Taking a “Bite ” Out of Bispecific Antibodies (BsAbs) in Diffuse Large B-Cell Lymphoma: Applications for Treatment Implementation

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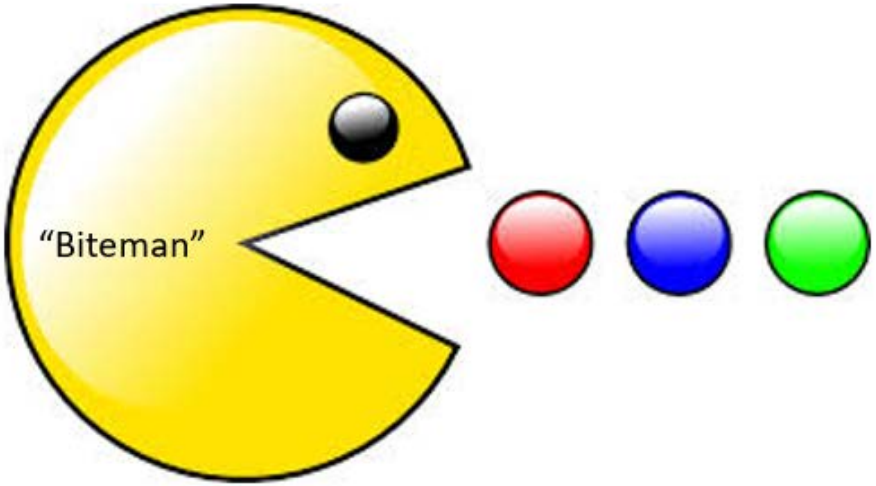
knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

Disclosures

- Speakers Bureau: Sanofi, BeiGene, Incyte and AbbVie/Genmab
- Advisory Board: Astellas, BMS and Incyte

Objectives



Indication, dosing and mechanism of action

Managing Toxicity

Preparation and administration

Outline

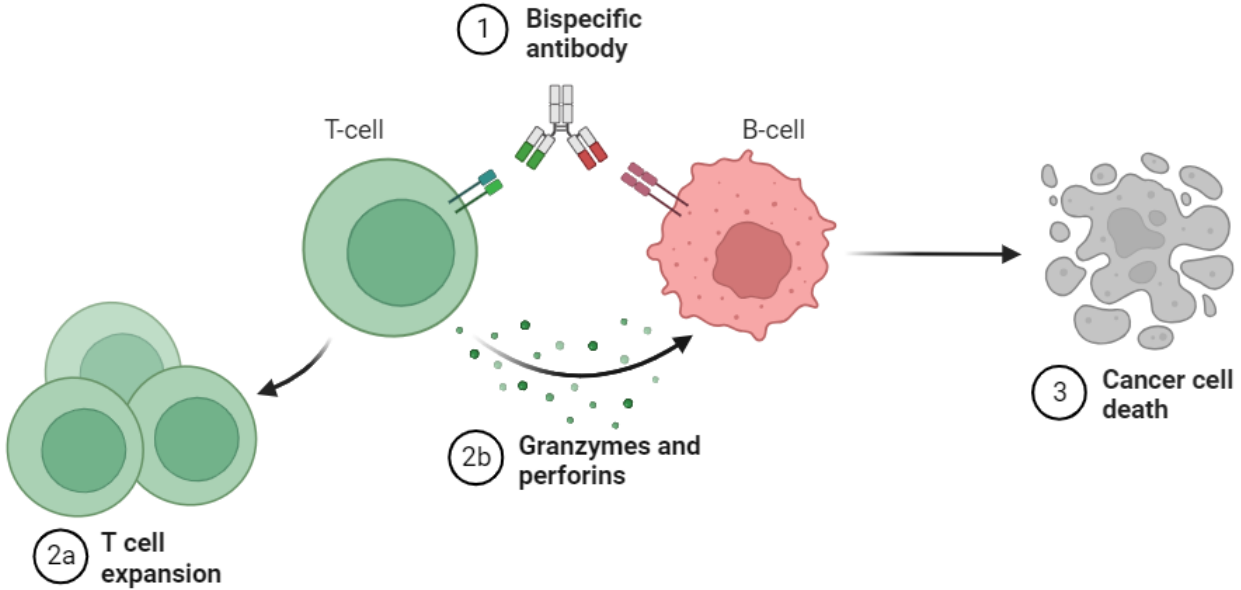
- Approval and Indication
- Mechanism of Action
- Administration and Pearls
- Managing Toxicity
- Implementation and Pharmacy Operations
- Navigating Cost of Care
- Future Applications

Approval and Indication

- Epcoritamab: indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from indolent lymphoma and high-grade B-cell lymphoma (HGBCL), after *two or more lines of systemic therapy*
  - FDA accelerated approval May 19, 2023
- Glofitamab: indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, or large B-cell lymphoma (LBCL) arising from follicular lymphoma, after *two or more lines of systemic therapy*
  - FDA accelerated approval June 15, 2023

EPKINLY™ (epcoritamab-bysp). [package insert]. Plainsboro, NJ USA: Genmab Inc, and AbbVie Inc.; 2023.
COLUMVI™ (glofitamab-gxbm). [package insert]. San Francisco, CA USA: Genentech Inc.; 2023.

Mechanism of Action



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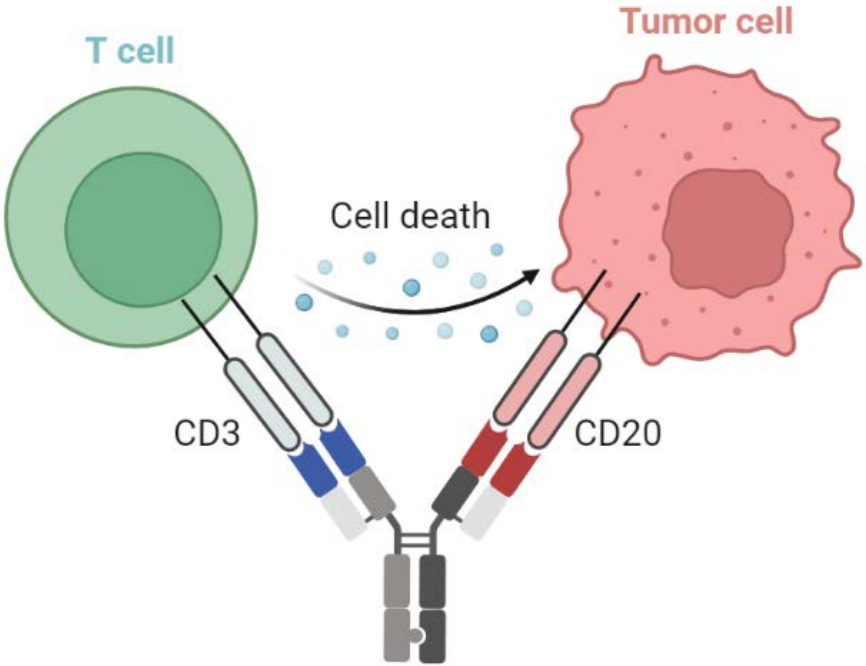
Mechanism of Action



