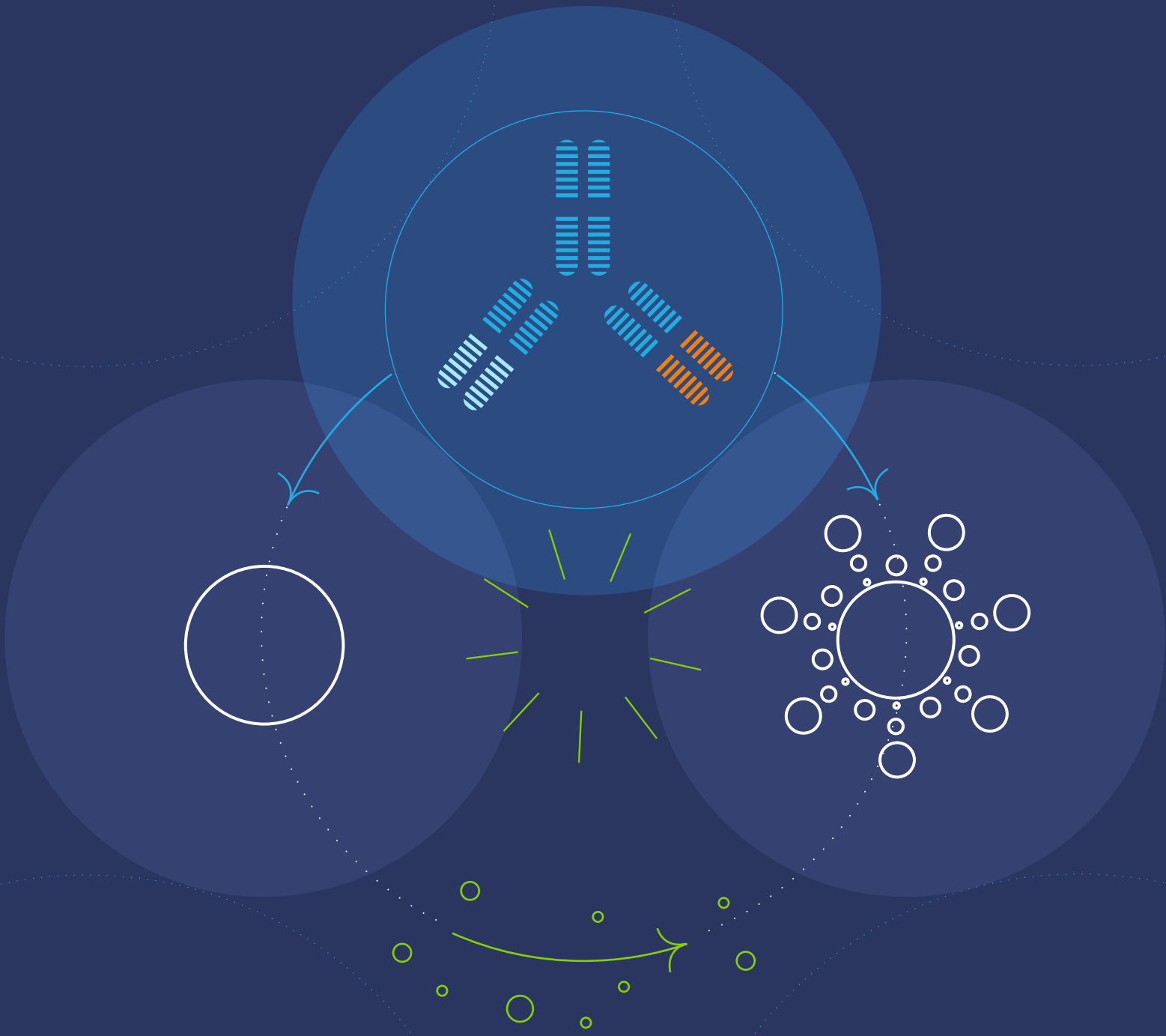
EPCORITAMAB-BYSP

(EPKINLY®)

PLAYBOOK



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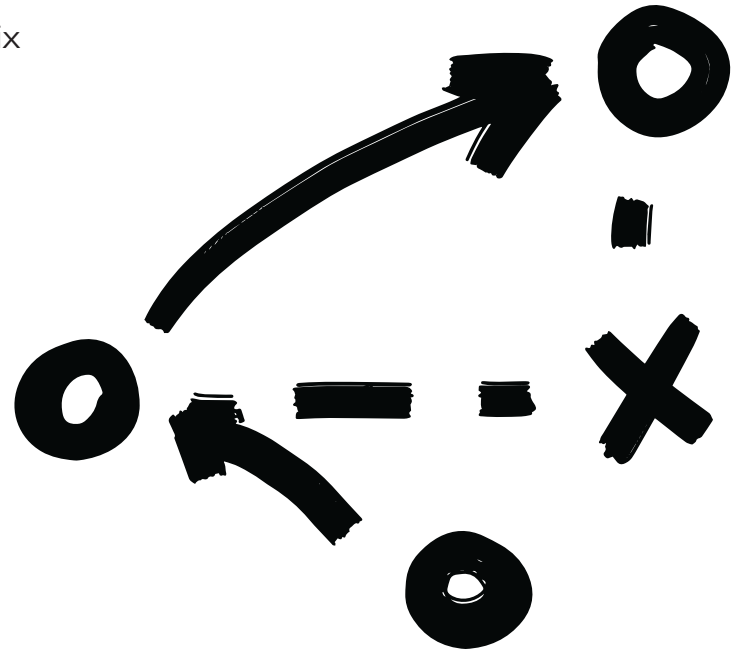
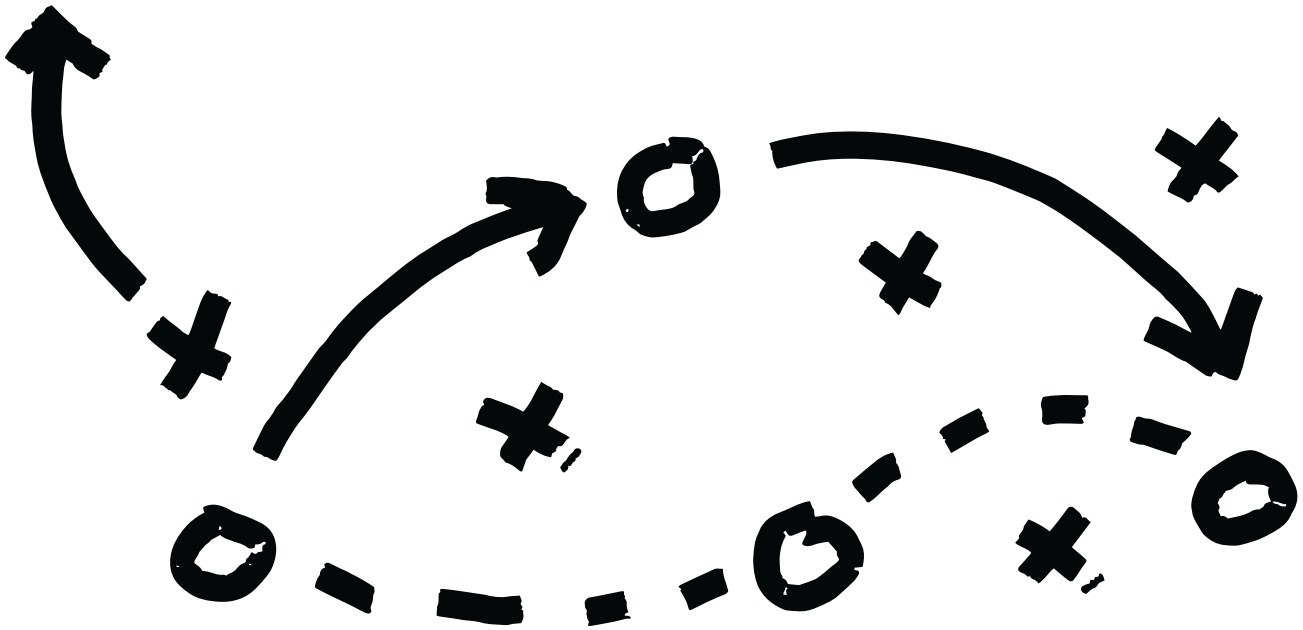


Introduction

Bispecific T-cell engagers represent a significant advancement in cancer treatment. These therapies work by directly linking immune cells to cancer cells and have been approved for various hematologic and solid tumors.[1] Numerous ongoing studies are exploring their use in earlier lines of therapy or in combination with other treatments, making the establishment of bispecific antibody therapy programs in both inpatient and outpatient settings essential to serve patients best.[2,3]

Developing these programs requires substantial effort, including creating protocols for adverse effect management, educating staff and patients, and careful financial planning to address logistical challenges. This undertaking demands interprofessional collaboration among various healthcare providers and efficient systems to ensure clear and timely communication.

