Multiple Myeloma

Note: Consider Clinical Trials as treatment options for eligible patients.

INITIAL DIAGNOSTIC WORK-UP

- History and physical
- CBC with differential, BUN, creatinine, electrolytes, LDH, calcium, albumin, beta-2 microglobulin, serum protein electrophoresis and immunofixation, serum free light chain assay (kappa and lambda), immunofixation, and quantitative immunoglobulins (IgG, IgM, IgA)
- 24 hour urine protein electrophoresis and immunofixation
- Whole body musculoskeletal MRI without contrast or PET/CT scan
- Unilateral bone marrow aspirate and biopsy
  - Bone marrow immunohistochemistry
  - Bone marrow flow cytometry
  - Cytogenetics
  - FISH (t(4:14), t(14:16), t(11:14), Del 13, Del 17p, Del 1p (CDKN2C), 1q21 gain/amplification
- Dental evaluation[1]
- Lifestyle risk assessment[2]

If indicated:

- IgD and IgE
- Diagnostic imaging:
  - MRI of spine (avoid gadolinium if CrCl < 30 mL/minute)
  - Bone densitometry
- Tissue biopsy to diagnose extraosseous plasmacytoma
- Congo red staining of bone marrow and abdominal fat pad for amyloidosis (with or without electron microscopy [EM])
- Gene expression profile (GEP)

TREATMENT

FOLLOW-UP/SURVEILLANCE

Smoldering (asymptomatic) myeloma[3]

- Low/ Intermediate risk → Observe at 2-3 month intervals
- High risk →
  - Consider clinical trial
  - Observation
  - Consider lenalidomide with or without dexamethasone

Progression?

- No → Smoldering (asymptomatic) myeloma[3]
- Yes → Active (symptomatic) myeloma[3]

Active (symptomatic) myeloma[3]

- Induction therapy (see Appendix B) **and**
- Adjunctive treatment as indicated (see Appendix C)
- Evaluation for autologous stem cell transplant (SCT)
- Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative[4]

Prior to each cycle, obtain the following labs:

- CBC with differential, BUN, creatinine, calcium
- Quantitative immunoglobulins
- Serum protein electrophoresis
- FLC as appropriate every month
- Urine protein electrophoresis

If clinically indicated, consider:

- Bone marrow aspirate and/or biopsy
- Whole body musculoskeletal MRI without contrast or PET/CT scan
- Consider MRI of spine if clinically indicated

See treatment based on response:

- Page 2 for ≥ partial response[5]

or

- Page 3 for < partial response[5]

CrCl = creatinine clearance
FISH = fluorescence in situ hybridization
FLC = free light chains

