Anti-BCMA Bispecific Practical Guidelines

Canadian Association of Nurses in Oncology
Association canadienne des infirmières en oncologie

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Multiple Myeloma in Canada

Approximately 4,100 new cases of multiple myeloma are diagnosed in Canada each year, with an estimated 1,750 deaths annually.

- Myeloma represents 1.7% of new cancers in men and 1.3% in women
- Myeloma is fairly rare before age 40; the average age of diagnosis is in the mid-60s
- Factors that may increase the risk of myeloma include:
  - Exposure to toxic chemicals
  - Exposure to radiation
  - Obesity
  - Older age
  - 1st degree relative affected
  - MGUS

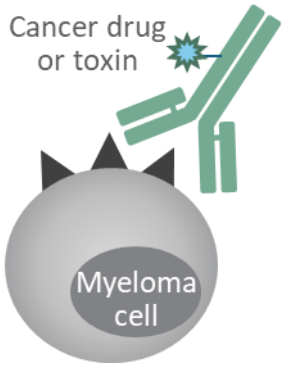
MGUS, monoclonal gammopathy of undetermined significance.
Statistics based on the Canadian Cancer Registry and Canadian Vital Statistics Death Database.
Brenner et al. *CMAJ* 2024;196:E615-23.

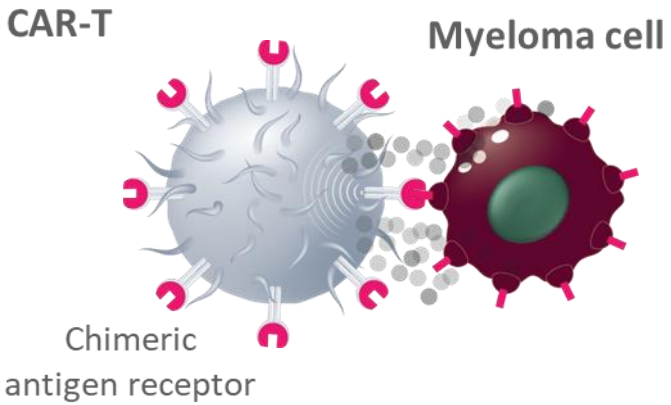
Myeloma Treatments Options Approved by Health Canada

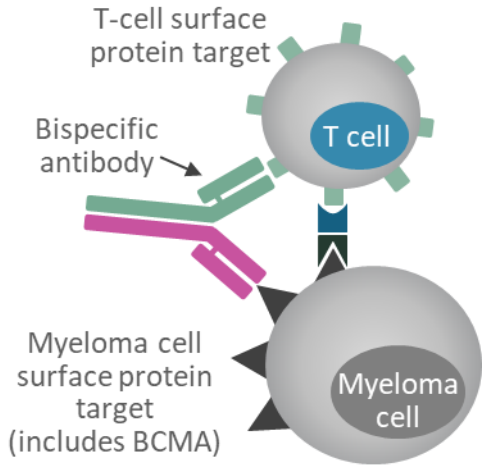
Drug Class	Generic Name
Proteosame inhibitors	Bortezomib
	Carfilzomib
	Ixazomib
Immunomodulatory (IMiDs)	Lenalidomide
	Pomalidomide
Monoclonal Antibodies (Anti-CD38)	Daratumumab
	Isatuximab
XPO1 Inhibitor	Selinexor
BCMA CAR-T	Ciltacabtagene autoleucel
CD3/GPRC5D bispecific antibody	Talquetamab
CD3/BCMA bispecific antibodies	Elranatamab
	Teclistamab

Health Canada

Classes of BCMA-Targeted Agents







Antibody-drug conjugates

- Consist of a monoclonal antibody fused to a chemotherapy agent, pro-drug, or radioactive isotope
- The antibody brings the toxic agent close to the myeloma cell to minimize off-target effects
- Repeat dosing schedule, frequency/duration differs by agent

CAR-Ts

- T cells from the patient are genetically modified to target BCMA
- Once bound, they activate to kill the tumour cell
- Must be manufactured for each individual patient; T cells collected by apheresis
- One-time dosing at certified centres

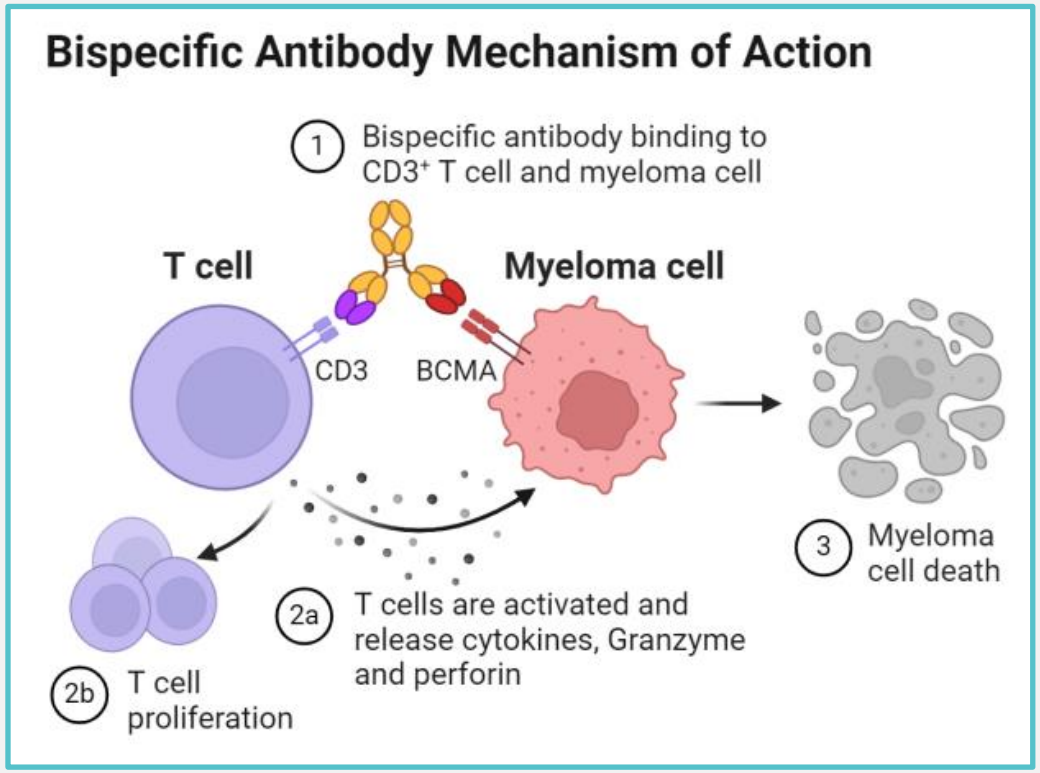
Bispecific T-cell–engaging antibodies

- Made from fragments of two different antibodies
  - One targets the myeloma cell (anti-BCMA)
  - The other binds to an immune cell (typically CD3)
- Can be used without modification or individual manufacturing
- Repeat dosing schedule, frequency/duration differs by agent

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation.

1. Multiple Myeloma Research Foundation. Multiple Myeloma Immunotherapy. Available at: https://themmrf.org/wp-content/uploads/2021/05/Immunotherapy_Booklet_2021_04132021.pdf. Accessed July 2024.

Mechanism of Action: CD3/BCMA Bispecific Antibodies



- Potent in vivo anti-tumor efficacy similar to CAR T
- Rapid kinetics of anti-tumor efficacy
- Rapid induction of T cell activation, expansion, and cytokine response

Characterization of the BCMA epitope bound by BCMA-CD3 T cell engager elranatamab.
ASCO 2024 (Poster 7546), Maria Josic, et al.
Also referenced: Panowski SH, et al. *Mol Cancer Ther* 2019; 18(11):2008-20.

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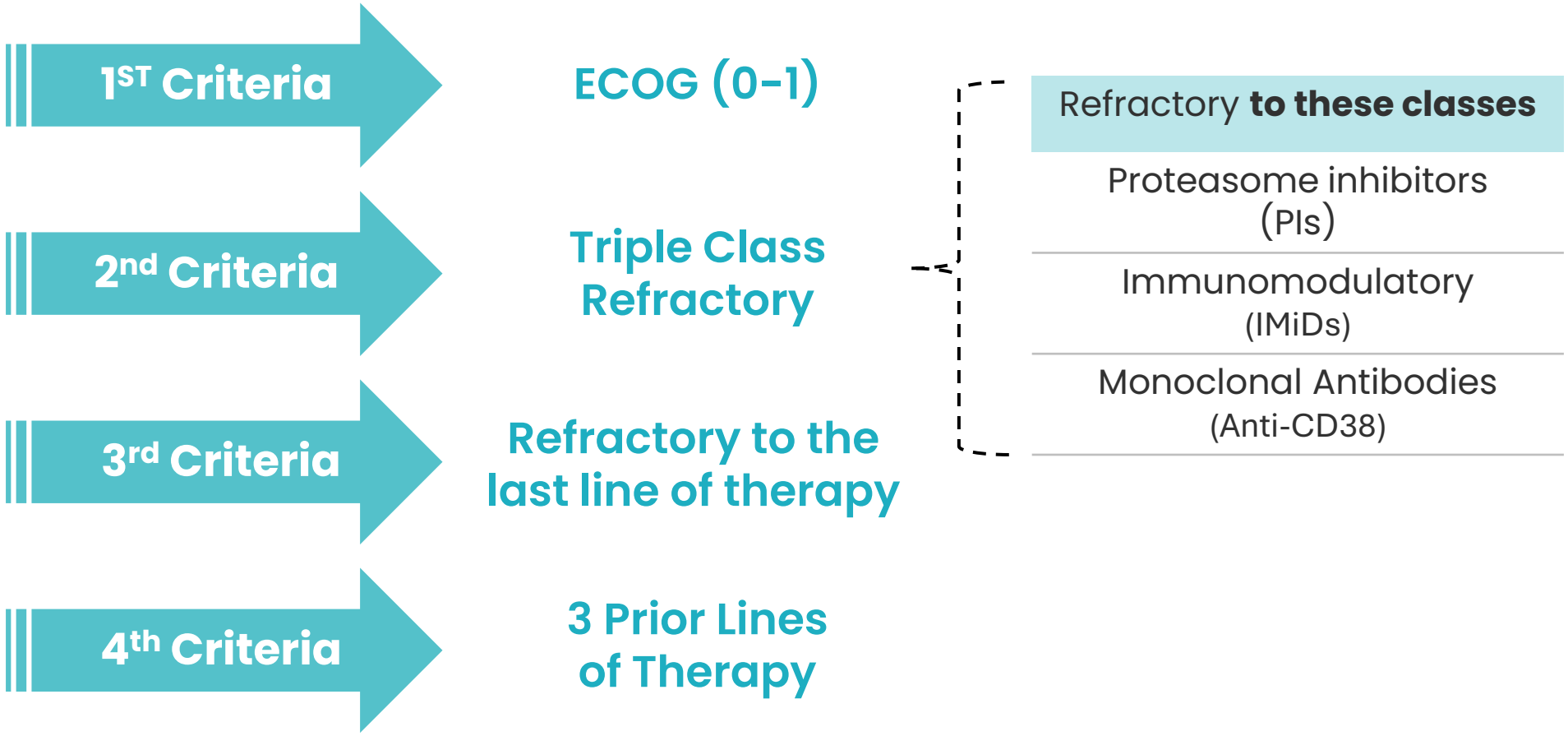
CD3/BCMA Bispecific Antibodies: Defining the Eligible Patient Population

