Engaging with Bispecific T-Cell Engagers

This document is a launchpad for exploring bispecific T-cell engagers (BTCEs).

⚙️ Mechanism of Action

💊 Step-Up Dosing Considerations

⚠️ Cytokine Release Syndrome

🧠 Neurotoxicity (including ICANS)

✅ REMS Certification

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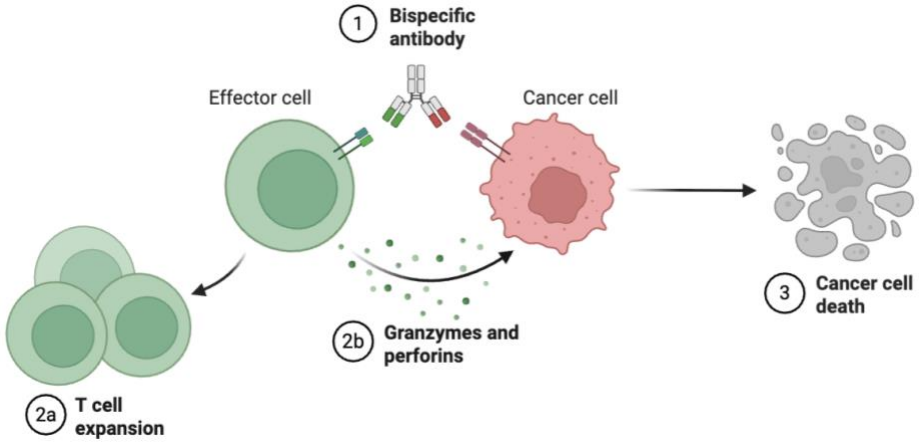
⚙ Mechanism of Action



Source: BioRender. 2025.

BTCEs are designed to bind two different targets: a protein on T cells (often CD3) and a protein on cancer cells (a tumor-associated antigen).

Why it matters: By binding to both cells, BTCEs physically bring T cells into close proximity with cancer cells, triggering T cell activation and leading to the release of cytotoxic molecules that kill the cancer cells.

Tumor-associated antigens of BTCEs approved in the US as of March 2025.

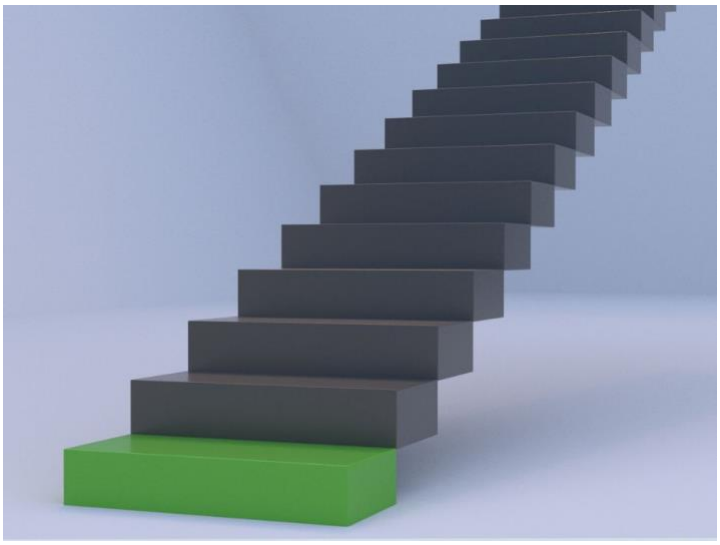
- BCMA (B-Cell Maturation Antigen): Elranatamab, Linvoseltamab, Teclistamab
- CD19 (Cluster of Differentiation 19): Blinatumomab
- CD20 (Cluster of Differentiation 20): Epcoritamab, Glofitamab, Mosenutuzumab
- DLL3 (Delta-like Ligand 3): Tarlatamab
- gp100 (glycoprotein 100): Tebentafusp
- GPRC5D (G Protein-Coupled Receptor Class C Group 5 Member D): Talquetamab

Advantages: BTCEs offer a targeted approach to cancer treatment, potentially minimizing the impact on healthy cells.

- Unlike Chimeric Antigen Receptor (CAR)-T cell therapy, which requires modifying a patient's own T cells, BTCEs are "off-the-shelf" products.

Challenges: Like other immunotherapies, BTCEs can cause severe side effects, such as cytokine release syndrome (CRS) and neurotoxicity.

💊 Step-Up Dosing Considerations



All commercially available BTCEs require step-up dosing (SUD) and pre-medications to mitigate the risk of cytokine release syndrome (CRS).

Why it matters: Institutions face significant challenges in managing the SUD period for BTCEs, necessitating:

- Meticulous patient monitoring
- Coordinated scheduling
- Consistent follow-up by multidisciplinary teams

Initial SUD for most BTCEs was conducted in inpatient settings. However, **institutions are gradually moving to outpatient SUD administration**, necessitating:

- Expansion of infrastructure
- Enhanced follow-up monitoring protocols

Notably, inpatient care remains essential for patients with high tumor burdens due to increased CRS risk.

