Bispecific Antibody (BsAb) Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)/ Neurotoxicity Guidance

February 2024

Collaboration of VHA Oncology Field Advisory Board and the
VHA National Formulary Committee

The following guidance is based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic. It will be reviewed on a quarterly basis and revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT.

Table of Contents

Definitions

BiSpecific Antibodies (BsAb): Contains 2 different target specific units in one antibody molecule. In oncology, these BsAbs generally link malignant cells to immune cells, blocking cell growth and activating the immune system (T cells).
Bispecific T-Cell Engager (BiTE): A BsAb that engages tumor-associated antigens on malignant cells and surface molecules on T-cells
Cytokines: Proteins that are produced and secreted by most cells that act as messengers facilitating multiple functions including the inflammatory response. Examples of cytokines includes interleukin, interferon, and tumor necrosis factor.
Cytokine Release Syndrome (CRS): An exaggerated systemic inflammatory response triggered by the effects of T-cell engaging therapies like BsAbs that cause release of inflammatory cytokines. CRS symptoms range from mild flu-like symptoms to severe multi-organ failure.
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): Neurologic toxicity caused by the inflammatory actions of cytokines released after BsAb therapy causing disruption of the blood-brain barrier and accumulation of inflammatory cytokines in the central nervous system. ICANS is a diagnosis of exclusion after other possibilities have been ruled out.

BsAbs and Indications
Blinatumomab (BLINCYTO): Relapsed or Refractory CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL)
Elranatamab (ELREXFIO): Relapsed or Refractory Multiple Myeloma (BCMA target) [REMS program]
Epcoritamab (EPKINLY): Relapsed or Refractory large B-cell lymphoma (CD20 target)
Glofitamab (COLUMVI): Relapsed or Refractory large B-cell lymphoma (CD20 target)
Mosunetuzumab (LONSUMIO): Relapsed or Refractory follicular lymphoma (CD20 target)
Talquetamab (TALVEY): Relapsed or Refractory multiple myeloma (GPRC5D target) [REMS program]
Tebentafusp (KIMMTRAK): HLA-A*02:01 unresectable or metastatic uveal melanoma
Teclistamab (TECVAYLI): Relapsed or Refractory multiple myeloma (BCMA target) [REMS program]

CRS Background

Basic CRS Pathophysiology

Cytokine Release Syndrome (CRS) is an exaggerated systemic inflammatory response due to the binding of BsAb to its antigen on the surface of target cells, causing activation of immune (e.g. T-cells) and non-immune cells that results in the immense release of inflammatory cytokines, fever and multiorgan dysfunction. Cytokines, such as interleukins, interferons, and tumor necrosis factor help to regulate immune responses, hematopoietic development, and response to infectious agents and inflammatory stimulation. Cytokines contribute to many of the clinical indicators of CRS. Symptoms may be progressive.

CRS Presentation, Diagnosis

I. **Clinical Presentation**

- **Time Course**- highest risk is **minutes to hours** after step-up or induction infusions, but it might occur once patient is discharged.

Bispecific	**Median Time to CRS onset after most recent dose**	**Median Duration of CRS**
Blinatumomab	2 days	5 days
Glofitamab	14 hours	2 days
Epcoritamab	24 hours	2 days
Tebentafusp	Day of infusion	2 days
Mosunetuzumab	4-46 hours	3 days
Teclistamab	2 days	2 days
Elranatamab	2 days	2 days
Telquetamab	27 hours	17 hours

- **Flu-like symptoms**: Fever (≥38.0°C/<100.4°F) (not attributable to any other cause); nausea; fatigue; headache; rash; diarrhea, arthralgia, myalgia
- **Hypotension**
- **Systemic inflammatory response syndrome** (circulatory collapse; vascular leakage; peripheral and/or pulmonary edema; renal failure; cardiac dysfunction; multiorgan failure)
- **Respiratory symptoms**: cough; tachypnea; hypoxia, ARDS
- **Rash and Urticaria** (allergic reaction)
- **Low-grade CRS is common and high-grade is rare**

