Learn Your Labs
June 20, 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

**Joshua Richter, MD**
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

**Craig Emmitt Cole, MD**
Michigan State University
College of Human Medicine
Karmanos Cancer Institute
East Lansing, Michigan
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

The clinical features that are characteristic of multiple myeloma

- **C**: High levels of calcium in the blood
- **R**: Decreased kidney (renal) function
- **A**: Low amount of red blood cells (anemia)
- **B**: Presence of bone damage
Effects of Myeloma and Common Symptoms

- Low blood counts
  - Weakness
  - Fatigue
  - Infection

- Decreased kidney function
  - Weakness

- Bone damage
  - Bone pain

About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.

Disease presentation and myeloma-related complications after myeloma diagnosis are different in patients by race

More common in Black patients
- Hypercalcemia
- Kidney dysfunction
  - Hemodialysis
- Anemia

Less common in Black patients
- Bone fractures

Blood, Urine, Bone Marrow, and Imaging Tests Used to Identify MGUS, SMM, or Active Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>SMM</th>
<th>Active MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein</td>
<td>&lt;3 g/dL in blood</td>
<td>≥3 g/dL in blood or ≥500 mg/24 hrs in urine</td>
<td>≥3 g/dL in blood or ≥500 mg/24 hrs in urine</td>
</tr>
<tr>
<td>Plasma cells in bone marrow</td>
<td>&lt;10%</td>
<td>≥10%–60%</td>
<td>≥60%</td>
</tr>
<tr>
<td>Clinical features</td>
<td>No myeloma-defining events*</td>
<td>No myeloma-defining events*</td>
<td>≥1 myeloma-defining event*, including either: • ≥1 CRAB feature or • ≥1 SLiM feature</td>
</tr>
</tbody>
</table>

*CRAB, calcium elevation, renal insufficiency, anemia, bone disease; SLiM, >60% plasma cells in bone marrow, free light chain involved to uninvolved ratio >100, >1 focal lesion on MRI
Anatomy of the Antibody

Immunoglobulin classes: IgG, IgA, and IgM

- **IgG**
  - Red – disulphide links
  - Green – light chains
  - Blue – heavy chains

- **IgA**
  - Red – disulphide links

- **IgM**

Quantitative Immunoglobulins and Immunofixation

- Quantitative serum immunoglobulins can detect *immunoparesis*
  - Quantitative immunoglobulins is a test to check the normal (uninvolved) antibody levels and the antibody produced by the myeloma plasma cells
  - Uninvolved immunoglobulins are reduced in 91% of myeloma patients
- The *type* of M protein is best determined by immunofixation
  - Immunofixation can also detect very small amounts of a serum and urine M-protein.
- **17% of patients with myeloma only produce light chains**
  - We always check the M protein on the SPEP and light chains in myeloma

Light Chain Monoclonal Gammopathy Detection

- **17% of patients with myeloma only produce light chains**
  - Light chain concentrations are too low to be detected by routine serum immunofixation
  - Light chains can be found either with 24-hr urine collection for Bence Jones urine protein electrophoresis (UPEP) or a blood test for the serum light chain analysis
  - Random (spot) Bence Jones UPEP alone is not considered adequate screening for monoclonal gammopathies
- A sensitive assay for immunoglobulin free light chains (FLCs) in the blood is available
  - Several studies have shown the serum FLC test equivalent or superior to the 24-hr urine collection.
  - Ratio helps in diagnosis; the total FLC total value assesses response


Light Chain Monoclonal Gammopathy Detection

- Serum FLC assay uses κ and λ polyclonal antibodies against specific epitopes that are hidden in intact immunoglobulins but exposed on FLCs
- FLCs independently quantify the two isotypes
- Monoclonality can be identified by the demonstration of an abnormal ratio of κ : λ FLCs

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Types of Multiple Myeloma Based on Blood or Urine Tests

**Intact M protein**
- Named for the type of immunoglobulin and light chain pair; for example, IgG kappa (κ) or IgG lambda (λ)
- 80% of patients
- Use M protein to follow disease

**Light chain only**
- Also known as Bence Jones protein
- Renal failure more common in light chain multiple myeloma
- 20% of patients
- Use free light chain (κ or λ) or Bence Jones protein to follow disease

**Non-secretory**
- No M protein present
- 3% of patients
- Use PET scan, bone marrow biopsy, ? mass spectrometry
Staging Myeloma: Serum Levels of β2 Microglobulin

β2 –Microglobulin

The higher the β2 microglobulin (>5.5), the more plasma cells and/or the worse the kidney function.

