

# SUSTAIN

Systematic Uptake and Standardization of Treatment  
Advances Through an Integrated Network for  
**BISPECIFIC ANTIBODY THERAPY**

Provided by  UK HealthCare

 The  
France  
Foundation

# Today's Faculty



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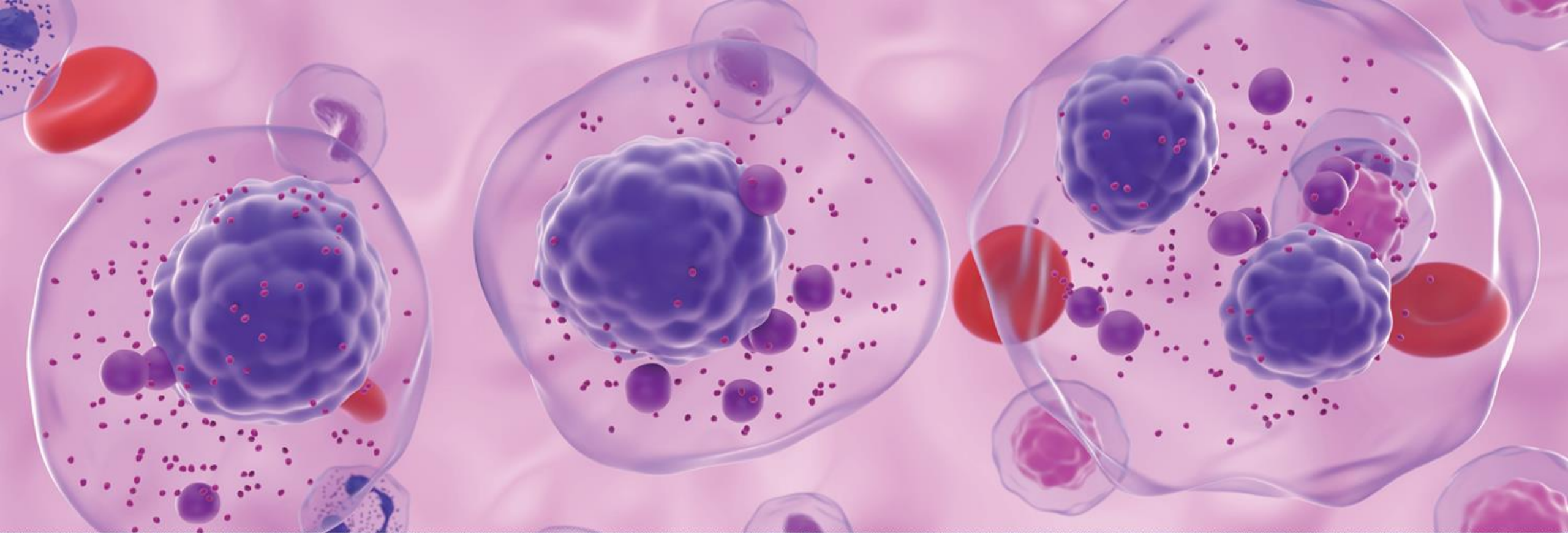
- **1.00 IPCE**

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information, visit:





# Session 3: Cytokine Release Syndrome— Pathophysiology, Recognition, and Management



# Curriculum Learning Objective

- Educate multidisciplinary teams on BsAb pharmacology; recognition and grading of adverse events; and appropriate interventions including, when to escalate care
- Establish emergency response protocols, multidisciplinary rapid response teams, and clear communication pathways with UKHC for complex cases
- Train providers in appropriate patient selection criteria, risk stratification, and patient/caregiver education regarding expectations, monitoring requirements, and symptom reporting

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# Session Objectives

- Recognize and grade CRS following bispecific antibody therapy
- Apply appropriate CRS management, including timely use of tocilizumab and corticosteroids
- Incorporate monitoring strategies to detect and manage CRS early

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# Based On What You Learned Last Session....

How confident do you feel in identifying and selecting patients for BsAbs?

- A. Very Confident
- B. Confident
- C. Neutral/unsure
- D. Somewhat confident
- E. Not at all confident

A vertical strip on the left side of the slide shows a microscopic view of cells. The cells are primarily purple and blue, with some red and orange structures. They appear to be in various stages of division or are different types of cells. The background is a light pinkish-purple.

# Based On What You Learned Last Session....

How confident do you feel in your skills to monitor or manage adverse events?

