

Cytokine Release Syndrome With Bispecific Antibodies:

A Pharmacist's Guide to Safe Management



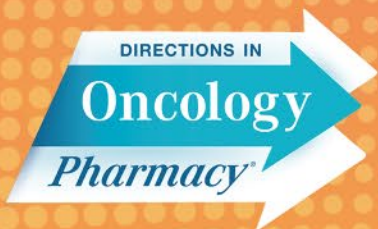
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Faculty and Staff Disclosures

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This activity is approved for 1.0 contact hour (0.10 CEU) under the ACPE universal activity number 0290-0000-24-252-L01-P.

Release Date: October 19, 2024

Activity Type: Application

Fee: Free



This activity is supported by MJH Life Sciences®, the parent company of *Pharmacy Times*® and *PTCE*.



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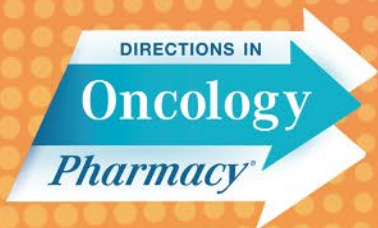
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Educational Objectives

After completion of this activity, participants will be able to:

- Identify patients at risk for cytokine release syndrome (CRS) by assessing factors related to the disease, patient characteristics, and treatment modality
- Implement evidence-based strategies for the prevention and management of CRS according to severity of the reaction
- Explore pharmacist-driven strategies to improve the safe administration of bispecific antibodies in relation to CRS



Pretest Questions



Pretest Question 1

In addition to fever, which of the following is one of the most common signs of cytokine release syndrome (CRS)?

- A. Hypotension
- B. Vomiting
- C. Confusion
- D. Seizures



Pretest Question 2

LD is a 67-year-old man who is receiving talquetamab for his multiple myeloma. He calls the cancer center the day after receiving his talquetamab to report a fever of 101.7 °F and difficulty breathing. Which is the most appropriate strategy to manage his suspected grade 2 CRS?

- A. Instruct him to take acetaminophen and call back if his fever returns.
- B. Direct him to the emergency department for workup and management of CRS.
- C. Inform him that his symptoms will likely resolve without intervention.
- D. Permanently discontinue and record talquetamab as a patient allergy.



Pretest Question 3

Your pharmacy department is considering formulary addition of tarlatamab, a new bispecific antibody for patients with small cell lung cancer. Which is an important pharmacy consideration regarding CRS administration and safety?

- A. One-time infusion of cells mitigates risk of CRS.
- B. Risk Evaluation and Mitigation Strategies enrollment is required.
- C. Develop product-specific CRS management guidelines/policies.
- D. Continuous infusion of the drug mitigates risk of CRS.



Pretest Question 4

Before participating in this activity, confident are you with the recognition and management of CRS from bispecific antibody therapy?

- A. Not at all
- B. Somewhat
- C. Moderately
- D. Very
- E. Extremely



Pathophysiology of CRS



But First, The Why?

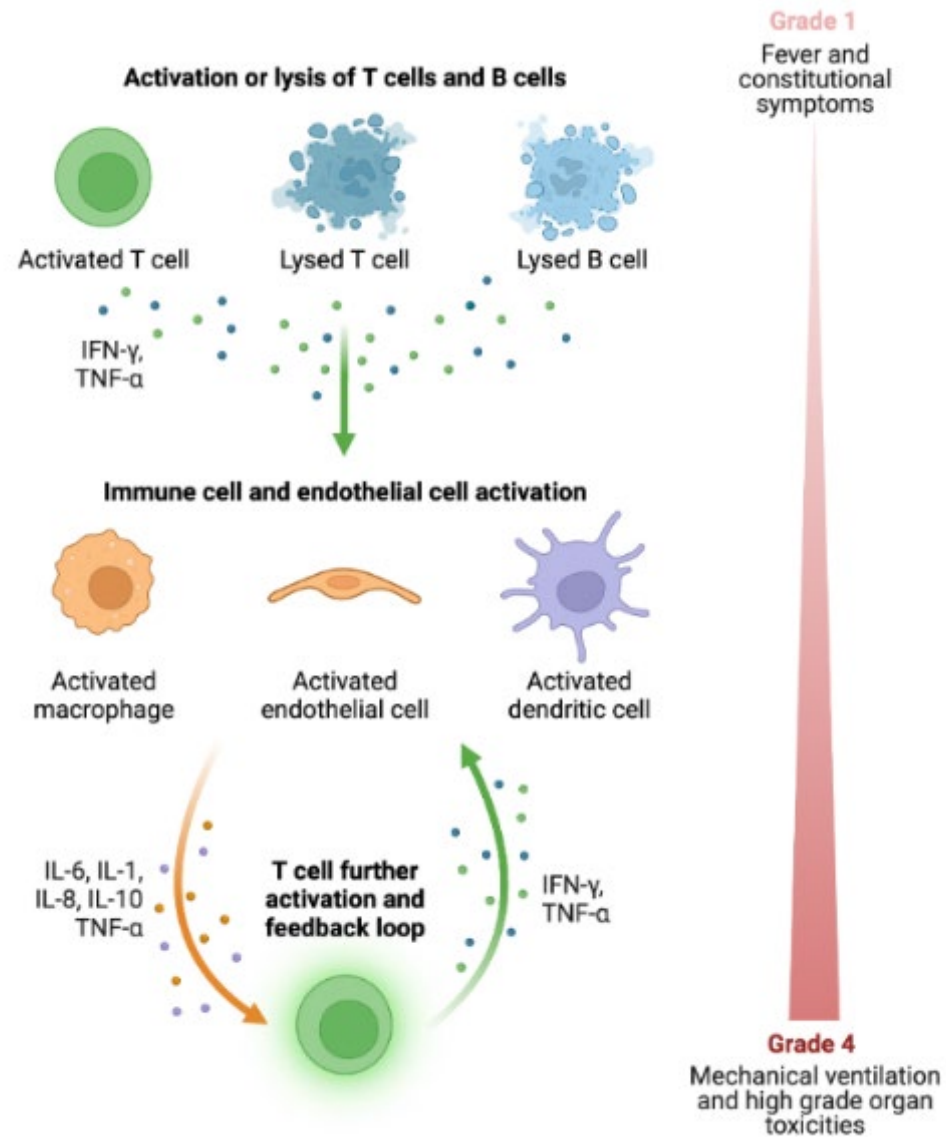
- Pharmacists have appreciated many treatment advances in hematology and oncology, including approvals of novel immunotherapies (eg, bispecific antibodies [BsAbs])
- With novel immunotherapies, significant new toxicities have emerged, including cytokine release syndrome (CRS)
- CRS can be fatal if not managed appropriately and in a timely manner



