Mitigating Adverse Events:
Bispecifics in Lymphoma

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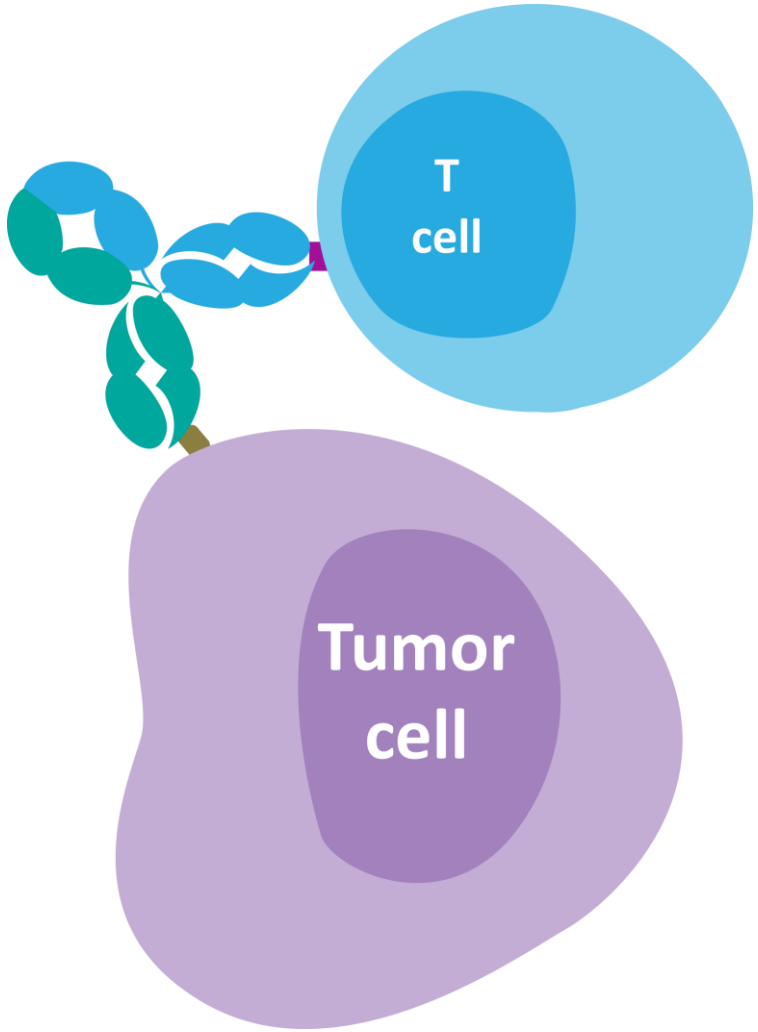
Learning Objectives

At completion of this session, participants should be able to:

1) Identify currently approved bispecific antibodies for follicular and diffuse large B cell lymphomas and their most common toxicities.
2) Recognize signs/symptoms of CRS and neurotoxicity/ICANS, be familiar with grading criteria, and identify mitigation strategies for these toxicities to address safety outcomes.
3) List management strategies for myelosuppression and infection secondary to bispecific antibody treatment.
4) Outline essential education for patients receiving bispecific antibody treatments.
5) Describe strategies for effective coordination of care for patients on bispecific antibody treatments, including between tertiary cancer centers and community settings.

Bispecific Antibodies



Why Bispecific Antibodies?

Three bispecific antibodies are currently FDA approved for the treatment of follicular lymphoma (FL) or diffuse large B cell lymphoma (DLBCL)

- All approved in 3rd line setting and beyond
- All are anti CD20 x CD3 T cell engaging therapies
- All are “off the shelf” antibodies that create an immune synapse between patients’ healthy T cells and the CD20+ malignant B cells
- Bispecific antibodies have similarities to but a more favorable toxicity profile than CART cell therapy.
- Do not require administration at a tertiary cancer care center

FDA APPROVED AGENTS

FL mosunetuzumab

(FDA approved 12/22/20220

DLBCL epcoritamab

(FDA approved 5/19/2023)

glofitamab

(FDA approved 6/15/2023)

Novel Toxicities: Cytokine Release Syndrome (CRS)

Cytokine Release Syndrome (CRS)

- An acute systemic inflammatory syndrome caused by a large release of pro-inflammatory cytokines from immune cells.
- Characterized by fever and multiple organ dysfunction.
- Since common symptoms of CRS are not specific to CRS, imperative to distinguish from other inflammatory disorders (such as: infection, sepsis, HLH, TLS, PE, allergic reaction, heart failure, disease progression)
- Due to risk of CRS, bispecific antibodies are administered on a step-up dosing schedule to reduce incidence and severity of symptoms.
- Pre-medications administered to mitigate CRS include antipyretic, antihistamine and steroid (specific to each bispecific, refer to PI).
- Treatment should be withheld until CRS resolves or permanently discontinued based on severity (always with grade 4).

