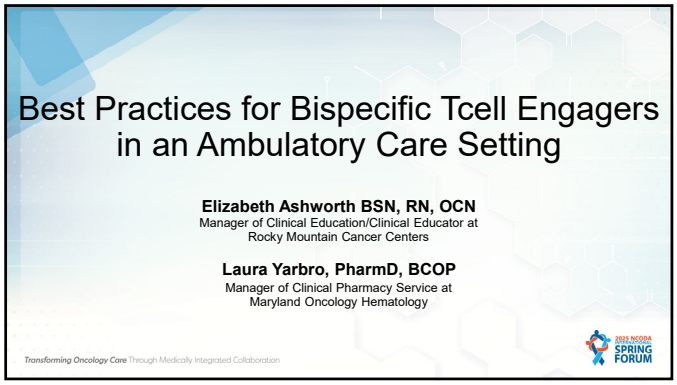
Best Practices for Bispecific Tcell Engagers in an Ambulatory Care Setting
Elizabeth Ashworth BSN, RN, OCN
Manager of Clinical Education/Clinical Educator at Rocky Mountain Cancer Centers
Laura Yarbro, PharmD, BCOP
Manager of Clinical Pharmacy Service at Maryland Oncology Hematology
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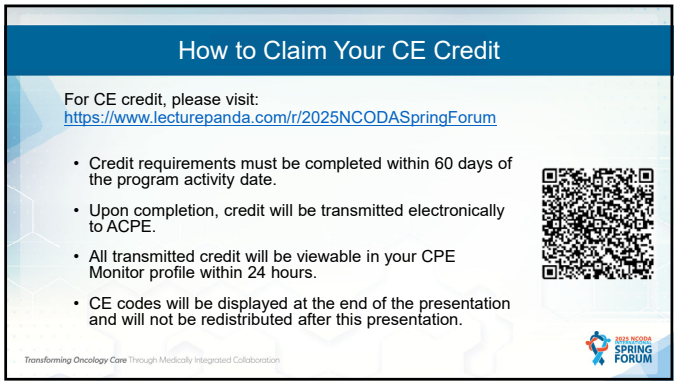
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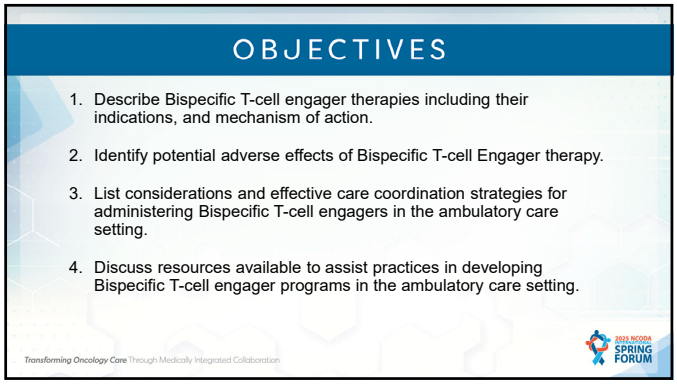
OBJECTIVES
1. Describe Bispecific T-cell engager therapies including their indications, and mechanism of action.
2. Identify potential adverse effects of Bispecific T-cell Engager therapy.
3. List considerations and effective care coordination strategies for administering Bispecific T-cell engagers in the ambulatory care setting.
4. Discuss resources available to assist practices in developing Bispecific T-cell engager programs in the ambulatory care setting.
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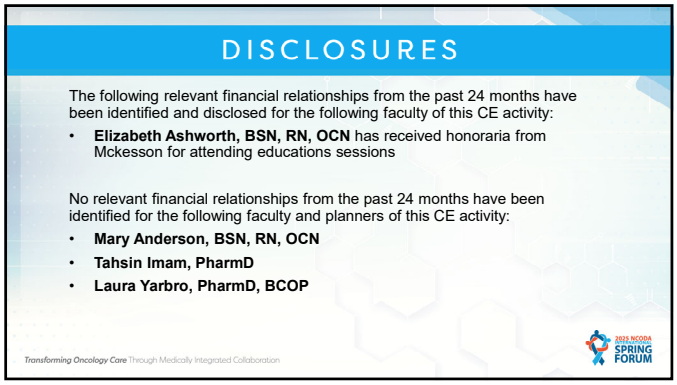
DISCLOSURES
The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty of this CE activity:
• Elizabeth Ashworth, BSN, RN, OCN has received honoraria from Mckesson for attending educations sessions
No relevant financial relationships from the past 24 months have been identified for the following faculty and planners of this CE activity:
• Mary Anderson, BSN, RN, OCN
• Tahsin Imam, PharmD
• Laura Yarbro, PharmD, BCOP
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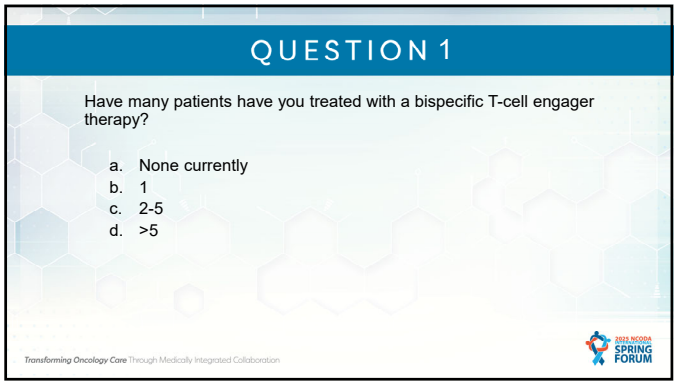
QUESTION 1
Have many patients have you treated with a bispecific T-cell engager therapy?
a. None currently
b. 1
c. 2-5
d. >5
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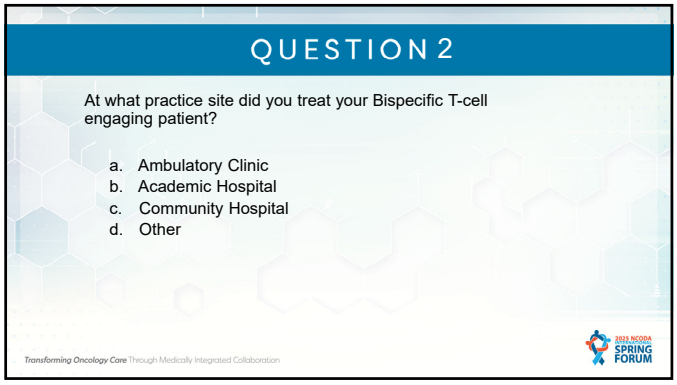
5