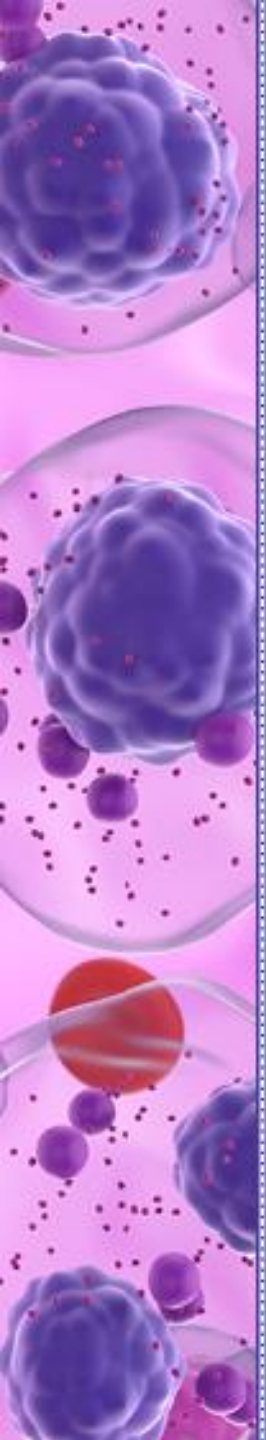
- A. Very Confident
- B. Confident
- C. Neutral/unsure
- D. Somewhat confident
- E. Not at all confident

# What Do You Know?



A patient receiving a bispecific antibody develops fever and requires **low-flow oxygen via nasal cannula** but remains normotensive. How should this CRS be graded and managed?

- A. Grade 1; supportive care only
- B. Grade 2; consider tocilizumab
- C. Grade 3; immediate ICU transfer
- D. Grade 4; permanent discontinuation



# Adverse Events Associated With BsAbs

BsAbs are associated with potentially serious and fatal adverse events, including:



ECHO #4 will review how to identify and manage ICANS!



Cytokine release syndrome (CRS)



Immune effector cell-associated neurotoxicity syndrome (ICANS)



Cytopenias



Infection



# Patient and Caregiver Education

- Patients should be educated on the benefits and risks of BsAbs to make an informed decision about treatment
  - Social workers and caregivers should also be included in the conversation
- BsAbs require patient/caregiver compliance and early recognition of side effects, which can lead to improved patient outcomes
- Clinicians should provide educational materials to patients

ECHO #2 reviewed important considerations for discussing eligibility for BsAbs with your patients

Society for Immunotherapy of Cancer (SITC) and Association of Community Cancer Centers (ACCC).

[https://higherlogicdownload.s3.amazonaws.com/SITCANCER/2c19e5a6-3adb-4d01-b46c-](https://higherlogicdownload.s3.amazonaws.com/SITCANCER/2c19e5a6-3adb-4d01-b46c-c01e11745b3a/UploadedImages/Policy/SITC_ACCC_Expanding_Access_Workshop_Report.pdf)

[c01e11745b3a/UploadedImages/Policy/SITC\\_ACCC\\_Expanding\\_Access\\_Workshop\\_Report.pdf](https://higherlogicdownload.s3.amazonaws.com/SITCANCER/2c19e5a6-3adb-4d01-b46c-c01e11745b3a/UploadedImages/Policy/SITC_ACCC_Expanding_Access_Workshop_Report.pdf); Association of Community Cancer Centers (ACCC).

[https://www.accc-cancer.org/docs/projects/bispecific-antibodies/using-bispecific-antibodies-in-community-practice.pdf?sfvrsn=f5b5ac13\\_0](https://www.accc-cancer.org/docs/projects/bispecific-antibodies/using-bispecific-antibodies-in-community-practice.pdf?sfvrsn=f5b5ac13_0)

# Pre-Medications Reduce the Risk of CRS Prior to Infusion

	Teclistamab and Talquetamab	Elranatamab	Linvoseltamab
Pre-Medications	<ul style="list-style-type: none"> <li>Acetaminophen 650-1000 mg PO</li> <li>Diphenhydramine 50 mg PO/IV (PO defaulted)</li> <li>Dexamethasone 16 mg PO/IV (PO defaulted)</li> </ul>	<ul style="list-style-type: none"> <li>Acetaminophen 650 mg PO</li> <li>Diphenhydramine 25 mg PO/IV (PO defaulted)</li> <li>Dexamethasone 20 mg PO/IV (PO defaulted)</li> </ul>	<ul style="list-style-type: none"> <li>Acetaminophen 650 mg PO</li> <li>Diphenhydramine 25 mg PO/IV (PO defaulted)</li> <li>Dexamethasone 40 mg PO/IV</li> </ul>
	<ul style="list-style-type: none"> <li>Given 1 hour prior to BsAb dose</li> <li>Required for <b>all step-up doses</b> and the <b>first treatment dose</b></li> <li>PRN thereafter if CRS with prior dose or delay in treatment schedule</li> </ul>		

ECHO #5 will review how to treat and manage patients with infections!

