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

S. Vincent Rajkumar, Jesus San Miguel, and Jean Luc Harousseau on behalf of the International Myeloma Workshop Consensus Panel I

Goal

- The goal of the 2008 IMW Consensus Panel I was to develop a set of guidelines for the uniform reporting of clinical trial results
- We propose that future clinical trials in myeloma adhere to the guidelines proposed by this panel.

I. RESPONSE CRITERIA

- The International Myeloma Working Group (IMWG) uniform response criteria should be used in future clinical trials, with additional clarifications

IMWG Criteria: Key Features

- Corrects inadvertent errors in EBMT criteria
- Clarifies omissions
- Addition of FLC criteria
- Modification of the definition for disease progression for patients in CR
- Addition of VGPR and stringent CR categories.

IMWG Criteria: No changes in key response definitions

- PR, VGPR, CR, PD, SD defined according to IMWG.
  - Note PD for patients in CR should be defined as per the IMWG criteria.

Bone Marrow Confirmation for CR

- Up to 13% of patients with IF- CR may have ≥5% plasma cells in the marrow.
- Bone marrow confirmation is required for coding CR, and the panel recommends no change to the CR definition.

New Additions/Updates

- MR
- Definition of stringent CR
- Molecular CR

Minor Response

- MR as defined by EBMT criteria, be reported for patients with relapsed, and refractory myeloma
- When MR is reported, the specific rate of MR should be given distinctly from the overall response rate

Stringent CR: Update of definition

- Requires negative clonal cells by multiparametric flow cytometry (with ≥4 colors).
- Normal FLC ratio
- All other requirements of CR

Molecular CR

- Molecular CR is defined as stringent CR plus negative ASO-PCR (sensitivity 10^{-5})

Additional clarifications:
Measurable Disease by FLC only

- CR: Negative serum and urine IFE plus a normal FLC ratio
- VGPR: ≥90% decrease in the difference between involved and uninvolved FLC levels

PET and MRI

- Not be incorporated formally into the response criteria for purposes of assessing depth of response, but additional single center studies are encouraged.

Reporting Response Data

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

Reporting Response Data

- Duration of CR and PR should each be reported.

IMWG Criteria

- The IMWG criteria for response and progression incorporating published errata, updated definition of stringent CR, and additional clarifications published in Kyle et al. Leukemia 2009.

II. LINES OF THERAPY

- A line of therapy is defined as one or more cycles of a planned treatment program.
  - *single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner.*

- ***A new line of therapy starts*** when (on-therapy) a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression or toxicity.
- *A new line of therapy also starts* when (off-therapy) a planned period of observation is interrupted by a need for additional treatment for the disease.

III. DEFINITION OF PATIENT POPULATIONS

- The terms used to define patient populations studied must be standardized.
- The definitions are based on a recent ASH-FDA panel on endpoints in myeloma.

Disease Categories

- Newly Diagnosed
- Refractory
  - Primary refractory
  - Relapsed and refractory
- Relapsed

Refractory Myeloma

- Defined as disease that is non-responsive *(failure to achieve MR)* while on salvage therapy, or progresses within 60 days of last therapy.

- There are 2 categories of refractory myeloma:
  - Primary refractory myeloma
  - Relapsed-and-refectory myeloma

Primary refractory myeloma

- Patients who have never achieved a *MR with any therapy*
  - *non-responding, non-progressive*
  - *progressive disease*

Relapsed-and-refractory myeloma

- Patients who have achieved minor response (MR) or better at some point in their disease course, but them relapse and become non-responsive *(failure to achieve MR)* while on salvage therapy,

Relapsed myeloma

- 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 for relapsed-refractoy Myeloma

- 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.

IV. 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 ITT 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.

REPORTING OF EFFICACY RESULTS

- Response assessments should be performed before next therapy is initiated.
- Patients should be followed every 1-2 months until PD to enable accurate calculation of TTP and PFS

V. ESSENTIAL EFFICACY MEASURES IN PHASE III TRIALS

- All phase III studies should report:
  - OS
  - TTP
  - PFS
  - Duration of response (DOR)
- If possible, time to next treatment (TNT), 5 year OS rate and 10 year OS rate.

Time to Next Treatment (TNT)

- Ideally double-blind studies needed
- 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.
- Next treatment should start when there is either clinical relapse or a significant paraprotein relapse.

Clinical Relapse

- Defined using the definition of clinical relapse in the IMWG criteria (CRAB features).

Significant Paraprotein Relapse

- Defined as doubling of the M-component in two consecutive measurements separated by ≤ 2 months;
- Or increase in the absolute levels of serum M protein by ≥1gm/dl, or urine M protein by ≥500mg /24h, or involved FLC level by ≥20mg/dl (plus an abnormal FLC ratio) in two consecutive measurements separated by ≤ 2 months.

Plan

- Consensus Panel I report will be published
- Recommend all new and if possible existing trials follow the guidelines for reporting results recommended by the panel