Multiple Myeloma Care

Translating Evolving Practices to Oncology Nurses in Community Settings

Preassessment
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Objectives

1. Review evolving treatment options in RRMM and clinical implications
2. Examine how academic and tertiary care centers have integrated new treatments into practice in the setting of RRMM
3. Identify the most common and the unique chronic adverse events associated with long-term treatment of multiple myeloma
4. Describe the core principles surrounding mitigating and managing chronic adverse events in patients being treated in the RRMM setting
5. Outline the expanding roles of nurses, advanced practice providers (APPS), and nurse navigators when patients are treated with newer options in the RRMM setting

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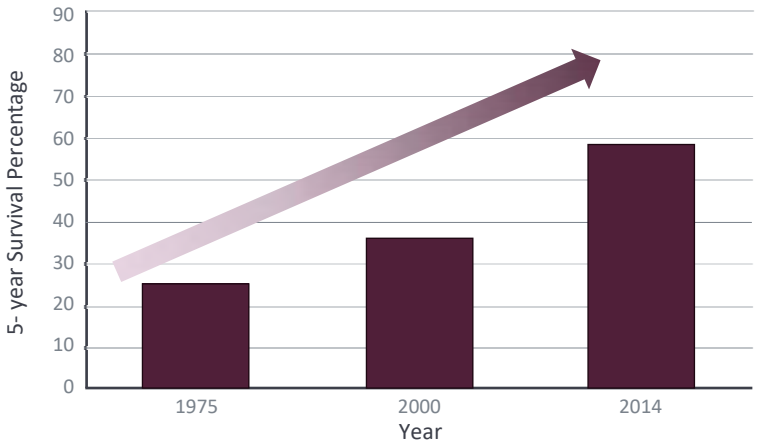
Patients With Multiple Myeloma Are Living Longer Than Ever



≈60%
LIVE MORE THAN
5 YEARS
after their diagnosis[1]

As novel treatments are more broadly adopted into clinical practice, MM management is evolving to comprise long-term patient care and management, which, in turn, is expanding the roles of nurses, nurse navigators, and APPs in the RRMM setting.

1. SEER Cancer Stat Facts: Myeloma. Accessed March 19, 2023. https://seer.cancer.gov/statfacts/html/mulmy.html.

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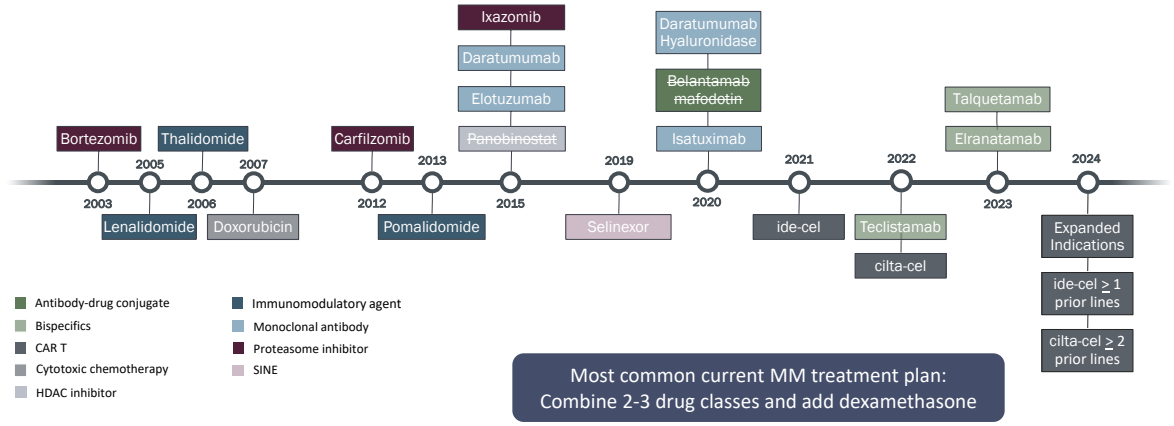
FDA-Approved Therapy for Multiple Myeloma Since 2000



Most common current MM treatment plan:
Combine 2-3 drug classes and add dexamethasone

CAR, chimeric antigen receptor; HDAC, histone deacetylase; MM, multiple myeloma; SINE, selective inhibitor of nuclear transport

Cancer.gov website. Drug therapy for multiple myeloma.

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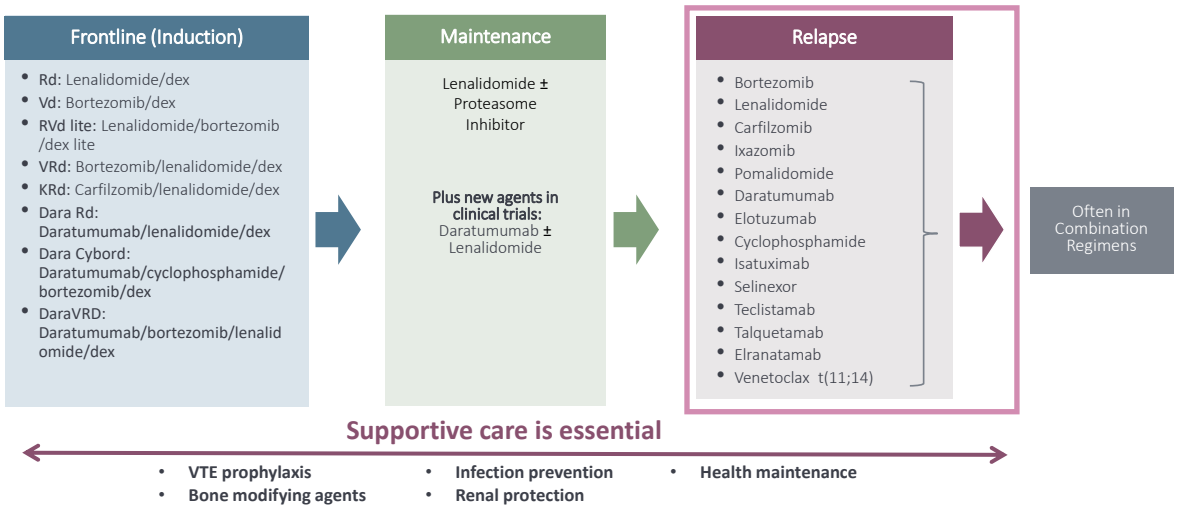
Common Treatments for Multiple Myeloma[1,2]



