radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.
† Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).
‡ Bone marrow MFC should follow NGF guidelines. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.
¶ Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identifi ed by CT and present on at least two consecutive slices. Alternatively, an SUVmax=2x5 within osteolytic CT areas >1 cm in size, or SUVmax=1x5 within osteolytic CT areas ≤1 cm in size were considered positive.

Standard IMWG response criteria	
Response subcategory[a]	*Response criteria*
Stringent complete response	Complete response as defined below plus ▪ Normal FLC ratio (0.26-1.65)[b] and ▪ Absence of clonal cells in bone marrow[c] by immunohistochemistry or immunophenotyping[d]
Complete response	▪ Negative immunofixation of 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 h (0.1 g/ 24 h)
Partial response	▪ ≥ 50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h (0.2 g/ 24h) ▪ When the only method to measure disease is by serum FLC levels: PR is defined as a ≥ 50% decrease in the difference between involved and uninvolved sFLC levels ▪ In addition to the these criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas (SPD) is also required[e] ▪ If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline plasma-cell percentage was ≥ 30%
Minimal response	▪ ≥25% but ≤ 49% reduction of serum M-protein and reduction in 24 h urine M-protein by 50–89%. ▪ In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required[e]
Stable disease[f]	▪ Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease[g,h]	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 ≥5 g/dL; ▪ Urine M-protein (absolute increase must be ≥200 mg/24 h); ▪ In patients without measurable serum and urine M-protein levels, the diff erence 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[e] of >1 lesion, or ≥50% increase 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 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 SPD[e] 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 ≥5% plasma cells in the bone marrow; ▪ Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)

[a] All response categories require two consecutive assessments made any time before starting any new therapy; All categories of response require no known evidence of progressive disease or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements .

[b] All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

[c] Confirmation with repeat bone marrow examination not needed.

[d] Presence/absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistryrequires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

[e] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

[f] Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates.

[g] Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

[h] In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

NOTES:

- **Parameters that are considered measurable at baseline (serum and urine, FLC serum if both serum and urine are not measurable) should be performed at each assessment**
- **Urine M-protein is not needed to document partial response or minor response if baseline urine M-protein was not measurable; however, it is still required very good partial and complete response**
- **Once (s)CR is established, response remains (s)CR until relapse or progression is documented.**
- **Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category.**
- **Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring; otherwise the patient is classified as inevaluable until the size of the plasmacytoma is measured again.**
- **Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone.**
- **When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal serum FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed above.**
- **When the only method to measure disease is by serum FLC levels: VGPR is defined as a ≥ 90% decrease in the difference between involved and uninvolved serum FLC levels**
- **To achieve VGPR, if present at baseline, a ≥ 90% reduction in the size of soft tissue plasmacytomas (SPD) is also required**