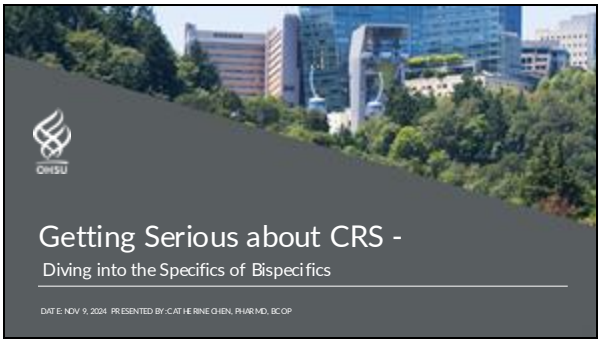

Getting Serious about CRS -

Diving into the Specifics of Bispecifics

DATE: NOV 9, 2024 PRESENTED BY: CATHERINE CHEN, PHARMD, BCOP

Objectives

- Compare and contrast the different commercially available bispecific T-cell engager therapies available in the United States
- Evaluate management strategies for complications that can arise from bispecific T-cell engager therapies including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)
- Discuss supportive care considerations relating to bispecific T-cell engager therapies
- Explain how bispecific T-cell engager therapies are utilized in the treatment of various malignancies

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Disclosure Statement

- Catherine Chen has no relevant financial relationship(s) with ineligible companies to disclose

3

Mechanism of Action

- Bispecific T-cell engager therapy targets CD3 molecule on T-cell receptor and specific tumor antigen simultaneously, activating T cells
- Activated T-cells secrete pro-inflammatory cytokines as well as cytolytic proteins that form pores on cancer cell membrane leading to cancer cell lysis

4 TianZ, et al. *J Hematol Oncol* 2021;14(1):75.

Advantages of Bispecific T-cell Engager Therapies

- Less time to manufacture:
  - Other therapies (e.g. CAR-T) requires additional time (20-40 days) to remove T-cells (via apheresis), engineer T-cells, give lymphodepletion chemotherapy, then re-infuse new T-cells
- Less cytotoxic compared to conventional chemotherapy
- Often given subcutaneously (exceptions): less risk for line infections, easier administration, etc.

5 Trabolsi A, etal. *Blood Cancer J.* 2021;14(1):27.

Commercially Available Products (selected)

Name (FDA approval year)	Disease State	Line of therapy	T Cell Target	Cancer Cell Target
Mosunetuzumab-axgb (**LUNSUMIO**), 2022	**Follicular Lymphoma**	After 2+ lines of systemic therapy	CD3	Cluster of differentiate 20 (CD20)
Teclistamab-cqyv (**TECVAYLI**), 2022	**Multiple Myeloma**	After 4+ lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and anti-CD38 monoclonal antibody		B-cell maturation antigen (BCMA)
Talquetamab-tgvs (**TALVEY**), 2023	**Multiple Myeloma**	After 4+ lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and anti-CD38 monoclonal antibody		G PRCSD (G protein-coupled receptor class C group 5 member D)
Glofitamab-gxbm (**COLUMVI**), 2023	**Diffuse large B-cell lymphoma (DLBCL)**	After 2+ lines of systemic therapy		Cluster of differentiate 20 (CD20)
Tebentafusp-tebn (**KIMMTRAK**), 2022	**Uveal melanoma**	Unresectable or metastatic, HLA-A*02:01 positive		Glycoprotein 100 (gp100) peptide
Elranatamab-bcmm (**ELREXFIO**), 2023	**Multiple Myeloma**	After 4+ prior lines of therapy including a PI, an IMiD, and an anti-CD38 monoclonal antibody		B-cell maturation antigen (BCMA)
Epcoritamab-bysp (**EPKINLY**), 2023	**DLBCL and high-Grade B-cell lymphoma** **Follicular lymphoma**	After 2+ prior lines of systemic therapy		Cluster of differentiate 20 (CD20)
Tarlatamab-dlle (**IMDELLTRA**), 2024	**Extended-stage small cell lung cancer**	After progression on or after platinum-based chemotherapy		Delta-like ligand 3 (DLL3)

6 Research Cfor DE and. Bispecific Antibodies An Area of Research and Clinical Applications. *FDA*. Published online March 12, 2024. Package Inserts.