dex, dexamethasone; VTE, venous thromboembolism

1. Faiman B, et al. *J Adv Pract Oncol.* 2016:7(suppl 1):17-29; 2. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma—v.4.2024.

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NCCN Recommendations for Adjunctive Treatment

Infection
- IVIG for recurrent infections
- Pneumococcal and influenza vaccine
- PJP, herpes and antifungal prophylaxis for high-dose or long-term steroids and teclistamab
- Herpes zoster prophylaxis with proteasome inhibitors, transplant, monoclonal antibodies, bispecific T-cell engagers

Bone disease
- Bisphosphonates, denosumab
- Radiation therapy
- Orthopedic consultation
- Vertebroplasty or kyphoplasty
- Calcium and Vitamin D supplementation

Renal dysfunction
- Avoid aggravating factors: contrast, NSAIDs, dehydration
- Not a contraindication to HCT
- Monitor bisphosphonates closely

Coagulation/thrombosis
- Prophylactic anticoagulation with IMiDs

Hypercalcemia
- Hydration, steroids, furosemide
- Zoledronic acid preferred
- Denosumab, calcitonin

Hyperviscosity
- Plasmapheresis

Anemia
- Consider erythropoietin
- Transfusion
- Type and screen patients prior to daratumumab administration

HCT, hematopoietic stem cell transplantation; ImiD, immunomodulatory drug; IVIG, intravenous immunoglobulin; NSAID, non-steroidal anti-inflammatory drug; PJP, pneumocystis jiroveci pneumonia
NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma—v.4.2024.

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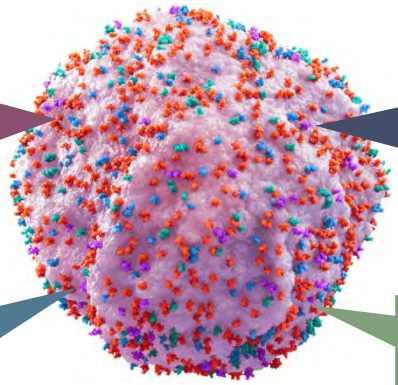
Antigen Targets in Multiple Myeloma (MM)

BCMA[1-3]
Activates signal transduction pathways, upregulates anti-apoptotic proteins, and induces the expression of immunosuppressive molecules to drive MM cell proliferation and survival



SLAMF7[6]
Highly expressed on MM cells
Has a role in interactions between MM and stromal cells, as well as MM growth and survival and regulation of the immune response

GPRC5D[4,5]
G protein-coupled receptor family C group 5 member D (GPRC5D) primarily expressed on myeloma cells, and limited to the hair follicle of skin and hard keratinizing tissues

CD38[7,8]
MM cells express high levels of CD38
Regulates migration and receptor-mediated adhesion and has ectoenzyme activity

SLAMF, signaling lymphocytic activation molecule family

1. D'Agostino M, et al. *Curr Hematol Malig Rep*. 2017;12(4):344-357; 2. Cho SF, et al. *Front Immunol*. 2018;9:1821; 3. Sanchez E, et al. *Br J Haematol*. 2012;158(6):727-738; 4. Mailankody S, et al. *N Engl J Med*. 2022;387:2296-1206; 5. Chari A, et al. *N Engl J Med*. 2022;387:2232-2244; 6. Tai YT, et al. *Blood*. 2008;112(4):1329-1337; 7. Malavasi F, et al. *Physiol Rev*. 2008;88:841-886; 8. Deaglio S, et al. *J Immunol*. 1998;160:395-402.

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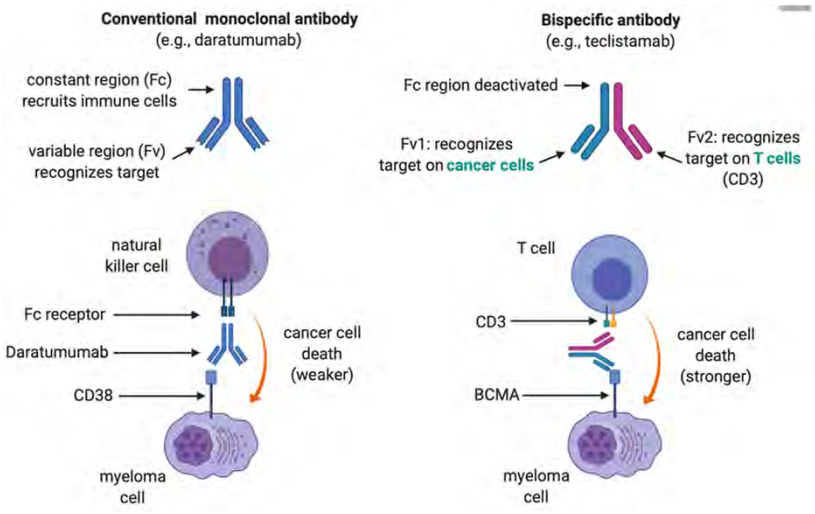
Bispecifics vs Conventional Monoclonal Antibodies



