

**Guidelines for the Uniform Reporting of Clinical Trials: Report of the 2008  
International Myeloma Workshop Consensus Panel I**

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International Myeloma Workshop Consensus Panel I**

## **BACKGROUND**

The treatment of myeloma has evolved rapidly in the last decade.<sup>1</sup> The introduction of several active new drugs and novel targeted investigational agents has resulted in numerous active clinical trials in every stage of the disease. Studies are being conducted worldwide, including an increasing number of multi-center, international trials.<sup>2,3</sup> It is essential that there be consistency in the conduct, analysis, and reporting of clinical trial results. Unless uniform reporting requirements are adhered to, it will be impossible to compare results across trials, or to accurately determine if reported results are valid and reliable. The goal of the 2008 International Myeloma Workshop Consensus Panel I was to develop a set of guidelines for the uniform reporting of clinical trial results in myeloma. We recognize that some compromises have to be made to ensure that adherence to requirements is practical in most countries, academic and community practices, and various groups conducting clinical trials in myeloma. We propose that future clinical trials in myeloma adhere to the guidelines proposed in this manuscript.

## **LINES OF THERAPY**

A line of therapy is defined as one or more cycles of a planned treatment program.<sup>4</sup> This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a

planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

## **DEFINITION OF PATIENT POPULATIONS**

The terms used to define patient populations studied should be standardized. The term relapsed, refractory, relapsed and refractory when used to describe patient populations tested in clinical trials should adhere to the definitions listed below. The definitions are based on a recent ASH-FDA panel on endpoints in myeloma.<sup>5</sup> We also propose that when new clinical trials are initiated that these definitions be used in eligibility criteria to ensure uniformity across trials.

### **Refractory Myeloma**

Refractory myeloma is defined as disease that is non-responsive while on salvage therapy, or progresses within 60 days of last therapy. Non-responsive disease is defined as either failure to achieve minor response or development of progressive disease while on therapy. There are two categories of refractory myeloma: “Relapsed-and-refractory myeloma” and “Primary refractory myeloma”

**Relapsed-and-refractory myeloma:** Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have *achieved minor response (MR) or better at some point in their disease course.*<sup>5</sup>

**Primary refractory myeloma:** Primary Refractory myeloma is defined as disease that is non-responsive in patients who have never achieved a *minor response with any therapy*. It includes patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression; as well as primary refractory, progressive disease where patients meet criteria for true progressive disease.<sup>5</sup>

### **Relapsed myeloma**

Relapsed myeloma is defined as previously treated myeloma which after a period of being off-therapy requires the initiation of salvage therapy but does not meet criteria for either “primary refractory myeloma” or “relapsed-and-refractory myeloma” categories.

### **Additional Qualifiers**

When possible if a clinical trial is targeted to a specific population, it would be best to provide additional qualifiers that describe more precisely the population being studied. For example, “relapsed and refractory to immunomodulatory therapy” or “relapsed and refractory to bortezomib” etc.

### **RESPONSE CRITERIA**

The International Myeloma Working Group (IMWG) uniform response criteria should be used in future clinical trials, with additional clarifications as listed below.<sup>6</sup> The IMWG uniform response criteria were developed to be similar to the European Group for Blood and Bone Marrow Transplant/ International Bone Marrow Transplant Registry/ American Bone Marrow Transplant Registry (EBMT/ IBMTR/ ABMTR) published criteria, commonly referred to as the Blade

criteria or the EBMT criteria,<sup>7</sup> with revisions, correction of inadvertent errors, and improvements that aid uniform reporting. These include the addition of free light chain (FLC) response and progression criteria for patients without measurable disease, modification of the definition for disease progression for patients in complete response, and addition of very good partial response and stringent response categories.

The panel recommends endorsed the definitions of partial response (PR), very good partial response (VGPR), complete response (CR), progressive disease (PD), and stable disease (SD) according to IMWG. Of note, there was unanimous consensus that progressive disease for patients in CR should be defined as per the IMWG criteria. CR patients will need to progress to the same level as VGPR and PR patients to be considered PD. A positive immunofixation alone is not sufficient.<sup>8,9</sup>

The need for bone marrow confirmation of complete response was discussed in detail, but new data showed that up to 13% of patients with immunofixation negative CR may have 5 or more percent plasma cells in the marrow.<sup>10</sup> Bone marrow confirmation is required for coding CR, and the panel recommends no change to the CR definition.