Assessment Question #1

True or False: Bispecific T-cell engager therapies are effective in treatment of various malignancies by utilizing the body's own immune system to attack cancer cells. This occurs by its unique mechanism of simultaneously binding an antigen on tumor cells and a surface molecule on T cells (e.g. CD3 on T-cells)

A. True
B. False

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Assessment Question #1

True or False: Bispecific T-cell engager therapies are effective in treatment of various malignancies by utilizing the body's own immune system to attack cancer cells. This occurs by its unique mechanism of simultaneously binding an antigen on tumor cells and a surface molecule on T cells (e.g. CD3 on T-cells)

A. True
B. False

8

Complications of Bispecific T-Cell Engager therapies

9

Cytokine Release Syndrome (CRS)

- "A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells..." - ASTCT Consensus Grading, 2018

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Lee,D.W, etal. *Biology ofBlood andMarrow Transplantation*. 2019;25(4), 625-638.

CRS Presentation

Fever at onset (>38 C)

Hypotension

Tachycardia

Hypoxia

Can also be associated with cardiac, hepatic and/or renal dysfunction leading to end organ dysfunction.

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Lee,D.W, etal. *Biology ofBlood andMarrow Transplantation*. 2019;25(4), 625-638.
Management of Immunotherapy-related toxicities. NCCN. Version 1.2024

CRS Grading

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
			With:	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or:	
Hypoxia	None	Requiring low-flow nasal cannula[b] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

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Lee,D.W, etal. *Biology ofBlood andMarrow Transplantation*.2019;25(4), 625-638.

Assessment Question #2

RN is a 67-year old male with relapsed/refractory multiple myeloma status post 4 previous lines of therapy, who received first dose of teclistamab 5 days ago. Today, his vitals are as follows:

BP	T	RR	O2 Sat
85/55	38.2°C (100.8°F)	18 bpm	99% (room air)

The patient was given 650 mg of acetaminophen followed by 1 liter of normal saline given over 30 minutes. Vitals were repeated one hour after receiving fluids, and were as follows:

BP	T	RR	O2 Sat
110/70	37.2°C (98.9°F)	18 bpm	99% (room air)

Mentation remains stable with ICE Score 10/10. **What is the patient presenting with?**

A. Grade 1 cytokine release syndrome as evidenced by temperature of 100°F (38°C) or higher with hypotension (SBP <90 mmHg) responsive to fluids.

B. Grade 2 cytokine release syndrome as evidenced by temperature of 100°F (38°C) or higher with hypotension (SBP <90 mmHg) responsive to fluids and not requiring vasopressors.

C. Grade 1 immune-effector cell-associated neurotoxicity syndrome (ICANS) as evidenced by depressed level of consciousness.

D. Relapsed disease requiring next line of therapy as evidenced by hypotension and fever.

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D. Relapsed disease requiring next line of therapy as evidenced by hypotension and fever.

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Management of CRS (example)**:

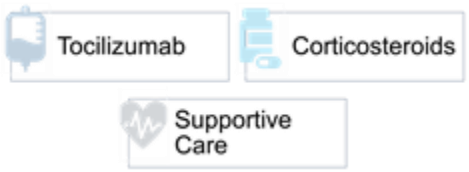
Teclistamab

Grade	Action
1	**Withhold teclistamab until CRS resolves** Administer **pretreatment medications prior to next dose of teclistamab**
2	Treat the same as Grade 1, patients should also be **hospitalized for 48 hours** following the next dose of teclistamab
3	First occurrence of Grade 3 CRS with duration < 48 hours: • Treat same as Grade 2. Patient should also be provided **supportive therapy,** which may include intensive care First occurrence of Grade 3 CRS with duration 48 hours or longer: • **Permanently discontinue teclistamab** • Provide supportive therapy, which may include intensive care
4	Permanently discontinue teclistamab Provide supportive therapy, which may include intensive care

*** follow specific medication package insert instruction/institutional guidelines for more specific management of therapy*

15 Package Insert. Teclistamab (TECVAYLI)

Management of CRS



- Fluids, supplemental oxygen, acetaminophen, antihistamines, etc.