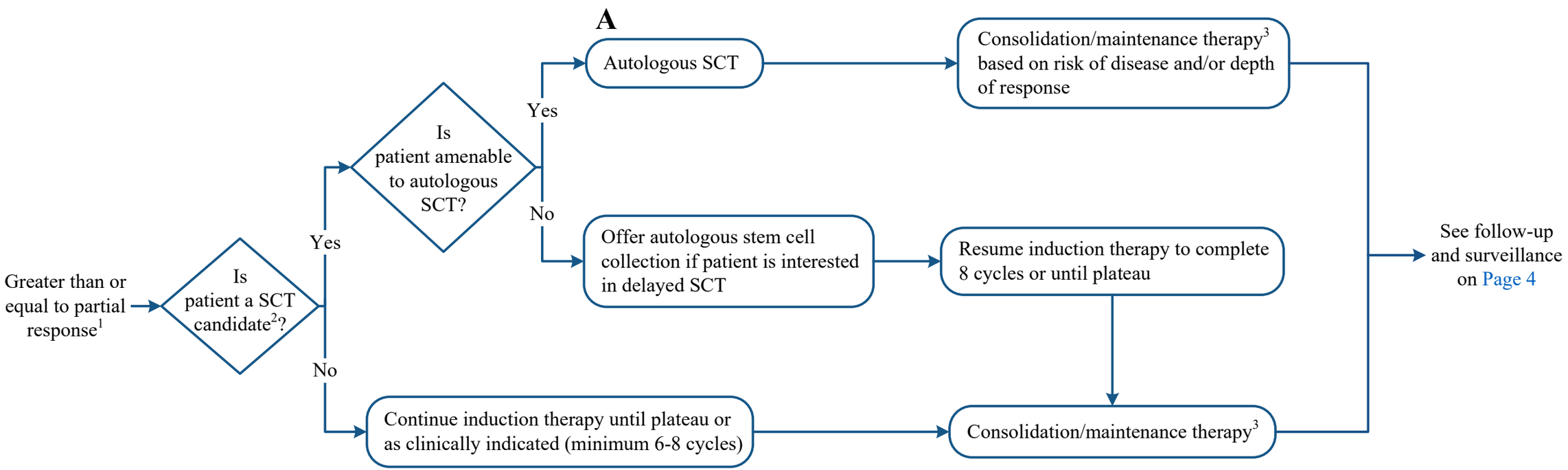
[1] Screening evaluation prior to initiation of bone modifying therapy and/or stem cell transplant (SCT)
[2] See Physical Activity, Nutrition, and Tobacco Cessation Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[3] See Appendix A for Definitions
[4] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).
[5] See Appendix D for Response Criteria

Department of Clinical Effectiveness V5
Approved by The Executive Committee of Medical Staff 07/16/2024

Multiple Myeloma

Note: Consider Clinical Trials as treatment options for eligible patients.

