

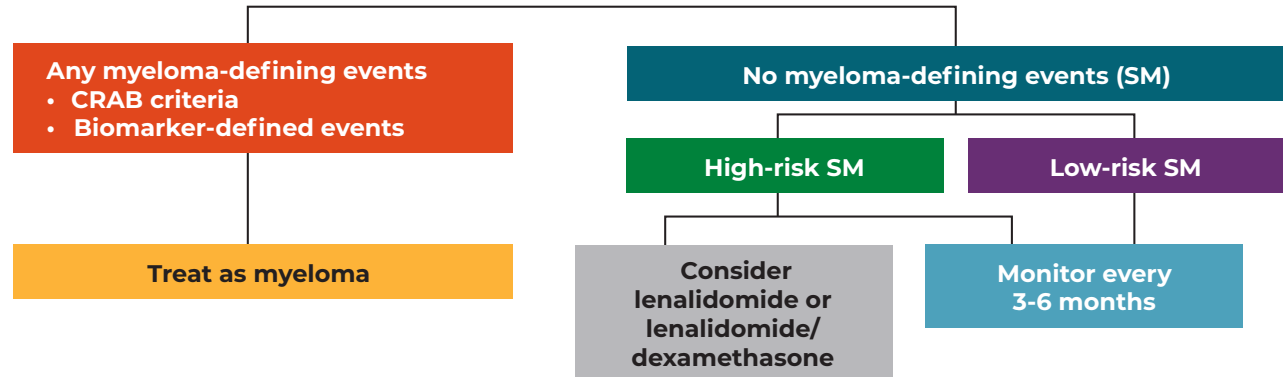
Multiple Myeloma Diagnosis and Treatment for 2023



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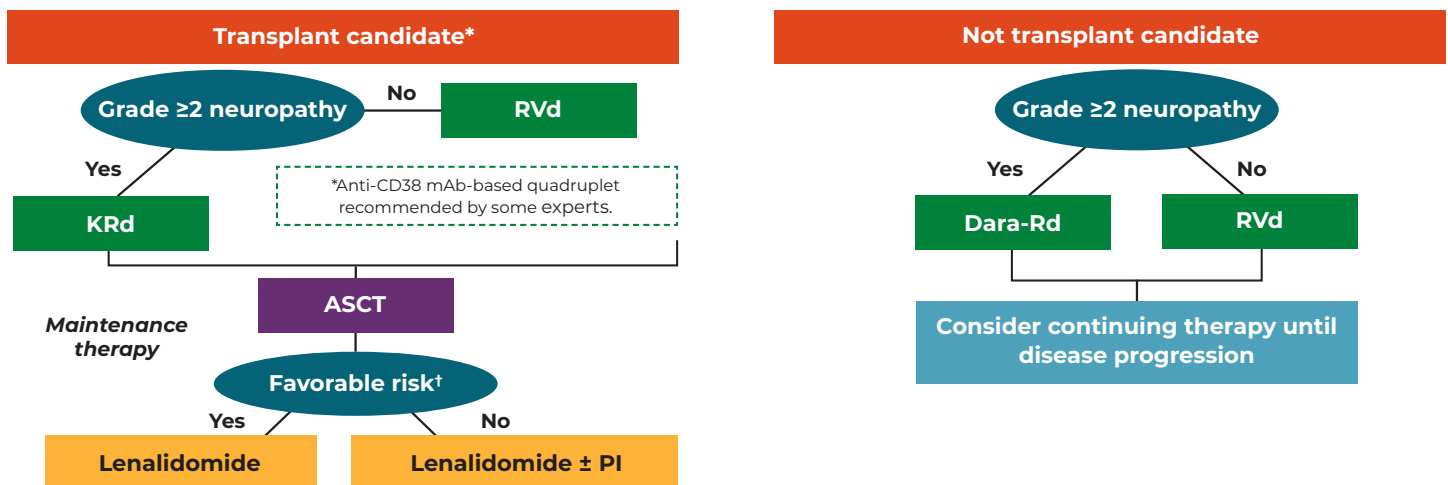
Potential New Myeloma or Smoldering Myeloma^{1,2}

- Clinical trials are always an option



Newly Diagnosed Multiple Myeloma^{1,2}

- Clinical trials are always an option



†Risk assessment including R-ISS, cytogenetic abnormalities, measure of monoclonal protein, and other risk factors.