16

Lee, D W, et al. *Biology of Blood and Marrow Transplantation*. 2019;25(4), 625-638.
Management of Immunotherapy-related toxicities. NCCN. Version 1.2024

Tocilizumab

Mechanism of Action: Humanized IgG1 kappa anti-IL-6R antibody

- Binds to both soluble and membrane-bound IL-6 receptor
- Blocks downstream signal transduction pathways

Approved by the FDA in 2017 for treatment of severe/life-threatening CAR T-cell induced CRS in adults and pediatric patients ages 2 years and older (off-label indication for bispecific T-cell engager induced CRS)

Dosing

- < 30 kg: 12 mg/kg
- ≥ 30 kg: 8 mg/kg (max 800 mg/dose)
- May repeat up to 3 additional doses with at least 8 hour interval in between

$$$

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Package Insert. Tocilizumab

Corticosteroids

- Effect on reducing the cytokine and chemokine release, reducing inflammatory processes
- Can be utilized for management or prophylaxis without interfering with response to treatment – able to preserve antitumor efficacy

18

Brattsand R, et al. *Aliment Pharmacol Ther*. 1998;10 Suppl2:81-92.
Ledeneq-Cohen G, et al *Clin Cancer Res*. 2023;29(21):4449-4463

Neurotoxicity, including Immune effector cell-associated neurotoxicity (ICANS)

- A pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells.

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Lee,D W, etal. *Biology ofBlood andMarrow Transplantation*. 2019;25(4), 625-638.
Management of Immunothe apy-related toxicities. NCC N. Versin 1.2024

Neurotoxicity Presentation

- Risk factors: CRS (strongest), high disease burden, high baseline inflammatory state, pre-existing neurologic comorbidities

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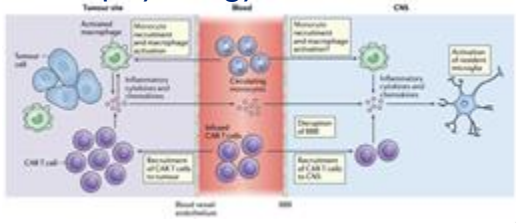
Lee,D W, etal. *Biology ofBlood andMarrow Transplantation*. 2019;25(4), 625-638.
Management of Immunothe apy-related toxicities. NCC N. Versin 1.2024

Pathophysiology of ICANS



21

Morris, EC et al. *Nature Reviews Immunology* 20211-12.

ICANS Grading Scale

ICE **Lower score=worse neurotoxicity**

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

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Lee,D W, etal. *Biology ofB Bod andMarrow Transplantatn.* 2019;25(4), 625-638.

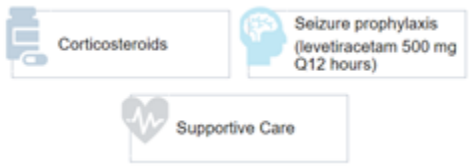
ICANS Grading Scale

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 seizure 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

23

Lee,D W, etal. *Biology ofB Bod andMarrow Transplantatn.* 2019;25(4), 625-638.

Management of ICANS



24

Lee,D W, etal. *Biology ofB Bod andMarrow Transplantatn.* 2019;25(4), 625-638.
Management of Immunotherapy-related toxicities. NCC N. Versin 1.2024

Management of ICANS (example)**: Teclistamab

Grade	Action
Grade 1 (ICE Score 7-9)	• **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 (ICE Score 3-6)	• Same management as Grade 1 PLUS • **Administer dexamethasone 10 mg IV q6H** Continue dexamethasone use **until resolution to grade 1 or less then taper** • Patient should be **hospitalized for 48 hours following the next dose** of teclistamab
Grade 3 (ICE Score 0-2)	First occurrence of Grade 3 ICANS: • Same management as Grade 2 PLUS • Provide supportive therapy, which may include **intensive care** Recurrent Grade 3 ICANS: • Same management as first occurrence of Grade 3 PLUS: • **Permanently discontinue teclistamab**
Grade 4 (ICE 0)	• Same management as Recurrent Grade 3 PLUS: • Instead of dexamethasone, consider administration of **methylprednisolone 1000 mg per day IV** and continue for 2 or more days.