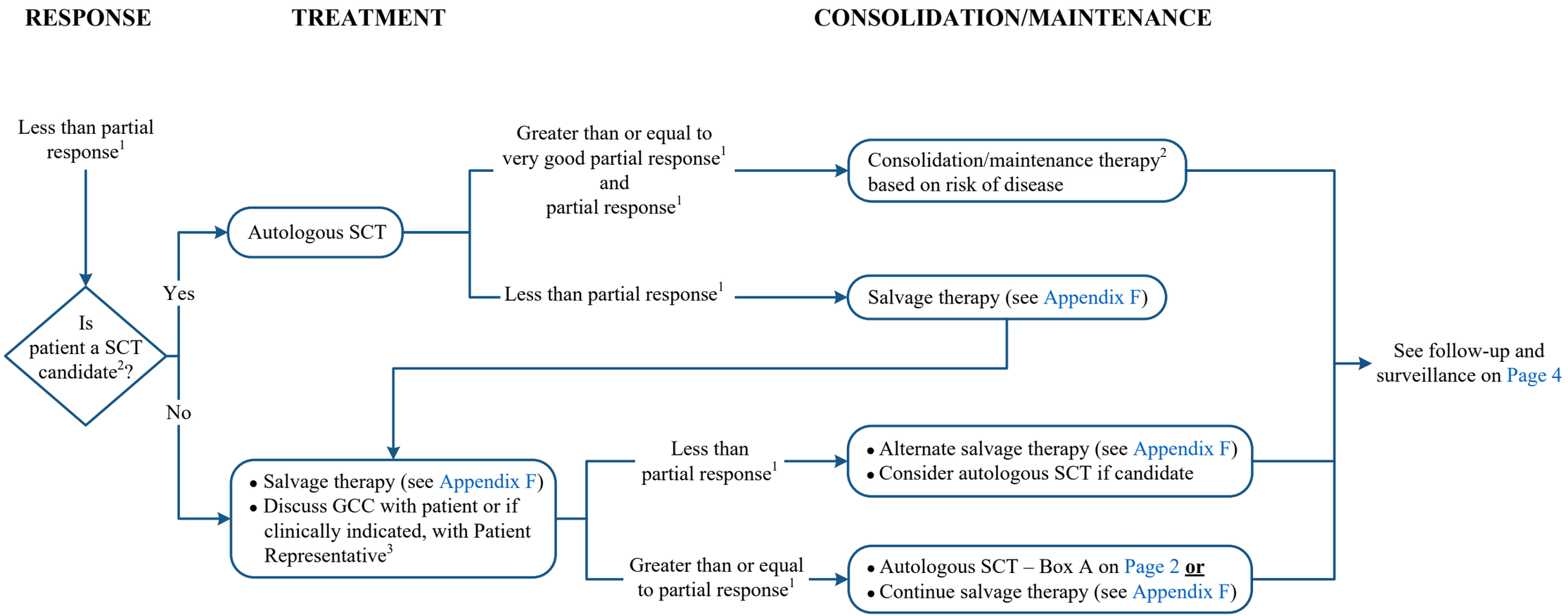
RESPONSE | **STEM CELL TRANSPLANT** | **CONSOLIDATION/MAINTENANCE**



[1] See Appendix D for Response Criteria
[2] See Appendix E for Considerations For Undergoing SCT
[3] See Appendix B for Treatment

Multiple Myeloma

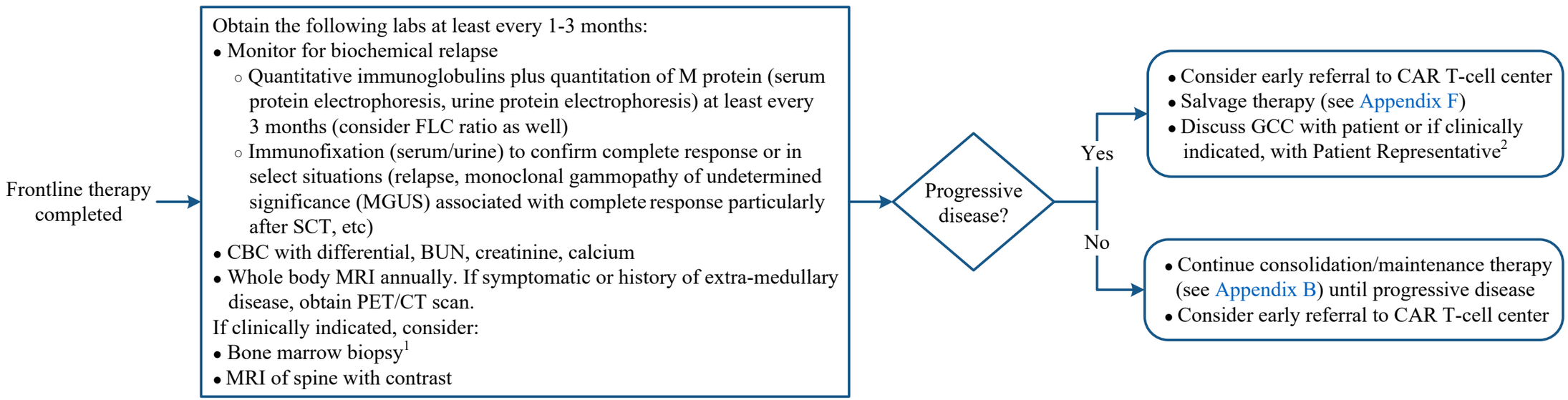
Note: Consider Clinical Trials as treatment options for eligible patients.



[1] See Appendix E for Response Criteria
[2] See Appendix B for Treatment
[3] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

Note: Consider Clinical Trials as treatment options for eligible patients.

FOLLOW-UP/SURVEILLANCE



CAR = chimeric antigen receptor

[1] If patient is in complete response, consider obtaining bone marrow biopsy to confirm minimal residual disease (MRD) status

[2] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

Multiple Myeloma

Note: Consider Clinical Trials as treatment options for eligible patients.

