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Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma

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Abstract

New systems have emerged for diagnosis, staging and response assessment in multiple myeloma (MM). The diagnostic and response criteria recommended are primarily derived from the International Myeloma Working Group, with certain updates and clarifications. The International Staging System is the current standard for staging of myeloma. A new risk stratification model is provided to specifically define high-risk patients who may benefit from novel therapeutic strategies. This paper provides the current criteria for diagnosis, staging, risk stratification and response assessment of MM.

Keywords

diagnosis; myeloma; prognosis; response; staging; treatment

Multiple myeloma (MM) is a malignant disorder characterized by the proliferation of a single clone of plasma cells derived from B cells in the bone marrow. Frequently, there is invasion of the adjacent bone, which destroys skeletal structures and results in bone pain and fractures. Occasionally, plasma cells infiltrate multiple organs and produce a variety of symptoms. The plasma cell clone produces a monoclonal (M) protein that can lead to renal failure caused by light chains (Bence Jones protein) or hyperviscosity from excessive amounts of M protein in the blood. The diagnosis depends on the identification of abnormal monoclonal plasma cells in the bone marrow, M protein in the serum or urine, evidence of end-organ damage and a clinical picture consistent with MM. The key clinical and laboratory features are summarized in Table 1.[1] This paper summarizes the current international consensus criteria for diagnosis, staging, risk stratification and response assessment of MM.

Recommended laboratory tests for diagnosis, prognosis and risk stratification

Standard laboratory and imaging modalities

A complete blood count, peripheral blood smear, chemistry screen including calcium and creatinine determinations, β_2-microglobulin (β_2M), lactate dehydrogenase and routine urinalysis are essential. In addition, serum protein electrophoresis, immunofixation, nephelometric quantitation of immunoglobulins and measurement of free light chains (FLCs) are needed. A bone marrow aspiration and biopsy with immunophenotyping, conventional cytogenetics, and fluorescence *in situ* hybridization (FISH) are required in all patients for diagnosis and risk stratification; bone marrow plasma cell labeling index, if available may be

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of additional value. A radiological skeletal bone survey, including spine, pelvis, skull, humeri and femurs is necessary. A magnetic resonance imaging (MRI) or computerized tomography (CT) scan may be needed to evaluate symptomatic bony sites, even if the skeletal survey is negative. In addition, either is essential if spinal cord compression is suspected.

Role of the serum FLC assay

The serum FLC assay has three main uses. First, it has prognostic value in MM,[2] monoclonal gammopathy of undetermined significance (MGUS),[3] smoldering MM (SMM)[4] and solitary plasmacytoma of bone.[5] Second, it can be used in conjunction with serum protein electrophoresis and immunofixation when screening for the presence or absence of a monoclonal plasma cell disorder such as myeloma in place of a 24-h urine protein study. However, if a plasma cell proliferative disorder is diagnosed, then a 24-h urine protein electrophoresis and immunofixation are needed, and the serum FLC assay cannot be used in place of urine studies. Finally, the serum FLC test is useful in monitoring disease course and response to therapy in patients who do not have measurable disease on serum and protein electrophoresis (including non-secretory myeloma). Measurable disease is defined as serum monoclonal (M) protein ≥1 g/100 ml or urine M protein ≥200 mg per 24 h. In patients without measurable disease, there are few options available to monitor disease and the FLC levels will be useful as described in the section below on response criteria.

