Strategies for MRD in MM - Goals

To develop a manuscript i.e., a perspective or white paper, the purpose of which is to document/clarify the role of MRD in improving multiple myeloma patient care and enhancing the development of new therapies. This document will cover:

• State of the science and technology supporting the use of MRD in multiple myeloma.
• Summary of findings from recent meta-analyses of MRD.
• A pathway including clinical trial designs to further establish the value of MRD in management of cancer patients and its value as a response biomarker/surrogate endpoint for multiple myeloma.

The manuscript will help inform design of future clinical trials and, therefore, assist pharma and diagnostics companies in product development.
Strategies for MRD in MM - Team

Co-chairs: Kenneth Anderson, Daniel Auclair

**Sub-Group 1**
Data Science & Technology

- Lead: Hervé Avet-L’Oiseau (CHU-Toulouse)

**Sub-Group 2**
Meta-Analysis

- Leads: Nikhil Munshi (DFCI)
  - Ola Landgren (MSKCC)

**Sub-Group 3**
Clinical Trial Designs

<table>
<thead>
<tr>
<th>3A. New Drug Approval Evidence</th>
<th>3B. Changing Clinical Practice with Existing Drugs</th>
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<tr>
<td>Lead: Nicole Gormley (FDA)</td>
<td>Lead: Shaji Kumar (Mayo)</td>
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**Members**

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Strategies for MRD in MM - Timelines


- Subteams Teleconf.
- Subteams drafts
- First full draft
- Final Doc.
- Submission
- F2F Meeting NYC June 23rd

White Paper

Development of Novel Trials Concepts
Sub-Group I: Data Science and Technology

Flow vs NGS MRD – At the beginning
Sub-Group I: Data Science and Technology

Flow vs NGS MRD - Now
Sub-Group I: Data Science and Technology

Minimal Residual DISEASE
Sub-Group II: Meta-Analyses

Munshi N et al., JAMA Oncol, in press
Sub-Group II: Meta-Analyses

How much is enough?

“You must not use a steam hammer to crack a nut if a nutcracker will do”
- Lord Diplock
Sub-Group IIIA: Trial Designs – New Drugs Evidence

**Single Trial Model**

- Surrogate/ MRD
- Accelerated Approval
- PFS/OS
- Regular Approval

**Multiple Trial Model**

- Surrogate/ MRD
- Accelerated Approval
- Regular Approval
Sub-Group IIIB: Changing Clinical Practice with Existing Drugs

New IMWG Criteria that include MRD

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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>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>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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<tr>
<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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<tr>
<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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<tr>
<th>Endpoint</th>
<th>Definition</th>
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<td>TTP</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>PFS</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>EFS</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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<tr>
<td>DFS</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>DOR</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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Sub-Group III B: Changing Clinical Practice with Existing Drugs

Impact on patients?