Clinical Practice Resource: CD3/BCMA Bispecific Antibodies for Relapsed/Refractory Multiple Myeloma

Literature review current as of: 4 April 2025

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IMPORTANT:

- Safe delivery of CD3/BCMA BsAbs requires attention to preparation, administration, monitoring, and coordination of care.
- This clinical resource is intended to provide practical guidance where local resources may not exist; institutional guidelines around dose reductions, toxicity management, and infusion line and intravenous catheter care should be followed.

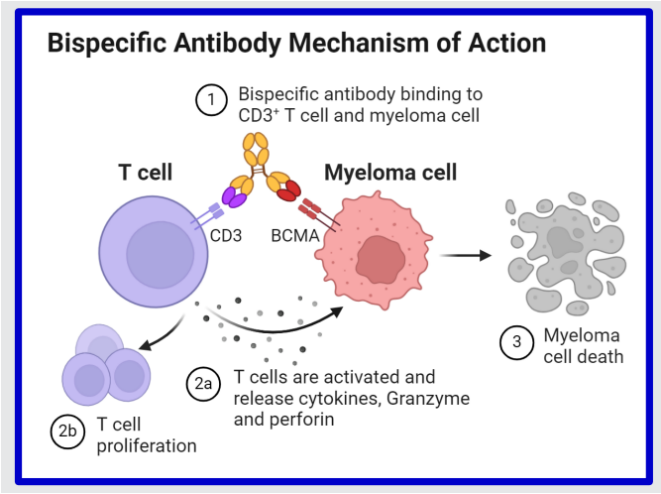
1. Introduction: BCMA-targeted agents for multiple myeloma

There are three classes of BCMA-targeted therapies for treatment of multiple myeloma in Canada:[1]

Antibody-drug conjugates	CAR-Ts	Bispecific T-cell-engaging antibodies

• 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
	• 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
		• 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

Mechanism of action of CD3/BCMA BsAbs:[2,3]



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

2. CD3/BCMA BsAbs approved for use in multiple myeloma

2.1.1 Indications

Two CD3/BCMA BsAbs are approved in Canada for the treatment of multiple myeloma:[4,5]

Elranatamab and **Teclistamab** are each indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

2.2 Clinical trials of CD3/BCMA BsAbs in RRMM

	Elranatamab (Pfizer; MagnetisMM-3)[6,7,8,9] Phase 2	Teclistamab (J&J; MajesTEC-1)[10,11,12] Phase 1/2
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) (Cohort C: prior BCMA n= 40)
	Cohort A	**Cohort A**
Median age (range)	68 (36-89)	64 (33-84)
Disease stage, ISS		
I	30%	52%
II	37%	35.2%
III	20%	12%
High-risk cytogenetics	25.2%	25.7%
Prior lines of therapy, median (range)	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%
ORR	61.0%	63%
VGPR	18.7%	13.9%
PR	4.9%	3.6%
≥CR	37.4%	45.5%
MRD-	MRD-negativity at the threshold of 10^{-5} was achieved by 90.3% in patients with CR or better who were evaluable for MRD (n=31)	44/54 (81.5%) MRD-evaluable patients were MRD- at any point
mPFS, months	17.2	11.3
mDOR, months	The median DORs by LOT were not reached (NR), and the probability of maintaining a response at 18 months was 83.3% (95% CI, 56.8-94.3)	mDOR for all patients: 21.6
mOS, months	24.6	21.9

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.

CI, confidence interval; CR, complete response; ISS, International Staging System; LOT, line of treatment; mDOR, median duration of response; MRD, minimum residual disease; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; ORR, objective response rate; PR, partial response; VGPR, very good partial response.

