Minimal Residual Disease
July 14, 2023

Tech Support
1-719-234-7952
Resources

• Resource tab includes
  – Speaker bios
  – Copy of the slide presentation
  – Exhibit Hall

Submit your questions throughout the program!
MMRF Research Initiatives

For more information, visit themmrf.org

Speakers

Benjamin A. Derman, MD
University of Chicago
Chicago, Illinois

Rafael Fonseca, MD
Mayo Clinic
Phoenix, Arizona
Goals of Multiple Myeloma Therapy

- Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible.
- Eliminate myeloma cells (as measured via minimal residual disease [MRD] testing).
- Improve quality of life with as few treatment side effects as possible.
- Provide the longest possible period of response before first relapse.
- Prolong overall survival.
Measuring Response to Therapy

Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

Stable disease
Minor response
Partial response
Very good partial response
Complete response (CR): (100% decrease in M protein/<5% plasma cells in bone marrow biopsy)
Stringent CR (no plasma cells in bone marrow biopsy)
Minimal residual disease negative

Myeloma cell burden

What is MRD?

The presence of small amounts of myeloma cells in the body after treatment

The most sensitive MRD tests can detect at least 1 myeloma cell out of 1,000,000 cells.
Why should we measure MRD?

- With increasingly effective treatments, more patients can achieve a CR/sCR (no myeloma proteins in the blood or bone marrow by conventional tests)...
- ...but low levels of myeloma cells may remain and may be responsible for disease progression

How is MRD measured?

- Diagnostic
- Tumor burden
- MRD
- Flow cytometry
- Next-generation DNA sequencing
Techniques Available to Measure MRD in Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>Next-generation flow (NGF)</th>
<th>Next-generation sequencing (NGS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Availability</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Diagnostic sample</td>
<td>Helpful but not mandatory</td>
<td>Mandatory</td>
</tr>
<tr>
<td>Applicability</td>
<td>Universal (~100%)</td>
<td>High (~90%)</td>
</tr>
<tr>
<td>Turnaround time</td>
<td>2 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>Cost</td>
<td>~250 USD</td>
<td>~700 USD</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>With ~10 million cells</td>
<td>With around 2+ million cells</td>
</tr>
<tr>
<td>Quantitative</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fresh sample</td>
<td>Needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Patchy sample</td>
<td>Impacts</td>
<td>Impacts</td>
</tr>
<tr>
<td>Global cell characterisation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Standardisation</td>
<td>Ongoing (EuroFlow)</td>
<td>Yes (Adaptive)</td>
</tr>
</tbody>
</table>

Adapted from Paiva B et al. Blood. 2015;125:3059.

Key Terms for MRD

**MRD positive or MRD positivity (MRD+)**
- Myeloma cells are still detectable

**MRD negative or MRD negativity (MRD-)**
- Myeloma cells are not detected

**Sustained MRD-**
- Two measurements of MRD negativity performed at least 12 months apart

*Level of sensitivity can be different depending on methodology used (flow cytometry or NGS) and the number of cells analyzed*
Right now, measurement of MRD depends on counting cells or DNA sequences in bone marrow samples.

What if myeloma is present outside of the bone marrow?

Imaging (PET/CT or DW-MRI) may detect MRD outside the bone marrow. Peripheral blood tests are also under investigation.

Patients Who Achieve MRD Negativity Following Treatment Live Longer Than Those Who Are MRD Positive

Key points from 44 studies analyzed

- MRD negativity is associated with longer progression-free and overall survival.
- This association stands regardless of disease risk, MRD assay used, sensitivity threshold, disease setting, and conventional disease response.

Where is the MRD field going?

- MRD-driven therapy
- New MRD assays that do not depend on bone marrow samples

Three Types of MRD Blood Tests

- Cell-free DNA
  - DNA sequencing
- Mass spectrometry
- Single-cell sequencing
- Circulating myeloma cells
Blood-Based MRD Testing: Mass Spectrometry

Induction: KRD × 4 → Melphalan 200 mg/m² + ASCT → Consolidation: KRD × 14 → Maintenance: lenalidomide

Mass spectrometry (MS) is being evaluated as a method to detect free light chains (FLCs) in the blood as a potentially more sensitive test to detect MRD in patients after therapy. There are several different methods to do this.


A study was performed in patients with newly diagnosed myeloma who had both bone marrow (NGS) and blood (MS) MRD samples drawn at the same time.

In some cases, MS from the blood was able to detect disease when bone marrow testing was not—AND this identified patients who would later have disease progression.

