


Antibody-Drug Conjugates and Bi-specifics: A Guide for Oncology Pharmacy Technicians

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Transforming Oncology Care Through Medically Integrated Collaboration




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DISCLOSURES


The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty and planners of this CE activity:

- C. Brooke Adams, PharmD, BCOP
 - Advisory board member for Johnson and Johnson and Genmab
 - Consultant for Bristol-Myers Squibb
 - Speaker for Pfizer

No relevant financial relationships from the past 24 months have been identified for the following planners of this CE activity:

- Tahsin Imam, PharmD
- Diasy Doan, PharmD
- Taryn Newsome, CPhT

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OBJECTIVES

1. Review the mechanisms of action and federal drug administration (FDA) approvals for antibody-drug conjugates (ADCs) and bi-specifics used in hematology/oncology.

2. Discuss common adverse events and management strategies for ADCs and bi-specifics.

3. Identify emerging ADCs and bi-specifics in the pipeline.

4. Summarize strategies to increase patients' access to ADCs and bi-specifics.

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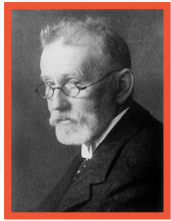

Introduction to ADCs

• ADC research has been conducted for more than a century.

• Paul Ehrlich first introduced the concept of the "magic bullet" in 1913.

• In 1997, the first monoclonal antibody, rituximab was FDA approved.

• In 2000, the first ADC came to market.



Dr. Paul Ehrlich

Strebhardt K, et al. Nat Rev Cancer 2008 (8): 473-480.

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ADCs FDA Approvals

Gemtuzumab ozogamicin*

Ado-trastuzumab emtansine

Moxetumomab pasudotox**

2000

2011

2013

2017

2018

Brentuximab vedotin

Inotuzumab ozogamicin
Gemtuzumab ozogamicin

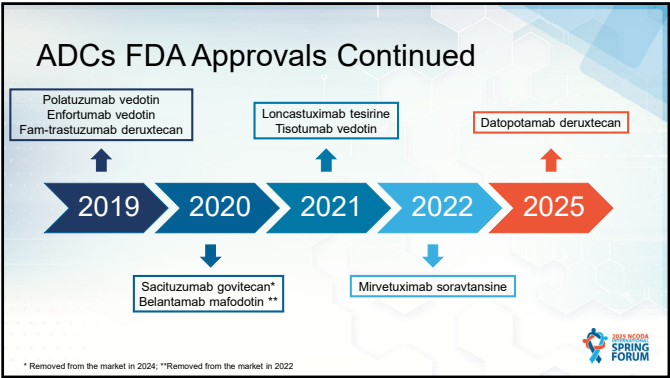
*Removed from the market in 2010; **Removed from the market in 2023

