New IMWG Response Criteria

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Limitations of current criteria
Response depth and outcome

CR, complete response; MR, minor response; MRD, minimal residual disease; nCR, near complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

CR
nCR
VGPR
PR
MR
Diagnosis
sCR
CR
nCR
Cure?

Time to disease progression

CR, complete response; MR, minor response; MRD, minimal residual disease; nCR, near complete response; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
Therapy and depth of response

CR, complete response; CVD, cyclophosphamide, bortezomib, and dexamethasone; CVRD, bortezomib, dexamethasone, cyclophosphamide and lenalidomide; KRd, carfilzomib, lenalidomide and dexamethasone; nCR, near complete response; ORR, overall response rate; PAD, bortezomib, doxorubicin, and dexamethasone; PR, partial response; RD, lenalidomide and dexamethasone; RVD, lenalidomide, bortezomib and dexamethasone; sCR, stringent complete response; TD, thalidomide and dexamethasone; VAD, vincristine, doxorubicin and dexamethasone; VGPR, very good partial response; VTD, bortezomib, thalidomide, and dexamethasone

Transitioning from conventional CR

**Complete Response (CR)**
- Negative serum and urine immunofixation
- <5% PCs in marrow

**Stringent Complete Response (sCR)**
- Normal FLC ratio
- No clonal plasma cells in marrow

**MRD negative**
- Flow negative MRD
- Sequencing negative MRD
- Imaging negative MRD
How do we define MRD negativity?

*The tools:*

- Flow cytometry
- NextGen sequencing
- Imaging
Depth of response and outcome

**PFS**
- Time to progression (%)
- Median: 80
- Median: 45
- Median: 27
- MRD– <10^-5 (n=30)
- MRD+ 10^{-3}–10^{-5} (n=37)
- MRD+ >10^{-3} (n=43)

**OS**
- Survival (%)
- Median: NR
- Median: 55

NR, not reached; OS, overall survival; PFS, progression free survival

Deeper response... better outcome

MRD after novel combinations

VRD induction → VRD or HDT consolidation → VRD consolidation → Len maintenance for 1 year

MRD at pre-maintenance

MRD at post-maintenance

HDT, high-dose therapy; Len, lenalidomide; VRD, bortezomib, lenalidomide and dexamethasone

Role of imaging
Post-induction PET

Elena Zamagni et al. Blood 2011;118:5989-5995

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Post ASCT PET

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Elena Zamagni et al. Blood 2011;118:5989-5995

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PET-CT normalisation Pre-maintenance: PFS

$p < 0.001$

69%

51.6%
PET-CT normalisation Pre-maintenance: OS

$p = 0.003$

94.6%

69.9%
PET and Flow negative: PFS

\( p = 0.02 \)

89.6%

54.5%
Durability of response

**TT2 overall survival by 3-year CR status**

- **Deaths/N 5-year estimate (%)**
  - a) sus–CR: 38/258, 82
  - b) non–CR: 78/218, 59
  - c) los–CR: 27/37, 24

Log-rank P-value <0.0001

P-values:
- a vs b <0.001
- a vs c <0.001
- b vs c <0.001

Revised IMWG response criteria

<table>
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<tr>
<th>IMWG MRD negativity criteria</th>
<th>Response subcategory</th>
<th>Response criteria</th>
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<tbody>
<tr>
<td>MRD negativity criteria</td>
<td>Sustained MRD-negative</td>
<td>MRD –ve in the marrow (next-generation flow cytometry [NGFC] and/or next-generation sequencing [NGS]) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity</td>
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<tr>
<td></td>
<td>Flow MRD-negative</td>
<td>Absence of phenotypically aberrant clonal plasma cells by NGFC on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells or higher</td>
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<td>Sequencing MRD-negative</td>
<td>Absence of clonal plasma cells by NGS on bone marrow aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in $10^5$ nucleated cells or higher</td>
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<td>Imaging + MRD-negative</td>
<td>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 &lt; mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue</td>
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</tbody>
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CT, computed tomography; IMWG, International Myeloma Working Group; MM, multiple myeloma; PET, positron emission tomography; SUV, standard uptake value Kuma, et al. Lancet Oncol; in press.
## Endpoints

<table>
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<th>Definition</th>
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<td><strong>TTP</strong></td>
<td>Duration from start of treatment to disease progression, with deaths from causes other than progression censored.</td>
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<tr>
<td><strong>PFS</strong></td>
<td>Duration from start of the treatment to disease progression or death (regardless of cause of death), whichever comes first.</td>
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<td><strong>EFS</strong></td>
<td>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.</td>
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<td><strong>DFS</strong></td>
<td>Duration from the start of MRD negativity to the time of reappearance of MRD. DFS applies only to patients in MRD negative state.</td>
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<tr>
<td><strong>DOR</strong></td>
<td>Duration from first observation of PR to the time of disease progression, with deaths from causes other than progression censored.* Duration of MRD, CR and PR should each be reported as appropriate.</td>
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</tbody>
</table>
Questions