Trials With Anti-CD38 mAb Added to Induction Therapy in Newly Diagnosed Transplant-Eligible Myeloma³⁻⁷

Trial	Phase (N)	Induction and Consolidation Arms	Maintenance Arms	Results of Primary Endpoint
CASSIOPEIA	III (1085)	Dara-VTd vs VTd	Dara vs observation	sCR 100 days after ASCT: 29% vs 20% ($P = .0010$)
GRIFFIN	II (207)	Dara-RVd vs RVd	Dara-R vs R	sCR at final analysis: 67% vs 48% ($P = .068$)*
GMMG-HD7	III (662)	Isa-RVd vs RVd	Isa-R vs R	MRD negativity after induction: 50% vs 36% ($P = .00017$)
GMMG-CONCEPT	II (125)	Isa-KRd in TE and TNE patients	Isa-KRd	MRD negativity after induction: 67.7% in TE patients and 54.2% in TNE patients

*Statistically significant at preset 1-sided α of 0.10.

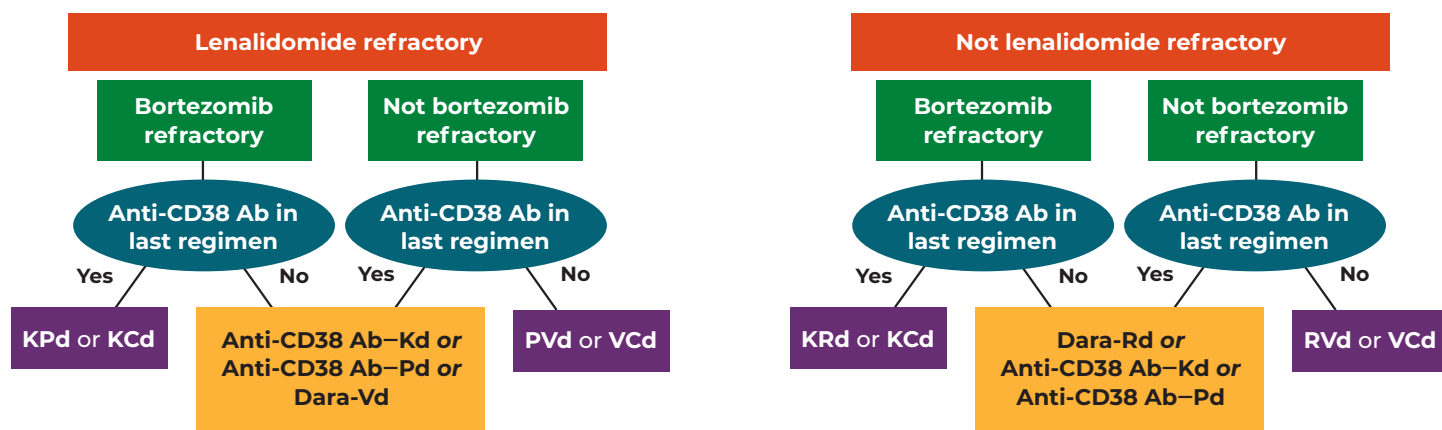
- CASSIOPEIA and GMMG-HD7 are 2-part trials with rerandomization for maintenance
- In GRIFFIN trial, Dara-RVd arm received Dara-based maintenance
- Daratumumab is approved in combination with Rd in patients with newly diagnosed MM ineligible for ASCT or in patients with relapsed or refractory MM after ≥ 1 prior therapy