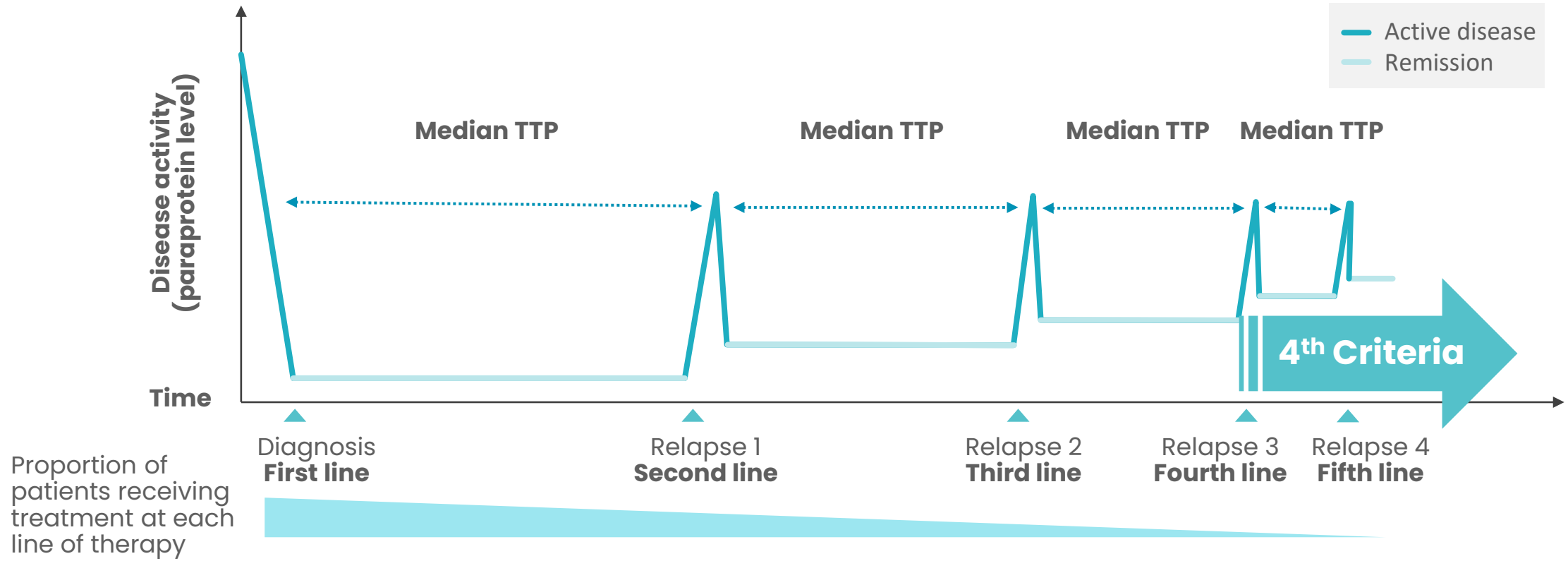
Four criteria must be met for patients to be eligible to CD3/BCMA Bispecifics



1. ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023. 2. Lesokhin et al. *Nat Med* 2023;29:2259-67; 3. TECVAYLI® (Teclistamab Injection) Product Monograph, August 2024; 4. Moreau P, et al. *N Engl J Med* 2022;387(6):495-505.

3 Prior Lines of Therapy

Median remission times (measured by TTP) and number of patients receiving treatment diminishes with each subsequent line of MM therapy

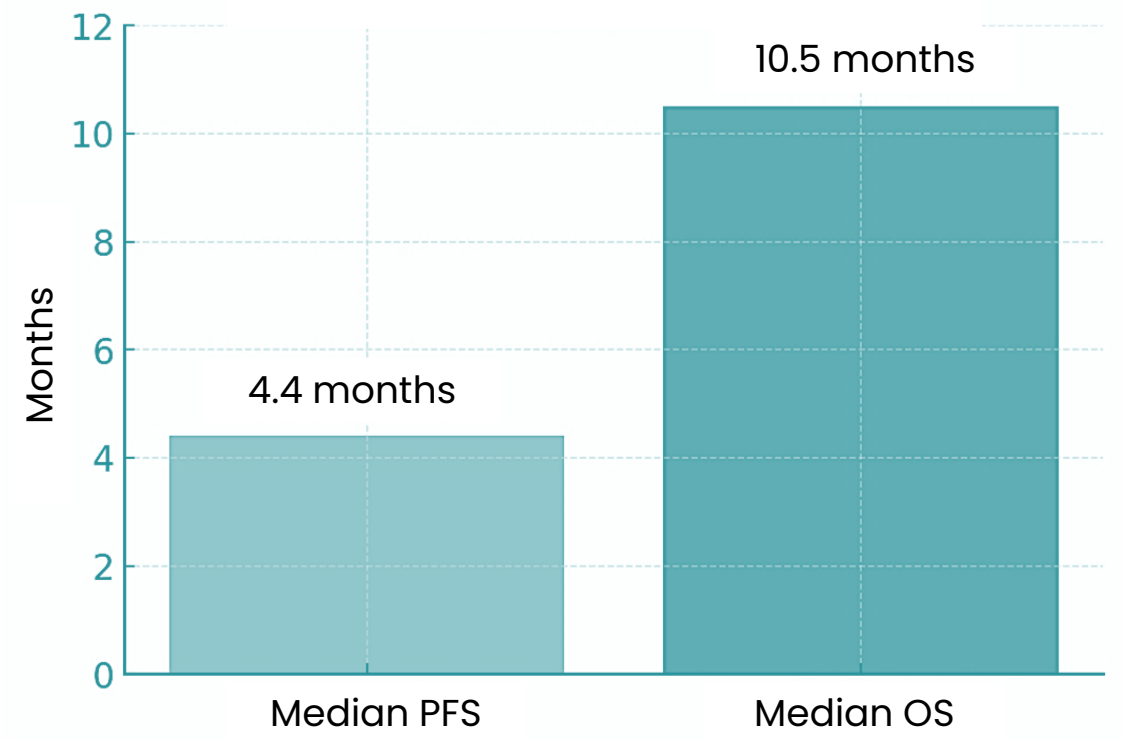


MM, multiple myeloma; TTP, time to progression.
Figure adapted from Bird SA, Boyd K. *Palliat Care Soc Pract* 2019;13:1178224219868235.
1. Bird SA, Boyd K. *Palliat Care Soc Pract* 2019;13:1178224219868235. 2. Yong K, et al. *Br J Haematol* 2016;175:252-264. 3. Shah N, et al. *Leukemia* 2020;34:985-1005.

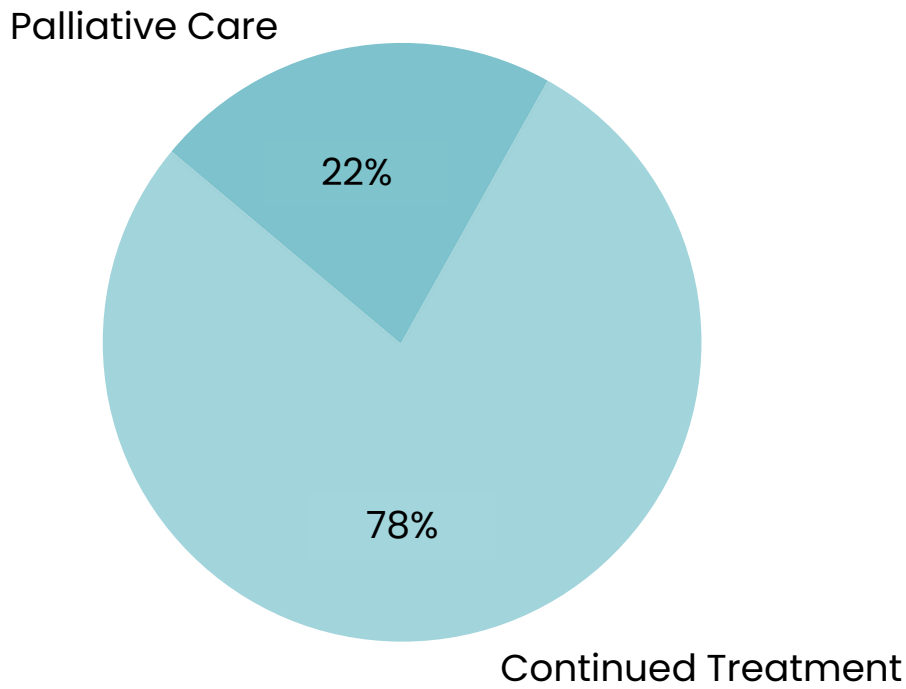
Poor Outcomes in TCR Multiple Myeloma

High unmet need for more effective therapies in this patient population

PFS and OS Outcomes in TCR MM



Patient Attrition Post Anti-CD38 mAB Failure



Measured from initiation of subsequent standard-of-care (SoC) treatment after progression on anti-CD38 mAb

Visram A, et al. *Blood Cancer J* 2023;13(1):181; McCurdy A, et al. *Blood Cancer J* 2023;13(1):111.

Anti-BCMA Trials – Patient Demographics

	Elranatamab (Pfizer; MagnetisMM-3)[1,2] Ph2	Teclistamab (J&J; MajesTEC-1)[3,4] Ph1/2
N treated/target	N=187 (Cohort A: BCMA-naïve n=123) (Cohort B: BCMA-exposed n=64)	N=205[4] (Cohort A: no prior BCMA n=165) (Cohort C: prior BCMA n= 40)
	Cohort A n=123	**Cohort A n=165**
Median age	68 (36-89)	64 (33-84)
Disease Stage	ISS[2]	ISS
I	30%	52%
II	37%	35.2%
III	20%	12.%
High-risk Cytogenetics	25.2%	25.7%

Data are shown side by side for reference only. Cross-trial comparisons cannot be made due to differences in trial design, patient population, study sites, etc.

ISS, International Staging System

1. Lesokhin et al. *Nat Med* 2023;29:2259-67. 2. Mol et al. *Leukemia Lymphoma* 2024;65(5):660-668. 3. Moreau et al. *N Engl J Med* 2022;387:495-505. 4. Touzeau et al. *Blood* 2024;144(23):2375-88.

Anti-BCMA Trials – Patient Demographics

	Elranatamab (Pfizer; MagnetisMM-3)[1] Ph2	Teclistamab (J&J; MajesTEC-1)[2,3] Ph1/2
N treated/target	N=187 (Cohort A: BCMA-naïve n=123) (Cohort B: BCMA-exposed n=64)	N=205 (Cohort A: no prior BCMA n=165)(NEJM) (Cohort C: prior BCMA n= 40)(BLOOD 2024) 0
	Cohort A n=123	**Cohort A n=165**
Prior lines of therapy, median	5 (2-22)	5 (2-14)
Extramedullary disease	31.7%	17.0%
Triple Class Exposed	100%	100%
Triple Class Refractory	96.7%	77.6%
Penta Drug Exposed	70.7%	70.3%
Penta Drug Refractory	42.3%	30.3%

Data are shown side by side for reference only. Cross-trial comparisons cannot be made due to differences in trial design, patient population, study sites, etc.

1. Lesokhin et al. *Nat Med* 2023;29:2259-67. 2. Moreau et al. *N Engl J Med* 2022;387:495-505. 3. Touzeau et al. *Blood* 2024;144(23):2375-88.