Cytokine Release Syndrome

- Systemic inflammatory response driven by the release of inflammatory cytokines due to immune activation
- First defined in the 90s with the utilization of OKT3 (monoclonal Ab immunosuppressant), which elicited strong release of cytokines in kidney transplant patients
- Symptoms can range from mild to more severe
- Result in laboratory abnormalities: cytopenias, kidney and liver function, coagulopathies, and a high C-reactive protein

Pathophysiology of CRS



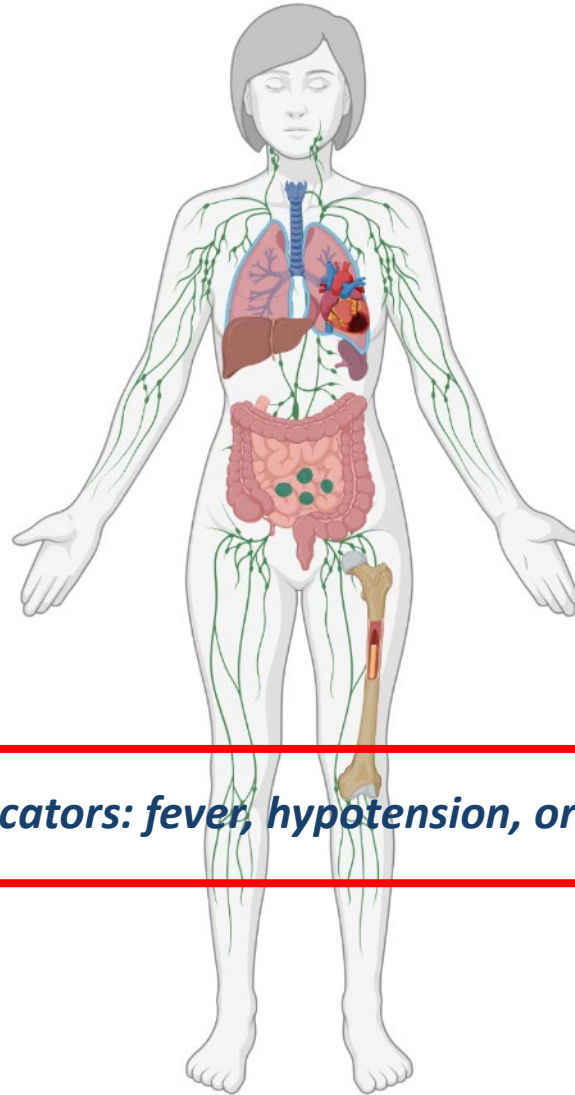
Presentation

Tachycardia
Hypotension
Troponin elevation
Arrhythmia
Acute heart failure

Hepatomegaly
Hypofibrinogenemia
Liver failure

Headaches
Confusion
Hallucinations
Delirium

Fever
Fatigue
Anorexia



Cytopenias
Coagulopathy
Febrile neutropenia
DIC

Tachypnea
Hypoxia
Respiratory failure

Myalgia
Arthralgia
Rash
Edema

Nausea
Vomiting
Acute kidney failure

DIC, disseminated intravascular coagulation.

Shimabukuro-Vornhagen A et al. *J Immunother Cancer*. 2018;6(1):56; Image created with BioRender.

CRS: Risk Factors

Drug-target-disease factors

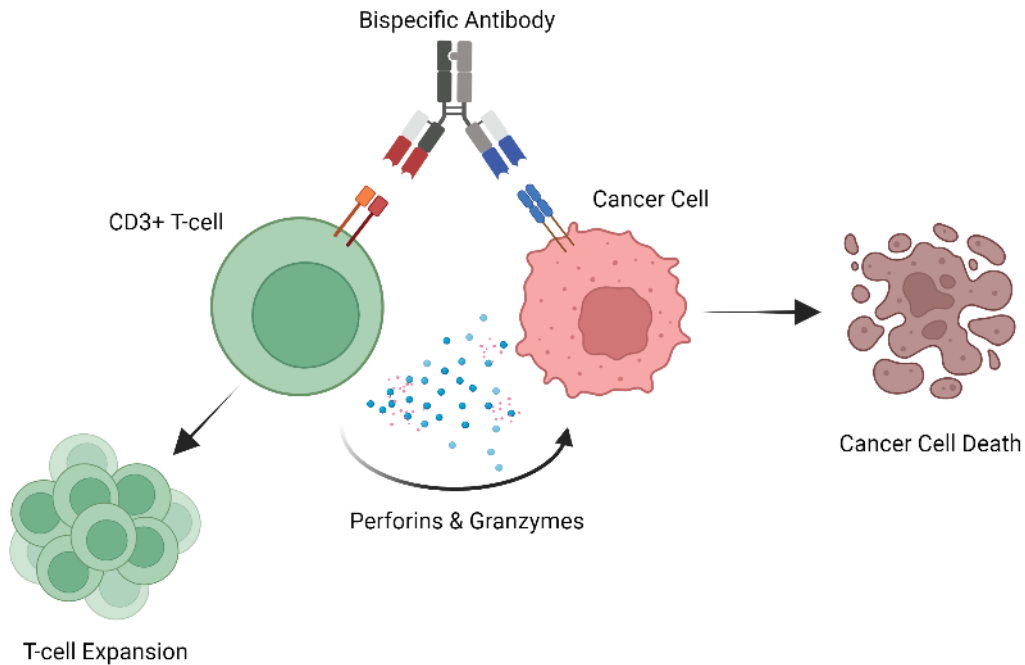
- Tumor antigen affinity
- CD3 affinity
- Tumor burden
- Expression level
- Target accessibility
- Indication
- Cell types