QUESTION 2
At what practice site did you treat your Bispecific T-cell engaging patient?
a. Ambulatory Clinic
b. Academic Hospital
c. Community Hospital
d. Other
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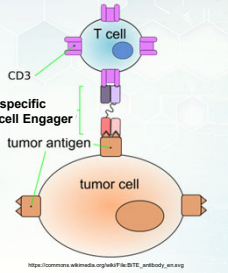
What is a Bispecific?

- Bispecifics are a new drug class within immunotherapy pantheon
- Antibodies targeting two different antigens
- Antibodies targeting two immune-related molecules
- **Antibodies targeting one tumor antigen and one immune-related molecule**
  1. CD3 arm
  2. Target antigen arm



https://commons.wikimedia.org/wiki/File:BiTE_antibody_en.svg

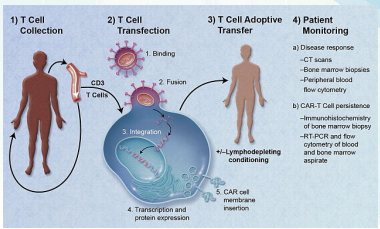
Tian, Z., Liu, M., Zhang, Y. *et al.* Bispecific T cell engagers: an emerging therapy for management of hematologic malignancies. *J Hematol Oncol* 14, 75 (2021).