3. Establishing a CD3/BCMA BsAb programme

3.1 Before prescribing Elranatamab or Teclistamab

- Coordinate with pharmacy, hospital and financial departments to add Elranatamab and/or Teclistamab and tocilizumab to formulary
- Educate providers, nurses and support staff on Elranatamab/Teclistamab administration and adverse reaction monitoring
- Establish protocols and / or order sets for Elranatamab/Teclistamab 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 screening, monitoring and prophylaxis based on current guidelines
    - Guidelines on the management of adverse reactions that may develop while on Elranatamab/Teclistamab, such as CRS or neurotoxicity

4. Initiating CD3/BCMA BsAb therapy

4.1 Pre-administration checklist

For each patient, prior to administration:

- Secure payer coverage
- Confirm that the patient has care partner support for step-up dosing
- Send baseline laboratory studies, including complete blood cell count with differential[4,5], in addition to standard laboratory and organ function tests performed prior to initiating a new anti-myeloma regimen[13]
- Verify the pregnancy status of females of reproductive potential prior to initiating treatment[4,5]
- Assess vaccination history and ensure immunizations are up to date per local guidelines[13,14,15]
- Screen patients for active infections – if present, do not initiate BsAbs[4,5]
- Collect baseline history of chronic viral infections (e.g., CMV, HBV, HIV)[13,14]
- Monitor patients for reactivation of chronic viral infections (e.g., CMV, HBV, HIV) and/or new onset viral infections based on clinical presentation and clinician judgment (e.g., influenza, COVID-19, EBV)[13,14,15]
- Establish a plan for monitoring for 48 hours after step-up dosing[4,5]
- Review the **Adverse Events and Clinical Management** section for recommendations on monitoring and prophylaxis while on Elranatamab/ Teclistamab therapy

4.2 Patient education

Prior to treatment initiation, patient education should include the following:[4,5]

- 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 Emergency 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

5. Dosing of CD3/BCMA BsAbs

5.1 Practical dosing considerations:

- Establish a plan for monitoring for 48 hr after each step-up dose[4,5]
    - 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
- Premedications administered ~1 hour (Elranatamab)[4] or 1-3 hours (Teclistamab)[5] before each step-up dose and the first treatment dose:

CD3/BCMA BsAb	Corticosteroid	Antihistamine	Antipyretic
Elranatamab[4]	Dexamethasone (or equivalent) 20 mg PO or IV	Diphenhydramine (or equivalent) 25 mg PO	Acetaminophen (or equivalent) 650 mg PO
Teclistamab[5]	Dexamethasone 16 mg PO or IV	Diphenhydramine (or equivalent) 50 mg PO or IV	Acetaminophen (or equivalent) 650-1000 mg PO or IV

5.2 Elranatamab dosing schedule[4]

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, c, 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 elranatamab. [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.

5.3 Teclistamab dosing schedule[5]

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
	Day 5[d]	First treatment dose	1.5 mg/kg single dose
Weekly dosing schedule[b]	One week after first treatment dose and weekly thereafter[e]	Subsequent treatment doses	1.5 mg/kg once weekly
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 teclistamab 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.

6. Dose modifications

6.1 Practical considerations for dose modifications

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

6.2 Recommended dose modifications

The following dose modifications are recommended for adverse reactions other than CRS or neurotoxicity, including ICANS:[4,5]

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	Withhold until recovery to Grade ≤1 or baseline
Grade 4	Consider permanent discontinuation

ANC, absolute neutrophil count.

6.3 Resuming Elranatamab dosing after dosage delay[4]

Last administered dose	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)

6.4 Resuming Teclistamab dosing after dosage delay[5]

Last administered dose	Duration of delay from the last dose administered	Action
Step-up Dose 1 (12 mg)	≤7 days >7 days	Restart teclistamab step-up dosing schedule at step-up dose 2 (0.3 mg/kg) Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06 mg/kg)
Step-up Dose 2 (32 mg)	≤7 days 8–28 days >28 days	Restart teclistamab step-up dosing schedule at treatment dose (1.5 mg/kg) Restart teclistamab step-up dosing schedule at step-up dose 2 (0.3 mg/kg) Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06 mg/kg)
Any Full Treatment Dose (76 mg)	≤28 days >28 days	Restart teclistamab at treatment dose (1.5 mg/kg) once weekly Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06 mg/kg)