PO = by mouth; PRN = as needed

Teclistamab-cqyv (Tecvayli) [prescribing information]. Janssen Biotech, Inc; March 2026; Elranatamab-bcmm (Elrexio) [prescribing information]. Pfizer Inc; July 2025; Talquetamab-tgvs (Talvey) [prescribing information]. Janssen Biotech, Inc; August 2023. Linvoseltamab-gcpt (Lynozytic) [prescribing information]. Regeneron Pharmaceuticals, Inc; July 2025.

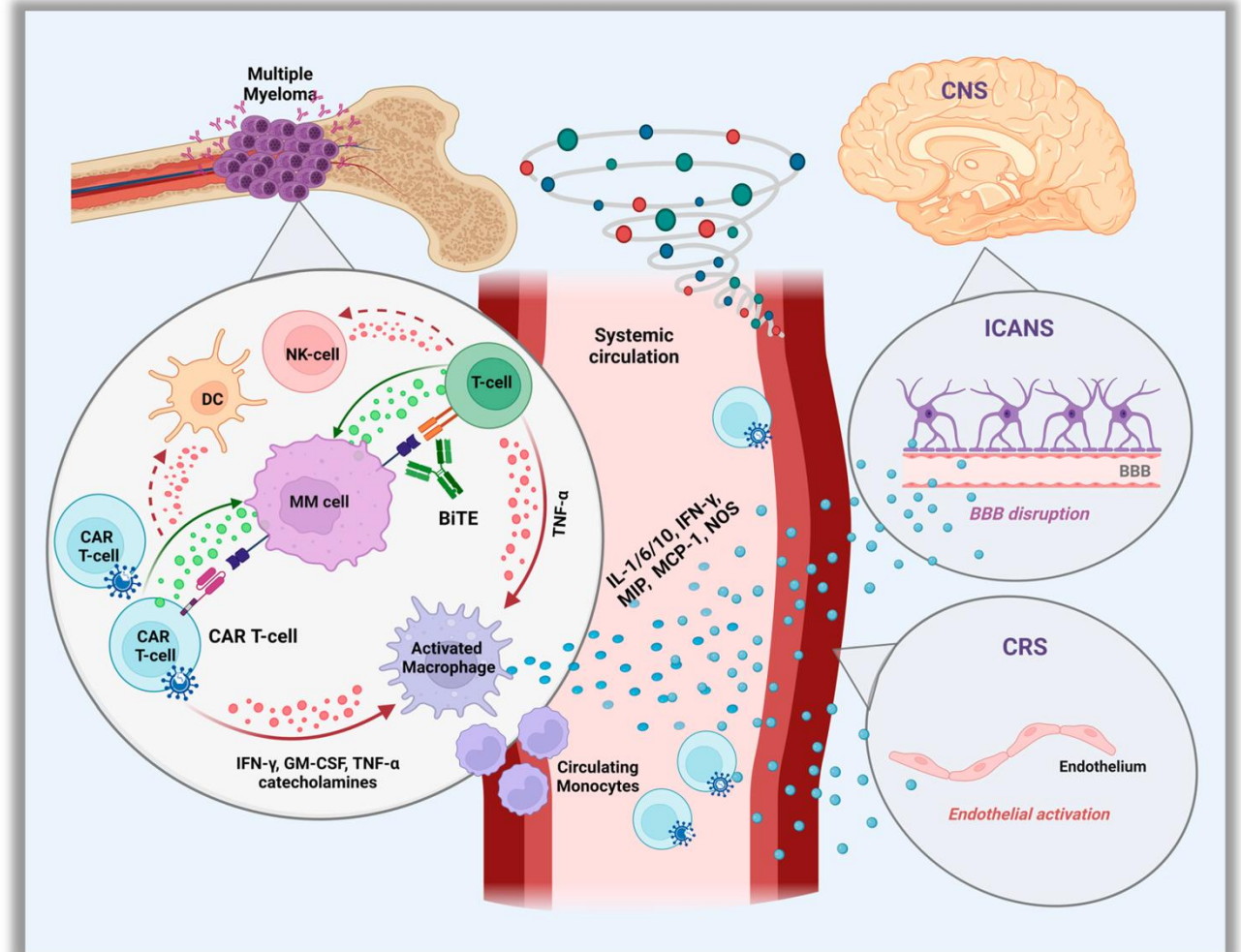
# Risk Factors for CRS

Risk Factors for CRS	
Disease related	<ul style="list-style-type: none"><li>• Tumor burden</li></ul>
Treatment related	<ul style="list-style-type: none"><li>• Higher dose of BsAbs or high affinity to CD3</li></ul>
Comments	<ul style="list-style-type: none"><li>• Occurs early (step-up dosing)</li><li>• Mostly grade 1 (50-75% of cases)</li><li>• Can become serious (1-5% of cases)</li></ul>

**CRS often precedes ICANS—it is important to promptly recognize the signs and symptoms!**

# Pathophysiology of CRS

- Occurs when BsAbs engage T cells with target cells →
  - T cells release cytokines (eg, IFN- $\gamma$ , TNF- $\alpha$ )
- Secondary activation of immune and non-immune cells amplifies cytokine production
- Can progress to systemic cytokine storm and inflammatory response
- Severity and incidence vary by BsAb construct and target