MS may provide a useful alternative to bone marrow testing to detect MRD in patients and may even help identify patients at increased risk of early relapse if they are MRD negative but MS positive during maintenance therapy.


Summary

MRD is the deepest response after myeloma treatment, including bone marrow MRD and imaging MRD. Flow cytometry and NGS are the two most commonly used marrow MRD tests. Blood-based MRD is under investigation.

MRD has been associated with longer progression-free and overall survival to predict lower risk of progression.

MRD response–directed therapy is being assessed in clinical studies to explore how to guide treatment decisions in myeloma.

MRD status is under investigation as an end point in clinical studies helping to expedite new drug approval in myeloma.
# Achieving MRD Negativity

**Rafael Fonseca, MD**  
Mayo Clinic  
Phoenix, Arizona

## MRD Negativity Achieved in Patients With NDMM by Various Regimens

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>ASCT</th>
<th>MR -negativity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triplet regimen</strong>¹²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRd 8 cycles</td>
<td>Yes</td>
<td>58%</td>
</tr>
<tr>
<td>KRd 12 cycles</td>
<td>No</td>
<td>54%</td>
</tr>
<tr>
<td>VRd ×6 cycles</td>
<td>Yes</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Quadruplet regimen</strong>²³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRd-daratumumab ×6 cycles</td>
<td>Yes</td>
<td>51%</td>
</tr>
<tr>
<td>KRd-daratumumab ×8 cycles</td>
<td>No</td>
<td>71%</td>
</tr>
</tbody>
</table>

3. Landgren O et al. JAMA Oncol. 2021;7:862
MRD Negativity Achieved in Patients With NDMM by Various Regimens

**DETERMINATION phase 3 study**

Newly diagnosed myeloma patients

365 patients - 357 patients

EARLY-TRANSPLANT ARM

Revlimid + Velcade + dex (RVd)

Stem cell collection

ASCT

RVd

R

LATE-TRANSPLANT ARM

Revlimid + Velcade + dex (RVd)

Induction

Transplant

Consolidation

RVd

R

*Patients who achieve MRD negativity following treatment experience longer remission than those who are still MRD positive after treatment.*

MRD by next-generation sequencing (sensitivity $1 \times 10^{-5}$)

Revlimid Maintenance Therapy: Improves Depth of Response

Disease response

Before Maintenance

During/After Maintenance

Number of Patients

- MRD negative
- CR
- VGPR
- ≤PR

Cumulative Survival

PFS (Months)

At maximal response during or after maintenance treatment with Revlimid

Maintenance Duration

Myeloma XI Study

Newly diagnosed myeloma patients

Induction

CTD/CRD

KCRD

Consolidation

CVD

No CVD

ASCT

730 patients

518 patients

Maintenance

Revlimid

Observation

Median PFS (mos) at time of randomization to maintenance therapy (median follow up 44.7 mos)

<table>
<thead>
<tr>
<th></th>
<th>All patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revlimid</td>
<td>64</td>
</tr>
<tr>
<td>Observation</td>
<td>32</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.52</td>
</tr>
<tr>
<td>P Value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*PFS benefit across all patient subgroups on Revlimid maintenance therapy: standard risk; molecular high risk, which included the presence of del(17p), gain(1q), t(4;14), t(14;16), or t(14;20); MRD positive; and MRD negative.

More evidence for the benefit of longer duration of Revlimid maintenance in patients who are MRD positive than MRD negative. And evidence of ongoing benefit beyond 2–3 years for patients with both standard- and high-risk disease.
Using MRD Negativity to Guide Discontinuation of Maintenance Therapy

**MRD2STOP Study**

- Complete response and MRD negative by PET and NGF or NGS on at least 1 year of maintenance
- MRD and PET/CT negative: N=38

**Active Surveillance**

- 1-yr MRD
- 2-yr MRD
- 3-yr MRD

**Discontinue maintenance**

**Continue maintenance**

After median follow-up of 14 months, 89% remain on study (5% with PD, 6% withdrew).

MRD resurgence occurred in 13% of patients (2 patients had resurgence of M protein and disease progression).

MRD negativity (at $10^{-6}$ and $10^{-7}$) is sustained even after discontinuation of maintenance therapy.