Individual patient factors

- Obesity
- Hyperlipidemia
- Hypertension
- Age
- Smoking
- Endothelial dysfunction and inflammation

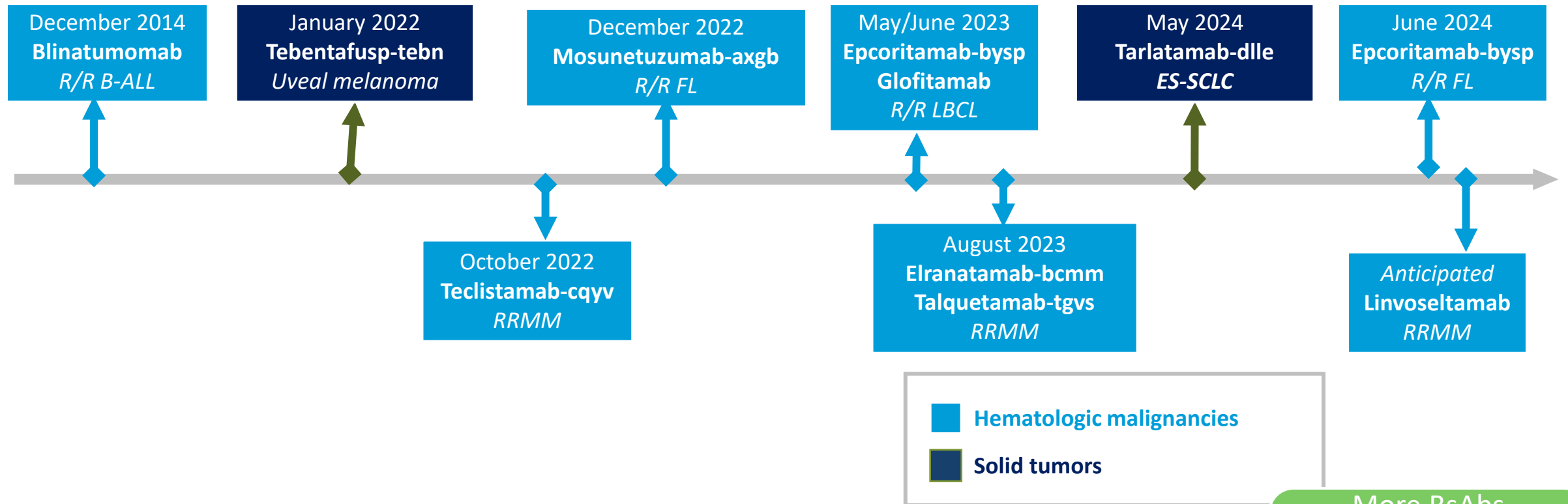


What Are Bispecific Antibodies?



- 2 distinct antigen binding sites that can exert multiple mechanisms of action at the same time
- Binding results in:
 - Immune cell recruitment mediated by the release of perforins and granzymes, leading to cell death
 - Interference with receptor signaling
 - T-cell expansion resulting in increased immune response

Bispecific Antibodies Approvals at a Glance



B-ALL, B-cell acute lymphoblastic leukemia; FL, follicular lymphoma; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; RRMM, relapsed/refractory multiple myeloma; ES-SCLC: extensive-stage small cell lung cancer.

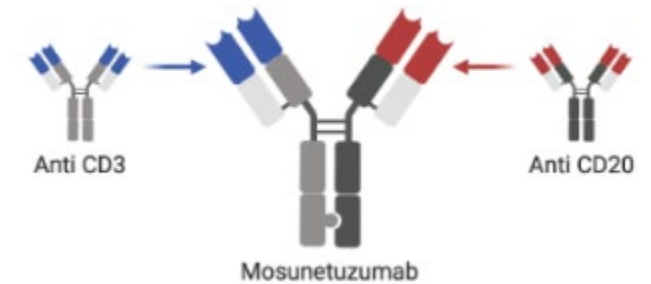
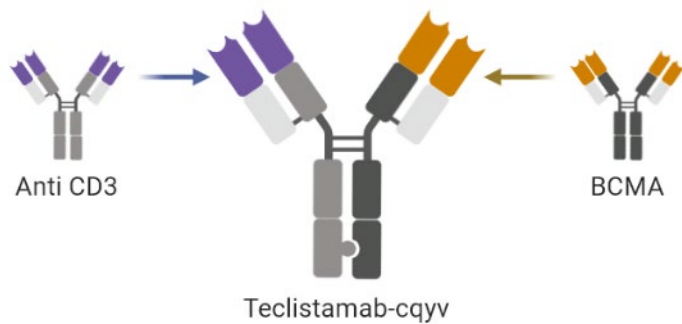
Oncology (cancer)/hematologic malignancies approval notifications. FDA. Updated August 20, 2024. Accessed October 16, 2024. www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications; Liu J, Zhu J. *Int Immunopharmacol*. 2024;138:112609.

