Markey Cancer Center

NCI Comprehensive Cancer Center

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BEST HOSPITALS U.S.News & WORLD REPORT CANCER 2023-2024

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Best Practices in the Delivery of Bispecific Antibody Therapies

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DISCLOSURES

- Hiffsa Taj no disclosures
- Christopher Gates no disclosures
- Sarah Sertich no disclosures
- Allison Mueller no disclosures
- Seth Roller has no disclosures
- Bryant Clemons no disclosures
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Learning Objectives

- 1. Describe the mechanism of action of bispecific antibodies and their role in hematologic and solid malignancies

- 2. Differentiate bispecific therapies from monoclonal antibodies, cellular therapies, and immunotherapies

- 3. Identify indications and approved agents in current oncology practice

- 4. Discuss implementation of interdisciplinary communication and coordination of care to ensure patient education, symptom management, and follow up across the care continuum


Bispecific Antibody
Therapies

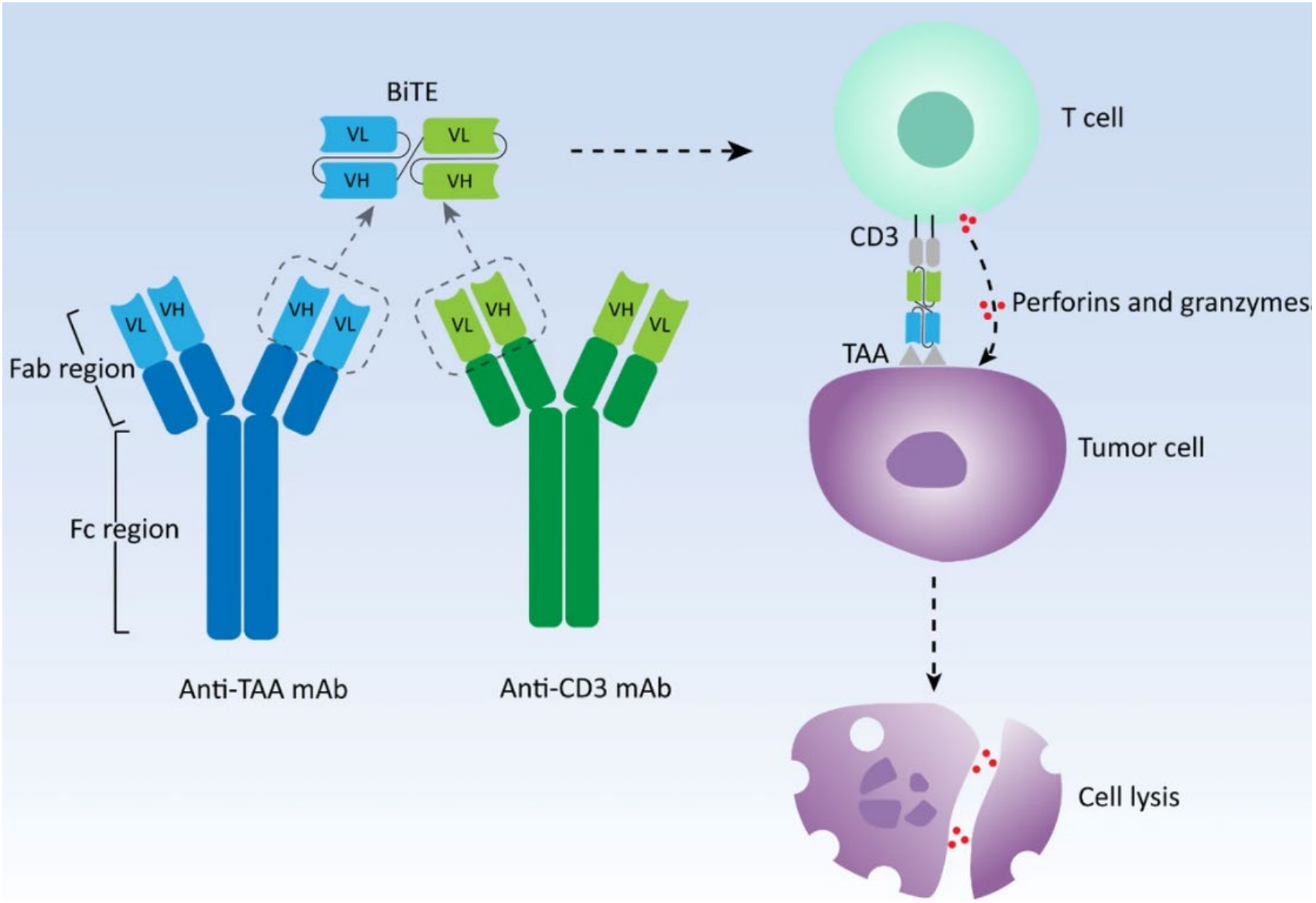
What are Bispecific Antibodies?