Evaluating the Efficacy of Bispecifics in Anti-BCMA Naïve Patients

Anti-BCMA exposed patients have Lower Responses

	Elranatamab (Pfizer; MagnetisMM-3)[1,2] Ph2	Teclistamab (J&J; MajesTEC-1)[3,4] Ph1/2
ORR	61.0%[1]	63%[3]
VGPR	18.7[1]	13.9%[3]
PR	4.9%[1]	3.6%[3]
≥CR	37.4%[1]	45.5%[3]
MRD⁻	MRD negativity (10^{-5}) rate was 90.3% in patients with CR or better who were evaluable for MRD (n=31)[1]	44/54 (81.5%) MRD-evaluable patients were MRD- at any point[4]
mPFS	17.2 months[1]	11.3 months[3]
DOR	The median DORs by LOT were not reached (NR), and the probability of maintaining a response at 18 mos was 83.3% (95% CI, 56.8-94.3)[2]	mDOR for all patients: 21.6 months[3]
mOS	24.6 months[1]	21.9 months[3]

Data are shown side by side for reference only. Cross-trial comparisons cannot be made due to differences in trial design, patient population, study sites, etc.

ASCO, American Society of Clinical Oncology; BCMA, B-cell maturation antigen; CR, complete response; DOR, duration of response; EHA, European Hematology Association; LOT, line of treatment; MRD, minimum residual disease; mPFS, median progression-free survival; mOS, median overall survival; MRD, minimal residual disease; ORR, objective response rate; PR, partial response; VGPR, very good partial response.
See notes for references.

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Elranatamab Dosing Schedule

Establish a plan for monitoring for 48 hr after step-up dose 1 and step-up dose 2

- Current Canadian practice is to give step-up dosing for RRMM in the inpatient setting so that patients are closely monitored for CRS and ICANS

Premedication: PO acetaminophen 650 mg, PO/IV dexamethasone 20 mg, PO diphenhydramine 25 mg or an equivalent of each

Dosing Schedule	Week/Day	Dose	
Step-Up Dosing[a,b]	Week 1: Day 1	Step-up dose 1	12 mg SC
	Week 1: Day 4	Step-up dose 2	32 mg SC
Weekly Dosing[a, b, d]	Week 2-24: Day 1	Treatment dose	76 mg SC once weekly
Every 2 Weeks Dosing[d, e]	Week 25 onward: Day 1	Treatment dose	76 mg SC once every two weeks

[a] Administer pre-pretreatment medications prior to the first 3 doses of Elrexfio. [b] A minimum of 2 days should be maintained between step-up dose 1 (12 mg) and step-up dose 2 (32 mg). [c] A minimum of 3 days should be maintained between step-up dose 2 (32 mg) and the first full treatment (76 mg) dose. [d] Maintain a minimum of 6 days between treatment doses. [e] For patients who have achieved and maintained a partial response or better for 2 months.

ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023.

Teclistamab Dosing Schedule

Establish a plan for monitoring for 48 hr after step-up dose 1 and step-up dose 2

- Current Canadian practice is to give step-up dosing for RRMM in the inpatient setting so that patients are closely monitored for CRS and ICANS

Premedication: PO/IV acetaminophen 650-1000 mg or equivalent, dexamethasone 16 mg, diphenhydramine 50 mg or equivalent

Dosing Schedule	Day	Dose[a]	
All patients			
Step-Up dosing schedule[b]	Day 1	Step-up dose 1	0.06 mg/kg single dose
	Day 3[c]	Step-up dose 2	0.3 mg/kg single dose
Weekly dosing schedule[b]	Day 5[d]	First treatment dose	1.5 mg/kg single dose
Patients who have a complete response or better for a minimum of 6 months.			
Biweekly (every two weeks) dosing schedule[b]	Consider reducing the dosing frequency to 1.5 mg/kg every two weeks		

A Dose is based on actual body weight and should be administered subcutaneously. [b] Refer to recommendations for restarting Tecvayli after dose delays. [c] Step-up dose 2 may be given 2 to 7 days after step-up dose 1. [d] First treatment dose may be given between 2 to 7 days after step-up dose 2. This is the first full treatment dose (1.5 mg/kg). [e] Maintain a minimum of 5 days between weekly treatment doses.
TECVAYLI® (Teclistamab Injection) Product Monograph, August 2024.

BsAb Dose Modifications

Dose **reductions** are **not recommended**
Dose delays may be required **to manage toxicities** related to BsAbs, including cytopenias and laboratory abnormalities

Recommended dose modifications for adverse reactions other than CRS or neurotoxicity, including ICANS

Adverse Reaction	Actions
ANC <0.5 x 10^9/L	Withhold until ANC ≥0.5 x 10^9/L
Febrile neutropenia	Withhold until ANC ≥1 x 10^9/L and fever resolves
Hemoglobin <8 g/dL	Withhold until hemoglobin ≥8 g/dL
Platelets <25,000/µL (<25 x 10^9/L) or Platelets 25,000–50,000/µL (25-50 x 10^9/L) with bleeding	Withhold until platelet count ≥25,000/µL **(≥25 x 10^9/L)** and no evidence of bleeding
Non-hematologic adverse reaction **Grade 3** **Grade 4**	Withhold until recovery to Grade ≤1 or baseline Consider permanent discontinuation

ANC, absolute neutrophil count; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023; TECVAYLI® (Teclistamab Injection) Product Monograph, August 2024.

Resuming Elranatamab After Dose Interruption

Last dose administered	Duration of delay from the last dose administered	Action
Step-up Dose 1 (12 mg)	≤14 days	Restart elranatamab at Step-up Dose 2 (32 mg) If tolerated, increase to 76 mg 4 days later
	>14 days	Restart elranatamab Step-up Dosing Schedule at Step-up Dose 1 (12 mg)
Step-up Dose 2 (32 mg)	≤14 days	Restart elranatamab at 76 mg
	15–28 days	Restart elranatamab at Step-up Dose 2 (32 mg) If tolerated, increase to 76 mg 1 week later
	>28 days	Restart elranatamab Step-up Dosing Schedule at Step-up Dose 1 (12 mg)
Any Full Treatment Dose (76 mg)	≤6 weeks	Restart elranatamab at 76 mg
	>6 to ≤12 weeks	Restart elranatamab at Step-up Dose 2 (32 mg) If tolerated, increase to 76 mg 1 week later
	>12 weeks	Restart elranatamab Step-up Dosing Schedule at Step-up Dose 1 (12 mg)

Administer the following medications ~1 hour prior to Step-up Dose 1, Step-up Dose 2 and the first Full Treatment Dose, to reduce the risk of CRS:

- Acetaminophen 650 mg PO or IV (or equivalent)
- Dexamethasone 20 mg PO or IV (or equivalent)
- Diphenhydramine 25 mg PO (or equivalent)

IV, intravenously; PO, orally.

ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023.

Resuming Teclistamab After Dose Interruption

Last administered dose	Duration of delay from the last administered dose	Action
Step-up dose 1 (0.06 mg/kg)	≤7 days	Restart teclistamab step-up dosing schedule at step-up dose 2 (0.3 mg/kg)
	>7 days	Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06 mg/kg)
Step-up dose 2 (0.3 mg/kg)	≤7 days	Restart teclistamab step-up dosing schedule at treatment dose (1.5 mg/kg)
	8-28 days	Restart teclistamab step-up dosing schedule at step-up dose 2 (0.3 mg/kg)
	>28 days	Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06 mg/kg)
Any full treatment dose (1.5 mg/kg)	≤28 days	Restart teclistamab at treatment dose (1.5 mg/kg) once weekly
	>28 days	Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06 mg/kg)

Administer the following medications 1-3 hours prior to Step-up Dose 1, Step-up Dose 2 and the first Full Treatment Dose, to reduce the risk of CRS:

- Acetaminophen 650-1000 mg PO or IV (or equivalent)
- Dexamethasone 16 mg PO or IV
- Diphenhydramine 50 mg PO or IV (or equivalent)

IV, intravenously; PO, orally.

TECVAYLI® (Teclistamab Injection) Product Monograph. August 2024.

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Overview of Safety of BCMA BsAbs

Early events

CRS*

ICANS*

Injection site reactions

Later events

Anemia, neutropenia, thrombocytopenia, hypokalemia

Fatigue

URTI, pneumonia

Diarrhea, nausea

Decreased appetite

Rash

Arthralgia

Dry skin

All events occurred at a rate of ≥20% except neutropenia and anemia which occurred at a rate of ≥30%.
*Requiring monitoring during step-up dosing.

BCMA, B-cell maturation antigen; BsABs, bispecific antibodies; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; URTI, upper respiratory tract infection.

ELREXFIO® (elranatamab) Product Monograph, December 2023. TECVAYLI® Product Monograph. August 2024

Anti-BCMA Trials – AEs of Interest

	Elranatamab (Pfizer; MagnetisMM-3)[1] **Cohort A n=123**	Teclistamab (J&J; MajesTEC-1)[2] **Cohort A n=165**
CRS		
All grades	71 (57.7%)	119 (72.1%)
Grade 3/4	0	1 (0.6%)
CRS onset	Onset: 2.0d (1.0-9.0d); Duration/resolution: 2.0d (1.0-19.0d)	2d (1-6d); 2d (1-9d)
ICANS		
All grades	4 (3.4%)	5 (3.0%)
Grade 3/4	0	0
Grade 5	0	0

Use of steroids and tocilizumab was permitted in all trials

Data are shown side by side for reference only. Cross-trial comparisons cannot be made due to differences in trial design, patient population, study sites, etc.

AE, adverse event; ASH, American Society of Hematology; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

1. Lesokhin et al. *Nat Med* 2023;29:2259-67; 2. Moreau et al. *N Engl J Med* 2022;387:495-505.

Anti-BCMA Trials – AEs of Interest (2/2)

	Elranatamab (Pfizer; MagnetisMM-3)[1] **Cohort A n=123 Median duration of treatment 5.6 months (0.03-24.4)**	Teclistamab (J&J; MajesTEC-1)[2] **Cohort A n=165 Median duration of treatment 8.5 months (0.2 to 24.4)**
Infections		
All grades	69.9%	78.8%
Grade 3/4	39.8%	55.2%;
Grade 5 (Including % Covid)	6.5% (1.6% from Covid)	13.3% (6.1% from Covid)
Hematologic Grade 3/4		
Neutropenia	48.8%	64.2%
Anemia	37.4%	37.0%
Thrombocytopenia	23.6%	21.2%
Lymphopenia	25.2%	32.7%
Leukopenia	NR	7.3%

Data are shown side by side for reference only. Cross-trial comparisons cannot be made due to differences in trial design, patient population, study sites, etc.

AE, adverse event; ASH, American Society of Hematology

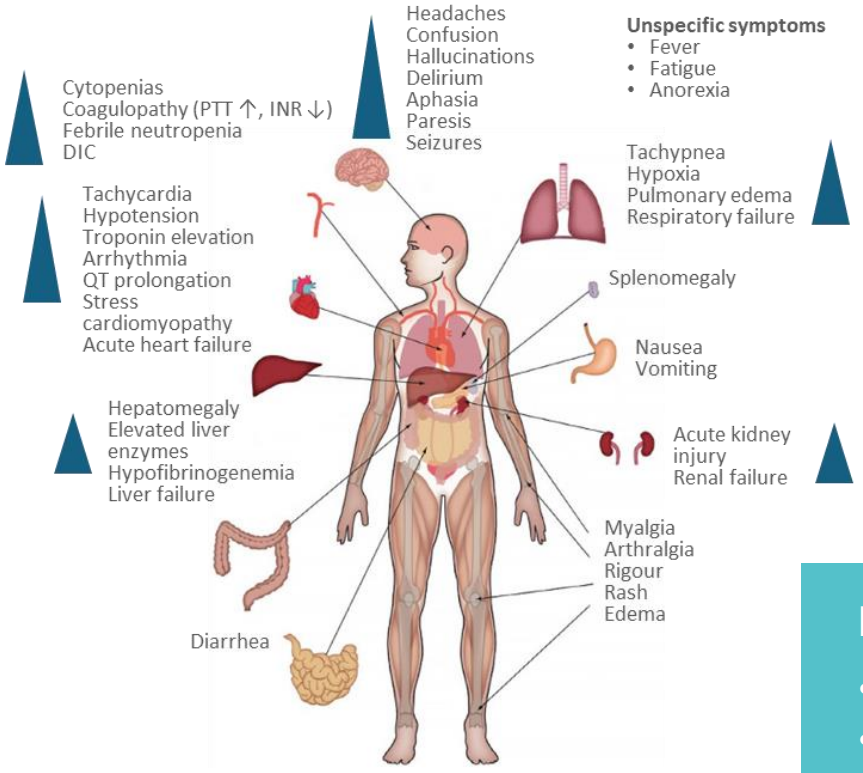
1. Lesokhin et al. *Nat Med* 2023;29:2259-67; 2. Moreau et al. *N Engl J Med* 2022;387:495-505.