REMINDER:

Administer premedications prior to step-up doses and after the first full treatment dose to reduce the risk of CRS.[4,5]

7. Administration of CD3/BCMA BsAbs

7.1 Pre-administration checklist[16]

Step-up dose and cycle 1 (4 weeks)

- Baseline ICE assessment
- Monitor vitals
- Educate patients with clear explanations of potential side effects

Cycle 2 and beyond

- Baseline ICE assessment
- Monitor vitals
- Counsel patients with clear explanations of potential side effects

7.2 Considerations for drug preparation[4,5]

- Elranatamab and Teclistamab are each supplied as ready-to-use solutions that do not need dilution prior to administration
- Use aseptic technique to prepare and administer Elranatamab and Teclistamab
- To minimize errors, follow the preparation instructions for each CD3/BCMA BsAb as documented below

7.3 Preparation of Elranatamab[4]

Required Dose	Dose Volume
76 mg (Full treatment dose)	1.9 mL
32 mg (Step-up dose 2)	0.8 mL
12 mg (Step-up dose 1)	0.3 mL

7.4 Preparation of Teclistamab[5]

Use the table below to determine total dose, injection volume, and number of vials required based on patient's body weight for **Step-up Dose 1 using Teclistamab 30 mg/3 mL (10 mg/mL) vial**:

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial=3 mL)
Step-Up Dose 1 (0.06 mg/kg)	35-39	2.2	0.22	1
	40-44	2.5	0.25	1
	45-49	2.8	0.28	1
	50-59	3.3	0.33	1
	60-69	3.9	0.39	1
	70-79	4.5	0.45	1
	80-89	5.1	0.51	1
	90-99	5.7	0.57	1
	100-109	6.3	0.63	1
	110-119	6.9	0.69	1
	120-129	7.5	0.75	1
	130-139	8.1	0.81	1
	140-149	8.7	0.87	1
	150-160	9.3	0.93	1

Use the table below to determine total dose, injection volume, and number of vials required based on patient's body weight for **Step-up Dose 2 using Teclistamab 30 mg/3 mL (10 mg/mL) vial**:

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial=1.7 mL)
Treatment Dose (1.5 mg/kg)	35-39	56	0.62	1
	40-44	63	0.7	1
	45-49	70	0.78	1
	50-59	82	0.91	1
	60-69	99	1.1	1
	70-79	108	1.2	1
	80-89	126	1.4	1
	90-99	144	1.6	1
	100-109	153	1.7	1
	110-119	171	1.9	2
	120-129	189	2.1	2
	130-139	198	2.2	2
	140-149	216	2.4	2
	150-160	234	2.6	2

Use the table below to determine total dose, injection volume, and number of vials required based on patient's body weight for **Treatment Dose using Teclistamab 30 mg/3 mL (10 mg/mL) vial**:

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial=1.7 mL)
Treatment Dose (1.5 mg/kg)	35-39	56	0.62	1
	40-44	63	0.7	1
	45-49	70	0.78	1
	50-59	82	0.91	1
	60-69	99	1.1	1
	70-79	108	1.2	1
	80-89	126	1.4	1
	90-99	144	1.6	1
	100-109	153	1.7	1
	110-119	171	1.9	2
	120-129	189	2.1	2
	130-139	198	2.2	2
	140-149	216	2.4	2
	150-160	234	2.6	2

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[4,5]
- Administer Elranatamab/Teclistamab subcutaneously[4,5]
    - Preferred site: Abdomen; alternatively, Elranatamab/ Teclistamab may be injected into subcutaneous tissue at other sites (e.g., thigh) [4,5]
- 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[4,5]
    - 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[17]
- Monitor **complete blood counts, renal and liver function, and infectious symptoms** periodically[4,5,13,14]
- Monitor for toxicity or drug concentrations of CYP substrates when coadministered with elranatamab/teclistamab[4,5]