Diagnosing and Monitoring Myeloma: Learn Your Labs!

- **Number of red blood cells, white blood cells, and platelets**
- **Comprehensive panel: measure levels of albumin, calcium, and creatinine; assess function of kidney, liver, and bone status and the extent of disease**
- Determine the level of a protein that indicates the presence/extent of MM and kidney function: **USED FOR STAGE**
- Determine the level of myeloma cell production and extent of MM: **USED FOR STAGE**
- **Detect the presence and level of M protein = how much myeloma**
- **Identify the type of abnormal antibody proteins: IgG, IgA, κ, or λ**
- **Freelite test measures free light chains (kappa or lambda) in blood = how much myeloma**
- **Detect Bence Jones proteins (otherwise known as myeloma light chains) in urine (present or not present)**
- **Determine the presence and levels of M protein and Bence Jones protein in the urine = how much myeloma**
The Iceberg Model of Myeloma

Summary

Unlike other types of cancer, multiple myeloma is diagnosed, staged, and monitored through blood tests, x-rays, and bone marrow biopsies.

Blood tests allow you and your doctor to not only track the myeloma but also the function of the bone marrow, kidneys, liver, immune system, and electrolytes.

Know how to read your myeloma (M) protein level.

Understanding and monitoring your M protein and/or free light chains will allow you to know when and how well you have responded to therapy.

Understanding your blood work informs and empowers you!

You can cope with the diagnosis of multiple myeloma by empowering yourself to learn what you need to gain control, knowledge, and support!
Bone Marrow Biopsy and Staging

Joshua Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

Bone Marrow Biopsy

Types of chromosomal abnormalities

Translocation  Deletion  Gain or Amplification

*Images of bone marrow aspiration and biopsy, types of chromosomal abnormalities.*
Why is genomic sequencing important in myeloma risk assessment?

- Genetic changes in myeloma cells may affect prognosis and treatment selection
- Using samples from the bone marrow—specific tests look at these genetic changes
- Some tests are used routinely and look at the **chromosomal** changes (FISH)
- Newer tests assess changes in the **DNA** (gene expression profiling and next-generation sequencing)
  - Ask your doctor if these tests are available
- All patients in the MMRF CoMMpass study had **genomic sequencing** from diagnosis to relapse. The resulting data provides detailed genetic profiles for every myeloma patient at every stage of their disease!

Actionable Alterations in MM

**Personalized medicine efforts have identified molecular alterations for which there are drugs in the clinic**

These alterations may be the Achilles’ heel of myeloma cells.
MyDRUG Trial

Functional high-risk patients

Profiling for alterations (NCT02884102)

- No detectable actionable alterations
- RAF/RAS mutations
- CDK pathway-activating alterations
- FGFR3-activating alterations
- t(11;14)

Daratumumab + IPd

Cobimetinib + dexamethasone

Abemaciclib + dexamethasone

Erdafitinib + dexamethasone

2 cycles

2:1

Venetoclax + IPd

IPd control

*Assess single-agent activity after 2 cycles: after cycle 2, add backbone to single agent

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)

Stringent CR

Minimal residual disease negative

Myeloma cell burden

ClonoSEQ is an FDA-approved next-generation sequencing (NGS) test to measure MRD in MM patients

How is MRD measured?

Techniques Available to Measure MRD in MM

<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>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Diagnostic sample</td>
<td>Important but not mandatory</td>
<td>Mandatory</td>
</tr>
<tr>
<td>Applicability</td>
<td>Universal (~ 100%)</td>
<td>High (~ 90%)</td>
</tr>
<tr>
<td>Time</td>
<td>2 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>Cost</td>
<td>~ 250 USD</td>
<td>~ 700 USD</td>
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<tr>
<td>Sensitivity</td>
<td>$10^{-6}$–$10^{-6}$</td>
<td>$10^{-6}$</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: next-generation sequencing (NGS) or next-generation flow cytometry (NGF).*

Comprehensive Response Assessment

- Right now, measurement of MRD depends on counting cells in bone marrow samples

- What about other areas of the body?

