NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the Diagnosis and Treatment of Multiple Myeloma (MM)

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The diagnosis of **symptomatic MM** requires the following clinical findings[1]:

- Clonal bone marrow plasma cells (BMPCs) ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:



Hypercalcemia
Serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)



Renal insufficiency
Creatinine clearance <40 mL per min or serum creatinine >177 µmol/L (>2 mg/dL)



Anemia
Hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L



Bone lesions
One or more osteolytic lesion(s) on skeletal radiography, CT, or PET-CT

  - Any one or more of the following biomarkers of malignancy:
    - Clonal BMPC percentage ≥60%
    - Involved:uninvolved serum free light chain ratio ≥100
    - >1 focal lesions on MRI studies

- Following diagnosis of symptomatic MM, primary myeloma therapy is initiated, along with bone-targeting treatment and supportive care treatment for symptom management
- Patient transplant candidacy is assessed, with reassessments for transplant as performance status improves
  - Refer to hematopoietic cell transplant (HCT) center
  - Harvest hematopoietic stem cells (consider for 2 transplants if appropriate)

Principles of T-cell redirecting therapy

General Principles

- Treatment selection should be individualized based on disease characteristics, patient comorbidities and social circumstances, urgency of intervention, and available healthcare infrastructure
- All patients with myeloma should be referred to a T-cell therapy capable center at time of first relapse for consideration of available therapies
- For patients with clinical relapse, consider starting therapy that will not compromise T-cell fitness, such as alkylator therapy
- When both BCMA CAR-T-cell therapy and BCMA TCEs are viable options, current data suggest that CAR-T-cell is preferred given the established efficacy of TCE following CAR-T-cell therapy failure[2]
- If sequencing BCMA-targeted therapies, a TFI of at least 6 months from prior BCMA-directed therapy is associated with improved response rates[3]
- Infections remain the most common cause of non-relapse mortality, and prophylaxis is crucial[4,5]
  - Prophylaxis for VZV/HSV, PJP, antibacterial and anti-fungal when ANC <500 (units), HBV/CMV screening, and IVIG prophylaxis
- Avoid bendamustine or high-dose alkylator therapy prior to TCR therapy[2]
- Prophylactic tocilizumab can be utilized to reduce risk of CRS[6]

Bridging Therapy

- T-cell health at the time of leukapheresis is a critical determinant of CAR-T product quality and efficacy. CD4+ CAR-T cell exhaustion has been directly linked to early relapse after BCMA-directed CAR-T therapy.[7] The selection of bridging therapy should be individualized based on disease burden, pace of progression, and prior treatment history:
  - Hold therapy for 2 to 3 weeks prior to apheresis where feasible
  - Avoid high-dose corticosteroids for at least 1 week prior to leukapheresis
  - When selecting bridge therapy, prioritize agents that preserve T-cell fitness (avoid alkylator-based therapies such as bendamustine if possible)
  - Regimens combining anti-myeloma classes of drugs that patients are not refractory to are preferred
  - Talquetamab can be considered as an effective bridging option prior to CAR-T-cell therapy for triple-class refractory patients[8]

CAR-T-cell Therapy

- Minimize prior BCMA-directed therapies in patients planning to receive BCMA CAR-T-cell therapy
- When possible, avoid TCE prior to T-cell collection[2]
- Avoid BCMA TCE as bridging therapy prior to BCMA CAR-T-cell therapy
- Good response to bridging therapy does not obviate the need for CAR-T-cell therapy
- CAR-T-cell infusion in the setting of high disease burden can be associated with more severe CRS and neurotoxicity and bridging therapy is strongly recommended[9]

T-cell Engagers

- For patients with rapidly progressive disease, use of TCE recommended due to faster access[2]
- If being utilized as bridging, T-cell collection prior to TCE initiation is preferred[2]
- Bispecific antibodies have improved safety profile with regard to high-grade CRS and ICANS

ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; CMV, cytomegalovirus; CRS, cytokine release syndrome; CT, computed tomography; HBV, hepatitis B virus; HSV, herpes simplex virus; ICANS, immune effector cell–associated neurotoxicity syndrome; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; PJP, *Pneumocystis jirovecii* pneumonia; TCE, T-cell engager; TCR, T-cell receptor; TFI, treatment-free interval; VZV, varicella-zoster virus.