More BsAbs anticipated, especially in the solid tumor space!

Bispecific Antibodies

- Current T-cell engagers dually target CD3 and:

CD19	GP100	CD20	BCMA	GRPC5D	DLL3
• blinatumomab	• tebentafusp	• epcoritamab • glofitamab • mosunetuzumab	• elranatamab • linvoseltamab • teclistamab	• talquetamab	• tarlatamab



Klein C et al. *Nat Rev Drug Discov.* 2024;23(4):301-319; Images created with BioRender.

Bispecific Antibodies in Hematology

Agent	Cancer type	REMS program?	Ramp-up interval	Admission recommended with ramp-up?
Blinatumomab	ALL	Removed 2022	7 days	☒
Elranatamab	Myeloma	☒	Days 1, 4, 8	☒
Epcoritamab	DLBCL, FL		Weekly x 3	☒
Glofitamab	DLBCL		Day 1 obinutuzumab, then weekly x 2	☒
Mosunetuzumab	FL		Weekly x 3	
Teclistamab	Myeloma	☒	Days 1, 4, 7	☒
Talquetamab	Myeloma	☒	Days 1, 4, 7, ± 10	☒

All products recommend steroid, antipyretic, and H1 antagonist premedication with ramp-up.

DLBCL, diffuse large B-cell lymphoma; REMS, Risk Evaluation and Mitigation Strategies.

Blincyto. Prescribing information. Amgen Inc; 2024; Elrexfio. Prescribing information. Pfizer Inc; 2023; Epkinly. Prescribing information. Genmab US, Inc; 2024; Columvi. Prescribing information. Genentech; 2023; Lunsumio. Prescribing information. Genentech; 2022; Tecvayli. Prescribing information. Janssen Biotech, Inc; 2024; Talvey. Prescribing information. Janssen Biotech, Inc; 2023; Pradhan SM. Supplement approval for Blincyto. FDA. December 5, 2022. Accessed October 16, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/125557Orig1s025ltr.pdf

Details of CRS With BsAbs in Hematology

Agent	Study	CRS		Median time to CRS onset, hours
		All (%)	Grade ≥ 3 (%)	Any grade
Elranatamab	MagnetisMM-3	56	0	48
Epcoritamab	EPCORE NHL-1	50	2.5	20
Glofitamab	NP30179	63	4	13.5
Mosunetuzumab	GO29781	44	2	5-27
Teclistamab	MajesTEC-1	72	0.6	48
Talquetamab	MonumenTAL-1	77	3	48
Linvoseltamab	LINKER-MM1	57	2	11

****Key takeaway**:** CRS generally occurs earlier and tends to be less severe than other agents.

Bispecific Antibodies in Oncology

Agent	Cancer type	REMS program?	Ramp-up interval	Admission recommended with ramp-up?
Tebentafusp	Uveal melanoma	N/A	Days 1, 8, 15	☒
Tarlatamab	SCLC	N/A	Days 1 and 8	☒

All products recommend steroid, antipyretic, and H1 antagonist premedication with ramp-up.

Details of CRS With BsAbs in Oncology

Agent	Study	CRS		Median time to CRS onset, hours
		All (%)	Grade ≥ 3 (%)	Any grade
Tebentafusp	IMCgp100-202	89	1	NR
Tarlatamab	DeLLphi-301	61	6	13.1 hours

****Key takeaway**:** CRS generally occurs earlier and tends to be less severe than other agents.



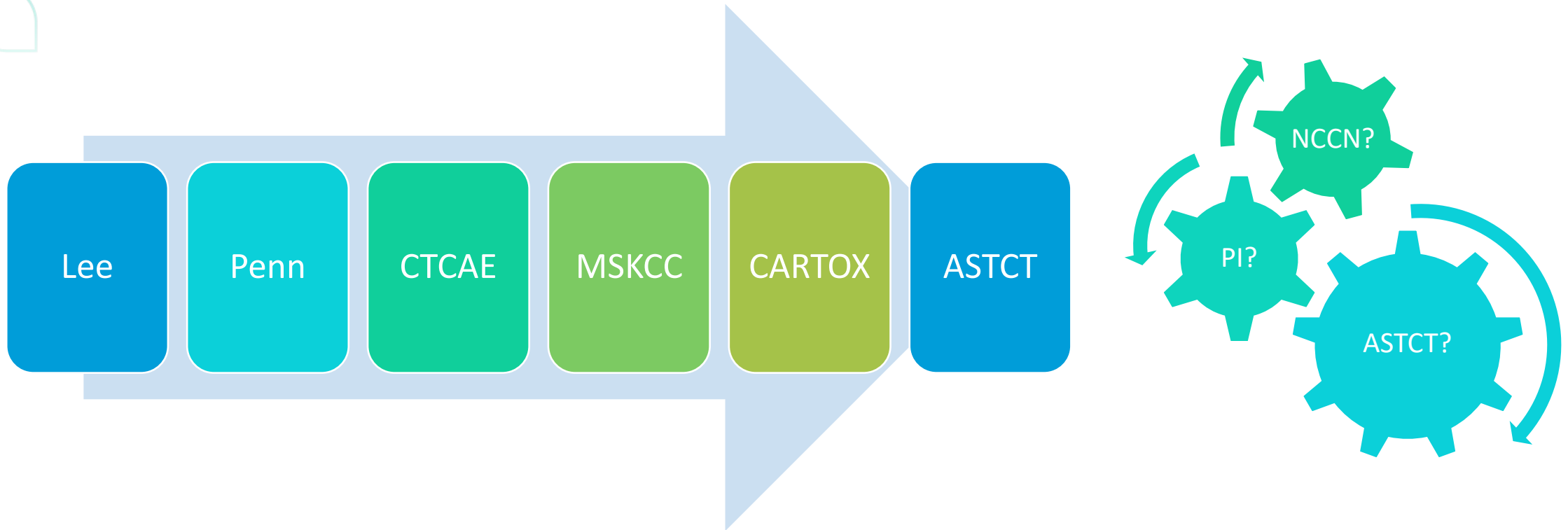
Prevention, Recognition, and Management of CRS