To assist programs planning to initiate a bispecific antibody therapy program, this playbook offers essential guidance on epcoritamab-bysp (EPKINLY®), an off-the-shelf bispecific CD20/CD3 T-cell engager approved for treating diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), and follicular lymphoma (FL).[4] By providing this information, we aim to facilitate the successful integration and accessibility of this drug into oncology practices, both in inpatient and outpatient settings.



Epcoritamab Dosage and Supportive Care[4]

Epcoritamab is subcutaneously administered.

Each cycle is 28 days long.
Administration frequency varies depending on the cycle number.

Cycles 1-3:
Administered weekly

Cycles 4-9:
Administered biweekly

Cycle 10 and Beyond:
Administered once every four weeks until disease progression or unacceptable toxicity

Cycle 1 is given as a step-up dosage schedule to reduce the incidence and severity of cytokine release syndrome (CRS). The number of step-up doses are different for DLBCL and FL, where DLBCL has two step-up doses and FL has three step-up doses.

Step-Up Dosing (Cycle 1):

DLBCL:
Two step-up doses (0.16 mg, 0.8 mg)
First full dose (48 mg): Cycle 1, Day 15

FL:
Three step-up doses (0.16 mg, 0.8 mg, 3 mg)
First full dose (48 mg): Cycle 1, Day 22

Recommended Dosage:

Cycle of treatment (Cycle = 28 days)	Day of treatment	Dose of Epcoritamab		
			DLBCL	FL
Cycle 1	1	Step-up dose 1	0.16 mg	0.16 mg
	8	Step-up dose 2	0.8 mg	0.8 mg
	15	Step-up dose 3 or first full dose	48 mg (full dose)	3 mg (step-up dose 3)
	22	Full dose	48 mg	48 mg
Cycle 2 and 3	1, 8, 15 and 22	48 mg		
Cycle 4 to 9	1 and 15	48 mg		
Cycle 10 and beyond	1	48 mg		

Note: If a dose of epcoritamab is missed or delayed, step-up dosing may need to be restarted.

4-week dosing cycles for Epcoritamab for DLBCL

CYCLE 1	CYCLE 2-3	CYCLE 4-9	Monthly maintenance dosing CYCLE 10+
W1 ●	W1 ●	W1 ●	W1 ●
W2 ●	W2 ●	W2	W2
W3 ●	W3 ●	W3 ●	W3
W4 ●	W4 ●	W4	W4

STEP-UP DOSAGE: ● **0.16 mg ON DAY 1** > ● **0.8 mg ON DAY 8**
FULL DOSE: ● **48 mg ON DAYS 15+**

Administer epcoritamab subcutaneously in 28-day cycles to well-hydrated patients until disease progression or unacceptable toxicity.

4-week dosing cycles for Epcoritamab for FL

CYCLE 1	CYCLE 2-3	CYCLE 4-9	Monthly maintenance dosing CYCLE 10+
W1 ●	W1 ●	W1 ●	W1 ●
W2 ●	W2 ●	W2	W2
W3 ●	W3 ●	W3 ●	W3
W4 ●	W4 ●	W4	W4

STEP-UP DOSAGE: ● **0.16 mg ON DAY 1** > ● **0.8 mg ON DAY 8** > ● **3 mg ON DAY 15**
FULL DOSE: ● **48 mg ON DAYS 22+**

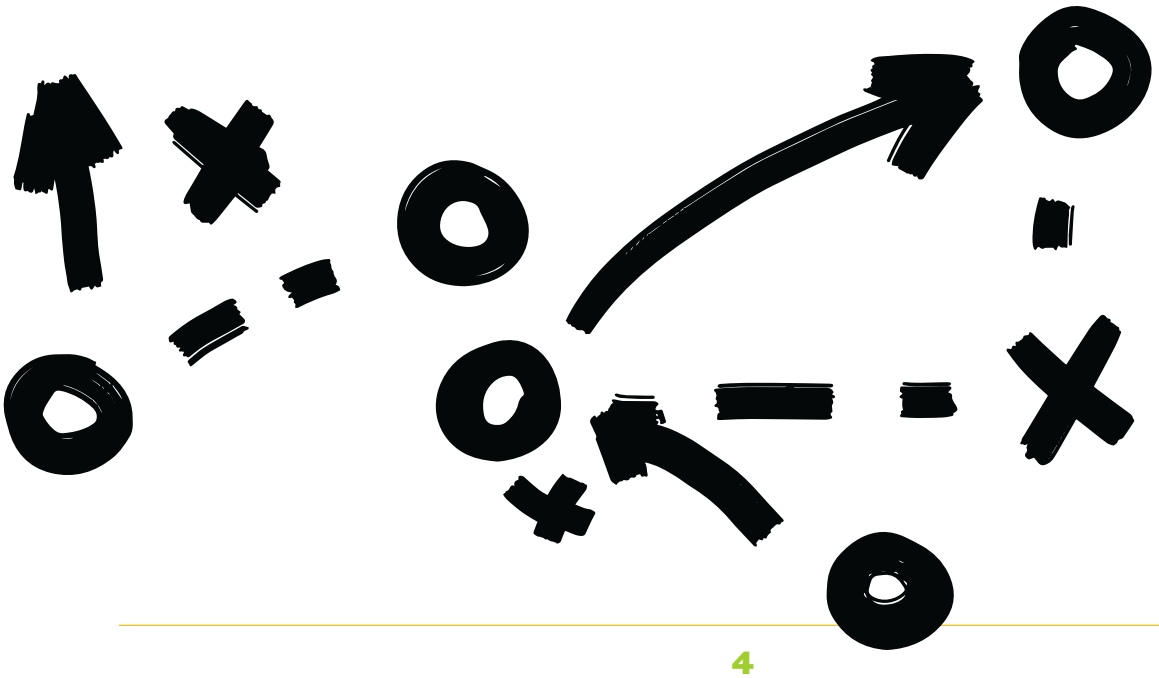
Administer epcoritamab subcutaneously in 28-day cycles to well-hydrated patients until disease progression or unacceptable toxicity.

Supportive Care

Infection prevention: Prior to starting epcoritamab, provide *Pneumocystis jirovecii pneumonia* prophylaxis and consider initiating prophylaxis against herpes virus to prevent herpes zoster reactivation.

Reducing the incidence and severity of CRS: Provide pre- and post-administration medications before and after each dose in cycle 1. For patients who experience grade 2 or 3 CRS with previous dose, some of these medications may be continued.