Cytokine Release Syndrome (CRS)

Symptoms of Systemic CRS Events

CRS is a systemic inflammatory response triggered by the release of large amounts of cytokines into the bloodstream

Organ systems and presentation



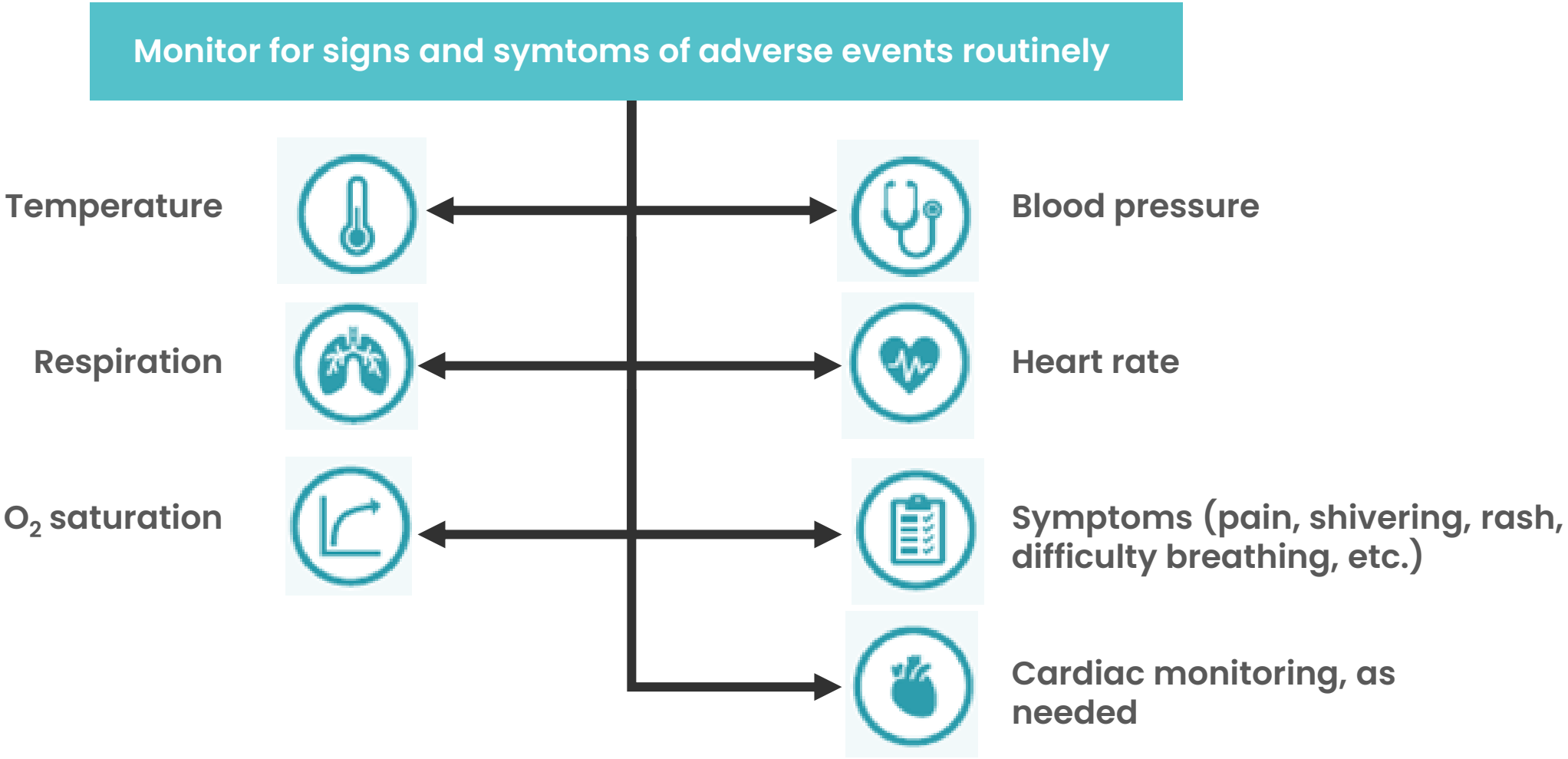
Monitor for:

- Fever
- Hypotension
- Hypoxia

CRS, cytokine release syndrome; DIC, disseminated intravascular coagulation; INR, international normalized ratio; PTT, partial thromboplastin time.

1. Zhou X, et al. *Front Immunol* 2020;11:620312. 2. Shimabukuro-Vornhagen A, et al. *J Immunother Cancer* 2018;6(1):56.

Best Practices in Monitoring for Early Systemic Events Following Anti-BCMA Bispecific Antibody Administration



BCMA, B-cell maturation antigen.

1. Catamero D, et al. *Semin Oncol Nurs* 2024;40(3):151621.

Occurrence and Timing of CRS

In clinical trials, most patients experienced CRS:

	MagnetisMM-3 (elranatamab)[1]		MajesTEC-1 (teclistamab)[2]	
Patients affected (percentage of participants, all grades)	57.7%	Grade 1, 42.0% Grade 2, 14.3% Grade 3, 0%	72.1%	Grade 1, 50.3% Grade 2, 21.2% Grade 3, 0.6%
Median time until onset of CRS (relative to most recent dose)	2 days (range: 1.0-9.0)		2 days (range: 1.0-6.0)	
Median duration of CRS Add interval	2 days (range: 1.0-19.0)		2 days (range: 1.0-9.0)	

CRS, cytokine release syndrome.

1. Lesokhin AM, et al. *Nat Med* 2023;29(9):2259-2267. 2. Moreau P, et al. *N Engl J Med* 2022;387(6):495-505.

CRS Grading

Grade	CTCAE v5.0	ASTCT consensus		
		Fever	Hypotension	Hypoxia
1	Fever +/- constitutional systems	≥38°C	None	None
2	With hypotension responding to fluids and/or hypoxia responding to <40% FiO2	≥38°C	Not requiring vasopressors	Requiring low-flow nasal cannula
3	With hypotension managed with 1 vasopressor and/or hypoxia requiring ≥40% FiO2	≥38°C	Requiring vasopressors +/- vasopressin	Requiring high-flow nasal cannula
4	Life-threatening consequences; urgent intervention needed	≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; FiO2, fraction of inspired oxygen.

1. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed July 2024. 2. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25(4):625-638.

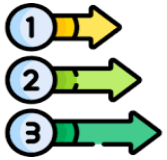
Mitigating CRS Events With Anti-BCMA Bispecific Antibodies

Premedication

- Administered prior to each step-up dose and with first full dose
- **Dexamethasone, diphenhydramine, acetaminophen**
- When restarting after a dose delay (any time after step-up dose 1 and >2 weeks after step-up dose 2), administered prior to restarting therapy

Use of premedication and step-up dosing reduces incidence of CRS, with 98.8% of CRS events occurring within the first 3 doses

Step-up dosing



Reduces the incidence and severity of CRS

Monitoring

Monitor patients for 48 hours after step-up doses (note: patients are currently monitored in inpatient setting)

BCMA, B-cell maturation antigen; CRS, cytokine release syndrome.

1. ELREXFIO® Product Monograph. December 2023. 2. Lesokhin AM, et al. *Nat Med* 2023;29(9):2259-2267. 3. Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15(1):47-62. 4. Catamero D, et al. *Semin Oncol Nurs* 2024;40(3):151621. 5. TECVAYLI® Product Monograph. August 2024.

Tocilizumab prophylaxis in RRMM patients treated with anti-BCMA BsAbs: Exploratory data

- Single-centre, real-world study of RRMM patients treated with BsAbs from 25 Oct 2022 to 21 Jun 2024
- Patients treated with teclistamab (n=36) or elranatamab (n=16) who received prophylactic tocilizumab had low rates of CRS and ICANS:
  - CRS: 14%
  - ICANS: 8%
- Among patients experiencing ICANS, most events were grade 1 or 2

BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; RRMM, relapsed or refractory multiple myeloma.
Kowalski et al. *Blood* 2024;144 (Suppl 1):932.

Management of CRS Events

Rule out other etiologies: infection, heart failure, pulmonary edema; possibly treat for infection

Grade	Bispecific antibody therapy
	Supportive care + intervention
1	Withhold until CRS resolution and administer pretreatment medications prior to next dose ± tocilizumab
2	± tocilizumab* + 48-hour monitoring following next dose according to institutional and manufacturer guidelines
3	*First grade 3 occurrence or with duration ≤48 hours*: Tocilizumab ± corticosteroid + ICU/critical care as needed *Recurrent grade 3 or grade 3 with duration >48 hours*: Tocilizumab + high-dose corticosteroid; ICU/critical care
4	Permanently discontinue; provide ICU/critical care as needed

*High-burden, high-risk products; older; comorbidities; etc.

CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICU, intensive care unit.

1. ELREXFIO® (Elranatamab Injection) Product Monograph. December 2023. 2. TECVAYLI® (Teclistamab Injection) Product Monograph. August 2024. 3. Brudno JN, Kochenderfer JN. *Blood Rev* 2019;34:45.

Sample CRS Management Protocol: Grade 1

Grade 1 management

Page the admitting or covering prescriber

Administer the following as ordered

- Acetaminophen 650 mg or 975 mg PO Q4H PRN
- Diphenhydramine 50 mg IV Q4H PRN
- Metoclopramide 10 mg PO/IV Q4H PRN
- Ondansetron 8 mg PO/IV Q8H PRN

Monitor for CRS symptoms, including vital signs and pulse oximetry at least every hour for
12 hours or until resolution of symptoms, whichever is earlier

If febrile, initiate concurrent septic workup and consider empiric coverage with broad-spectrum antibiotics, particularly if immunocompromised and/or neutropenic

Consider IV fluids if required

CRS, cytokine release syndrome; IV, intravenous; PO, by mouth; PRN, as needed; Q#H, every # hours.
Adapted from BC Cancer. Protocol for Cytokine Release Syndrome Management. Available at: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCCRS_Protocol.pdf. Accessed December 2023.

Sample CRS Management Protocol: Grade 2

Grade 2 management

Page the admitting physician or covering prescriber if not already done

Administer the following as ordered
- 0.5–1 L NaCl 0.9% IV fluid bolus or continuous infusion
- Acetaminophen 650 mg or 975 mg PO Q4H PRN
- Diphenhydramine 50 mg IV Q4H PRN
- Metoclopramide 10 mg PO/IV Q4H PRN
- Ondansetron 8 mg PO/IV Q8H PRN

Vital signs and pulse oximetry frequency should increase to at least every hour, and more frequently if necessary, until resolution of CRS symptoms

If BP does not respond to IV fluids (i.e., after 2 fluid boluses), tocilizumab and/or steroids should be strongly considered

Early administration of tocilizumab decreases risk of progression to grade ≥3 CRS
- Tocilizumab 8 mg/kg (maximum 800 mg) IV in 100 mL NS over 1 hour. Repeat Q8H PRN if not responding to IV fluids or supplemental oxygen (limit 3 doses in 24 hours, 4 doses total)

Steroids:
- Methylprednisolone 1 mg/kg IV Q12H or
- Dexamethasone 10 mg IV Q6H

Continue steroids until grade ≤1, then taper over 3 days

If required:
- Salbutamol 5 mg inhalation by nebulizer Q20MIN (maximum 3 doses)

BP, blood pressure; CRS, cytokine release syndrome; IV, intravenous; NaCl, sodium chloride; NS, normal saline; PO, by mouth; PRN, as needed; Q#H, every # hours; Q20MIN, every 20 minutes.
Adapted from BC Cancer. Protocol for Cytokine Release Syndrome Management. Available at: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCCRS_Protocol.pdf. Accessed December 2023.

