Multiple Myeloma Guidelines adopted from NCCN and ESMO

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Tests for multiple myeloma:

Tests needed for all patients	Tests that may be useful for some patients
Medical history and physical exam	Tissue biopsy
CBC with differential	Bone densitometry
Blood chemistry(creatinine, BUN, ca, electrolytes, LDH, albumin, β_2 micro globulin)	PET/CT (positron emission tomography/computed tomography)scan
Serum free light chain assay	MRI (magnetic resonance imaging)
Serum quantitative immunoglobulin	Amyloid protein staining
Serum protein electrophoresis	Serum viscosity test
Serum immunofixation	Plasma cell labeling index
24 hours urinary protein	HLA(human leukocyte antigen) typing
Urine protein electrophoresis	
Urinary immunofixation	
Bone marrow aspirate & biopsy	
Standard metaphase cytogenetics & FISH (del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21)	
Flow cytometry &/or immunohistochemistry	
Bone survey	

Revised IMWD (international myeloma work group) diagnostic Criteria:

Plasma cell disorder	Definition
Smouldering multiple myeloma	Both criteria must be met: • Serum M protein (IgG or IgA) ≥30 g/l or urinary M protein ≥500 mg per 24 h and/or clonal BM plasma cells 10%–60% • Absence of myeloma-defining events or amyloidosis
Multiple myeloma	Clonal BM plasma cells ≥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: - Hypercalcaemia: serum calcium > 0.25 mmol/l (>1 mg/dl) higher than the upper limit of normal of > 2.75 mmol/l (>11 mg/dl) - Renal insufficiency: CrCl <40 ml/min or serum creatinine >177 μmol/l (>2 mg/dl) - Anaemia: haemoglobin value of > 20 g/l below the lower limit of normal, or a haemoglobin value <100 g/l - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT • Any one or more of the following biomarkers of malignancy: - ≥60% clonal BM plasma cells - Involved/uninvolved serum-free light chain ratio ≥100 - ≥1 focal lesion on MRI studies (each focal lesion must be ≥5 mm in size)

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BM, bone marrow; CrCl, creatinine clearance; CT, computed tomography; M protein, monoclonal protein; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.

Standard risk factors for MM and the revised ISS (International Staging System):

Prognostic factor	Criteria
ISS stage	
I	Serum β2M < 3.5 mg/l, serum albumin ≥3.5 g/dl
II	Not ISS stage I or III
III	Serum β2M ≥ 5.5 mg/l
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

β2M, β2 microglobulin; CA, chromosomal abnormalities; iFISH, interphase fluorescent *in situ* hybridisation; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

Standard IMWG response criteria:

Response subcategory	Response criteria
Molecular CR	CR plus negative ASO-PCR, sensitivity 10^{-5}
Immunophenotypic CR	Stringent CR plus Absence of phenotypically aberrant PCs (clonal) in BM with a minimum of 1 million total BM cells analysed by multiparametric flow cytometry (with > 4 colours)
Stringent CR	CR as defined below plus Normal FLC ratio and Absence of clonal PCs by immunohistochemistry or 2- to 4-colour flow cytometry
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤ 5% PCs in BM
VGPR	Serum and urine M protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M protein plus urine M protein level <100 mg per 24 h
PR	≥ 50% reduction of serum M protein and reduction in 24h urinary M protein by ≥ 90% or to < 200 mg per 24 h 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 unmeasurable, ≥50% reduction in PCs is required in place of M protein, provided baseline BM PC percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Progressive disease	Increase of 25% from lowest confirmed response value in one 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 ≥ 5 g/dl Urine M protein (absolute increase must be ≥ 200 mg/24 h)

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ASO-PCR, allele-specific polymerase chain reaction; BM, bone marrow; CR, complete response; FLC, free light chain; M protein, monoclonal protein; PCs, plasma cells; PR, partial response; VGPR, very good partial response.

IMWG response criteria including minimal residual disease:

Response subcategory		Response criteria
IMWG MRD negativity criteria	*Sustained MRD-negative*	MRD-negative in the marrow (next-generation flow and/or NGS) and by imaging as defined below, confirmed one 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 next-generation flow cytometry on BM aspirates using the EuroFlow standard operation procedure for MRD detection in MM (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 BM aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of BM aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Imaging + MRD-negative	MRD-negative as defined by next-generation flow cytometry or NGS plus Disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to < mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

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BM, bone marrow; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRD, minimal residual disease; NGS, next-generation sequencing; PET-CT, positron emission tomography-computed tomography; SUV, standardised uptake value.

Guidelines for myeloma therapy:

1- Primary treatment for plasmacytoma:

Local radiotherapy is the preferred treatment of choice with surgical removal in case of extra-osseous plasmacytoma, but about two-thirds of patients develop MM at 10 years' follow-up.