Diagnostic criteria

Standard diagnostic criteria

The International Myeloma Working Group (IMWG) and Mayo Clinic have established almost identical criteria for the diagnosis of the plasma cell proliferative disorders.[6] Table 2 lists the current IMWG diagnostic criteria for MM with minor clarifications (as referenced); it also lists the diagnostic criteria for related plasma cell disorders that need to be differentiated from MM. MGUS is defined by an intact immunoglobulin < 3 g/100 ml and < 10% bone marrow plasma cells and absence of end-organ damage. End-organ damage includes hypercalcemia, *r*enal failure, *a*nemia and *b*one (CRAB) lesions that are felt related to a plasma cell proliferative disorder and not explained by another unrelated disease or disorder. Patients with only free serum κ and λlight chains (idiopathic Bence Jones proteinuria) should be excluded. Symptomatic MM is differentiated from MGUS and SMM (asymptomatic) based on the presence or absence of end-organ damage attributable to the underlying plasma cell proliferative process. Note that although a bone marrow biopsy is indicated at diagnosis in all patients with myeloma, in patients with clinical MGUS with a small monoclonal protein (less than 1.5 g/100 ml) and no end-organ damage it can be deferred. Conventional radiographs showing lytic lesions, osteoporosis or pathologic fractures are used to detect the presence of bone lesions.

Role of additional imaging procedures

Skeletal lesions may also be detected by MRI, fluoro-deoxyglucose positron emission tomography (PET) or CT. CT and MRI scans are more sensitive than conventional radiography in detecting bone and bone marrow involvement. Among asymptomatic MM patients with normal roentgenograms, up to 50% may have tumor-related abnormalities on MRI of the lower spine. One or more of these studies are indicated when symptomatic areas show no abnormality on routine radiographs. However, the routine use in assessing the extent of bone disease in addition to skeletal radiographs is unclear, and is not recommended on a routine basis in most patients except those with apparent solitary plasmacytoma. The specific role of new imaging modalities in management needs further investigation. The role of bone mineral density studies in myeloma and the use of these studies in identifying patients at risk for pathologic fractures and prophylactic bisphosphonate therapy also remain unresolved. We do not believe that

asymptomatic skeletal lesions detected only by MRI, CT or PET scanning are routine indications for therapy, but should be evaluated in the clinical context and followed closely. Therapeutic decisions must be based on a case-by-case basis.

Staging

Durie–Salmon staging system

The Durie–Salmon clinical staging system was developed over 30 years ago to provide a practical way to measure MM tumor burden.[17] Knowing the immunoglobulin production by each plasma cell and the half-life of the circulating immunoglobulin, it was possible to mathematically derive the total myeloma cell number and tumor burden. The tumor burden was then correlated with individual clinical, laboratory and X-ray features, including the levels of hemoglobin, serum calcium and creatinine, serum and urine M protein levels and the number and size of bone lesions to define the clinical staging system. This provided a simple and practical estimate of tumor burden. Patients were categorized as stage I, II or III, depending on the degree of anemia, hypercalcemia, levels of M protein in the serum and urine or bone lesions. In addition, patients with or without serum creatinine of 2 mg/100 ml or more were designated A or B.

International staging system

The Durie–Salmon staging was widely adopted as the standard staging system in MM. However, there are significant shortcomings with this system. The number of lytic lesions on routine radiographs, an important element of the Durie–Salmon system, is unfortunately observer dependent. In an effort to develop a more objective staging system, other features were proposed. Serum β_2M (Sβ_2M) is an easily reproducible readily available laboratory test. It has proven to be an important prognostic factor since its introduction more than 25 years ago.[18] More recently, the IMWG has reported using only the albumin level and β_2M (Table 3). Clinical and laboratory data were obtained on 10 750 previously untreated symptomatic MM patients from 17 worldwide institutions. The International Staging System (ISS) system consists of stage I: β_2M < 3.5 mg/l and serum albumin ≥3.5 g/100 ml (median survival 62 months); stage II, neither stage I nor stage III (median survival 44 months) and stage III β_2M ≥5.5 mg/l (median survival 29 months)[19]

Limitations of the ISS

The ISS has many advantages. It allows outcome in clinical trials to be compared with each other and is more reproducible than the Durie–Salmon system. However, the ISS also has many limitations. It is not useful unless the diagnosis of myeloma has already been made. The ISS has no role in MGUS, SMM or other related plasma cell disorders. It cannot be used to distinguish MGUS and SMM from myeloma. Stage III ISS is a composite group comprised of patients in whom the β_2M is elevated because of tumor burden as well as patients in whom the elevation is due to renal failure. Thus, the ISS cannot be used for therapeutic risk stratification, and does not provide a good estimate of tumor burden. Finally, the prognostic role of the ISS in the era of new drugs is not established. It is possible that the ISS may not retain prognostic significance in the era of new drugs.