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Administration: Epcoritamab

- Route: Subcutaneous
- Pre-medications (Cycle 1):
  - Prednisone 100 mg or dexamethasone 15 mg (PO or IV)
    - Continue 3 days after each weekly dose
  - Diphenhydramine 50 mg
  - Acetaminophen 650-1000 mg
- Cycle length = 28 days
- Duration = Until progression

Cycle	Day	Dose
Cycle 1	1	0.16 mg
	8	0.8 mg
	15	48 mg
	22	48mg
Cycle 2 and 3	1,8,15,22	48mg
Cycles 4-9	1,15	48mg
Cycle 10+	1	48mg

Thieblemont C, et al. *J Clin Oncol*. 2023;41(12):2238-2247.; EPKINLY™(epcoritamab-bysp). [package insert]. Plainsboro, NJ USA: Genmab Inc, and AbbVie Inc.; 2023.

Administration: Glofitamab

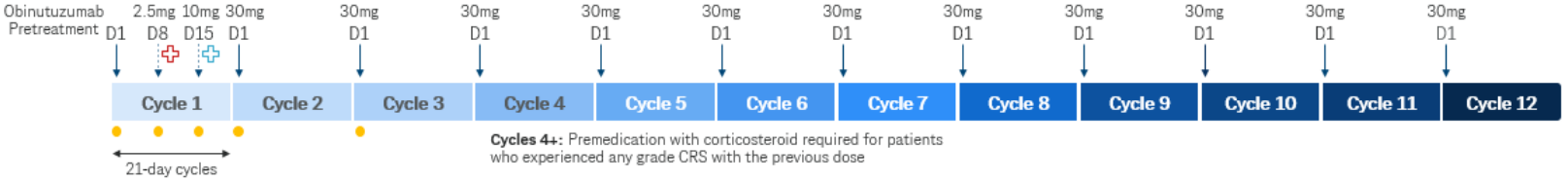
- Route: Intravenous
- Pre-medications (Cycle 1-3):
  - Dexamethasone 20 mg (IV)
  - Diphenhydramine 50 mg
  - Acetaminophen 500-1000 mg
- Cycle length = 21 days
- Duration = 12 cycles (fixed)

Cycle	Day	Dose
Cycle 1	1	Administer obinutuzumab
	8	2.5 mg over 4 hours
	15	10 mg over 4 hours
Cycle 2	1	30 mg over 4 hours
Cycles 3-12	1	30 mg over 2 hours

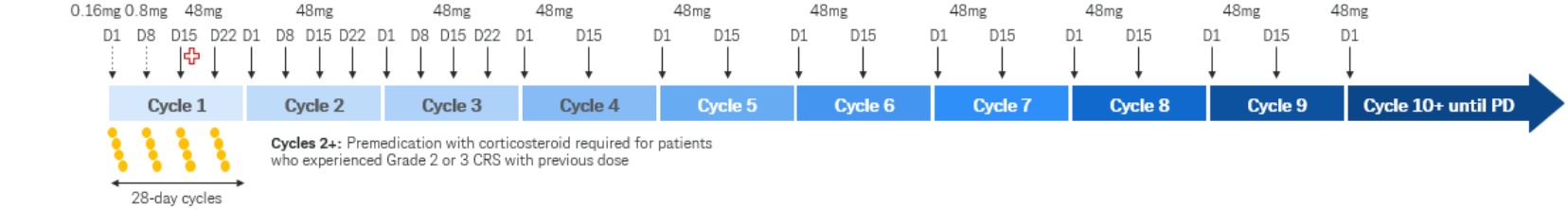
Dickinson MJ, et al. *N Engl J Med*. 2022;387(24):2220-2231. COLUMVI™ (glofitamab-gxbm). [package insert]. San Francisco, CA USA: Genentech Inc.; 2023.

Administration: Bispecific Antibodies in R/R DLBCL

Glofitamab IV Infusion[1] - Administer over a minimum of 4 hours for Cycles 1 and 2; administer over 2 hours for subsequent cycles if no CRS with the previous dose



Epcoritamab SC Injection[2]



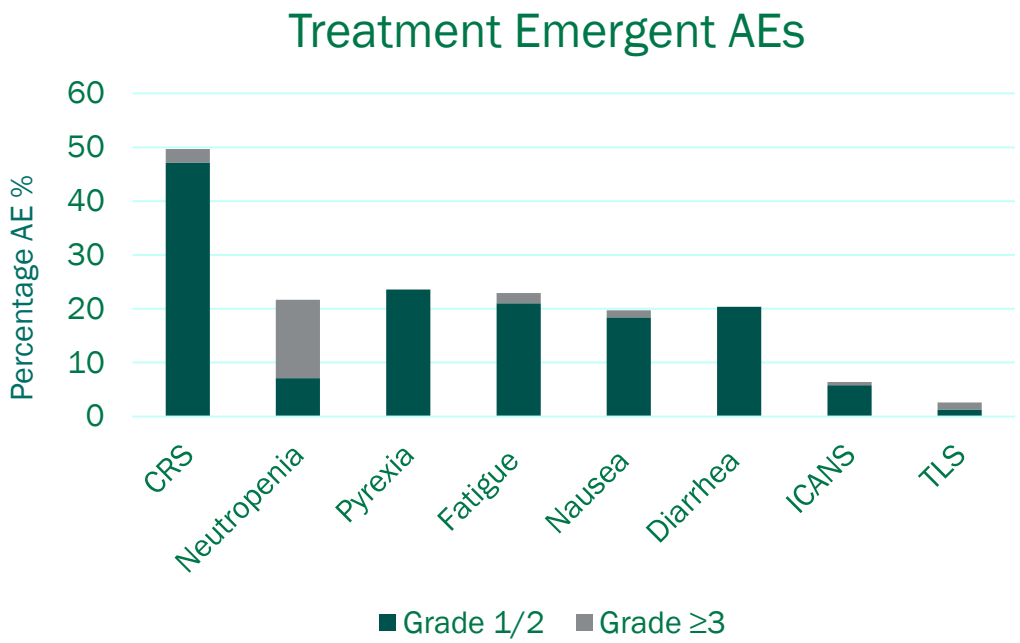
● = Required dose of corticosteroid premedication