Cycle 1 (all patients, each weekly administration)	Cycle 2+ (patients who experienced grade 2 or 3 CRS with previous dose)
Pre-administration medications (30-120 mins prior to epcoritamab administration): » Dexamethasone 15 mg oral or IV, prednisolone 100 mg oral or IV, or equivalent » Diphenhydramine 50 mg oral or IV, or equivalent » Acetaminophen 650 to 1000 mg oral	**Pre-administration medications** (30-120 mins prior to epcoritamab administration): » Dexamethasone 15 mg oral or IV, prednisolone 100 mg oral or IV, or equivalent
Post-administration medications (for 3 consecutive days following each weekly administration of epcoritamab in cycle 1) » Dexamethasone 15 mg oral or IV, prednisolone 100 mg oral or IV, or equivalent	**Post-administration medications** (for 3 consecutive days following the next administration of epcoritamab until it is given without subsequent grade 2 or higher CRS) » Dexamethasone 15 mg oral or IV, prednisolone 100 mg oral or IV, or equivalent



Epcoritamab Monitoring and Adverse Effect Management

Epcoritamab has boxed warnings for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[4] Other warnings and precautions include infections, cytopenia, and embryo-fetal toxicity. For DLBCL and HGBCL, the most common (≥ 20%) adverse reactions are cytokine release syndrome, fatigue, musculoskeletal pain, injection site reactions, pyrexia, abdominal pain, nausea, and diarrhea. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) are decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin, and decreased platelets. For FL, the most common (≥ 20%) adverse reactions are injection site reactions, cytokine release syndrome, COVID-19, fatigue, upper respiratory tract infection, musculoskeletal pain, rash, diarrhea, pyrexia, cough, and headache. The most common Grade 3 to 4 laboratory abnormalities (≥ 10%) are decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, and decreased hemoglobin. See the Adverse Reactions Management Guide for more information. Because of the risk of CRS and ICANS, all patients should be monitored for signs and symptoms of these syndromes. According to FDA-approved labeling, the hospitalization recommendations vary depending on the specific indication.[4]

- **DLBCL:** Patients should be hospitalized for 24 hours after administration of Cycle 1, Day 15—the first full dose (48 mg) of epcoritamab
- **FL:** Hospitalization is NOT required

Healthcare systems can determine the appropriate level of monitoring for patients who will receive epcoritamab, which does not necessarily mean inpatient admission if suitable alternatives are available.

REAL-WORLD APPLICATION

Many sites administer all doses in the outpatient setting—even the first full dose for patients with DLBCL—by ensuring systems are in place for safe observation when the risks of CRS are highest.

Cytokine Release Syndrome

CRS is a systemic inflammatory response that can occur when the immune system is activated and releases large amounts of cytokines—proteins that help regulate immune responses.[5]

Common Features of CRS:

Symptoms: range from mild to severe and may include:

Fever	**Rash**
Fatigue	**Shortness of breath**
Nausea	**Low blood pressure**
Headache	**Rapid heart rate**

Onset: In the EPCORE NHL-1 trial, the median time to CRS onset varied between DLBCL and FL.[6,7] CRS occurred approximately 24 hours after administration in patients with DLBCL, while in patients with FL, it occurred around 60 hours after administration (Table 1).

Duration: In the EPCORE NHL-1 trial, the median duration of CRS was 2 days.[6,7]

Severity: CRS with epcoritamab is primarily low grade, predictable, and manageable

- In the EPCORE NHL-1 trial, CRS occurred in ~50% of patients. Most CRS events occurred during Cycle 1, with the highest events occurring on the day of the first full 48 mg dose (Figure 1 and Figure 2).[6,7]
- The majority of cases of CRS in DLBCL were grade 1 or 2, and all cases of CRS in FL were grade 1 or 2 [6,7]

Figure 1: CRS in DLBCL

Distrubution of CRS Events by Dose

Cycle 1 (92% of all events)

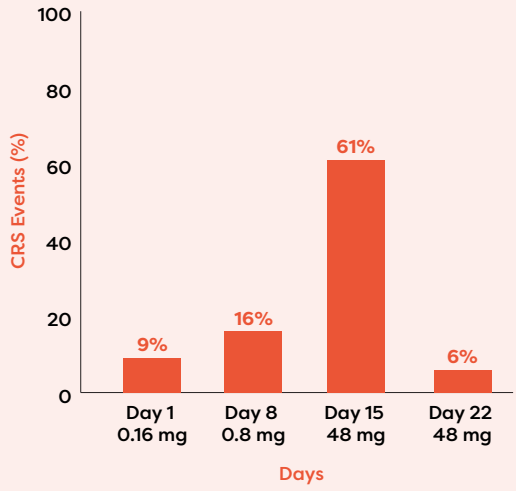


Figure 2: CRS in FL

Distrubution of CRS Events by Dose

Cycle 1 (88% of all events)

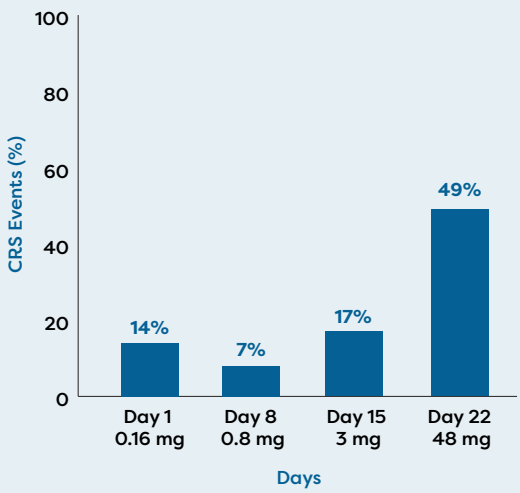


Table 1: CRS

	DLBCL	FL
Onset		
Across all doses	24 hours (range 0-10 days)	59 hours (range 0.1-7 days)
First full 48 mg dose	21 hours (range 0-7 days)	61 hours (range 0.1-7 days)
Resolution	98%	100%
Duration	2 days (range 1-27 days)	2 days (range 1-14 days)
All grades	51%	49%
Grade 1	37%	45%
Grade 2	17%	9%
Grade 3	2.5%	0%

Management:

Monitoring: Close monitoring of blood pressure, blood oxygen, and body temperature is essential, especially when patients are at highest risk of CRS.

Treatment Options: Treatment may include medications such as corticosteroids or tocilizumab, which can help manage inflammation and mitigate symptoms. For refractory cases, medications such as anakinra and siltuximab.[8,9] See the Appendix for an example protocol for grading and managing CRS.

BEST PRACTICES

If patients receive Cycle 1 in the outpatient setting, provide them with a thermometer, pulse oximeter, and blood pressure monitor. Additionally, supply patients and caregivers with a written log or a device to record vital signs for the first 2-3 days after each Cycle 1 dose.

Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS is characterized by various neurological symptoms resulting from the activation of the immune system and the resultant inflammatory processes.[5]

Common Features of ICANS:

Symptoms: range from mild to severe and may include:

Encephalopathy	**Motor deficits**
Headaches	**Ataxia**
Seizures	**Tremors**
Aphasia	

Onset: In EPCORE NHL-1, the onset of ICANS symptoms occurred after 2-3 weeks of therapy, and 3 days from the most recent administration.[6,7]

Duration: In EPCORE NHL-1, the duration was around 2-4 days.[6,7]

Severity: Similar to CRS, the severity of ICANS can vary significantly, with some patients experiencing mild symptoms while others may have severe or life-threatening effects.

- In EPCORE NHL-1, around 6% of patients experienced ICANS.[6,7]
  - The majority of cases were grade 1 or 2. There was one grade 5 ICANS event in the DLBCL group.

Management:

Monitoring: Patients receiving epcoritamab should be closely monitored for any neurological changes.

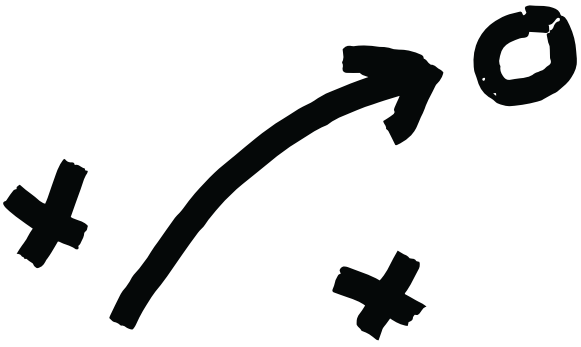
Treatment Options: Management may involve supportive care, symptom management, and potentially the use of corticosteroids or other medications to reduce inflammation. See the Appendix for an example protocol for grading and managing ICANS.