Recommendations regarding staging

We recommend that both the Durie–Salmon staging and the ISS be reported in clinical trials. Although the Durie–Salmon Staging System has several shortcomings, we believe that it remains useful in comparing patients in clinical trials and allows a better assessment of the disease burden of patients in a given study.

Risk stratification

Conventional cytogenetic studies show an abnormal karyotype in only one-third of patients with MM.[20] However, the presence of hypodiploidy[21] or the deletion of chromosome 13 predicts a significantly reduced survival.[22] FISH reveals abnormalities in more than 90% of patients with MM (Table 4).[20] In an Eastern Cooperative Oncology Group (ECOG) clinical trial of 351 patients, the presence of t4;14, t(14;16) or 17p– was associated with poor prognosis (median survival 25 months).[25] The combination of monosomy and/or deletion of chromosome 13 by FISH and a $S\beta_2M$ level greater than 2.5 mg/l resulted in shorter survival.[26] An elevated plasma cell labeling index also confers a significantly adverse prognosis.[27] Gene expression profiling has been utilized to aid in the differentiation between normal plasma cells and those in MGUS, MM, amyloid light-chain amyloidosis, and extramedullary plasmacytomas. It has also been used to identify high risk patients with MM, and to further classify risk in poor prognosis MM patients such as those with t(4;14).

Recommendations on risk stratification

As discussed earlier, the Durie–Salmon Staging System and the ISS are important for prognosis, but are not useful for therapeutic risk stratification. Independent prognostic markers discussed above provide a better estimate of differences in underlying myeloma biology. Either FISH or conventional cytogenetics, or preferably both, should be done at diagnosis in all patients. However, modifying therapy based on underlying risk factors remains controversial and needs further study. Gene expression profiling is also useful in risk stratification, but is limited by the lack of a uniform platform across many centers in the world and widespread availability.

Response criteria

The European Group for Blood and Bone Marrow Transplant/International Bone Marrow Transplant Registry/American Bone Marrow Transplant Registry (EBMT/IBMTR/ABMTR) published criteria for the response and progression of MM treated by stem cell transplantation, commonly referred to as the Blade criteria or the EBMT criteria.[28] In addition, other commonly used response criteria were those developed by the Chronic Leukemia-Myeloma Task Force, Southwest Oncology Group (SWOG) and the ECOG. All these have been largely abandoned. In 2006, the IMWG recognized the need for uniformity and published uniform response criteria that are to be used in future clinical trials.[29]

The IMWG uniform response criteria were developed similarly to the EBMT criteria with several major exceptions: addition of FLC response and progression criteria for patients without measurable disease, modification of the definition for disease progression for patients in complete response (CR), addition of very good partial response (VGPR) and stringent response categories, elimination of the minor response category, elimination of the mandatory 6-week wait time to confirm response, and some additional clarifications and correction of errors. The IMWG criteria for response and progression are listed in Table 5.

Recommendations on response criteria

We believe that the IMWG supplements and clarifies some of the problems with the EBMT criteria, and is now the standard criteria that should be used in future clinical trials. It overcomes some significant limitations of the EBMT criteria that have become a significant issue recently such as the definition of progressive disease in patients achieving CR. However, we also recommend that for patients with relapsed refractory myeloma, the minor response category be reported (see below) in addition. Some of the main points pertaining to the assessment of response in myeloma are further discussed below.

VGPR

The VGPR category is a useful measure of depth of response. It identifies patients with a better outcome who have achieved excellent response but are not yet in CR. VGPR has gained additional clinical significance by the finding that patients who obtained at least a VGPR with the first autologous stem cell transplant do not benefit from a second (tandem) transplant. It distinguishes patients who have had near disappearance in their M-spike but are still immunofixation positive from those patients who merely have a 50% reduction in their serum M-spike. The VGPR or better rate should be reported in clinical trials to enable comparison of regimens.

