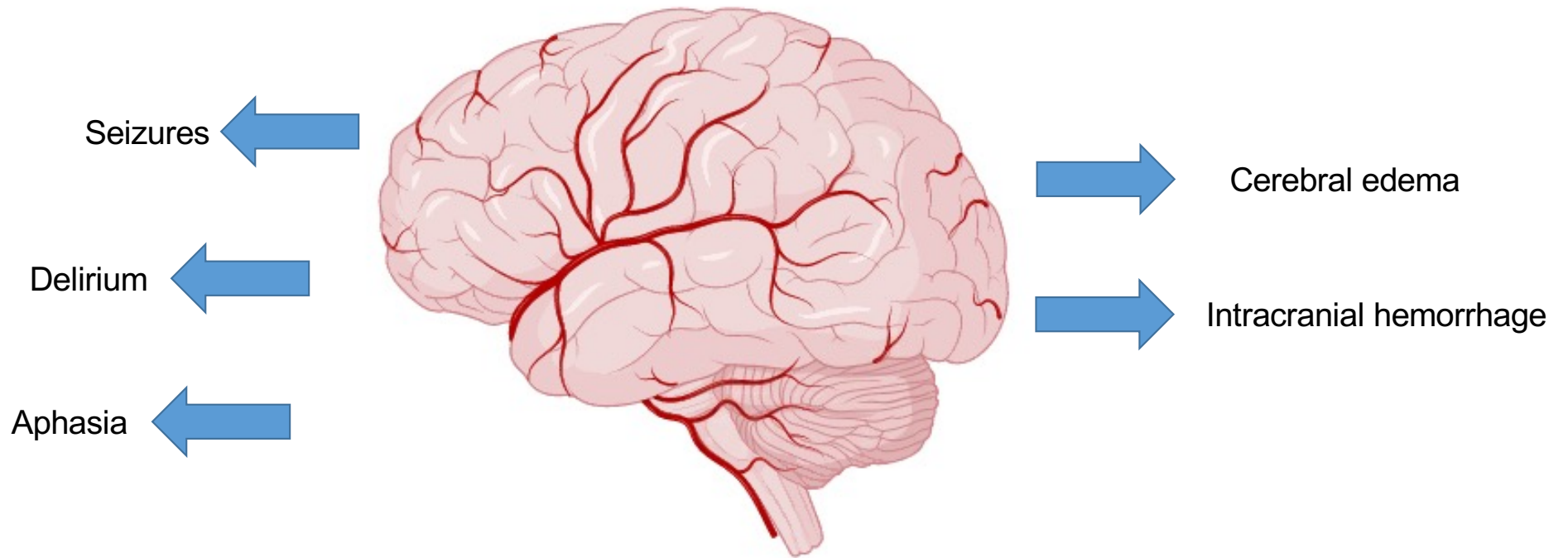


VS



Helman, A. Koblic, P. Reid, A. Kovacs, G. Emergency Management of Status Epilepticus. Emergency Medicine Cases. December, 2019. <https://emergencymedicines.com/status-epilepticus>.

# Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)