Sample CRS Management Protocol: Grade ≥3

Grade ≥3 management

Page the admitting physician or covering prescriber if not already done.
Arrange emergent transfer to higher level of care

Administer the following as ordered
- 0.5-1 L NaCl 0.9% IV fluid bolus or continuous infusion
- Acetaminophen 650 mg or 975 mg PO Q4H PRN
- Diphenhydramine 50 mg IV Q4H PRN
- Metoclopramide 10 mg PO/IV Q4H PRN
- Ondansetron 8 mg PO/IV Q8H PRN

Vital signs every 15 minutes or more frequently as ordered by physician until resolution to grade 2 or less, then every hour until complete resolution of CRS

All patients should receive BOTH steroids and tocilizumab:
- Tocilizumab 8 mg/kg (maximum 800 mg) IV in 100 mL NS over 1 hour. Repeat Q8H as needed if not responding to IV fluids or supplemental oxygen (limit 3 doses in 24 hours, 4 doses total)
- Methylprednisolone 1 mg/kg IV Q12H or
- Dexamethasone 10 mg IV Q6H or
- Methylprednisolone 1 g IV QD × 3 days

Continue steroids until grade ≤1, then taper over 3 days

If required:
- Epinephrine 1 mg/mL (1:1000) 0.5 mg IM Q5MIN (maximum 3 doses)
- Nebule for inhalation by nebulizer Q20MIN (maximum 3 doses)

CRS, cytokine release syndrome; IM, intramuscular; IV, intravenous; NaCl, sodium chloride; NS, normal saline; PO, by mouth; PRN, as needed; Q#H, every # hours; Q#MIN, every # minutes; QD, every day.
Adapted from BC Cancer. Protocol for Cytokine Release Syndrome Management. Available at: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCCRS_Protocol.pdf. Accessed December 2023.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Neurological side effects associated with BCMA BsAbs

There are 3 general clinical presentations of neurological complications with BsAbs:

Headache, a nonspecific neurotoxic event that can be associated with CRS and often responds to acetaminophen

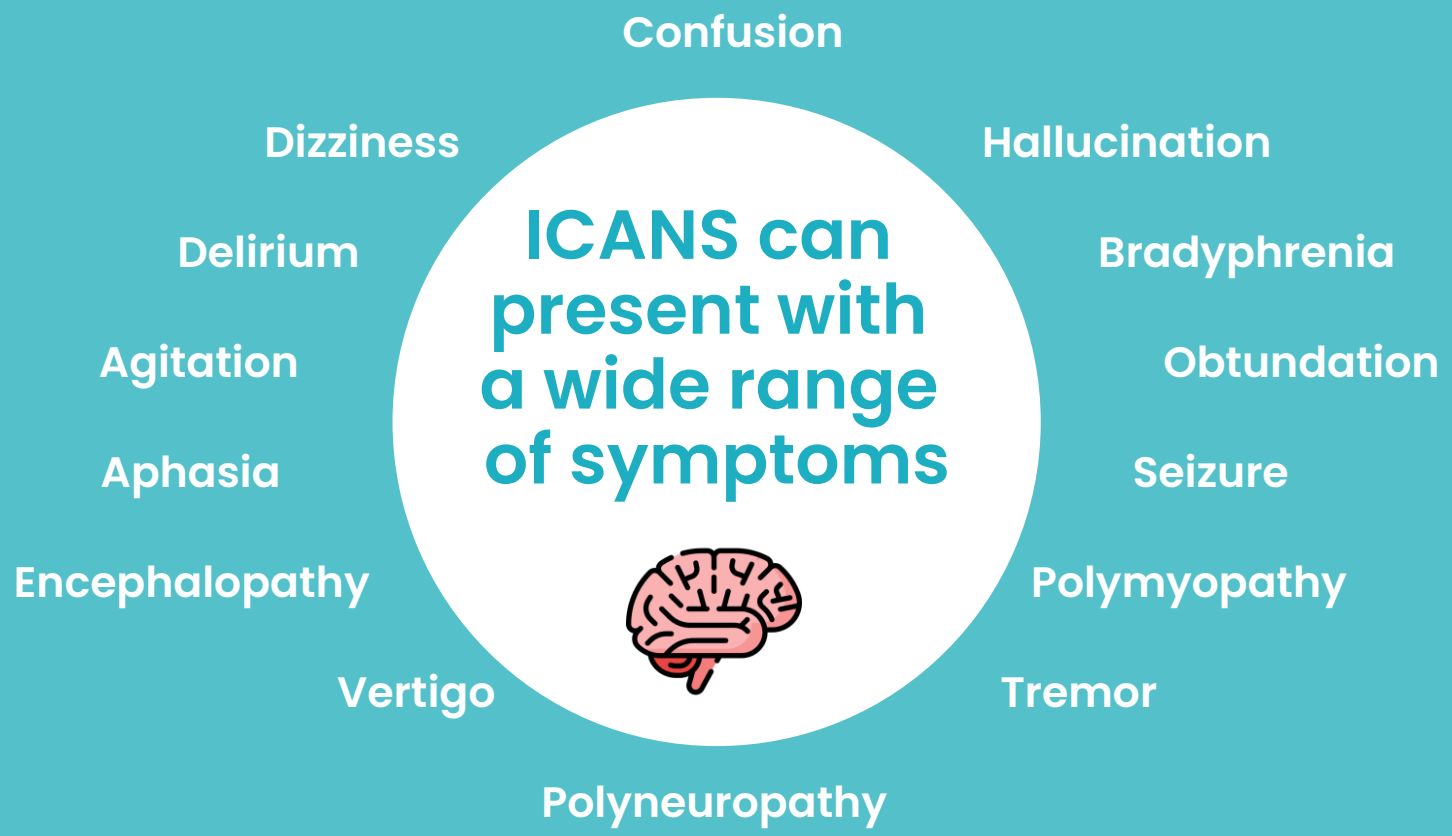
Immune effector cell-associated neurotoxicity syndrome (ICANS), which is less common and triggered by influx of cytokines and T cells into the CNS

Peripheral neuropathies are usually associated with prior history of neuropathy

BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; CNS, central nervous system; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.
Rodriguez-Otero P, et al. *Lancet Oncol* 2024;25:e205-16.

Symptoms of ICANS Events

CRS symptoms typically precede those of ICANS



On MRI, cerebral edema may also be present

CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; MRI, magnetic resonance imaging.

1. Zhou X, et al. *Front Immunol*. 2020;11:620312.

Occurrence and Timing of ICANS

In clinical trials, few patients experienced ICANS:

	Bispecific antibodies	
	MagnetisMM-3 (elranatamab)[1]	**MajesTEC-1 (teclistamab)[2]**
Patients affected (percentage of participants)	3.4% (Grade 1, 0.8%; Grade 2, 2.5%; Grade 3, 0%)	3.0% (Grade 3, 0.6%)
Median time until onset of ICANS (relative to most recent dose)	2.5 days (range: 1.0–4.0)	(not reported specifically for ICANS)
Median duration of ICANS	2 days (range: 1.0–6.0)	(not reported specifically for ICANS)

ICANS, immune effector cell–associated neurotoxicity syndrome.

1. Lesokhin AM, et al. *Nat Med* 2023;29(9):2259-2267 and supplement. 2. Moreau P, et al. *N Engl J Med* 2022;387(6):495-505.

ICANS Grading

ASTCT ICANS consensus grading for adults

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

ASTCT, American Society for Transplantation and Cellular Therapy; EEG, electroencephalogram; ICANS, immune effector cell–associated neurotoxicity syndrome; ICE, immune effector cell encephalopathy; ICP, intracranial pressure.

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

Management of ICANS Events

Grade	Bispecific antibody therapy	
	Neurologic toxicity excluding ICANS	ICANS
1	Withhold until symptoms resolve or stabilize	Withhold until resolution Consider steroids
2	Withhold until symptoms improve to grade ≤1	Withhold until resolution + steroids + 48-hour monitoring with next dose
3	*First occurrence*: grade 2 actions + supportive therapy *Recurrence*: grade 4 actions	*First occurrence*: grade 2 actions + supportive therapy + steroids *Recurrence*: grade 4 actions + Steroids
4	Permanently discontinue + steroids (dexamethasone or methylprednisolone) ICU/critical care	

*High-burden, high-risk products; older, comorbidities; etc.
CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; ICU, intensive care unit.
1. ELREXFIO® Product Monograph. December 2023. 2. TECVAYLI® Product Monograph. August 2024. 3. Neelapu SS, et al. *Nat Rev Clin Oncol* 2018;15:47. 4. Neelapu SS, et al. *Hematol Oncol* 2019;37(suppl 1):48.

Counselling Patients on CRS and ICANS

Nurses and pharmacists should provide a clear explanation of potential symptoms associated with CRS and ICANS, with instructions on when and how to inform the care team

Written information, including leaflets, should be provided to patients to reinforce prior verbal communications

CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome.

1. Catamero D, et al. *Semin Oncol Nurs* 2024;40(3):151621.

Infections

Risk Factors for Infections in Patients on Anti-BCMA Bispecific Antibodies

PATIENT-RELATED FACTORS

- Age
- Performance status
- Comorbidities (e.g., renal failure and chronic heart failure)
- Immunoparesis
- Cytopenia (neutropenia and lymphopenia)

DISEASE-RELATED FACTORS

- Tumour burden
- Refractory to ≥3 lines of treatment
- Disease type (e.g., antibody type [full antibody or light-chain only, IgD, IgE], secretory status [yes vs. no], genetic status [hyperdiploid vs. hypodiploid])
- Renal dysfunction

RISK FACTORS FOR INFECTION in patients with MM receiving bispecific antibodies

- Glucocorticoid cumulative dose/prior glucocorticoid use and duration
- Previous intensive treatment such as autologous transplant, allogeneic transplant, or transplant <1 year ahead of starting bispecific antibody/antibodies
- Previous treatment with: chemotherapy, PIs, IMiDs, anti-CD38 monoclonal antibodies, or bispecific antibody/antibodies
- Recent CAR-T therapy
- Most recent line of MM treatment

TREATMENT-RELATED FACTORS

- Number of previous infections
- Type of previous infection
- History of hospitalization due to infection
- Severity of previous infections
- Baseline DNA-virus exposure, including VZV, CMV and HBV

INFECTIOUS HISTORY

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; CMV, cytomegalovirus; HBV, hepatitis B virus; Ig, immunoglobulin; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteosome inhibitor; VZV, varicella-zoster virus.

