

IN PURSUIT OF *YOUR CURE.*[®]

Management of Infections and More By The Multidisciplinary Team

Immunotherapy in Multiple Myeloma

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**MYELOMA
INSTITUTE**



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Outline

- Case: 71-year-old patient with multiple myeloma
- CRS and ICANS: management and prophylaxis
- Infections: management and prophylaxis

Case: Newly Diagnosed Multiple Myeloma

- 71-year-old female. Diagnosed with multiple myeloma in April 2011. Pain in left femur and fatigue. Hgb 8.5 g/dL. M spike 3.2 g/dL IgG k, kappa sFLC 95 mg/dL, lambda sFLC 0.30 mg/dL, all other labs WNL, PET/CT showing lytic lesions in left femur with SUV 6.8. Bone marrow biopsy: 50% kappa restricted plasma cells, FISH found chrom 3+, 5+ and 11+

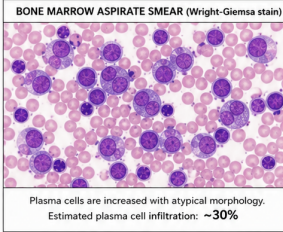
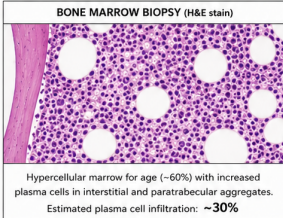
- **Initial therapy:** Bortezomib/lenalidomide/dexamethasone light x 8 cycles followed by lenalidomide maintenance (10 mg). Best response: CR

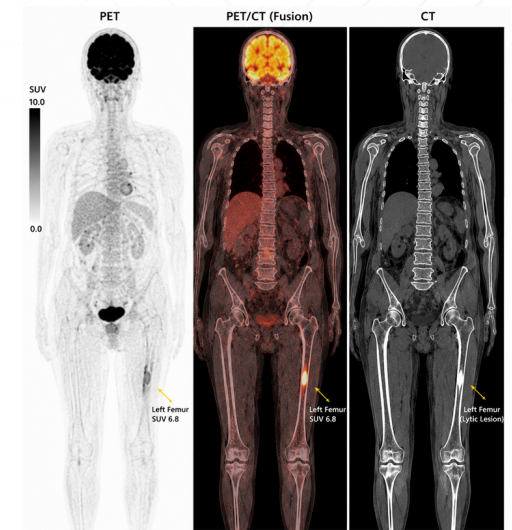


Case: Now Relapsed/Refractory Multiple Myeloma (5th Line)

- Patient has relapsed several times and is now relapsing while on her 4th line of therapy (she has received lenalidomide, pomalidomide, bortezomib, carfilzomib, elotuzumab, daratumumab, isatuximab, and cyclophosphamide in various combinations)
- At this time, sFLC kappa levels are 78 mg/dL, sFLC lambda 0.25 mg/dL, all other labs WNL. Bone marrow biopsy show 30% kappa restricted plasma cells, FISH found chrom 3+, 5+ and 11+. PET/CT showing lytic lesions in left femur with SUV 6.8
- **What to do next? What treatment may be reasonable?**

- **Fifth line:** Started on elranatamab 76 mg, weekly dosing x 4 cycles. Then planned restaging, depending on labs

BONE MARROW ASPIRATE SMEAR (Wright-Giemsa stain)	FISH ANALYSIS (Plasma Cells)			
	Probe	Normal	Patient (Myeloma Cells)	Result
 <p>Plasma cells are increased with atypical morphology. Estimated plasma cell infiltration: ~30%</p>	CEP 3 (3q26) Spectrum Green	2G	≥3G	GAIN (≥3 copies) Detected
	CEP 5 (5p15) Spectrum Red	2R	≥3R	GAIN (≥3 copies) Detected
 <p>Hypercellular marrow for age (~60%) with increased plasma cells in interstitial and paratrabecular aggregates. Estimated plasma cell infiltration: ~30%</p>	CEP 11 (11q13) Spectrum Aqua	2A	≥3A	GAIN (≥3 copies) Detected
	CEP 17 (17p13) Spectrum Gold	2G	2G	NORMAL (2 copies)



Case: Now Relapsed/Refractory Multiple Myeloma (5th Line)

What would we consider going forward with elranatamab single drug 76 mg dosing?