- Imaging (with PET/CT scan) is also required to detect residual disease outside of the bone marrow
Know Your Imaging Tests!

Assess changes in the bone structure and determine the number and size of tumors in the bone

X-ray  MRI  CT scan  PET scan

Putting the Results Together

Staging, prognosis, and risk assessment
Multiple Myeloma Prognosis and Risk

**Revised International Staging System (R-ISS)**

<table>
<thead>
<tr>
<th>R-ISS stage</th>
<th>Laboratory measurements</th>
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<tbody>
<tr>
<td>I</td>
<td>Serum β2M level &lt;3.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>Serum albumin level ≥3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>No high-risk CA*</td>
</tr>
<tr>
<td></td>
<td>Normal LDH level</td>
</tr>
<tr>
<td>II</td>
<td>All other possible combinations</td>
</tr>
<tr>
<td>III</td>
<td>Serum β2M level ≥5.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>High-risk CA* or high LDH level</td>
</tr>
</tbody>
</table>

*High-risk chromosomal abnormality (CA) by FISH: del(17p) and/or t(4;14) and/or t(14;16)*

**Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines**

**High risk**
- High-risk genetic abnormalities
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p
  - p53 mutation
  - gain 1q
- R-ISS Stage 3
- High plasma cell S phase
- GEP: high-risk signature
- Double-hit myeloma: any two high-risk genetic abnormalities
- Triple-hit myeloma: three or more high-risk genetic abnormalities

**Standard risk**
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)

Currently cannot identify with great certainty all high-risk patients.

β2M: beta-2 microglobulin; LDH: lactate dehydrogenase; GEP: gene-expression profiling

Multiple Myeloma Prognosis and Risk

Many blood test and bone marrow biopsy test results can determine a patient’s risk for myeloma that is aggressive (high risk) or not (standard risk) based on the R-ISS system.

**Standard risk**
- Serum β2M level <3.5 mg/L
- Serum albumin level ≥3.5 g/dL
- No high-risk chromosomal abnormality*
- Normal LDH level

**High risk**
- Serum β2M level ≥5.5 mg/L
- High-risk chromosomal abnormality* or high LDH level

All other possible combinations of the test results means that a patient is R-ISS stage II

*High-risk chromosomal abnormality by FISH: del(17p) and/or t(4;14) and/or t(14;16)
R-ISS, Revised International Staging System; β2M, beta-2 microglobulin; LDH, lactate dehydrogenase; FISH, fluorescence in situ hybridization
Additional High-Risk Features

**Disease Features**
- Other cytogenetic and genetic abnormalities
- Plasma cell leukemia
- Extramedullary disease
- Renal failure

**Patient Features**
- Comorbidities
- Frailty

**Response Features**
- Lack of response to therapy
- Short first PFS

Summary

Bone marrow biopsies are a pain in the butt; but give us key insight into the biology of your myeloma.

The genetic information we obtain from the biopsy can give us not only prognostic information but also guide us towards the optimal drug choice.

Ongoing trials are looking at utilizing drugs typically used for other cancers for treating myeloma.

Bone marrow biopsies can also let us know how deep your remission is

There are multiple ways of staging myeloma, with the newer ones using genetic information.

X-rays, CTs, PET scans, and MRIs are all used to stage and re-stage myeloma.
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.
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>Patient Summit</td>
<td>Saturday, June 24 9:00 AM to 3:30 PM</td>
<td>Peter Voorhees, MD Cindy Varga, MD Craig Cole, MD Monique Hartley-Brown, MD Jordan Robinson, PA</td>
</tr>
<tr>
<td>American Society of Clinical Oncology 2023 FAQs Livestream</td>
<td>Wednesday, June 28 2:30 PM to 3:30 PM</td>
<td>Nisha Joseph, MD Roseann Pruitt, PA-C Danielle Roberts, PA-C</td>
</tr>
<tr>
<td>Webinar: Minimal Residual Disease</td>
<td>Friday, July 14 1:00 PM to 2:00 PM</td>
<td>Benjamin Derman, MD Rafael Fonseca, MD</td>
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For more information or to register, please visit themmrf.org/resources/education-program
Resources

- Resource tab includes
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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 trials.
- 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!