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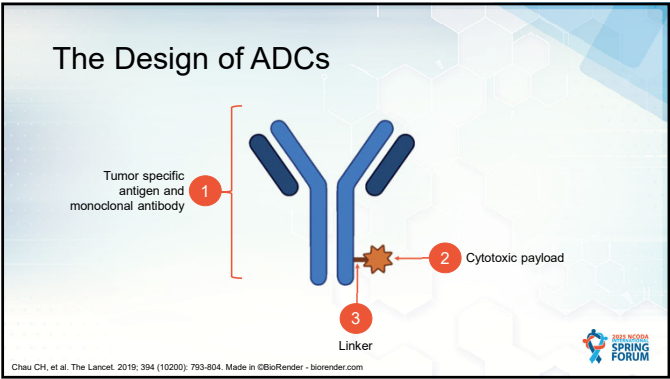
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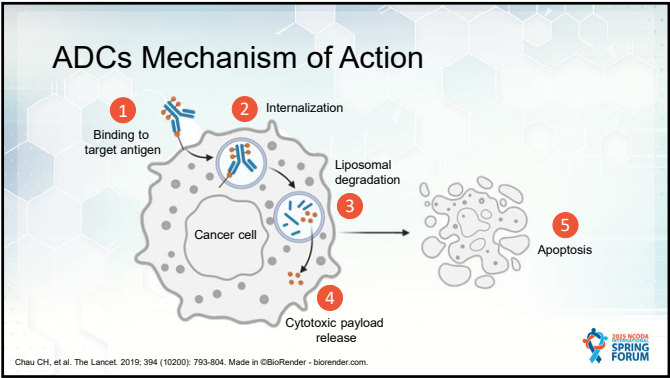
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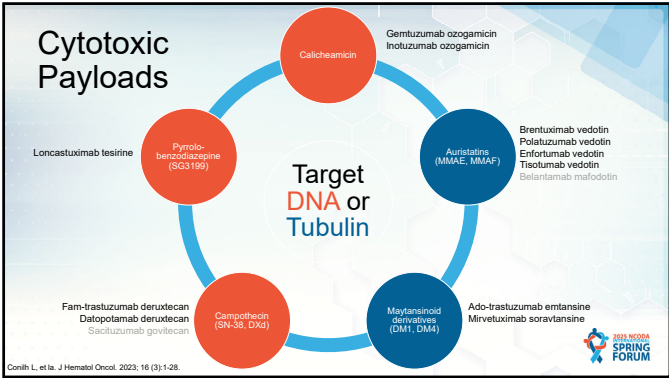
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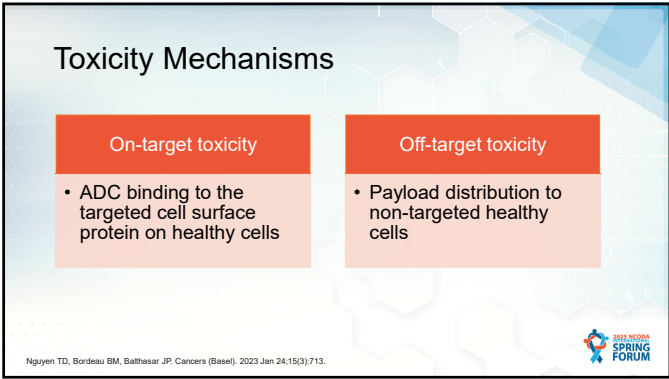
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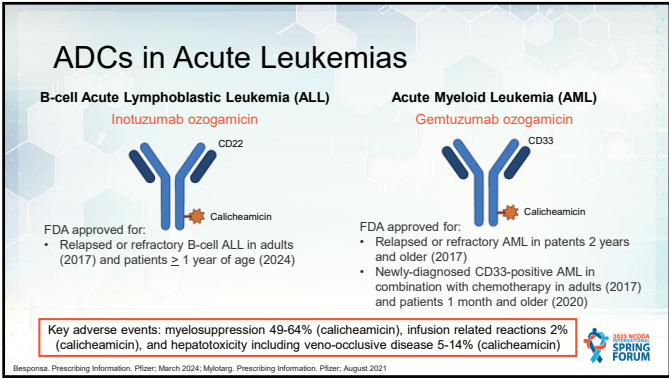
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ADCs in Breast Cancer

Metastatic Breast Cancer

Ado-trastuzumab emtansine

FDA approved for human epidermal growth factor receptor 2 (HER2)-positive, metastatic breast cancer patients who previously received trastuzumab and a taxane, separately or in combination and have received prior therapy for metastatic disease or progressed within 6 months of completing adjuvant therapy (2013).

Fam-trastuzumab deruxtecan

FDA approved for HER2-positive, metastatic or unresectable breast cancer, who have received a prior chemotherapy in the metastatic setting, or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (2019).

Datopotamab deruxtecan

FDA approved for adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease (2025).

Kadcyla. Prescribing Information. Genentech. February 2022. Enhertu. Prescribing Information. Daiichi-Sankyo and AstraZeneca. January 2025. Datrovy. Prescribing Information. AstraZeneca. January 2025.

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ADCs in Breast Cancer

Early Breast Cancer

Ado-trastuzumab emtansine

FDA approved for the adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment (2019).