Bispecific antibody (BsAb):

monoclonal antibody with two distinct binding domains allowing it to bind to two antigens or two epitopes of the same antigen simultaneously

Bispecific T-cell engager (BiTE™):

bispecific molecule or antibody designed to form an immune synapse between T-cells (via the CD3 receptor) and tumor cells (via tumor-associated antigens)



Zhou S, et al. Biomarker Res. 2021; 9:38

True or False: Bispecific Antibody Edition

All monoclonal antibodies are bispecifics.

FALSE: Most bispecifics are monoclonal antibodies ("-mab"), but most monoclonal antibodies only target one antigen (e.g., rituximab targets CD20).

All bispecific therapies are monoclonal antibodies.

FALSE: While most commercially available bispecific T-cell engagers are monoclonal antibodies, tebentafusp-tebn is not technically an antibody product.

All bispecific antibodies are bispecific T-cell engagers.

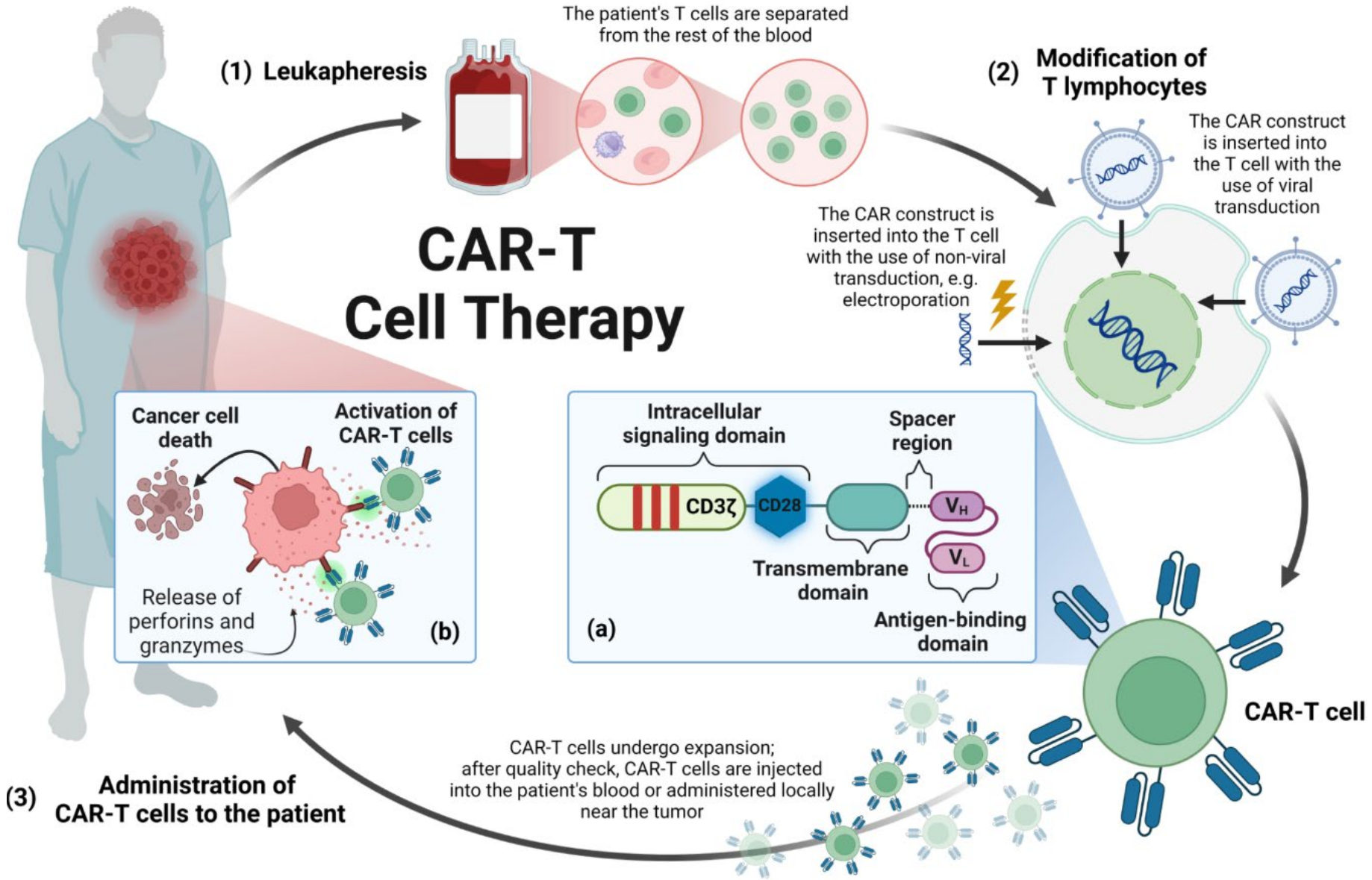
FALSE: This is a common mechanism of action for bispecifics, but there are bispecific antibodies that do not involve T-cells.