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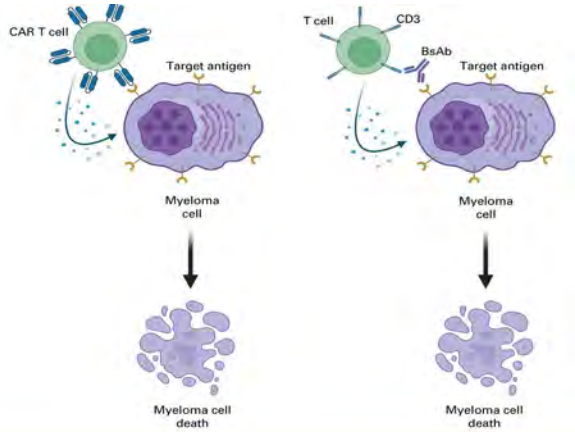
CAR T Cell and Bispecific Antibodies

Mechanism of Action[1]



1. Holstein SA, et al. *J Clin Oncol*. 2023;41(27):4416-4429. Epub 2023 Jul 20.

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FDA-approved T Cell-directed Therapies

Efficacy Data – Registrational Trials[1-3]

Therapy	N	Median Previous Lines of Therapy, No. (range)	Triple Class Refractory, %	Penta-Drug Refractory, %	High-Risk, %	ORR, %	≥CR, %	PFS	DOR	OS
Ide-cel[5]	128	6 (3-16)	84	26	35	73	33	Median 8.8 months	Median 10.7 months	Median 19.4 months
Cilta-cel[3,16,17]	97	6 (4-8)	88	42	24	98	82.5	Median 34.9 months	Median 33.9 months	63% at 3 years
Teclistamab[18]	165	5 (2-14)	78	30	26	63	39.4	Median 11.3 months	Median 18.4 months	Median 18.3 months
Talquetamab	232	6 (2-20)	75 SC 85 IV	25 SC 35 IV	16	63-72	21-28	Not reported	Median 7.8 - 10.2 months	Not reported
Elranatamab	123	5 (2-22)	100	87	25	61	35	Not reached at median follow up of 14.7 months	Not reached at median follow up of 14.7 months	Not reached at median follow up of 14.7 months

The FDA has mandated a black box warning for all marketed CAR-T therapies, citing a potential risk of inducing malignant T-cell tumors.

CR, complete response; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

1. Holstein SA, et al. *J Clin Oncol*. 2023;41(27):4416-4429. Epub 2023 Jul 20; 2. Chari A, et al. *N Engl J Med*. 2022;387:2232-2244; 3. Lesokhin AM, et al. *Nat Med*. 2023;29(9):2259-2267.

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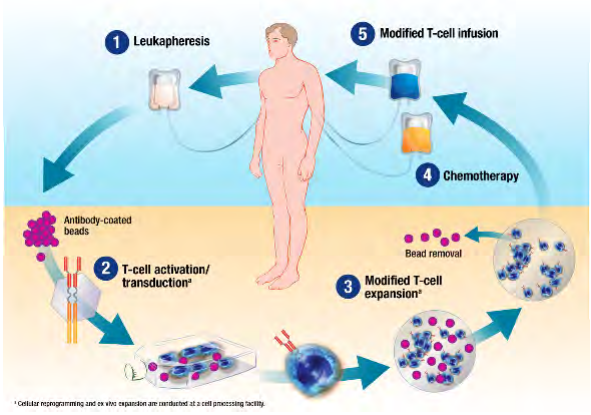
Overview of CAR T Cell Therapy



Manufacturing time can take up to 2-8 weeks

Courtesy of David Porter MD

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Bridging Therapy Goals:

Disease Control and to Decrease Tumor Burden

Regimens
- Steroids (eg, dexamethasone)
- Previous treatment
- Selinexor/pomalidomide/ dexamethasone
- D-PACE or D-ACE
- Salvage auto transplant
- Radiation

Indications
- Control disease/rapidly growing disease
- Bulky disease
- Symptomatic patient (pain)
- Major organ involvement or obstruction
- Expected delay in CAR T cell production

Regimen selection
- Prior therapies
- Regimen-related AEs
- Site(s) of disease
- Comorbidities
- Blood counts
- Simplicity of administration

D-ACE, dexamethasone/doxorubicin/cyclophosphamide/etoposide; D-PACE, dexamethasone/cisplatin/doxorubicin/cyclophosphamide/etoposide

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Lymphodepletion

Lymphodepletion is necessary for expansion of CAR T cells:

- Lymphodepletion creates a "favorable" environment for CAR T cell expansion and survival *in vivo*
- Administered on D-5, D-4, D-3 before CAR T cells are infused on D + 0
  - **Fludarabine 30 mg/m^2** IV daily and **cyclophosphamide 300-500 mg/m^2** IV x 3 days.[1-3]

1. Locke FL, et al. *Lancet Oncol.* 2019;20:31-42; 2. Neelapu SS, et al. *N Engl J Med.* 2017;377:2531-2544; 3. Svaboda J, et al. *Blood.* 2019;134(supp1):1606.