BEST PRACTICES

If patients receive Cycle 1 in the outpatient setting, ensure that caregivers are trained to perform an ICE score, which assesses changes in speech, orientation, handwriting, attention, and receptive aphasia.

Table 2: ICANS

	DLBCL	FL
Onset		
From start of treatment, median	16.5 days (range: 8-141 days)	21.5 days (range 14-66 days)
From most recent administration, median	3 days (range 1-13 days)	3 days (range 0.4-7 days)
Resolution, Duration, median	90%, 4 days (range 0-8 days)	100%, 2 days (range 1-7 days)
Duration of exposure, median	5 cycles (range: 1-20 cycles)	8 cycles (range: 1-33 cycles)
All grades	6%	6%
Grade 1	4.5%	3.9%
Grade 2	1.3%	2.4%
Grade ≥ 3	0.6%	0%



Workflow for Implementing Epcoritamab in the Clinic

1. **Designate a Practice Champion:**
Appoint a "Practice Champion" to serve as the primary contact for integrating epcoritamab into the clinic.

2. **Engage Pharmacy and Financial Departments:**
Collaborate with the pharmacy and finance teams on adding a new drug to the formulary:
   - Confirm the existence of payer contracts
   - Review the prescribing information, including the medication guide
   - Watch the pharmacy preparation video for epcoritamab
   - Review the dosing and administration guidelines for epcoritamab
   - Create an electronic treatment plan or paper order form to facilitate medication ordering by providers

3. **Follow Clinic Protocols:**
Adhere to clinic policies regarding product ordering, including the necessary equipment (e.g., vials) and other procedures for onboarding new medications.

4. **Verify Safe Administration Protocols:**
Ensure there is a protocol in place for the safe administration of epcoritamab.

5. **Educate Clinic Staff:**
Provide ongoing education to clinic staff on dose preparation, administration, and adverse event (AE) monitoring and management:
   - Include training for call center staff on prompt symptom triage
   - Educate staff who may see patients urgently, such as ER personnel
   - If applicable, educate satellite sites within the network that will administer epcoritamab
   - Consider establishing an EMR alert for providers accessing patient charts to raise awareness of CRS/ICANS risk due to bispecific antibody therapy
   - Supply on-call staff with relevant training and resources, such as prescribing information, AE management guides, and dosing and administration guidelines

6. **Facilitate Transitions of Care:**
If applicable, prepare sites for transitions between community and hospital settings:
   - Confirm that the local hospital has access to epcoritamab in case a transition is necessary
   - Consider developing a memorandum of understanding with supportive sites to receive patients back for maintenance doses.

REAL-WORLD APPLICATION

Some sites administer all step-up doses in an outpatient setting with coordinated observation at a nearby hospital. Others manage the process entirely outpatient by equipping patients with monitoring tools like pulse oximeters, thermometers, and blood pressure monitors, and providing instructions for tracking and responding to abnormal signs, supported by a contact line for questions.

7. **Prepare for Adverse Reaction Management:**
Consider the following aspects:

- Schedule specific touchpoints (calls or telehealth) with patients between doses, especially for Cycle 1
- Provide instructions for patients/caregivers on how to monitor for AEs
- Designate whom patients should contact to report symptoms, including after hours
- Develop a workup plan for rapid response if CRS or ICANS is suspected
- Identify key phrases or symptoms for the on-call team to monitor, which may warrant a hospital evaluation
- Determine necessary pre-medications
- Ensure availability of medications for managing potential adverse effects
- Identify hospitals best equipped for patient management in case hospitalization is required
- Establish a strong communication channel between the Community Oncology Clinic and the hospital for prompt support

8. **Prepare Patients for Treatment Initiation:**
Conduct a physical exam, routine lab tests, and prophylaxis for PJP and possibly herpes virus.

- Discuss the care plan with patients and caregivers, covering:
  - The importance and methods of adequate hydration before administration
  - Premedications, step-up dosing, and the overall treatment schedule
  - Signs and symptoms of potential adverse events, when to reach out to the clinic, what to do in emergencies, and the significance of carrying the patient wallet card
- Consider enrolling patients in MyNavCare™ patient support program
- Provide a starter kit for patients, including the patient wallet card, available from AbbVie/Genmab
- Offer patient and care partner support resources provided by AbbVie/Genmab.

9. **Tailor Support for Each Patient:**

- Assess the type of support the patient will need throughout treatment (e.g., attentive care partners, transportation, psychological support access)
- Determine if the patient requires follow-up calls after 24 and/or 48 hours post-dose to monitor for symptoms
- Consider the necessity of visiting nurse or social worker services

10. **Coordinate Dosing and Appointment Scheduling:**

- Arrange for the administration of prophylactic medications and premedications
- Ensure that medication is on hand to manage CRS if required
- For patients with DLBCL, consider reserving a hospital bed in an inpatient unit for at least 24 hours following the administration of the first full dose

11. **Set Up Follow-Up Appointments:**
Establish a follow-up appointment schedule with the patient that includes both clinic visits and telehealth consultations.

Workflow for Implementing Epcoritamab in the Hospital

1. **Designate a Hospital Champion:**
Appoint a "Hospital Champion" to act as the primary contact for the integration of epcoritamab into hospital protocols.

2. **Engage Pharmacy and Finance Teams:**
Collaborate with pharmacy and financial departments to add epcoritamab to the formulary:
   - Confirm existing payer contracts
   - Review the prescribing information, including the medication guide
   - Watch the pharmacy preparation video focused on epcoritamab
   - Review the dosing and administration guidelines
   - Create an electronic treatment plan or paper order form to assist healthcare providers in ordering the medication

3. **Follow Hospital Protocols:**
Adhere to hospital policies concerning product ordering, including any required equipment (e.g., vials) and other procedures for onboarding new medications.

4. **Verify Safe Administration Protocols:**
Ensure that there are established protocols for the safe administration of epcoritamab within the hospital setting.

5. **Educate Hospital Staff:**
Provide regular education to hospital staff on dose preparation, administration, and AE management:
   - Include training for nursing staff on prompt symptom triage
   - Educate emergency room personnel on urgent patient care related to epcoritamab
   - Ensure that all relevant departments, including outpatient or infusion centers, receive appropriate training
   - Consider implementing EMR alerts for clinical staff to raise awareness about the risks of CRS and ICANS associated with bispecific antibody therapy
   - Equip on-call staff with important resources such as prescribing information, adverse event management guides, and dosing and administration protocols

6. **Prepare for Transitions of Care:**
If applicable, facilitate smooth transitions between community oncology clinics and the hospital:

- Consider developing a memorandum of understanding with supportive sites to receive patients back for maintenance doses.
- Steps for Academic Centers or Health Systems upon Receiving Patient Referrals for Epcoritamab:
    - Identify a Hospital Champion to ensure ongoing communication with both the patient and the Community Clinic's care team
    - Verify that epcoritamab is included in the institution's formulary and establish a process for ordering the product, such as creating order sets
    - Educate the patient and their care partners about the treatment process and the resources available, and consider enrolling the patient in the manufacturer's support program, such as MyNavCare™
    - Check whether the patient's dose of epcoritamab is on schedule or delayed. If delayed, restart epcoritamab therapy according to the package insert recommendations.
    - Ensure that the recommended prophylaxis has been administered, or order it as needed, and conduct a comprehensive physical exam and routine baseline lab work
    - Regarding reimbursement considerations, conduct a patient benefits verification and complete any requirements for medical exceptions or prior authorizations
- Preparing to hand off a patient back to the community oncology clinic for subsequent treatment requires meticulous coordination
    - The Hospital Champion should lead this process by ensuring seamless communication with the Clinic Practice Champion
    - It is important to send complete medical records to the community oncology clinic, detailing dates of epcoritamab administration, premedications given and patient response details, including any adverse events
    - Facilitate peer-to-peer communication with the receiving community oncology clinic provider or care team member to discuss the patient's treatment and ongoing needs
    - Ensure all necessary medications, including epcoritamab, pre-medications, and drugs needed to manage potential adverse events, are available at the Community Clinic before transitioning the patient
    - Maintain open communication lines with the receiving clinic to provide consultation if needed

BEST PRACTICES

Standardizing management protocols and training staff to quickly address adverse events is crucial. Integrating approved toxicity management into BsAb order sets enhances confidence and reduces errors.