Select Adverse Events and Prophylaxis by Drug Class^{1,7,8-11}

Proteasome Inhibitors	Immunomodulatory Agents	Anti-CD38 Monoclonal Antibodies	Corticosteroids
• Herpes zoster prophylaxis • Peripheral neuropathy (bortezomib) • Monitor/manage cardiac conditions carefully (carfilzomib) • Thromboprophylaxis (carfilzomib)	• Prophylactic anticoagulation ◦ 81-mg aspirin for patients with no risk factors ◦ Warfarin or LMWH for higher-risk individuals ◦ Possible role for DOACs • 2 birth control methods required • Cytopenias	• Premedicate with corticosteroids, antipyretics, and antihistamines prior to daratumumab • Herpes zoster prophylaxis • Consider <i>Pneumocystis jirovecii</i> pneumonia prophylaxis per institutional practice • Interference with blood typing and response monitoring	• Hyperglycemia • Fatigue • Hyperactivity • Infection risk • Muscle wasting

Multiple Myeloma Selected Second-line Alternatives^{1,2}

- Clinical trials are always an option

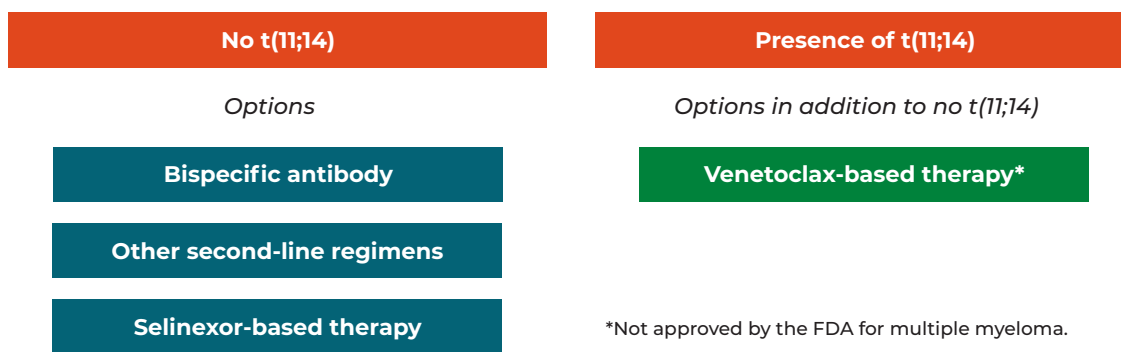


- Other alternatives in this setting include Elo-Pd, Ixa-Pd, and Selinexor-Vd

If candidate, consider ASCT

Multiply Relapsed Multiple Myeloma^{1,2}

- If patient is penta refractory or triple-class refractory and is a candidate, refer for anti-BCMA CAR T-cell therapy
- Following shared decision-making and assessment of comorbidities:



*Not approved by the FDA for multiple myeloma.

- Clinical trials are always an option

Currently Approved Options in R/R Multiple Myeloma¹²⁻¹⁷

Agent	Type	Indication(s) in R/R Multiple Myeloma
Idecabtagene vicleucel	BCMA CAR T-cell therapy	After ≥4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
Ciltacabtagene autoleucel	BCMA CAR T-cell therapy	After ≥4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
Teclistamab	Bispecific antibody to BCMA x CD3	After ≥4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
Elranatamab	Bispecific antibody to BCMA x CD3	After ≥4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
Talquetamab	Bispecific antibody to GPRC5D x CD3	After ≥4 prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
Selinexor	Exportin 1 inhibitor	In combination with Vd in adults who have received ≥1 prior therapy In combination with dexamethasone after ≥4 therapies and disease refractory to ≥2 PIs, ≥2 IMiDs, and an anti-CD38 mAb

Studies of Approved Options for Patients After ≥4 Prior Therapies¹⁸⁻²¹

Agent	Trial Phase	Patients, n	ORR, %	Median PFS, Mo	Median OS, Mo	CRS, % Any Grade	NT, % Any Grade
Selinexor	II	122	26	3.7	8.6	NA	NA
Idecabtagene vicleucel	II	128	73	8.8	24.8	84	18
Ciltacabtagene autoleucel	Ib/II	97	98	NR	NR	95	22
Teclistamab	I/II	165	63	11.3	18.3	72.1	14.5
Elranatamab	II	123	61	NR	NR	57.7	3.4*
Talquetamab	I/II	0.4 mg/kg QW: 143 0.8 mg/kg Q2W: 145	74 72	NR	NR	79 74.5	10.7* 11.0*

*ICANS.