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Premedication and Prophylaxis Considerations[1]

Cell infusion premedication:
Acetaminophen and diphenhydramine (**NO steroids**)

Infection prophylaxis:
- Antiviral
- Antifungal and fluoroquinolone during neutropenic period
- PJP prophylaxis

Seizure prophylaxis may be considered

PJP, pneumocystis jiroveci pneumonia
1. Raje NS, et al. *Lancet Haematol*. 2022;9(2):e143-e161

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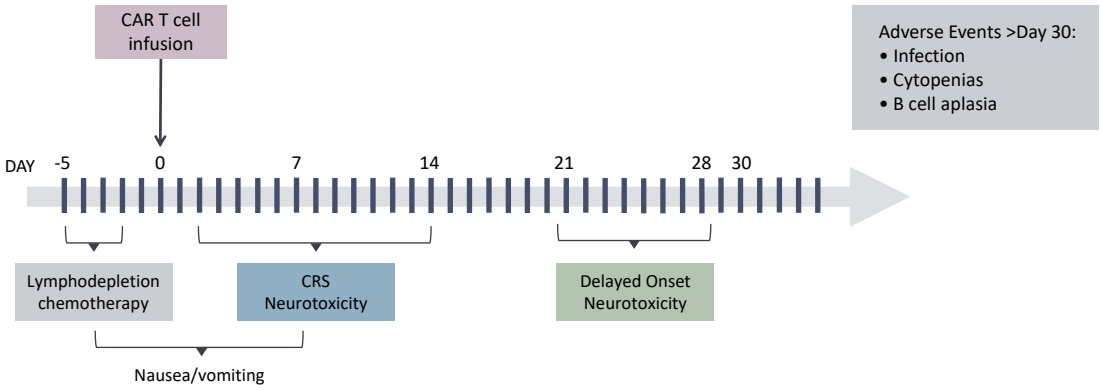
CAR T Adverse Events and Timelines[1,2]



1. Brudno JN, et al. *Blood.* 2016;127:3321-3330; 2. Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018; 15:47-62.

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CAR T-Cell AEs Onset

Acute AEs[1]

- Cytokine-release syndrome
- Immune effector cell–associated neurotoxicity syndrome
- Cytopenias
- Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome

Typically managed by CAR T Cell Center

Delayed AEs[2,3]

- B-cell aplasia/hypogammaglobulinemia
- Prolonged cytopenias
- Late infections
- Long-term neurologic events/ movement and neurocognitive treatment-emergent AEs
- Transient cardiac AEs

Typically managed by primary oncology team

1. Maus MV, et al. *J Immunother Cancer.* 2020;8(2):e001511; 2. Cohen AD, et al. *Blood Cancer J.* 2022;12:32; 3. Chakraborty R, et al. *Transplant Cell Ther.* 2021;27:222-229.

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CRS[1]

Cause: Activation/expansion of CAR T cells increases levels of cytokines (IL-6, IL-15, INF-γ, GM-CSF, others)

Onset: variable; 1 to 5 days

Duration: 3 to 5 days

Risk: Variable up to 5% in >/= grade 3

- Disease burden
- Peak CAR T cell levels
- Pre-treatment and peak cytokine levels

Biochemical Findings:

- Organ-specific markers
  - Creatinine, blood urea nitrogen
  - Troponin
  - Aminotransferases (AST/ALT), bilirubin
- Cytokine panels not readily available for "real-time" clinical use
- Easy to measure surrogates: ferritin, C-reactive protein
  - Trend to monitor the tempo of CRS

In the end, CRS is a clinical, rather than laboratory diagnosis
Cytokine levels do not influence grading or treatment

Teachey DT, et al. *Cancer Discov*. 2016;6:664-679.

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Treatment of CRS: Tocilizumab

Description	Humanized anti-IL-6 receptor $IgG1_{\kappa}$ monoclonal antibody
Mechanism of action	Inhibits IL-6 mediated signaling by binding to both soluble and membrane-bound human IL-6 receptors
FDA Expanded Approval 8/30/17	For the treatment of CAR T cell-induced severe or life-threatening CRS in patients 2 years of age and older
Dose	• Adults: 8 mg/kg once (max dose of 800 mg) • As frequent as every 8 hours, max of 4 doses total
Administration	Intravenous over 1 hour
Required doses	Ensure that 2 doses of tocilizumab are available prior to infusion of CAR T cells
Monitor	• For 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS • Monitor patients for signs or symptoms of CRS for 4 weeks after infusion and if present, seek immediate medicate attention

CAR, chimeric antigen receptor

Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:47-62. Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:218.

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Neurotoxicity Associated with CAR T Therapy[1-4]

Cause: Mechanism of toxicity is not clear

- T cell vs cytokine mediated??
- CAR T cells are seen in the CSF

Onset: 5-7 days after infusion; later than CRS

Duration: 5-10 days

- Fully reversible except in cases of fatal cerebral edema

Risk:

- High disease burden
- High IL-6 on Day 1
- Pre-treatment and peak cytokine levels
- Early or high-grade CRS
- Peak CAR T-cell levels

Neuro assessments

Wide range of symptoms from headache to encephalopathy, seizures

- Decreased attentiveness, anxiety, tremors, somnolence, disorientation, aphasia, nonsensical/tangential speech
- Parkinson-like movement disorders

Treatment:

- No clear response to anti-cytokine therapy
- Use of steroids and anti-seizure medications

CAR, chimeric antigen receptor; CRS, cytokine release syndrome; CSF, cerebrospinal fluid; DIC, disseminated intravascular coagulation

1. Maude SL, et al. *N Engl J Med*. 2014;371(16):1507-1517; 2. Davila ML, et al. *Sci Transl Med*. 2014;6(224):224ra25; 3. Lee DW, et al. *Lancet*. 2015;385(9967):517-528; 4. Kochendorfer JN, et al. *J Clin Oncol*. 2015;33(6):540-549.