Response assessment using the serum FLC assay

The serum FLC assay criteria come into play only in patients who do not have evidence of measurable disease. As discussed earlier, measurable disease is defined as serum M protein ≥1 g/100 ml or urine M protein ≥200 mg per 24 h. The FLC assay is not to be used for response assessment in patients who have evidence of measurable disease in the serum or urine. In addition, the baseline level of the involved FLC should be at least ≥10 mg/l and the FLC assay should have an abnormal ratio (clonal).

The serum FLC assay consists of two separate assays, one to detect free-κ (normal range, 3.3–19.4 mg/l) and the other to detect free-λ (normal range, 5.7–26.3 mg/l) light chains. The test assesses clonality based on the ratio of κ/λ light chain levels (normal reference range, 0.26–1.65). Patients with κ/λ FLC ratio <0.26 are defined as having monoclonal λ FLC and those with ratios >1.65 are defined as having a monoclonal κ FLC. The monoclonal light chain isotype is referred to as the ‘involved’ FLC isotype, and the opposite light chain type is the ‘uninvolved’ FLC type.

FLC levels vary considerably with changes in renal function and do not solely represent monoclonal elevations. Thus, both the level of the involved and the uninvolved FLC isotypes (that is, the involved-uninvolved difference) are considered in assessing response.

Definition of disease progression in patients with CR

The IMWG uniform response criteria have clarified that patients in CR need to meet the same criteria for disease progression as other patients not in CR for purposes of calculating progression-free survival and time to progression.[29] The relapse from CR definition should not be used to define progression in these patients as had been done earlier in the EBMT criteria. The immunofixation results used to define CR can vary significantly due to laboratory variation. Thus, using relapse from CR criteria would erroneously result in shorter time to progression and progression-free survival for CR patients as compared to those not in CR with regimens that produce high CR rates.

Definition of disease progression in SMM

The criteria used for MM cannot be used to determine disease progression in SMM. A recent American Society of Hematology/Food and Drug Administration (ASH-FDA) panel has defined specific criteria for disease progression in SMM (Table 5).

Minor response

The IMWG response criteria deleted the category of minor response, as it was not felt to be reliable. However, a recent ASH-FDA panel proposed that the category of minor response as defined in the EBMT criteria (Table 6) be used in patients with relapsed refractory myeloma to obtain a signal of activity in phase I/II trials of novel agents. Table 5 also defines relapsed myeloma and relapsed and refractory myeloma recommended by the ASH-FDA panel.

Survival estimates

Several estimates of survival such as overall survival, disease-free survival, progression-free survival, time to progression and event-free survival are used to describe outcome in myeloma. The specific definitions of these terms and their respective role in myeloma are listed in Table 7.

Summary

We provide a summary of current criteria and definitions that are used in diagnosis, prognosis, risk stratification and response assessment in myeloma. We have highlighted the limitations of current criteria, and corrected any inadvertent errors that have been identified in the various published criteria over time. The paper also provides input in areas where there is controversy or lack of clarity.

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Table 1

Clinical and laboratory abnormalities in myeloma[1]

Clinical/laboratory features	Proportion of patients with abnormality (%)
Anemia <12 g/100 ml	72
Bone lesions (lytic lesions, pathologic fractures or severe osteopenia)	80
Renal failure (serum creatinine ≥2 mg/100 ml)	19
Hypercalcemia (≥11 mg/100 ml)	13
Monoclonal protein on serum protein electrophoresis	82
Monoclonal protein on serum protein immunofixation	93
Monoclonal protein on serum plus urine protein immunofixation (or serum immunofixation plus serum free light chain assay)	97
Type of M protein	
IgG	52
IgA	21
Light chain only	16
Increased ≥10% clonal bone marrow plasma cells	96