Huehls AM, Coupet TA, Sentman CL. Bispecific T-cell engagers for cancer immunotherapy. Immunol Cell Biol. 2015 Mar;93(3):290-6

7

How does CAR-T Therapy Compare

- Chimeric Antigen Receptor Therapy (CAR-T)
  - Individualized T-cell therapy
  - Leukapheresis
  - Manufactured T-cells
  - T-cell are re-infused
- Warnings
  - CRS
  - ICANS
  - Increased incidence compared to bispecific t-cell engager



Shah VG, Gauthier J. Turning the beast: CRS and ICANS after CAR T-cell therapy for ALL. Bone Marrow Transplant. 2021 Mar;56(3):552-566.

https://upload.wikimedia.org/wikipedia/commons/thumb/a/a2/CAR-Engineered_T-Cell_Adoptive_Transfer.jpg/640px-CAR-Engineered_T-Cell_Adoptive_Transfer.jpg

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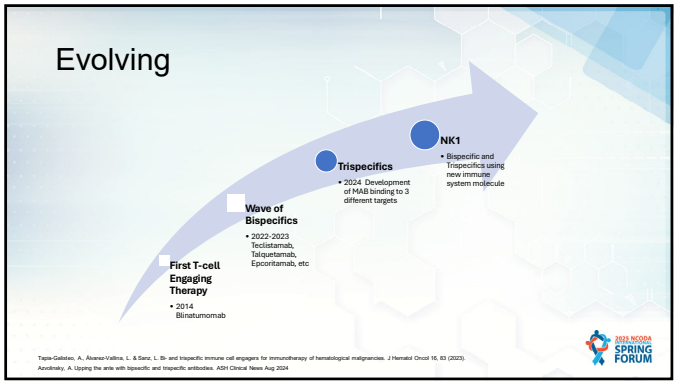
Indications

Hematology	
• Acute Lymphoblastic Leukemia – Blinatumomab • Multiple Myeloma – Elranatamab, Teclistamab, Talquetamab	• Diffuse Lymphoblastic B-Cell Lymphoma (DLBCL)/Follicular Lymphoma - Epcoritamab • DLBCL – Glofitamab • Follicular Lymphoma - Mosunetuzumab
Solid Tumor	
• Small Cell Lung Cancer - Tarlatamab	• Uveal Melanoma - Tebentafusp

9


Evolving
First T-cell Engaging Therapy
• 2014
Blinatumomab
Wave of Bispecifics
• 2022-2023
Teclistamab, Talquetamab, Epcoritamab, etc
Trispecifics
• 2024 Development of MAB binding to 3 different targets
NK1
• Bispecific and Trispecifics using new immune system molecule
Tapia-Galisteo, A., Álvarez-Vallina, L. & Sanz, L. Bi- and trispecific immune cell engagers for immunotherapy of hematological malignancies. J Hematol Oncol 16, 83 (2023).
Arvindsky, A. Upping the ante with bispecific and trispecific antibodies. ASH Clinical News Aug 2024
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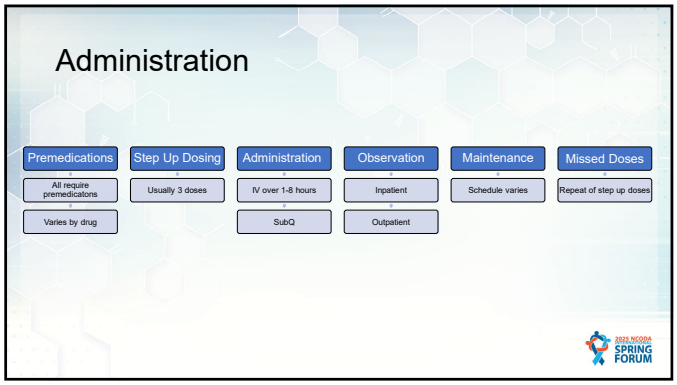
10