Management of CRS With CAR T-Cell Therapy and Bispecific Antibody Therapy^{12-16,22}

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

Grade	CAR T-Cell Therapy	Bispecific Antibody Therapy
	Supportive Care + Intervention	Supportive Care + Intervention
1	± tocilizumab*	Withhold until CRS resolution and administer pretreatment medications prior to next dose
2	Tocilizumab ± corticosteroid	Grade 1 interventions + 48-hour hospitalization following next dose according to institutional and manufacturer guidelines
3	Tocilizumab + corticosteroid	<i>First grade 3 occurrence with duration ≤48 hours:</i> grade 2 interventions + ICU/critical care as needed <i>Recurrent grade 3 or grade 3 with duration >48 hours:</i> grade 4 interventions
4	Tocilizumab + high-dose corticosteroid ICU/critical care	Permanently discontinue; provide ICU/critical care as needed

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

Management of Neurologic Toxicity and ICANS With CAR T-Cell and Bispecific Antibody Therapy^{12-16,23-24}

Grade	CAR T-Cell Therapy		Bispecific Antibody Therapy	
	Neurotoxicity	CRS + Neurotoxicity	Neurologic Toxicity Excluding ICANS	ICANS
1	Supportive care ± steroids	Supportive care ± tocilizumab*	Withhold until symptoms resolve or stabilize	Withhold until resolution
2	Steroids (dexamethasone or methylprednisolone)	Tocilizumab + steroids (dexamethasone)	Withhold until symptoms improve to grade ≤1	Withhold until resolution + steroids + 48-hour hospitalization with next dose
3	Steroids (dexamethasone)	Tocilizumab + steroids (dexamethasone)	<i>First occurrence:</i> grade 2 actions + supportive therapy <i>Recurrence:</i> grade 4 actions	<i>First occurrence:</i> grade 2 actions + supportive therapy + steroids <i>Recurrence:</i> grade 4 actions + steroids
4	High-dose steroids (methylprednisolone) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone) ICU/critical care	Permanently discontinue + steroids (dexamethasone or methylprednisolone) ICU/critical care	

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

Add anticonvulsants (levetiracetam, benzodiazepines)
Low threshold for inpatient management (if outpatient at time of onset)
Multidisciplinary team approach

Infection Prophylaxis and Vaccinations With CAR T-Cell Therapy and Bispecific Antibody Therapy^{12-16,19,25-30}

Toxicity, %	Ide-Cel	Cilta-Cel	Teclistamab	Elranatamab	Talquetamab
Infections (bacterial, viral, fungal)	69	58	80	70	62
Hypogammaglobulinemia	21	12	21	13	Not reported
Grade ≥3 neutropenia	89	95	64	64	35

- Complete outstanding vaccinations at least 2 weeks prior to starting CAR T-cell therapies or bispecific antibodies (eg, influenza, pneumococcal, COVID-19)
- Delay postinfusion vaccinations for at least 3-6 months (1 year for live)
- Consider checking antibody titers

Antibacterial Prophylaxis	Antiviral Prophylaxis	Antifungal Prophylaxis
Recommend for patients with high risk of infection	HSV/VZV prophylaxis in all patients	• PJP prophylaxis recommended • Other antifungal prophylaxis recommended for patients with high risk of fungal infection