Package Insert. Teclistamab (TECVAYLI)

*** follow specific medication package insert instruction/institutional guidelines for more specific management of therapy*

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Assessment Question #3

DP is a 72-year old male with relapsed/refractory DLBCL who started next line of treatment of epcoritamab (D1 was 16 days ago). The day after receiving his first full dose of epcoritamab (48 mg, given on C1D15, yesterday), he becomes disoriented and incoherent, not oriented to self, time, or place. ICE score is 6/10 (baseline 10/10). What are some next steps to consider?

A. Consult neurology for further evaluation and management
B. Consider starting a prophylactic non-sedating anti-seizure medication (e.g. levetiracetam)
C. Initiate steroid burst – dexamethasone 10 mg every 6 hours until symptoms resolve to grade 1 or less (taper as appropriate)
D. Withhold therapy until ICANS resolves
E. All of the above

DLBCL: Diffuse Large B-Cell Lymphoma
C1D15: Cycle 1, Day 15
ICE: Immune Effector Cell Encephalopathy

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Mitigating Risk of CRS/ICANS: Considerations

- Pre-medications
- Step-up dosing
- Inpatient monitoring for first cycle

28 Ball K, et al. *MAbs*. 2023;15(1):2181016.

Assessment Question #4

What are some additional safety measures that are in place for some bispecific T-cell engager therapy products to prevent/monitor the incidence of CRS/ICANS?

A. Step-up dosing (incrementally increasing dose of therapy to a patient before reaching the target dose level
B. Inpatient administration and monitoring
C. Frequent vital checks and neurological assessments
D. Pre-medication with a corticosteroid, an antihistamine, and acetaminophen prior to step up doses
E. All of the above

29

Assessment Question #4

What are some additional safety measures that are in place for some bispecific T-cell engager therapy products to prevent/monitor the incidence of CRS/ICANS?

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B. Inpatient administration and monitoring
C. Frequent vital checks and neurological assessments
D. Pre-medication with a corticosteroid, an antihistamine, and acetaminophen prior to step up doses
E. All of the above

30

Assessment Question #5

How is tocilizumab utilized in the treatment of bispecific T-cell engager complications?

A. Tocilizumab is used to treat either cytokine release syndrome or immune effector cell-associated neurotoxicity (or both), often if symptoms are grade 2 or higher
B. Tocilizumab is dosed as 8 mg/kg IV (not to exceed 800 mg/dose) every 8 hours as needed for a 4-dose maximum limit
C. Tocilizumab is an interleukin-6 inhibitor (IL-6) that lowers the body's immune response and reduces inflammation.
D. B+C
E. All of the above

31

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D. B+C
E. All of the above

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Additional Considerations

- Long term steroids: what are some complications?
  - Osteoporosis, infection risk, gastritis, hyperglycemia, insomnia, etc.
  - Consider tapering steroids if on prolonged course
- Neurotoxicity: if patient unable to take medications orally, consider changing to intravenous route
- Fever: could have multiple etiologies outside of CRS – should consider infection work up and empiric antibiotics if necessary (e.g. if concerns for infection or neutropenic)

33

Yasir M, et al Corticosteroid Adverse Effects. [Updated 2023 Jul 3].

Conclusion

- Bispecific T-cell engager therapies have achieved durable responses in patients with malignancies
- Two major toxicities arising from bispecific T-cell engager therapies include CRS and neurotoxicity
- Each therapy has a specific onset and treatment algorithm, though some institutions may standardize their treatment approach. Grading is based on severity of symptoms
- Primary management of CRS include fluids, supplemental oxygen, steroids, and tocilizumab, whereas neurotoxicity is managed with steroids, supportive care and initiation of seizure prophylaxis

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Thank You