[Clinic or Hospital Logo]			
		SOP #	[Number]
		Effective	[Date]
		Approved	[Date]
		Next Review	[Date]
		Owner	[Name]
		Department	[Name]
		Tags	[Tags]
		Applicability	[Name of sites]

Inpatient Use of Bispecific T-Cell Engagers

Where Did This Resource Come From?	
Clinic/Hospital Type	Large, academic medical center with affiliated community satellites
What's Unique?	• Inpatient administration of BTCEs necessitates varying schedules for monitoring vital signs and neurochecks based on symptom severity, with more frequent checks for higher severity symptoms. • Lists criteria for considering outpatient BTCE administration. • Provides a unique transitions-of-care checklist.

1. Purpose

To outline the procedure for inpatient administration of bispecific T-cell engagers.

2. Scope

This standard operating procedure (SOP) applies to healthcare professionals involved in the administration and monitoring of bispecific T-cell engagers for patients in an inpatient setting.

3. Definitions

- **Bispecific T-Cell Engager (BTCE)**: Synthetic proteins that bind two distinct antigens: one targets the CD3 protein on T cells, and the other targets a specific cancer antigen, redirecting T cells to activate an antitumor immune response.
- **Step-Up Dose**: A dosing strategy that starts with a lower dose and gradually increases it to effectively prime the immune system while minimizing adverse effects.
- **Cytokine Release Syndrome (CRS):** A potentially severe inflammatory response that occurs when immune effector cell therapy leads to the release of cytokines into the bloodstream. This syndrome causes symptoms such as fever, hypotension, hypoxia, chills, tachycardia, dyspnea, nausea, rash, headache, and myalgia.
- **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):** A neurological complication caused by inflammation in the central nervous system following immune

effector cell therapy. Symptoms can range from mild, such as headache and confusion, to severe, including seizures and coma, which may be life-threatening.

- **Neurotoxicity**: Side effects that impact the nervous system, including those caused by immunotherapy.
- **Immune Effector Cell Encephalopathy (ICE) Score**: A clinical scoring tool for assessing the severity of neurological symptoms associated with immune effector cell therapies.

4. Procedure

- **Step 1:** Patient Assessment
    - Confirm diagnosis and prior treatment(s).
        - Confirm dosing sequence and monitoring timeframe (e.g., step-up dose, first full dose).
        - Review prior dose(s) and date.
    - Assess patient performance status and laboratory test results.
    - Workup and evaluation:
        - Pertinent history and physical examination including vital sign evaluation and evaluation of respiratory symptoms.
    - Decide on whether the patient is a candidate for outpatient treatment.

Outpatient Criteria	
	Eastern Cooperative Oncology Group (ECOG) performance status 0-1
	Adequate organ function per treating physician
	Caregiver available 24/7 with reliable transportation
	Living within 30 minutes of the health system throughout step-up dosing
	No other significant comorbidities requiring admission
	No history of severe CRS or ICANs with previous CAR-T or BTCE therapy

- **Step 2:** Preparation and Administration
    - Obtain and confirm informed consent.
    - Pharmacist submits the drug on the health system “high cost” log for approval by a health system administrator.
    - Initiate supportive care.
    - Confirm supply of tocilizumab.
    - Administer the BTCE.

- **Step 3:** Monitoring and Managment for Adverse Events
    - CRS
        - Risk factors for severe CRS

High Risk for Severe CRS	
	Age ≥ 60 years
	High tumor burden
	Comorbidities (>3) using the Hematopoietic Cell Transplantation Comorbidity Index

        - Grading of CRS

CRS Parameters	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature >38°C not attributable to any other cause			
	With either:			
Hypotension	None	Not requiring vasopressors, responsive to fluids	Requiring 1 vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
	And/or[b]			
Hypoxia	None	Requiring low-flow nasal canula (<6 L/min) or blow-by	Requiring high-flow nasal canula (>6 L/min), facemask, non-breather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)

[a]Fever is NO LONGER required to grade subsequent CRS severity in patients who have CRS then receive antipyretics or anti-cytokine therapy (e.g., tocilizumab or steroids). In this case, CRS is driven by hypotension and/or hypoxia.