McAndrew NP, et al. Medscape. 2020 (https://emedicine.medscape.com/article/2500111)

CRS Symptoms

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.

MILD	SEVERE
Fever (hallmark)	Hypotension
Fatigue and malaise	Capillary leak (hypoxia)
Nausea	Circulatory shock
Headache	Febrile neutropenia
Myalgia and arthralgia	Pulmonary edema
Rash	Acute respiratory distress syndrome
Shortness of breath	Cardiac dysfunction
Diarrhea (Anxiety)	Multiorgan system failure

CRS Grading Based on 2019 ASTCT Consensus Guidelines

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.

CRS Grade 1	CRS Grade 2	CRS Grade 3	CRS Grade 4
Fever ≥38.0°C (100.4F)	Fever ≥38.0°C (100.4F)	Fever ≥38.0°C (100.4F)	Fever ≥38.0°C (100.4F)
No hypotension	Hypotension not requiring vasopressors	Hypotension requiring a vasopressor (with or without vasopressin)	Hypotension requiring ≥ 2 vasopressors, excluding vasopressin
No hypoxia	Hypoxia requiring low-flow oxygen	Hypoxia requiring high-flow nasal cannula, facemask, nonrebreather mask, or Venturi mask	Hypoxia requiring positive pressure ventilation

Novel Toxicities: Neurotoxicity (including ICANS)

- ICANS: Immune effector cell-associated neurotoxicity syndrome
  - Occurs when cytokines disrupt the blood-brain barrier
  - Incidence varies and generally coincides with but can occur after CRS
- Note: CRS is distinct from ICANS but symptoms can overlap
- Expressive aphasia is a characteristic early sign of severe neurotoxicity and was the first neurologic symptom in 86% of patients on epcoritamab who developed severe neurotoxicity.

(Santomasso BD, et al. *Cancer Discov*. 2018;8(8):958–971. 2. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638).

ICANS Symptoms

Santomasso BD, et al. *Cancer Discov*. 2018;8(8):958–971. 2. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.

EARLY SYMPTOMS	LATE SYMPTOMS
Expressive aphasia (especially in naming objects)	Impairment of cognitive skills
Dysgraphia	Altered Level of Consciousness
Impaired Attention	Seizure
Apraxia	Stupor
Lethargy	Coma
Tremor	Cerebral Edema
Headache	Motor Weakness

ICE Score

ASTCT Consensus Encephalopathy Assessment Tool

Immune-Effector Cell-Associated Encephalopathy (ICE) Tool

- **Orientation:** Orientation to year, month, city, hospital: 4 points
- **Naming:** Name 3 objects (e.g., point to clock, pen, button): 3 points
- **Following commands:** (e.g., Show me 2 fingers or Close your eyes and stick out your tongue): 1 point
- **Writing:** Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
- **Attention:** Count backwards from 100 by ten: 1 point

Score 10: No impairment

Lee et al. *Biol Blood Marrow Transplant*, Dec 2018

ICANS Grading for Adults Based on 2019 ASTCT Consensus

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.

Grade 1	Grade 2	Grade 3	Grade 4
ICE Score 7-9	ICE Score 3-6	ICE Score 0-2	ICE Score 0 (pt unable to perform)
Awakens spontaneously	Awakens to voice	Awakens only to tactile stimuli	Unarousable or requires vigorous, or repetitive tactile stimuli to arouse
		Clinical seizure that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	**Life-threatening prolonged seizure** or repetitive clinical or electrical seizures without return to baseline in between
		Focal/local edema on neuroimaging	**Diffuse cerebral edema** on imaging, decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad
			Deep focal motor weakness (eg, hemiparesis or paraparesis)

Mosunetuzumab

Mosunetuzumab

- Approved for 3L+ relapsed/refractory follicular lymphoma. NCCN category 2A recommendation.
- Approval based on phase 2 clinical trial (90 patients with third line plus FL).
- ORR of 78.9% with CR rate of 57.8%.
- Majority of patients (either w/ OR or CR) maintained response at 18 months
- Administered IV in 21-day cycles with cycle 1 step-up dosing: 1 mg on cycle 1 day 1, 2 mg on cycle 1 day 8, 60 mg on cycle 1 day 15 and cycle 2 day 1, and 30 mg on day 1 of cycle 3 and onwards.
- Fixed duration therapy: patients who achieve CR receive 8 cycles, those with PR/SD receive 17 cycles (or until disease progression/unacceptable toxicity).