Non-T-cell Engaging Bispecific Antibodies

- Amivantamab-vmjw (non-small cell lung cancer)
  - Targets both *EGFR* and *MET*
- Emicizumab-kxwh (hemophilia A)
  - Targets/bridges coagulation factors IXa and X
- Faricimab-svoa (macular edema/degeneration)
  - Targets both Ang-2 and VEG-A
- Zanidatamab-hrii (*HER2* positive biliary tract cancer)
  - Targets two distinct extracellular sites on *HER2*
- Zenocutuzumab-zbco (non-small cell lung cancer & pancreatic cancer)
  - Targets both *HER2* and *HER3*

FDA-approved Bispecific T-cell Engagers

Disease state	Drug	FDA approval date	Tumor-associated antigen	Offered at UK?
Acute lymphoblastic leukemia	Blinatumomab	2014	CD19	✓
Lymphoma	Mosunetuzumab-axgb	2022	CD20	✓
	Epcoritamab-bysp	2023		✓
	Glofitamab-gxbm	2023		✓
Multiple myeloma	Teclistamab-cqyv	2022	BCMA	✓
	Elranatamab-bcmm	2023		✓
	Linvoseltamab-gcpt	2025		
	Talquetamab-tgvs	2023	GPRC5D	✓
Small cell lung cancer	Tarlatamab-dlle	2024	DLL3	✓
Uveal melanoma	Tebentafusp-tebn	2022	gp100	✓



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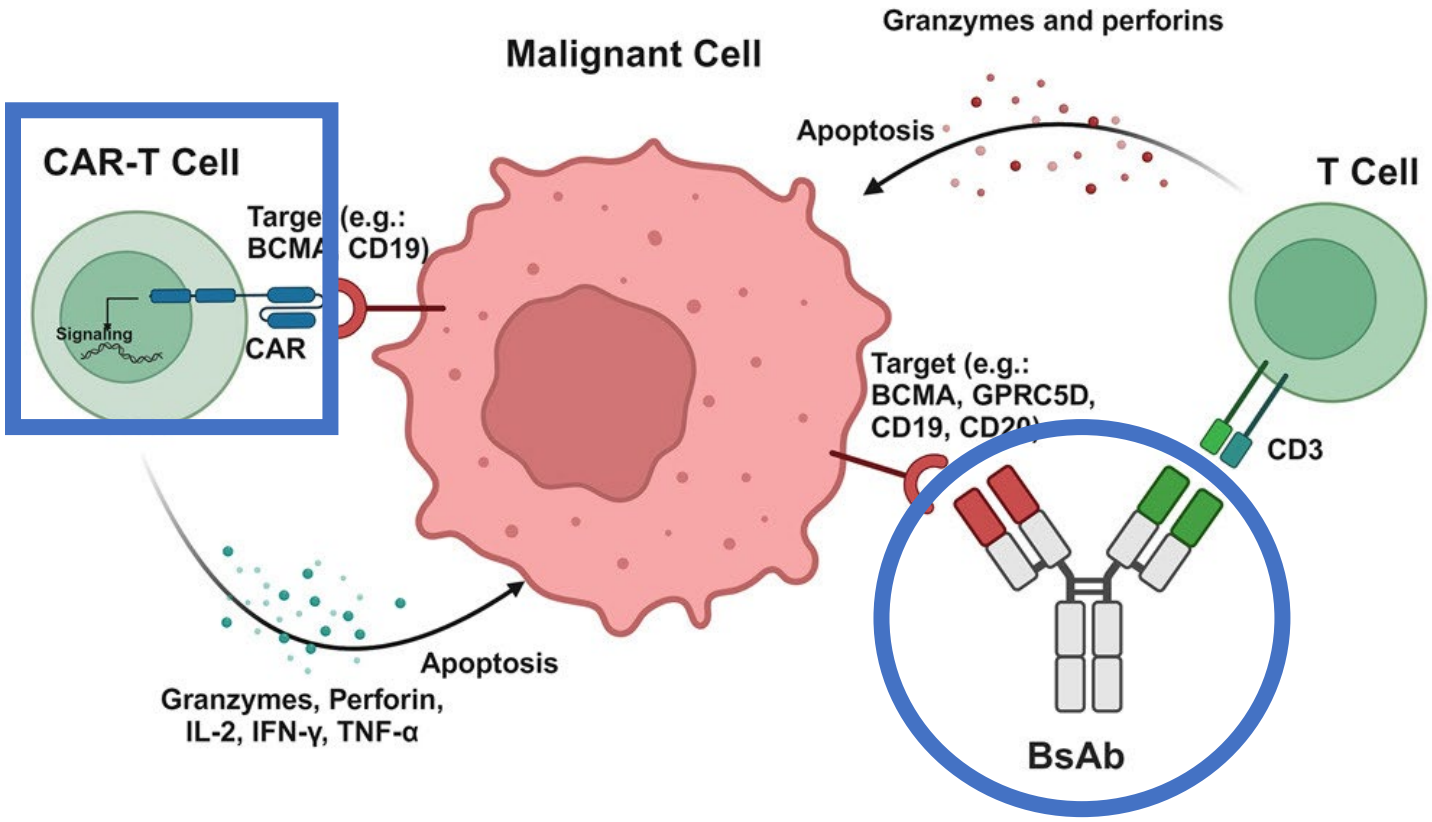