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Medications Can Reduce Infection Risk

Type of Infection Risk	Medication Recommendation(s) for Healthcare Team Consideration[1]
Viral: HSV/VZV	Acyclovir prophylaxis
Bacterial: blood, pneumonia, and urinary tract infection	Consider prophylaxis with levofloxacin
PJP (P. jirovecii pneumonia)	Consider prophylaxis with trimethoprim-sulfamethoxazole
Fungal infections	Consider prophylaxis with fluconazole
COVID-19 and Influenza	Antiviral therapy if exposed or positive for COVID per institution recommendations
IgG < 400 mg/dL (general infection risk)	Consider IVIg
ANC < 1000 cells/µL (general infection risk)	Consider GCSF 2 or 3 times/wk (or as frequently as needed) to maintain ANC > 1000 cells/µL and maintain treatment dose intensity

Some people receiving BCMA-targeting therapies have experienced infections that are less common like CMV, PJP, EBV and fungal infections

ANC, absolute neutrophil count; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GCSF, granulocyte colony-stimulating factor; HSV, herpes simplex virus; VZV, varicella zoster virus.

1. Raje NS, et al. *Lancet Haematol*.2022;9(2):143–161.

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Bispecific Treatment Timeline

Week 1: Step-up dosing to mitigate incidence and severity of CRS and neurotoxicity
- Allow 48 hours between doses to assess for emerging CRS or ICANS
- Observation recommended as inpatient during step-up dosing at a REMS certified facility
- Hold dose for evidence of CRS or ICANS or active infection
- Premedicate 1-3 hours prior to all step-up doses and first full dose, or if prior dose was associated with CRS or ICANS
- Recommended pre-medications: glucocorticoid steroid, antihistamine, and antipyretic

- **Week 2 and onward: requires coordination of care with the community team and facility**

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Teclistamab Safety

	Any Grade	Grade 3 or 4
	no. of patients (%)	no. of patients (%)
Neutropenia	118 (71.5)	108 (65.5)
Anemia	90 (54.5)	62 (37.6)
Thrombocytopenia	70 (42.4)	37 (22.4)
Infections	132 (80.0)	91 (55.2)
Cytokine release syndrome	119 (72.1)	1 (0.6)
Diarrhea	56 (33.9)	6 (3.6)
COVID-19	48 (29.1)	35 (21.2)
ICANS	5 (3.03)	0

van de Donk N, et al. J Clin Oncol. 2023;41(November 16_suppl):8011.

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Teclistamab: CRS and ICANS Prevention and Management

- Step-up dosing: 0.06 mg/kg, 0.3 mg/kg, 1.5 mg/kg separated by at least 48 hours
- Hospitalization recommended but may not be essential with robust outpatient monitoring
- Dexamethasone (16 mg), acetaminophen, and diphenhydramine pre-medication before step-up and first full dose.
- Tocilizumab is preferred for CRS management, although tocilizumab is not mentioned in teclistamab's FDA prescribing information or REMS
- Dexamethasone is preferred for ICANS management

Teclistamab PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761291s000lbl.pdf. Accessed May 22, 2024.

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Infections and Hypogammaglobulinemia

- Teclistamab phase 2 (N = 165)[1,2]
  - 80% developed infections, 55.2% grade 3-4
  - 74.5% developed hypogammaglobulinemia (IgG <500 mg/dL)
  - 12 deaths from COVID-19
  - 8 additional deaths from infections including one PML (JC virus)
  - 6 cases of pneumocystis pneumonia
- Talquetamab phase 2 (N = 232)[3]
  - ~40% developed infections, 7% grade 3-4
  - ~80% developed hypogammaglobulinemia
  - 1 fatal infection, and no COVID-19 deaths

Understanding of infection risk evolved during these studies, and many patients did not receive prophylaxis

IgG, immunoglobulin G; JC, human polyomavirus 2; PML, progressive multifocal leukoencephalopathy.

1. Moreau P, et al. *N Engl J Med.* 2022;387:495-505; 2. van de Donk N, et al. *J Clin Oncol*. 2023;41(November 16_suppl):8011; 3. Chari A, et al. *N Engl J Med*. 2022;387:2232-2244.

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Infection Prophylaxis With Bispecifics *

- Herpes zoster prophylaxis (FDA prescribing information)[1]
- Intravenous immune globulin
- Pneumocystis prophylaxis for teclistamab
- Evaluate for CMV reactivation with cytopenias or other suggestive clinical symptoms
- Consider reduction in frequency to Q2W after stable response is achieved[2]

* Will probably be the same for all anti-BCMA bispecific agents

1. Teclistamab PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761291s000lbl.pdf. Accessed May 22, 2024; 2. Usmani SZ, et al. *J Clin Oncol*.2023;41(suppl 16; abstr 8034).

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Management of Oral AEs[1]

Taste Changes
Dexamethasone oral solutions "swish and spit" have been tried but with no proven benefit yet. Sour citrus or candies before meals are also recommended.

Dry Mouth
OTC dry mouth rinse, gel, spray are recommended. Consider saliva substitute. Advise patients to avoid hot beverages.

Dysphagia
Dietary modifications with small bites, eating upright, and sips with food can help manage symptoms.

Glossitis and Thrush
EARLY initiation of nystatin or mycelex is key to manage symptoms.