1. Raje N, et al. *Blood Cancer J* 2023;13(1):116.

Respiratory Infections Were the Most Common Types of Infections Associated With BCMA-Targeted BsAbs

Elranatamab[1]

Infections occurring in ≥10% of patients in the total safety population in MagnetisMM-3 (N=123)

Median duration of treatment 5.6 mos (0.03-24.4)

COVID-19	29.3% (15.4% Grade 3/4, 1.6% grade 5)
Pneumonia	16.3% (8.1% Grade 3/4)
URTI	16.3% (0% Grade 3/4)
Sinusitis	10.6% (1.6% Grade 3/4)

Teclistamab[2]

Infections occurring in ≥10% of patients in MajesTEC-1 (N=187)

Median duration of treatment 8.5 mos (0.2 to 24.4)

Pneumonia	18.2% (12.7% Grade 3/4)
COVID-19	17.6% (12.1% Grade 3/4, 6.1% Grade 5)
Bronchitis	13.3% (0% Grade 3/4)
URTI	10.9% (0% Grade 3/4)

BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; URTI, upper respiratory tract infection; UTI, urinary tract infection.

1. Lesokhin et al. *Nat Med* 2023;29:2259-67; 2. Moreau P, et al. *N Engl J Med* 2022;387(6):495-505.

Adverse Events Associated With Higher Risk of Infection: Neutropenia

BCMA-targeted agents can induce the death of neutrophil cells, resulting in neutropenia and elevated risk of infection

BCMA-targeted agent	Clinical trial	Study population	Rate of neutropenia, n (%)		
			All grades	Grade 3/4	Febrile
Elranatamab[1]	MagnetisMM-3	N=123	60 (48.8)	60 (48.8)	4 (2.2)
Teclistamab[2]	MajesTEC-1	N=165	117 (70.9)	106 (64.2)	4 (2.4)

Dose modifications for elranatamab and teclistamab[3,4]

Absolute neutrophil count less than 0.5×10^9/L

Withhold until absolute neutrophil count is 0.5×10^9/L or higher

Febrile neutropenia

Withhold until absolute neutrophil count is 1.0×10^9/L or higher and fever resolves

BCMA, B-cell maturation antigen.

1. Lesokhin et al. *Nat Med* 2023;29:2259-67; 2. Moreau P, et al. *N Engl J Med* 2022;387(6):495-505. 3. Raje N, et al. *Blood Cancer J* 2023;13(1):116. 4. Nooka AK, et al. *Cancer* 2024;130:886-900.

Adverse Events Associated With Higher Risk of Infection: Hypogammaglobulinemia

BCMA-targeted agents can reduce Ig levels, resulting in hypogammaglobulinemia and elevated risk of infection

BCMA-targeted agent	Clinical trial	Study population	Rate of hypogammaglobulinemia, n (%)	
			All grades	Grade 3/4
Elranatamab[1]	MagnetisMM-3	N=123	138 (75.5)	NR
Teclistamab[2]	MajesTEC-1	N=165	123 (74.5)	3 (1.8)

Suggested guidance for elranatamab and teclistamab[3,4]

Monitor Ig levels during/after treatment and administer Ig therapy for IgG <4 g/L.
Manage per local clinical guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection.

BCMA, B-cell maturation antigen; Ig, immunoglobulin; NR, not reported.

1. Lesokhin et al. *Nat Med* 2023;29:2259-67; 2. Moreau P, et al. *N Engl J Med* 2022;387(6):495-505.. 3.Raje N, et al. *Blood Cancer J* 2023;13(1):116. 4. Nooka AK, et al. *Cancer* 2024;130:886-900.

Monitoring, Prophylaxis, and Treatment Modification for Viral Infections

	CMV	EBV	VZV
Monitoring	• If suspected, use CMV DNA copies	• In cases of persistent fever and fatigue, monitor EBV DNA copies to exclude EBV DNA reactivation	–
Prophylaxis	–	–	• Acyclovir or valacyclovir • Vaccination
Treatment	• Oral valganciclovir for CMV reactivation • Alternatives: IV ganciclovir or foscarnet	• Rituximab	• Valacyclovir or IV acyclovir for VZV reactivation
BCMA-targeted antibody modification	Withhold for grade ≥3 infection until resolves to grade 1		

BCMA, B-cell maturation antigen; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; HBV, hepatitis B virus; IV, intravenous; VZV, varicella zoster virus.

1. Raje N, et al. *Blood Cancer J* 2023;13(1):116.

Monitoring, Prophylaxis, and Treatment Modification for Viral Infections (cont.)

	HBV	Influenza	SARS-COV-2
Prophylaxis	• If core antibody positive, administer prophylaxis, or monitor for HBV DNA copies, with pre-emptive antiviral treatment for those with positive DNA tests/viremia • If surface antigen positive, administer antiviral prophylaxis: entecavir, tenofovir, lamivudine under the control of specialists, as per standard treatment guidelines	• Vaccination of patients and close contacts • 2-dose series, at least 1 month apart, of high-dose influenza vaccine may increase likelihood of seroprotection	• Vaccination of patients and close contacts • Canada Immunization Guide recommends a 2-dose series, 4-8 weeks apart (a 3rd dose may be considered for moderately to severely immunocompromised individuals)
Monitoring	• Screen for core antibodies prior to starting treatment, monitor HBV DNA copies in core antigen positive patients	• Direct testing of nasopharyngeal or respiratory secretions by PCR if suspected	• PCR test on nasal, nasopharyngeal, or respiratory secretions if suspected
Treatment	-	• Oseltamivir or baloxavir, if influenza is confirmed	• Treat with available therapies, with consideration of concurrent medications; treatment is based on symptoms and physician assessment
BCMA-targeted antibody modification	• Maintain dosing during prophylaxis • Discontinue if patient experiences reactivation	-	• Temporary discontinuation in patients with COVID-19 until clinical resolution, together with RT-PCR clearance

BCMA, B-cell maturation antigen; HBV, hepatitis B virus; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction.

1. Raje N, et al. *Blood Cancer J* 2023;13(1):116; 2. Canadian Immunization Guide (February 5, 2025 update).

Monitoring, Prophylaxis, and Treatment Modification for Bacterial Infections

	Bacterial
Prophylaxis	• Recommended in patients with: – Prolonged neutropenia – High risk of infections – History of recurrent bacterial infections • Treat with levofloxacin, stopping treatment once patient no longer has neutropenia • Risk of developing resistant pathogens should be considered with use of antibacterial prophylaxis • Combining antibacterial prophylactic treatments is not recommended
Monitoring	• Blood, urine, sputum, and fecal cultures • Imaging to provide greater insight and confirm extent of infection • For further confirmation: CT or PET scans for pneumonia evaluation, suspected colitis, diverticulitis or abdominal abscesses, or procedural biopsy based on the infection site
Treatment	• Dependent on infectious agent, targeted therapy recommended if agent can be identified – Broad-spectrum antibiotics for patients with concomitant neutropenia – Levofloxacin or equivalent, based on site of infection, for patients who do not have concomitant neutropenia – For older patients or those with QT prolongation: third-generation cephalosporins • Treat until symptoms resolve • Treating microbial colonizations is not recommended; however, treatment may be used in very immunocompromised patients
BCMA-targeted antibody modification	• Maintain dosing during prophylaxis • Temporary discontinuation during antibacterial treatment until infection resolution

BCMA, B-cell maturation antigen; CT, computed tomography; PET, positron emission tomography.

1. Raje N, et al. *Blood Cancer J* 2023;13(1):116.

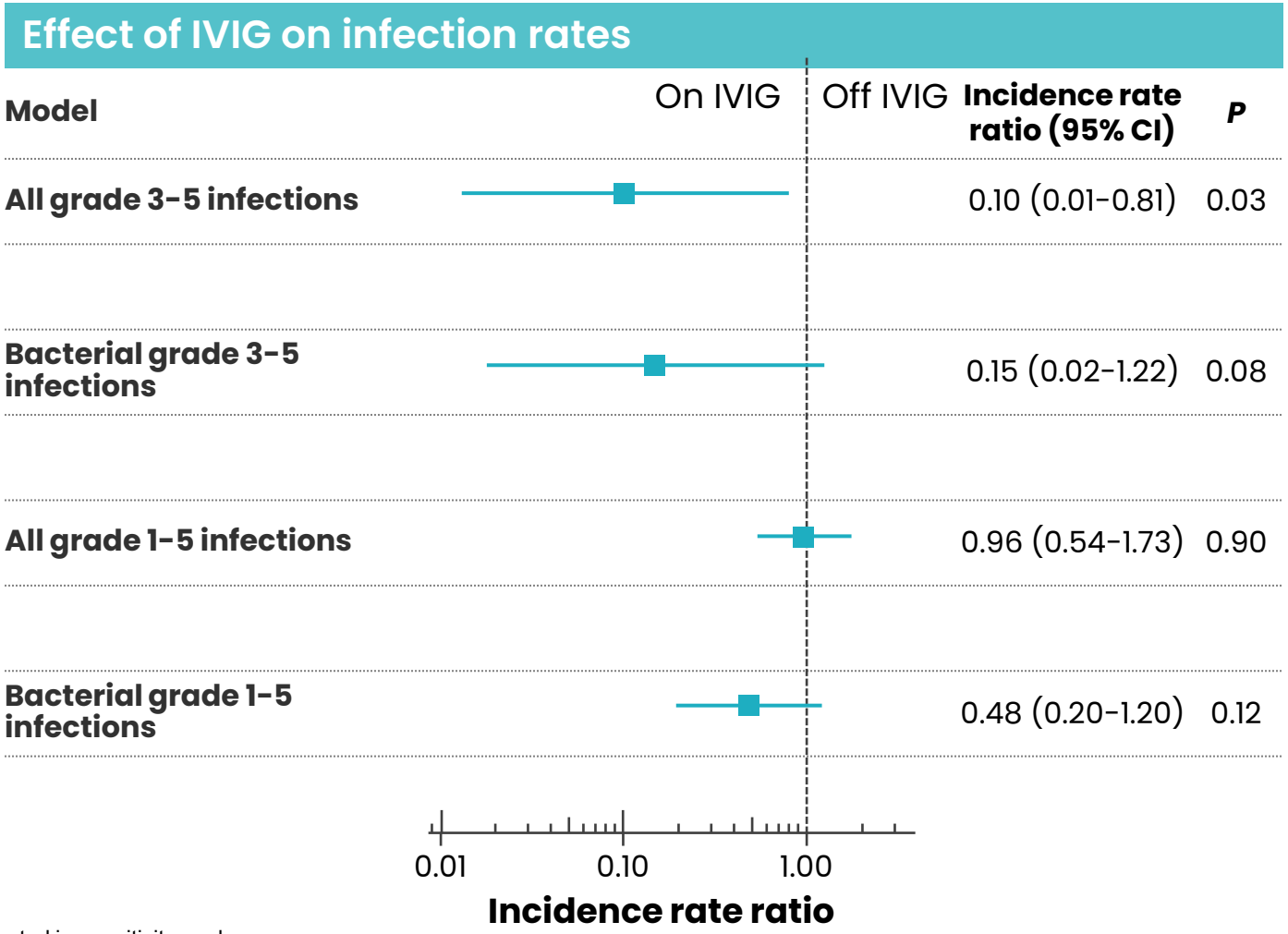
Monitoring, Prophylaxis, and Treatment Modification for Fungal Infections

	Fungal (general)	Fungal (*P. jirovecii*)
Prophylaxis	• Not recommended unless patient has: – Previous history of fungal infections – Prolonged neutropenia – History of prolonged high-dose corticosteroid use (<2 weeks) • Consult infectious disease specialist • If using prophylaxis: fluconazole is recommended • Itraconazole and voriconazole can be considered • Monitoring during antifungal prophylaxis is not recommended, unless for suspected aspergillosis	• Recommended prophylaxis for all patients • Trimethoprim-sulfamethoxazole, dapsone, or atovaquone if allergic to sulfonamide • Inhaled or intravenous pentamidine for patients with neutropenia
Monitoring	• Routine monitoring is not recommended • Serum galactomannan testing if aspergillosis is suspected • Cultures, imaging, and diagnostic tests help identify the fungal infection, if suspected • Biopsy to confirm mold in patient with sinusitis	• Routine monitoring is not recommended
Treatment	• Dependent on infectious agent and investigations • Treat as per infectious disease guidelines, and consult with an infectious disease provider	• Treat as per standard antimicrobial regimens for PJP: – Trimethoprim-sulfamethoxazole for 21 days – Oral atovaquone 750 mg BID for 21 days (for mild cases, sulfonamide allergy) – Clindamycin and primaquine for 21 days (for moderate/severe cases, sulfonamide allergy)
BCMA-targeted antibody modification	• Maintain dosing during prophylaxis • Temporary discontinuation during antifungal treatment until resolution	• Maintain dosing during prophylaxis

BCMA, B-cell maturation antigen; BID, twice daily; PJP, *Pneumocystis jirovecii* pneumonia.