Al Hadidi S, et al. Mol Ther. 2024 Aug 7;32(8):2444-2460

Bispecifics vs. CAR-T

	Bispecifics	CAR-T
Structure	Recombinant antibodies/molecules	Genetically re-engineered T-cell
Anti-tumor mechanisms	Inducing tumor cell lysis by the formation of immune synapse between T-cells and tumor cells	Inducing tumor cell lysis by the formation of immune synapse between T-cells and tumor cells
Recruitment of T-cells	Passive – dependent on endogenous T-cells and redirecting them to kill tumor cells	Active – redirecting engineered T-cells outside of body to kill tumor cells
Advantages	Off-the-shelf	Endogenous T-cell independent; longer half-life
Disadvantages	Antigen-dependent; continuous administration due to shorter half-life	Antigen-dependent; complex pre-infusion process

Zhou S, et al. Biomarker Res. 2021; 9:38

Bispecific Toxicities

- Cytokine release syndrome
- Neurologic toxicity
- Cytopenias
- Infection

Toxicities

Cytokine release syndrome (CRS)

- Condition occurring as a result of rapid cytokine release into the bloodstream from immune cells
- Fever, hypoxia, hypotension, tachycardia, etc.

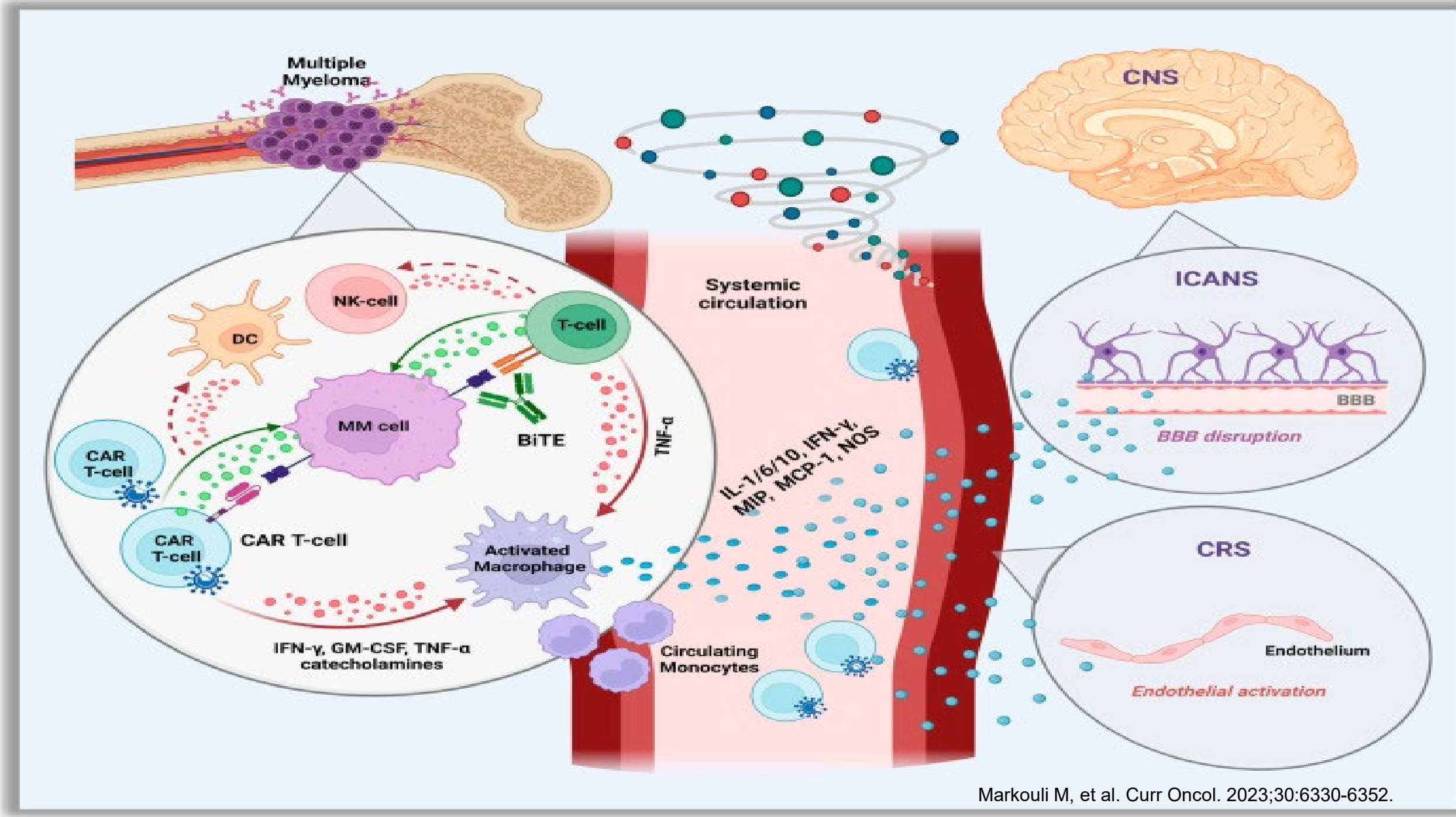
Neurologic toxicity

- Immune effector-cell associated neurotoxicity syndrome (ICANS)
  - Headache, confusion, tremor, seizure, comatose, etc.
- Other manifestations:
  - Parkinsonism, Guillain-Barré, sensory neuropathy, etc.