- **Weight loss and anorexia** are associated with taste changes. **Nutritionist** involvement and dietary modifications are recommended to support patients. An appetite stimulant with Marinol, if indicated, can also be utilized.
- **Education and emotional support are key strategies to manage oral toxicities.**

OTC, over-the-counter

1. Catamero D, Purcell K, Ray C, et al. Presented at the 20th International Myeloma Society (IMS) Annual Meeting Nurse Symposium; September 27–30, 2023; Athens, Greece.

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Management of Dermatological AEs[1]

Dry Skin	Heavy moisturizers
Hand and/or foot peeling	Ammonium lactate 12% lotion to soles and palms BID
Nail thinning and peeling	Nail hardeners, topical vitamin E oil, and triamcinolone 0.025% ointment
Pruritus	Loratadine 10 mg PO daily for 3–5 days post talquetamab dose and triamcinolone 0.1% cream BID
Injection site reaction	
Body rash/ drug rash	Above plus consider methylprednisolone taper and betamethasone 0.05% cream BID

- Consider dose HOLD for other grade 3 dermatologic AEs
- Dermatology consults may be helpful as an early strategy
- **With experience, dermatologic AEs can be managed more easily vs oral AEs**
- These interventions were successful at reducing or resolving dermatologic AEs

1. Catamero D, Purcell K, Ray C, et al. Presented at the 20th International Myeloma Society (IMS) Annual Meeting Nurse Symposium; September 27–30, 2023; Athens, Greece.

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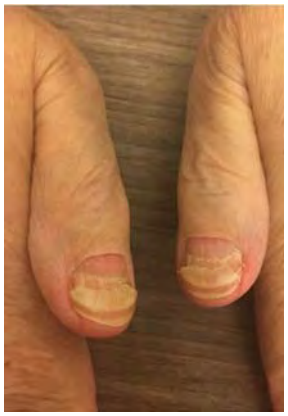
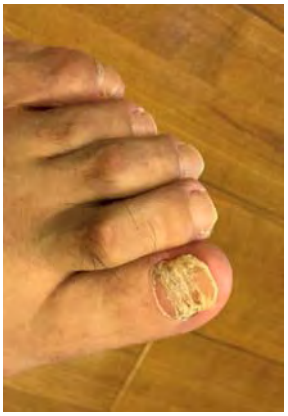
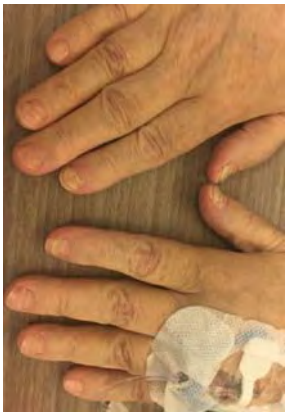
Nail Changes (Associated with Talquetamab – GPRC5D)

Courtesy of Donna Catamaro, CRNP

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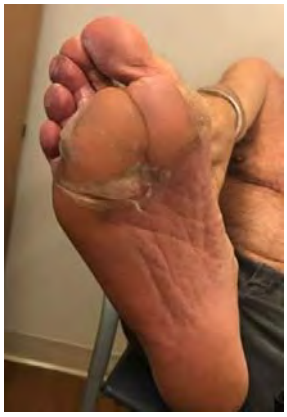
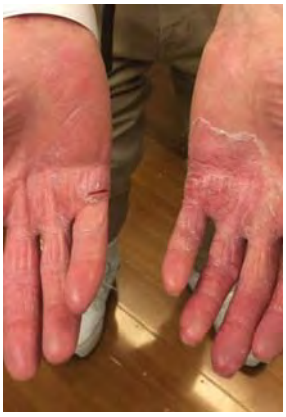
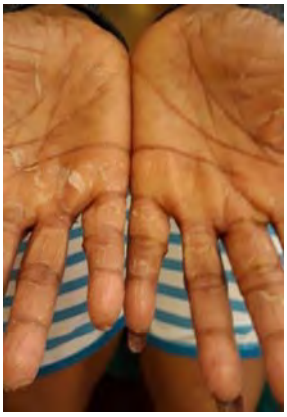
Palmar Plantar Desquamation (Associated with Talquetamab – GPRC5D)

Courtesy of Donna Catamaro, CRNP

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Comparison of Immunotherapy Approaches

	MoABs	CARs	BiTEs
Off-the-shelf	YES	No	Yes
Ease of administration	+++	+	+ to ++
Repeated dosing required	Yes	No	Yes
Dependent on patient T cell "fitness"	No	Yes	Yes
Adverse events	IRR	CRS, neuro	CRS, neuro
Adverse event duration	NA	~14-21 days	Ongoing
Durable clinical activity seen	Yes	Yes	Yes
Requires LD chemotherapy	No	Yes	No

LD, lymphodepleting; IRR, infusion-related reaction; MoAB, monoclonal antibody

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Conclusion

- Significant advances in the treatment of myeloma continue to improve survival
- Highly effective immunotherapies, including CAR T and bispecifics, recently FDA approved for RRMM are showing great promise and are now moving earlier in lines of therapy at relapse.
- Close monitoring and aggressive management of the unique adverse events associated with these T cell-directed therapies is essential
- Adaption of these agents in RR disease is successfully moving to the community setting. Nurses, in community and CAR T centers, are essential in the successful coordination, symptom management and patient/family education.
- Myeloma patients are "Survivors"

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Claim Credit

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Resources

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MM Treatment: Key AEs, Considerations