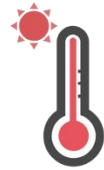


BiTE = bispecific T cell engager; DC = dendritic cell; IFN- $\gamma$  = interferon gamma; IL = interleukin; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; NK = natural killer; NOS = nitric oxide synthase; TNF- $\alpha$  = tumor necrosis factor alpha

Markouli M, et al. *Curr Oncol.* 2023;30(7):6330-6352; Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-638.

# Symptoms of CRS

Pyrexia



Nausea/  
vomiting



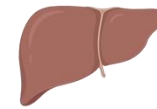
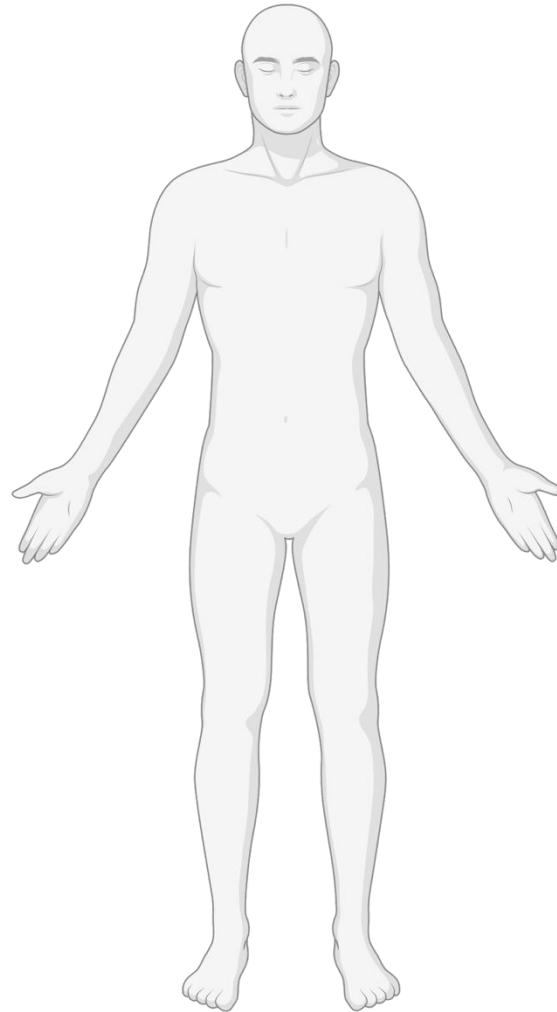
Fatigue



Rash  
and  
Urticaria



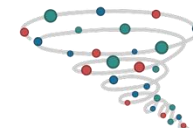
Arthralgia/  
Myalgia



Elevated  
Liver  
Enzymes



Hypotension



Systemic  
Inflammatory  
Response



Respiratory  
symptoms



Diarrhea

# Timing of CRS

- Highest risk occurs minutes to hours after step-up or induction infusions
  - CRS can sometimes occur after patient is discharged

BsAb	Median Time to CRS Onset After Most Recent Dose	Median Duration of CRS
Teclistamab	2 days	2 days
Elranatamab	2 days	2 days
Talquetamab	27 hours	17 hours
Linvoseltamab	11 hours	15.6 hours

A vertical strip on the left side of the slide shows a microscopic view of cells, likely cancer cells, with various colors (purple, red, blue) and textures, set against a pinkish background.