II. **Differential Diagnoses**

- Tumor Lysis Syndrome (TLS): discriminate based on lab findings: hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia with TLS
- Infection, Sepsis: may coexist with CRS and simultaneous treatment for both may be considered
- Tumor progression

CRS Presentation, Diagnosis (continued)

III. **Evaluation and Diagnosis**-Unspecific symptoms and difficult to diagnose.

A. Evaluation

- Physical Examination- to include temperature, blood pressure, pulse oximetry or arterial blood gas (or mixed venous blood gas/O2 saturation), examination of skin, heart and lungs
- Labs- 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. Do not wait for lab results to initiate t
- Imaging: Chest X-ray, cross-sectional imaging (e.g., CT scan), or echocardiogram as clinically indicated.

B. **Lab findings**: cytopenias, elevated creatinine, elevated liver enzymes, dysregulated coagulation parameters, increased C-Reactive Protein

- CRS Management (see Management Section below) does not require lab testing and should not be delayed waiting for lab results

CRS Grading and Management

CRS Management by Grade-CRS is not well described with BsAb therapy; consensus guidelines from ASCTC for CRS with CAR-T therapy are utilized. Severity is determined by hypotension and hypoxia[2]

- CRS with BsAbs is less severe than CRS with CAR T therapy.
- Early management of CRS may prevent escalation to a higher grade.
- For ALL Grades Hold BsAb therapy until CRS resolves then resume except for Grade 4
- If Outpatient, admit to inpatient if Grade >1 (Grade 1 might be managed as an outpatient). During initial step-up therapy, patient may need to be admitted to inpatient service depending on the BsAb.

CRS Grading and Management [1,2]

Grade	Management*
1 1. Temp >100.4F (not attributable to other causes) 2. Hypotension: None	• Symptomatic/Supportive Care • Antipyretics-Acetaminophen 650mg orally Q6 hours prn • Blood and urine cultures; initiate broad spectrum IV antibiotics as for neutropenic patients • IV hydration (for general support; if needed for hypotension treat as Grade 2) • If persistent or refractory fever (<3 days), manage as Grade 2
2 1. Fever>/=100.4F 2. Hypotension responsive to fluid bolus. May use 1 low dose vasopressor 3. O2 needs <6L	• Continue Symptomatic/Supportive Care as for Grade 1 • Include IV bolus and supplemental oxygen as needed; consider transfer to ICU if unresponsive to fluid bolus • Tocilizumab 8mg/kg IV over 1 hour (not to exceed 800mg/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 10mg IV every 8-12 hours. • If no improvement 24 hours after starting tocilizumab, manage as Grade 3
3 1. Fever >/=100.4 2. Hypotension requiring a vasopressor with or without vasopressin 3. O2 needs >6L (high-flow nasal canula, facemask, non-rebreather mask, or Venturi mask)	• 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 10mg IV every 6 hours for 3 days, and rapidly taper when symptoms improve. • Tocilizumab as per Grade 2 if maximum dose not reached and no improvement on high-dose steroids. If refractory, manage as Grade 4
4 1. Fever>/=100.4 2. Hypotension requiring multiple vasopressors excluding vasopressin 3. Positive Pressure Ventilation (CPAP, BiPAP, Intubation, or mechanical intubation)	• Admit to ICU • Discontinue Bispecific Antibody • Continue Supportive Care as in Grade 3 plus mechanical ventilation as needed • Initiate high-dose methylprednisolone at 500mg every 12 hours for 3 days, followed by 250mg every 12 hours for 2 days, followed by 125mg every 12 hours for 2 days, followed by 60mg every 12 hours until symptoms improve to Grade 1 • Tocilizumab as per Grade 2 if maximum dose not reached • If no improvement methylprednisolone 1000mg every 12 hours or other cytokine directed therapy (e.g. siltuximab).