Kadcyla. Prescribing Information. Genentech. February 2022.

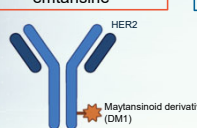
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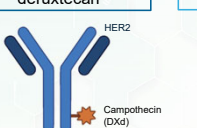
ADCs in Breast Cancer

Ado-trastuzumab emtansine



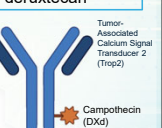
Key adverse events: peripheral neuropathy 32% (DM1), myelosuppression 31% (DM1), cardiotoxicity 22% (HER2), and pneumonitis 1.1% (HER2)

Fam-trastuzumab deruxtecan



Key adverse events: moderate-high emetogenicity (DXd), myelosuppression 72% (DXd), cardiotoxicity 8% (HER2), and pneumonitis 12% (HER2)

Datopotamab deruxtecan



Key adverse events: moderate emetogenicity (DXd), myelosuppression 41% (DXd), ocular toxicity 51% (trop2), skin toxicity 19% (trop2), and stomatitis 59% (trop2)

Kadcyla. Prescribing Information. Genentech. February 2022. Enhertu. Prescribing Information. Daiichi-Sankyo and AstraZeneca. January 2025. Datrovy. Prescribing Information. AstraZeneca. January 2025.

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ADCs in Lymphoma

Large B-cell Lymphoma (LBCL)

Loncastuximab tesirine

FDA approved for adult patients with relapsed or refractory (R/R) LBCL after 2 prior lines of systemic therapy (2021).

Brentuximab vedotin

FDA approved for adults patients in combination with lenalidomide and rituximab for R/R LBCL after 2 prior lines of systemic therapy and ineligible for an autologous stem cell transplant or chimeric antigen receptor T-cell therapy (2025).

Polatuzumab vedotin

FDA approved for adult patients in combination with rituximab, cyclophosphamide, doxorubicin, prednisone (R-CHP) for newly diagnosed LBCL (2023) and adult patients with R/R LBCL in combination with bendamustine, rituximab (BR) that have failed 2 prior line of systemic therapy (2019).

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ADCs in Lymphoma

Classical Hodgkin Lymphoma (cHL)

Brentuximab vedotin

FDA approved for:

- Newly diagnosed cHL adult patients with stage III or IV disease in combination with doxorubicin, vinblastine, and dacarbazine (2018).
- Newly diagnosed high risk cHL pediatric patients 2 years and older in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide (2022).
- Maintenance after auto-HCT for high-risk adult patients (2015).
- Adult patients with R/R cHL after failure of auto-HCT or at least two prior multi-agent chemotherapy regimens in patients who are not auto-HCT candidates (2011).

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ADCs in Lymphoma Continued

Loncastuximab tesirine

Brentuximab vedotin

Polatuzumab vedotin

CD19

Pyrrulobenzodiazepine (SG3199)

CD30

Auristatin (MMAE)

CD79b

Auristatin (MMAE)

Key adverse events: fluid retention 20% (SG3199), skin and nail reactions 30% (SG3199)

Key adverse events: peripheral neuropathy 20-30% (MMAE), myelosuppression 37-46% (MMAE)

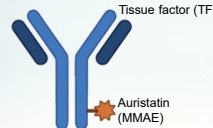
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ADC in Cervical Cancer

Tisotumab vedotin

FDA approved for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy (2021).




Tissue factor (TF)

Auristatin (MMAE)

Key adverse events:

- Peripheral neuropathy 39% (MMAE)
- Myelosuppression 16% (MMAE)
- Ocular toxicity including dry eye, keratitis, blurry vision, and excessive lacrimation 55% (TF)
- Cutaneous reactions including skin rashes, Stevens-Johnson syndrome and toxic epidermal necrolysis 17% (TF)

Tivdak. Prescribing Information. Pfizer and Genmab; April 2024

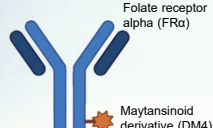


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ADC in Ovarian Cancer

Mirvetuximab soravtansine

FDA approved for adult patients with FR α positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received 1-3 systemic treatment regimens (2024).