The proposed clarifications and minor changes are recommended and approved by the panel to the IMWG criteria.<sup>11</sup> The IMWG criteria for response and progression incorporating published errata, updated definition of stringent CR (see below) and additional clarifications are listed on Table 1.<sup>6</sup>

**Stringent CR:** The panel approved an update to the definition of stringent CR in the IMWG criteria to require negative clonal cells by multiparametric flow cytometry (with  $\geq 4$  colors). Stringent CR is defined as CR plus absence of phenotypically aberrant PC in bone marrow with a

minimum of 3000 total PC analyzed by multiparametric flow cytometry (“immunophenotypic CR”)<sup>3,12</sup> (Table 1).

**Molecular CR:** The panel approved a definition of molecular CR to be incorporated into the IMWG criteria. Molecular CR is defined as stringent CR plus negative ASO-PCR (sensitivity 10<sup>-5</sup>)(Table 2).

**Minor Response:** The panel concurred with a recent ASH-FDA panel<sup>5</sup> that for patients with relapsed, and refractory myeloma, MR should be reported separately in clinical trials (Table 2). When MR is reported, the specific rate of MR should be given distinctly from the overall response rate (partial response or better) to make clinical trial comparisons possible.

**Additional clarifications:** The following clarifications to IMWG criteria were made for coding CR in patients in whom the only measurable disease is by serum FLC levels. In these patients, CR requires negative serum and urine immunofixation plus a normal FLC ratio of 0.26-1.65, on two consecutive assessments. Similarly to code VGPR in such patients, a >90% decrease in the difference between involved and uninvolved free light chain FLC levels is required on two consecutive assessments. These were inadvertently omitted from the IMWG criteria.<sup>11</sup>

Secondly, after much discussion the panel agreed that MRI and PET-CT findings will not be incorporated formally into the response criteria for purposes of assessing depth of response, but additional single center studies are encouraged.<sup>13</sup>

Finally, the time at which response assessment was conducted should be reported. In addition, the time to best response should also be reported.

## **REPORTING OF EFFICACY RESULTS**

All efficacy results for primary endpoints should be reported only on intent to treat basis. In the case of secondary endpoints, in addition to intent to treat results, results based on actual treatment received can also be reported. The reporting of results in subsets of patients restricted to those who completed certain duration of therapy should be avoided. All patients who were registered and met eligibility criteria regardless of whether they actually received therapy for a meaningful period (or not at all) should be in the denominator for all efficacy calculations. Response assessments should be performed before next therapy is initiated.

In all clinical trials, patients should be followed every 1-2 months until PD to enable accurate calculation of time to progression (TTP), and progression free survival (PFS).

## **ESSENTIAL EFFICACY MEASURES IN PHASE III TRIALS**

Regardless of the primary endpoint studies, all phase III studies should report overall survival (OS), TTP, PFS, duration of response (DOR) and if possible, time to next treatment (TNT), 5 year OS rate and 10 year OS rate. The definitions of TTP, PFS, DOR are listed on Table 3.<sup>6</sup> It is particularly important that both TTP and PFS be reported. Where possible, details of any crossover should be provided.

**Time to next treatment:** Time to next treatment is difficult to accurately compare except in double-blind studies. But is clearly important to report TNT in future phase III trials. TNT is defined time from registration on trial to next treatment or death due to any cause, whichever comes first. To accurately defined TNT, next treatment should start uniformly. The consensus is

that next treatment should start when there is either biological relapse or a significant paraprotein relapse. Biological relapse will be defined using the definition of clinical relapse in the IMWG criteria.<sup>6</sup> In the IMWG criteria clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease and/or end organ dysfunction (CRAB features) that are felt related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, MRI or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l]
4. Decrease in hemoglobin of >2 g/dl [1.25 mmol/l] or to less than 10g/dL
5. Rise in serum creatinine by 2 mg/dl or more [177 mmol/l or more]
6. Hyperviscosity

In some patients, bone pain may be the initial symptom of relapse in the absence of any of the above listed features.