2- Smouldering myeloma

Immediate treatment is not recommended at the present time for patients with indolent myeloma. Clinical trials for high-risk smouldering myeloma are strongly encouraged.

3- Active Multiple myeloma:

Avoidance of myelotoxic agents to reserve stem cells prior to transplantation
Primary therapy for transplant candidates (Assess after 2 cycles)
• Bortezomib /dexamethasone • Bortezomib /doxorubicin/dexamethasone • Bortezomib /thalidomide/dexamethasone • Lenalidomide/dexamethasone • Bortezomib/ Lenalidomide /dexamethasone
Primary therapy for non-transplant candidate
• Lenalidomide/low-dose dexamethasone • Bortezomib / Lenalidomide /dexamethasone • Bortezomib / cyclophosphamide /dexamethasone • Carfilizomib/Lenalidomide/dexamethasone • Ixazomib/ Lenalidomide/dexamethasone
Maintenance therapy
Bortezomib Lenalidomide

For patients in good clinical condition (e.g. fit patients), induction followed by high-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is the standard treatment. Four to six courses of induction are recommended before proceeding to stem cell collection. Melphalan [200 mg/m2 intravenous (i.v.)] is the standard preparative regimen before ASCT. Peripheral blood progenitor cells are the preferred source of stem cells, rather than BM. In young patients following ASCT, phase III randomised trials have demonstrated that maintenance therapy with immunomodulatory drugs (IMiDs), either thalidomide or lenalidomide. Allogeneic SCT is not indicated as part of front-line therapy and should only be carried out in the context of a clinical trial. In elderly patients following induction, maintenance therapy using either IMiDs or bortezomib is recommended with or without thalidomide maintenance.

Therapy for previously treated multiple myeloma	
Preferred regimens	**others**
• Repeat primary induction therapy (if relapse > 6 months) • Bortezomib / dexamethasone • Bortezomib / Lenalidomide /dexamethasone • Bortezomib/cyclophosphamide/dexamethasone • Carfilizomib/Lenalidomide/dexamethasone • Carfilizomib/dexamethasone • Daratumumab • Daratumumab/ Bortezomib / dexamethasone • Daratumumab/ Lenalidomide/dexamethasone • Elotuzumab/ Lenalidomide/dexamethasone • Ixazomib/ Lenalidomide/dexamethasone • Lenalidomide/dexamethasone • Pomalidomide/ Bortezomib / dexamethasone • Pomalidomide / dexamethasone	• Bendamustine • Bendamustine/ Bortezomib / dexamethasone • Bendamustine/ Lenalidomide/dexamethasone • Bortezomib/liposomal doxorubcindexa/ cyclophos/vepside/cisplatin • Panobinostat/bortizomib/dexa • Panobinostat/carfilizomib • Pamolidomide/cyclophos/dexa

In young patients, a second ASCT may be considered, provided that the patient responded well to the previous ASCT. In the relapse setting, allogeneic SCT should only be carried out in the context of a clinical trial.

Adjuvant therapy:

Bone disease:

The I.V. agents pamidronate and zoledronic acid are of clinical benefit in the treatment of bone disease in patients with MM. Orthopaedic surgery is required in patients with pathological fractures or at risk of long bones, and may need to be complemented with radiotherapy. Spinal cord compression is an emergency that requires treatment with high-dose dexamethasone and simultaneous local radiotherapy should be started as soon as possible; surgery should be used in the case of bone fragments within the spinal route.

Anemia, BM failure and infections:

Recombinant human erythropoietin and darbepoetin alfa can be used for the treatment of myeloma-associated anaemia (hemoglobin level<10 g/dl), once other causes of anaemia have been excluded. The target is to maintain hemoglobin around 12 g/ dl (below 14 g/dl to avoid thromboembolic complications and hypertension). Treatment with granulocyte colony-stimulating factor (G-CSF) may be required to treat chemotherapy-induced severe granulocytopaenia. Infectious episodes require immediate therapy with broad spectrum antibiotics. Prophylaxis of infection remains controversial but may be beneficial within the first 2–3 months of initiation of therapy, especially in patients receiving lenalidomide or pomalidomide, or in patients at high risk of infection (previous serious infections or neutropenia).

Renal failure:

Bortezomib-based therapies (in combination with dexamethasone with/without

thalidomide or doxorubicin or cyclophosphamide) are the treatment of choice in patients with renal failure. The current recommendations for patients with MM who are due to start IMiD therapy are to use aspirin (100 mg) in the absence of risk factors for thrombosis and to use full dose anticoagulants for those at higher risk (low molecular weight heparin or full-dose warfarin).