Effective outpatient administration requires:

- Comprehensive monitoring by clinical teams
- Education and engagement of caregivers

Earlier lines of therapy with lower disease burdens may enable more outpatient treatments.

Novel combination therapies of BTCEs with other traditionally outpatient-administered medications make outpatient administration more desirable.

Scheduling flexibility. Specific dosing protocols for SUDs exist, but flexibility exists to allow institutions to optimize administration strategies:

- Example: Teclistamab permits the second SUD to be given 2-4 days after the first dose and the third SUD to be given 2-4 days after the second, enabling potential outpatient care.
    - Institutions may adopt compressed dosing schedules, such as administering teclistamab three times a week (e.g., **Monday-Wednesday-Friday**).

Monitoring and Support Needs

- Example: Tarlatamab requires longer monitoring intervals and poses unique challenges for outpatient administration, especially regarding observation periods.
- Institutional strategies and operating hours for monitoring vary, affecting patient care continuity.

Resource Considerations for Outpatient SUD

- Implementing outpatient SUD can yield cost savings but requires:
    - Medical staff availability after hours
    - Preparedness for urgent or emergency care needs
- Follow-up for toxicity assessment is essential, ideally through in-person or virtual visits.

Access to Supportive Care

- Timely access to medications like dexamethasone and tocilizumab is critical for managing CRS and ensuring patient safety.
- Collaborations with local emergency departments can facilitate prompt access to necessary treatment(s).

Patient and Caregiver Education

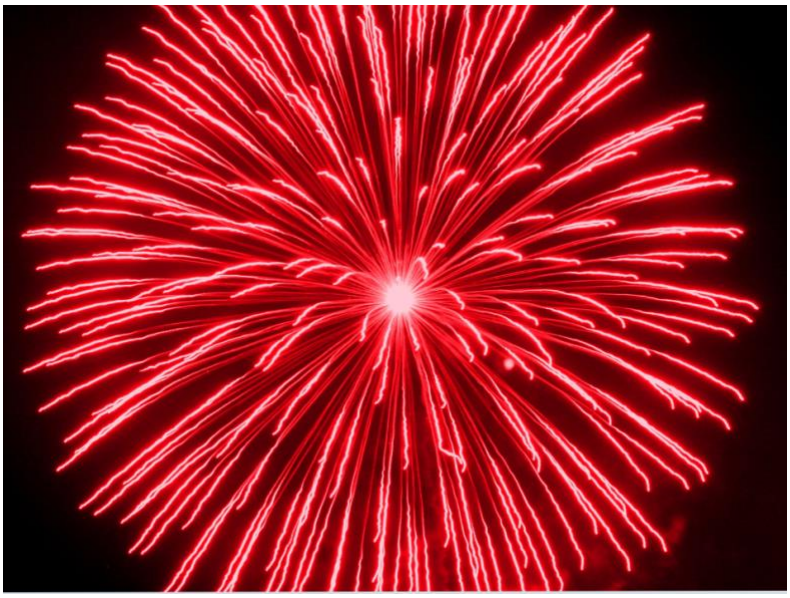
- Caregiver must attend education sessions to prepare for home monitoring and identify when to seek medical help.
- Recommendations include keeping patients within a specified radius (typically between a 30-to-45-minute drive) from treatment centers for safety.

Monitoring Tools and Protocols

- Monitoring body temperature, blood oxygen levels, and blood pressure is essential.
    - While some institutions supply thermometers, pulse oximeters, and blood pressure monitors directly to patients, others utilize vendor-provided wearable technology for continuous monitoring.
- Institutions should have clear pathways for admitting patients with severe CRS or neurotoxicity, ensuring comprehensive care management.

The bottom line: Ensuring safe and effective use of BTCEs hinges on institutions' capabilities to monitor and manage patient responses effectively.

⚠ Cytokine Release Syndrome



What is it? 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.

- **Deeper dive**: The connection between cancer cells and T-cells triggers the release of proinflammatory cytokines, particularly IL-6, IL-1, TNF-alpha, and IFN-γ. This creates a positive feedback loop between activated adaptive and innate immune cells, leading to excessive cytokine release and hyperinflammation.
- **Signs and symptoms:** chills, fever, headache, low blood pressure, low tissue oxygen level, muscle and joint aches, nausea, rapid heartbeat, rash, trouble breathing

How common is it? When does it occur?

- CRS is relatively common with BTCEs. However, the rates of higher-grade CRS are lower than those associated with CAR-T.