# Monitoring for CRS in an Outpatient Setting

1. Record vital signs daily
2. Obtain daily weights
3. Evaluate daily CBC with differential and complete metabolic profile
4. Record coagulation parameters twice a week
5. Measure C-Reactive protein and ferritin daily during step-up therapy and first full dose, then as needed
6. Assess and Grade CRS at least daily and with any change in clinical status

CBC = complete blood count

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638; Santomasso BD, et al. *J Clin Oncol* 2021; 39: 3978-3992; Ludwig H, et al. *Lancet Oncol*. 2023;24: e255-69; VHA Guidance. Accessed April 15, 2026. [https://www.va.gov/formularyadvisor/DOC\\_PDF/CRE\\_Bispecific\\_Antibody\\_CRS\\_and\\_ICANS\\_Neurotoxicity\\_Guidance\\_Feb2024.pdf](https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Bispecific_Antibody_CRS_and_ICANS_Neurotoxicity_Guidance_Feb2024.pdf)



# Monitoring for CRS in an Inpatient/Intensive Care Setting

**During initial step-up therapy, patient may need to be admitted to inpatient service depending on the BsAb utilized**

1. Obtain vital signs every 4 hours (while awake if stable)
2. Monitor oral and IV fluid inputs and outputs
3. Weigh daily
4. Evaluate daily CBC with differential and complete metabolic profile
5. Measure coagulation parameters twice a week
6. Record C-Reactive Protein level daily during step-up, then continue until CRS resolves
7. Assess and grade CRS every 12 hours and whenever there is a change; call the covering physician with any changes
8. Perform cardiac/hemodynamic monitoring by telemetry

A vertical decorative strip on the left side of the slide features a microscopic view of cells. The cells are primarily purple and blue, with some red and orange cells interspersed. They appear to be in various stages of division or are different types of cells, possibly related to the medical context of the slide.

# Monitoring for CRS in a Home Setting

1. Provide team contact information and guidance on when to call for symptoms
2. Obtain oral temperature every evening; if the patient feels unwell or lethargic, increase oral temperature to three times a day
3. Encourage oral fluid intake

# Evaluation and Diagnosis of CRS

## Physical examination should include:

- Temperature
- Blood pressure
- Pulse oximetry or arterial blood gas (or mixed venous blood gas/O<sub>2</sub> saturation)
- Examination of skin, heart, and lungs



## Labs should include:

- CBC with differential
- Coagulation: (PT/PTT, fibrinogen, fibrin D-dimer)
- Chemistry: serum electrolytes, kidney and liver function, uric acid, lactate, LDH
- C-reactive protein and ferritin (inflammation)
- Microbiologic testing, especially in neutropenic patients (blood and urine cultures)
- Cardiac markers as clinically indicated



## Imaging should include:

- Chest X-ray
- Cross-sectional imaging (eg, CT scan), or echocardiogram as clinically indicated

**CRS Management does not require lab testing and should not be delayed waiting for lab results**

LDH = lactate dehydrogenase; PT = prothrombin time; PTT = partial thromboplastin time

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638; Santomaso BD, et al. *J Clin Oncol* 2021; 39: 3978-3992; Ludwig H, et al. *Lancet Oncol*. 2023;24: e255-69; VHA Guidance. Accessed April 15, 2026. [https://www.va.gov/formularyadvisor/DOC\\_PDF/CRE\\_Bispecific\\_Antibody\\_CRS\\_and\\_ICANS\\_Neurotoxicity\\_Guidance\\_Feb2024.pdf](https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Bispecific_Antibody_CRS_and_ICANS_Neurotoxicity_Guidance_Feb2024.pdf)



# Lab Findings With CRS

- Lab findings may include:
  - Cytopenias
  - Elevated creatinine
  - Elevated liver enzymes
  - Dysregulated coagulation parameters
  - Increased C-Reactive Protein