✚ = **For glofitamab:** Hospitalize all patients during and for 24 hours after completion of infusion
For epcoritamab: Hospitalize all patients for 24 hours after administration

✚ = **For glofitamab:** Patients who experienced any grade CRS during the 2.5 mg dose should be hospitalized during and for 24 hours after completion of the 10 mg dose
For subsequent doses, patients who experienced Grade ≥2 CRS with their previous infusion should be hospitalized during and for 24 hours after the completion of the next glofitamab infusion

COLUMVI™ (glofitamab-gxbm). [package insert]. San Francisco, CA USA: Genentech Inc.; 2023.
EPKINLY™(epcoritamab-bysp). [package insert]. Plainsboro, NJ USA: Genmab Inc, and AbbVie Inc.; 2023

EPCORE NHL-1: Safety

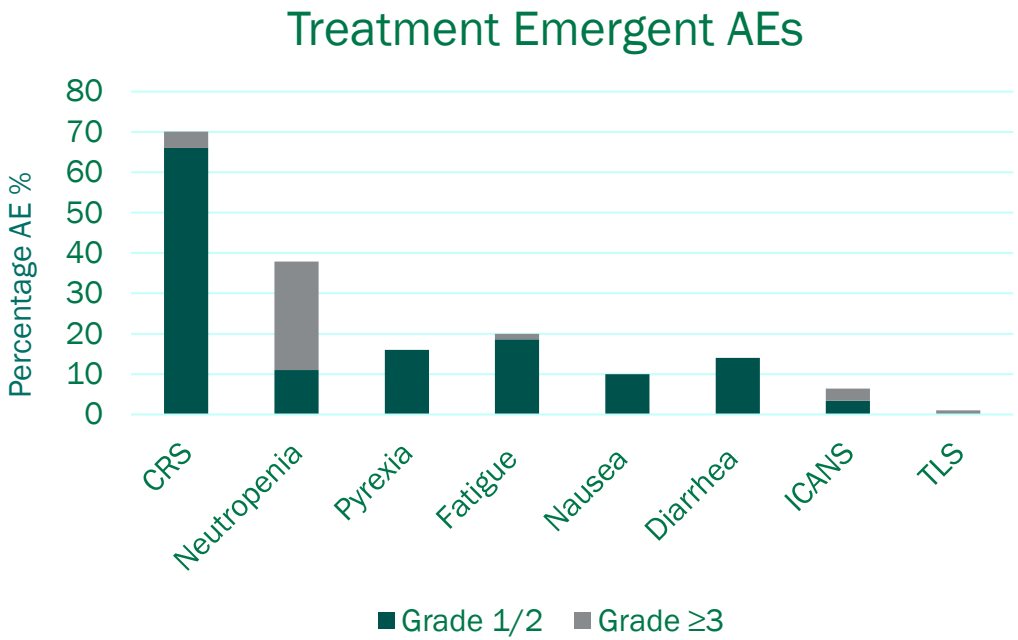


- CRS = 49.7% (N = 78)
  - Median time to onset = 20 hours post-first full dose (C1D15)
  - Median duration = 48 hours
  - Tocilizumab use = 28.2%
  - Corticosteroid use = 20.5%
- ICANS = 6.4% (N = 10)
  - Median time to onset = 16.5 days
  - Median duration = 4 days
  - One fatal case
- Fatal AEs = 5.7%

CRS = Cytokine Release Syndrome
ICANS = Immune Effector Cell Associated Neurotoxicity Syndrome
AE = Adverse Event

Thieblemont C, et al. *J Clin Oncol*. 2023;41(12):2238-2247.