- Observation (not admission) for step-up dosing
- Short-course step-up dosing (D1,4,8)*
- Management of CRS/ICANS during step-up dosing (tocilizumab prophylaxis)
- Antiviral prophylaxis
- Antibiotic prophylaxis
- Monthly IVIG
- Recommend seasonal vaccinations
- Consider less frequent dosing of elranatamab over time (driven by response/assessments)

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BCMA-Targeted Bispecific Antibodies: Safety Profiles

	AMG-701 ¹	CC-93269 ²	Teclistamab ³	Elranatamab ⁴	REGN5458 ⁵	TNB383B ⁶
CRS (G 3-4)	61% (9%)	76.7% (3.3%)	71.5% (0.6%)	60.6% (0%)	38% (0%)	69% (4%)
Median Onset	-	1 (1-9)	2(1-6)	3	10.1(6-47) hours	1(1-2)
Duration	- 29%	2 (1-6)	2(1-9)	4(1-10)	14 (0-96) hours	1(1-8)
Tocilizumab		43%	36.4%	50%	43%	
NTS			15%	6.4%		
Grade 3-4			0.6%	1.1%	0%	0%
ICANs	Not reported	Not reported	3%	0%	4% (g2)	
Median Onset			2.5 (1-7)	NR		
Duration			3 (1-37)	NR		
Treatment required			7.3%	NR		
Cytopenias						
Grade 3-4						
Neutropenia	23%	37%	57%	67.3%	22%	24%
Anemia	43%	43%	34.5%	47.3%	23%	15%
Thrombopenia	20%	17%	21.2%	27.3%	13%	9%
Infections			63%			
Grade 3-4	17%	30%	35%		5 exitus infec	28%

Hypogammaglobulinemia as AEs observed in most patients treated with BCMA-CD3 mABs along the therapy.

NOTE: Cross-trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results.

1. Harrison SJ, et al. ASH 2020. Abstract 181; 2. Costa LJ, et al. EHA 2020. Abstract S205; 3. Moreau P, et al. ASH 2021. Abstract 896;
4. Sebag M, et al. ASH 2021. Abstract 895; Zonder, ASH 2021. Abstract 160; Kumar SK, et al. ASH 2021. Abstract 900.

CRS: It's a Learning Process!

- After the first/second step-up dose..... **We have to think of CRS if fever appears but....**
- **There is no symptom/sign/lab abnormality that is pathognomonic for CRS**

- Clinical symptomatology
- Physical examination

- Hemogram
- Biochemistry including
 - CRP
 - Ferritin
 - Creatinine
 - Uric acid
 - Electrolytes
 - Liver enzymes
 - Coagulation: fibrinogen and D-dimers

- X-ray
- Cultures
 - Blood, urine, sputum...
- Additional explorations based on clinical symptomatology

- Differential diagnosis with TLS, infections,..... Or coexistence
- **Early detection and early intervention**

CRS: Early Detection and Gradation Is Crucial to Start Therapy

ASTCT CRS consensus grading (adapted from Lee et al/ASTCT, BBMT, 2019)				
CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$	Temperature $\geq 38^{\circ}\text{C}$
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or†				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow nasal cannula, face mask, non-rebreather mask, or venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)
<p>Organ toxicities associated with CRS may be graded according to CTCAE V.5.0, but they do not influence CRS grading.</p> <p>*Fever is defined as a temperature of $\geq 38^{\circ}\text{C}$ not attributable to any other cause. In patients who have CRS who then undergo antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.</p> <p>†CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with a temperature of 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.</p> <p>ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome.</p>				

- G1: symptomatic treatment
 - G1 persistent or G2: tocilizumab
 - Toci can be considered earlier on in elderly patients with comorbidities
 - If CRS does not improve, steroids should be given with a second dose of tocilizumab
 - If CRS does not improve, third line can include high-dose MP, siltuximab, anakinra... But it would be highly recommended to consider other diagnosis
- ** Management may differ between BsAabs