**CRS Management does not require lab testing and should not be delayed waiting for lab results**



# Grading CRS

	Grade 1	Grade 2	Grade 3	Grade 4
<b>Fever with</b>	Temperature $\geq 38^{\circ}$			
<b>Hypotension and/or</b>	None	Requiring up to 1 low dose of vasopressor	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors excluding vasopressin
<b>Hypoxia</b>	None	Requiring low-flow oxygen $\leq 6$ L/min	Requiring high-flow oxygen $\geq 6$ L/min	Requiring positive pressure ventilation (CPAP, BiPAP, Intubation, or mechanical intubation)

BiPAP = bilevel positive airway pressure; CPAP = central positive airway pressure

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638; Santomaso BD, et al. *J Clin Oncol* 2021; 39: 3978-3992; Ludwig H, et al. *Lancet Oncol*. 2023;24: e255-69; VHA Guidance. Accessed April 15, 2026. [https://www.va.gov/formularyadvisor/DOC\\_PDF/CRE\\_Bispecific\\_Antibody\\_CRS\\_and\\_ICANS\\_Neurotoxicity\\_Guidance\\_Feb2024.pdf](https://www.va.gov/formularyadvisor/DOC_PDF/CRE_Bispecific_Antibody_CRS_and_ICANS_Neurotoxicity_Guidance_Feb2024.pdf)

# Teclistamab, Elranatamab, and Talquetamab Guidance for Managing CRS

Grade	Action
1	<ul style="list-style-type: none"><li>• Withhold BsAb until CRS resolves</li></ul>
2	<ul style="list-style-type: none"><li>• Withhold BsAb until CRS resolves</li><li>• Administer pretreatment medications prior to next dose of BsAb</li><li>• Monitor patients for 48 hours following the next dose of BsAb</li></ul>
3	<ul style="list-style-type: none"><li>• Withhold BsAb until CRS resolves</li><li>• Provide supportive therapy, which may include intensive care</li><li>• Administer pretreatment medications prior to the next dose</li><li>• Patients should be hospitalized for 48 hours following the next dose</li><li>• If recurrent Grade 3 CRS or duration is 48 hours or longer<ul style="list-style-type: none"><li>— Permanently discontinue BsAb</li></ul></li></ul>
4	<ul style="list-style-type: none"><li>• Permanently discontinue BsAb</li><li>• Provide supportive therapy, which may include intensive care</li></ul>

Teclistamab-cqyv (Tecvayli) [prescribing information]. Janssen Biotech, Inc; March 2026; Elranatamab-bcmm (Elrexio) [prescribing information]. Pfizer Inc; July 2025; Talquetamab-tgvs (Talvey) [prescribing information]. Janssen Biotech, Inc; August 2023.

# Linvoseltamab Guidance for Managing CRS

Grade	Action
1	<ul style="list-style-type: none"><li>• Withhold BsAb until CRS resolves</li><li>• Provide supportive care, which may include intensive care</li><li>• When CRS resolves resume BsAb</li></ul>
2	<ul style="list-style-type: none"><li>• Follow guidance for Grade 1</li><li>• When CRS resolves, resume treatment<ul style="list-style-type: none"><li>— Consider a decrease in infusion rate up to 50% (no more than 6 hours total) when resuming treatment</li><li>— Increase the rate on subsequent infusions if tolerated</li></ul></li><li>• Monitor patients within proximity of a health care facility for 24 hours following this dose, and consider hospitalization</li></ul>
3	<ul style="list-style-type: none"><li>• Follow guidance for Grade 2</li><li>• When CRS resolves, resume treatment at a reduced dose<ul style="list-style-type: none"><li>— Decrease in infusion rate up to 50% (no more than 6 hours total) when resuming treatment</li><li>— If tolerated, continue with the next recommended dose</li><li>— If full dose is tolerated, the infusion rate can be increased to the rate prior to CRS</li></ul></li><li>• Monitor patients within proximity of a health care facility for 24 hours following this dose, and consider hospitalization</li><li>• Permanently discontinue if Grade 3 CRS reoccurs</li></ul>
4	<ul style="list-style-type: none"><li>• Permanently discontinue if Grade 3 CRS reoccurs</li><li>• CRS should be managed per Grade 3 recommendations</li></ul>

# Treating and Managing CRS



## Grade 1

- Provide symptomatic/supportive care
- Administer antipyretics (acetaminophen 650 mg orally Q6 PRN)
- Obtain blood and urine cultures; initiate broad-spectrum IV antibiotics as for neutropenic patients
- IV hydration
- If persistent or refractory fever < 3 days, manage as Grade 2