In patients who do not have biological relapse, a significant paraprotein relapse is defined doubling of the M-component in two consecutive measurements separated by  $\leq 2$  months; or an increase in the absolute levels of serum M protein by  $\geq 1$  gm/dl, or urine M protein by  $\geq 500$ mg /24h, or involved FLC level by  $\geq 20$ mg/dl (plus an abnormal FLC ratio) in two consecutive measurements separated by  $\leq 2$  months.

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**Table 1. International Myeloma Working Group Uniform Response criteria for multiple myeloma<sup>6</sup>**

<b>Response subcategory</b>	<b>Response criteria</b>
<b>Complete response* (CR)</b>	<ul style="list-style-type: none"> <li>• Negative immunofixation of serum and urine, and</li> <li>• Disappearance of any soft tissue plasmacytomas, and</li> <li>• &lt; 5% plasma cells in bone marrow</li> </ul>
<b>Stringent complete response (sCR)**</b>	CR as defined above plus <ul style="list-style-type: none"> <li>• Normal FLC ratio, and</li> <li>• Absence of phenotypically aberrant PC in bone marrow with a minimum of 3000 total PC analyzed by multiparametric flow cytometry (with <math>\geq 4</math> colors)</li> </ul>
<b>Very good partial response (VGPR)*</b>	<ul style="list-style-type: none"> <li>• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or</li> <li>• <math>\geq 90\%</math> or greater reduction in serum M-component plus urine M-component &lt;100 mg per 24 h</li> </ul>
<b>Partial Response (PR)</b>	<ul style="list-style-type: none"> <li>• <math>\geq 50\%</math> reduction of serum M-protein and reduction in 24-h urinary M-protein by <math>\geq 90\%</math> or to &lt;200 mg per 24 h</li> <li>• If the serum and urine M-protein are unmeasurable a <math>\geq 50\%</math> decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria</li> <li>• If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, <math>\geq 50\%</math> reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was <math>\geq 30\%</math></li> <li>• In addition to the above criteria, if present at baseline, <math>\geq 50\%</math> reduction in the size of soft tissue plasmacytomas is also required</li> </ul>
<b>Stable disease (SD)</b>	<ul style="list-style-type: none"> <li>• Not meeting criteria for CR, VGPR, PR or progressive disease</li> </ul>
<b>Progressive Disease (PD)*</b>	Increase of 25% from lowest response value in any one or more of the following: <ul style="list-style-type: none"> <li>• Serum M-component (absolute increase must be <math>\geq 0.5</math> g/dl)<sup>c</sup> and/or</li> <li>• Urine M-component (absolute increase must be <math>\geq 200</math> mg/24 h) and/or</li> <li>• Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels(absolute increase must be &gt;10 mg/L)</li> <li>• Bone marrow plasma cell percentage (absolute % must be <math>\geq 10\%</math>)</li> <li>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas</li> <li>• Development of hypercalcemia (corrected serum calcium &gt;11.5 mg/dl) that can be attributed solely to the plasma cell proliferative disorder</li> </ul>

All response categories (CR, sCR, VGPR, PR) require two consecutive assessments made at anytime before the institution of any new therapy; complete and 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.

**\*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 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.

\*\*Note stringent CR definition updated to reflect need for multiparametric flow cytometry rather than immunofluorescence or immunohistochemistry

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**Table 2. Additional Response Criteria and Updates**

CATEGORY	CRITERIA
<b>Minor Response (MR) in patients with relapsed refractory myeloma adopted from the EBMT criteria<sup>7</sup></b>	<ul style="list-style-type: none"> <li>• <math>\geq 25\%</math> but <math>&lt; 49\%</math> reduction of serum M protein <i>and</i> reduction in 24 hour urine M-protein by 50 to 89% which still exceeds 200 mg per 24 h</li> <li>• In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required</li> <li>• No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)</li> </ul>
<b>Molecular CR</b>	Stringent CR plus <ul style="list-style-type: none"> <li>• negative ASO-PCR, sensitivity <math>10^{-5}</math></li> </ul>

**Table 3. Definitions of Time to Event Endpoints<sup>5,6</sup>**

<b>Endpoint</b>	<b>Definition</b>
Time to progression (TTP)	Duration from start of treatment to disease progression, with deaths due to causes other than progression censored.
Progression-free survival (PFS)	Duration from start of the treatment to disease progression or death (regardless of cause of death), whichever comes first.
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.
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.
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.

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