Prevention

- Workup
 - Required
 - Comprehensive physical examination
 - Routine laboratory testing: complete blood count, complete metabolic panel, lactate dehydrogenase +/- ferritin, C-reactive protein
 - Optional
 - Cardiac workup: baseline cardiac ultrasound or multigated acquisition scan
- Proximity to treatment facility at least during step-up dosing
- Patient and care partner education
 - Overview of toxicities
 - Home monitoring of vitals and symptoms
 - When and how to call the health care team
- Supportive care medications with steroids, antipyretics, and H1 antagonists

CRS Grading: An Evolving Tale



ASTCT, American Society for Transplantation and Cellular Therapy; CARTOX, CAR T-Cell Therapy–Associated Toxicity; CTCAE, Common Terminology Criteria for Adverse Events; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; PI, prescribing information.

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

ASTCT Guidelines: CRS Grading

Grade	Presenting symptoms
1	Temperature $\geq 100.4^{\circ}\text{F}$
2	Temperature $\geq 100.4^{\circ}\text{F}$ with: • Hypotension responsive to fluids, not requiring vasopressors, and/or • Oxygen requirement of low-flow nasal cannula or blow-by
3	Temperature $\geq 100.4^{\circ}\text{F}$ with: • Hypotension requiring 1 vasopressor with or without vasopressin, and/or • Oxygen requirement of high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask
4	Temperature $\geq 100.4^{\circ}\text{F}$ with: • Hypotension requiring multiple vasopressors (excluding vasopressin), and/or • Oxygen requirement of positive pressure (ie, CPAP, BiPAP, intubation, mechanical ventilation)

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure.

CRS Management

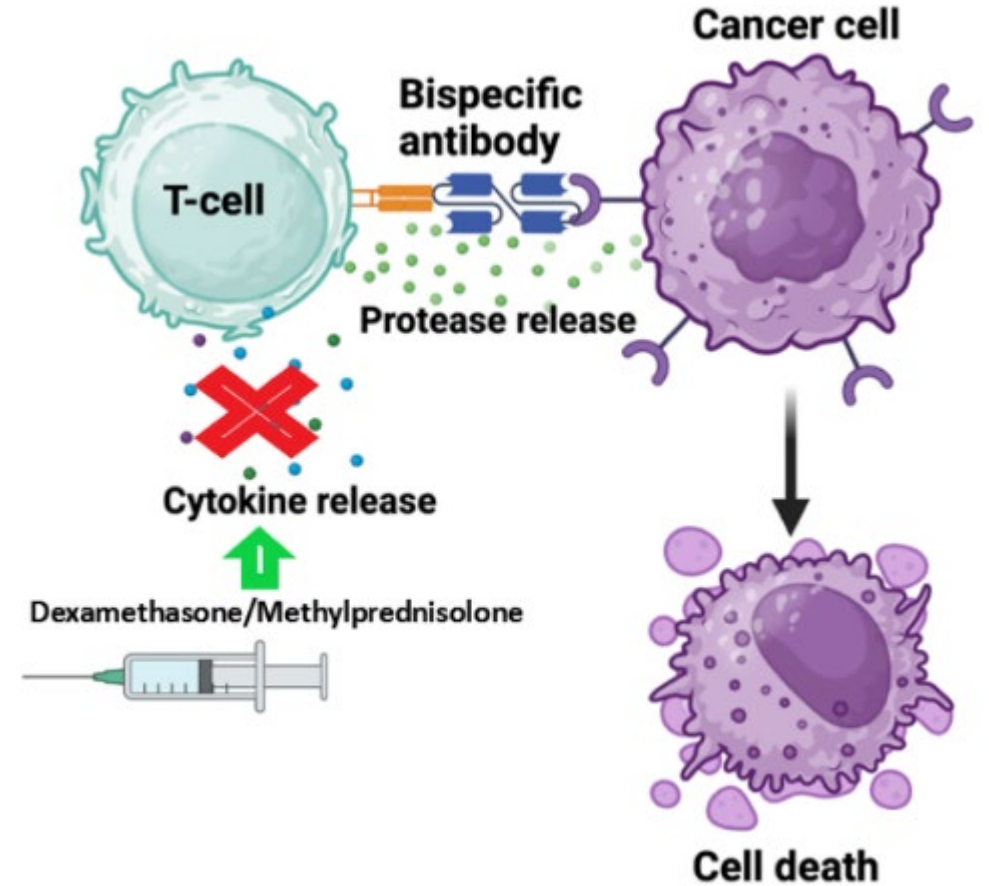
Grade	Site of care	Management
1	OP/IP	• Acetaminophen 650-1000 mg orally, repeat if recurrent fever, $\geq 6-8$ hours if clinically stable • Oral hydration • Check temperature every 1-2 hours and other vitals. If OP, should notify team if blood pressure drops >10 mm Hg below baseline and <90 mm Hg systolic, new weakness, confusion, dizziness or hypoxia ($<90\%$) • Consider dexamethasone if refractory/recurrent fever ($<6-8$ hours) • Consider tocilizumab in cases of protracted fever (>48 hours despite steroids)
2	IP floor	• Acetaminophen 650-1000 mg as needed, up to 3-4x daily • Dexamethasone 10 mg every 12 hours • IV fluids and supplemental oxygen as needed • Consider tocilizumab if persistent symptoms despite IV fluids and steroids
3	IP floor or ICU	• Acetaminophen 1000 mg IV as needed up to 3-4x daily when safe • Dexamethasone 10 mg IV every 6 hours, until resolution to grade ≤ 1, followed by taper • Evaluate for sepsis and consider empiric antibiotics • Administer tocilizumab
4	ICU	• Acetaminophen 1000 mg IV as needed up to 3-4x daily when safe • Dexamethasone 20 mg IV every 6 hours, until resolution to grade ≤ 1, followed by taper • Administer tocilizumab

ICU, intensive care unit; IP, inpatient; IV, intravenous; OP, outpatient.