Administration
Premedications
All require premedicatons
Varies by drug
Step Up Dosing
Usually 3 doses
Administration
IV over 1-8 hours
SubQ
Observation
Inpatient
Outpatient
Maintenance
Schedule varies
Missed Doses
Repeat of step up doses
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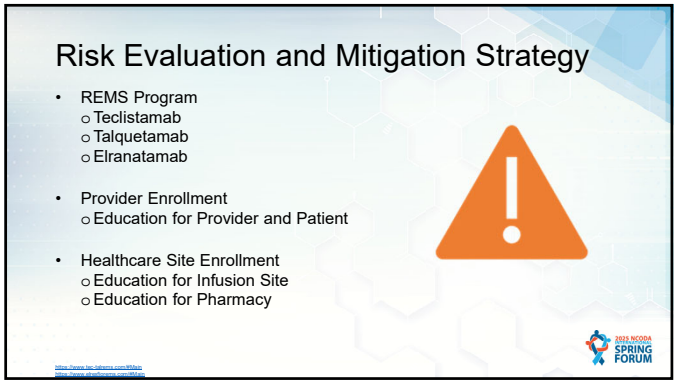
Risk Evaluation and Mitigation Strategy
• REMS Program
o Teclistamab
o Talquetamab
o Elranatamab
• Provider Enrollment
o Education for Provider and Patient
• Healthcare Site Enrollment
o Education for Infusion Site
o Education for Pharmacy
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Side Effects

- Cytokine Release Syndrome (CRS)
- Immune Effector Cell Associated Neurotoxicity (ICANS)
- Infections
- Cytopenias
- Oral toxicity, Dermatological toxicity – **Talquetamab**
- Hepatotoxicity

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Infection Assessment

- Consequence of disease state and therapy
- Monitor
  - CBC
  - IgG levels – primarily multiple myeloma
  - Patient Symptoms
- Prevention/Treatment
  - IVIG
  - Antibiotics
  - Vaccinations

Jourdes A. et al. Characteristics and incidence of infections in patients with multiple myeloma treated by bispecific antibodies: a national retrospective study, Clinical Microbiology and Infection, Volume 30, Issue 6, 2024, Pages 764-771
Maurice F. et al. Risk of infections associated with the use of bispecific antibodies in multiple myeloma: a pooled analysis, *Blood Adv* Vol 7 Issue 13, 2023 pages 3069-3074
Raje, N., Anderson, K., Einsele, H. *et al.* Monitoring, prophylaxis, and treatment of infections in patients with MM receiving bispecific antibody therapy: consensus recommendations from an expert panel. *Blood Cancer J.* 13, 116 (2023).

14

What is a Cytokine?

- A type of **protein** that is made by certain immune and non-immune cells and has an **effect on the immune system.** Some cytokines stimulate the immune system and others slow it down.
  - Examples of cytokines are interleukins, interferons, and colony-stimulating factors.
- When there is a large release of cytokines, this can cause cytokine release syndrome (CRS)

National Cancer Institute. Cytokine. National Cancer Institute Dictionary of Cancer Terms. Accessed March 18, 2025. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cytokine.

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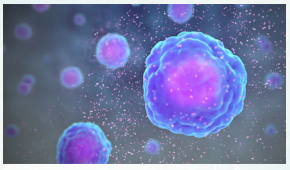
What is Cytokine Release Syndrome?

- **Cytokine release syndrome** is caused by a large, rapid release of cytokines into the blood from immune cells affected by the immunotherapy
- Signs and symptoms of cytokine release syndrome;
  - Fever
  - Nausea
  - Headache
  - Rash
  - Rapid heartbeat
  - Low blood pressure
  - Trouble breathing



http://www.scientificanimations.com/wiki-images/ Creative Commons Attribution-Share Alike 4.0 International

https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cytokine-release-syndrome

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Cytokine Release Syndrome Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38C (100.4F)	Temp ≥ 38C (100.4F)	Temp ≥ 38C (100.4F)	Temp ≥ 38C (100.4F)
			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 <90% O2 saturation	Requiring high-flow nasal cannula facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

From 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 Apr;25(4):625-638. doi: 10.1016/j.bbmt.2018.12.758

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How do you determine if a patient needs vasopressors?

- Vasopressor Indications
  - Mean Arterial Pressure (MAP) < 65
  - Not responsive to fluid resuscitation
- MAP Calculations
- **MAP= (Systolic + Diastolic + Diastolic) ÷ 3**
- MAP = DP + 1/3(SP – DP) or
- MAP = DP + 1/3(PP)
- Many blood pressure machines have a MAP score on the machine, but it is important to know how to calculate when a patient is calling in with their blood pressure.