Drug	CRS Rate (Any Grade)	Median Time to CRS Onset	Median Duration of CRS
Leukemia			
Blinatumomab	14% of rrALL (up to 5% w/ grade 3+), 7% of MRD+ ALL	~4 days	3 days
Lymphoma			
Epcoritamab	~50% (2.5% grade 3) in DLBCL and 49% (0% grade 3+) in follicular lymphoma	~1–2 days	~1–3 days
Glofitamab	63% (4% grade 3+)	~1–2 days	~1–3 days
Mosunetuzumab	39% (17% grade 3+)	~1–2 days	~1–3 days
Multiple Myeloma			
Elranatamab	14% (0% grade 3+)	~2 days	~2 days
Linvoseltamab	46% (0.9% grade 3+)	~11 hours	~15 hours
Talquetamab	76% (1.5% grade 3+)	~1 day	~1 day
Teclistamab	72% (0.6% grade 3+)	~2 days	~2 days
Small Cell Lung Cancer			
Tarlatamab	55% (1.6% grade 3+)	~1 day	~2-6 days
Uveal Melanoma			
Tebentafusp	89% (0.8% grade 3+)	Within the first 3 weekly infusions	~2 days

Abbreviations: ALL, acute lymphocytic leukemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; MRD, measurable residual disease; r/r, relapsed/refractory

How is it graded? The most common grading used is the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading.

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Yes	Yes	Yes	Yes
	With			
Hypotension	None	Requiring IV fluids but not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
	And/or †			
Hypoxia	None	Requiring low-flow O_2 via nasal cannula‡ or blow-by	Requiring O_2 via high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring O_2 via positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation)

* Fever is defined as a temperature ≥100.4 °F (38°C) not attributable to any other cause. In patients who have CRS and then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring a low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 liters/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 liters/minute.

Management of CRS: Each institution may have a unique way of managing CRS, but basic principles generally include:

- Holding future BTCE administration until symptoms resolve.
- Administering supportive care to maintain normal blood pressure and blood oxygen.

Below are the management recommendations for CRS from each commercially approved agent, as stated in their US package inserts.

Leukemia BTCE

Blinatumomab	
Grade 1	No recommendations
Grade 2	No recommendations
Grade 3	**Patients Weighing 45 kg or More** • Interrupt blinatumomab. • Administer dexamethasone 8 mg every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 9 mcg/day, and escalate to 28 mcg/day after 7 days if the adverse reaction does not recur. **Patients Weighing Less Than 45 kg** • Interrupt blinatumomab. • Administer dexamethasone 5 mg/m^2 (maximum 8 mg) every 8 hours intravenously or orally for up to 3 days and taper thereafter over 4 days. • When CRS is resolved, restart blinatumomab at 5 mcg/m^2/day, and escalate to 15 mcg/m^2/day after 7 days if the adverse reaction does not recur.
Grade 4	• Discontinue blinatumomab permanently. Administer dexamethasone as instructed for Grade 3 CRS.

Lymphoma BTCEs

	Epcoritamab	Glofitamab	Mosunetuzumab
Grade 1	Withhold epcoritamab and manage per current practice guidelines. Ensure CRS symptoms are resolved prior to next dose of epcoritamab.	Withhold glofitamab and manage per current practice guidelines. If symptoms resolve, restart infusion at a slower rate. Ensure CRS symptoms are resolved for at least 72 hours before next dose. Consider slower infusion rate for next dose.	Withhold current infusion of mosunetuzumab and manage per current practice guidelines. If symptoms resolve, restart infusion at the same rate. Ensure CRS symptoms are resolved for at least 72 hours prior to the next dose of mosunetuzumab. Administer premedication prior to next dose of mosunetuzumab and monitor patient more frequently.
Grade 2	Withhold epcoritamab and manage per current practice guidelines. Ensure CRS symptoms are resolved prior to next dose of epcoritamab. Administer premedication prior to next dose of epcoritamab. (Note: Pre- and post-administration medications are given for all patients before Cycle 1, but are not recommended for subsequent cycles, unless a patient experiences Grade 2 or 3 CRS with the previous dose. If they experience Grade 2 or 3 CRS, they should receive dexamethasone 15 mg (or equivalent) as a premedication AND daily dexamethasone 15 mg (or equivalent) for 3 consecutive days until epcoritamab is given without subsequent CRS of Grade 2 or higher. For the next dose of epcoritamab, monitor more frequently and consider hospitalization.	Withhold glofitamab and manage per current practice guidelines. If symptoms resolve, restart infusion at a slower rate. Ensure CRS symptoms are resolved for at least 72 hours before next dose. For the next dose, consider a slower infusion rate, monitor more frequently, and consider hospitalization. For recurrent Grade 2 CRS, manage per Grade 3 CRS.	Withhold current infusion of mosunetuzumab and manage per current practice guidelines. If symptoms resolve, restart infusion at 50% rate. Ensure CRS symptoms are resolved for at least 72 hours prior to the next dose of mosunetuzumab. Administer premedication prior to next dose of mosunetuzumab and consider infusing the next dose at 50% rate. For the next dose of mosunetuzumab, monitor more frequently and consider hospitalization. **Recurrent Grade 2 CRS** Manage per Grade 3 CRS.
Grade 3	**First Occurrence**		
	Withhold epcoritamab and manage per current practice guidelines, which may include intensive care. Ensure CRS symptoms are resolved prior to the next dose of epcoritamab. Administer premedication prior to next dose of epcoritamab. (Note: Pre- and post-administration medications are given for all patients before Cycle 1, but are not recommended for subsequent cycles, unless a patient experiences Grade 2 or 3 CRS with the previous dose. If they experience Grade 2 or 3 CRS, they should receive dexamethasone 15 mg (or equivalent) as a premedication AND daily dexamethasone 15 mg (or equivalent) for 3 consecutive days until epcoritamab is given without subsequent CRS of Grade 2 or higher. Hospitalize for the next dose of epcoritamab.	Withhold glofitamab and manage per current practice guidelines, which may include intensive care. Ensure CRS symptoms are resolved for at least 72 hours before next dose. Hospitalize for the next dose, monitor more frequently, and consider a slower infusion rate.	Withhold mosunetuzumab, manage per current practice guidelines and provide supportive therapy, which may include intensive care. Ensure CRS symptoms are resolved for at least 72 hours prior to the next dose of mosunetuzumab. Administer premedication prior to next dose of mosunetuzumab and infuse the next dose at 50% rate. Hospitalize for the next dose of mosunetuzumab.
	Recurrent Grade 3 CRS		
	Permanently discontinue epcoritamab. Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.	Permanently discontinue glofitamab.	Permanently discontinue mosunetuzumab. Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.