* Inpatients receiving corticosteroids, consider antifungal prophylaxis

Monitoring for CRS[3]

I. Clinic/Outpatient
- A. Record vital signs daily
- B. Daily weights
- C. Daily CBC with differential and complete metabolic profile
- D. Coagulation parameters twice a week
- E. C-Reactive Protein and ferritin daily during step-up therapy and first full dose, then as needed
- F. Assess and Grade CRS at least daily and if a change in status in clinic

II. Inpatient/Intensive Care Setting
- A. During initial step-up therapy, patient may need to be admitted to inpatient service depending on the BsAb utilized.
- B. Vital signs every 4 hours (while awake if stable)
- C. Monitor oral and IV fluid inputs and outputs
- D. Weigh daily
- E. Daily CBC with differential and complete metabolic profile
- F. Coagulation parameters twice a week
- G. C-Reactive Protein level daily during step up then continue until CRS resolves (i.e. all signs and symptoms leading to diagnosis are resolved)
- H. Assess and Grade CRS every 12 hours and whenever there is a change; call covering physician with any changes
- I. Cardiac/hemodynamic monitoring by telemetry

III. Home Setting
- A. Provide Team contact information and guidance on when to call for symptoms
- B. Oral temperature every evening; if patient feels unwell or lethargic, increase oral temperature to three times a day
- C. Encourage oral fluid intake (e.g. 1.5-2.0 liters per day as tolerated)

ICANS/Neurologic Toxicity Background

Pathophysiology

Similar to cytokine release syndrome (CRS), the pathophysiology of immune effector cell-associated neurotoxicity syndrome (ICANS) starts with the production of pro-inflammatory cytokines by chimeric antigen receptor (CAR) T cells and the activation of bystander immune cells such as macrophages in the tumor microenvironment.
Inflammatory cytokines and chemokines produced by CAR T cells and myeloid cells diffuse into the bloodstream and, eventually, result in disruption of the blood–brain barrier (BBB), with accumulation of cytokines and CAR T cells in the CNS together with activation of resident microglial cells.[8]

The neurologic toxicity (NT) of BsAb therapy has been described as ICANS, which was coined for the neurologic toxicity associated with CAR-T cell therapy. This description may not be accurate as the pathophysiology and clinical findings of BsAb-related vs. CAR-T cell therapy-related neurologic toxicity are not believed to be the same. In both settings, these toxicities are thought to be related to T-cell overactivation. Yet CAR-T cells are known to cross into the CNS, leading to increased protein and cytokine levels.[6] BsAb, especially those with the IgG backbone, are not expected to cross into the CNS. Therefore, neurologic adverse events within the BsAb clinical trial setting have been mild and rare events.

Although the neurotoxicity intensity and severity may vary among these immune therapies, there are similar management strategies. This document will focus on ICANS with noted differences that may exist for BsAb.

ICANS/Neurologic Toxicity Presentation, Diagnosis, Grading

I. **Clinical Presentation**

ICANS is typically associated with CRS, though few patients may develop ICANS without previous or concomitant CRS, ICANS may develop after CRS symptoms have resolved; rarely both complications can occur simultaneously. ICANS will typically manifest within 2-3 days of the onset of CRS. ICANS can present with varying degrees of neurologic changes. Initial presentation may be subtle with loss of attentiveness and language dysfunction. Other symptoms may include delirium, dysphasia, lethargy, difficulty concentrating, agitation, confusion, aphasia, depressed level of consciousness, encephalopathy, seizures, tremor, ataxia, loss of coordination or cerebral edema.

II. **Diagnosis**

- The diagnosis of ICANS should be considered while all other potential causes are being ruled out
- Suspect ICANS if new or worsening neurologic symptoms in the setting of recent immune effector cell (IEC), such as CAR-T cell therapy or BsAb therapy
- Initial presenting symptoms could be subtle as loss of attentiveness and/or speech dysfunction or tremors
- Additional investigation to r/o other potential causes should include review of concomitant medications or receipt of recent CNS-acting agents (i.e. opiates, benzodiazepines). Investigation may include head CT or brain MRI, lumbar puncture to r/o infectious causes

III. **Grading**

The ASTCT grading scale for CAR-T cell therapy-associated ICANS should also be used for BsAb therapy.

The process of grading ICANS involves evaluating the most severe symptom a patient has experienced, secondary to ICANS, among five domains: encephalopathy, level of consciousness, seizure, motor findings and elevated intracranial pressure/cerebral edema. Utilizing the ICE (**I**mmune effector **C**ell-associated **E**ncephalopathy) score, a 10-point encephalopathy assessment tool, patients are graded on the most severe symptom secondary to ICANS in five components: orientation, naming, following commands, writing and attention.