Toxicities in Multiple Myeloma – Bispecifics vs. CAR-T

Bispecific	CRS any grade	CRS grade ≥ 3	ICANS	Neurotoxicity any grade	Neurotoxicity grade ≥ 3
Elranatamab	58%	0.5%	3.3%	59%	7%
Talquetamab	76%	1.5%	9%	55%	6%
Teclistamab	72%	0.6%	6%	57%	2.4%
CAR-T	**CRS any grade**	**CRS grade ≥ 3**	**ICANS**	**Neurotoxicity any grade**	**Neurotoxicity grade ≥ 3**
Idecabtagene vicleucel	89%	7%	15%*	40%	4.6%
Ciltacabtagene vicleucel	84%	4%	13%	24%	7%

*pulled from real world data presented at ASCO 2022



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Trends in Bispecific-related CRS & ICANS

Cytokine release syndrome	Bispecifics	CAR-T
Frequency	Common	Common
Onset	Typically in step-up dosing or with 1st treatment-dose	Typically within 1 week
Intensity	Very rarely ≥ Grade 3	Rarely ≥ Grade 3
ICANS	**Bispecifics**	**CAR-T**
Frequency	Very uncommon	Uncommon
Onset	Typically in step-up dosing or with 1st treatment dose	Typically within 1 week
Manifestations of neurotoxicity	Most commonly headache, dizziness; ICANS rare	More commonly confusion/ICANS-related

Patient Education

Adverse effects

CRS / ICANS
Infectious

Temperature, symptom monitoring, and RTC precautions

Frequency of treatment

Expectations for hospitalization

Contact information for clinic and after-hours on call physician

Provider Education

Inpatient nursing staff

Outpatient infusion staff

Medical oncology inpatient team (attending, fellow, PA/APRNs, PharmD)

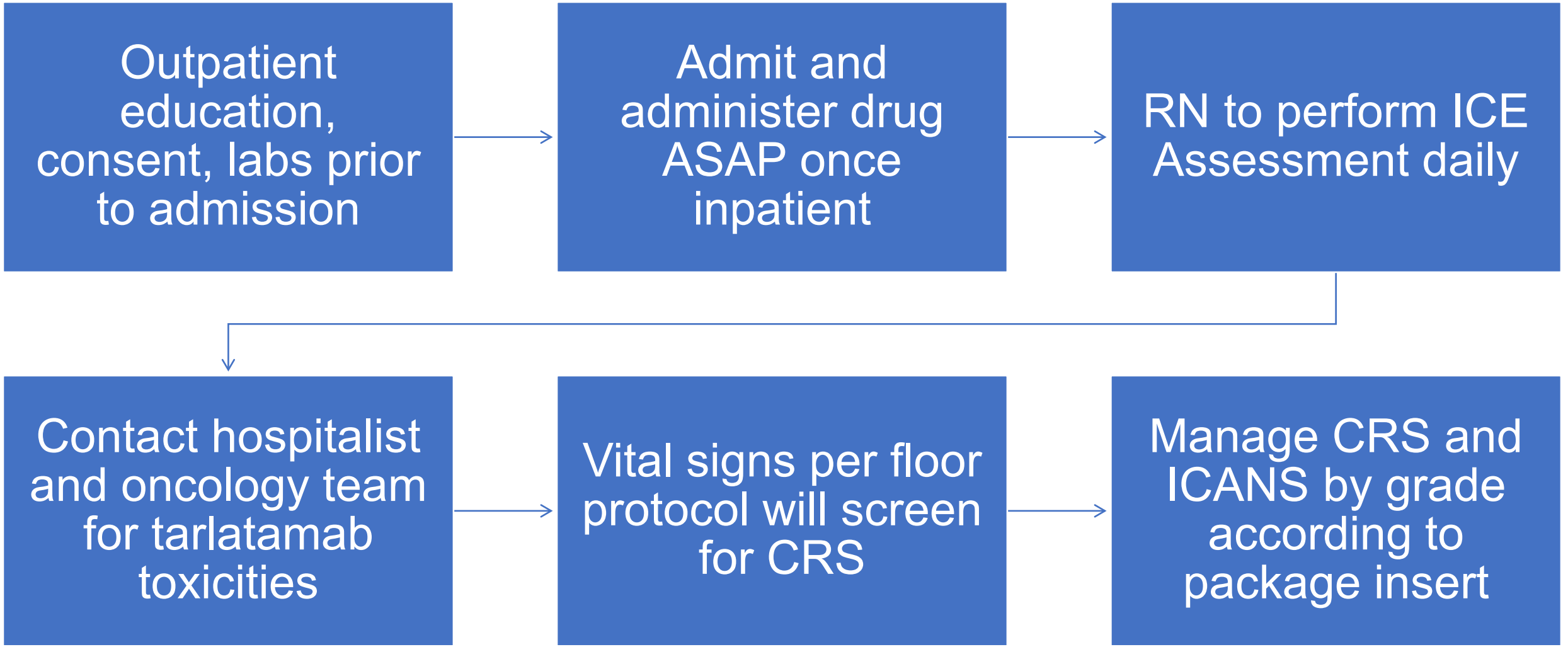
On-call physicians

Hospitalists and other consulting physicians who might be called for toxicities (neurology, intensivists, etc.)