Folate receptor alpha (FR α)

Maytansinoid derivative (DM4)

Key adverse events:

- Moderate emetogenicity (DM4)
- Peripheral neuropathy 36% (DM4)
- Myelosuppression 22% (DM4)
- Ocular toxicity including dry eye, keratitis, blurry vision, and excessive lacrimation 59% (FR α)

Elihere. Prescribing Information. AbbVie; October 2024

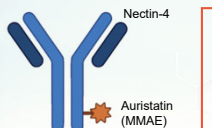


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ADC in Bladder Cancer

Enfortumab vedotin

FDA approved in combination with pembrolizumab for patients with locally advanced or metastatic urothelial cancer who are ineligible for cisplatin-containing chemotherapy (2019).




Nectin-4

Auristatin (MMAE)

Key adverse events:

- Peripheral neuropathy 50% (MMAE)
- Myelosuppression (MMAE)
- Ocular toxicity including dry eye, keratitis, blurry vision, and excessive lacrimation 24% (nectin-4)
- Cutaneous reactions including skin rashes, Stevens-Johnson syndrome and toxic epidermal necrolysis 54% (nectin-4)
- Dysgeusia 26% (nectin-4)

Padcev. Prescribing Information. Astellas and Pfizer; August 2024



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QUESTION 1

Which of the following would be an **on-target** toxicity of an ADC?

a) MMAE causing peripheral neuropathy

b) Binding to HER2 on the heart leading to heart failure

c) DM4 causing nausea and vomiting

d) SG3119 causing fluid retention

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Strategies to Prevent Toxicity

Ocular toxicity

- Baseline ophthalmologic exam then as needed/recommended
- Lubricant eye drops QID
- Corticosteroid and vasoconstrictor eye drops prior to infusion
- Cooling eye pads
- Avoid contact lenses
- Dose reduce or hold therapy based on severity

Dermatologic toxicity

- Early intervention with topical or systemic corticosteroids.
- Dose reduce or hold therapy based on severity

Peripheral neuropathy

- Monitoring prior to each dose
- Dose reduce and hold therapy based on severity

Cardiotoxicity

- Baseline echocardiogram (ECHO) then as needed

Veno-occlusive disease

- Ursodiol prophylaxis
- Liver function monitoring

Infusion-related reactions

- Pre-medications 30-60 minutes prior to the infusion

Nguyen TD, Bordeau BM, Balhassar JP. Cancers (Basel). 2023 Jan 24;15(3):713.

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ADCs in the Pipeline

ADC	Target	Payload	Most advance clinical phase	Disease
Telisotuzumab adizutecan	c-MET	adizutecan	II	Metastatic colorectal cancer
ARX517	PSMA	amberstatin-269	II	Metastatic prostate cancer
CMG901	Claudin 18.2	MMAE	II	Metastatic gastroesophageal and biliary cancers
AZD8205	B7-H4	TOP1i	II	Advanced breast biliary, ovarian, endometrial, and squamous non-small cell lung cancers
CX-2051	EpCAM	CAMP59	I	Advanced solid tumors
IBI3009	DLL3	TOP1i	I	Metastatic SCLC

MET, mesenchymal-epithelial transition factor receptor; PSMA, prostate-specific membrane antigen; EpCAM, epithelial cell adhesion molecule; DLL3, delta-like Ligand 3; TOP1i, Top1 inhibitor 1

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Introduction to Bi-specifics

Bi-specific antibodies (BsAbs)

- Antibody that binds to two different targets

Bi-specific T-cell Engagers (BTCEs)

- Binds to surface tumor antigen on malignant cell and CD3 on T-cell

Spless C et al. Mol Immunol. 2015;67(2 Pt A):95-106

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BTCE FDA Approvals

Blinatumomab

2014

Tebentafusp
Teclistamab
Mosunetuzumab

2022

Glofitamab
Epcoritamab
Elranatamab
Talquetamab

2023

Tarlatamab

2024

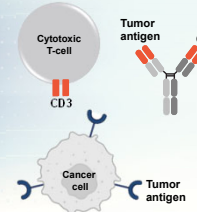
Herrera M, et al. Trends in Cancer. 2024;10(10):893-919.