Supportive Care Principles for Patients With Multiple Myeloma^{1,31-33}

Thromboembolic Events	Infection	Bone Health
• May occur when receiving IMiDs: ◦ Low risk (<2 risk factors*): low-dose aspirin (81 mg) ◦ High risk (≥2 risk factors*) or IMiD + high-dose Dex: LMWH or therapeutic warfarin (target INR 2-3) • Educate patients on preventive strategies and early detection • Can consider DOACs, but not well studied in this population	• Stay current on appropriate vaccinations, including COVID-19 and annual influenza vaccine • Herpes prophylaxis when receiving Pls, mAbs, and CAR T-cell or BsAb therapy; consider PJP prophylaxis if using high-dose Dex • Antibacterial and antifungal prophylaxis while neutropenic after CAR T-cell or BsAb therapy • Consider IVIG for recurrent, life-threatening infections	• All patients should receive bisphosphonates or denosumab • Bisphosphonates: pamidronate and zoledronic acid (greater risk for ONJ with zoledronic acid; monitor for renal impairment on bisphosphonates) • SC denosumab preferred when renal disease is present • Baseline dental exam and ONJ monitoring while using bone-modifying therapy

*Risk factors include older age, history of thrombotic event, BMI ≥30 kg/m², prior central venous catheter or pacemaker, immobilization, CV/renal disease, diabetes, trauma, blood clotting disorders, hyperviscosity, acute infection.

Selinexor	Venetoclax
• Thrombocytopenia, neutropenia: Consider platelet transfusion/growth factor support as needed • Gastrointestinal toxicity ◦ 5-HT₃ antagonist ± olanzapine ◦ Antidiarrheal agents and IV fluids • Hyponatremia: Monitor sodium throughout treatment • Infections: Monitor white blood cell count; consider antimicrobials	• Toxicities: diarrhea, nausea, constipation, cough, and cytopenias • Prophylactic antibiotics ◦ PJP ◦ Antibacterial ◦ Antiviral • Tumor lysis prophylaxis ◦ Consider allopurinol • Monitor for infections • Monitor outpatient for blood counts and tumor lysis syndrome • Avoid moderate or strong CYP3A4 inhibitors (prolong bioavailability of venetoclax) such as clarithromycin, grapefruit

Ab, antibody; ASCT, autologous stem cell transplant; BsAb, bispecific antibody; Cilta-cel, ciltacabtagene autoleucel; CRAB, calcium elevation, renal insufficiency, anemia, bone abnormalities; CRS, cytokine-release syndrome; CV, cardiovascular; Dara, daratumumab; Dex, dexamethasone; DOAC, direct oral anticoagulant; Elo, elotuzumab; HSV, herpes simplex virus; ICANS, immune effector cell–associated neurotoxicity syndrome; Ide-cel, idecabtagene vicleucel; IMiD, immunomodulatory agent; INR, international normalized ratio; Isa, isatuximab; IVIG, IV immunoglobulin; Ixa, ixazomib; KCd, carfilzomib/cyclophosphamide/dexamethasone; Kd, carfilzomib/dexamethasone; KPd, carfilzomib/pomalidomide/dexamethasone; KRd, carfilzomib/lenalidomide/dexamethasone; LMWH, low-molecular-weight heparin; mAb, monoclonal antibody; MRD, measurable residual disease; NA, not applicable; NR, not reached; NT, neurotoxicity; ONJ, osteonecrosis of the jaw; ORR, overall response rate; OS, overall survival; Pd, pomalidomide/dexamethasone; PFS, progression-free survival; PI, proteasome inhibitor; PJP, pneumocystis jirovecii pneumonia; Pvd, pomalidomide/bortezomib/dexamethasone; R, lenalidomide; R-ISS, Revised International Staging System; R/R, relapsed/refractory; Rd, lenalidomide/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; sCR, stringent complete response; SM, smoldering myeloma; TE, transplant eligible; TNE, transplant noneligible; Vcd, bortezomib/cyclophosphamide/dexamethasone; Vd, bortezomib/dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; VZV, varicella virus.

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