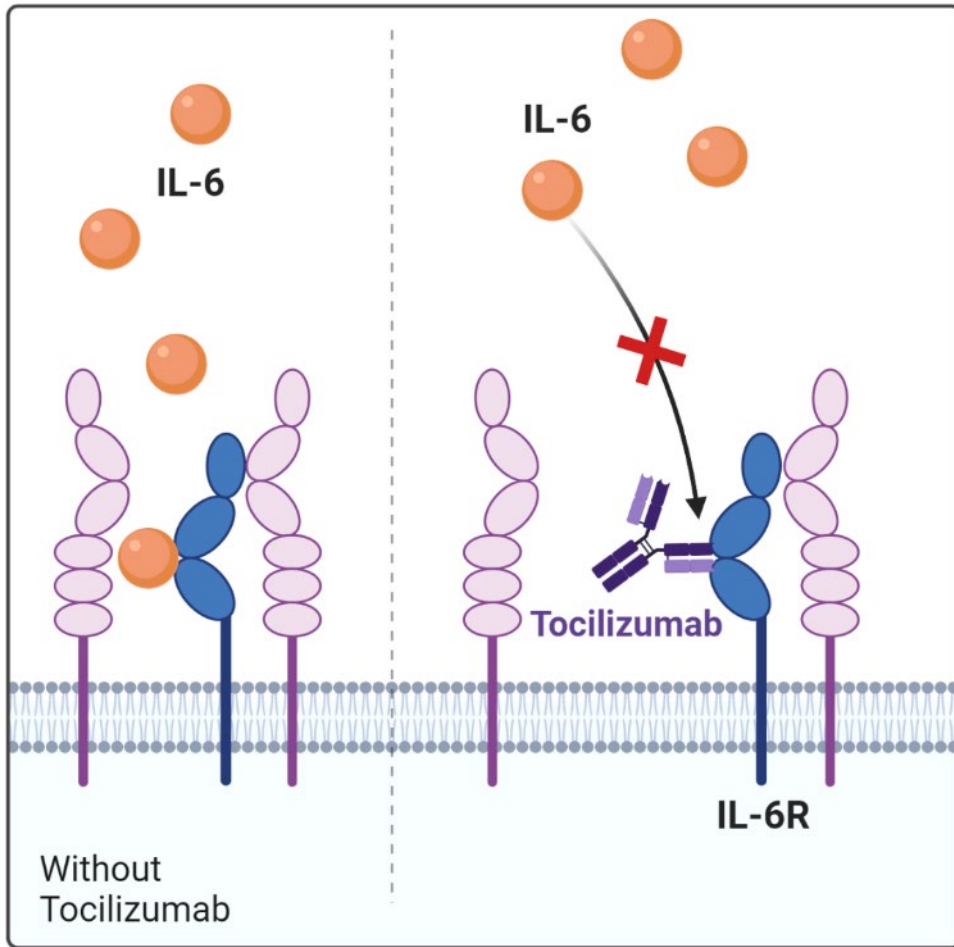
Crombie JL et al. *Blood*. 2024;143(16):1565-1575.

CRS Treatment: Steroids

- Responsible for decreased production of inflammatory mediators
- Can reduce incidence of severe CRS
- Dexamethasone generally preferred due to a lower incidence of CRS than with other steroids
- Falchi L et al reported:
 - A reduction in CRS in patients receiving dexamethasone as a premedication (48.5%) vs in the non-dexamethasone cohort (73.2%)
 - A shorter time to CRS resolution
 - Less tocilizumab use