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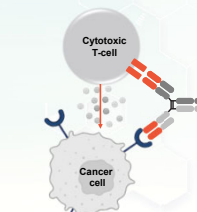
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BTCE Mechanism of action

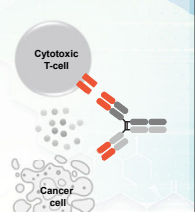
1 T-cell activation



2 Immune synapse formation



3 Apoptosis



Made in CbioRender - biorender.com

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BTCE in B-cell Acute Lymphoblastic Leukemia

Blinatumomab

FDA approved for those \geq 1 month with:

Relapsed or refractory CD19-positive B-cell ALL (2014)

CD19-positive B-cell acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% (2018)

CD19-positive Philadelphia chromosome-negative B-cell ALL in the consolidation phase of multiphase chemotherapy (2024)

mAb for CD3

Binds to CD3

mAb for CD19

Binds to CD19

BITE[®] molecule

Blinato

Prescribing Information, Amgen, December 2024. Made in CBioRender - biorender.com

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BTCE in Multiple Myeloma (MM)

Teclistamab

Elranatamab

Talquetamab

BCMA

GPRC5D

BCMA GPRC5D

CD3

FDA approved for relapsed or refractory MM in adults who have received \geq 4 lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody (teclistamab: 2023; elranatamab and talquetamab: 2024).

BCMA: B-cell maturation antigen; GPRC5D: G protein - coupled receptor, class C, group 5, member D

Tecvay®. Package Insert. Janssen, November 2024; Talvey. Package Insert. Janssen, August 2023; Elrexfio. Package Insert. Pfizer, August 2023.

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GPRC5D Expression

Variable expression in the lungs

Plasma cells

Hard keratinized tissue of the tongue and plasma cells in the salivary glands and tonsils

Keratin-expressing hair follicles

Keratogenous zone of the nail

Smith EL, et al. Sci Transl Med. 2019;11(485):eaau7746.

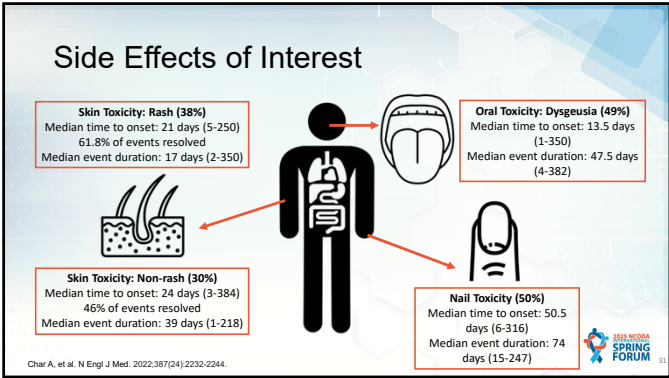
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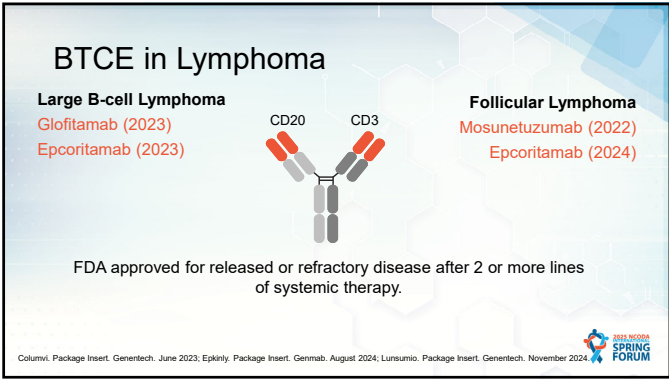
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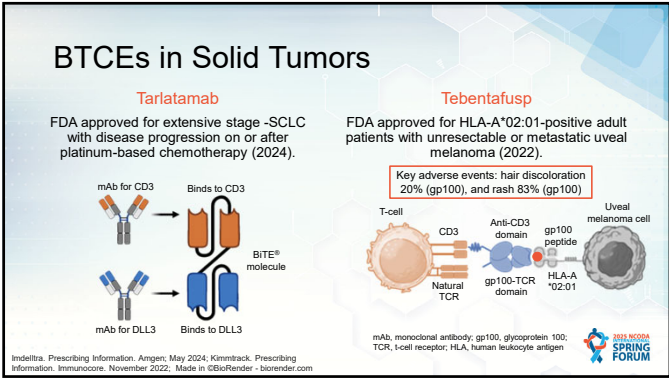
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Key BTCE Adverse Events