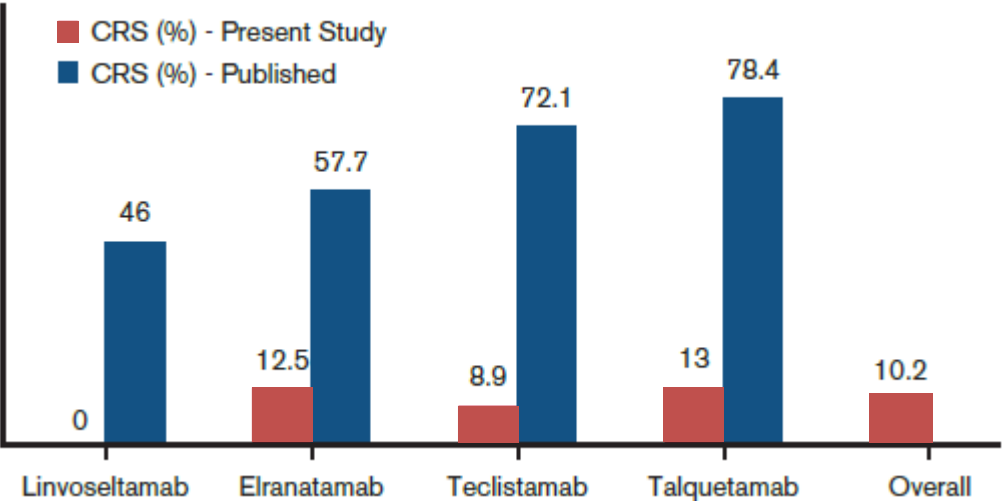
- G-CSF is not recommended during the step-up doses and first full dose
- It is not recommended to give more than 2 doses of tocilizumab because of the blockade of IL-6R
- The TLS can be prevented with adequate hydration and allopurinol as part of the routine
- In selected patients with high tumor burden, it would be recommended to prescribe rasburicase as prophylaxis
- If TLS is suspected, it is highly recommended to prescribe rasburicase.

1. Biol blood marrow transplant 25 2019 625-638

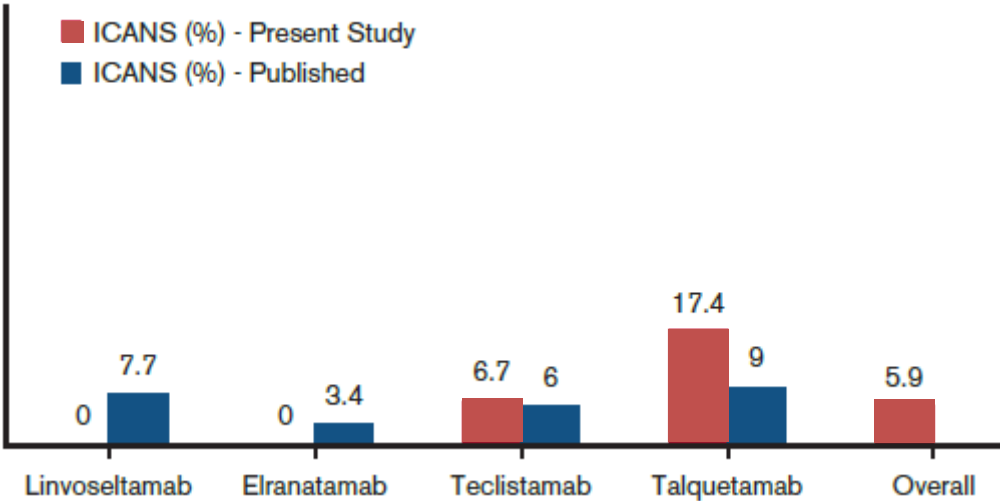
Prophylactic IL-6 Blockade Prior to Bispecific Antibodies

- This **single-center real-world** study of patients who were given a **single dose of prophylactic tocilizumab 1 hour prior to starting treatment** with teclistamab, elranatamab, linvoseltamab, talquetamab, or a combination through the University of Miami Hospital and Clinics between October 25, 2022, and December 16, 2024

Rate of CRS by drug in present study and trial comparator



Rate of ICANS by drug in present study and trial comparator



Without compromising efficacy, a single dose of prophylactic tocilizumab resulted in an overall CRS rate of 10.1% and an overall rate of ICANS of 5.9%

ICANS: Diagnostic Workup & Grading

- BASELINE neurological examination that it is not usually done by neurologist
- **ROUTINE neurological examination following BsAbs administration**
 - Attention, alertness & language (**earliest signs**)
 - Important insight from **family members** and **nursing team**

IMMUNE EFFECTOR CELL-ASSOCIATED ENCEPHALOPATHY SCORE



ICE Score

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

Score 10: no impairment; score 7–9: Grade 1 ICANS; score 3–6: Grade 2 ICANS; score 0–2: Grade 3 ICANS; score 0 due to patient unarousable and unable to perform ICE assessment: Grade 4 ICANS

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

ICANS: Diagnostic Workup & Grading (cont.)