Budde L et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;8:1055-1065

Mosunetuzumab (Cont.)

- CRS is most likely to occur in cycle 1. 5% occurred with cycle 2 day 1 and 1% following subsequent doses.
- CRS rate is relatively low grade, with 44% any grade CRS (26% grade 1, 16.7% grade 2, and only 2.5% grade 3 or 4 CRS).
- Recurrent CRS occurred in 11% of patients.
- Neurotoxicity of any grade occurred in 30% of patients, with 3% grade 3 events.
- ICANS occurred in 1% of patients (grades 1 and 2).
- NO hospitalization requirement for any doses, but hospitalization should be considered following a grade 2 CRS event and recommended for subsequent infusions following a grade 3 CRS event.

Budde L et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;8:1055-1065

Mosunetuzumab – Side Effect Profile

- Other common (≥20%) AEs were fatigue (36.7%), headache (31.1%), neutropenia and pyrexia (28.9% each), hypophosphatemia (22.2%), and pruritus (21.1%).
- Common (≥5%) Gr 3-4 AEs (66.7% overall) were neutropenia (26.6%), hypophosphatemia (13.3%), hyperglycemia and anemia (7.8% each), and elevated ALT (5.6%).

- Infections:
  - Serious infections, including opportunistic infections, occurred in 17% of patients (grade 3 or 4 infections in 14%, and fatal infections in 0.9%).
  - Most common grade 3 or higher infections were PNA, sepsis and URTI.

- Budde L et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol. 2022;8:1055-1065

Epcoritamab

Epcoritamab

- Indicated for the treatment of adult patients with relapsed or refractory DLBCL, NOS, including DLBCL arising from indolent lymphoma, and high-grade B-cell lymphoma in 3rd line + setting. NCCN Category 2A recommendation.
- Approval based on results of phase 1/2 trial of 157 patients with R/R DLBCL. ORR was 61%, with 38% of patients achieving complete response. Median DOR 15.6 months.
- Administered **subcutaneously** in 28 day cycles until disease progression or unacceptable toxicity:
  - Cycle 1 administered with step up dosing
    - Day 1 – 0.16 mg
    - Day 8 – 0.8 mg
    - Day 15 – first full dose – 48mg (requires hospitalization for 24 hours after dose)
  - Cycles 2 and 3: Days 1, 8, 15, 22 - 48 mg dose
  - Cycles 4 through 9: Days 1 and 15 – 48mg dose
  - Cycles 10 and beyond: Day 1 – 48mg dose

PI, epcoritamab, retrieved 10/12/23

Epcoritamab – Side Effect Profile

- CRS occurred in 51% of patients, with grade 1 occurring in 37%, grade 2 in 17%, and grade 3 in 2.5%.
- Most CRS events occurred in cycle 1 (92%) and were associated with the first full dose.
- Median time to onset across all doses was 24 hours (range 0 to 10 days). Median time to onset with first full dose was 21 hours (range 0 to 7 days).
- Recurrent CRS occurred in 16% of patients. 98% of patients experienced resolution of CRS.
- During trial, serious infections (including opportunistic infections), were reported in 15% of patients with grade 3 or 4 infections in 14% and fatal infections in 1.3%. Most common grade 3 or higher infections were sepsis, COVID-19, UTI, PNA and URTI.

PI, epcoritamab, retrieved 10/12/23

Epcoritamab – Side Effect Profile (cont)

- ICANS occurred in 6% of patients on trial (10/157), with 9 of these events occurring during cycle 1 of treatment. Median time to onset was 16.5 days from start of treatment, with median duration 4 days.
- ICANS resolved in 90% of patients with supportive care.
- The most common (≥20%) AEs were CRS (51%), fatigue (29%), musculoskeletal pain (28%), injection site reactions, pyrexia (24%), abdominal pain (23%), nausea (20%) and diarrhea (20%).
- The most common grade 3 to 4 laboratory abnormalities (≥10%) were decreased lymphocyte count, decreased neutrophil count, decreased white blood cell count, decreased hemoglobin and decreased platelet counts.
- Grade 1 and 2 injection site reactions occurred in 27% of patients, no grade 3 or 4.