7. **Prepare for Managing Adverse Reactions:**
Discuss the following considerations:

- Schedule specific follow-up touchpoints (calls or telehealth) with patients after dosing, particularly after Cycle 1
- Provide guidelines for patients and caregivers on how to monitor for AEs
- Identify whom patients should contact to report symptoms, including after-hours
- Establish a rapid response protocol for suspected cases of CRS or ICANS
- Train staff to identify key symptoms or phrases indicating the need for hospital evaluation
- Determine necessary pre-medications and ensure they are available
- Keep medications on hand to manage potential adverse events
- Identify the most suitable hospitals equipped to manage potential complications if hospitalization is necessary
- Foster strong communication between the hospital and community oncology clinics for efficient patient support

8. **Prepare Patients for Treatment Initiation:**

- Conduct comprehensive physical exams and routine lab tests, including prophylaxis for PJP and possibly the herpes virus
- Review the care plan with patients and caregivers, covering:
  - Importance and methods of adequate hydration prior to administration
  - Overview of premedications, step-up dosing, and the overall treatment schedule
  - Signs and symptoms of potential adverse events, when to contact the hospital, what to do in an emergency, and the significance of the patient wallet card
- Consider enrolling patients in MyNavCare™ patient support program
- Provide a starter kit that includes the patient wallet card, available from AbbVie/Genmab
- Share patient and caregiver support resources provided by AbbVie/Genmab

9. **Tailor Support for Each Patient:**

- Evaluate the type of support each patient may need during treatment (e.g., attentive care partners, transportation services, access to psychological support)
- Determine whether patients require follow-up calls 24-48 hours after dosing to monitor for symptoms
- Assess the needs for visiting nurse or social worker services

10. **Coordinate Dosing and Appointment Scheduling:**

- Arrange for the administration of prophylactic medications and premedications prior to treatment
- Ensure the availability of medications to manage CRS if necessary
- Reserve a hospital bed in an inpatient unit for at least 24 hours following the administration of the first full dose

11. **Establish Follow-Up Appointment Schedule:**
Set up a comprehensive follow-up appointment schedule for patients that includes both in-person clinic visits and telehealth appointments.

Financial Considerations

BsAbs administered in outpatient settings offer potential cost savings for both patients and the healthcare system. Careful financial planning and management are essential to maximize these benefits.

BEST PRACTICE

Ensure the C-Suite fully understands the benefits and costs associated with bispecific therapies.

Formulary:

Adhere to site-specific procedures to prepare a drug information monograph or spreadsheet for presentation to the Pharmacy & Therapeutics (P&T) Committee or a similar clinical committee.

- If a formal review is not possible and a quick turnaround is required, consider non-formulary processes.
- Key considerations include cost, potential rebates, and discounts available through Group Purchasing Organizations (GPOs) or networks, as well as adverse event profiles.
- Additional pricing considerations may be offered by Clinically Integrated Networks (CIN) or provider networks.
- Costs may encompass administration, staff time, chair time, personnel and facility expenses, medication (including pre-meds and supportive medications), monitoring, and managing adverse events.

Procurement:

- Coordinate with the designated specialty distributor or GPO to ensure the product is stocked and available for order.
- Educate purchasing staff on proper ordering procedures.
- Arrange for the ordering and administration of pre-medications and epcoritamab.

Authorization:

- Review prescribing information to confirm on-label use and appropriateness for the patient.
- Conduct a thorough patient benefits investigation.
- Complete requirements for prior authorization or medical exceptions as needed.
- Consider enrolling patients in Epkinly's MyNavCare™ Patient Support program for assistance with benefits investigation and prior authorization support. Visit MyNavCare.com or call 1-866-NAV-CAR1 (1-866-628-2271) Monday-Friday, 8 am-8 pm ET for more information.

BEST PRACTICES

- Establish an authorization/financial task group within your EMR or email system that is alerted when a new patient is being considered for bispecific therapy.
- Implement a financial pre-screening process for every patient.
- Confirm payment for same-day services, both inpatient and outpatient if required.
- Ensure clinical documentation is updated regularly, including clinical data, indications, and guideline updates.

Reimbursement:

- Effective communication with payers is crucial
- Ensure accurate J-code data
- Be aware that prophylactic tocilizumab may not be reimbursed
- Explore copay assistance options, including manufacturer assistance and disease-specific grant assistance

Considerations Specific to Epcoritamab:

- Administered via subcutaneous injection
- Administered by a healthcare professional
- Falls under a buy-and-bill model
- Covered under the medical benefit
- Can be administered in an outpatient setting

Manufacturer Resources:

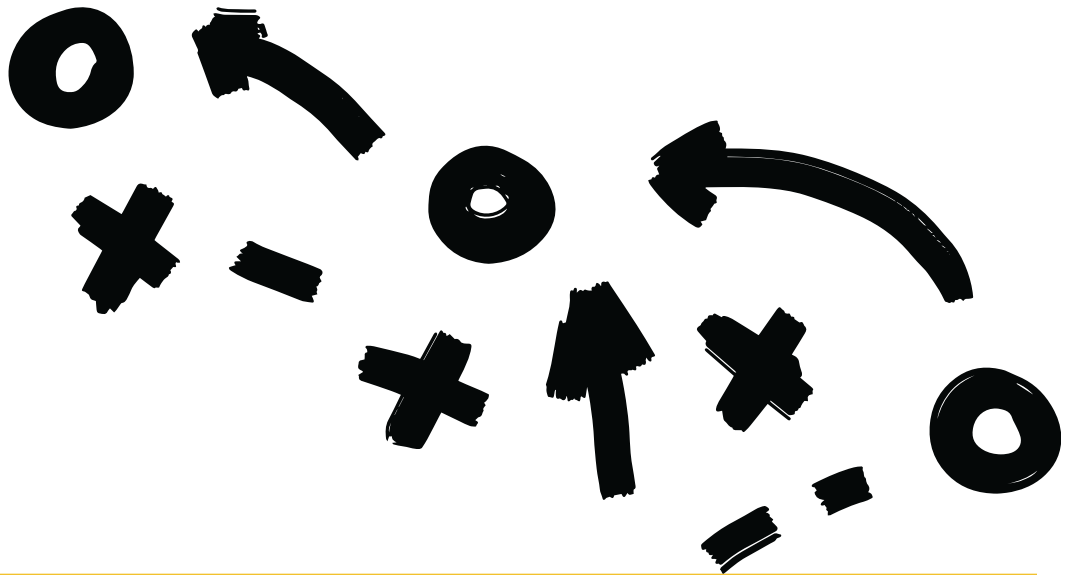
- Prior auth checklist
- Sample letter of medical necessity
- Sample letter of appeal
- Medicare-specific forms
- J-code Reimbursement and coding guide

BEST PRACTICES

To minimize denied claims and ensure proper reimbursement, include tocilizumab as a PRN order in the treatment plan and secure its precertification alongside outpatient authorization.