Grade 4	Permanently discontinue epcoritamab. Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.	Permanently discontinue glofitamab and manage per current practice guidelines, which may include intensive care.	Permanently discontinue mosunetuzumab. Manage CRS per current practice guidelines and provide supportive therapy, which may include intensive care.

Multiple Myeloma BTCEs

	Elranatamab	Linvoseltamab	Talquetamab	Teclistamab
Grade 1	Withhold elranatamab until CRS resolves. Administer pretreatment medications prior to next dose of elranatamab.	Withhold linvoseltamab until CRS resolves. Provide supportive care, which may include intensive care.	Withhold talquetamab until CRS resolves. Administer pretreatment medication prior to next dose.	Withhold teclistamab until CRS resolves. Administer pretreatment medications prior to next dose of teclistamab.
Grade 2	Withhold elranatamab until CRS resolves. Monitor patients daily for 48 hours following the next dose of elranatamab. Instruct patients to remain within proximity of a healthcare facility, and consider hospitalization. Administer pretreatment medications prior to next dose of elranatamab.	Withhold linvoseltamab until CRS resolves. Provide supportive care, which may include intensive care. Consider a decrease in infusion rate up to 50% (no more than 6 hours total) when resuming treatment. Increase rate on subsequent infusions if tolerated. Monitor patients within proximity of a healthcare facility for 24 hours following this dose, and consider hospitalization.	Withhold talquetamab until CRS resolves. Administer pretreatment medications prior to next dose. Patients should be hospitalized for 48 hours following the next dose.	Withhold teclistamab until CRS resolves. Administer pretreatment medications prior to next dose of teclistamab. Patients should be hospitalized for 48 hours following the next dose of teclistamab.
Grade 3				
	Withhold elranatamab until CRS resolves. Provide supportive therapy, which may include intensive care. Patients should be hospitalized for 48 hours following the next dose of elranatamab. Administer pretreatment medications prior to next dose of elranatamab.	Withhold linvoseltamab until CRS resolves. Provide supportive care, which may include intensive care. **Resume treatment at a decreased infusion rate up to 50% (no more than 6 hours total) and hospitalize for 24 hours after the administration for this dose**. After resuming treatment, if the administered dose is tolerated, continue with the next dose of the recommended dosing regimen. If the full dose is tolerated, infusion rate can be increased to the rate prior to the adverse reaction.	**Duration less than 48 hours** Withhold talquetamab until CRS resolves. Provide supportive therapy, which may include intensive care. Administer pretreatment medications prior to the next dose. Patients should be hospitalized for 48 hours following the next dose.	**Duration less than 48 hours** Withhold teclistamab until CRS resolves. Provide supportive therapy, which may include intensive care. Administer pretreatment medications prior to next dose of teclistamab. Patients should be hospitalized for 48 hours following the next dose of teclistamab.
	Permanently discontinue therapy with elranatamab. Provide supportive therapy, which may include intensive care.	Permanently discontinue therapy with linvoseltamab. Provide supportive care, which may include intensive care.	**Recurrent or duration greater than or equal to 48 hours** Permanently discontinue talquetamab. Provide supportive therapy, which may include intensive care.	**Recurrent or duration greater than or equal to 48 hours** Permanently discontinue teclistamab Provide supportive therapy, which may include intensive care.
Grade 4	Permanently discontinue therapy with elranatamab.	Permanently discontinue therapy with linvoseltamab.	Permanently discontinue talquetamab.	Permanently discontinue teclistamab.