1. Rajkumar SV, et al. *Lancet Oncol.* 2024;15:e538-e548. 2. Costa LJ, et al. *Leukemia.* 2025;39:543-554. 3. Sidana S, et al. *Blood.* 2025;145:85-97. 4. Raje N, et al. *Blood Cancer J.* 2023;13:116. 5. Rodriguez-Otero P, et al. *Lancet Oncol.* 2024;25:e205-e216. Erratum in: *Lancet Oncol.* 2024;25:e284. Erratum in: *Lancet Oncol.* 2025;26:e186. 6. Kowalski A, et al. *Blood Adv.* 2025;9:4979-4986. 7. Ledergor G, et al. *Blood Adv.* 2024;8:3562-3575. 8. Dhakal B, et al. *Blood.* 2025;146:2063-2072. 9. Freeman CL, et al. *Blood.* 2025;145:1645-1657.
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NCCN Guidelines® for the Diagnosis and Treatment of Multiple Myeloma (MM) (cont'd)

1L — Primary therapy for HCT candidates and those in whom HCT is deferred

Suggested treatment regimens*

Preferred

- D-VRd (NCCN category 1)
- Isa-VRd (category 1)

Other recommended

- Isa-KRd (category 1)
- D-KRd

Useful in certain circumstances

- VCd†
- D-VCd†
- D-VCRd† (for high-risk and PCL)
- VRd (category 1)
- KRd
- KCd†
- VTd-PACE‡

Maintenance therapy§

Preferred

- Lenalidomide‖ (category 1)

Other recommended

- KR (category 1)§,‖
- DR§,‖

Useful in certain circumstances

- V ± R (category 1)§,‖
- Daratumumab (category 1)
- Ixazomib (category 2B)

1L — Primary therapy if HCT is not indicated

Suggested treatment regimens*,¶

In general, continue primary therapy until progression with de-escalation of therapy (modification of dose and duration) as needed.

Preferred

- D-VRd (for patients <80 years old who are not frail) (category 1)
- Isa-VRd (for patients <80 years old who are not frail) (category 1)
- DRd (category 1)#

Other recommended

- VRd (category 1)
- KRd
- Isa-Rd

Useful in certain circumstances

- R + low-dose dexamethasone (category 1)
- VCd†
- Vd
- VRd-lite for patients assessed as being frail
- KCd†
- D-VCd†
- Isa-KRd (category 2B)
- IRd
- RCd

2L- 4L — Relapsed/Refractory MM after 1-3 prior therapies

Suggested treatment regimens*,**,††,‡‡,§§

Preferred

(Order of regimens does not indicate comparative efficacy)

T-cell redirection therapy‖‖

***CAR-T-cell therapy*¶¶**

- Cilta-cel (category 1)

Anti-BCMA therapy:

- Teclistamab-cqyv ± D## (category 1)

Anti-CD38-refractory

- KRd (category 1)
- KPd

Bortezomib-refractory

- KRd (category 1)
- DKd (category 1)
- Isa-Kd (category 1)
- DRd (category 1)
- Isa-Rd (category 1)
- DPd (category 1)
- Isa-Pd (category 1)
- KPd

Lenalidomide-refractory

- Bela-maf + Vd‖ (category 1)
- DVd (category 1)
- DKd (category 1)
- Isa-Kd (category 1)
- DPd (category 1)
- Isa-Pd (category 1)
- KPd

Other recommended

- PVd (category 1)
- SVd (category 1)
- PCd (category 1)
- D + talquetamab-d## (category 1)
- Ide-cel (category 1)
- IRd (category 1)
- ERd (category 1)
- Talquetamab + DPd## (category 1)
- EVd
- VCd
- D-VCd
- VRd
- KCd
- D-KPd
- RCd
- D + iberdomide-d
- ICd
- IPd
- EPd

HCT as indicated

- Autologous HCT
- Allogeneic HCT
  - Donor lymphocyte infusion can be considered in patients with disease relapse after allogeneic HCT

Useful in certain circumstances

- Vd (category 1)
- Kd (category 1)
- Rd (category 1)
- Pd (category 1)
- Bela-maf + Pd (category 1)
- KCTd
- KSd
- Kd + Bela-maf
- Daratumumab
- SPd
- DSd
- Venetoclax-d ± D or PI (only for patients with t(11;14))

For treatment of aggressive MM

- DCEP
- Td-PACE ± V
- Talquetamab-tgvs + teclistamab-cqyv##

NOTE: All therapy recommendations are category 2A unless otherwise indicated.

