THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-o]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Preferred Regimens*
Order of regimens does not indicate comparative efficacy

Anti-CD-38 Refractory	Bortezomib-Refractory	Lenalidomide-Refractory
• Carfilzomib/lenalidomide/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone • Pomalidomide/bortezomib/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone	• Carfilzomib/lenalidomide/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone	• Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) • Pomalidomide/bortezomib/dexamethasone (category 1) • Carfilzomib/pomalidomide/dexamethasone ***After one prior therapy including lenalidomide and a PI*** ▸ Daratumumab/pomalidomide/dexamethasone (category 1) ***After two prior therapies including lenalidomide and a PI*** ▸ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▸ Elotuzumab/pomalidomide/dexamethasone ***After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy*** ▸ Ixazomib/pomalidomide/dexamethasone

CAR T-Cell Therapy
After one prior line of therapy including IMiD and a PI, and refractory to lenalidomide
▸ Ciltacabtagene autoleucel (category 1)

After two prior lines of therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI
▸ Idecabtagene vicleucel (category 1)

* For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Relapsed/Refractory Disease After 1–3 Prior Therapies, see MYEL-G 4 of 5

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[l] 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.
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] 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.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.

Note: All recommendations are category 2A unless otherwise indicated.

Continued

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-p]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Other Recommended Regimens

- Carfilzomib (twice weekly)/dexamethasone (category 1)
- Elotuzumab/lenalidomide/dexamethasone (category 1)
- Ixazomib/lenalidomide/dexamethasone (category 1)
- Selinexor/bortezomib/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone
- Daratumumab/carfilzomib/pomalidomide/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib/cyclophosphamide/dexamethasone
- Lenalidomide/cyclophosphamide/dexamethasone

After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy

- Pomalidomide/cyclophosphamide/dexamethasone (category 1)

Useful in Certain Circumstances

- Bortezomib/dexamethasone (category 1)
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Lenalidomide/dexamethasone (category 1)
- Carfilzomib/cyclophosphamide/thalidomide/dexamethasone
- Carfilzomib (weekly)/dexamethasone
- Selinexor/carfilzomib/dexamethasone
- Selinexor/daratumumab/dexamethasone
- Venetoclax/dexamethasone ± daratumumab or PI only for t(11;14) patients

After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy

- Pomalidomide/dexamethasone (category 1)
- Selinexor/pomalidomide/dexamethasone

For treatment of aggressive MM

- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)

After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD

- Daratumumab

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[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[l] 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.
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] 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.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.
[p] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

Note: All recommendations are category 2A unless otherwise indicated.

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THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-o]
Relapsed/Refractory Disease After 3 Prior Lines of Therapy

Preferred Regimens[q]

- ***CAR T-cell Therapy:***
  - ◊ Ciltacabtagene autoleucel
  - ◊ Idecabtagene vicleucel

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

- *Bispecific Antibodies:*[r]
  - ◊ Elranatamab-bcmm
  - ◊ Talquetamab-tgvs
  - ◊ Teclistamab-cqyv

Other Recommended Regimens

- Bendamustine
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/carfilzomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- High-dose or fractionated cyclophosphamide

After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody

- Selinexor/dexamethasone

Useful in Certain Circumstances[q]

- Talquetamab-tgvs + teclistamab-cqyv[r]

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

- Belantamab mafodotin-blmf (if available through compassionate use program)

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[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[l] 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.
[m] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[n] 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.
[o] Alkylating agents can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.
[q] Patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy. Optimal sequencing of sequential BCMA targeted therapies is not known; however accumulated data suggests immediate follow on with second BCMA directed therapy after relapse may be associated with lower response rates
[r] Prophylactic tocilizumab may be considered prior to first dose to reduce the risk of cytokine release syndrome (CRS).

Note: All recommendations are category 2A unless otherwise indicated.