[b]CRS grade is determined by the more severe event, hypotension, or hypoxia not attributable to any other cause.

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

CRS can be downgraded in an afebrile patient treated with anti-cytokine therapy as their hemodynamic status improves.

ICANS should be excluded from the definition of CRS and the separate neurotoxicity scale be utilized as described below.

- Neurotoxicity
  - ICE score
    - **Orientation** to year, month, city, hospital: 4 points (1 point for each)
    - **Naming** 3 objects: 3 points (1 point for each)
    - **Following simple commands**: 1 point
    - **Writing standard sentence**: 1 point
    - **Attention** to count backward from 100 by 10: 1 point
    - Total score is out of 10 points
  - Grading for ICANS

ASTCT ICANS Consensus Grading for Adults				
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score[a]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed Level of Consciousness[b]	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
Motor Findings[c]	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[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ASTCT, American Society for Transplantation and Cellular Therapy; EEG, electroencephalogram; ICP, intracranial pressure.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

[a]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.

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

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

[d]Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

- Monitoring
  - Patients receiving BTCE therapy should be monitored for CRS and ICANS at the following frequency:

			Floor Status		**ICU Status**
Vital Signs			Every 4 hours		Every 1 hour
ICANS Grade	**0**	**1**	**2**	**3**	**4**
ICE Score	10	7-9	3-6	1-2	0
ICE Assessment	Q4	Q4	Q2	Q2 if not intubated Q1 if intubated	Q1
Neurocheck Frequency	Q4		Per institution SOC for patients with ICU status	Per institution SOC for patients in ICU and assess LOC, pupil, corneal, blink, grimace, cough, gag, and motor response in the limbs (graded on GCS)	

SOC, standard of care; ICU, intensive care unit; LOC, level of consciousness; GCS, Glasgow Coma Scale.

- More frequent monitoring is determined by the attending provider based on individual patient needs.
- The attending provider should be notified for:
  - Deviations from baseline in systolic blood pressure (SBP)
  - Heart rate of >120 or <60 beats per minute

        - Arrhythmia
        - Respiratory rates > 25 or <12 breaths/min
        - Arterial oxygen saturation <92% on room air
    - If admitted for reasons other than step-up dosing, ICE scores do not need to be completed at the above frequency and left to provider discretion.
  - Management of CRS and Neurotoxicity
    - See Bispecific T-Cell Engager CRS SOP; See Bispecific T-Cell Engager Neurotoxicity SOP
      - See agent-specific resources for additional side effects.
- **Step 4**: Documentation and Transitions
  - See Transitions of Care Checklist.

Transitions of Care Checklist	
	Identified where patient is going after discharge
	Patient has received copies of test results and documentation or orders for any pending tests (if applicable)
	Patient has received discharge packet
	Provided contact information in event of adverse effects during/after discharge, including on-call staff contacts
	Supportive medications instructions counseled
	Supportive medications picked up (in-house) or sent to external pharmacy
	Necessary follow-up appointments scheduled
	If patient is transferring to another facility, staff has been notified
	Patient has received BTCE wallet card (as applicable)

5. References

1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. doi:10.1016/j.bbmt.2018.12.758.
2. Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3×CD20 bispecific antibody therapy. *Blood*. 2024; 143 (16): 1565–1575. doi: https://doi.org/10.1182/blood.2023022432.
3. Saini NY, Cerny J, Furtado V, et al. Hematopoeitic cell transplant - comorbidity index (HCT-CI) score is a useful tool for predicting induction mortality and overall survival in newly diagnosed acute myeloid leukemia patients. *Blood.* 2018; 132 (Supplement 1): 1396. doi: https://doi.org/10.1182/blood-2018-99-112639.

6. Revision History

Version #	Date	Description of Changes	Reviewed / Approved By