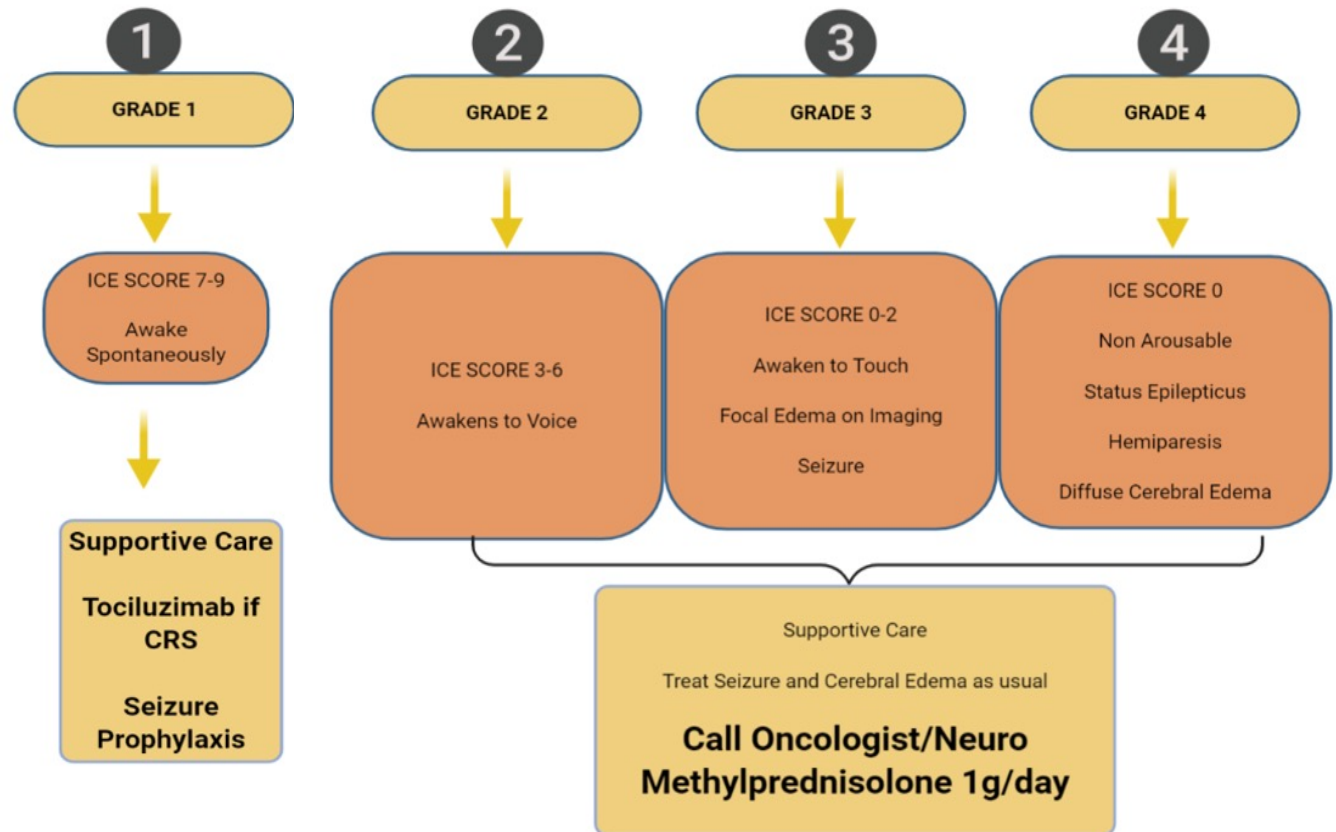
# ICANS Grading Includes the Immune Effector Cell-Associated Encephalopathy (ICE) Score

Points	Assessment
4	Orientation: year, month, city, and hospital
3	Naming: ability to name 3 objects correctly
1	Following simple commands: ex, close your eyes and smile
1	Writing: able to write a standard sentence
1	Attention: ability to count backwards from 100 by 10

- ICE scoring is as follows
  - 10 points: no impairment
  - 7-9 points: grade 1 ICANS
  - 3-6 points: grade 2 ICANS
  - 0-2 points: grade 3 ICANS
  - 0 points: assessment unable to complete due to severe AMS grade 4 ICANS

# ICANS Grading System

- ICE score
- Consciousness
- Weakness
- Seizure
- Cerebral edema



# CRS Treatment

Grade	Symptoms	Treatment
1	Temperature > 38°C Flu-like symptoms Nausea	Supportive care Sepsis workup and empiric abx treatment Consider tocilizumab for 1 dose for fever lasting greater than 3 days
2	Temperature > 38°C Hypotension not requiring vasopressors Hypoxia responding to < 40% FiO2	Manage fever and sx as in Grade 1 IVF Supplementary oxygen Tocilizumab 8mg/kg IV x1 Consider one dose of glucocorticoids such as methylprednisolone
3	Temperature > 38°C Hypotension requiring 1 vasopressor Hypoxia requiring ≥ 40% FiO2	Manage fever and sx as in Grade 1 Vasopressor High-flow oxygen support ICU admission Tocilizumab 8mg/kg IV x1 Corticosteroids: methylprednisolone 1mg/kg/day Dexamethasone 10mg/q6hr if more neurologic symptoms
4	Temperature > 38°C Hypotension requiring multiple pressors Hypoxia requiring positive airway pressure Life-threatening consequences	Manage fever and sx as in Grade 1 Vasopressor Mechanical ventilation ICU admission Tocilizumab 8mg/kg IV x1 Corticosteroids: methylprednisolone 1mg/kg/day Dexamethasone 10mg/q6hr if symptoms are more neurologic