NP30179 Trial: Safety

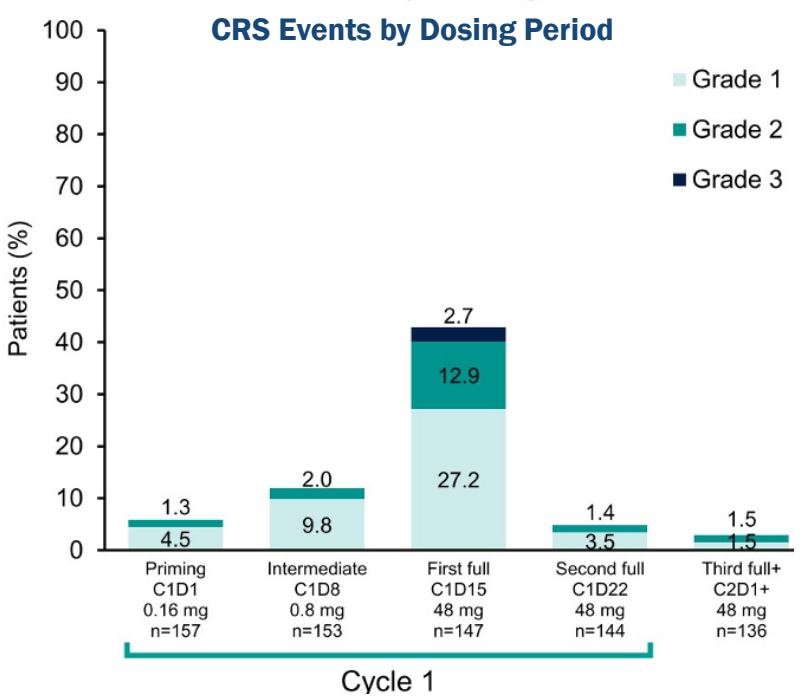


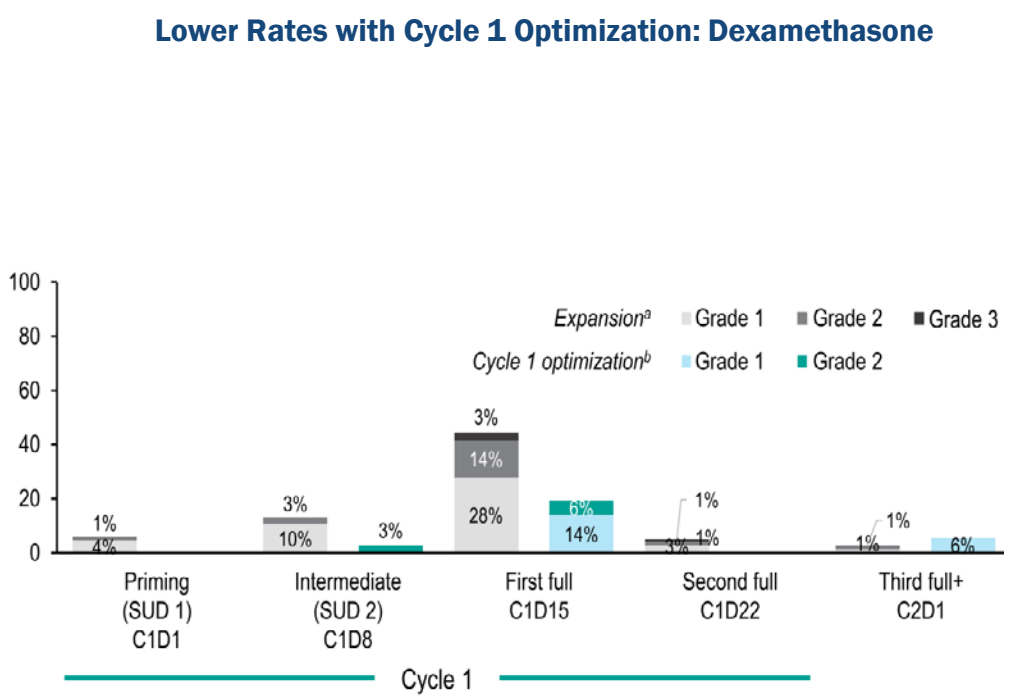
- CRS = 66% (N = 101)
  - Median time to onset = 13.5 hours post-first dose (C1D8)
  - Median duration = 30.5 hours
  - Tocilizumab use = 32 %
  - Corticosteroid use = 27.8 %
- ICANS = 8% (N = 12)
  - CTCAE-defined neurologic AEs
  - FDA adjudication = 4.8% (N = 7)
  - One fatal case
- Fatal AEs = 5%

CRS = Cytokine Release Syndrome
ICANS = Immune Effector Cell Associated Neurotoxicity Syndrome
AE = Adverse Event

Dickinson MJ, et al. *N Engl J Med*. 2022;387(24):2220-2231.

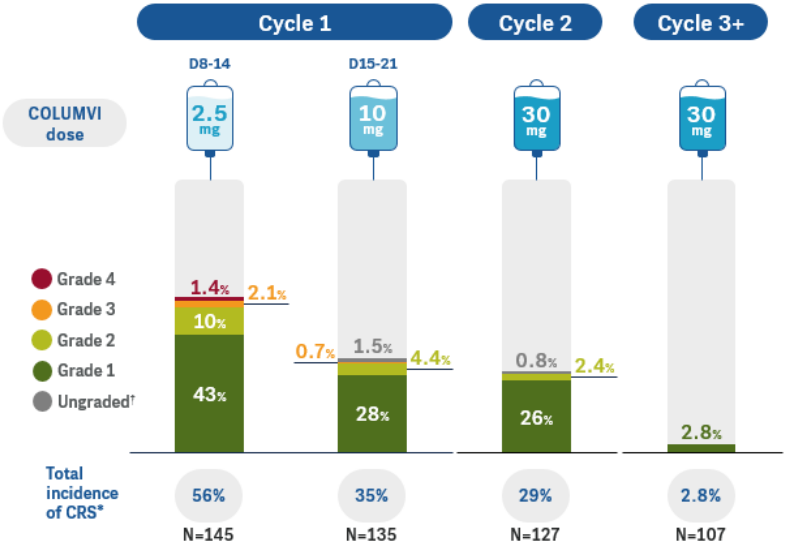
Managing Toxicity: Epcoritamab CRS



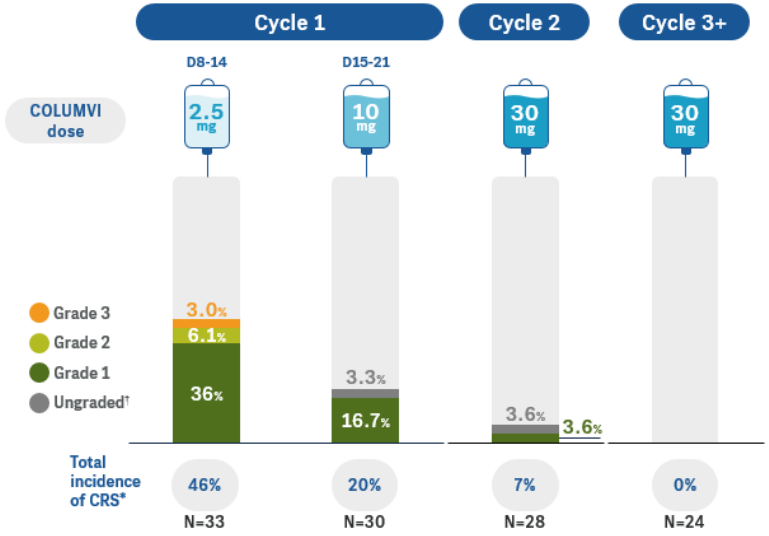


EPKINLY™(epcoritamab-bysp). [package insert]. Plainsboro, NJ USA: Genmab Inc, and AbbVie Inc.; 2023. Genmab data on file.

Managing Toxicity: Glofitamab CRS



USPI: CRS by Cycle



CRS By Cycle in Cohort of Patients who Received Dexamethasone Premedication

COLUMVI™ (glofitamab-gxbm). [package insert]. San Francisco, CA USA: Genentech Inc.; 2023. Genentech data on file.

Managing Toxicity: CRS

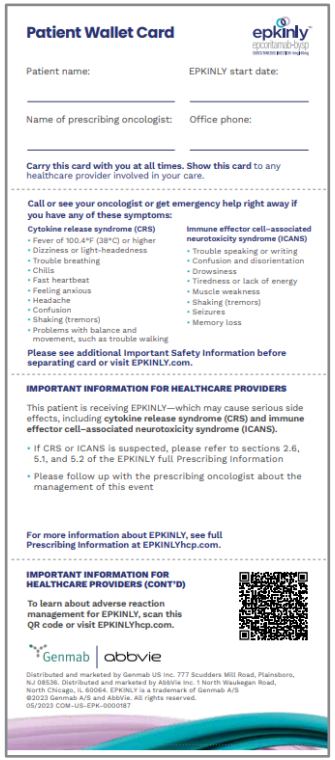
- "Manage CRS per current practice guidelines"
  - Graded using American Society for Transplantation and Cellular Therapy (ASTCT) 2019 consensus grading criteria
  - Supportive care
    - Continuation of corticosteroids for premedication and/or treatment
    - Antipyretic and fluid management
    - IL-6 receptor antagonists (tocilizumab)
    - Intensive care with Grade 3 and Grade 4 CRS (vasopressor, respiratory support)
  - Hospitalization when necessary for subsequent doses
  - Consideration of slower infusion rates for glofitamab
  - Delay of therapy and repeat step-up if necessary per protocol

Managing Toxicity: ICANS

- Infrequent in both the NP30179 and EPCOR-NHL1 trials
  - Approximately 5-8% (majority Grade 1 or 2)
  - Clinically different from CAR-T cell-induced ICANS, primarily headache and dizziness
  - Treat with corticosteroids and supportive care, consider anti-seizure prophylaxis
- Fatal cases – confounding factors
  - Epcoritamab (Day 25): hyperammonemia, possible microangiopathy (new cerebral infarcts, splenic infarct, thrombocytopenia and coagulopathy), and accumulation of morphine active metabolites
  - Glofitamab (Day 17): considered related to worsening pain and opioids by investigator

Counseling Tip: No driving or operating hazardous equipment until resolution!