Drug Class	Name	Key Potential AEs	Nursing Considerations
Proteasome inhibitors	Bortezomib	PN, T, M, F	IV, SC; monitor platelets; safe in renal failure; reduce dose for hepatic disease
	Carfilzomib	C, M, F, DVT, PN	Hydration, cardio/pulmonary; reduce dose for hepatic disease
	Ixazomib	PN, T, GI, R	Reduce dose for hepatic/renal disease
Immunomodulatory agents	Lenalidomide	DVT, M, BD, R, D, rash	ASA if low risk and DOACs and warfarin if high risk for clots; weekly CBC x 8 wks
	Thalidomide	DVT, M, BD, PN, drowsiness	As above
	Pomalidomide	DVT, M, BD, F	As above
Monoclonal antibodies	Daratumumab	IR, M, RD	Infusion reaction risk; pre/post med as directed; interrupt infusion if reaction
	Elotuzumab	IR, M, RD	As above
	Isatuximab	IR, M, RD	As above
	Daratumumab Hyaluronidase	ARR,M, RD	SQ administration over 5 minutes

AE, adverse event; ARR, administration related reaction ; ASA, acetylsalicylic acid; BD, birth defects; C, cardiac; D, diarrhea; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; F, fatigue; GI, gastrointestinal toxicities; IR, infusion reaction; IV, intravenous; LMWH, low molecular weight heparin; M, myelosuppression; MM, multiple myeloma; N, nausea; PN, peripheral neuropathy; R, renal dose adjustment necessary; RD, response disruption; SQ, subcutaneous; T, thrombocytopenia

US Food and Drug Administration. FDA approved drug products.

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MM Treatment: Key AEs, Considerations

Drug Class	Name	Key Potential AEs	Nursing Considerations
Alkylating agents	Melphalan	M, N, D	CBC diff monthly; renal dose adjustment
	Cyclophosphamide	M, N, D	Monitor CBC platelets and differential, antiemetics
Corticosteroids	Prednisone	H, MS	Monitor blood sugar, insomnia, weight gain
	Dexamethasone	H, MS	As above
Selective inhibitors of nuclear export (SINE)	Selinexor	D, N, T, F	Monitor Na+ and intake Prophylactic use of antiemetics

CBC, complete blood count; D, diarrhea; F, fatigue; H, hyperglycemia; M, myelosuppression; MM, multiple myeloma; MS, metabolic syndrome; N, nausea; T, thrombocytopenia

US Food and Drug Administration. FDA approved drug products.

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Options to Consider Regarding 4+ Prior Lines*

	Type of Immunotherapy	Availability/Logistics	Adverse Events
Ide-cel[1]	CAR--T (BCMA)	• Cellular therapy center • Manufacturing slot • Manufacturing time • One-time therapy • REMS and CRS/ICANS management	• CRS/NT (potentially severe) • Infections • Cytopenias (potentially severe)
Cilta-cel[2,3]	CAR-T (BCMA)		
Teclistamab[4,5]	Bispecific (BCMA)	• REMS and CRS/ICANS management • Readily available • Continuous therapy (SQ)	• CRS/NT (unlikely severe) • Infection risk (perhaps higher) • Cytopenias (unlikely severe)
Talquetamab[6] -	Bispecific (GPRC5D)		• CRS/NT • Skin-related events (rash) • Nail-related events • Dysgeusia • Weight loss
Elranatamab[7]	Bispecific (BCMA)		• CRS/NT • Infection risk • Cytopenias

*Ide-cel was recently approved for patients after one or more lines of therapy and cilta-cel after 2 or more lines of therapy.
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; GPRC5D, G protein–coupled receptor class C group 5 member D; ICANS, immune cell-associated neurotoxicity syndrome; NT, neurotoxicity; REMS, Risk Evaluation and Mitigation Strategy; SQ, subcutaneous

1. Munshi NC, et al. *N Engl J Med*. 2021;384:705-716; 2. Berdeja J, et al. *Lancet*. 2021;398:314-324; 3. Lin Y, et al. ASCO 2023, abstract 8009; 4. Moreau P, et al. *N Engl J Med*. 2022;387:495-505; 5. van de Donk N, et al. ASCO 2023, abstract 8011; 6. Chari A, et al. *N Engl J Med*. 2022;387(22):2232-2244; 7. Lesokhin AM, et al. *Nat Med. 2023;*29:2259–2267.

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MM Treatment: Key AEs, Considerations

Drug Class	Name	Key Potential AEs	Nursing Considerations
CAR T	Ide Cel Cilta Cel	C, N, M, I	• REMS • CRS and neurotoxicity • Hospitalize for close monitoring, near facility for one month • Monitor for cytopenias and infections • IVIG may be needed
Bispecifics	Teclistamab Talquetamab Elranatamab	C, N, I	• REMS • CRS and neurotoxicity • Monitor in hospital recommended • Monitor for cytopenias and infection on going • IVIG may be needed • Skin and nail and taste changes (talquetamab)

C, cardiac; I, immune-related AEs; M, myelosuppression; N, neurotoxicity

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CRS Grading: ASTCT Grading Scale[1]

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring vasopressor with or without vasopressin	Requiring multiple vasopressors
		And/Or		
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow cannula, face mask, nonrebreather mask or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure

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

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Management of CRS[1,2]

ASTCT CRS Grade	Management
Grade 1	• Antipyretics and IV hydration • Diagnostic work-up to rule out infection • Antibiotics if neutropenic
Grade 2	• Supportive care as in grade 1 • IV fluid boluses and/or supplemental oxygen • Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Consider monitoring in ICU • Vasopressor support and/or supplemental oxygen • Tocilizumab + dexamethasone 10 mg to 20 mg IV every 6 hours or its equivalent of methylprednisolone
Grade 4	• Supportive care as in grade 1 • Monitoring in ICU • Vasopressor support and/or supplemental oxygen via positive pressure ventilation • Tocilizumab + methylprednisolone 1,000 mg/day • Refractory CRS: anakinra, siltuximab, dasatinib, ruxolitinib, etanercept

ICU, intensive care unit; IV, intravenous

1. Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47-62; 2. Neelapu SS. *Hematol Oncol*. 2019;37:48-52.