PI, epcoritamab, retrieved 10/12/23

Glofitamab

Glofitamab

- Approved in 3L+ DLBCL, NOS or LBCL arising from FL. NCCN guidelines Category 2A recommendation.
- Approval based on phase 1/2 NP30179 trial of 145 patients (overall response rate of 56% and CR of 43%, median DOR 18.4 months).
- Administered **intravenously** in 21 day cycles:
  - 7 days prior to initiation of glofitamab, all pts must receive pre-treatment with a single IV dose of obinutuzumab 1000mg to reduce risk of CRS.
  - Step up dosing commences on day 8 (2.5mg) - patients should be hospitalized during infusion and for 24 hrs after.
  - Day 15 dose (10mg) – hospitalize during/24 hrs after infusion if CRS with 2.5mg dose
  - Dosing on cycle 2 day 1 and subsequent cycles is 30mg
    - Hospitalize during/24 hrs after infusion if experienced grade 2 or greater CRS during previous infusions
- Fixed duration treatment continues for 12 cycles (~ 8.5 months) or until disease progression/unacceptable toxicity.

PI, glofitamab, retrieved 10/12/23

Glofitamab – Side Effect Profile

- CRS occurred in 56% of patients after 2.5mg dose, 35% after 10mg dose, 29% after initial 30mg dose and 2.8% after subsequent doses.
- CRS generally low grade (52% grade 1, 14% grade 2)
- Median time to onset of CRS was 14 hours (range 5 to 74 hours)
- CRS after any dose resolved in 98% of cases, with median duration of CRS of 2 days (range 1-14 days)
- Recurrent CRS occurred in 34% of all patients.

Drugs. 2023 Jun 7 : 1–7.doi: 10.1007/s40265-023-01894-5 ; PI, glofitamab, retrieved 10/12/23

Glofitamab – Side Effect Profile (cont)

- Neurological adverse events grade 2 or higher occurred in 15% of patients, with grade 3 or higher events occurring in 3.2% of patients.
- Cases of ICANS of any grade occurred in 4.8% of patients.
- Most common AEs (≥20%) are CRS (70%), musculoskeletal pain (21%), rash (20%), and fatigue (20%).
- Most common grade 3 or 4 lab abnormalities are lymphocyte count decreased (83%), hypophosphatemia (28%), neutropenia (26%), hyperuricemia (23%), hypofibrinogenemia (21%).

Drugs. 2023 Jun 7 : 1–7.doi: 10.1007/s40265-023-01894-5 ; PI, glofitamab, retrieved 10/12/23

Toxicity Management
Patient Education
Coordination of Care

Special Considerations

- CNS disease
  - Exclusion criteria in clinical trials for all 3 bispecific antibodies
  - Can consider using but CNS disease needs to be controlled first
- Infections
  - Bispecific antibodies should not be administered to patients with active infections
  - Consider antibiotic prophylaxis w/ antiviral and anti-PJP
    - Antiviral if recurrent HSV, neutropenia or CD4 count <200
    - PJP prophy if steroids given for >4 days and for patients considered at increased risk
  - Can utilize G-CSF
  - Check IgG levels frequently, consider IVIG if <600 and especially if <400.
- Tumor flare
  - Patients can experience tumor flare, most events occurring during C1
  - Could manifest as new or worsening pleural effusions, pain or swelling at the sites of lymphoma lesions, and tumor inflammation
  - Hydration and pain medications can help
  - Reassurance that symptoms likely do not represent disease progression

Toxicity Management – CRS

- **For Grade 1 CRS**
  - Investigate for infection and rapidly startup broad-spectrum antibiotics, continue until fever and any existing neutropenia resolve.
  - Supportive care per institutional standard of care (antipyretics and IV hydration)
  - Closely monitor neurologic status
  - Consider anti-cytokine therapy in certain cases (advanced age, high tumor burden, circulating tumor cells, fever refractory to antipyretics)
    - Tocilizumab over 1h (not to exceed 800 mg per dose). Repeat after at least 8h as needed. Maximum of 2 doses in a 24h period.
    - For concurrent ICANS, choose alternative to tocilizumab (eg, siltuximab, anakinra
  - Consider corticosteroids
    - Dexamethasone 10–20 mg per day (or equivalent)
    - In case of concurrent ICANS, initiation of steroids is highly recommended

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.

Management of CRS (Cont.)

- Grade 2 CRS
  - All interventions for grade 1
  - Supplemental O2 as indicated
  - Continuous cardiac monitoring and pulse oximetry as indicated
  - Anti-cytokine therapy is recommended (For concurrent ICANS, choose alternative to tocilizumab)
  - If refractory CRS, increase/initiate corticosteroids (dex 10-20mg or equivalent daily and consider alternative anti-cytokine therapy
- Grade 3/4 CRS
  - All interventions for grade 1 and 2
  - Management in intensive care unit
  - Vasopressor support and/or supplemental oxygen
  - Grade 4 may require mechanical ventilation and/or renal replacement therapy
  - Dexamethasone (10-20mg IV q6h), if no response methylprednisolone 1000mg/day
  - Anti-cytokine therapy is recommended (For concurrent ICANS, choose alternative to tocilizumab)
  - Permanent discontinuation of therapy for Grade 4 CRS

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.