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

7.5 Administering maintenance 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[4,5]
- Monitor patients for signs and symptoms of infection prior to and during treatment[4,5,13,14]
- Monitor complete blood counts, renal function and liver function periodically[4,5,13,14]
- Monitor IgG levels monthly during treatment[14]
    - Expert recommendations include IVIG replacement for patients on BsAbs, particularly those with hypogammaglobulinemia (IgG <4 g/L) or in certain cases of infection[13,14] [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[4,5,13]
    - 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[17]

*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, or with Teclistamab if there is a complete response or better for a minimum of 6 months.

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

Post-administration monitoring checklist

Step-up dose and cycle 1

- Monitor vitals every 4-6 hours for 48 hours post-administration
- Neurologic assessment every shift or every visit
- Consult with physician

Cycle 2 and beyond

- Monitor vitals
- Patient education on side effects
- Instruct patients to self-monitor and contact hospital staff when specific symptoms are exhibited

8. Adverse events and clinical management

8.1 Safety overview of CD3/BCMA BsAbs

- Assessment and monitoring guidance provided in the following sections aim to support proactive management of potential toxicities associated with CD3/BCMA BsAb therapy.
- In addition to the common toxicities listed below, vigilance is required to proactively monitor for and manage less common but serious toxicities including CRS and ICANS.

8.2 Most common adverse reactions

Events occurring at a rate of ≥20% in clinical trials of Elranatamab and Teclistamab: [4,5]

Early events	Later events
CRS*	Cytopenias: anemia†, neutropenia†, thrombocytopenia,
ICANS*	Hypokalemia
Injection site reactions	Fatigue
	Infections: URTI, pneumonia
	Gastrointestinal: diarrhea, nausea
	Decreased appetite
	Rash
	Arthralgia
	Dry skin

*Require monitoring during step-up dosing. †Occurred at a rate of ≥20%.
CRS, cytokine release syndrome; ICANS, immune effector cell-mediated neurotoxicity syndrome; URTI, upper respiratory tract infection.

8.3 Adverse events of interest

	Elranatamab (Pfizer; MagnetisMM-3)[6] Cohort A n=123 Median duration of treatment 5.6 months (0.03-24.4)	Teclistamab (J&J; MajesTEC-1)[10] Cohort A n=165 Median duration of treatment 8.5 months (0.2 to 24.4)
CRS		
All grades	71 (57.7%)	119 (72.1%)
Grade 3/4	0	1 (0.6%)
CRS timing	Onset: 2.0d (1.0-9.0d) Duration/resolution: 2.0d (1.0-19.0d)	Onset: 2.0d (1.0-6.0d) Duration/resolution: 2.0d (1.0-9.0d)
ICANS		
All grades	4 (3.4%)	5 (3.0%)
Grade 3/4	0	0
Grade 5	0	0
Infections		
All grades	69.9%	78.8%
Grade 3/4	39.8%	55.2%
Grade 5 (including % COVID-19)	6.5% (1.6% from COVID-19)	13.3% (6.1% from COVID-19)
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.

Use of steroids and tocilizumab was permitted in all trials.