ICE score

Level of consciousness

Seizures

Motor

Intracranial
pressure

ASTCT ICANS Consensus Grading

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7–9	3–6	0–2	0 (patient is unarousable and unable to perform ICE)
Depressed level consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure			Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (e.g., no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

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

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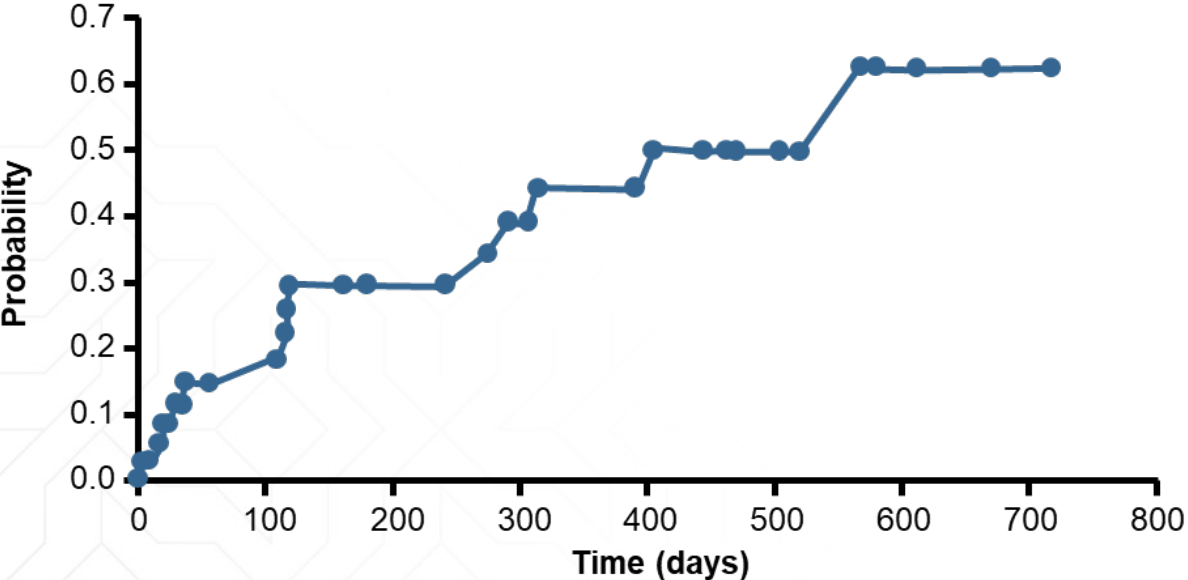
Bispecific Antibodies and Patterns of Infections

Clinical Variables	BsAb (N=36)	CAR-T (N=26)	Total (N=62)	P-value
CRS grade				0.52
1	12 (33.3%)	6 (23.1%)	18 (29.0%)	
2	2 (5.6%)	3 (11.5%)	5 (8.1%)	
Median time to therapy from diagnosis, y	6.6 (0.83-15.5)	2.6 (0.35-14.4)	5.2 (0.3-15.5)	0.04
Use of tocilizumab	4 (28.6%)	5 (55.6%)	9 (39.1%)	0.38
Median follow in months (range), mo	8.5 (3.5-10.5)	8.9 (3.1-18.1)	9 (3.1-18)	0.81
Median IgG levels (mg/L) at start of therapy (range)	889 (333-1931)	605 (259-1315)	673 (281-1826)	0.13
Baseline hypogammaglobinemia (≤ 700 mg/dL)	20 (80.0%)	13 (72.2%)	33 (76.7%)	0.551
Baseline severe hypogammaglobinemia (≤ 400 mg/dL)	11 (44.0%)	8 (44.4%)	19 (44.2%)	0.97
Baseline lymphopenia (≤ 300 /mL)	8 (23.5%)	8 (30.8%)	16 (26.7%)	0.53
IVIg supplementation	8 (22.9%)	6 (25.0%)	14 (23.7%)	0.84
Cumulative infections	25	5	30	0.01
Number of bacterial infections (n)	12	1	13	0.11
Number of viral infections (n)	8	2	10	0.69
Aggregated hospitalizations for infection (n)	15	3	18	0.03
Average length of stay per patient, mean (SD)	4.833 (3.460)	9.000 (5.196)	5.667 (4.030)	0.11
Best response				0.75
PD	7 (25.9%)	6 (30.0%)	13 (27.7%)	
\leq PR	20 (74.1%)	14 (70.0%)	34 (72.3%)	