Bispecific Therapy Monitoring

- Step-up doses planned
- Hospitalization often required (currently UK policy)
  - Varying admission length
- “Remain in the area” for 2-4 weeks
- Severe CRS / ICANS require re-admission
- Flat dosing with 2nd Cycle and beyond

Tarlatamab-dlle Protocol (C1D1, C1D8)

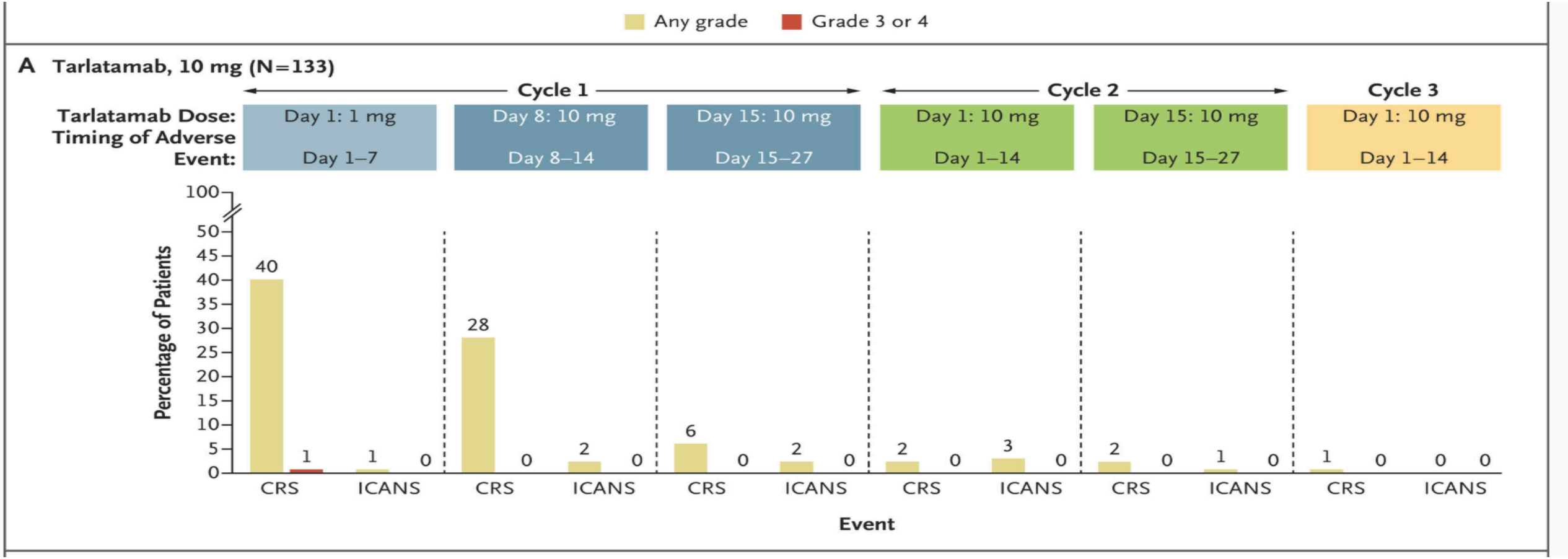


Tarlatamab-dlle Protocol (C1D1, C1D8)

1. Outpatient education, consent, labs prior to admission
2. Admit and administer drug ASAP once inpatient
3. RN to perform ICE Assessment daily
4. Contact hospitalist and oncology team for tarlatamab toxicities
5. Vital signs per floor protocol will screen for CRS
6. Manage CRS and ICANS by grade according to package insert

Tarlatamab-dlle CRS Onset

- Median onset to CRS: 13.5 hours
- Most frequent CRS within D1-8



Challenges to implementation

Each product has own protocol (REMS)

Requirement of 24/7 support

- Hospital bed availability
- On-call experts required
- Coordination with all teams
- Medications on site (tocilizumab)

How have some community centers offered Bispecific T cell engager therapies?

- Initial cycles at academic center
  - Remainder of cycles at community level
- REMS help / coordination from academic center
  - Share experiences
- Stepwise integration

Nursing & Psychosocial Care

Patient Monitoring

All patients are monitored with cardiac telemetry and continuous pulse oximetry and have vital signs ordered at specific frequencies during and following the infusion to monitor for hypotension, hypoxia, fever, tachycardia, and dysrhythmias.

All patients are assessed at baseline and then at ordered frequencies for Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Provider notified immediately of any changes in patient condition and patient treated per protocol.