8.4 Cytokine release syndrome (CRS)

CRS is 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;[13] symptoms can be mild, life-threatening or fatal.[18]

8.4.1 Hallmark symptoms of CRS

Fever

Hypoxia

Hypotension

Other symptoms include tachycardia, fatigue, headache and organ toxicity.[13]

8.4.2 Practical considerations

- During CD3/BCMA BsAb therapy, patients should be monitored for CRS to enable early intervention and prevent or minimize CRS symptoms[15,a]
- With CD3/BCMA BsAbs, CRS is commonly observed after the initial exposure but may occur with subsequent early doses[13]
- With the recommended Elranatamab dosing schedule, 57.7% of patients experienced CRS (Grade ≥3, 0%), with a **median time to onset of 2 days**[6]
    - Most patients experienced CRS after the first Step-up Dose (43.2%)[4]
- With the recommended Teclistamab dosing schedule, 72.1% of patients experienced CRS (Grade ≥3, 0.6 %), with a **median time to onset of 2 days**[10]
    - Most patients experienced CRS after the first Step-up Dose (44%)[5]

[a] Information included is from the International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations. Treatment of CRS should be guided by the available data and take into consideration the agent being administered.

8.4.3 Monitoring for CRS with CD3/BCMA BsAbs[16]

- Temperature
- Respiration
- O_2 saturation
- Symptoms: pain, shivering, rash, difficulty breathing, etc.
- Blood pressure
- Heart rate
- Cardiac monitoring (as needed)

8.4.4 Occurrence and timing of CRS in CD3/BCMA BsAbs clinical trials

	MagnetisMM-3 (Elranatamab)[6]	MajesTEC-1 (Teclistamab)[10]
Patients affected (percentage of participants, all grades)	57.7%	72.1%
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	2 days (range: 1.0-19.0)	2 days (range: 1.0-9.0)

8.4.5 Grading of CRS events[19]

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% FiO_2	≥38°C	Not requiring vasopressors	Requiring low-flow nasal cannula
3	With hypotension managed with 1 vasopressor and/or hypoxia requiring ≥40% FiO_2	≥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; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CD, cluster of differentiation; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; FiO_2, fraction of inspired oxygen.

8.4.6 Mitigating CRS events with CD3/BCMA BsAbs

- The incidence and severity of CRS related to BsAb administration can be diminished with stepwise dosing, premedication or temporary drug discontinuation.[13]
- Use of premedication and step-up dosing reduces the incidence of CRS, with 98.8% of CRS events occurring within the first 3 doses.[4,5]
- During CD3/BCMA BsAb therapy, patients should be monitored for CRS to enable early intervention and prevent or minimize symptoms.[20]

Premedication	Step-up Dosing	Monitoring
• 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	Reduces the incidence and severity of CRS	Monitor patients for 48 hours after step-up doses (note: patients are currently monitored in inpatient setting)

CRS, cytokine release syndrome.

8.4.7 Tocilizumab prophylaxis

Exploratory data on tocilizumab prophylaxis in RRMM patients treated with CD3/BCMA BsAbs:[20]

- 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 (14%) and ICANS (8%)
- Among patients experiencing ICANS, most events were grade 1 or 2

8.4.8 Management of CRS events with CD3/BCMA BsAbs[4,5]

- At sign of CRS, alert the treating physician, withhold Elranatamab/ Teclistamab and immediately evaluate the patient for hospitalization.
- Evaluate and treat other causes of fever, hypoxia and hypotension.
- Rule out other etiologies: infection, heart failure, pulmonary edema; possibly treat for infection.[21]
- Manage according to recommendations in Product Monograph and per current practice guidelines.

Grade	CD3/BCMA BsAb therapy: Supportive care + intervention[4,5]
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

BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CD, cluster of differentiation; CRS, cytokine release syndrome; ICU, intensive care unit.