Cytokine release syndrome (CRS)
Neurotoxicity including immune-effector cell neurotoxicity syndrome (ICANS)

Strategies to prevent CRS and ICANS:

- Step-up dosing
 - Hospitalization commonly required based on dose and product
 - Outpatient dosing with close monitoring may be considered
- Pre-medications
 - Commonly dexamethasone, acetaminophen, and diphenhydramine

van de Donk NWCJ, Zweegman S. Lancet. 2023;402(10396):142-156.

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CRS Clinical Presentation

Brain: headache, confusion, hallucinations, delirium, aphasia, paresis, seizures, ataxia, dysphagia

Blood and vasculature: cytopenias, coagulopathy, disseminated intravascular coagulation (DIC), capillary leak, fever

Heart: Tachycardia, hypotension, troponin elevation, arrhythmia, QT prolongation, stress cardiomyopathy, acute heart failure

Liver: Hepatomegaly, elevated liver enzymes, hypofibrinogenemia, liver failure

Colon: diarrhea

Lungs: tachypnea, hypoxia, pulmonary edema, respiratory failure

Spleen: splenomegaly

Stomach: nausea and vomiting

Kidneys: acute kidney injury, renal failure

Joints, muscles, and skin: myalgia, arthralgia, rigor, rash, and edema

Shimabukuro-Vornhagen A, et al. J Immunother Cancer. 2018;6(1):56.

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ASTCT Consensus CRS Grading

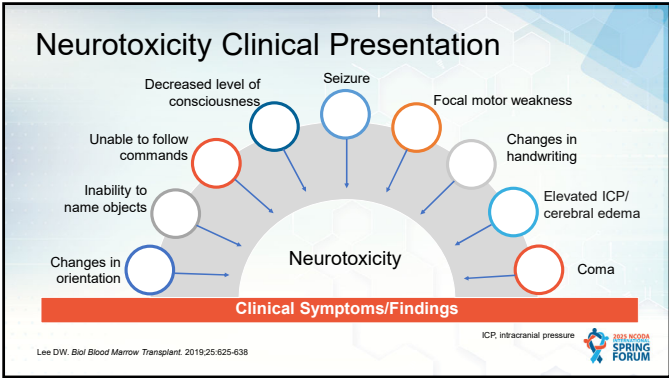
CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature $\geq 38^{\circ}\text{C}$			
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxemia	None	Requiring low-flow nasal cannula or blow-by (6L/minute or less)	Requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask ($> 6\text{L/minute}$)	Requiring positive pressure (CPAP, BiPAP, intubation and mechanical ventilation)

CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure

Lee DW, et al. Biol Blood and Marrow Transplantation 2019;25(4):625-638.

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ASTCT ICE Scoring Tool

The ICE score (10-point scale) can measure subtle changes in cognition by evaluating orientation, attention, writing, and language.

Assess	Orientation	Naming	Following commands	Writing	Attention
Task	Oriented to year, month, city, hospital	Name 3 objects (eg, point to clock, pen, button)	Eg, "show me 2 fingers" or "close your eyes and stick out your tongue"	Ability to write a standard sentence	Count backward from 100 by 10
Points assigned	4	3	1	1	1

Grade 1	Grade 2	Grade 3	Grade 4
7-9	3-6	0-2	0 (unusable)

Lee DW, et al. Biol Blood and Marrow Transplantation 2019;25(4):625-638.