Patient Monitoring

Baseline Assessment

- Cytokine Release Syndrome (CRS)
- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

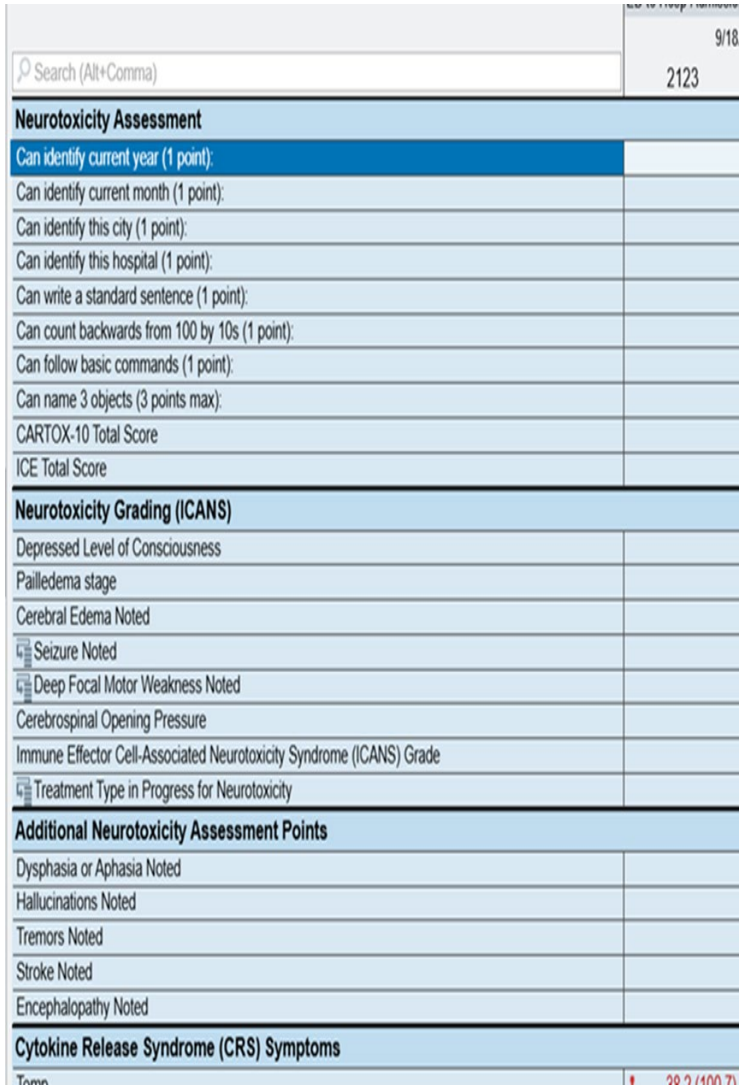
Ongoing Monitoring

- Cardiac telemetry
- Continuous pulse oximetry
- Vital signs
  - Hypotension, hypoxia, fever, tachycardia dysrhythmias

Assessing for CRS & ICANS

- Assessment tools in electronic health record

- ICANS:
  - Patient asked the same questions
  - Writes the same sentence when assessing for ICANS
  - Patient signature



Search (Alt+Comma)	9/18 2123
Neurotoxicity Assessment	
Can identify current year (1 point):	
Can identify current month (1 point):	
Can identify this city (1 point):	
Can identify this hospital (1 point):	
Can write a standard sentence (1 point):	
Can count backwards from 100 by 10s (1 point):	
Can follow basic commands (1 point):	
Can name 3 objects (3 points max):	
CARTOX-10 Total Score	
ICE Total Score	
Neurotoxicity Grading (ICANS)	
Depressed Level of Consciousness	
Pailledema stage	
Cerebral Edema Noted	
Seizure Noted	
Deep Focal Motor Weakness Noted	
Cerebrospinal Opening Pressure	
Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) Grade	
Treatment Type in Progress for Neurotoxicity	
Additional Neurotoxicity Assessment Points	
Dysphasia or Aphasia Noted	
Hallucinations Noted	
Tremors Noted	
Stroke Noted	
Encephalopathy Noted	
Cytokine Release Syndrome (CRS) Symptoms	
Temp	

Grading ICANS

- Graded similarly to other infusion reactions based on ICE score and severity
- Symptoms managed per protocol

ASTCT ICANS Consensus Grading for Adults

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

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; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.
* 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 (eg, 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.
§ 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.

Grading CRS

- Graded similar to hypersensitivity infusion reactions based on the severity
- Symptoms managed per protocol