	Provide supportive therapy, which may include intensive care.	CRS should be managed per Grade 3 recommendations.	Provide supportive therapy, which may include intensive care.	Provide supportive therapy, which may include intensive care.

Small Cell Lung Cancer BTCE

Tarlatamab	
Grade 1	• Administer symptomatic treatment (e.g., acetaminophen) for fever.
Grade 2	• Recommend hospitalization for a minimum of 24 hours with cardiac telemetry and pulse oximetry. • Administer symptomatic treatment (e.g., acetaminophen) for fever. • Administer supplemental oxygen and intravenous fluids when indicated. • Consider dexamethasone (or equivalent) 8 mg IV. • Consider tocilizumab (or equivalent). • When resuming treatment at the next planned dose, monitor patients from the start of the tarlatamab infusion for 22 to 24 hours in an appropriate healthcare setting.
Grade 3	**In addition to Grade 2 treatment:** • Recommend intensive monitoring, e.g., ICU care. • Administer dexamethasone (or equivalent) 8 mg IV every 8 hours up to 3 doses. • Vasopressor support as needed. • High flow oxygen support as needed. • Recommend tocilizumab (or equivalent) • Prior to the next dose, administer concomitant medications as recommended for Cycle 1. • When resuming treatment at the next planned dose, monitor patients from the start of the tarlatamab infusion for 22 to 24 hours in an appropriate healthcare setting.
Grade 4	• ICU care. • Per Grade 3 treatment. • Recommend tocilizumab (or equivalent).

Uveal Melanoma BTCE

Tebentafusp	
Grade 1	No recommendations
Grade 2	• If hypotension and hypoxia do not improve within 3 hours or CRS worsens, escalate care and manage according to next higher level of severity • For moderate CRS that is persistent (lasting 2-3 hours) or recurrent, administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 3	• Withhold tebentafusp until CRS and sequelae have resolved • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent) • Resume tebentafusp at same dose level (i.e., do not escalate if severe CRS occurred during initial dose escalation; resume escalation once dosage is tolerated) • For severe CRS, administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 4	• Permanently discontinue tebentafusp • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)

🧠 Neurotoxicity (including ICANS)

What is it? 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.

- **Non-ICANS neurotoxicity**: ICANS is a term that describes some, but not all, of these neurologic effects.
- **Signs and symptoms**: anxiety, confusion, dizziness, feeling very sleepy, headache, memory issues, shaking, trouble finding words or speaking, trouble sleeping

How common is it? When does it occur?

- BTCE-associated neurologic problems occur less frequently than CRS.
- Incidence and severity of ICANS is lower with BTCEs than with CAR-T.

Drug	ICANS rate	Median Time to ICANS Onset	Median Duration of ICANS
Leukemia			
Blinatumomab	Neurologic toxicities: 65% (13% grade 3+) ICANS: 7.5%	2 weeks	Not reported
Lymphoma			
Epcoritamab	6% in both DLBCL and FL	From start of treatment: DLBCL: 16.5 days FL: 21.5 days Relative to the most recent administration: DLBCL and FL: 3 days	DLBCL: 4 days FL: 2 days
Glofitamab	4.8%	Not reported	Not reported
Mosunetuzumab	2.1%	17 days	3 days
Multiple Myeloma			
Elranatamab	3.3%	Relative to the most recent administration: 3 days	2 days
Linvoseltamab	8%	Relative to the most recent administration: 1 day	2 days
Talquetamab	9%	Relative to the most recent administration: 2.5 days	2 days
Teclistamab	6%	Relative to the most recent administration: 4 days	3 days
Small Cell Lung Cancer			
Tarlatamab	9%	From start of treatment: 29.5 days	33 days
Uveal Melanoma			
Tebentafusp	Not reported	Not reported	Not reported

Abbreviations: ALL, acute lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; ICANS, immune effector cell–associated neurotoxicity syndrome; MRD, measurable residual disease; r/r, relapsed/refractory

How is it graded?

- ICANS grade is determined by the **most severe** event according to the:
  - ICE score
  - Level of consciousness
  - Seizure
  - Motor findings
  - Raised intracranial pressure/cerebral edema (not attributable to any other cause).
- Example: A patient with an ICE score of 3 who has a generalized seizure is classified as having Grade 3 ICANS.

What's an ICE (Immune Effector Cell-associated Encephalopathy) Score?