Table 2

Diagnostic criteria for plasma cell disorders

Disorder	Disease definition	References
Monoclonal gammopathy of undetermined significance (MGUS)	All three criteria must be met: Serum monoclonal protein <3 g/100 ml Clonal bone marrow plasma cells <10% and Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	6
Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥3 g/100 ml and/or clonal bone marrow plasma cells ≥10% and Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia or renal failure that can be attributed to a plasma cell proliferative disorder	6
Multiple myeloma	All three criteria must be met except as noted: Clonal bone marrow plasma cells ≥ 10% Presence of serum and/or urinary monoclonal protein (except in patients with true non-secretory multiple myeloma) and Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically Hypercalcemia: serum calcium ≥ 11.5 mg/100 ml or Renal insufficiency: serum creatinine >1.73 mmol/l) Anemia: normochromic, normocytic with a hemoglobin value of >2 g/100 ml below the lower limit of normal or a hemoglobin value <10 g/100 ml Bone lesions: lytic lesions, severe osteopenia or pathologic fractures	6,7
Waldenström's macroglobulinemia	Both criteria must be met: IgM monoclonal gammopathy (regardless of the size of the M protein) and ≥ 10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (e.g. surface IgM+, CD5+/−, CD10−, CD19+, CD20+, CD23−) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma. Note: IgM MGUS is defined as Serum IgM monoclonal protein <3 g/100 ml, and bone marrow lymphoplasmacytic infiltration <10% and No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly Smoldering Waldenström's macroglobulinemia (also referred to as indolent or asymptomatic Waldenström's macroglobulinemia) is defined as: Serum IgM monoclonal protein ≥ 3 g/100 ml and/or bone marrow lymphoplasmacytic infiltration ≥ 10%, and No evidence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly that can be attributed to a lymphoplasma cell proliferative disorder	8–12
Solitary plasmacytoma	All four criteria must be met: Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI of spine and pelvis (except for the primary solitary lesion)	13,14

Disorder	Disease definition	References
	Absence of end-organ damage such as CRAB lesions that can be attributed to a lymphoplasma cell proliferative disorder	
Systemic AL amyloidosis	All four criteria must be met:	15
	Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract or peripheral nerve involvement)	
	Positive amyloid staining by Congo red in any tissue (e.g. fat aspirate, bone marrow or organ biopsy)	
	Evidence that amyloid is light chain-related established by direct examination of the amyloid (immunohistochemical staining, direct sequencing, and so on) and	
	Evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal free light chain ratio or clonal plasma cells in the bone marrow).	
	Note: Approximately 2–3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed above; the diagnosis of AL amyloidosis must be made with caution in these patients	
POEMS syndrome	All three criteria must be met:	16
	Presence of a monoclonal plasma cell disorder	
	Peripheral neuropathy and	
	At least one of the following seven features: osteosclerotic bone lesions, Castleman's disease, organomegaly, endocrinopathy (excluding diabetes mellitus or hypothyroidism), edema, typical skin changes and papilledema.	
	Note: Not every patient meeting the above criteria will have POEMS syndrome; the features should have a temporal relationship with each other and no other attributable cause. The absence of osteosclerotic lesions should make the diagnosis suspect. Elevations in plasma or serum levels of vascular endothelial growth factor and thrombocytosis are common features of the syndrome and are helpful when the diagnosis is difficult.	

Abbreviations: AL, amyloid light chain; MRI, magnetic resonance imaging.

Modified and reproduced with permission from Rajkumar *et al.*[15] ©Mayo Clinic Proceedings PDEMS (Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).

Table 3

International staging system

Stage I
Serum β_2-microglobulin <3.5 mg/l and
Albumin ≥3.5 g/100 ml
Stage II
Not fitting stage I or II
Stage III
Serum β_2-microglobulin ≥5.5 mg/l

Table 4

Mayo risk stratification for myeloma: definition of high-risk disease[7]

High-risk characteristic	Percentage of newly diagnosed patients with the abnormality (%)[1,22,23]
Conventional cytogenetics	
Deletion of chromosome 13 (monosomy)	14
Hypodiploidy	9
Either hypodiploidy or deletion 13	17
Fluorescent in situ hybridization (FISH)	
t(4;14)	15
t(14:16)	5
17p–	10
Plasma cell labeling index (PCLI) studies: PCLI ≥3%	6
Any one of the above high-risk abnormalities	25–30