Managing Toxicity: Patient Education



Patient Wallet Card

epkinly epcoritamab-bysp

Patient name: EPKINLY start date:

Name of prescribing oncologist: Office phone:

Carry this card with you at all times. Show this card to any healthcare provider involved in your care.

Call or see your oncologist or get emergency help right away if you have any of these symptoms:

Cytokine release syndrome (CRS)
- Fever of 100.4°F (38°C) or higher
- Dizziness or light-headedness
- Trouble breathing
- Chills
- Fast heartbeat
- Feeling anxious
- Headache
- Confusion
- Shaking (tremors)
- Problems with balance and movement, such as trouble walking

Immune effector cell–associated neurotoxicity syndrome (ICANS)
- Trouble speaking or writing
- Confusion and disorientation
- Drowsiness
- Tiredness or lack of energy
- Muscle weakness
- Shaking (tremors)
- Seizures
- Memory loss

Please see additional Important Safety Information before separating card or visit EPKINLY.com.

IMPORTANT INFORMATION FOR HEALTHCARE PROVIDERS

This patient is receiving EPKINLY—which may cause serious side effects, including **cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS).**

- If CRS or ICANS is suspected, please refer to sections 2.6, 5.1, and 5.2 of the EPKINLY full Prescribing Information
- Please follow up with the prescribing oncologist about the management of this event

For more information about EPKINLY, see full Prescribing Information at EPKINLYhcp.com.

IMPORTANT INFORMATION FOR HEALTHCARE PROVIDERS (CONT'D)

To learn about adverse reaction management for EPKINLY, scan this QR code or visit EPKINLYhcp.com.

Genmab | abbvie

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Information for the Treating Doctor (cont'd)

Visit COLUMVI-hcp.com to learn more about CRS grading and management.

Genentech
A Member of the Roche Group

M-US-00019077(v1.0) Printed in USA. June 2023

Patient's name:

Prescribing doctor:

Prescribing doctor's phone number:

Date of **COLUMVI™ (glofitamab-gxbm)** initiation:

Carry this card with you at all times. Show to any doctor involved in your care.

COLUMVI can cause CRS, a serious side effect that is common during treatment with COLUMVI, and can also be serious and lead to death.

Call your healthcare provider or get emergency medical help right away if you develop any signs or symptoms of CRS, including:

- fever of 100.4°F (38°C) or higher
- chills or shaking
- fast or irregular heartbeat
- dizziness or light-headedness
- trouble breathing
- shortness of breath

Experiencing any of these symptoms could be due to cytokine release syndrome, which requires immediate evaluation by a doctor.

Please see Important Safety Information, including **Serious Side Effects**, as well as the accompanying COLUMVI full Prescribing Information and Medication Guide.

Information for the Treating Doctor

This patient has received **COLUMVI**—which can cause cytokine release syndrome (CRS).

- If CRS is suspected, please refer to Section 2.4 of the Prescribing Information for recommendations on CRS management
- Consider following up with the prescribing physician about how this event was managed

For more information about COLUMVI, see full Prescribing Information.

https://www.columvi.com/content/dam/gene/columvi/pdfs/columvi-wallet-card.pdf. Accessed February 2, 2024

https://www.epkinly.com/content/dam/epcoritamab/docs/wallet-card.pdf. Accessed February 2, 2024

Managing Toxicity: Patient Education

Who?

What?

When?

Figure 1: Sample educational sheet for patients

Patient Name:	DOB:
Diagnosis:	Current treatment:
Day 1 start of treatment:	My highest risk of side effects is on:
Treatment team: Contact information:	
CRS Symptoms to monitor for: - Temp 100.4 F or greater - Pulse Ox 90% or less or >5% change from baseline - Decrease in SBP >10 mmHg from baseline and/or SBP <90 mmHg - Increased HR >110 or more than 20 bpm from baseline while at rest	Neurotoxicity symptoms to monitor for: - Confusion - Difficulty with speech - Difficulty staying awake - Abnormal actions - Seizures
What do I monitor at home? - Temperature - Blood pressure - Heart rate - Oxygen levels	How often do I monitor?
When do I call my doctor's office? - Any symptom of CRS or change in thinking or speech When should I go straight to the ER?	What number should I call? - During office hours: - After office hours:

Crombie JL, et al. Consensus Recommendations on the Management of Toxicity Associated with CD3xCD20 Bispecific Antibody Therapy https://doi.org/10.1182/blood.2023022432

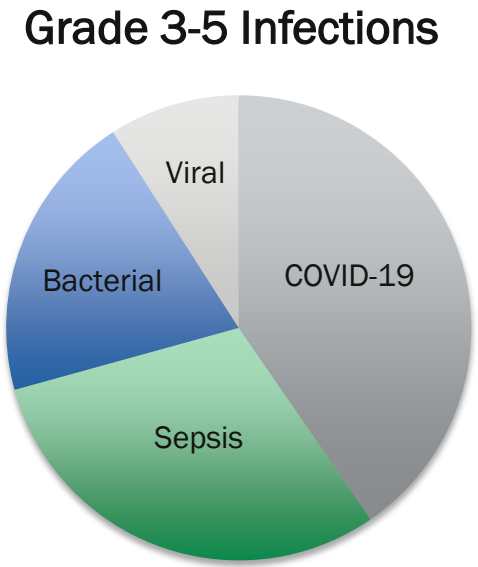
Managing Toxicity: Cytopenias

- Neutropenia
  - All Grade: 50-56 %
  - Grade 3 or 4: 26-32%
- Anemia
  - All Grade: 62-72%,
  - Grade 3 or 4: 8-12%
- Thrombocytopenia
  - All Grade: 48-56 %
  - Grade 3 or 4: 8-12%

- Low rates of febrile neutropenia (~3%)
- Granulocyte-colony stimulating factor (G-CSF) administration allowed
  - Median duration of neutropenia generally days to weeks (8-20 days)
    - Occurs most commonly with earlier cycles of therapy
  - Dose interruptions per protocol
    - Absolute neutrophil count < 0.5 x 10^9/L
    - Platelet count < 50 x 10^9/L
- Overall favorable profile compared to CAR-T cell therapy

Managing Toxicity: Infections

- Infections (all grade 39-45%)
  - Grade 3-5 15%
  - Low rates of febrile neutropenia ~ 3%
- Antibacterial and antifungal prophylaxis not routinely required
- Consider Immunoglobulin replacement therapy (IVIG)



Counseling Tip: Antiviral and PJP prophylaxis indicated!