Category	Assessment	Point(s)
Orientation	Orientation to year, month, city, hospital	4 (1 point each)
Naming	Name 3 objects (e.g., clock, pen, button)	3 (1 point each)
Following commands	(e.g., Show me 2 fingers or close your eyes and stick out your tongue)	1
Writing	Ability to write a standard sentence (e.g., Our national bird is the bald eagle)	1
Attention	Count backwards from 100 by 10	1
	Total	**____/10**

Grading by ICE score

- Score 10: No impairment
- Score 7-9: Grade 1 ICANS
- Score 3-6: Grade 2 ICANS
- Score 0-2: Grade 3 ICANS
    - A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia or may be classified as having Grade 4 ICANS if the patient is unarousable
- Score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

ASCTC 2019 Grading of ICANS

Symptom/Sign	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	None	None	Any clinical seizure (focal or generalized) that resolves rapidly (<5 minutes) or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (5 minutes or more) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	None	None	None	Deep focal motor weakness such as hemiparesis or paraparesis
Raised intracranial pressure/ cerebral edema	None	None	Focal/local edema or neuroimaging	Diffuse cerebral edema on neuroimaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

Management of Neurotoxicity: Each institution may have a unique way of managing neurotoxicity, including ICANS, but the main principles typically include:

- Holding future BTCE administration until symptoms resolve.
- Administering supportive care.

Below are the management recommendations for ICANS from each commercially approved agent, as stated in their US package inserts.

Leukemia BTCE

Blinatumomab		
	Patients Weighing 45 kg or More	**Patients Weight Less Than 45 kg**
Grade 1	No recommendations	No recommendations
Grade 2	• Interrupt blinatumomab until ICANS resolves. • Administer corticosteroids and manage according to current practice guidelines. • When ICANS is resolved, restart blinatumomab at 9 mcg/day. • Escalate to 28 mcg/day after 7 days if the adverse reaction does not recur.	• Interrupt blinatumomab until ICANS resolves. • Administer corticosteroids and manage according to current practice guidelines. • When ICANS is resolved, restart blinatumomab at 5 mcg/m^2/day. • Escalate to 15 mcg/m^2/day after 7 days if the adverse reaction does not recur.
Grade 3	• Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 mcg/day. • Escalate to 28 mcg/day after 7 days if the adverse reaction does not recur. • If the adverse reaction occurred at 9 mcg/day, or if the adverse reaction takes more than 7 days to resolve, discontinue blinatumomab permanently.	• Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 5 mcg/m^2/day. • Escalate to 15 mcg/m^2/day after 7 days if the adverse reaction does not recur. • If the adverse reaction occurred at 5 mcg/m^2/day, or if the adverse reaction takes more than 7 days to resolve, discontinue blinatumomab permanently.
	• Discontinue blinatumomab permanently if more than one seizure occurs. • If ICANS, administer corticosteroids and manage according to current practice guidelines.	
Grade 4	• Discontinue blinatumomab permanently. • If ICANS, administer corticosteroids and manage according to current practice guidelines.	

Lymphoma BTCEs

	Epcoritamab	Glofitamab	Mosunetuzumab
Grade 1	Withhold epcoritamab until ICANS resolves. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.	Continue glofitamab and monitor neurologic toxicity symptoms. If ICANS, manage per current practice guidelines.	Continue mosunetuzumab and monitor neurologic toxicity symptoms. If ICANS, manage per current practice guidelines.
Grade 2	Withhold epcoritamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.	Withhold glofitamab until neurologic toxicity symptoms improve to Grade 1 or baseline. Provide supportive therapy, and consider neurologic evaluation. If ICANS, manage per current practice guidelines.	Withhold mosunetuzumab until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 72 hours. Provide supportive therapy, and consider neurologic evaluation. If ICANS, manage per current practice guidelines.
Grade 3	**First Occurrence**		
	Withhold epcoritamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. Provide supportive therapy, which may include intensive care.	Withhold glofitamab until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 7 days. For Grade 3 neurologic events lasting more than 7 days, consider permanently discontinuing glofitamab. Provide supportive therapy, and consider neurology evaluation. If ICANS, manage per current practice guidelines.	Withhold mosunetuzumab until neurologic toxicity symptoms improve to Grade 1 or baseline for at least 72 hours. Provide supportive therapy, which may include intensive care, and consider neurology evaluation. If ICANS, manage per current practice guidelines. If recurrence of ICANS, permanently discontinue mosunetuzumab.
	Recurrent Grade 3 ICANS		
	Permanently discontinue epcoritamab. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. Provide supportive therapy, which may include intensive care.		
Grade 4	Permanently discontinue epcoritamab. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for	Permanently discontinue glofitamab. Provide supportive therapy, which may include intensive care, and consider neurology evaluation. If ICANS, manage per current practice guidelines.	Permanently discontinue mosunetuzumab. Provide supportive therapy, which may include intensive care, and consider neurology evaluation. If ICANS, manage per current practice guidelines.

	starting non-sedating, anti-seizure medicines for seizure prophylaxis. Provide supportive therapy, which may include intensive care.		