Courtesy of Elizabeth Ashworth

Scheeren, T.W.L., Bakker, J., De Backer, D. et al. Current use of vasopressors in septic shock. Ann. Intensive Care 9, 20 (2019). https://doi.org/10.1186/s13613-019-0496-7

DeMers, D. Wachs, D. Physiology, Mean Arterial Pressure. National Library of Medicine. (2023). Physiology, Mean Arterial Pressure - StatPearls - NCBI Bookshelf

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QUESTION 3

In the outpatient setting, you call a patient to follow up 3 days after they received a Bispecific T-cell engager therapy. They live in the mountains and were discharged from the hospital after meeting the inpatient monitoring observation requirement for the medication. Their caregiver reports a blood pressure of 80/50.

What would the MAP score be for this patient?

MAP= (Systolic + Diastolic + Diastolic) ÷ 3

a. **80**
b. **70**
c. **60**
d. **50**

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QUESTION 4

The caregiver also reports a temperature of 101.0 **°F** in addition to blood pressure of 80/50. What grade of CRS does this patient have?

Answer Choices:

a. Grade 1
b. Grade 2
c. Grade 3
d. Grade 4

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38C (100.4F)	Temp ≥ 38C (100.4F)	Temp ≥ 38C (100.4F)	Temp ≥ 38C (100.4F)
			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 <90% O2 saturation	Requiring high-flow nasal cannula facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation)

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Immune effector cell-associated neurotoxicity syndrome (ICANS)

- Occurs in the days to weeks following therapy administration
- Systemic **inflammation and high levels of circulating cytokine**
  - Result in endothelial cell activation and blood-brain barrier (BBB) disruption
  - Causes an inflammatory cascade within the central nervous system (CNS)
  - Subsequent alterations
    - Cortical and subcortical function
    - Diffuse cerebral edema in some cases

https://www.uptodate.com/contents/immune-effector-cell-associated-neurotoxicity-syndrome-icans?search=ICANS&source=search_result&selectedTitle=1~24&usage_type=default&display_rank=1

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ICANS

- ICANS usually occurs in the context of cytokine release syndrome (CRS)
  - Neurologic symptoms beginning within two to four days of the onset of CRS
  - CRS is not required for ICANS
  - Syndromes can occur at different times
- Tarlatomab median time to onset of ICANS from the first dose of was 29.5 days and median resolution around 33 days
- Initial neurologic symptoms are usually characterized by inattention and language deficits
- Clinical symptoms can be rapidly progressive within hours to a few days
- Close monitoring is critical

https://www.uptodate.com/contents/immune-effector-cell-associated-neurotoxicity-syndrome-icans?search=ICANS&source=search_result&selectedTitle=1~24&usage_type=default&display_rank=1

https://www.imdeltahcp.com/safety/common-adverse-reactions

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Neurologic Toxicity

Monitor for signs and symptoms of neurologic toxicities, including immune effector cell-associated neurotoxicity syndrome

If patient is arousable and able to perform **immune cell-associated encephalopathy score (ICE) assessment:**

- Orientation (oriented to year, month, city, hospital = 4 points)
- Naming (name 3 objects, eg, point to clock, pen, button = 3 points)
- Following commands (eg, “show me 2 fingers” or “close your eyes and stick out your tongue” = 1 point)
- Writing (ability to write a standard sentence = 1 point)
- Attention (count backwards from 100 by 10 = 1 point)
- If unarousable and unable to perform ICE assessment (grade 4 ICANS = 0 points).

- Speak to provider if ICE assessment score is less than 10

Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS

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Steroids

- Corticosteroids reduce the activity of the immune system
- Used together with tocilizumab to treat more severe CRS
- They are used to treat more severe neurologic side effects
- Dexamethasone and methylprednise are the commonly used steroids

NCCN Guidelines for Patients

Immunotherapy Side Effects: CAR T-Cell Therapy, 2024

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Tocilizumab for treatment of CRS

- For the treatment of Cytokine release syndrome and blocks interaction between IL-6 and its receptors.
  - It is essential for treating moderate to severe CRS grades 2,3,and 4
- Lowers the body's immune response and reduces inflammation.
- Dosing 8 mg per kg.
  - >800mg doses not recommended for CRS
- 60-minute IV infusion in 100mL NS
- Alone or in combination with corticosteroids
- Different dosing for patients less than 30 kg weight.