*Selected but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus. †Treatment option for patients with renal insufficiency and/or peripheral neuropathy. ‡Generally reserved for the treatment of aggressive MM. §Two-drug maintenance recommended for high-risk MM. ‖There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy versus secondary cancers should be discussed with patients. ¶Quadruplet regimen is preferred. Based on functional status, patients may be started with a 2- or 3-drug regimen with additional drugs added as performance status improves. #Consider early discontinuation of dexamethasone for older patients. **Regimens included under 1-3 prior therapies can also be used later in the disease course. Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior. ††Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT. ‡‡In order to maximize benefit of systemic therapy, agents/regimens may be reconsidered or repeated if relapse is after at least 6 months of stopping therapy. §§Alkylating agents can impact the ability to collect T cells for CAR-T-cell therapy. ‖‖Optimal sequencing of BCMA therapies is still under investigation. ¶¶Talquetamab-tgvs may be considered as a bridge to BCMA CAR-T therapy in relapsed and/or refractory multiple myeloma. ##Prophylactic tocilizumab may be considered prior to first dose to reduce the risk of CRS. ***Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

1L, first-line; 2L, second-line; 4L, fourth-line; NCCN, National Comprehensive Cancer Network; PCL, plasma cell leukemia.

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NCCN Guidelines for the Diagnosis and Treatment of Multiple Myeloma (MM) (cont'd)

4L+ — Relapsed/Refractory MM after ≥3 prior therapies

Suggested treatment regimens[*,†,‡,§,‖]

- Regimens included under 1-3 prior therapies can also be used later in the disease course
- Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior
- Combinations containing anti-CD38 should be considered if >6 months since last CD38 targeting

Preferred[¶]

CAR-T-cell therapy[#]

- Cilta-cel
- Ide-cel

After at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD

Bispecific antibodies**

BCMA-targeted:

- Elranatamab-bcmm
- Linvoseltamab-gcpt
- Teclistamab-cqyv

GPRC5D-targeted:

- Talquetamab-tgvs

Useful in certain circumstances

- Liposomal doxorubicin + Vd (NCCN category 1)
- Bela-maf-containing regimens
- Bendamustine[‖]
- BVd[‖]
- BKd[‖]
- BRd[‖]
- Talquetamab-tgvs + D**
- High-dose or fractionated cyclophosphamide
- Talquetamab-tgvs + P**
- Sd
- Talquetamab-tgvs + teclistamab-cqyv[#,‖]
- Venetoclax-d ± D or PI (only for patients with t(11;14))
- Alkylator therapy
- Autologous HCT

Therapy for relapsed/refractory disease after BCMA therapy

Important considerations:

- Time from most recent BCMA-targeted therapy; consider alternative target than BCMA if <6 months
- Combinations containing anti-CD38 should be considered if >6 months since last CD38 targeting
- Alkylator-based therapy may provide temporary disease control to allow for consideration of CAR-T therapy
- Selecting a different BCMA-targeted bispecific after progression on another BCMA-targeted bispecific unlikely to be helpful

T-cell redirecting therapies**

- Talquetamab-tgvs[#]
- Talquetamab-tgvs + teclistamab-cqyv[#]
- Teclistamab-cqyv
- Second BCMA CAR-T, if available

Standard chemotherapy

- VSd
- Belantamab-containing combinations
- Carfilzomib-containing regimens
- Venetoclax-d ± D or PI (only for patients with t(11;14))

HCT as indicated

- Autologous HCT

Therapy abbreviation key

B, bendamustine
Bela-maf, belantamab mafodotin-blmf
C, cyclophosphamide
Cilta-cel, ciltacabtagene autoleucel
D, daratumumab
DCEP, dexamethasone, cyclophosphamide, etoposide, cisplatin
d, dexamethasone
E, elotuzumab
I, ixazomib
Ide-cel, idecabtagene vicleucel
Isa, isatuximab-irfc
K, carfilzomib
P, pomalidomide
PACE, cisplatin, doxorubicin, cyclophosphamide, etoposide
R, lenalidomide
S, selinexor
T, thalidomide
V, bortezomib

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