ICANS/Neurologic Toxicity Assessment, Management & Monitoring

I. Inpatient setting

A. Daily clinical assessment for ICANS/Neurologic Toxicity includes:

- Physical exam and review of vital signs
- Neurologic examination.
    - Initial signs may include subtle deficits in attention, changes in alertness and language
    - Grade neuro assessment with ICE score and neurotoxicity domain of ASTCT
    - Repeat at least twice daily and with any change in status
    - Consider Neurology consult
- Assess for signs of increased intracranial pressure. Consider Ophthalmology consult to perform fundoscopy
- Labs should include CBC, chem profile, PT, aPTT, fibrinogen, ferritin and CRP
- Monitor and correct severe hyponatremia
- Consider antiseizure prophylaxis, such as a non-sedating antiepileptic agent, for those at higher seizure risk, such as previous seizure history, CNS disease, EEG findings or brain lesions[2]
- Multidisciplinary discussion regarding clinical care setting (e.g. evaluate need for intensive clinical care)
    - Consider transfer to intensive care setting if progressive mental status changes, suspected cerebral edema, status epilepticus and/or patients with grade 3 or 4 neurotoxicity
    - Consider Neurology consult
    - Consider Ophthalmology consult to perform fundoscopy

B. Rule out other possible etiologies for neurologic changes. Additional evaluations may include:

- Concomitant medications
- Head CT or brain MRI for $\geq$ Grade 2 neurotoxicity
- Lumbar puncture to evaluate CSF to r/o suspicion of infection and $\geq$ Grade 3 neurotoxicity

ICANS/Neurologic Toxicity Assessment, Management & Monitoring (continued)

Management and Treatment

ASTCT ICANS Consensus Grading & Management by Grading for Adults

Neurotoxicity Grade	Grade 1	Grade 2	Grade 3	Grade 4
	ICE score* 7-9	**ICE score*** 3-6	**ICE score*** 0-2	**ICE score*** 0 (patient unarousable; unable to perform ICE)
	And/or depressed level of consciousness: Awakens spontaneously	**And/or depressed level of consciousness:** Awakens to voice	**And/or depressed level of consciousness:** Awakens only to tactile stimulus	**Depressed level of consciousness:** Unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma.
			Seizure: Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	**Seizure:** Life-threatening prolonged seizure (> 5 min); or repetitive clinical or electrical seizures without return to baseline in between
			Elevated ICP/cerebral edema: Focal/local edema on neuroimaging	**Motor findings:** Deep focal motor weakness such as hemiparesis or paraparesis
				Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad
Management of ICANS without CRS	Supportive care with IV hydration and aspiration precautions	Supportive care with IV hydration and aspiration precautions; Administer dexamethasone 10 mg IV x 2 (or equivalent) and reassess; Repeat every 6-12 hours if no improvement; Rapidly taper once symptoms improve to Gr 1	Transfer to ICU; Administer dexamethasone 10mg IV every 6-12 hours (or equivalent)	Transfer to ICU; Consider mechanical ventilation for airway protection; Administer high-dose methylprednisolone IV 1000 mg one to two times daily for 3 days; if not improvement, can increase to two to three times daily; Continue corticosteroids until Gr 1, then taper as appropriate
Management of ICANS with Concurrent CRS	Above care + Tocilizumab 8mg/kg IV over 1 hour. Repeat every 8 hours as needed. Limit to maximum of 3 doses/24-hr period	Above care + Transfer to ICU if also has Gr 2 CRS; Administer tocilizumab as Gr 1	Above care + Administer tocilizumab as Gr 1	Above care + Administer tocilizumab as Gr 1

*** ICE Scoring. Immune Effector Cell-Associated Encephalopathy (ICE) Assessment and Scoring**

Scoring Elements	Evaluation/Assessment	Score
Orientation	Patient is oriented to year, month, city, hospital	4 points
Naming	Ability to name/identify specific objects	3 points
Following Commands	Ability to follow simple commands	1 point
Writing	Ability to write a standard sentence	1 point
Attention	Ability to count backwards from 100 by 10	1 point

