

Supplementary information

EHA–EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma

**In the format provided by
the authors and unedited**

Supplementary Table 1 | Levels of evidence and grades of recommendation

<i>Levels of evidence</i>	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
<i>Grades of recommendation</i>	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

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Supplementary Table 2 | 20-2-20 IMWG Classification of smouldering multiple myeloma

Model	Risk factors and proposed definition of high versus low risk	Categories	Number of risk factors
3-risk factor model	Serum M protein (>2 vs ≤2 g/dl)	<i>Low-risk</i>	0
	Serum FLC ratio (>20 vs ≤20 g/dl)	<i>Intermediate-risk</i>	1
	BMPC (>20 vs ≤20%)	<i>High-risk</i>	2–3
4-risk factor model	Serum M protein (>2 vs ≤2 g/dl)	<i>Low-risk</i>	0
	Serum FLC ratio (>20 vs ≤20 g/dl)	<i>Low-intermediate</i>	1
	BMPC (>20 vs ≤20%)	<i>Intermediate-risk</i>	2
	Presence versus absence of a chromosomal abnormality (t(4;14), t(14;16), +1q or del13q/monosomy 13)	<i>High-risk</i>	3–4

BMPC, bone marrow plasma cell; FLC, free light chain; vs, versus.

Adapted from ref. 45, Springer Nature Limited.

Supplementary Box 1 | IMWG response criteria³⁰

International Myeloma Working Group (IMWG) minimal residual disease (MRD)

- Sustained MRD-negative: MRD-negative in the bone marrow (BM) (next-generation flow cytometry (NGF) and/or next-generation sequencing (NGS)) and by imaging as defined below, negativity confirmed one year apart. Subsequent evaluations can be used to further specify the duration of criteria negativity (e.g. MRD-negative at 5 years).
- Flow MRD-negative: Absence of phenotypically aberrant clonal plasma cells by NGF on BM aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (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 LymphosightVR 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 NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET-CT or decrease to less than mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal.
 - MRD-negative 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 than mediastinal blood pool SUV or decrease to less than that of surrounding normal.

Stringent complete response (sCR): complete response (CR) as defined below plus normal involved to uninvolved serum free light chains (FLC) ratio and absence of clonal plasma cells (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 $\leq 5\%$ PCs in BM.

Very good partial response (VGPR): Serum and urine M protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M protein plus urine M protein level < 100 mg per 24 h.

Partial response (PR)

- $\geq 50\%$ reduction of serum M protein and reduction in 24h urinary M protein by $\geq 90\%$ or to < 200 mg per 24 h.
- If the serum and urine M protein are unmeasurable, a $\geq 50\%$ 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, $\geq 50\%$ reduction in PCs is required in place of M protein, provided baseline BM PC percentage was $\geq 30\%$.
- In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ 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)

Clinical relapse

Clinical relapse requires one or more of the following criteria:

- Direct indicators of increasing disease and/or end organ dysfunction (hypercalcaemia, renal failure, anaemia and bone disease (CRAB) features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;
- 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 by the sum of the products of the diameters (SPD) of the measurable lesion;
- Hypercalcaemia (>11 mg/dl);
- Decrease in haemoglobin of ≥ 2 g/dl not related to therapy or other non-myeloma-related conditions;
- Rise in serum creatinine by 2 mg/dl or more from the start of the therapy and attributable to myeloma;
- Hyperviscosity related to serum paraprotein.

Relapse from CR (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 $\geq 5\%$ plasma cells in the BM;
- Appearance of any other sign of progression (i. e, new plasmacytoma, lytic bone lesion or hypercalcaemia see above).

Relapse from MRD negativity (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 $\geq 5\%$ clonal plasma cells in the BM;
- Appearance of any other sign of progression (i. e, new plasmacytoma, lytic bone lesion or hypercalcaemia).