RELAPSE (PROGRESSIVE DISEASE) AFTER AUTOLOGOUS SCT

FOLLOW-UP/SURVEILLANCE

Relapse (progressive disease) < 2 year post autologous SCT →

- Consider early referral to CAR T-cell center
- Salvage therapy (see Appendix F)
- Discuss GCC with patient or if clinically indicated, with Patient Representative[1]

Relapse (progressive disease) ≥ 2 year post autologous SCT or any patient →

- Salvage therapy (see Appendix F) with or without autologous SCT
- Consider early referral to CAR T-cell center
- Discuss GCC with patient or if clinically indicated, with Patient Representative[1]

[1] GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

APPENDIX A: Definitions

Smoldering (Asymptomatic) Myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥ to 30 g/L or urinary monoclonal protein ≥ 500 mg per 24 hour and/or clonal bone marrow plasma cells 10-60%
- Absence of myeloma defining events or amyloidosis

Active (Symptomatic) Myeloma

Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma[1] 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: 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: CrCl < 40 mL per minute or 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 lesions on skeletal radiography, CT, or PET/CT[2]
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage[1] ≥ 60%
  - Involved:uninvolved serum FLC ratio[3] ≥ 100
  - > 1 focal lesions on MRI studies[4]

[1] Clonality should be established by showing k/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferable be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.
[2] If bone marrow has < 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement
[3] These values are based on the serum Freelite assay (The Binding Site Group, Birminham, UK). The involved FLC must be ≥ 100 mg/L.
[4] Each focal lesion must be 5 mm or more in size

APPENDIX B: Treatment

Stem Cell Transplant Candidates

Primary Therapy

Preferred Regimens:
- Daratumumab/bortezomib/lenalidomide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone

In certain circumstances:
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
- Daratumumab/bortezomib/cyclophosphamide/dexamethasone
- Daratumumab/carfilzomib/lenalidomide/dexamethasone

Maintenance Therapy

Preferred regimen:
- Lenalidomide

Other recommended regimens:
- Bortezomib
- Daratumumab
- Daratumumab/lenalidomide
- Ixazomib

In certain circumstances:
- Bortezomib/lenalidomide with or without dexamethasone
- Carfilzomib/lenalidomide

Special Considerations
- If neuropathy, consider lenalidomide/dexamethasone containing therapy or carfilzomib containing regimen
- If renal impairment:
  - Dose reduce lenalidomide according to guidelines
  - Use carfilzomib with caution; close renal monitoring is warranted
- Check 2D echocardiogram or equivalent prior to use of carfilzomib to ensure adequate baseline ejection fraction (EF)
- If diabetic, consider low-dose dexamethasone-based combination therapy and consultation to Endocrinology–Diabetes for diabetes management

Non- Stem Cell Transplant Candidates

Primary Therapy

Preferred Regimens:
- Daratumumab/lenalidomide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone

Other recommended regimens:
- Daratumumab/bortezomib/lenalidomide/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone
- Ixazomib/lenalidomide/dexamethasone

In certain circumstances:
- Lenalidomide/low-dose dexamethasone
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients
- Carfilzomib/cyclophosphamide/dexamethasone
- Cyclophosphamide/lenalidomide/dexamethasone

Maintenance Therapy

Preferred regimen:
- Lenalidomide

Other recommended regimens:
- Bortezomib
- Daratumumab/lenalidomide
- Ixazomib

In certain circumstances:
- Bortezomib/lenalidomide

Special Considerations
- If neuropathy, consider lenalidomide/dexamethasone containing therapy or carfilzomib containing regimen
- If renal impairment:
  - Dose reduce lenalidomide according to guidelines
  - Use carfilzomib with caution; close renal monitoring is warranted
- Check 2D echocardiogram or equivalent prior to use of carfilzomib to ensure adequate baseline EF
- If diabetic, consider low-dose dexamethasone-based combination therapy and consultation to Endocrinology–Diabetes for diabetes management

APPENDIX C: Adjunctive Treatment

Bone Disease:

- Prior to starting bisphosphonate/denosumab:
  - Comprehensive dental exam plus appropriate dentistry prior to treatment
  - Treatment and resolution of active oral infections prior to treatment
  - Check 25-hydroxyvitamin D and corrected calcium levels and supplement as needed