- NCCN Guidelines for Patients
- Immunotherapy Side Effects: CAR T-Cell Therapy. 2024

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QUESTION 5

What patient education should be considered when starting a patient on a T-cell engaging bispecific?

a. Wallet card
b. Monitoring supplies (i.e. blood pressure cuff, pulse oximeter, thermometer)
c. Hospital with Tocilizumab and clinical staff familiar with CRS/ICANS
d. Family support/caregiver
e. Contact numbers
f. All of the above

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Hospital and Wallet Cards

- Confirm with patient and caregiver they understand the hospital to report to if CRS or Neurologic changes
  - Within an hour of home
  - Do they carry Tocilizumab
  - Consider if the hospital staff had education to provide care for patient
- Wallet Card from manufacturer website
  - Download and fill out to give to the patient to present to ER if needed
  - Most pharmaceutical companies have wallet cards available upon request

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Nursing Considerations

- Communication
  - Work with local hospital oncology floor to confirm they are prepared for the admission for observation and have tocilizumab available
  - Baseline assessment before administration
  - Assess if caregiver to help monitor for symptoms of CRS and ICANS
  - If no caregiver, discuss nurse follow up assessment calls after discharged from hospital
- Develop guidelines at your institution for frequency of CRS/ICE assessment
- NCODA playbook may be used as a resource

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Home Monitoring

Confirm patient has a thermometer, blood pressure cuff, pulse oximeter and caregiver to assess for neurologic changes

- Temperature
- Blood pressure
- Oxygen saturation
- Mental status changes
- Sample Hand Writing-Sentence or name
- Caregiver available and appropriate to monitor
  - Vitals and ICE score log
  - Educate caregiver on ICE assessment and when to call

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Nursing Considerations-continued

- Recommend administration earlier in the week for outpatient administration
- Confirm correct vial size for step up doses
- Glofitimab is a very small volume for first ramp up IV infusion. *Consider priming line with medication*
- Tocilizumab was recently added in the NCCN guideline that it may be given for CRS prevention
- Blinatumomab education about what to do if pump difficulties. *Do not flush line
- Direct patients to appropriate hospitals if CRS symptoms and neurologic changes

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Pharmacy Considerations

- Admixture
  - Confirm correct vial sizes
  - 2-step dilution process
- REMS
- Dosing schedule
- Monitoring for delayed treatment
  - Possible resumption of step-up dosing
- Cost

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Two different outpatient approaches

INPATIENT STEP-UP DOSING

AMBULATORY STEP-UP DOSING

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Academic Center and Maintenance Administration

- Created a core team with providers and leadership (Nursing, Pharmacy, Operations)
- Developed policies and workflow
- Collaborated with Industry for provider and staff education
- Collaborated with community hospital for step-dosing
- Decided to work with academic centers to complete step up dosing
- Treatment continuity inpatient notes to review CRS/ICNS, dosing, treatment course, REMS completion
- Currently participating in clinical trials for full ambulatory administration

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Outpatient administration and inpatient admission for monitoring

- Communication. Notify Pharmacy, nursing and hospital staff of anticipated patient and schedule
- Educate staff. Complete REMS
- Assess and educate caregiver about T-cell engaging bispecifics
- Coordinate plan for hospital admission immediately after administration
- Communicate to clinical staff planned discharge date
- Confirm caregiver available to monitor for symptoms
  - If no caregiver, develop monitoring protocol. Example: Call patient multiple times a day to assess for CRS/ICANs

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Resources

- NCODA Playbook
- ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma Link
- NCCN Management of Immunotherapy-Related Toxicities Link
  - CRS Management
  - ICE Management

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Available Bispecific T-Cell Engager Medications