Questions to Consider:

- How will your practice manage formulary requests for bispecific antibodies?
- What information does your practice require for formulary review?
- Where will you source this information?
- How will your practice manage procurement of bispecific antibodies?
- Who will be part of your reimbursement team and how will you manage the process?



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Appendix

Example CRS protocol

Example ICANS protocol

Staff education

Inpatient Bispecific Order Set Recommendations

Telephone triage

RN Bispecific On-Call Tip Sheet Template

Additional resources

Example Protocol for Managing CRS

[Logo]	[Practice Name]	Version #: [Number] Effective Date: [Date]
[Department]	**Managing CRS associated with Bispecific T-Cell Engagers**	Owners: [Names and Titles] Revised/Reviewed Date: [Date]

Scope:
This policy applies to all clinical staff at [Program Name].

Purpose:
To establish a standard procedure for identifying and managing patients undergoing bispecific T-cell engager therapy who experience Cytokine Release Syndrome (CRS).

Definitions:
Cytokine Release Syndrome (CRS): A systemic inflammatory response caused by the rapid release of cytokines into the bloodstream. Symptoms vary from mild flu-like symptoms such as fever and fatigue, to severe, life-threatening conditions like hypotension, capillary leak syndrome, and multi-organ dysfunction.

Policy:

- **Patient and Caregiver Education**
  - Prior to initiating bispecific T-cell engager treatment, educate patients and caregivers about the potential symptoms of CRS, noting the higher likelihood of symptoms during step-up dosing phases, with the highest risk occurring at the first full treatment dose.
  - Ensure patient has a thermometer, pulse oximeter, blood pressure machine, and a prescription for as needed home dexamethasone. Instruct them on the importance of monitoring temperature, blood pressure, and pulse oximetry three times daily for 2-3 days following each dose of the step-up dosing, and as clinically indicated thereafter.
  - Stress the need to contact healthcare providers if there are changes in the patient's condition. Provide the after-hours clinic phone number and instructions for when to seek emergency help or call 9-1-1. Patients should receive written materials about their specific therapy and a patient card listing the therapy name and emergency instructions.
- **Healthcare Team Education and Management**
  - Clinical staff must check the patient's vitals before starting treatment. Abnormal readings require documentation of "okay to treat" by a qualified provider in the treatment plan.
  - If contacted by a patient, use the nurse triage checklist to assess symptoms, and promptly communicate any abnormal CRS findings to the covering provider for further evaluation and management.
  - If outpatient, admit to inpatient.
  - If Grade 1, consider managing patients in the outpatient setting. During initial step-up therapy, the patient may need to be admitted to the inpatient service depending on the bispecific T-cell engager.

Refer to the treatment chart below for management strategies of CRS in patients receiving bispecific T-cell engagers.

CRS Grade	Supportive Care	Glucocorticoids	Anti-cytokine therapy
Grade 1: Temp ≥ 100.4°F (38°C)	Support with antipyretics & encourage hydration » APAP 1000 mg every 8 hours PRN for elevated temperature » Monitor neurologic status » Assess for infections with cultures and chest radiography (if able) » If grade 1, pt will check temp and BP every 2hrs while awake at home, call clinic for advisement if BP goes less that 10mm HG below baseline AND <90mmHg systolic, new orthostatic symptoms, weakness, confusion, dizziness or new hypoxia (SpO_2 <90%)	Dexamethasone 16 mg PO may be given & repeated daily if grade 1 CRS continues » Consider for administration for refractory fever, must be reviewed with clinical team or covering MD prior to administration » Must be seen for clinical evaluation same day or next day	May consider tocilizumab for high risk patients (advanced age, high tumor burden, heart failure, pulmonary disease) or fever persisting > 48hr » Must be evaluated in clinic and reviewed with clinical team or covering MD prior to administration
Grade 2: Temp ≥ 100.4°F (38°C) plus hypotension not requiring a vasopressor and/or hypoxia requiring low flow nasal cannula requiring low flow oxygen by nasal cannula or blow-by	Must be evaluated urgently in clinic or ED » APAP 1000 mg Q8H for elevated temperature » NS 1000 ml over 30-60 minutes (may bolus as needed for BP) » Monitor neurologic status » O_2 to maintain O_2 Sats	Dexamethasone 16 mg PO (take at home before coming to clinic or ED) » If hypotension continues despite tocilizumab and fluids then administer 10 mg IV every 12 hours	Administer tociluzumab 8 mg/kg (max 800 mg) » May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total if not responsive to IV fluids or increasing supplemental oxygen

Grade 3: Temp ≥ 100.4°F (38°C) plus hypotension requiring one vasopressor (with or without vasopressin) and/or or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask or Venturi mask	Hospital admission (consider ICU) » Management per grade 2 » Hemodynamic monitoring, IV fluids, O_2 support, vasopressor support	Dexamethasone 10 to 20 mg every 6 hours (or equivalent) & continue until event is grade 1 or less. Taper over 3 days once patient is grade 1	» As per grade 2 recommendations
Grade 4: Temp ≥ 100.4°F (38°C) plus hypotension requiring greater than one vasopressor (excluding vasopressin) and/or hypoxia requiring positive pressure (CPAP, BiPAP, intubation, and mechanical ventilation)	Hospital admission (ICU) » Manage per grade 3 » Mechanical ventilation may be required	Dexamethasone 10 to 20 mg every 6 hours (or equivalent) & continue until event is grade 1 or less. Taper over 3 days once patient is grade 1 » Alternatively may administer methylprednisolone 1000 mg IV daily X 3 days	» As per grade 2 recommendations

** Atypical CRS presentations: (i.e., persistent CRS-like symptoms for >1 week despite appropriate supportive measures; febrile illness outside of the normal CRS timeframes, or with accompanying significant organ dysfunction) consider diagnostic work up to rule out alternative diagnosis such as infections or Hemophagocytic lymphohistiocytosis (HLH)/ Macrophage activation syndrome (MAS)

Example Protocol for Managing ICANS

[Logo]	[Practice Name]	Version #: [Number] Effective Date: [Date]
[Department]	**Managing ICANS with Bispecific T-Cell Engagers**	Owners: [Names and Titles] Revised/Reviewed Date: [Date]

Scope:
This policy is applicable to all clinical staff at [program name].

Purpose:
To establish a standard procedure for identifying and managing patients undergoing bispecific T-cell engager therapy who experience Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Definition(s):

- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS): a disorder characterized by a pathologic process affecting the central nervous system that occurs after certain immune therapy, leading to the activation or involvement of natural or introduced T cells and/or other immune response cells. Symptoms may worsen over time and can encompass aphasia, changes in consciousness, cognitive impairment, muscle weakness, seizures, and swelling of the brain.

Policy:
ICANS assessment and grading scale will be completed prior to initiation of bispecific T-cell engagers.

- If normal baseline neurologic assessment, patients and caregivers should be educated on potential manifestations of neurological toxicity and monitor or and changes in neurological status from baseline
  - Reassess with any changes and follow recommendations per grading scale
- If abnormal baseline neurologic assessment, clinical team to review and make recommendations regarding need for more frequent ICANS assessment

Grading:

ICE Score

Orientation	Orientation to year, month, city, hospital: **4 points**
Naming	Ability to name 3 objects (e.g., point to clock, pen, button): **3 points**
Following Commands	Ability to follow simple commands (e.g., “Show me 2 fingers” or “Close your eyes and stick out your tongue”): **1 point**
Writing	Ability to write a standard sentence (e.g., “Our national bird is the bald eagle”): **1 point**
Attention	Ability to count backwards from 100 by 10: **1 point**

Scoring:

- **10**, no impairment
- **7-9**, grade 1 ICANS
- **3-6**, grade 2 ICANS
- **0-2**, grade 3 ICANS
- **0,** grade 4 ICANS due to patient unarousable and unable to perform ICE assessment

ASTCT Consensus ICANS Grading Chart

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	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	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

See the below treatment chart for managing ICANS.