Sample CRS management protocols[22]

Grade	Medications	Monitoring	Actions
1	• 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	At least Q4H x 12H or until resolution of symptoms, whichever is earlier: • CRS symptoms • Vital signs • Pulse oximetry	• Page the admitting or covering prescriber • If febrile, initiate concurrent septic workup and consider empiric coverage with broad-spectrum antibiotics, particularly if immunocompromised and/or neutropenic
2	• 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	At least every hour, and more frequently, if necessary, until resolution of CRS symptoms: • Vital signs • Pulse oximetry	• Page the admitting physician or covering prescriber if not already done • 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, continued until grade ≤1, then taper over 3 days • If required: Salbutamol 5 mg inhalation by nebulizer Q20MIN (maximum 3 doses)
≥3	• 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	Q15MIN or more frequently as ordered by physician until resolution to grade 2 or less, then every hour until complete resolution of CRS: • Vital signs • Pulse oximetry	• Page the admitting physician or covering prescriber if not already done • Arrange emergent transfer to higher level of care 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)

BP, blood pressure; CRS, cytokine release syndrome; IM, intramuscular; IV, intravenous; NaCl, sodium chloride; NS, normal saline; PO, by mouth; PRN, as needed; QxH, every X hours; QxMIN, every X minutes; QD, once daily.

8.5 Immune effector cell-mediated neurotoxicity syndrome (ICANS)

ICANS is a poorly understood pathological process affecting the central nervous system (CNS) following immune effector therapy characterized by disruption of the blood–brain barrier, allowing permeation of cytokines, immune cells and T cells into the cerebrospinal fluid (CSF).[18,23]

8.5.1 Neurological side effects associated with CD3/BCMA BsAbs

There are three general clinical presentations of neurological complications with CD3/BCMA BsAbs:[15]

Headache	ICANS	Peripheral neuropathies
A nonspecific neurotoxic event that can be associated with CRS and often responds to acetaminophen	Less common and triggered by influx of cytokines into the CNS	Usually associated with prior history of neuropathy

CNS, central nervous system; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

8.5.2 Signs and symptoms of ICANS[24]

Early	Progressive
Expressive aphasia	Global aphasia
Tremor/ dysgraphia	Obtundation
Impaired attention	Stupor
Loss of motor skills	Cerebral edema
Altered consciousness	Seizures

8.5.3 Practical considerations

- ICANS often occurs following CRS, but may also occur concurrent with, or even in the absence of, CRS.[4,5]
- With the recommended Elranatamab dosing schedule, ICANS occurred in 3.3% of patients.[4]
- With the recommended Teclistamab dosing schedule, ICANS occurred in 3.0% of patients.[5]
- On MRI, cerebral edema may also be present.[24]

8.5.4 Occurrence and timing of ICANS in CD3/BCMA BsAbs clinical trials

	MagnetisMM-3 (Elranatamab)[6]	MajesTEC-1 (Teclistamab)[10]
Patients affected (percentage of participants, all grades)	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
Median duration of ICANS	2 days (range: 1.0-6.0)	Not reported

8.5.5 Grading of ICANS events

ASTCT ICANS consensus grading for adults[18]

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; CTCAE, Common Terminology Criteria for Adverse Events; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune effector cell encephalopathy; ICP, intracranial pressure.

ICE score assessment tool for ICANS[18]

If the patient's ICE score is 9 or below, notify physician immediately		
Orientation	Orientation to year, month, city, hospital	4
Naming	Ability to name 3 objects (e.g., point to clock, pen, button)	3
Following	Ability to follow simple commands (e.g., "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1
Writing	Ability to write a standard sentence (e.g., "Our national symbol is the maple leaf")	1
Attention	Abilify to count backward from 100 by 10s	1

8.5.6 Mitigating ICANS events with CD3/BCMA BsAbs[16]

- Nurses and pharmacists should provide a clear explanation of potential symptoms associated with ICANS (and CRS), 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

8.5.7 Management of neurotoxicity with CD3/BCMA BsAbs[4,5]

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

8.6 Infectious complications

8.6.1 Risk factors for infections in patients on CD3/BCMA BsAbs[14]

Patient-related factors	Disease-related factors
• Age • Performance status • Comorbidities (e.g., renal failure and chronic heart failure) • Immunoparesis • Cytopenia (neutropenia and lymphopenia)	• Tumor 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
Treatment-related factors	**Infectious history**
• 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	• 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

CAR-T, chimeric antigen receptor T cell; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; HBV, hepatitis B virus; IMiD, immunomodulatory drug; Ig, immunoglobulin; MM, multiple myeloma; PI, proteasome inhibitor; VZV, varicella zoster virus.