Management of Neurologic Toxicity (including ICANS)

- At the first sign of ICANS, withhold drug.
  - Consider Neurology evaluation
  - Rule out other causes of neurologic symptoms
  - Provide supportive therapy, which may include intensive care
  - Consider starting non-sedating, anti-seizure medications for seizure prophy
  - No role for tocilizumab or other anti-cytokine therapies unless concomitant CRS
  - For grade 2-4, administer IV steroids (dexamethasone 10mg IV q6h). For grade 4, can also consider methylprednisolone 1000mg daily
- Permanently discontinue for grade 4 ICANS (epcoritamab, glofitamab, mosunetuzumab), recurrent grade 3 ICANS (epcoritamab, mosunetuzumab), grade 3 ICANS lasting >7 days (glofitamab)
- Please see PI for each bispecific for detailed ICANS management protocols

Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625–638.; PI glofitamab, epcoritamab, mosunetuzumab, retrieved 10/12/23

Coordination of Care: Clinical Pearls

- Patients are required to be admitted to hospital during administration and for 24 hours for first full dose of epcoritamab on cycle 1 day 15 and for cycle 1 day 8 of glofitamab.
- Be aware of recommendations for hospitalization for subsequent doses of epcoritamab and glofitamab and for mosunetuzumab depending on severity of CRS with prior doses.
- Be familiar with time to onset and duration of CRS for each drug.
- Check inflammatory markers including CRP and ferritin prior to each dose.
- Ensure that on-call providers are aware of the administration of bispecific antibody and risk of CRS and ICANS.
- If a patient needs ER referral, report should be called to the treating provider to make them aware of the possibility of CRS and to **ensure the availability of tocilizumab.**
  - **Bispecific antibodies should not be administered in a facility without access to tocilizumab**

Coordination of Care: Clinical Pearls (cont.)

- Patient wallet cards are available for all 3 available FDA approved therapies – information includes therapy name/start date, name/contact information of treating oncologist, information about AEs and link to PI.
- Refer to each drug's PI for information re: pre-medications and for recommendations for restarting therapy after dose delays, indications for hospitalization, and discontinuation of therapy for severe toxicities.
- Assess caregiver availability and willingness, provide specific education regarding side effects, ensure that they have contact information to seek medical assistance.
- Patients need to be evaluated in person prior to each dose of bispecific antibody, or as clinically indicated. Chart documentation should include assessment and grading of CRS and ICANS score.
- Assess for any history of steroid induced behavioral changes or psychosis as steroid premedication (usually dexamethasone) could induce symptoms which can be mistaken for (or exacerbate) CRS and neurotoxicity.

Patient Education: Clinical Pearls

- Patients must be educated about signs/symptoms of CRS
  - They will need to have a thermometer at home and consider purchasing a pulse oximeter
- Patients must be educated about the increased risk of infection while on treatment and to call with any fevers or infectious symptoms.
  - If within window of CRS, we need to evaluate CRS vs infection.
  - If they have respiratory symptoms, they should be instructed to test for COVID-19 and if positive, be treated promptly and not resume treatment until symptoms have resolved.
  - Emphasize neutropenic precautions
  - Initiate conversation about use of IVIG with appropriate patients
- Patients must be educated about signs/symptoms of neurotoxicity/ICANS and should be cautioned to avoid driving or use of potentially dangerous equipment/machinery if they develop dizziness, confusion, tremors, drowsiness or other symptoms that impair consciousness.

Patient Education Clinical Pearls (Cont.)

- Epcoritamab requires patients to take oral steroids at home on days 2-4 for at least first cycle of treatment (and with subsequent cycles if experience grade 2/3 CRS with previous dose
- Review parameters for oral hydration to help with CRS and TLS.
- Consider allopurinol for TLS prophy if high tumor burden and/or circulating disease.
- Emphasize fall precautions, minimize concomitant medications causing sedation, dizziness or mental status changes.
- Employ usual side effect management strategies for chemoimmunotherapy to address other common toxicities of bispecifics:
  - Antiemetics
  - Antidiarrheals
  - Exercise and pacing of activities for fatigue
  - Topical corticosteroids for mild rash
  - Cold compresses to injection site reactions (epcoritamab)

Thank you!

Contact information:

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