Managing Toxicity: TLS and Tumor Flare

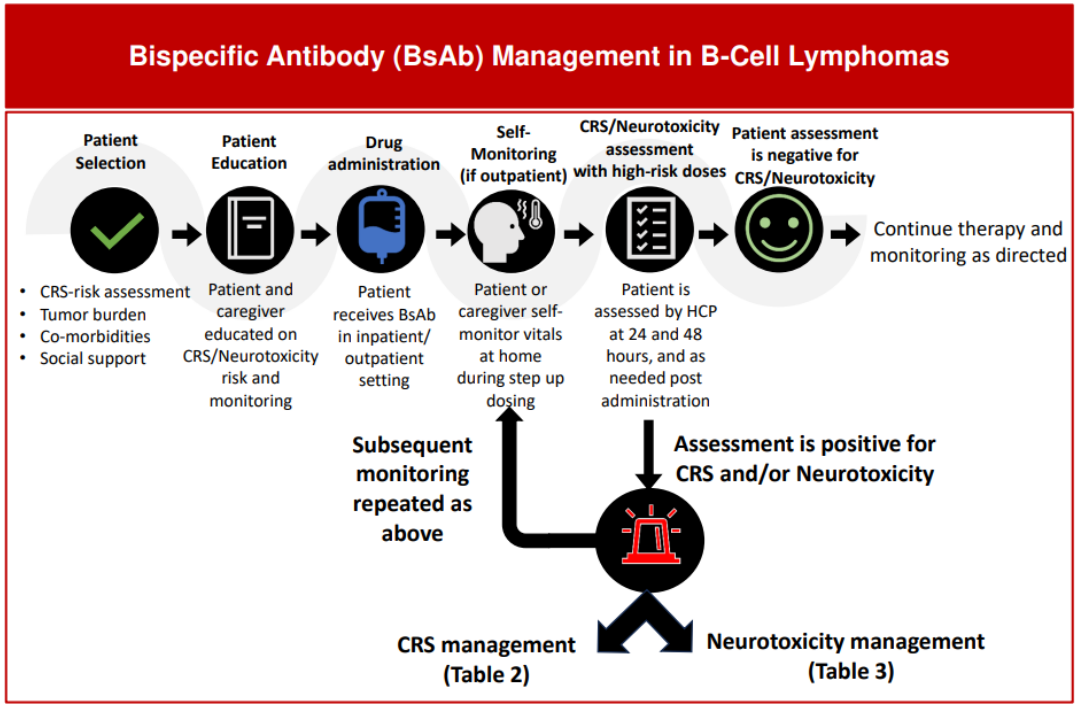
- Tumor Lysis Syndrome (TLS)
  - Epcoritamab: Grade 3 TLS in 2 patients (1%)
  - Glofitamab: Grade ≥3 TLS in 2 patients (1%)
- Tumor Flare or pseudoprogression
  - Typically after first dose or target dose
  - Assessed by Lymphoma Response to Immunotherapy Criteria (LYRIC)
    - Epcoritamab: 10 % of patients achieving objective response (9 patients)
    - Glofitamab: 12 % all grade, Grade ≥ 3 3%

Counseling Tip: Consider anti-hyperuricemic medications for prophylaxis!

BsAbs Pearls

	Epcoritamab	Glofitamab
Inpatient Admission	24 hours after C1D15	During and 24 hours after C1D8
CRS Peak Incidence	C1D15	C1D8
CRS Timing (median onset)	20 hours (C1D15)	13.5 hours (C1D8)
Viral and PJP Prophylaxis	Recommended	Recommended
Route	SQ	IV
Duration of therapy	Until progression	Maximum 12 cycles

Implementation: To Admit or Not to Admit



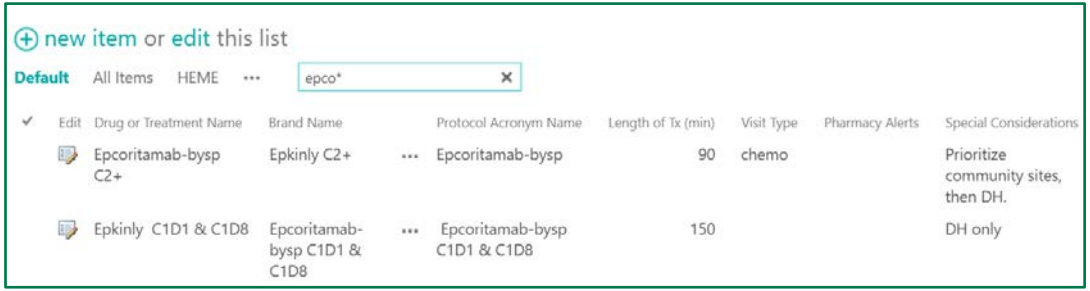
Crombie JL, et al. https://doi.org/10.1182/blood.2023022432

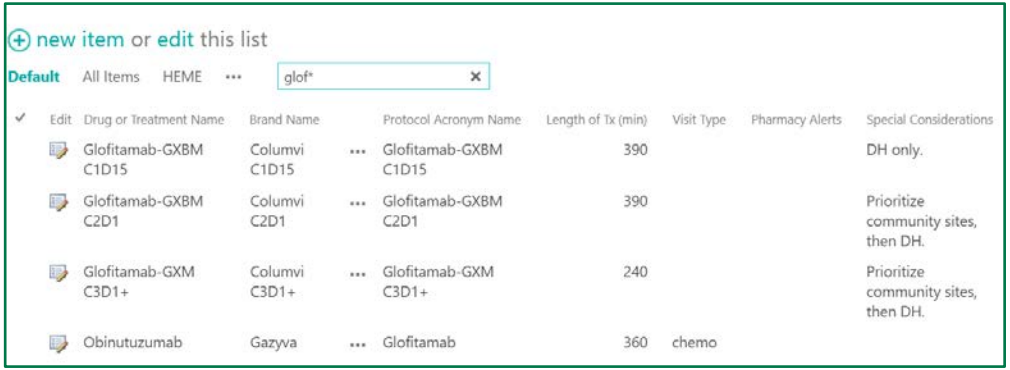
Implementation: To Admit or Not to Admit

- Site of monitoring should generally follow the prescribing label
- Specific to each clinical site's capabilities
- Workflow delineation key to escalation of care
  - Post-dose monitoring protocols
  - Emergency transfer when necessary
- Capitalizing on electronic health record systems
- Education of community emergency department staff
- Always consider the patient!