Multiple Myeloma BTCEs

	Elranatamab	Linvoseltamab	Talquetamab	Teclistamab
Grade 1	Withhold elranatamab until ICANS resolves. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis.	Withhold linvoseltamab until neurologic symptoms resolve or return to baseline. Provide supportive therapy and manage per current practice guidelines. Consider non-sedating, anti-seizure medications for seizure prophylaxis.	Withhold talquetamab until ICANS resolves. Monitor neurologic symptoms, and consider consultation with neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	Withhold teclistamab until ICANS resolves. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis.
Grade 2	Withhold elranatamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. Monitor patients daily for 48 hours following the next dose of elranatamab. Instruct patients to remain within proximity of a healthcare facility, and consider hospitalization.	Withhold linvoseltamab until neurologic symptoms resolve or return to baseline. Provide supportive therapy and manage per current practice guidelines. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Consider non-sedating, anti-seizure medications for seizure prophylaxis. Monitor patients within proximity of a healthcare facility for 24 hours following the next dose of linvoseltamab and consider hospitalization.	Withhold talquetamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Patients should be hospitalized for 48 hours following the next dose of talquetamab.	Withhold teclistamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. Patients should be hospitalized for 48 hours following the next dose of teclistamab.
Grade 3	**First Occurrence**			
	Withhold elranatamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care. Patients should be hospitalized for 48 hours following the next dose of elranatamab.	Withhold linvoseltamab until neurologic symptoms resolve or return to baseline. Provide supportive therapy and manage per current practice guidelines. Consider neurology evaluation. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Consider non-sedating, anti-seizure medications for seizure prophylaxis. Resume treatment with linvoseltamab at a reduced dose and hospitalize for 24 hours after the administration of the dose. After resuming treatment, if the administered dose is tolerated, continue with the next dose of the recommended dosing regimen.	Withhold talquetamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care. Patients should be hospitalized for 48 hours following the next dose of talquetamab.	Withhold teclistamab until ICANS resolves. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. Provide supportive therapy, which may include intensive care. Patients should be hospitalized for 48 hours following the next dose of teclistamab.

	Recurrent Grade 3 ICANS			
	Permanently discontinue elranatamab. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care.	Permanently discontinue linvoseltamab. Provide supportive therapy and manage per current practice guidelines. Consider neurology evaluation. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Consider non-sedating, anti-seizure medications for seizure prophylaxis.	Permanently discontinue talquetamab. Administer dexamethasone 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care.	Permanently discontinue teclistamab. Administer dexamethasone 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. Provide supportive therapy, which may include intensive care.
Grade 4	Permanently discontinue elranatamab. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously for 3 days. Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medications (e.g., levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care.	Permanently discontinue linvoseltamab. Provide supportive therapy and manage per current practice guidelines. Consider neurology evaluation. Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Consider non-sedating, anti-seizure medications for seizure prophylaxis.	Permanently discontinue talquetamab. Administer dexamethasone 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. Provide supportive therapy, which may include intensive care.	Permanently discontinue teclistamab. Administer dexamethasone 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. Alternatively, consider administration of methylprednisolone 1,000 mg per day intravenously and continue methylprednisolone 1,000 mg per day intravenously for 2 or more days. Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. Provide supportive therapy, which may include intensive care.

Small Cell Lung Cancer BTCEs

Tarlatamab	
Grade 1	• Withhold tarlatamab until ICANS resolves, then resume tarlatamab at the next scheduled dose. • Supportive care.
Grade 2	• Withhold tarlatamab until ICANS resolves, then resume tarlatamab at the next scheduled dose. • Supportive care. • Dexamethasone (or equivalent) 10 mg IV. Can repeat every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours if symptoms worsen. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management. • Monitor patients for 22 to 24 hours following the next dose of tarlatamab.
Grade 3	• Withhold tarlatamab until the ICANS resolves, then resume tarlatamab at the next scheduled dose. • If there is no improvement to grade ≤ 1 within 7 days or grade 3 toxicity reoccurs within 7 days of reinitiation, permanently discontinue tarlatamab. • For recurrent grade 3 events, permanently discontinue. • Recommend intensive monitoring, e.g., ICU care. • Consider mechanical ventilation for airway protection. Dexamethasone§ (or equivalent) 10 mg IV every 6 hours or methylprednisolone 1 mg/kg IV every 12 hours. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Monitor patients for 22 to 24 hours following the next dose of tarlatamab.
Grade 4	• Permanently discontinue tarlatamab. • ICU care. • Consider mechanical ventilation for airway protection. • High dose corticosteroids. • Consider repeat neuroimaging (CT or MRI) every 2-3 days if patient has persistent Grade ≥ 3 neurotoxicity. • Treat convulsive status epilepticus per institutional guidelines.