1. Raje N, et al. *Blood Cancer J* 2023;13(1):116.

Effect of IVIG on Rates of Grade 3-5 Infections



Similar outcomes were demonstrated in sensitivity analyses.
IVIG, intravenous immunoglobulin; Q4W, every 4 weeks.
1. Lancman G, et al. *Blood Cancer Discov* 2023;4(6):440-451.

Vaccinations in Patients on BCMA-Targeted Agents

Live vaccines are contraindicated in patients with RRMM on BCMA-targeted agents

Patients should be up to date on vaccinations against VZV, influenza, SARS-CoV-2 and pneumococcus

Caregivers should be fully immunized and receive seasonal vaccines

Prior to travelling to endemic areas of infection, patients should receive travel vaccinations and consult a disease specialist

BCMA, B-cell maturation antigen; RRMM, relapsed/refractory multiple myeloma; VZV, varicella-zoster virus.

1. Raje N, et al. *Blood Cancer J* 2023;13(1):116. 2. Canadian Immunization Guide (February 5, 2025 update).

Counselling Patients to Prevent Infections

Provide patients taking BCMA-targeted agents with guidance on how to prevent infections while on therapy

- Wash hands regularly
- Avoid crowded areas, especially with people who are sick
- Wear a mask if crowded areas cannot be avoided or in contact with symptomatic individuals
- Do not share food or personal items
- Shower or bathe daily and use unscented lotion to prevent skin from becoming dry and cracking
- Cook meat and eggs thoroughly
- Wash raw fruits and vegetables
- Protect skin from direct contact with pet bodily waste
- Clean teeth and gums with an ultrasoft toothbrush and use mouthwash to prevent sores
- Keep household surfaces clean

BCMA, B-cell maturation antigen.

1. Centers for Disease Control and Prevention (CDC). What You Need to Know: Neutropenia and Risk for Infection. Available at: https://www.cdc.gov/cancer/preventinfections/pdf/neutropenia.pdf. Accessed July 2024.

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Summary

- High unmet need for effective therapies for patients with RRMM, particularly for TCR BCMA-targeted BsAbs have been shown to prolong median PFS by 11.3-17.2m and median OS by 21.9-24.6m in 4th line treatment and beyond
- Patients taking BsAbs have an increased risk for CRS, ICANS, and infections
  - CRS and ICANS often appear within days of starting treatment, while infections take longer to appear
  - Use of step-up dosing, premedication, and prophylaxis helps prevent the onset of side effects associated with BCMA-targeted BsAbs
- Provide patients with information regarding the risks and benefits of treatment
  - Including the signs and symptoms of potential side effects
  - Additional resources to help guide them if an event occurs (e.g., Wallet card)

BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; OS, overall survival; PFS, progression-free survival; RRMM, relapsed and/or refractory multiple myeloma; TCE, triple class exposed.

Glossary

AE	Adverse event
BCMA	B-cell maturation antigen
BsAb	Bispecific antibody
CR	Complete response
CRS	Cytokine release syndrome
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell-associated encephalopathy
ISS	International Staging System
IVIG	Intravenous immunoglobulin
MGUS	Monoclonal gammopathy of undetermined significance
MRD	Minimum residual disease
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PR	Partial response
RRMM	Relapsed/refractory multiple myeloma
TCR	Triple class refractory
VGPR	Very good partial response

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Establishing an anti-BCMA BsAb Programme

Before Prescribing Elranatamab or Teclistamab:

- Coordinate with pharmacy, hospital and financial departments to add elranatamab and/or teclistamab and tocilizumab to formulary [remove/edit as applicable to local healthcare system]
- Educate providers, nurses and support staff on BsAbs administration and adverse reaction monitoring
- Establish protocols and / or order sets for BsAbs administration and adverse reaction management. Items to consider for inclusion in protocols or order sets:
  - Screening checklist
  - Premedication and monitoring schedule
  - Schedule for monitoring vital signs, neurological status and laboratory studies
  - Infectious disease monitoring and prophylaxis based on current guidelines
  - Guidelines on the management of adverse reactions that may develop while on BsAbs, such as CRS or neurotoxicity

BsAbs, bispecific antibodies; CRS, cytokine release syndrome.

Pre-administration/Post-administration Checklist for anti-BCMA Bispecific Antibodies

	Step-up dose and cycle 1	Cycle 2 and beyond
Pre-administration	• Baseline ICE assessment • Monitor vitals • Educate patients with clear explanations of potential side effects	• Baseline ICE assessment • Monitor vitals • Counsel patients with clear explanations of potential side effects
Post-administration	• Monitor vitals every 4-6 hours for 48 h post-administration • Neurologic assessment every shift or every visit • Consult with physician	• Monitor vitals • Patient education on side effects • Instruct patients to self-monitor and contact hospital staff when specific symptoms are exhibited

BCMA, B-cell maturation antigen; ICE, immune effector cell encephalopathy.

1. Catamero D, et al. *Semin Oncol Nurs* 2024;40(3):151621.

Initiating Anti-BCMA BsAb Therapy

For Each Patient, Prior to Administration:

- Secure payer coverage [remove if not applicable to local healthcare system]
- Confirm that the patient has care partner support for step-up dosing
- Establish a plan for monitoring for **48 hours after Step-up Dosing**[1,2]
- Send baseline laboratory studies, including complete blood cell count with differential[1,2], in addition to standard laboratory and organ function tests performed prior to initiating a new anti-myeloma regimen[3]
- Verify the pregnancy status of females of reproductive potential prior to initiating treatment[1,2]
- Assess vaccination history and ensure immunizations are up to date per local guidelines[3-5]
- Screen patients for active infections – if present, do not initiate BsAbs[1,2]
- Collect baseline history of chronic viral infections (e.g., CMV, HBV, HIV)[3,4]
- Monitor patients for reactivation of chronic viral infections and/or new onset viral infections (e.g., influenza, COVID-19, EBV) based on clinical presentation and clinician judgment[3-5]
- Review the **Prevention and Management of Possible Adverse Reactions** section for recommendations on monitoring and prophylaxis while on anti-BCMA BsAb therapy

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

1. ELREXFIO® (Elranatamab Injection) Product Monograph. December 2023. 2. TECVAYLI® (Teclistamab Injection) Product Monograph. August 2024. 3. Ludwig H, et al. *Lancet Oncol* 2023;24:e255–e269. 4. Raje N, et al. *Blood Cancer J* 2023;13:116. 5. Rodriguez-Otero P, et al. *Lancet Oncol* 2024;25(5):e205-e216.

Initiating Anti-BCMA BsAb Therapy

Patient Education Should Include the Following:

- Provide patient / care partner with the Patient Alert Card; inform them to carry the card at all times and to show it to any HCP involved in care, including at the hospital and / or A&E unit
- Advise patient to remain within proximity of a healthcare facility for monitoring of signs and symptoms of CRS and neurotoxicity, including ICANS, for **48 hours after Step-up Dosing**
- Organize short stay lodging in proximity to hospital (e.g., within driving distance) for outpatient administration
- Educate patient and care partner on risks of, and how to recognize, CRS and neurotoxicity, including ICANS
- Emphasize the need for the patient / care partner to report all symptoms suggestive of these events to their HCP or emergency department immediately
- No driving or operating heavy or potentially dangerous machinery during the step-up dosing schedule and for 48 hours after completing each of the two step-up doses, and in the event of new onset of any neurologic toxicity symptoms
- Advise females of reproductive potential of the possible risk to the fetus during pregnancy and to use effective contraception

A&E, accident and emergency; BCMA, B-cell maturation antigen; BsAbs, bispecific antibody; CRS, cytokine release syndrome; HCP, healthcare provider; ICANS, immune effector cell-associated neurotoxicity syndrome.

1. ELREXFIO® (Elranatamab Injection) Product Monograph. December 2023. 2. TECVAYLI® (Teclistamab Injection) Product Monograph. August 2024..

Anti-BCMA BsAb Administration

Administering the Step-up Dosing Schedule

- Perform **vital signs** prior to each dose
- Perform exam, including the level of consciousness, prior to the first dose, and repeat as clinically indicated; document baseline ICE score [see the **Adverse Events and Clinical Management** section]
- Administer **premedication** approximately 1 hour prior to dose to reduce CRS risk[1,2]
- Administer anti-BCMA BsAbs subcutaneously
  - **Preferred site: Abdomen**; alternatively, anti-BCMA BsAbs may be injected into subcutaneous tissue at other sites (e.g., thigh)[1,2]
- Patients should be monitored for signs and symptoms of CRS and ICANS **for 48 hours after** administration of each **step-up dose** and instructed to remain within proximity of a healthcare facility[1,2]
  - During elranatamab clinical trial, patients were monitored with vital signs every 4 hours and neurologic exams* prior to each dose of the step-up regimen[4]
- Monitor **complete blood counts, renal and liver function, and infectious symptoms** periodically[1–3,5]
- Monitor for toxicity or drug concentrations of CYP substrates when coadministered with anti-BCMA BsAbs[1,2]

*Neurologic exam components: Assessment of mental status, motor function, sensory function, gait, deep tendon reflexes, cranial nerve function, station and coordination.

BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; CNS, central nervous system; CRS, cytokine release syndrome; CYP, cytochrome P450; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune Effector Cell-Associated Encephalopathy; SC, subcutaneously.

1. ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023. 2. TECVAYLI® (Teclistamab Injection) Product Monograph. August 2024. 3. Ludwig H, et al. *Lancet Oncol* 2023;24:e255–e269. 4. Pfizer. An Open-label, Multicenter, Non-randomized Phase 2 Study of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One Proteasome Inhibitor, One Immunomodulatory Drug, and One Anti-CD38 Antibody. Protocol C1071003. Final Protocol Amendment 10, 22 March 2023. 5. Raje N, et al. *Blood Cancer J* 2023;13:116.