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Table 5

International Myeloma Working Group uniform response criteria for multiple myeloma[29]

Response subcategory	Response criteria
Complete response[a] (CR)	Negative immunofixation of serum and urine and Disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above plus
	Normal FLC ratio and
	Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)[a]	Serum and urine M-component detectable by immunofixation but not on electrophoresis or ≥90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h
Partial response (PR)	≥50% reduction of serum M protein and reduction in 24-h 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 bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥30%
	In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease
Progressive disease (PD)[a]	Increase of 25% from lowest response value in any one or more of the following:
	Serum M-component (absolute increase must be ≥0.5 g/100 ml)[c] and/or
	Urine M-component (absolute increase must be ≥200 mg per 24 h) and/or
	Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved
	FLC levels (absolute increase must be >10 mg/l)
	Bone marrow plasma cell percentage (absolute % must be ≥10%)
	Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	Development of hypercalcemia (corrected serum calcium >11.5 mg/100 ml) that can be attributed solely to the plasma cell proliferative disorder

[a]Note clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

All response categories (CR, sCR, VGPR and PR) require two consecutive assessments made at any time before the institution of any new therapy; complete, PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

Adapted with permission from Durie *et al*.[29]

[c]for progressive disease, serum M-component increases of ≥1 gm/100 ml are sufficient to define relapse if starting M-component is ≥5 gm/100 ml.

Table 6

Additional response criteria for specific disease stages[30]

Category	Criteria
Definition of relapsed myeloma and relapsed and refractory myeloma	Relapsed myeloma: at least one prior regimen, and not meeting criteria for relapsed and refractory myeloma
	Relapsed and refractory myeloma: relapse of disease while on salvage therapy, or progression within 60 days of most recent therapy
Minor response (MR) in patients with relapsed refractory myeloma	≥25% but <49% reduction of serum M protein *and* reduction in 24 h urine M protein by 50–89%, which still exceeds 200 mg per 24 h
	In addition to the above criteria, if present at baseline, 25–49% reduction in the size of soft tissue plasmacytomas is also required
	No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progression to active myeloma in patients with smoldering myeloma	Evidence of progression based on the IMWG criteria for progressive disease in myeloma (Table 5) *and*
	Any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder
	Development of new soft tissue plasmacytomas or bone lesions
	Hypercalcemia (>11 mg/100 ml)
	Decrease in hemoglobin of ≥2 g/100 ml
	Serum creatinine level ≥2 mg/100 ml

Abbreviation: IMWG, International Myeloma Working Group. Adapted with permission from Anderson *et al.*[30]

Table 7

Definitions of time to event end points[30]

End point	Definition	Comment
Time to progression (TTP)	Duration from start of treatment to disease progression, with deaths due to causes other than progression censored	TTP is useful in assessing the activity of a drug and the durability of treatment benefit, but does not take into account the fact that a treatment may be associated with increased treatment-related deaths and hence should be assessed in conjunction with progression-free survival
Progression-free survival (PFS)	Duration from start of the treatment to disease progression or death (regardless of cause of death), whichever comes first	Should be reported in conjunction with TTP
Event-free survival (EFS)	The definition for EFS depends on how 'event' is defined. In many studies, the definition of EFS used is the same as PFS. EFS may include additional 'events' that are considered to be of importance besides death and progression, including serious drug toxicity	In general in myeloma, most studies reporting EFS are in fact referring to PFS. PFS is a more specific term and is the preferred term to be used, unless the definition of EFS includes additional 'events' besides progression or death that are considered important to take into account
Disease-free survival (DFS)	Duration from the start of CR to the time of relapse from CR. DFS applies only to patients in complete response	Unlike TTP and PFS, the end point of DFS applies only to the subset of patients in complete response, and as such has limited value in myeloma at present
Duration of response (DOR)	Duration from first observation of partial response to the time of disease progression, with deaths due to causes other than progression censored. Duration of CR and PR should each be reported	Unlike TTP and PFS, the end point of DOR applies only to a subset of patients in the study who achieve at least partial response. It expresses the durability of response

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