The sum of all elements totals the ICE score, a component of ASTCT ICANS Consensus Grading

Note that suggested management based upon recommendations for CAR-T cell therapy-associated ICANS

- Refer to prescribing information and clinical data for the BsAb product to ascertain potential risk for ICANS/neurotoxicity. Pay particular attention to:
    - Whether BsAb should be held, dose-reduced or discontinued
    - Supportive measures are recommended (i.e. IV hydration, corticosteroids)
    - Specialty consults suggested or transfer to intensive care unit

ICANS/Neurologic Toxicity Assessment, Management & Monitoring (continued)

II. Intensive Care setting

- Reserve intensive care setting for patients with worsening condition likely secondary to cerebral edema, status epilepticus and/or grade 3-4 ICANS/neurotoxicity. Patients will need close monitoring of neurologic, respiratory and cardiovascular functions.

III. Patient education on ICANS/Neurologic toxicity

- Discuss the possibility of ICANS/neurotoxicity associated with BsAb therapy
- Inform the patient/caregiver to be aware of signs and symptoms, which may include headache, confusion/ disorientation, attention loss/unable to focus, trouble speaking, sleepiness, problems with memory, dizziness, mental status changes.
- Advise patient and/or caregiver to immediately contact their provider should they experience any signs or symptoms that could indicate neurologic toxicity
- Instruct patient/caregiver to avoid driving or operating machinery if experiencing signs and symptoms related to neurotoxicity

Communication Plan for Management of CRS and ICANS/Neurologic Toxicity

- Prior to patient admission, ensure communication with nursing, pharmacy, intensive care unit.
- Consider notification to neurology service, as consult may be necessary.

I. Oncology Service

- ☐ Provider enters necessary forms (i.e. Prior Auth Drug Request and/or REMS forms)
- ☐ Orders entered for CRS and ICANS medications, including support medications need on PRN basis
- ☐ Notify inpatient medical team attending or service chief about plan to admit for CRS/ICANS management

II. Nursing

- ☐ Education for nurses (clinic and inpatient)
- ☐ Checklist for nursing (clinic and inpatient)
- ☐ REMS training and requirements met, if necessary (not every BsAb has a REMS)

III. Intensive care/step down units

- ☐ Notified of patient treatment on site (clinic or inpatient) with potential for CRS and/or ICANS
- ☐ Participate in multidisciplinary discussion for symptomatic patients
- ☐ Assist/manage transfer of care

IV. Pharmacy

- ☐ Education for pharmacists
- ☐ Checklist for pharmacy
- ☐ Support medication such as acetaminophen and corticosteroids should be available for immediate administration
- ☐ Necessary drugs in stock, including at least 2 doses of tocilizumab if available or can be obtained quickly
- ☐ Necessary forms completed (i.e. REMS)
- ☐ REMS training and requirements met, if necessary (not every BsAb has a REMS)

V. Inpatient Medicine Teams

- ☐ Consider education for medicine teams

VI. Patient /caregiver

- ☐ Educate on signs and symptoms of CRS
- ☐ Educate on signs and symptoms of ICANS/neurologic toxicity
- ☐ Provide Patient Wallet Card (pertaining to receipt of immune therapy) and/or Medication Guide from Prescribing Information

  Note: Patient Wallet Cards are not a part of FDA labeling for every BsAb

Nursing Education / Checklist

Administration

Step-Up Dosing: Since CRS occurs most often in the first several days of BiTE therapy (but can occur at any time during therapy), the strategy of using step-wise increases during initial administration helps to decrease the risk of CRS. Package labels recommend step-up dosing in the inpatient setting due to long observation times for CRS or ICANS. CRS symptoms tend to subside with subsequent doses.