Anti-BCMA BsAb Administration

Administering Weekly and Biweekly Treatment Doses

- Perform **vital signs** prior to each dose
- Perform physical exam periodically and as clinically indicated
- Administer **premedication** approximately 1 hour prior to the **first Full Treatment Dose** to reduce CRS risk[1,2]
- Monitor patients for **signs and symptoms of infection** prior to and during treatment[1–4]
- Monitor complete blood counts, renal function and liver function periodically[1–4]
- Monitor IgG levels monthly during treatment[3]
  - Expert recommendations include IVIG replacement for patients on anti-BCMA BsAbs, particularly those with hypogammaglobulinemia (IgG <4 g/L) or in certain cases of infection[3,4] [see the **Adverse Events and Clinical Management** section]
- Instruct patient / care partner to watch for signs or symptoms of CRS and neurotoxicity, including ICANS, particularly during early treatment doses or after dose interruption[1,2,4]
  - In the elranatamab clinical trial, neurologic exams† were performed weekly up to Week 12, every other week up to Week 24, and monthly from Week 25 and beyond[5]

*The dose frequency can be reduced to Q2W for patients who have received at least 24 weeks of treatment with elranatamab and have achieved a response.
†Neurologic exam components: Assessment of mental status, motor function, sensory function, gait, deep tendon reflexes, cranial nerve function, station and coordination.
BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; Q2W, every 2 weeks; QW, weekly; SC, subcutaneously.
1. ELREXFIO® (Elranatamab Injection) Produce Monograph, December 2023. 2. TECVAYLI® (Teclistamab Injection) Product Monograph. August 2024. 3. Raje N, et al. *Blood Cancer J* 2023;13:116. 4. Ludwig H, et al. *Lancet Oncol* 2023;24:e255–e269. 5. Pfizer. An Open-label, Multicenter, Non-randomized Phase 2 Study of Elranatamab (PF-06863135) Monotherapy in Participants With Multiple Myeloma Who Are Refractory to at Least One Proteasome Inhibitor, One Immunomodulatory Drug, and One Anti-CD38 Antibody. Protocol C1071003. Final Protocol Amendment 10, 22 March 2023.

Cytokine Release Syndrome

A systemic inflammatory response mediated by the activation of T lymphocytes, with host immune cells as the source of cytokines such as IL-6, IFN-γ and IL-10[1]; symptoms can be **mild, life-threatening or fatal**[2]

HALLMARK SYMPTOMS OF CRS[2]

Fever

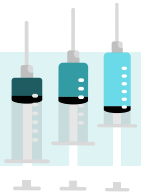
Hypoxia

Hypotension

Other symptoms may include tachycardia, fatigue, headache and organ toxicity[1]

The incidence and severity of CRS related to anti-BCMA BsAb administration can be diminished with **stepwise dosing, premedication or temporary drug discontinuation**[1]

During BsAb therapy, patients should be **monitored** for CRS to enable **early intervention** and prevent or minimize CRS symptoms[3,a]



With BsAbs, CRS is commonly observed after the **initial exposure** but may occur with subsequent early doses[1]

With the recommended **elranatamab** dosing schedule, 58% of patients experienced CRS (Grade ≥3, 0.5%), with a **median time to onset of 2 days**[4]

Most patients experienced CRS **after the first Step-up Dose** (43.2%)[4]

With the recommended **teclistamab** dosing schedule, 72% of patients experienced CRS (Grade ≥3, 0.6%), with a **median time to onset of 2 days**[5]

Most patients experienced CRS **after the first Step-up Dose** (44%)[5]

Management of CRS with anti-BCMA BsAbs[4,5]:

- At first sign of CRS, alert the treating physician, withhold anti-BCMA BsAb and immediately evaluate the patient for hospitalization
- Evaluate and treat other causes of fever, hypoxia and hypotension
- Manage according to recommendations in Product Monograph and per current practice guidelines

Please find footnotes, references and abbreviations included in the slide notes.

CRS Grading

Grade	CTCAE v5.0	ASTCT consensus		
		Fever	Hypotension	Hypoxia
1	Fever +/- constitutional systems	≥38°C	None	None
2	With hypotension responding to fluids and/or hypoxia responding to <40% FiO2	≥38°C	Not requiring vasopressors	Requiring low-flow nasal cannula
3	With hypotension managed with 1 vasopressor and/or hypoxia requiring ≥40% FiO2	≥38°C	Requiring vasopressors +/- vasopressin	Requiring high-flow nasal cannula
4	Life-threatening consequences; urgent intervention needed	≥38°C	Requiring multiple vasopressors (excluding vasopressin)	Requiring positive pressure

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; FiO2, fraction of inspired oxygen.

1. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed July 2024. 2. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25(4):625-638.

ICANS

ICANS is a poorly understood **pathological process affecting the CNS** following immune effector therapy characterized by disruption of the blood–brain barrier, allowing permeation of cytokines, immune cells and T cells into the CSF[1,2]

Signs and symptoms of ICANS[1,3,4,5]

Early:

- Expressive aphasia
- Tremor / dysgraphia
- Impaired attention
- Loss of motor skills
- Altered consciousness

Progressive:

- Global aphasia
- Obtundation
- Stupor
- Cerebral oedema
- Seizures

Management of neurotoxicity with anti-BCMA BsAbs[3]:

- At first sign of neurotoxicity (including ICANS), alert the treating clinician, **evaluate and treat based on severity**; evaluation should include ICE score (see next slide)
- Rule out **other causes** of neurologic symptoms
- Follow recommendations in the **label** and per **current practice guidelines**

CRS IS A RISK FACTOR FOR ICANS

ICANS often occurs following CRS, but may also occur concurrent with, or even in the absence of, CRS[3,4]

With the recommended **elranatamab** dosing schedule, **ICANS occurred in 3.3% of patients[3]**

With the recommended **teclistamab** dosing schedule, **ICANS occurred in 3.0% of patients[5]**

CNS, central nervous system; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, Immune Effector Cell-Associated Encephalopathy.

1. Lee DW, et al. *Biol Blood Marrow Transplant* 2019;25(4):625–638. 2. Sterner RC, Sterner RM. *Front Immunol* 2022;13:879608. 3. ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023. 4. Ludwig H, et al. *Lancet Oncol* 2023;24:e255–e269. 5. TECVAYLI® (Teclistamab Injection) Product Monograph, August 2024.

ICE Score Assessment Tool for ICANS

Orientation	orientation to year, month, city, hospital	**4** points
Naming	ability to name 3 objects (e.g., point to clock, pen, button)	**3** points
Following commands	ability to follow simple 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 symbol is the maple leaf")	**1** point
Attention	ability to count backward from 100 by 10s	**1** point

ICANS, immune effector cell–associated neurotoxicity syndrome; ICE, immune effector cell encephalopathy.

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

Infectious Complications

Infections

Infections with anti-BCMA BsAb therapy can occur and include pneumonia, upper respiratory tract infection, COVID-19, UTI and sepsis[1–5]

In the clinical trials, **39.8%/44.8%** of patients receiving elranatamab/teclistamab developed Grade 3 or 4 infection on study[6,7]

Hypogammaglobulinemia

Patients with multiple myeloma may experience hypogammaglobulinemia due to **plasma cell aplasia** and further **depletion of normal plasma cells** by targeted therapies[6]

Low serum IgG levels (<400 g/L), including **severe hypogammaglobulinemia** (<2 g/L), are common with BCMA-targeted therapy[1,2]

Management of infections with anti-BCMA BsAbs[4,5]:

- ❑ Do not initiate BsAb in patients with active infections
- ❑ **Monitor patients for infection** prior to and during treatment
- ❑ Administer **prophylactic anti-infectives** and **treat active infections** according to current practice guidelines

Management of hypogammaglobulinemia[4]:

- ❑ **Monitor Ig levels** during treatment
- ❑ Consider SCIg or IVIg for **IgG levels ≤4 g/L**
- ❑ Treat according to local institutional guidelines, including **infection precautions and antimicrobial prophylaxis**

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; COVID-19, coronavirus disease 2019; Ig, immunoglobulin; IV; intravenous; SC, subcutaneous; UTI, urinary tract infection.

1. Raje N, et al. *Blood Cancer J* 2023;13:116. 2. Ludwig H, et al. *Lancet Oncol* 2023;24:e255–e269. 3. Tomasson MH, et al. *HemaSphere* 2024;8(7):e136. 4. ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023. 5. TECVAYLI® (Teclistamab Injection) Product Monograph, August 2024; 6. Mohan M, et al. *Br J Haematol* 2023;203:736–746. 6. Lesokhin AM, et al. *Nat Med* 2023;29:2259-67. 7. Moreau P, et al. *N Engl J Med* 2022;387:495-505.

Laboratory Abnormalities

Cytopenias

Cytopenias with BsAbs are **caused by cytokines** in the bone marrow microenvironment that **impair hematopoiesis,** often in patients with **pre-existing myelosuppression** due to multiple myeloma and prior therapy[1,2]

After treatment with elranatamab/teclistamab, **neutropenia** occurred in 48.8%/70.9% of patients (Grade 3 or 4, 48.8%/64.2%)[3,4]

Febrile neutropenia occurred in 2.2%/2.4% of patients[3,4]

Anemia occurred in 48.8%/52.1% of patients (Grade 3 or 4, 37.41%/37.0%) [3,4]

Thrombocytopenia occurred in 30.9%/40.0% of patients (Grade 3 or 4, 23.6%/21.2%)[3,4]

- Check **complete blood cell count at baseline and periodically** during therapy[3,4]
- Monitor neutropenic patients for signs of infection and provide supportive care according to current guidelines[3,4]
  - Expert recommendations include **G-CSF** for Grade ≥3 neutropenia. **Administration should be avoided when the patient is at risk of CRS**[5]

AST, aspartate aminotransferase; BsAb, bispecific antibody; CRS, cytokine release syndrome; G-CSF, granulocyte colony-stimulating factor; PK, pharmacokinetics; QOD, every other day; TIW, three times weekly; ULN, upper limit of normal.

1. Ludwig H, et al. *Lancet Oncol* 2023;24:e255–e269. 2. Sheu M, et al. *Hematol Oncol* 2023;41:718–724. 3. Lesokhin AM, et al. *Nat Med* 2023;29:2259-67. 4. Moreau P, et al. *N Engl J Med* 2022;387:495-505. 5. Raje N, et al. *Blood Cancer J* 2023;13:116.

Organ Dysfunction

Hepatic Impairment

No formal studies of elranatamab/teclistamab have been conducted in patients with hepatic impairment. **Mild hepatic impairment** (total bilirubin >1–1.5 x ULN and any AST, or normal total bilirubin and AST > ULN) **did not influence the PK** of elranatamab/teclistamab in population PK analyses[1,2]

Increased transaminases were reported in 15.8%/35-41% of patients (Grade 3 or 4, 4.9%/3.0-4.2%) in the elranatamab/ teclistamab clinical trials[1,2]

- No dose adjustments are required for **mild** hepatic impairment[1,2]
- No data are available in patients with **moderate** (total bilirubin >1.5–3 x ULN and any AST) or **severe** (total bilirubin >3 x ULN and any AST) hepatic impairment[1,2]

AST, aspartate aminotransferase; BsAb, bispecific antibody; CRS, cytokine release syndrome; G-CSF, granulocyte colony-stimulating factor; PK, pharmacokinetics; QOD, every other day; TIW, three times weekly; ULN, upper limit of normal.

1. ELREXFIO® (Elranatamab Injection) Product Monograph, December 2023; 2. TECVAYLI® (Teclistamab Injection) Product Monograph, August 2024.

Sponsorship

This program meets Canadian Association of Nurses in Oncology (CANO) guidelines and is expected to support nurses in their understanding of mCRC. Endorsement is provided by CANO for a time period of two years, ending February 7th, 2027.

CANO/ACIO has made every effort to ensure that information included within this program is accurate at the time of endorsement. The information included cannot substitute for the advice or direction of a health care professional, and the association makes no guarantees, nor can it assume any legal liability for the accuracy, completeness, or usefulness of such information or for any damage incurred directly or indirectly from the information. Reference to any specific product does not imply its endorsement, recommendation or preference by the Canadian Association of Nurses in Oncology.

This program has been accredited by the Faculty of Nursing of Laval University for 1.5 continuing education units per 90 minutes of activity ending November 15th, 2025. **Faculty of Nursing of Laval University:** Please note that in order to claim the 1.5 continuing education units attributed to this program, you must view all twelve videos. Once done, please refer to the following link in order to claim your certificate by the Faculty: www.uec.fsi.ulaval.ca

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