Advances in minimal residual disease testing in myeloma

Ola Landgren, M.D., Ph.D.
Chief of Myeloma Service, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Cornell Medical College, New York

New York, June 24, 2016
Advances in MRD testing in myeloma

2015-2016
What we accomplished the past year

• MRD is meaningful in myeloma: formal evidence

• MRD = MRD: IMWG guidelines

• White paper in progress: collaboration
2 meta analyses
Meta analysis show MRD is valid

MRD positivity (vs. MRD negativity) and progression-free survival*

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard Ratio</th>
<th>HR</th>
<th>95%-CI</th>
<th>W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korde 2015</td>
<td></td>
<td>10.40</td>
<td>[1.63; 66.35]</td>
<td>2</td>
</tr>
<tr>
<td>Mateos 2014</td>
<td></td>
<td>2.50</td>
<td>[1.54; 4.05]</td>
<td>31</td>
</tr>
<tr>
<td>Paiva 2008</td>
<td></td>
<td>2.85</td>
<td>[2.01; 4.05]</td>
<td>60</td>
</tr>
<tr>
<td>Silvennoinen 2013</td>
<td></td>
<td>3.52</td>
<td>[1.13; 10.98]</td>
<td>5</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td>2.85</td>
<td>[2.17; 3.74]</td>
<td>10</td>
</tr>
</tbody>
</table>

*A higher hazard ratio indicates increased risk for each survival endpoint (i.e. risk of progression)

Landgren et al. (in press)
prospective trials
Determination trial (IFM/DFCI 2009) show MRD is valid

RVd arm, PFS

Transplant arm, PFS

Post consolidation (9/2015)

What we accomplished the past year

• MRD is meaningful in myeloma: formal evidence

• MRD = MRD: IMWG guidelines

• White paper in progress: collaboration
International Myeloma Working Group Consensus Criteria for Response and Minimal Residual Disease Assessment in Multiple Myeloma

Short title: Multiple Myeloma Response Criteria

Word count: Abstract: 200; Text: 8300; Tables: 7; References: 115

Correspondence to: Prof. Shaji K. Kumar, M.D.
Division of Hematology
MAYO CLINIC
200 First St, SW
Rochester, MN USA 55905
kumar.shaji@mayo.edu


Affiliations: Division of Hematology, Mayo Clinic, Rochester, MN, USA (Prof. S Kumar, MD, Prof. S V Rajkumar, MD, Prof. Robert A. Kyle, MD); Dana-Farber Cancer Institute, Boston, MA, USA (Prof. K.C. Anderson, MD, Prof. Paul G. Richardson, MD, Prof. N Munshi, MD); Clinica Universidad de Navarra, Centro de Investigacion Medica Aplicada (CIMA), Pamplona, Spain (B. Paiva, Ph.D., Prof. J F San Miguel, MD); Cedars-Sinai Comprehensive Cancer Center, Los Angeles, CA, USA (Prof. B GM Durie, MD); Memorial Sloan Kettering Cancer Center, New York, NY, USA (O. Landgren, MD); University Hospital, Nantes, France (Prof. P. Moreau, MD, Prof. J L Harousseau, MD); University Hospital of Salamanca/BSAL, Salamanca, Spain (Prof. A Orfao, PhD., Prof MV Mateos MD); Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitària Città della Salute e della Scienza di Torino, Torino, Italy (Prof. A Palumbo, MD, Prof. M Boccadoro, MD);
Which is better? We have options!
Kumar et al. (in press)
<table>
<thead>
<tr>
<th>IMWG MRD negativity criteria</th>
<th>Response subcategory</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Requires complete response as originally defined)</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>
</tr>
<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>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td></td>
<td>Imaging &amp; 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>
</tr>
</tbody>
</table>

Kumar et al. *(in press)*
What we accomplished the past year

• MRD is meaningful in myeloma: formal evidence

• MRD = MRD: IMWG guidelines

• White paper in progress: collaboration
Teleconference to discuss the writing of a White Paper on MRD in multiple myeloma
What is next?
Practical next steps

Future steps
Will MRD become a regulatory endpoint in myeloma?

A) Yes

B) A

C) B
MRD as a regulatory end-point

Surrogate/ MRD

Accelerated approval

PFS/OS

Regular approval

Single trial model
Key factors to make MRD a regulatory end-point

- MRD done the same way
- MRD done for all patients
- Complete followup
Future steps
MRD biology?
Every patient has several parallel myelomas already at diagnosis

>10% light-chain restricted plasma cells

Many sub-clones in every myeloma patient at diagnosis

Fraction of patients (%)

Sub-clones respond differently to given drugs

Lohr et al Cancer Cell 2014
Significantly recurrent mutations of individual genes in multiple myeloma

- KRAS
- NRAS
- BRAF
- CYLD
- FAM46C
- TRAF3
- DIS3
- IRF4
- HIST1H1E
- ACTG1
- TP53
- LTB
- PRDM1
- RB1
- MAX

2. Walker BA. et al., *JCO*, 2015; 33(33): 3911-20
when to start therapy?
Patients with mutations in significantly recurrent multiple myeloma genes

Mailankody et al. (oral presentation, June 3) ASCO 2016

Newly diagnosed multiple myeloma

Smoldering myeloma

Newly diagnosed multiple myeloma versus smoldering myeloma, Fisher’s exact test: P=0.005
when to modify therapy?
MRD-driven treatment for newly diagnosed myeloma patients

Footnote: Modern combination therapy: e.g., carfilzomib, lenalidomide, and dexamethasone (reference: (8)); maintenance therapy: e.g., lenalidomide

Landgren and Giralt. Bone Marrow Transplantation 2016
stop therapy?
Longitudinal MRD testing

- Ensure maintained MRD $10^{-6}$ negativity
- Dissect mechanisms of MRD positivity, develop targets
- Develop strategies when MRD $10^{-6}$ negativity $\rightarrow$ positivity

Landgren et al. *unpublished data*
Modern combination therapy → rapid, deep and sustained MRD-
Quality of life
WELCOME
TO
NEW YORK
Let’s get the party started!