FiO2 = fraction of inspired oxygen; abx = antibiotics; sx = symptoms; IVF = intravenous fluids; ICU = intensive care unit

# ICANS Treatment

Grade	Description	Treatment
1	ICE score 7-9 Spontaneously awake	Supportive care Seizure prophylaxis Tocilizumab ONLY if concurrent CRS present
2	ICE score 3-6 Awakens to voice	<b>Grade 2-4 Treatment:</b>
3	ICE score 0-2 Awakens to touch Focal edema on neuroimaging seizure	Methylprednisolone 1gram/day
4	ICE score 0 Non-arousable Status epilepticus Hemiparesis Diffuse cerebral edema on neuroimaging	Treat seizure and cerebral edema as per usual protocols

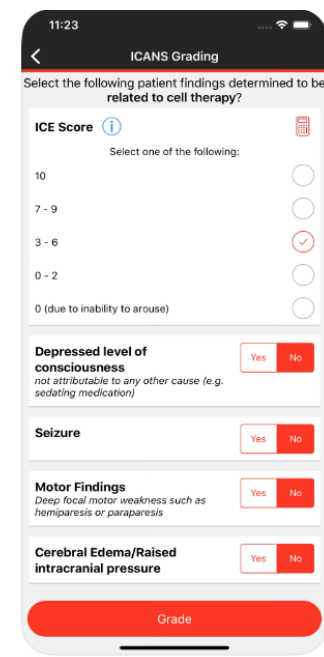
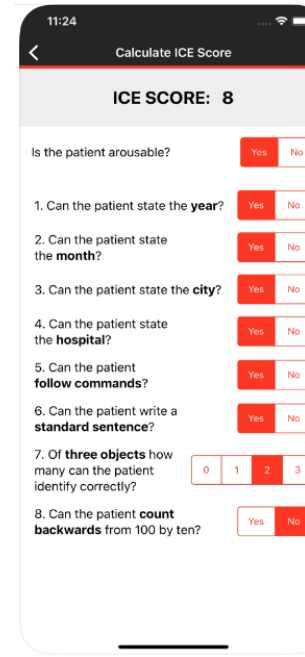
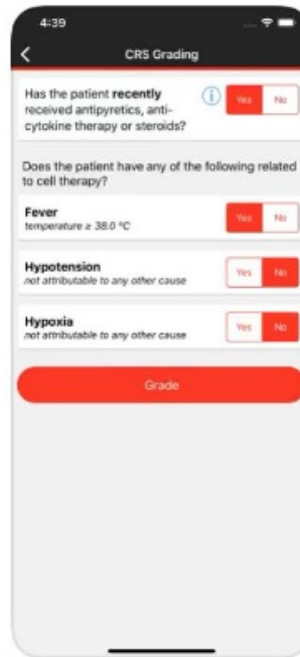
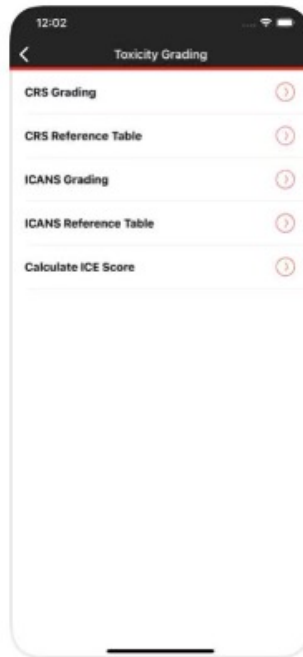
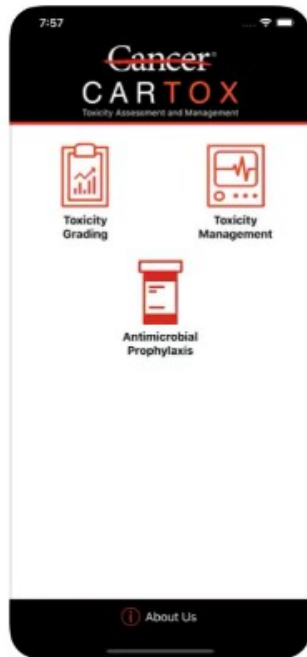
# An App Exists for CAR T Toxicities