**MRD-guided discontinuation of maintenance may carry significant cost savings.**

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MRD Response-Adapted Consolidation and Treatment Cessation

**MASTER Trial**

- Newly diagnosed myeloma patients

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)</td>
</tr>
<tr>
<td>Consolidation</td>
<td>Dara-KRd</td>
</tr>
<tr>
<td>Consolidation</td>
<td>Dara-KRd</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Revlimid</td>
</tr>
</tbody>
</table>

**MRD SURE**

- 80% of patients achieved MRD negativity (at $<1 \times 10^{-5}$) and 66% achieved MRD negativity at $<1 \times 10^{-6}$.
- 86% of patients achieved a CR or better.
- Responses deepened with each phase of treatment—and were similar in patients with zero, one, or two or more high-risk genetic abnormalities.
- ASCT increased the rates of MRD negativity following induction therapy, benefitting patients with highest-risk disease features.
- Nearly all patients with no or only one high-risk genetic abnormality and confirmed MRD negativity had no disease progression or MRD resurgence since stopping treatment.

**27**

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*MRD assessment performed with PET, flow cytometry ($10^{-5}$), NGS ($10^{-6}$), and CD138-selected NGS ($10^{-7}$)


*24 and 72 weeks after completion of therapy (by NGS)


**28**
Ongoing Studies Using MRD Results to Direct Therapy

**Phase 3 DRAMMATIC Study**

- Patients post-ASCT
  - Maintenance
    - Revlimid
    - Revlimid + Darzalex
    - MRD assessment
      - Positive: Continued assigned therapy
      - Negative: Stop assigned therapy

**Phase 3 OPTIMUM Study**

- Patients post-ASCT
  - MRD assessment
    - Positive: Revlimid + Ninlaro
    - Negative: Revlimid
    - Maintenance
      - Continue treatment until progression or unacceptable toxicity
      - Off study

MRD Is Important for Clinical Care and New Drug Registration

- Currently assessed by BM-based technologies
  - Flow cytometry
  - Next-generation sequencing

- Progress being made with blood-based technologies
  - MS
  - Cell-free DNA

- A surrogate for patient outcome in clinical trials

- Many clinical trials are using MRD-driven strategies

- Accelerate innovative trials leading to regulatory approval

BM, bone marrow; MS, mass spectrometry
Optimal Timing of MRD Testing for Newly Diagnosed Multiple Myeloma

Induction therapy → Transplant with high-dose chemotherapy → Maintenance therapy

Induction therapy → Maintenance therapy

MRD Isn’t Everything; It’s the Only Thing!

Depth

MRD Boundary 1

Duration of treatment

MRD Boundary 2

PAX ROMANA
Means "Roman Peace" in Latin
ALL-Like Myeloma and FL-Like Myeloma

**Key Points**

- Modern combination therapies result in increasingly higher MRD negativity rates, which are associated with better clinical outcomes (progression-free survival).

- To determine MRD status, patients need easy access to sensitive, reliable MRD assays that can be used in the standard-of-care setting.

- In the future, treatment strategies may be driven by increased access to modern combination therapies paired with novel FDA-approved MRD assays.

- Sustained MRD negativity could become the central definition of a cure for multiple myeloma in the future.
Questions & Answers

For more information, please visit https://themmrf.org/resources/education-programs/

Check out our High-Impact Topic videos
MMRF Patient Resources

Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.
To Learn More & Find Your Event today!
www.theMMRF.org/Events

Upcoming Patient Education Events
Save the Date

<table>
<thead>
<tr>
<th>Topic</th>
<th>Date and Time (ET)</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal Residual Disease FAQs Livestream</td>
<td>Friday, August 4 1:00 – 2:00 PM</td>
<td>Luciano J. Costa, MD, PhD</td>
</tr>
<tr>
<td>Learn Your Labs FAQs Livestream</td>
<td>Friday, August 9 2:00 – 3:00 PM</td>
<td>Hans C. Lee, MD Rebecca Lu, NP</td>
</tr>
</tbody>
</table>

For more information or to register, visit themmrf.org/resources/education-program
Resources

- Resource tab includes
  - Speaker bios
  - Copy of the slide presentation
  - Exhibit Hall
Need help with travel to a clinical study?

• The MMRF has partnered with the Lazarex Cancer Foundation to help provide more equitable access to clinical studies for multiple myeloma patients
• This partnership is one facet of the MMRF’s commitment to improve diversity and representation in myeloma clinical studies
• MMRF has provided $100,000 over 2 years to Lazarex to fund travel, lodging, and food for patients (and a travel companion) so that they can participate in clinical studies that are appropriate for them
• Patients are funded according to income guidelines and will be reimbursed for allowed expenses
• For more information on this program and to be connected with Lazarex, call our Patient Navigation Center at 1-888-841-6673

Thank you!