## Grade 2

- Continue symptomatic/supportive care as in Grade 1
- Include IV bolus and supplemental oxygen as needed
  - Consider transfer to ICU if unresponsive to fluid bolus
- Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose); repeat every 8 hours
  - Limit to 3 doses per 24 hours with a maximum of 4 doses
- If no improvement in hypotension after fluid bolus consider adding dexamethasone 10 mg IV every 8-12 hours
- If no improvement 24 hours after starting tocilizumab, manage as Grade 3

## Grade 3

- **Admit to ICU**
- Continue Supportive Care as in Grade 2 and add vasopressors if needed
- Cardiac ECHO of not already performed to assess cardiac function; begin hemodynamic monitoring
- Initiate dexamethasone 10 mg IV every 6 hours for 3 days, and rapidly taper when symptoms improve
- Tocilizumab as per Grade 2 if the maximum dose is not reached and there is no improvement on high-dose steroids
  - If refractory, manage as Grade 4

## Grade 4

- **Admit to ICU**
- **Discontinue BsAb**
- Continue supportive care as in Grade 3 plus mechanical ventilation as needed
- Initiate high-dose methylprednisolone at 500 mg every 12 hours for 3 days, followed by 250 mg every 12 hours for 2 days, followed by 125 mg every 12 hours for 2 days, followed by 60 mg every 12 hours until symptoms improve to Grade 1
  - If no improvement methylprednisolone 1000 mg every 12 hours or other cytokine directed therapy
- Tocilizumab as per Grade 2 if maximum dose not reached



# Role of the Pharmacist

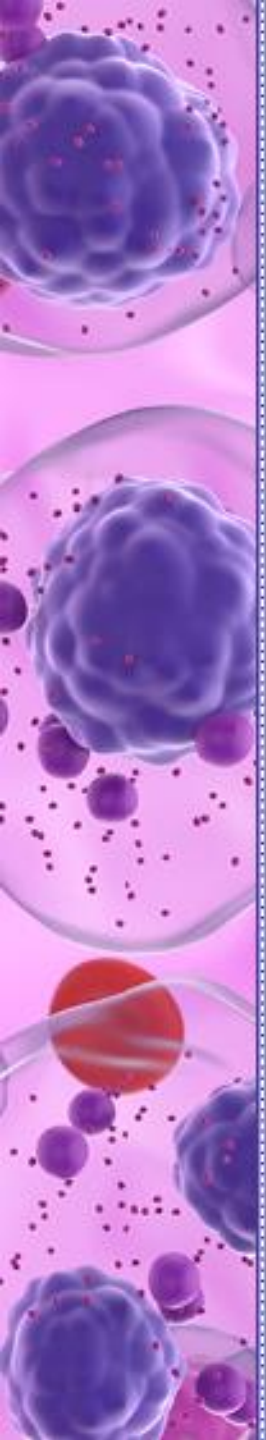
- Review patient's home medication regimen
  - Consider holding antihypertensives for 1-2 days following step-up doses
  - Clinically-significant drug interactions with BsAbs are rare
- Manage inventory of both BsAbs and tocilizumab
  - Ensure quick access to tocilizumab for cases where it is needed
- Collaboration in development of institutional protocols for CRS management

# What Did You Learn?



A patient receiving a bispecific antibody develops fever and requires **low-flow oxygen via nasal cannula** but remains normotensive. How should this CRS be graded and managed?

- A. Grade 1; supportive care only
- B. Grade 2; consider tocilizumab
- C. Grade 3; immediate ICU transfer
- D. Grade 4; permanent discontinuation





# Key Takeaways

- Anticipate early CRS, particularly during step-up dosing, and ensure appropriate inpatient monitoring for initial doses
- Grade CRS promptly using standardized criteria to guide management decisions
- Initiate timely treatment, including supportive care and early use of tocilizumab for  $\geq$  grade 2 CRS, with corticosteroids for refractory cases
- Use mitigation strategies, including step-up dosing, premedication, and treatment holds/resumption per protocol to reduce severity and recurrence



# Based On What You Just Learned....

How confident do you feel in your ability to deliver continuation of treatment in an outpatient community setting?

- A. Very Confident
- B. Confident
- C. Neutral/unsure
- D. Somewhat confident
- E. Not at all confident



# Based On What You Just Learned....

How confident do you feel in your ability to coordinate as-needed follow-up care with academic centers?