CARTOX

Toxicity assessment tool

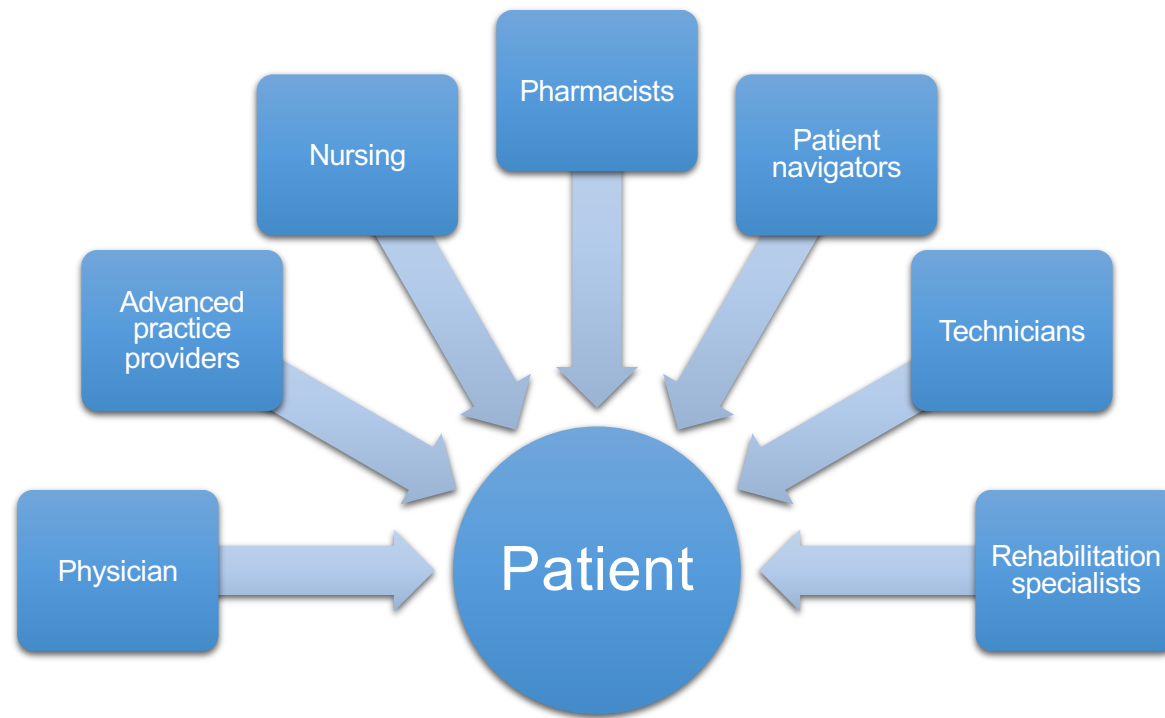
★★★★★ 1



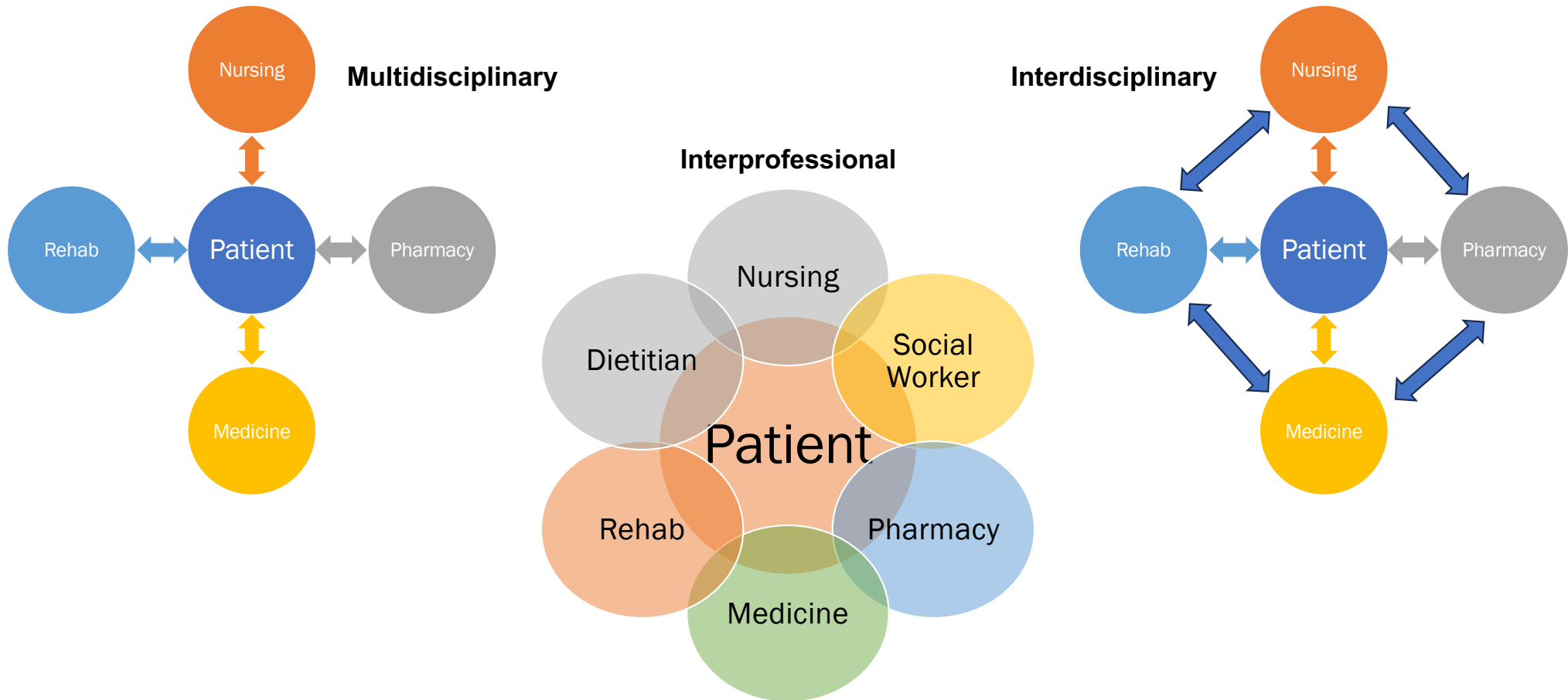


# A Multidisciplinary Team Approach to Care

# Shared Decision-Making for Improved ED Management



# Shared Decision-Making for Improved ED Management



# ED Management Summary

- High Clinical Index of Suspicion
- Calling consultants early
- Transferring to higher level of care early
- Ordering labs/images to help colleagues on admission

# Post-Activity Survey

Scan the QR Code below or at your table



We appreciate your participation.

# Question 1

Which of the following targets both CD3 T-cell receptors and the GPRC5D MM receptor and has been associated with CRS and ICANS?

1. Elranatamab
2. Isatuximab
3. Teclistamab
4. Talquetamab



## Question 2

CRS and ICANS were seen in \_\_\_\_, respectively, of patients treated with cilta-cel in the CARTITUDE-1 trial.

1. ~20% and ~60%
2. ~40% and ~80%
3. ~60% and ~40%
4. ~80% and ~20%



## Question 3

All of the following may be considered as a therapeutic approach to CAR T- and BsAb-associated CRS except?

1. CD-20 blockade with rituximab
2. IL-6 inhibition with siltuxumab
3. IL-6 inhibition with tocilizumab
4. IL-1 inhibition with anakinra
5. Unsure



## Question 4

How confident are you in your ability to incorporate and implement a multidisciplinary team (MDT) approach to improve MM patient outcomes and quality of life?

1. Very confident
2. Confident
3. Somewhat confident
4. Not very confident
5. Not at all confident



# Questions?



Access accreditation information, or claim CE credit by scanning the QR code