Grade	Management
Grade 1	» MRI imaging of the brain (if available), ICE scoring every 6 hours, EEG » Vigilant supportive care, aspiration precautions, IV hydration » Avoid medications that cause CNS depression » Dexamethasone 4-10 mg x 1 dose and reassess in 6 hours » If associated with concurrent CRS, add tocilizumab*
Grade 2	» Neurological work-up as Grade 1 ICANS » Supportive care as in Grade 1 ICANS » Dexamethasone 4-10 mg IV every 6-12 hours » If associated with concurrent CRS, administer tocilizumab 8 mg/kg (max 800 mg). May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total. » Once ICANS improves, taper steroids
Grade 3	» Transfer to ICU level of care » Neurological work-up and supportive care as Grade 1 ICANS » Consider diagnostic lumbar puncture » Treat seizures and cerebral edema as appropriate » Dexamethasone 10 mg IV every 6 hours » If associated with concurrent CRS, add tocilizumab* » If encephalopathy persists, increase dexamethasone to 20 mg every 6 hours » Once ICANS improves, taper steroids
Grade 4	» Transfer to ICU level of care » Neurological work-up and supportive care as Grade 1 ICANS » Consider diagnostic lumbar puncture » Treat seizures and cerebral edema as appropriate » Methylprednisolone 1 g/day IV in divided doses for 3 days » If associated with concurrent CRS, add tocilizumab* » Once ICANS improves, taper steroids

*tocilizumab 8 mg/kg (max 800 mg). May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total.

Example Guidance Document for Staff Education for Epcoritamab

1. **Establish training schedule (e.g., quarterly, biannually, annually)**
2. **In the clinic**
    a. Training for call center staff
        - Dedicate a direct call line for patients and/or caregivers
        - Provide patients and/or caregivers with contact information to their care team
        - If able, dedicate on-call staff for 24/7 availability

3. In the hospital

    a. Training for nursing staff on prompt symptom triage
        - Dedicate a direct call line for patients and/or caregivers
        - Determine triage schedule for on-call staff
        - Provide patients and/or caregivers with contact information to their care team

4. Dosage form

    a. Epcoritamab is prepared and administered by a health care provider as a subcutaneous injection.

    b. Patients with diffuse large B-cell lymphoma/high grade B-cell lymphoma (DLBCL/HGBCL) receive epcoritamab in a 2-step up dosage schedule (0.16 mg and 0.8 mg).

    c. Patients with follicular lymphoma (FL) receive epcoritamab in a 3-step up dosage schedule (0.16, 0.8, 3.0 mg)

4 mg/0.8 mL vial for step up doses	48 mg/0.8 mL vial for full doses
	
Step up dose 1 (0.16 mg) and step up dose 2 (0.8 mg) of epcoritamab 4 mg/0.8 mL require **dilution** by a healthcare provider **For patients with FL only:** Step up dose 3 of epcoritamab (3 mg) **does not** require dilution	The 48-mg full dose of epcoritamab 48 mg/0.8 mL vial **does not** require dilution

5. Dose preparation

    a. Watch Step-By-Step Instructional Video for Epkinly Dilution Methods: Empty Sterile Vial and Sterile Syringe

6. Storage and handling

a. Single-dose vials

- Refrigerate at 2°C to 8°C (36°F to 46°F)
- Keep in the original carton and protected from light
- Do NOT freeze or shake epcoritamab

b. Storage of epcoritamab solution in the syringe

- Use epcoritamab solution in the syringe immediately
- If not used immediately, store in a **refrigerator** at 2°C to 8°C (36°F to 46°F) for up to **24 hours** or at **room temperature** at 20°C to 25°C (68°F to 77°F) for up to **12 hours**
- The total storage time from the start of dose preparation to administration should not exceed **24 hours**
- Discard unused epcoritamab solution beyond the allowable storage time

7. Managing other adverse reactions

Adverse Reaction	Severity	Action
Infections	Grades 1-4	Withhold Epkinly » In patients with active infection, until the infection resolves » For grade 4, consider permanent discontinuation of Epkinly
Neutropenia	Absolute neutrophil count (ANC) <0.5 x 10^9/L	Withhold Epkinly » Until ANC ≥0.5 x 10^9/L
Thrombocytopenia	Platelet count <50 x 10^9/L	Withhold Epkinly » Until platelet count ≥50 x 10^9/L
Other adverse reactions	Grade 3 or higher	Withhold Epkinly » Until the toxicity resolves to grade 1 or baseline
Severity is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0		

8. Counseling patients

	3L+ DLBCL/HGBCL	3L+ FL

CRS	» Inform patients and their care partners of the risk of CRS
	» Advise them to immediately contact their healthcare provider should signs and symptoms associated with CRS occur
	  » These can include pyrexia, hypotension, hypoxia, chills, tachycardia, headache, and dyspnea
	» Advise patients with DLBCL or HGBCL that they should be hospitalized for 24 hours after administration of the cycle 1, day 15 dosage of 48 mg
	» Advise patients who experience symptoms that impair consciousness not to drive and refrain from operating heavy or potentially dangerous machinery until events resolve
		» Inform patients and their care partners of the risk of CRS
		» Advise them to immediately contact their healthcare provider should signs and symptoms associated with CRS occur
		  » These can include pyrexia, hypotension, hypoxia, chills, tachycardia, headache, and dyspnea
		» Advise patients who experience symptoms that impair consciousness not to drive and refrain from operating heavy or potentially dangerous machinery until events resolve

ICANS	» Advise patients and their care partners of the risks of ICANS, and to immediately contact their healthcare provider for signs and symptoms of ICANS » The onset of events may be delayed and can include: confusional state, lethargy, tremor, dysgraphia, aphasia, nonconvulsive status epilepticus » Advise patients who experience symptoms of ICANS that impair consciousness to refrain from driving or operating heavy or potentially dangerous machinery until symptoms of ICANS resolve	
Other Adverse Reactions	» Advise patients of the risk of serious infections, and to contact their healthcare professional for signs or symptoms of serious infection » Discuss the signs and symptoms associated with cytopenias, including neutropenia and febrile neutropenia, anemia, and thrombocytopenia	

3L+ DLBCL/HGBCL, third line+ diffuse large B-cell lymphoma/high grade B-cell lymphoma
3L+ FL, third line+ follicular lymphoma
CRS, cytokine release syndrome
ICANS, immune effector cell-associated neurotoxicity syndrome

Example of an Inpatient Bispecific T-Cell Engager Order Set

GENERAL ORDERS:

Vital signs and assessments:

- Assess every 8 hours if patient is admitted but not to have suspected CRS/ICANS and anytime there is a change in status
- Assess if patient is located on FLOOR or ED with suspected CRS/ICANS, recommend vital sign monitoring hourly x4, followed by every 2 hrs x4, then per MD guidance or hospital protocol and anytime there is a change in patient status
- Assess every 1 hour if patient is located in ICU with suspected CRS/ICANS and anytime there is a change in status

Assessment and grading of CRS

- Assess every 8 hours if patient is admitted but not to have suspected CRS/ICANS for change in patient's status (see attached assessment tool)

Assessment and grading of ICANS

- Assess every 8 hours if patient is admitted but not to have suspected CRS/ICANS for change in patient's status or when there is a change in patient's status (see attached assessment tool)

Daily Weight

Daily labs and as needed:

- CBC, CMP, LDH, uric acid daily and ferritin (PRN)

DVT/VTE prophylaxis

Notify oncologist of any of the following:

- SBP greater than 140 or less than 90 mmHg
- Heart rate greater than 120 or less than 60 bpm or an arrhythmia
- Respiratory rate greater than 25 or less and 12 breaths/min
- Oxygen saturation less than 92% on room air
- Change in weight > 5 lbs
- Upward trend in serum creatinine or liver function test
- Tremor or jerking movement in the extremities
- Any increase in CRS or ICANS overall grade
- Temperature greater than or equal to 100.4 °F (38°C)