Crombie JL, et al. https://doi.org/10.1182/blood.2023022432

Implementation: Scheduling





Implementation: How to Handle?

- Hazardous? – No, NIOSH does not categorize as hazardous
- USP 800? – No, follow USP 797 standards for sterile compounding
  - Ability to compound in central pharmacy
  - "Chemotherapy hood" negative pressure room not required
- Complexity of preparation
  - Epcoritamab subcutaneous injection
    - 0.16 mg dose requires 2 dilutions
    - 0.8 mg dose requires 1 dilution
  - Glofitamab intravenous infusion
    - Drug volume added to 50-100 mL mini-bags

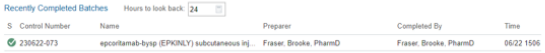
NIOSH = National Institute for Occupational Safety and Health
Image credit: https://www.halyardhealth.com/wp-content/uploads/Chemo-Compounding-PPE-Guidelines-Poster-02902.pdf

Implementation: Preparation

Epcoritamab Preparation Steps – 0.16 mg dose

Dilution A (epcoritamab-bysp (Epkinly) subcutaneous injection 1st dilution) – is the first step for both the 0.16 mg doses and 0.8 mg doses and should be done in compounding and repackaging – the CNR record is 750533

- Use an appropriately sized syringe, vial, and needle for each transfer step.
- Prepare epcoritamab vial
  - Retrieve one 4 mg/0.8 mL epcoritamab vial from the refrigerator.
  - Allow the vial to come to room temperature
    - This will take approximately 30 minutes
    - The vial cannot be at room temperature for longer than an hour before you start the dilution
  - Gently swirl the epcoritamab vial. DO NOT invert, vortex, or vigorously shake the vial.
- Perform dilution
  - Label an appropriately sized empty vial as "Dilution A".
  - Transfer 0.8 mL of epcoritamab into the Dilution A vial.
  - Transfer 4.2 mL of 0.9% Sodium Chloride Injection, USP into the Dilution A vial to make a final concentration of 0.8 mg/mL.
  - Gently swirl the Dilution A vial for 30 to 45 seconds.
- After completing the dilution in compounding and repackaging, the pharmacist will need to check the vial in Dispense Prep
  - In order to see if the pharmacist has checked the vial, go into Compounding & Repackaging and look for the dose to be completed under recently completed batch



- Save the epcoritamab vial as it will need to be scanned for the dispense preparation step in Epic.

0.16 mg dose

- After ensuring a pharmacist has checked the CNR for Dilution A, Perform second dilution (complete in Epic dispense prep)
  - Label an empty vial "Dilution B"
  - Transfer 2 mL of solution from the Dilution A vial into the Dilution B vial. Then discard Dilution A vial.
  - Transfer 8 mL of 0.9% NaCl into the Dilution B vial
  - The resultant concentration is 0.16 mg/mL
  - Gently swirl the Dilution B vial for 30-45 seconds
- Withdraw dose:
  - Withdraw 1 mL from Dilution B vial into a 3 mL syringe
- Label dose and note expiration on label
  - 12 hours at room temperature for outpatient doses
  - 24 hours refrigerated for inpatient doses

Show Me the Money $$$!

- Epcoritamab or glofitamab cost for 10+ cycles estimated ~ $200,000 - 300,000 for drug cost alone*
- Cost of continuous therapy could be > CAR-T
  - Limited cost-effectiveness data
    - QALT threshold
  - NTAP designation for Medicare patients as of October 2023

* WAC (Wholesale Acquisition Cost in 2023)
QALY: quality adjusted life year
NTAP: new technology add-on payment

Future Directions

First-Line

- Epcoritamab +R-CHOP vs R-CHOP in patients with newly diagnosed DLCBL (EPCOR™ NHL-2; *NCT05578976*)
- Epcoritamab +R-mini-CHOP in DLBCL patients ineligible for full-dose anthracycline (Arm 8 *NCT04663347)*
- Glofitamab +R-CHOP in previously untreated DLBCL (NP40126, *NCT03467373*)
- Glofitamab + Pola-RCHP vs Pola-RCHP in previously untreated LBCL (RO7082859, *NCT06047080*)

Second-Line

- Epcoritamab +GemOx in patients with R/R DLBCL ineligible for ASCT (Arm 5 *NCT04663347)*
- Epcoritamab +R-ICE in patients with R/R DLBCL eligible for ASCT (Arm 10 *NCT04663347*)
- Glofitamab + GemOx vs Rituximab + GemOx in R/R DLBCL (STARGLO, GO41944, *NCT04408638)*
- Glofitamab +R-ICE in patients with R/R transplant or CAR-T eligible DLBCL (*NCT05364424*)

www.clinicaltrials.gov

Thank You!

Appendix

Implementation: CRS Management

Table 2: Proposed management of CRS for CD3xCD20 BsAbs according to severity

Definition: CRS is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction

Symptoms: Fever (required) with possible hypoxia, hypotension, tachypnea, nausea, headache, fatigue, myalgias or malaise

Work up and evaluation:
- Pertinent history and physical exam including vital sign evaluation and evaluation of respiratory symptoms.
- Review medications including BsAb received, last dose of anti-pyretic therapy, steroids, or anti-cytokine administration.
- Assess for concurrent symptoms of neurotoxicity.
- Assess for alternate diagnosis including infection (including neutropenic fever), venous thromboembolism, respiratory infection (including COVID-19, influenza), volume overload or dehydration, exacerbation of underlying cardio-pulmonary condition. Treat as appropriate.
- For duration of symptoms over 1 week, consider excluding HLH/MAS[12]

Monitoring: Consider monitoring patient for 1-2 hours post infusion if outpatient administration of BsAb on day of step-up dosing

Next dose: Follow prescribing label

Grade and definition	Management
Grade 1: Fever[a] ≥100.4 F +/- constitutional symptoms requiring symptomatic treatment, no hypotension or hypoxia	Home: - A/P 650-1000 mg PO, can repeat if recurrent fever ≥ 6-8h later if clinically stable - Recommend aggressive oral hydration - Continue to check temperature every 1-2 hours and other vitals if able. Patients should recontact the clinic urgently or present to ED if BP goes less than < 10 mm Hg below baseline AND < 90 mm Hg systolic, new orthostatic symptoms, weakness, confusion, dizziness, or new hypoxia (<90%). Home versus outpatient/ED evaluation: - If refractory or recurrent fever (< 6-8h) consider dexamethasone 10 mg once. Home management may be appropriate if vital signs remain stable and no other concerning symptoms. Otherwise, patients should be evaluated in a healthcare facility. - Consider earlier administration of steroids and immediate in-person evaluation for patients with multiple disease risk factors or comorbidities (See text). - Consider daily dexamethasone with persistent symptoms.