Uveal Melanoma BTCE

- Tebentafusp has no specific recommendations regarding neurotoxicity.

✅ REMS Certification

REMS (Risk Evaluation and Mitigation Strategies) programs are implemented to ensure that the benefits of a drug outweigh its risks. As of March 2025, only the BTCEs approved for multiple myeloma have REMS programs.

Why it matters: Four BTCEs (elranatamab, linvoseltamab, talquetamab, and teclistamab) have REMS requirement due to the risk of cytokine release syndrome and neurotoxicity. Prescribers, pharmacies, and healthcare settings have specific requirements that need to be met in order to use these agents.

Although 4 BTCEs have REMS requirements, 2 of the agents (talquetamab and teclistamab) fall under the same REMS programs. As such, there are only 3 BTCE-associated REMS programs.

1. ELREXFIO™ REMS
2. LYNOZYFIC™ REMS
3. TECVAYLI® and TALVEY® REMS

What do these programs require?

Here is a general overview of what these programs require:

- **Prescriber**
  - Complete a knowledge assessment
  - Complete the prescriber enrollment form
  - Before treatment initiation, counsel and provide the patients and/or their caregivers using the Patient Wallet Card, which outlines risk of CRS and neurologic toxicities
- **Pharmacy and Healthcare Settings**
  - Designate an Authorized Representative (AR) for Pharmacy and Healthcare Setting
    - Can be any responsible individual assigned by the Pharmacy or Healthcare setting (e.g., pharmacist, pharmacy technician, registered nurse).
    - Exception: The AR cannot be the same person that's a certified prescriber of the BTCE.
  - AR completes and submits the Pharmacy and Healthcare Setting Enrollment Form
  - Train all relevant staff involved in dispensing the BTCEs.

Go deeper. Below is a list of general responsibilities of pharmacy and healthcare setting.

- Report serious adverse events of CRS and neurologic toxicities of the REMS
- Maintain records of staff training
- Maintain records that processes and producers are in place and are being followed
- Maintain records of ALL dispenses of the BTCE and provide data to the REMS and Wholesalers-distributors, as requested.
- Comply with audits carried out by the drug manufacturer or third party acting on behalf of the drug manufacturer to ensure that all training, processes, and procedures are in place and being followed
- Do NOT distribute, transfer, loan, or sell the BTCE expect to certified pharmacies and healthcare settings
- Confirm prescriber certification for ALL dispenses
  - Log into the online REMS website
  - Select REMS Dispense Authorization (RDA)
  - Enter the prescriber's NPI number or name and confirm their certification status
  - The BTCE may only be dispensed upon generation of an RDA
  - Maintain records of all BTCE dispenses in a log or medical record for audit purposes.

Package Inserts Referenced in Alphabetical Order

1. BLINCYTO (blinatumomab). Thousand Oaks, CA. Amgen Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2024/125557s030lbl.pdf. Published December 17, 2024. Accessed March 27, 2025.
2. COLUMVI (glofitamab-gxbm). South San Francisco, CA. Genentech, Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2023/761309s000lbl.pdf. Published June 15, 2023. Accessed March 27, 2025.
3. ELREXFIO (elranatamab-bcmm). New York, NY. Pfizer Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2023/761345Orig1s000lbl.pdf. Published August 14, 2023. Accessed March 27, 2025.
4. EPKINLY (epcoritamab-bysp). Plainsboro, NJ. Genmab US, Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2024/761324s003lbl.pdf. Published June 26, 2024. Accessed March 27, 2025.
5. IMDELLTRA (tarlatamab-dlle). Thousand Oaks, CA. Amgen Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2024/761344s000lbl.pdf. Published May 16, 2024. Accessed March 27, 2025.
6. KIMMTRAK (tebentafusp-tebn). Conshohocken, PA. Immunocore Commercial LLC. www.accessdata.fda.gov/drugsatfda_docs/label/2024/761228s003lbl.pdf. Published June 27, 2024. Accessed March 27, 2025.
7. LUNSUMIO (mosunetuzumab-axgb). South San Francisco, CA. Genentech, Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2024/761263s005lbl.pdf. Published November 22, 2024. Accessed March 27, 2025.
8. LYNOZYFIC (linvoseltamab-gcpt). Tarrytown, NY. Regeneron Pharmaceuticals, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761400s000lbl.pdf. Published July 2, 2025. Accessed August 12, 2025.
9. TALVEY (talquetamab-tgvs). Horsham, PA. Janssen Biotech, Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2023/761342s000lbl.pdf. Published August 9, 2023. Accessed March 27, 2025.
10. TECVAYLI (teclistamab-cqyv). Horsham, PA. Janssen Biotech, Inc. www.accessdata.fda.gov/drugsatfda_docs/label/2024/761291s008lbl.pdf. Published Mary 28, 2024. Accessed March 27, 2025.

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