- A. Very Confident
- B. Confident
- C. Neutral/unsure
- D. Somewhat confident
- E. Not at all confident



# Ask the Audience!

**Please unmute or use the chat feature to discuss with your colleagues.**

What are your top 3 concerns on recognizing, assessing, and managing CRS in your clinical practice?



# Case Studies

Please come off mute or use the chat feature to discuss with your colleagues and ask questions about your patient cases



# Case Review: CRS

- 81-year-old male with history of R-ISS **stage III IgG Lambda MM**
  - t(11;14); monosomy 13
- **RVd initiated** 10/2016 - through January 2017
  - May 2017 His monoclonal protein increased off therapy and reached 1.8 g/dL
- Patient developed worsening fatigue and pancytopenia
  - **Ixazomib Rd** 1/2018 - July 2018
    - » Poor tolerance and continued to have pancytopenia
- July 3, 2018, which demonstrated:
  - **Peripheral blood, bone marrow aspirate and biopsy (right posterior iliac crest)**, and
  - Flow cytometry: hypercellular bone marrow infiltrated by **lambda-restricted plasma cells**
  - **Neoplasm** (70-80% plasma cells by cd138 immunohistochemistry),
  - Cytogenetic FISH analysis demonstrated **t(11;14) and monosomy 13**

FISH = fluorescence in situ hybridization; IgG = immunoglobulin G; R-ISS = Revised International Staging System; RVd = lenalidomide, bortezomib, and dexamethasone; Rd = lenalidomide and dexamethasone.



# Case Review: CRS

- July 2018-Dec 2023: **Initiated daratumumab, bortezomib, and dexamethasone**
  - Due to increasing light chains, the decision was made to discontinue daratumumab maintenance
- Bone Marrow Biopsy 1/2024: Final Diagnosis
  - **Plasma cell neoplasm** with increased, **variably distributed lambda light chain-restricted plasma cells**
    - » Approximately 50% of aspirate cellularity, 70-80% of core biopsy cellularity
  - **Virtual absence of storage iron**
  - **Hypercellular bone marrow** with essentially unremarkable background trilineage hematopoiesis
  - ClonoSEQ: **4 dominant sequences** suitable for monitoring

# Case Review: CRS

- CT CAP shows a **retroperitoneal mass concerning for extramedullary disease**
- 02/2024: admitted for **teclistamab step-up dosing**
  - Day 5 dose: Patient developed **tachycardia with a MAP in the 70's on vasopressors**
- 1/20/24 infectious workup:
  - **Blood cultures:** ordered
  - **UA:** negative for infection
  - **CXR:** negative for infection
  - **Lactate:** 4.6
  - **CRP:** 247
  - **MRSA PCR:** neg
  - **MDR test/candida PCR:** neg
  - **Beta-glucan:** negative
  - **Strep pneumonia/legionella urinary antigens:** negative
  - **Nasopharyngeal respiratory panel/Covid-19 PCR:** negative
  - **Thyroid labs:** normal
  - **ProBNP:** 2,144
  - **ECG:** sinus tachycardia, 121 BPM, QTc 443 ms
  - **Echocardiogram:** LVEF 45%

BPM = beats per minute; CAP = chest, abdomen, and pelvis; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CXR = chest x-ray; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; MDR = multidrug-resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; PCR = polymerase chain reaction; QTc = corrected QT interval; UA = urinalysis

# What Happened Next?

- Patient started on **empiric cefepime 2 g IV q8h**.
- Started on **vasopressin 0.03 units/min IV** to maintain **MAP >65** and **norepinephrine 0.2–0.4 mcg/kg/min IV** to maintain **MAP >65**
- Continued **prophylactic acyclovir**
- Over the next 2 days:
  - s/p **tocilizumab 800 mg IV × 1 dose** (dose #1) at 21:47 PM → **ongoing hypotension**
  - s/p **tocilizumab 800 mg IV × 1 dose** (dose #2) at 11:30 AM the following day (<48 hours later)
- **Infectious workup broadened**: EBV, *Rickettsia*, *Ehrlichia/Anaplasma*, *Babesia*, and *Francisella tularensis* testing → all negative
- Patient escalated to **cefepime, metronidazole, and vancomycin**
- **Vasopressor support** was subsequently **discontinued**, and patient was eventually **de-escalated from antibiotics**

EBV = Epstein-Barr virus; IV = intravenous; MAP = mean arterial pressure; ppx = prophylaxis; q8h = every 8 hours; s/p = status post

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