Agents	Indication	REMS	Frequency	Route	Step-up dosing	Pre-medications	Monitoring post infusion
Epcoritomab-busp	Relapsed or refractory Diffuse Large B-cell Lymphoma; after 2 or more lines of therapy	No	Every 28 days, until disease progression. Cycle 1-3 (days 1,8,15,22), Cycles 4-9 (days 1, 15), Cycles 10+ (day 1)	SubQ	Yes	Yes	Hospitalization for 24 hrs post C1D15
Mosunetuzumab-axgb	Relapsed or Refractory Follicular Lymphoma; after 2 or more lines of therapy	No	Every 21 days x 8 Cycles or disease progression. Cycle 1 (days 1, 8, 15), Cycles 2+ (day 1)	IV over 4 hours Cycle 1, then over 2 hours, if tolerated	Yes	Yes	Consider hospitalization for subsequent infusions following Grade 2 CRS. Recommended hospitalization for infusions following Grade 3 CRS.
Tebentafusp-tebn	HLA-A*02:01 Positive adults with unresectable or metastatic Uveal Melanoma	No	Every 7 days	IV over 15-20 mins. Low protein binding 0.2-micron in-line filter	Yes	No	In office week 4*. Monitor at least 30 mins post infusion w/VS checked twice. **Weeks 1-3 hospitalization required**
Teclistamab-cqyv	Relapsed or refractory Multiple Myeloma; after 4 or more lines of therapy	Yes	Every 7 days, after step-up dosing, until progression or unacceptable toxicity	SubQ	Yes	Yes	Hospitalization recommended for 48 hours post each Tx during step-up dosing.
Glofitamab-gxbm)	Relapsed or refractory Diffuse Large B-cell Lymphoma, or Large B-Cell Lymphoma arising from Follicular lymphoma	No	Every 21 days x 12 Cycles max. or disease progression. Cycle 1 (day 1 Obinituzumab, day 8, 15), Cycles 2+ (day 1)	IV over 4 hours Cycles 1 & 2, then over 2 hours if no CRS experienced) Cycles 3-12	Yes	Yes	Hospitalization recommended x 24 hours following step-up dose 1 and 2 (if CRS experienced w/dose 1)
Talquetamab-tgvs	Relapsed or refractory Multiple Myeloma; after 4 or more lines of therapy	Yes	Every 7 days or every 14 days, until disease progression or unacceptable toxicity	SubQ	Yes	Yes	Hospitalization recommended for 48 hours post each Tx during step-up dosing.
Elranatamab-bcmm	Relapsed or refractory Multiple Myeloma; after 4 or more lines of therapy	Yes	**See step-up dosing for clarification** Weekly and every 2 weeks until disease progression or unacceptable toxicity	SubQ	Yes	Yes	Hospitalization recommended for 48 hours post step-up dose 1, and 24 hours post step-up dose 2.
Tarlatamab	Small cell lung cancer, extensive stage	No	Every 14 days Cycle 1 (days 1, 8, 15), Cycle 2 and beyond Days 1, 15	IV over 1 hour	Yes	Yes	Monitor patients in an appropriate health care setting during infusion and for 22 to 24 hours after the cycle 1 day 1 and cycle 1 day 8 infusions

Table Courtesy of Laura Yerbro

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SUMMARY

- Bispecific T-cell engager therapy is new form of immunotherapy with activity in several hematologic and solid tumor indications
- They require step-up dosing to ensure patient tolerability and limit serious adverse events
- Bispecific medications are associated with serious toxicities including cytokine release syndrome and immune effector cell-associated neurotoxicity
- REMS are required to be completed before administration
- It is important to provide education and teach patient/caregiver how to monitor for potential serious side effects and when to call clinic or report to the emergency room in the event they occur

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QUESTION & ANSWER

Best Practices for Bispecific T-cell Engagers in an Ambulatory Care Setting

Elizabeth Ashworth BSN, RN, OCN
Manager of Clinical Education/Clinical Educator at Rocky Mountain Cancer Centers
Laura Yarbro, PharmD, BCOP
Manager of Clinical Pharmacy Service at Maryland Oncology Hematology

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CE CODES

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