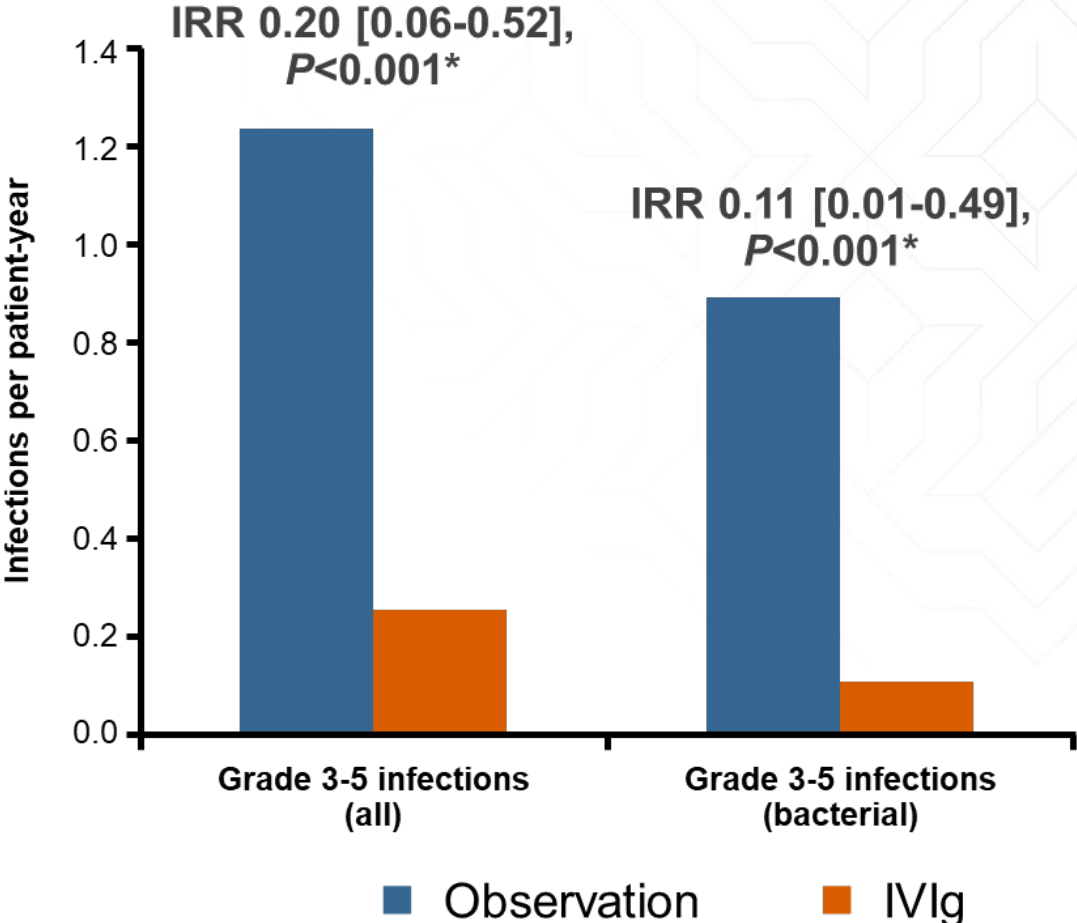
Mohan, et al. *Blood Adv.* 2022 Apr 26;6(8):2466-2470

Bispecific Antibodies and Patterns of Infections (cont.)

Probability of Grade 3-5 Infection



Lancman, et al. ASH 2022.



Infection Prevention and Management Strategies

Antimicrobial Prophylaxis

All patients

- HSV and VZV prophylaxis
- PJP prophylaxis
- VZV vaccination
- Influenza vaccination
- SARS-COV-2 vaccination per CDC/local guidelines

Antibacterial/antifungal indications

- Prolonged or G-CSF-resistant neutropenia
- High risk or history of recurrent infection
- History of prolonged high-dose steroid use (antifungal)

Management

Hypogammaglobulinemia

IVIG therapy monthly for

- IgG <400 mg/dL
- ≥ 2 severe recurrent infections by encapsulated bacteria
- Life-threatening infection
- Treatment-resistant bacterial infection

Neutropenia

- G-CSF for grade ≥ 3 neutropenia
- Avoid G-CSF during periods of CRS risk

Active Infection

- Treat with available therapy depending on infectious agent
- Antibiotic should be targeted when possible

Bispecific Antibody Dosing

Maintain dosing

- During prophylaxis
- During IVIG treatment

Temporarily withhold

- ANC < $0.5 \times 10^9/L$ or febrile neutropenia
- Active infection, including COVID-19

Discontinue

- HBV reactivation

ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; HBV, hepatitis B virus; IVIG, intravenous immunoglobulin; VZV, varicella zoster virus.

Raje N, et al. Blood Cancer J. 2023;13:116.

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And many, many more!





Thank you for your attention!

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