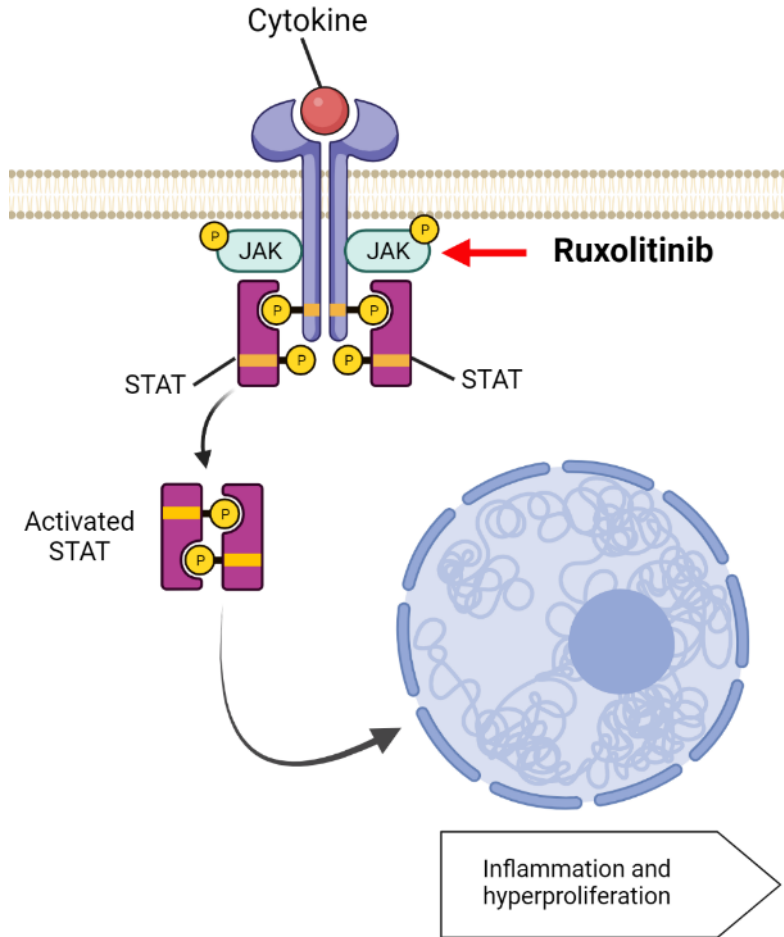


CRS Treatment: Tocilizumab



- Interleukin (IL)-6 receptor antagonist causes rapid symptomatic improvement
- 8 mg/kg (max 800 mg) actual body weight
- Should not be administered more than twice per CRS event (at least 8 hours apart) or 3x within a 6-week period

CRS Treatment: Investigational Agents



- **Siltuximab:** IL-6 antagonist
- **Anakinra:** IL-1 antagonist
- **Ruxolitinib:** JAK/STAT pathway antagonist



The Role of the Pharmacist in CRS Management

Role of the Pharmacist: Education

- Pharmacists play a key role in the education of both patients and the health care team
- Chemotherapy teaching
- REMS education
- CRS management

FOR THE PATIENT

Call your healthcare provider or get emergency help right away if you have any of these symptoms:

• Fever 100.4°F (38°C) or higher	• Trouble speaking, remembering things
• Trouble breathing	• Problems walking, weakness
• Chills	• Shaking, loss of balance, muscle spasms
• Dizziness or light-headedness	• Numbness and tingling
• Fast heartbeat	• Burning or stinging
• Headache	• Changes in hand/foot
• Agitation, trouble staying awake, confusion, disorientation	

IMPORTANT TO REMEMBER:

 If you have **any** of these symptoms, your doctor or seek emergency medical attention right away! These are not possible symptoms of bi-specific antibody therapy. Tell your doctors if you have any symptoms that bother you or does not go away.

You should always ask your doctor about other medications while on treatment.

FOR HEALTHCARE PROVIDERS

Bi-specific Antibody Patient Wallet Card
The University of Kansas Health System

Carry this card with you at all times.

Show this card to any health care provider involved in your care and if you go to the emergency room.



IMPORTANT SAFETY INFORMATION FOR PATIENTS RECEIVING BI-SPECIFIC ANTIBODIES

This patient has received: _____
 Name of Treating Oncologist: _____
 Office Phone Number: _____
 After Hours Phone Number: _____
 Step-up dose 1: _____
 Step-up dose 2: _____
 First treatment dose: _____

IMPORTANT SAFETY INFORMATION YOU SHOULD KNOW:
 Bi-specific antibody therapy can cause cytokine release syndrome (CRS) or neurotoxicity (ICANS) which may be fatal or life threatening. CRS may involve multiple organ systems.

Role of the Pharmacist: Policy

- Pharmacists play a key role in policy/protocol development
- CRS management protocols
- Serve on pharmacy and therapeutics committee
- REMS enrollment/management

▪ Management:		
CRS Grade	Signs or Symptoms	General Management
Grade 1	Fever or grade 1 organ toxicity	▪ Symptomatic management of constitutional symptoms & organ toxicities [IV fluids, antibiotics PRN] ▪ Consider checking a DIC panel and replacing fibrinogen if <100 mg/dL as needed ▪ For refractory or recurrent fevers dexamethasone 10 mg x1 can be considered. Additional doses can be considered every 24 hours until resolution of symptoms ▪ Consider tocilizumab 8 mg/kg (max 800 mg/dose) for persistent fever despite supportive care and dexamethasone (Refractory to supportive management x 24 hours OR lasting greater than 2 days). Can be repeated every 8 hours for up to 3 doses in a 24-hr period, max 4 doses total
	Hypotension	▪ IV fluid bolus 500-1000 mL normal saline, may repeat as necessary to keep SBP >90 mmHg ▪ If hypotension unchanged after 2 fluid boluses (maximum 2 L): consider additional intervention ▪ Consider rapid response and possible ICU transfer, start norepinephrine ▪ Obtain ECHO ▪ Administer dexamethasone 10 mg every 12 hours while symptoms persist ▪ Administer Tocilizumab 8 mg/kg (max 800 mg/dose) IV. Tocilizumab can be repeated every 8 hours for up to 3 doses in a 24-hr period, max 4 doses total if symptoms persist despite corticosteroids (4-6 hours after dose) or if clinically unstable ◦ If no improvement on tocilizumab after 2 doses within 24 hrs or rapid deterioration: anakinra 100 mg IV every 12 hours x 7 days (renally dose if CrCl <30 ml/min), if not responding may increase to 200 mg IV every 8 hours
	Hypoxia	▪ Use supplemental oxygen as needed to keep O2 sat >90% ▪ Administer tocilizumab as above

Role of the Pharmacist: Informatics

- Pharmacists play a key role in development of electronic health records
- Treatment plans: bispecifics
- CRS supportive care plans

The screenshot displays the Epic Report Viewer interface. At the top, the Epic logo is visible on the left, and navigation links for 'Orders Only', 'Orders', 'Remind Me', 'In Basket', 'My i-Vents', 'Epic Tip Sheets', and 'SHIELD' are on the right. Below the navigation bar, the title 'Report Viewer' is centered. A toolbar with icons for back, refresh, and document actions is present. The main content area is titled 'IP/OP HEME TECLISTAMAB'. Under the 'Protocol Summary' section, there are fields for 'Version Comment' (containing 'adding bactrim, updating dex dose') and 'Protocol Notes' (containing a reference to a study by Moreau P, et al.). The 'Protocol Types' section lists 'ONCOLOGY TREATMENT'. The 'Dosing' section includes several system default settings: a warning for weight differences, a warning for BSA differences, default formulas for CrCl (Cockcroft-Gault) and BSA (Mosteller), a 40% correction factor, and a default dosing option to use documented weight and BSA. The 'Target AUC' is set to 'None'. The 'Other Information' section lists 'Synonyms' as 'TECLISTAMAB' and 'MULTIPLE MYELOMA'.