CRS Grade	Management
Grade 1 Symptoms are not life threatening and require symptomatic treatment only (ie. fever, nausea, fatigue, headache, malaise)[1]	Supportive care[1] and rule out infection.
Grade 2 Symptoms require and respond to moderate intervention: - Oxygen requirement < 40% or < 3L nasal cannula to maintain oxygen saturation >90% - Hypotension responsive to fluids or one low dose vasopressor[6] - Grade 2 organ toxicity[7]	Administer **tocilizumab IV once;** may repeat dose every 8 hours. Limit to a maximum of 3 doses in 24 hours if no clinical improvement in 8 hrs. Maximum total of 4 doses. **<u>If no improvement within 24 hours after starting tocilizumab</u>:** Administer dexamethasone 10mg IV every 6 hours. Continue until Grade 1 or less, taper over 3 days. Patients who experience Grade ≥2 CRS should be monitored with continuous cardiac telemetry and pulse oximetry.
Grade 3 Symptoms require and respond to aggressive intervention: - Oxygen requirement ≥ 40% or > 3L nasal cannula to maintain oxygen saturation >90% - Hypotension requiring high dose[6] or multiple vasopressors or rapid and/or frequent vasopressor escalation - Grade 3 organ toxicity[7] - Grade 4 transaminitis (AST or ALT > 20 x ULN)[7] - New-onset altered mental status without other explanation - New cardiomyopathy without wall motion abnormality	Administer **tocilizumab IV once;** may repeat dose every 8 hours. Limit to a maximum of 3 doses in 24 hours. Maximum total of 4 doses. Administer dexamethasone 10mg IV every 6 hours. Continue until Grade 1 or less, taper over 3 days. Patients who experience Grade ≥2 CRS should be monitored with continuous cardiac telemetry and pulse oximetry.
Grade 4 Life threatening symptoms: • Requirements for ventilator support or continuous renal replacement therapy • Grade 4 organ toxicity (excluding transaminitis)[7]	Administer **tocilizumab IV once;** may repeat dose every 8 hours. Limit to a maximum of 3 doses in 24 hours. Maximum total of 4 doses. Administer high-dose methylprednisolone 1000mg IV every 24 hours for 3 days. If improves, manage as above. Continue until Grade 1 or less, taper as appropriate. Patients who experience Grade ≥2 CRS should be monitored with continuous cardiac telemetry and pulse oximetry.

Protocol

All team members involved in administration need to be familiar with the protocol for the therapy they are administering and have it readily available.

This aids in responding quickly and appropriately when infusion reactions do occur.

Especially helpful for providers unfamiliar with management of bispecific antibody toxicities who may be providing overnight coverage.

Protocol

Familiarity and readily available protocol for the therapy being administered

Timely response to manage symptoms

Helpful for providers unfamiliar with management of bispecific antibody toxicities providing overnight coverage.

Chain of Communication

Any changes in patient condition quickly communicated to provider.

Clear delineation of who should be contacted for specific concerns: oncology providers for issues related to bispecific antibody therapy, non-oncology hospitalist for issues not related to bispecific antibody therapy, hospitalist or fellow to contact oncology attending for severe reactions, etc.

0700-1700 APP (NP or PA) (Medical Oncology)

1700-1900 Fellow (Medical Oncology)

1900-2000 Hospital Medicine (swing coverage)

2000-0700 Hospital Medicine (night cross cover)

Integrating Psychosocial Care: Addressing Social Determinants of Health (SDOH) to Optimize Bispecific Therapy Outcomes

- Identify and address SDOH: housing, transportation, finances, social support
- Early social work involvement ensures patients can start and complete therapy
- Engage caregivers to support adherence and safe treatment
- Coordinate lodging, transportation, address food insecurity, and financial support

Ensuring Patients Can Get to Treatment

Lodging: American Cancer Society Hope Lodge, hospital vouchers, local housing programs (e.g., Open Arms)

Transportation: insurance-based transport (if eligible), paratransit, local and national volunteer driver programs, fuel reimbursement (through institutional grants or insurance)

Supports patients for step-up dosing and repeated visits

Psychosocial interventions enable consistent outpatient BsAb treatment attendance

Reducing Financial Toxicity to Maintain Treatment

National grants: Blood Cancer United, Multiple Myeloma Research Foundation, American Cancer Society, Cancer Cartel

Local grants: Shirley's Way, Kentucky Cancer Link, Gilda's Club Kentuckiana, hospital foundation funded grants

Copay assistance, SSDI/SSI resource navigation/ short-term disability & employer support

Travel stipends or lodging assistance for repeated visits

Prevents financial barriers from interrupting BsAb treatment

Supporting Basic Needs for Treatment Readiness

Food insecurity: grocery gift cards, meal delivery, pantries

Hygiene & clothing assistance through local community programs

Ensures patients have the resources to tolerate and complete BsAb treatment

Strengthening Emotional & Psychosocial Resilience

- Counseling provided by clinical social worker
- Connection to local and national support groups
- Referral to mental health therapist or psychiatrist for additional support
- Assess caregiver readiness, educate on monitoring side effects, provide caregiver support & counseling resources
- Goals-of-care discussions, survivorship planning, caregiver guidance
- *Supports emotional resilience, mental well-being, and home monitoring during BsAb treatment*

When Psychosocial Needs Are Addressed, Patient Outcomes Improve

TRANSPORTATION INSECURITY → HIGHER RISK OF MISSED VISITS

FINANCIAL DISTRESS → EARLY TREATMENT DISCONTINUATION

NAVIGATION & PSYCHOSOCIAL SUPPORT → IMPROVED ADHERENCE & SATISFACTION

STABLE SUPPORT SYSTEMS → FEWER ER VISITS AND HOSPITALIZATIONS

PROACTIVE PSYCHOSOCIAL CARE IMPROVES TREATMENT COMPLETION

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THANK **YOU**

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