Monoclonal Antibodies (denosumab)

For prevention of skeletal-related events:

- Denosumab 120 mg SQ every 4 weeks for 2 years, then every 6 months thereafter
  - Recommend intake of calcium carbonate 1,200-1,500 mg PO daily
- Monitoring during therapy:
  - Check creatinine, calcium, phosphorus and magnesium during the first weeks of therapy initiation
- CrCl < 30 mL/minute: Use is not recommended[1]

Bisphosphonates (pamidronate or zoledronic acid)

- Zoledronic acid 4 mg every 3 months (preferred) or pamidronate 90 mg once monthly for 2 years, then re-evaluate. If skeletal related event (SRE) occurs, reinstitute treatment.
- All patients treated with bisphosphonate should receive a ≥ 2 hour infusion of pamidronate and ≥ 15 minute infusion of zoledronic acid
- Renal impairment dose adjustments:
  - Zoledronic acid
    - CrCl 50 - 60 mL/minute: Reduce dose to 3.5 mg
    - CrCl 40 - 49 mL/minute: Reduce dose to 3.3 mg
    - CrCl 30 - 39 mL/minute: Reduce dose to 3 mg
    - CrCl < 30 mL/minute: Use is not recommended
  - Pamidronate - consider dose reduction to 30 mg-60 mg if creatinine > 3 mg/dL or CrCl < 30 mL/minute

Bone Disease – continued

- Monitoring during therapy:
  - Check creatinine prior to each infusion (hold bisphosphonate if creatinine has risen ≥ 0.5 mg/dL change or twice the baseline value if original creatinine was < 1.4 mg/dL)
  - Every 3-6 months check for albuminuria; if > 500 mg/24 hours hold treatment until return to baseline. If reinitiating, infuse zoledronic acid over 30 minutes and pamidronate over 4 hours.
- Discontinue bone modifying therapy if osteonecrosis of the jaw develops

Infection:

- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection, hypogammaglobulinemia, and/or if ≥ 3 infections/year
- Consider pneumococcal vaccinations per CDC guidelines[2]
- Recommend COVID-19 vaccinations per CDC guidelines[2]
- Consider annual influenza vaccine
  - Consider high-dose influenza vaccine for patients ≥ 65 years old and patients who have previously undergone a SCT
- Herpes zoster prophylaxis is indicated for patients treated with proteasome inhibitors, daratumumab, and/or high dose dexamethasone
  - Consider use in patients receiving elotuzumab
- Consider avoiding concomitant quinolone therapy for patients on bortezomib-containing regimens
- Antifungal, antibacterial, and anti-zoster prophylaxis is indicated for patients receiving hyperfractionated cyclophosphamide-based therapy

CDC = Centers for Disease Control and Prevention

[1] Patients with CrCl < 30 mL/minute were excluded in myeloma studies

[2] Refer to CDC vaccine schedules

Continue on next page

APPENDIX C: Adjunctive Treatment - continued

Renal Dysfunction:
- Dose reduction for anti-myeloma agents
- Maintain hydration to avoid renal failure
- Avoid use of nonsteroidal anti-inflammatory drugs (NSAID)
- Avoid gadolinium if CrCl < 30 mL/minute
- Avoid iodine IV contrast

Coagulation/thrombosis:
- Patients receiving thalidomide, lenalidomide, or pomalidomide and dexamethasone and/or anthracyclines should be given appropriate thromboprophylaxis according to International Myeloma Working Group Guidelines

Hypercalcemia:
- Prompt treatment with steroid containing chemotherapy
- Hydration, furosemide, and/or calcitonin
- Bone modifying therapy
  - Dose adjustments for renal impairment not required but use with caution and monitor for hypocalcemia

Symptomatic Hyperviscosity:
- Plasmapheresis should be used as adjunctive therapy

GI Prophylaxis:
- Patients receiving steroids should receive prophylaxis with a proton pump inhibitor or H_2-receptor antagonist