Pre-Medication & Supportive Meds: The use of pre-medications and supportive medications is drug-specific and is outlined in the package label. Refer to Page 14 for chart outlining supportive medications, including pre-meds. There may be differences in recommended pre-medications during initial step-up dosing, during subsequent cycles, and after the occurrence of CRS. In general, pre-medication falls into the following categories when recommended and should be given 60 minutes prior to the BsAb:

- Corticosteroid (usually prednisone or dexamethasone)
- Antihistamine (H1 antagonist) (usually diphenhydramine)
- Antipyretic (Acetaminophen)

Monitoring/Management of Toxicities

CRS-Outpatient/Clinic Setting

- ☐ Generally supportive care
- ☐ Daily vital signs and weights
- ☐ Daily CBC with differential and complete metabolic profile
- ☐ Coagulation parameters twice a week
- ☐ C-Reactive Protein daily during step-up and first dose, then as needed
- ☐ Assess CRS Grade daily and if a change in status occurs
- ☐ Corticosteroids or tocilizumab (Interleukin-6 inhibitor) therapy may be needed for CRS greater than or equal to Grade 2
- ☐ Transfer to Intensive Care if needed for intensive monitoring or progressing severe toxicity

CRS-Inpatient/Intensive Care Setting

- ☐ Vital signs every 4 hours
- ☐ Monitor IV and oral fluid intake and output
- ☐ Daily weights
- ☐ Daily CBC with differential and complete metabolic profile
- ☐ Coagulation parameters twice a week
- ☐ C-Reactive Protein daily during step-up and first dose, then as needed
- ☐ Assess CRS Grade every 12 hours and if a change in status occurs
- ☐ Grade neuro assessment with ICE score and neurotoxicity domain of ASTCT

CRS-Patient Home Setting

- ☐ Provide Team contact information and guidance on when to call for symptoms
- ☐ Oral temperature every evening; if feeling unwell or lethargic take oral temperature three times a day
- ☐ Encourage oral fluid intake

Nursing Education / Checklist (continued)

ICANS/Neurotoxicity-Clinic and/or Inpatient Setting

- ☐ Physical exam and review of vital signs daily
- ☐ Neurologic exam every 8-12 hours or if there is a change: initial signs may be subtle (deficits in attention, changes in alertness, changes in language). More frequent neurologic exam if intensive care setting is required.
- ☐ Grade neuro assessment with ICE score and neurotoxicity domain of ASTCT
- ☐ Consider transfer to intensive care setting if progressive mental status changes, suspected cerebral edema, status epilepticus and/or patients with grade 3 or 4 neurotoxicity
- ☐ Notify heme/onc and primary service attendings immediately if patient experiences any neurologic or hemodynamic changes or changes in ICE score
    - RR <10 or >24 breaths per minute
    - Respiratory distress (cyanosis, wheezing)
    - SBP <90 mmHg
    - Temperature >38°C (100.4°F)

Pharmacy Checklist

I. Patient review

- ☐ Confirm name & identifier in CPRS
- ☐ Current age, height, weight, BSA
- ☐ Allergies, prior treatment-related reactions, comorbid conditions noted
- ☐ Diagnosis
- ☐ History of prior therapies, if appropriate

II. Treatment plan review

- ☐ Goal of therapy
- ☐ BsAb dose and regimen
- ☐ Duration of treatment/# cycles
- ☐ PADR adjudication
- ☐ Pertinent labs are current and within limits for treatment
- ☐ Anticipated start date of cycle #1, day #1
- ☐ Forecast date(s) of additional treatment days within a cycle and/or subsequent cycle

III. Drug order review

- ☐ Note facility area(s) where step-up and full BsAb dose(s) are planning to be administered (i.e. outpatient clinic vs. inpatient ward)
- ☐ Medication order for BsAb [will vary per BsAb; include dose, route, rate, etc.] step up and full doses
- ☐ Ensure appropriate supportive medications are ordered (see chart below)
- ☐ Antiseizure prophylaxis may be ordered based upon patient risk
- ☐ Note start date of cycle #1, day #1 and additional treatment days within cycle
- ☐ Note that not all BsAb start on cycle #1, day #1. For example, obinutuzumab is given cycle #1, day #1, followed by first dose of glofitamab on cycle #1, day #8 to deplete circulating and lymphoid tissue B cells
- ☐ If a dose is delayed, refer to prescribing information for recommendations to restart; review new orders to reflect these changes