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Treatment of CRS: Tocilizumab

Description	Humanized anti-IL-6 receptor $IgG1_{\kappa}$ monoclonal antibody
Mechanism of action	Inhibits IL-6 mediated signaling by binding to both soluble and membrane-bound human IL-6 receptors
FDA Expanded Approval 8/30/17	For the treatment of CAR T cell-induced severe or life-threatening CRS in patients 2 years of age and older
Dose	• Adults: 8 mg/kg once (max dose of 800 mg) • As frequent as every 8 hours, max of 4 doses total
Administration	Intravenous over 1 hour
Required doses	Ensure that 2 doses of tocilizumab are available prior to infusion of CAR T cells
Monitor	• For 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS • Monitor patients for signs or symptoms of CRS for 4 weeks after infusion and if present, seek immediate medicate attention

CAR, chimeric antigen receptor

Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47-62. Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15:218.

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ICANS Assessment: What is Your ICE Score?

Orientation	Orientation to year, month, city, hospital: 4 points
Following commands	Ability to follow simple commands: 1 point
Naming	Ability to name 3 objects: 3 points
Writing	Ability to write a standard sentence: 1 point
Attention	Ability to count backwards from 100 by 10: 1 point

Grade 1: 7-9 points; Grade 2: 3-6; Grade 3: 0-2; Grade 4: unarousable, unable to complete assessment [1]

ICE, immune effector cell-associated encephalopathy

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

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ICANS Assessment[1]

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (unable to perform)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable, requires vigorous or repetitive stimuli to arouse. Stupor or coma.
Seizure	N/A	N/A	Any clinical seizure that resolves rapidly or nonconvulsive seizures on EEG that resolve without intervention	Life-threatening prolonged seizure; or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging, papilledema

EEG, electroencephalogram

1. Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625-38.

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ICANS Management

ASTCT ICANS Grade	Management
Grade 1	• Aspiration precautions and IV hydration • Seizure prophylaxis and levetiracetam • EEG • Image of brain • Consider tocilizumab
Grade 2	• Supportive care as in grade 1 • Consider dexamethasone or its equivalent of methylprednisolone
Grade 3	• Supportive care as in grade 1 • Dexamethasone 10 mg to 20 mg IV every 6 h or its equivalent of methylprednisolone • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • High-dose methylprednisolone 1000 mg/day for focal/local edema
Grade 4	• Supportive care as in grade 1 • High-dose methylprednisolone 1000 mg/day • Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide • Imaging of spine for focal motor weakness • For diffuse cerebral edema, lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt

ICP, intracranial pressure

Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15:47-62. Neelapu SS. *Hematol Oncol.* 2019;37:48-52.

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Medications Can Reduce Infection Risk

Type of Infection Risk	Medication Recommendation(s) for Healthcare Team Consideration[1]
Viral: HSV/VZV	Acyclovir prophylaxis
Bacterial: blood, pneumonia, and urinary tract infection	Consider prophylaxis with levofloxacin
PJP (P. jirovecii pneumonia)	Consider prophylaxis with trimethoprim-sulfamethoxazole
Fungal infections	Consider prophylaxis with fluconazole
COVID-19 and Influenza	Antiviral therapy if exposed or positive for covid per institution recommendations
IgG < 400 mg/dL (general infection risk)	Consider IVIg
ANC < 1000 cells/µL (general infection risk)	Consider GCSF 2 or 3 times/wk (or as frequently as needed) to maintain ANC > 1000 cells/µL and maintain treatment dose intensity

Some people receiving BCMA-targeting therapies have experienced infections that are less common like CMV, PJP, EBV and fungal infections

ANC, absolute neutrophil count; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GCSF, granulocyte colony-stimulating factor; HSV, herpes simplex virus; VZV, varicella zoster virus.

1. Raje NS, et al. *Lancet Haematol.*2022;9(2):143–161.

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Comparison of Immunotherapy Approaches

	MoABs	CARs	BiTEs
Off-the-shelf	YES	No	Yes
Ease of administration	+++	+	+ to ++
Repeated dosing required	Yes	No	Yes
Dependent on patient T cell "fitness"	No	Yes	Yes
Adverse events	IRR	CRS, neuro	CRS, neuro
Adverse event duration	NA	~14-21 days	Ongoing
Durable clinical activity seen	Yes	Yes	Yes
Requires LD chemotherapy	N0	Yes	No

LD, lymphodepleting; IRR, infusion-related reaction; MoAB, monoclonal antibody

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MM Treatment: Key AEs, Considerations

Drug Class	Name	Key Potential AEs	Nursing Considerations
CAR T	Ide Cel Cilta Cel	C, N, M, I	• REMS • CRS and neurotoxicity • Hospitalize for close monitoring, near facility for one month • Monitor for cytopenias and infections • IVIG may be needed
Bispecifics	Teclistamab Talquetamab Elranatamab	C, N, I	• REMS • CRS and neurotoxicity • Monitor in hospital recommended • Monitor for cytopenias and infection on going • IVIG may be needed • Skin and nail and taste changes (talquetamab)

C, cardiac; I, immune-related AEs; M, myelosuppression; N, neurotoxicity

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