8.6.2 Practical considerations

- Infections with BsAb therapy can occur and include pneumonia, upper respiratory tract infection, COVID-19, urinary tract infection, and sepsis[4,5,13, 14,25]
- In the clinical trials of CD3/BCMA BsAbs in RRMM, 39.8%/44.8% of patients receiving Elranatamab/Teclistamab developed Grade 3 or 4 infection on study[6,10]
- Do not initiate CD3/BCMA BsAbs in patients with active infections[4,5]

8.6.3 Occurrence and timing of infections in CD3/BCMA BsAbs clinical trials

Infections occurring in ≥10% of patients in the total safety population of each trial:

MagnetisMM-3 (Elranatamab)[6]		MajesTEC-1 (Teclistamab)[10]	
Median duration of treatment 4.1 months (0.03-14.9)		**Median duration of treatment 8.5 months (0.2 to 24.4)**	
COVID-19	29.3% (15.4% Grade 3/4, 1.6% Grade 5)	Pneumonia	18.2% (12.7% Grade 3/4)
Pneumonia	16.3% (8.1% Grade 3/4)	COVID-19	17.6% (12.1% Grade 3/4, 6.1% Grade 5)
URTI	16.3% (0% Grade 3/4)	Bronchitis	13.3% (0% Grade 3/4)
Sinusitis	10.6% (1.6% Grade 3/4)	URTI	10.9% (0% Grade 3/4)

COVID-19, coronavirus disease 2019; URTI, upper respiratory tract infection.

8.6.4 Adverse events associated with a higher risk of infection

Cytopenias

- Cytopenias with CD3/BCMA 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[13,26]
- BCMA-targeted agents can induce the death of neutrophil cells, resulting in neutropenia and elevated risk of infection

	MagnetisMM-3 (Elranatamab; N=123)[6]	MajesTEC-1 (Teclistamab; N=165)[10]
Neutropenia		
All grades	60 (48.8%)	117 (70.9%)
Grade 3/4	60 (48.8%)	106 (64.2%)
Febrile	4 (2.2%)	4 (2.4%)
Anemia		
All grades	60 (48.8%)	86 (52.1%)
Grade 3/4	46 (37.4%)	61 (37.0%)
Thrombocytopenia		
All grades	38 (30.9%)	66 (40.0%)
Grade 3/4	29 (23.6%)	35 (21.2%)

Hypogammaglobulinemia

- Patients with multiple myeloma may experience hypogammaglobulinemia due to plasma cell aplasia and further depletion of normal plasma cells by targeted therapies[27]
- Low serum IgG levels (<400 g/L), including severe hypogammaglobulinemia (<2 g/L), are common with BCMA-targeted therapy[13,14]
- BCMA-targeted agents can reduce Ig levels, resulting in hypogammaglobulinemia and elevated risk of infection

	MagnetisMM-3 (Elranatamab; N=123)[6]	MajesTEC-1 (Teclistamab; N=165)[10]
Hypogammaglobulinemia		
All grades	138 (75.5%)	123 (74.5%)
Grade 3/4	Not reported	3 (1.8%)

8.6.5 Monitoring, prophylaxis, and treatment modifications for infections during treatment with CD3/BCMA BsAbs

General monitoring strategies

- Check complete blood cell count at baseline and periodically during therapy
- Monitor neutropenic patients for signs of infection and provide supportive care according to current guidelines[4,5]
- Expert recommendations include G-CSF for Grade ≥3 neutropenia[14]
    - Administration should be avoided when the patient is at risk of CRS

Viral infections[14]