CRS ORDER SET:

Grade 1: Temp ≥ 100.4°F (38°C)

- Vital Signs per general orders as above
- Encourage hydration
- Acetaminophen 1000 mg every 8 hours PRN for elevated temperature
- Monitor neurologic status
- Vital Signs every 2hrs while awake
  - Notify MD if BP goes less than 10mm HG below baseline AND <90mm Hg systolic, new orthostatic symptoms, weakness, confusion, dizziness or new hypoxia (SpO^2 <90%)
- Dexamethasone 16 mg PO daily if grade 1 CRS continues
  - Consider for administration for refractory fever, must be reviewed with clinical team or covering MD prior to administration
- Tocilizumab 8 mg/kg (max 800 mg) for high-risk patients (advanced age, high tumor burden, heart failure, pulmonary disease) or fever persisting > 48hr
  - Review with MD prior to administration

Grade 2: Temp ≥ 100.4°F (38°C) plus hypotension not requiring a vasopressor and/or hypoxia requiring low flow nasal cannula

- Vital Signs every 2hrs
- Acetaminophen 1000 mg Q8H PRN elevated temperature
- NS 1000 ml over 30-60 minutes (may bolus as needed for BP)
- Monitor neurologic status
- O_2 to maintain O_2 Sats
- Dexamethasone 16 mg PO daily
  - Dexamethasone 10mg IV every 12hr if hypotension persistent
- Administer tociluzumab 8 mg/kg (max 800 mg)
  - May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total if not responsive to IV fluids or increasing supplemental oxygen

Grade 3: Temp ≥ 100.4°F (38°C) plus hypotension requiring one vasopressor and/or requiring high flow nasal cannula (evaluate for ICU admission)

- Vital Signs every 1hr
- Same management as grade 2
- Acetaminophen 1000 mg Q8H PRN elevated temperature
- NS 1000 ml over 30-60 minutes (may bolus as needed for BP)
- Monitor neurologic status
- O_2 to maintain O_2 Sats
- Vasopressor management if needed
- Dexamethasone 10 to 20 mg every 6 hours (or equivalent) & continue until event is grade 1 or less
- Taper over 3 days once patient is grade 1
- Administer tociluzumab 8 mg/kg (max 800 mg)

- May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total if not responsive to IV fluids or increasing supplemental oxygen

Grade 4: Temp ≥ 100.4°F (38°C) plus hypotension requiring greater than one vasopressor and/or requiring positive pressure (CPAP, BiPAP, intubation, and mechanical ventilation) (ICU management required)

- Vital Signs every 1hr
- Same management as grade 3
- Acetaminophen 1000 mg Q8H PRN elevated temperature
- NS 1000 ml over 30-60 minutes (may bolus as needed for BP)
- Monitor neurologic status
- O_2 to maintain O_2 Sats, mechanical ventilation as needed
- Vasopressor management if needed
- Dexamethasone 10 to 20 mg every 6 hours (or equivalent) & continue until event is grade 1 or less. Taper over 3 days once patient is grade 1
  - Alternatively may administer methylprednisolone 1000 mg IV daily X 3 days
- Administer tociluzumab 8 mg/kg (max 800 mg)
  - May repeat every 8 hours to a max of 3 doses in 24 hours and 4 doses total if not responsive to IV fluids or increasing supplemental oxygen

Example of a Telephone Triage Template

****This template ensures all staff members follow standardized steps to manage patients undergoing bispecific therapy and escalate cases promptly. It is for example only, please adjust according to the specific needs of the clinic.*

PATIENT COMPLAINT: BISPECIFIC THERAPY

Important Note:

Patients on bispecific therapy, particularly during the induction phase, may develop Cytokine Release Syndrome (CRS) and/or Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which can progress to serious, life-threatening conditions. It is critical to appropriately triage these patients and expedite their evaluation and care.

Ensure that the patient has a blood pressure cuff, thermometer, and pulse oximeter at home. Encourage the patient to check BP, pulse ox, and temperature during the call.

Assessment Questions:

- Any fevers or chills?
- Any of the following symptoms: dizziness, shortness of breath, racing heart, feeling anxious or restless, headache, confusion, memory loss, difficulty speaking, difficulty staying awake, abnormal actions, seizures, tremor, difficulty writing, or muscle weakness?

Patient Details:

- Onset:
- Location:
- Duration:
- Characteristics:
- Associated Factors:
- Relieving Factors:
- Treatment Tried:

RECOMMENDATIONS:
(EXAMPLES ONLY, PLEASE REFER TO SITE-SPECIFIC INTERNAL MEDICAL POLICIES)

Same Day Office Appointment:

1. Temperature of 100.4°F (38°C) or higher
2. Pulse oximetry reading ≤90% or a >5% decrease from baseline
3. Blood pressure drop >10 points from baseline or BP <90/70 mmHg
4. Resting heart rate >110 beats per minute
5. Any neurological symptoms (e.g., confusion, memory loss, seizures)

Urgent ER Evaluation:

1. Unable to awaken to voice
2. Seizure
3. Hypotension resulting in syncope

Action Plan:
If the patient reports any concerning symptoms, DO NOT simply relay the message to the team Advanced Practitioner (AP) for advisement.

- Place a phone call** to the team AP
- If the AP is unreachable, **have the patient come into the office immediately**.
- Coordinate with infusion charge to schedule ASAP hydration and reach out to the infusion AP for an evaluation upon patient arrival.
- Notify the "Bispecifics team" via email to inform them of the patient's urgent condition.

Lab Orders:

- CBC, CMP, Magnesium, Phosphorus, Uric Acid, LDH
- Blood cultures x2 (if febrile)

If unable to schedule as above, consult leadership for further guidance.

If the patient already has an appointment scheduled for that day, encourage them to come in sooner and alert the team and provider

Example of a Nurse On-Call Tip Sheet

Adjust for practice-specific roles and procedures

Preparation:
Before taking on-call responsibilities, the RN should print and review the Bispecific Grading Scale Baseline, along with the patient's chart, for baseline assessments and vital signs.

Call Schedule:

- Check-In Calls:
  - 7:30 PM
  - 11:30 PM
- Availability: The RN will be available to answer any calls from 5:00 PM to 7:30 AM via the bispecific phone.

Assessment:
Use the **After Hours Bispecific Assessment Tool** during designated calls and whenever the patient calls to report symptoms.

Reporting:
If vitals are stable and no new/concerning symptoms:

- Send a message to the MD with:
  - Patient name and bispecific drug
  - Vital signs: BP, Temp, O_2 sat, HR (with values)
  - Note absence of neurological symptoms or other concerns

If there are changes in vital signs, symptoms, or neurological issues:

- Call the MD and provide:
  - Patient name and bispecific drug.
  - Summary of assessment and reasons for concern.
  - Vitals, especially noting:
    - Temp ≥100.4°F (38°C)
    - Pulse Ox <90% or a >5% change from baseline
    - SBP <90mmHg or a >10mmHg decrease from baseline
    - HR >110 or a >20 bpm increase from baseline at rest
    - Neurological symptoms: confusion, speech issues, drowsiness, tremor, weakness, etc.

Office Visit:
If the MD decides the patient needs to come to the office:

- Call the patient to inform and ask for their vehicle details.
- Notify the Bispecific AP of the need for an office visit.
- Follow safety protocols for after-hours visits (e.g., park close to the building, enter together). The RN, AP, and patient should arrive within one hour, or sooner if safely possible.

Documentation:
All information should be recorded and scanned into EMR by the next morning.

Additional Resources

EPKINLY Dose Preparation and Administration Guide

Bispecific Antibodies Checklist for Community Providers

HOACNY Bispecifics Therapeutic Management Tools

IEC Therapy Toxicity Assessment and Management, MD Anderson Cancer Center, Houston, Texas

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