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Implementation: CRS Management

	Additional management: - Consider anti-cytokine therapy (e.g., tocilizumab) in cases of protracted fever (e.g. >48 hours despite corticosteroids). - Early tocilizumab after trial of dexamethasone should be considered in patients with multiple medical risk factors (e.g. comorbidities).
Grade 2: Fever ≥100.4 F with either hypotension not requiring pressors and/or hypoxia managed with low flow nasal canula or blow-by.	- All patients should be urgently evaluated in-person. Recommend inpatient management for most cases of Grade 2 CRS unless qualified outpatient day hospital/infusion center and no hypoxia. - If after hours without access to appropriate outpatient treatment area or if clinical scenario dictates, recommend ED evaluation. - A/P 650-1000 mg as need, up to 3-4 times daily. - Dexamethasone 10 mg every 12 hours. - Administer intravenous fluids/supplemental oxygen as appropriate. - Administer tocilizumab* if symptoms persist despite IV fluids and dexamethasone (approximately 4-6 hours after dosing) or if clinically unstable. Consider alternative agent (e.g. anakinra or siltuximab) if persistent symptoms despite maximal dosing
Grade 3: Fever ≥100.4 F with either hypotension (BP less than 90/60 or < 10 mmHg below not responsive to fluids and/or hypoxia requiring high-flow nasal canula, face mask or venturi mask	- Emergent inpatient admission (floor or ICU) for hemodynamic monitoring, IV fluids, oxygen therapy and vasopressors. - A/P 1000 mg IV as needed up to 3-4 times daily when safe. - Dexamethasone (e.g. 10 mg IV Q 6 hours), until resolution to grade ≤ 1, followed by dexamethasone taper. - Evaluate for sepsis and consider empiric antibiotics. - Administer tocilizumab* and consider alternative agent (e.g. anakinra or siltuximab) if persistent grade 3 CRS despite maximal dosing. - If refractory hypotension/hypoxia admit to ICU.
Grade 4: Fever ≥100.4 F with any of the following: Life threatening consequences, urgent intervention required; requiring multiple pressors and/or positive pressure respiratory support or mechanical intubation.	- Inpatient admission to ICU for hemodynamic monitoring, IV fluids, oxygen therapy and vasopressors. - A/P 1000 mg IV as needed up to 3-4 times daily when safe. - Dexamethasone (e.g. 20 mg IV Q 6 hours), until resolution to grade ≤ 1, followed by dexamethasone taper. - Administer tocilizumab and if repeated doses of tocilizumab have been utilized, consider alternative agent (e.g. anakinra or siltuximab) if persistent grade 4 CRS despite maximal dosing of first agent.

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Implementation: ICANS Management

Table 3: Neurotoxicity grading and proposed management for CD3xCD20 BsAbs

Definition: Neurological AE after BsAb therapy most frequently consist of headache and dizziness. Occasionally ICANS-like symptoms occur. These may or may not accompany CRS. Symptoms: Delirium, dysgraphia, tremor, lethargy, difficulty concentrating, agitation, confusion, expressive aphasia, apraxia, depressed level of consciousness, encephalopathy, seizures Recommendations: Patients and caregivers need to be educated on symptoms and that patients cannot operate drive or operate heavy machinery if symptomatic Work up and evaluation: - Pertinent history and PE - Review medications including last dose of anti-pyretic therapy, steroids, or anti-cytokine therapy. - Perform ICE score on all patients with neurologic symptoms. - Assess for alternate cause of symptoms. Consider performing CT head, EEG, MRI, or LP as appropriate. - Assess for concurrent symptoms of CRS (fever, hypoxia, hypotension). Treatment of CRS can occur concurrently if appropriate. - If any concern for neurological AEs exists patient should be evaluated in outpatient center or ED. If any worsening symptoms (e.g. somnolence, worsening confusion, weakness, etc.), patients should be promptly referred to the ED.	
ICE scoring system	
Orientation to year, month, city, hospital	4 points
Naming 3 objects	3 points
Following simple commands	1 point
Writing standard sentence	1 point
Attention to count backwards from 100 by 10	1 point
ICANS Grading	Management

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Implementation: ICANS Management

Grade 1: ICE 7-9 or depressed level of consciousness but awakens spontaneously.	- Pending clinical scenario and social situation, can consider observation or close monitoring in outpatient setting. Can consider dexamethasone 10 mg x 1.
Grade 2: ICE 3-6 or depressed level of consciousness but awakens to voice.	- Admit patient to hospital for monitoring. - Dexamethasone 10mg IV Q 12 hours, followed by taper once grade 1 or better.
Grade 3: ICE 0 to 2 or depressed level of consciousness but awakens to tactile stimulus or any clinical seizure that resolves rapidly or focal/local edema on neuroimaging.	- Monitor in ICU setting. - Neurology consult. - Dexamethasone 10 mg IV Q 6 hours, followed by taper once grade 1or better. - Use antiepileptics for seizure management as needed. - Consider adding anakinra 100 mg every 12 hours if symptoms persist beyond 24 hours, continue until resolution.
Grade 4: ICE is 0 or patient is unarousable or requires vigorous or repetitive tactile stimuli or life-threatening prolonged seizure (greater than 5 minutes) or repetitive seizures without return to baseline or deep focal motor weakness or diffuse cerebral edema on neuroimaging.	- Monitor in ICU setting. - Neurology consult. - Dexamethasone 10 mg IV Q 6 hours, followed by taper once grade 1or better. - Use antiepileptics for seizure management as needed. - Consider adding anakinra 100 mg every 12 hours if symptoms persist beyond 24 hours, continue until resolution.

CT: computed tomography, EEG: electroencephalogram, MRI: magnetic resonance imaging, LP: lumbar puncture

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Implementation: Logistical Considerations

- Insurance authorization (BsAb and supportive care medications)
- Ensure a facility is available close by with two doses of tocilizumab
- Designated location for treatment of low grade CRS if outpatient
- Dedicated pathway for escalation of care for ≥ Grade 2 CRS
- Electronic medical records (EMR) to create standard order sets
- Education to multidisciplinary staff, patients and caregivers
- Appointed team to monitor and manage complications
  - Oncologist, APP, RN, PharmD

Implementation: Patient Resources

- Access to thermometer
  - Suggested monitoring three times daily post step-up doses (48 hours)
- Blood pressure cuff and pulse oximeter when available
- Education sheet and/or wallet card
- Prescription for dexamethasone as needed for CRS
  - Start only after discussion with treatment team
- Clear call instructions and contact information