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ASTCT Consensus ICANS Grading (Adults)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score	7-9	3-6	0-2	0 (unusable)
Level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	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 electroencephalogram 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 Intracranial pressure/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.

Lee DW, et al. Biol Blood and Marrow Transplantation 2019;25(4):625-638.

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Risk Evaluation and Mitigation Strategies (REMS) Certification

REMS requirements for Prescribers

Online training and enrollment

- Review the following materials:
 - Prescribing Information
 - Prescriber Training Program
 - Adverse Reaction Management Guide
- Successfully complete the Knowledge Assessment, and submit it to REMS
- Complete the Prescriber Enrollment Form, and submit it to REMS

Patient counseling

Before treatment initiation (first step-up dose), counsel patients and/or their caregivers. Complete and provide patients or their caregivers with the Patient Wallet Card.

REMS requirements for Pharmacies and Healthcare Settings

Designation

Designate an **Authorized Representative** for the Pharmacy and Healthcare Setting.

Online training and enrollment


Authorized Representative must review the Pharmacy and Healthcare Setting Training Program.

Authorized Representative must complete the Pharmacy and Healthcare Setting Enrollment Form and submit it to REMS.

Staff training

Train all relevant staff involved in dispensing on the REMS requirements using the Pharmacy and Healthcare Setting Training Program.

Required for teclistamab, elranatamab, and talquetamab




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QUESTION 2

Which of the following is a common adverse event seen with **ALL** bi-specific T-cell engagers?

- a) Hair loss
- b) Weight loss
- c) Taste changes
- d) Cytokine release syndrome


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Institutional Considerations

- Infrastructure & resources**
 - What is needed to implement a new therapy like BTCEs
 - Who are the key players involved in multidisciplinary team
 - What resources should be created and available to staff
 - What type of infrastructure and workflows are needed to provide these therapies
- Formulary decisions**
 - How do you handle having multiple BCTEs with different indications
 - How do you prepare staff for the differences between products
- Financial impact and considerations**
 - Site of care considerations
 - Chair time



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BCTEs in the Pipeline			
Bi-specific	Target	Most advance clinical phase	Disease
Catumaxomab	EpCAM x CD3	III	Gastric, ovarian, bladder, malignant ascites, fallopian tube neoplasms, peritoneal neoplasms
Brenetafusp	PRAME x CD3	III	Ovarian, uterine, melanoma, NSCLC, SCLC, breast
BNT-142	Claudin-6 x CD3	II	Ovarian, NSCLC, testicular
Cibisatamab	CEA x CD3	II	NSCLC
CX-904	EGFR x CD3	I	Advanced solid tumors
EMB-07	ROR1 x CD3	I	Advanced solid tumors or relapsed/refractory lymphoma

PRAME, Preferentially Expressed Antigen in Melanoma; CEA, carcinoembryonic antigen; EGFR, Epidermal Growth Factor Receptor; ROR1, receptor tyrosine kinase-like orphan receptor 1; NSCLC, non small cell lung cancer

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QUESTION 3

Which of the following therapies may pose an access issue in a rural community setting?

a) Tarlatamab

b) Brentuximab vedotin

c) Polatuzumab vedotin

d) Loncastuximab tesirine

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SUMMARY

ADCs and BTCEs have changed the treatment paradigm for a number of hematological and solid tumor malignancies.

BTCEs offer several advantages including decreased risk of adverse events, increased access, and improved patient convenience.

BTCEs are not without unique challenges including logistical complexities especially in the community.

ADCs and BTCEs are here to stay with hundreds in the pipeline.

Pharmacy technicians play a critical role in the successful implementation of these therapies.

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QUESTION & ANSWER

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C. Brooke Adams, PharmD, BCOP

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CE CODES

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