Pharmacy Checklist (continued)

Supportive medications per FDA Package Labeling

Drug	*Pre-medications*	*Other meds*
Blinatumomab	Dexamethasone 16 mg IV	
Teclistamab	Dexamethasone 16mg PO/IV Diphenhydramine 50mg PO/IV Acetaminophen 650-1000mg PO	Antiviral prophylaxis
Glofitamab	Dexamethasone 20mg IV Diphenhydramine 50mg PO/IV Acetaminophen 500-1000 mg PO	Obinutuzumab day 1 Tumor lysis prophylaxis, if at risk Antiviral prophylaxis PJP prophylaxis
Epcoritamab	Dexamethasone 15mg PO/IV Diphenhydramine 50mg PO/IV Acetaminophen 650-1000mg PO	PJP prophylaxis Antiviral prophylaxis
Tebentafusp	None specified	
Mosunetuzumab	Dexamethasone 20mg IV Diphenhydramine 50-100 mg PO/IV Acetaminophen 500-1000 mg	
Elranatamab	Dexamethasone 20mg PO/IV Diphenhydramine 25mg PO Acetaminophen 650mg PO	PJP prophylaxis Antiviral prophylaxis
Talquetamab	Dexamethasone 16mg PO/IV Diphenhydramine 50mg PO Acetaminophen 650-1000mg PO	Antiviral prophylaxis

IV. Procurement process

- ☐ Review procedure to procure BsAb. Check PBM Formulary Management - Specialty Distribution Meds - All Documents (sharepoint.com)
- ☐ Ensure necessary forms are submitted, if appropriate (e.g. REMS)
- ☐ Confirm REMS Dispense Authorization (RDA) code, if necessary (e.g. teclistamab)
- ☐ Order BsAb in anticipation of identified start date
- ☐ Order ancillary medications needed to manage CRS, if needed
    - Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg/dose). Repeat every 8 hours, prn. Limit to maximum of 3 doses/24-hour period and max of 4 doses total.
    - Dexamethasone 10 mg IV or equivalent

V. BsAb preparation

- ☐ Review entire Preparation and Administration section of BsAb prescribing information
- ☐ Note dilution process may vary for each step-up dose, which may differ from the full dose
- ☐ Also note that within a BsAb product line preparation instructions may vary (e.g. epcoritamab 4 mg/0.8ml SDV must be diluted, but 48 mg/0.8ml SDV does not)
- ☐ Note storage and handling instructions of packaged product as well as diluted/reconstituted product

References

1. Lee DW, et al. ASCTC Consensus Grading for cytokine release syndrome neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019; 25: 625-638.
2. Santomasso BD, et al. Management of immune-related adverse events in patients treated with chimeric antigen receptor T-cell therapy: ASCO Guideline. J Clin Onc 2021; 39: 3978-3992.
3. IEC Therapy Toxicity Assessment and Management (also known as CARTOX) – adult. MD Anderson Cancer Center. V4 rev 9/2020
4. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf (Accessed March 27, 2018).
5. Ludwig H, Terpos E, van de Donk N, et al. Prevention and management of adverse events during treatment with bispecific antibodies and CAR-T cells in multiple myeloma: a consensus report of the European Myeloma Network. Lancet Oncol 2023; 24: e255-69.
6. Gust J, Finney OC, Li D, et al. Glial injury in neurotoxicity after pediatric CD19-directed chimeric antigen receptor T-cell therapy. Ann Neurol. 2019; 86: 42-54.
7. Morris EC, Neelapu SS, Giavridis T, Sadelain M. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. Nat Rev Immunol 2022; 22: 85-96.
8. Anderson K, et al. Associated Toxicities-Assessment and Management Related to CAR T-cell therapy. Clin J Onc Nursing 2019; 23 (Supplement): 13-19.
9. Breslin S. Cytokine-Release Syndrome: Overview and Nursing Implications. Clin J Onc Nursing 2007; 11 (Supplement): 37-42.
10. Mucha SR, et al. Management and Prevention of Cellular-Therapy-Related Toxicity: Early and Late Complications. Curr Oncol 2023; 30: 5003-5023.