	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
BsAb dose modification	Withhold for grade ≥3 infection until resolves to grade 1		
	HBV	**Influenza**	**SARS-CoV-2**
Monitoring	• Screen for core Ab prior to starting treatment, monitor HBV DNA copies in core Ag+ patients	• Direct testing of nasopharyngeal or respiratory secretions by PCR if suspected	• PCR test on nasal, nasopharyngeal, or respiratory secretions if suspected
Prophylaxis	• If core Ab+, administer prophylaxis, or monitor for HBV DNA copies, with pre-emptive antiviral treatment for those with positive DNA tests/viremia. • If sAg+, 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)[28]
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
BsAb dose 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

Ab+, core antibody positive; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HBV, hepatitis B virus; IV, intravenous; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction; sAg+, surface antigen positive; VZV, varicella zoster virus.

Bacterial infections[14]

	Bacterial
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
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
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
BsAb dose modification	• Maintain dosing during prophylaxis • Temporary discontinuation during antibacterial treatment until infection resolution

CT, computed tomography; PET, positron emission tomography.

Fungal infections[14]

	General	Invasive
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
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
Treatment	• Dependent on infectious agent and investigations • Treat as per infectious disease guidelines, and consult with an infectious disease provide	• 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)
BsAb dose modification	• Maintain dosing during prophylaxis • Temporary discontinuation during antifungal treatment until resolution	• Maintain dosing during prophylaxis

BID, twice daily; PJP, *Pneumocystis jirovecii* pneumonia.

Monitoring and management of hypogammaglobulinemia:[4,5]

- Monitor Ig levels during treatment
- Consider subcutaneous or intravenous immunoglobulin for IgG levels ≤4 g/L
- Treat hypogammaglobulinemia according to local institutional guidelines, including infection precautions and antimicrobial prophylaxis

Vaccinations in patients on CD3/BCMA BsAbs[14,28]

- 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

Checklist: Counselling patients to prevent infections while on CD3/BCMA BsAbs[29]

- 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

8.7 Organ dysfunction

8.7.1 Practical considerations for hepatic impairment[4,5]

- 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 pharmacokinetics (PK) of Elranatamab/Teclistamab in population PK analyses
- 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
- No dose adjustments are required for mild hepatic impairment
- 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

9. Acronyms and abbreviations

Ab+	Core antibody positive
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BCMA	B-cell maturation antigen
BID	Bid in diem (twice daily)
BsAb	Bispecific antibody
CAR-T	Chimeric antigen receptor T cell
CD	Cluster of differentiation
CMV	Cytomegalovirus
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common Technology Criteria for Adverse Events
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
DOR	Duration of response
EBV	Epstein Barr virus
FiO_2	Fraction of inspired oxygen
G-CSF	Granulocyte colony-stimulating factor
HBV	Hepatitis B virus
HCP	Healthcare professional
HIV	Human immunodeficiency virus
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Immune effector cell encephalopathy
ICP	Intracranial pressure
ICU	Intensive care unit

Ig	Immunoglobulin
IFN	Interferon
IL	Interleukin
IM	Intramuscular
IMiD	Immunomodulator drug
IV	Intravenous
LOT	Line of therapy
MM	Multiple myeloma
MRD	Minimal residual disease
NaCl	Sodium chloride
NS	Normal saline
O_2	Oxygen
ORR	Objective response rate
PCR	Polymerase chain reaction
PET	Positron emission tomography
PJP	*Pneumocystis jirovecii* pneumonia
PK	Pharmacokinetics
PO	Per os (by mouth)
PR	Partial response
PRN	Pro re nata (as needed)
QxH	Every x hours
QxMIN	Every x minutes
RRMM	Relapsed or refractory multiple myeloma
RT-PCR	Reverse transcriptase polymerase chain reaction
sAg+	Surface antigen positive
SC	Subcutaneous
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
UTI	Urinary tract infection
VGPR	Very good partial response
VZV	Varicella zoster virus

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