Report Viewer

IP/OP HEME TECLISTAMAB

Protocol Summary

Version Comment
adding bactrim, updating dex dose

Protocol Notes
145.Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. New England J

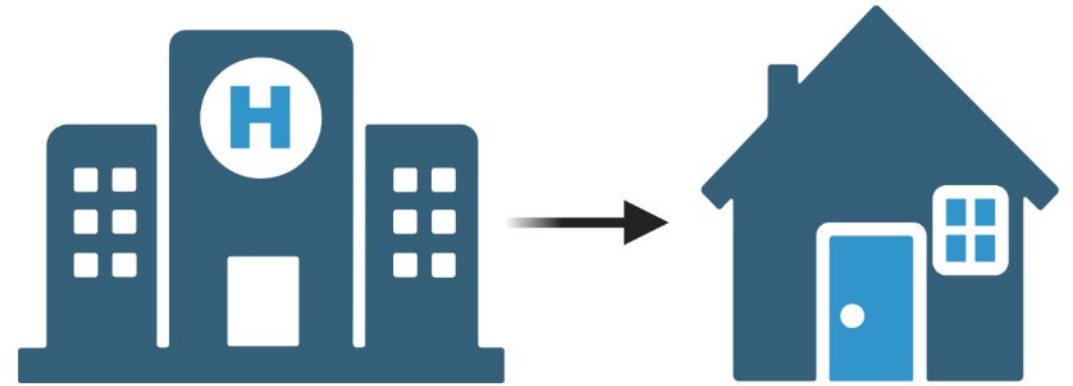
Protocol Types
ONCOLOGY TREATMENT

Dosing
Show a warning if the patient's documented weight differs from the treatment plan weight by: 10% (System Default)
Show a warning if the patient's documented BSA differs from the treatment plan BSA by: 10% (System Default)
Default CrCl Formula: MIN SCR 0.8 Cockcroft-Gault
Default BSA Formula: Mosteller (System Default)
Correction Factor: 40% (System Default)
Default Dosing Option: Use documented weight and BSA (System Default)
Target AUC: None

Other Information
Synonyms
TECLISTAMAB
MULTIPLE MYELOMA

Role of the Pharmacist: Operations

- **Procurement, handling, storage**
- **Order verification**
- **Medication reconciliation**
- **Adequate tocilizumab supply**
- **Transitions of care**
- **Quality**





Conclusions

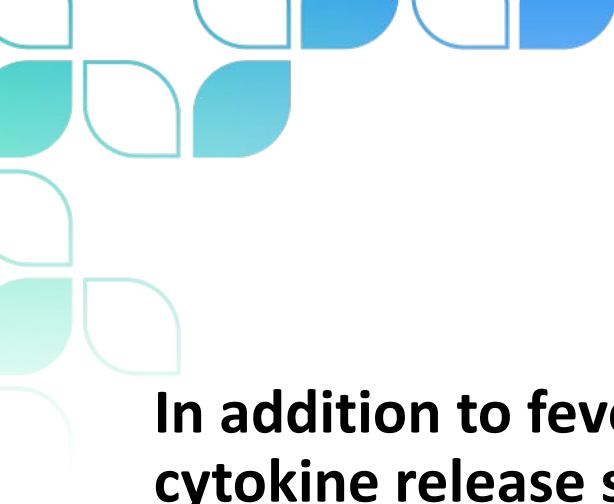
- CRS can occur with BsAb therapies, but important prevention and management strategies can be implemented to ensure success
- Pharmacists play a significant role in CRS recognition and management
- Pharmacists can be a key member of the multidisciplinary care team working through operational and practical challenges associated with these novel therapies

Additional Resources

Resource	Website
National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. Management of immunotherapy-related toxicities, version 1.2024	https://www.nccn.org/login?ReturnURL=https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf
Lee DW, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. <i>Biol Blood Marrow Transplant</i> . 2019;5(4):625-638.	https://www.sciencedirect.com/science/article/pii/S1083879118316914?via%3Dihub
Crombie JL, et al. Consensus recommendations on the management of toxicity associated with CD3 x CD20 bispecific antibody therapy. <i>Blood</i> .2024;143(16):1565-1575.	https://doi.org/10.1182/blood.2023022432
Mahmoudjafari Z, et al. Seamless Navigation of Bispecific Therapies: Optimizing Management and Outpatient Access With a Focus on Coordination. <i>J Adv Pract Oncol</i> . 2024:1-16.	https://doi.org/10.6004/jadpro.2024.15.8.15



Posttest Questions



Posttest Question 1

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- B. Vomiting
- C. Confusion
- D. Seizures



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- B. Risk Evaluation and Mitigation Strategies enrollment is required.
- C. Develop product-specific CRS management guidelines/policies.
- D. Continuous infusion of the drug mitigates risk of CRS.



Posttest Question 4

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- A. Not at all
- B. Somewhat
- C. Moderately
- D. Very
- E. Extremely

Thank you!