Radiation Therapy:
- Low-dose radiation therapy (20-30 Gy) can be used as palliative treatment for uncontrolled pain, impending or overt pathologic fracture, and/or impending or overt cord compression
- Limited involved sites should be used to decrease the impact of radiation on stem-cell harvest and potential future treatments

Orthopedic or Neurosurgical:
- Consider vertebroplasty or kyphoplasty for symptomatic vertebral compression fractures
- Consultation with orthopedic surgery should be sought as appropriate for impending or overt long bone fractures
- Consultation with neurosurgery should be sought in the setting of impending or overt spinal cord compression or vertebral column instability

APPENDIX D: Response Criteria for Multiple Myeloma

Standard IMWG Criteria	Response Criteria
Stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (k/λ ratio ≤ 4:1 or ≥ 1:2 for k and λ patients, respectively, after counting ≥ 100 plasma cells)
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours
Partial response	• ≥ 50% reduction of serum M-protein plus reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required
Minimal response	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24 hour urine M-protein by 50-89%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas is also required.
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.

IMWG = International Myeloma Working Group
SPD = sum of the produce of the maximal perpendicular diameters of measured lesions

Continued on next page

APPENDIX D: Response Criteria for Multiple Myeloma - continued

Standard IMWG Criteria	Response Criteria
Progressive disease	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: ◦ Serum M-protein (absolute increase must be ≥ 0.5 g/dL) ◦ Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5g/dL ◦ Urine M-protein (absolute increase must be ≥ 200 mg/24 hour) ◦ In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) ◦ In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%) • Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% decrease in the longest diameter of a previous lesion > 1 cm in short axis • ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression-free survival but is listed as something that can be reported optionally or for use in clinical practices: • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially buy the SPD of the measurable lesion • Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% plasma cells in the bone marrow • Appearance of any other sign of progression (*i.e.,* new plasmacytoma, lytic bone lesions, or hypercalcemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: • Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS or positive imaging study for recurrence of myeloma) • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • Development of ≥ 5% clonal plasma cells in the bone marrow • Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

CRAB features = calcium elevation, renal failure, anaemia, lytic bone lesions
NGF = next-generation flow NGS = next-generation sequencing

Continued on next page

APPENDIX D: Response Criteria for Multiple Myeloma - continued

IMWG MRD Criteria	Response Criteria
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (*e.g.,* MRD-negative at 5 years).
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirate using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 nucleated cells or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

MRD = minimal residual disease
NGF = next-generation flow
NGS = next-generation sequencing
SUV = maximum standardized uptake value

APPENDIX E: Considerations For Undergoing Autologus SCT

Clinical Eligibility Criteria

- No uncontrolled cardio/pulmonary conditions
- Adequate peripheral venous access or adequate option for central venous access for autologous apheresis donors
- Negative pregnancy test for women of child-bearing potential
- No known allergy to cytokines if cytokines are to be used
- Patients with sickle cell anemia and other hemoglobinopathies are candidates for autologous stem cell transplant as long as their clinical condition permits the collection of sufficient stem cells
- Labs:
  - White blood cell count - recommend > 3 K/microliter (minimum > 2 K/microliter)
  - Platelets - recommend > 75 K/microliter (minimum > 50 K/microliter)
- Negative pregnancy test for women of child-bearing potential
- No known allergy to cytokines if cytokines are to be used

Clinical Suitability Criteria

- Partial response to prior therapy (defined as a 50% decrease either in measurable serum and/or paraprotein or in bone marrow infiltration sustained for at least one month)
- Adequate cardiac, renal, pulmonary, and hepatic function

APPENDIX F: Salvage Therapy

Early Relapses (1-3 prior therapies)[1]

Preferred regimens:

- Bortezomib refractory
  - Daratumumab/lenalidomide/dexamethasone
  - Daratumumab/carfilzomib/dexamethasone
  - Carfilzomib/lenalidomide/dexamethasone
  - Isatuximab-irfc/carfilzomib/dexamethasone
  - Carfilzomib/promalidomide/dexamethasone
- Lenalidomide refractory
  - Daratumumab/carfilzomib/dexamethasone
  - Daratumumab/bortezomib/dexamethasone
  - Isatuximab-irfc/carfilzomib/dexamethasone
  - Carfilzomib/promalidomide/dexamethasone
- Ciltacel autoleucel (approved in 2L+)
- Idecabtagene vicleucel (approved in 3L+)

Other recommended regimens:

- Ixazomib/lenalidomide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone
- Carfilzomib (twice weekly)/dexamethasone
- Elotuzumab/lenalidomide/dexamethasone
- Selinexor/bortezomib/dexamethasone (once weekly)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab/cyclophosphamide/bortezomib/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Ixazomib/cyclophosphamide/dexamethasone

Subsequent therapy considerations:

- Bortezomib refractory
  - After one prior therapy including lenalidomide and a PI
    - Daratumumab/pomalidomide/dexamethasone
  - After two prior therapies including lenalidomide and a PI
    - Isatuximab-irfc/pomalidomide/dexamethasone
- Lenalidomide refractory
  - After one prior therapy including lenalidomide and a PI
    - Daratumumab/pomalidomide/dexamethasone
  - After two prior therapies including lenalidomide and a PI
    - Isatuximab-irfc/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
    - Pomalidomide/bortezomib/dexamethasone
    - Ixazomib/pomalidomide/dexamethasone
- Other recommended regimens
  - After two prior therapies including an IMiD and a PI **and** with disease progression on/within 60 days of completion of last therapy
    - Pomalidomide/cyclophosphamide/dexamethasone
  - After two prior therapies including lenalidomide and a PI
    - Elotuzaumab/pomalidomide/dexamethasone

IMiD = Immunomodulatory drug PI = Proteasome Inhibitor

[1] If a regimen listed for previously treated multiple myeloma was used as a primary induction therapy and relapse > 6 months, the same regimen may be repeated

Continued on next page

APPENDIX F: Salvage Therapy - continued

Early Relapses (1-3 prior therapies)[1]

In certain circumstances:

- Bortezomib/dexamethasone
- Lenalidomide/dexamethasone
- Carfilzomib/cyclophosphamide/thalidomide/dexamethasone
- Carfilzomib (weekly)/dexamethasone
- Selinexor/daratumumab/dexamethasone
- Selinexor/carfilzomib/dexamethasone
- Venetoclax/dexamethasone only for t(11:14) patients

Subsequent therapy considerations:

- In certain circumstances
  - After two prior therapies including an IMiD and a PI **and** with disease progression on/within 60 days of completion of last therapy
    - Pomalidomide/dexamethasone
    - Selinexor/pomalidomide/dexamethasone
  - For treatment of aggressive multiple myeloma
    - Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
    - Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) with and without bortezomib (VTD-PACE)
  - After tat least three prior therapies including a PI and an IMiD or are double refractory to a PI or an IMiD
    - Daratumumab

Late Relapses (> 4 prior therapies)

- After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD
  - Teclistamab-cqy
  - Elranatamab
  - Talquetamab
  - Idecabtagene vicleucel (approved in 3L+)
  - Ciltacabtagene autoleucel (approved in 2L+)
  - Belantamab mafodotin-blmf (if available through compassionate use program)
- 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

Post T-cell redirection therapy:

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

IMiD = Immunomodulatory drug PI = Proteasome Inhibitor

[1] If a regimen listed for previously treated multiple myeloma was used as a primary induction therapy and relapse > 6 months, the same regimen may be repeated

SUGGESTED READINGS

The following is not meant to be a comprehensive list of available effective treatments for myeloma. Myeloma treatments are changing rapidly and new treatments and added information regarding previous treatment treatments are available frequently. As a result, updates should be taken into consideration and for similar reasons, regimens reported only by abstract have been included on this reference list.

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