Multiple Myeloma Precursor Conditions

April 5, 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

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Speakers

Sagar Lonial  
Winship Cancer Institute  
Emory University School of Medicine  
Atlanta, Georgia

Omar Nadeem, MD  
Harvard Medical School  
Dana-Farber Cancer Institute  
Boston, Massachusetts
Overview of Multiple Myeloma Precursor Conditions

Omar Nadeem, MD
Harvard Medical School
Dana-Farber Cancer Institute
Boston, Massachusetts

1. What are plasma cells?
Function as immune cells responsible for making antibodies

2. What are plasma cell disorders?
Clonal population of abnormal plasma cells that originate in the bone marrow

3. What is an “abnormal protein” in my blood?
Detected in the blood when searching for underlying plasma cell disorder (IgG, IgA, light chain, IgD, IgM)

4. What is the problem?
The abnormal protein and the abnormal population of cells can lead to organ damage in multiple myeloma.

FAQs
Plasma Cell Disorders: Classification

**Updated IMWG criteria for diagnosis of multiple myeloma**

<table>
<thead>
<tr>
<th>MGUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• M protein &lt;3 g/dL</td>
</tr>
<tr>
<td>• Clonal plasma cells in bone marrow &lt;10%</td>
</tr>
<tr>
<td>• No myeloma-defining events</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoldering myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• M protein ≥3 g/dL (serum) or ≥500 mg/24 hrs (urine)</td>
</tr>
<tr>
<td>• Clonal plasma cells in bone marrow ≥10% to 60%</td>
</tr>
<tr>
<td>• No myeloma-defining events</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Multiple myeloma</th>
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</thead>
<tbody>
<tr>
<td>• Underlying plasma cell proliferative disorder AND</td>
</tr>
<tr>
<td>• 1 or more myeloma-defining events</td>
</tr>
<tr>
<td>• ≥1 CRAB* feature</td>
</tr>
<tr>
<td>• Clonal plasma cells in bone marrow ≥60%</td>
</tr>
<tr>
<td>• Serum free light chain ratio ≥100</td>
</tr>
<tr>
<td>• &gt;1 MRI focal lesion</td>
</tr>
</tbody>
</table>

*C: Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
A: Anemia (Hb <10 g/dL or 2 g/dL < normal)
B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)


MGUS is a Very Common Condition

- 3% of the general population at age 50 has MGUS
- This rate is 3 times higher for individuals of African descent
- This rate is 2–3 times higher for first-degree family members of myeloma patients

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Monoclonal gammopathy of undetermined significance (MGUS)
- Risk of progression to multiple myeloma or related conditions: 1% per year

Smoldering multiple myeloma (SMM)
- Risk of progression to active myeloma: 10% per year

High-risk SMM
- Risk of progression to active myeloma: 50% in 2 years

High-risk MGUS
- Non-IgG M protein
- Abnormal serum free light chain ratio
- M protein >1.5 g/dL

SMM
- Current standard of care is to observe only for low- and intermediate-risk patients.

Smoldering Multiple Myeloma: Heterogeneous Disease

51% will convert to MM in first 5 years (~10%/yr)
27% more will convert to MM in remaining 15 years (~2%/yr)

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Risk Assessment in Smoldering Myeloma

Mayo risk model¹
Plasma cell bone marrow infiltration, serum M-component level, and serum free light chain ratio

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>N</th>
<th>Rel. Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>114</td>
<td>1.9 (1.2–2.9)</td>
</tr>
<tr>
<td>3</td>
<td>78</td>
<td>4.0 (2.6–6.1)</td>
</tr>
</tbody>
</table>


Spanish model²
Aberrant PCs by immunophenotype plus immunoparesis

- >95% aPC/BMPC + paresis
- >95% aPC/BMPC or paresis
- No adverse factors

2/20/20 Model to Identify High-Risk SMM Patients

<table>
<thead>
<tr>
<th>2/20/20</th>
<th>Risk assessment for SMM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>&gt;2 g/dL M protein</td>
</tr>
<tr>
<td>20</td>
<td>&gt;20 free light chain ratio</td>
</tr>
<tr>
<td>20</td>
<td>&gt;20% bone marrow plasma cells</td>
</tr>
</tbody>
</table>

Model does not include any biological or immune factors that may account for interpatient heterogeneity.


Risk of progression at 2 Years

- High-risk group (2–3 risk factors) 44.2%
- Intermediate-risk group (1 risk factor) 17.9%
- Low-risk group (no risk factors) 6.2%
Can we identify everyone who has a precursor condition?

Identifying Patients Who Have Myeloma Precursor Conditions

Nationwide Screening Studies

Iceland

United States and Canada
Prevalence of MGUS and SMM

**Prevalence of MGUS and SMM**

- **iStopMM Study**
  - 148,704 individuals 40 years of age or older in Iceland enrolled
  - 75,422 screened for M protein and abnormal free light chain
  - 3,725 individuals with MGUS

**Arm 1**
- No further work-up

**Arm 2**
- Management by guidelines

**Arm 3**
- 1,279 patients
- Intensive follow-up

- 4.9% of individuals screened have MGUS
- 10.8% of individuals screened have SMM; SMM prevalence is 0.53%
- One third of SMM patients have an intermediate or high risk* of progression to myeloma

*High prevalence of SMM has implications for future treatment policies and underlines the need for accurate risk stratification in SMM.

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**Additional iStopMM Study Findings**

- After 3 years of follow-up, active screening identifies a significantly higher number of individuals with malignancies and smoldering disease.

- MGUS was **not** associated with COVID-19 susceptibility or COVID-19 severity.

- These findings suggest that immunosuppression in MGUS is different than in myeloma.

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*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma:
(1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow.


Nationwide Study of Myeloma Screening and Prevention: PROMISE

Screen 30,000 high-risk individuals
- Screen negative 26,100
- Screen positive 3,900
  - Prospective follow-up

Genetics and genomics
- Viktor Adalsteinsson
- Gad Getz
- Irene Ghobrial

Epidemiology
- Tim Rebbeck
- Lorelei Mucci
- Catherine Marinac

Bone marrow niche
- Ivan Borrello
- Irene Ghobrial

Imaging and therapeutics
- Jeremiah Johnson
- Irene Ghobrial

Develop novel biomarkers for diagnosis
Establish new risk stratification tools
Generate new tools to prevent disease progression

Promise Study Eligibility Criteria

2 groups of U.S. adults, age 30 or older, qualify for a free screening:

1. African Americans
   AND / OR
2. People of Any Race Who Have a Parent, Sibling, or Child with:
   Multiple myeloma, another blood cancer, OR one these related conditions:
   - Monoclonal Gammapathy of Undetermined Significance (MGUS)
   - Smoldering Multiple Myeloma
   - Waldenstrom Macroglobulinemia

We are also enrolling individuals who are 18 years of age or older and have a strong family history of blood cancer (2 or more first- and second-degree relatives).

Please sign up for the study if you qualify.

Note: The PROMISE study is for people who may have higher risks, but have not been diagnosed with any of these conditions.

If you have been diagnosed with one of these conditions, please visit our PCROWD study or similar project for people with precursor conditions.
High Prevalence of Monoclonal Gammopathy in a Population at Risk

The PROMISE Study

7,622 individuals screened*

6,305 patients

1,317 patients

High-risk features for myeloma

Non-Blacks with family history of HM (n=3,866)

Blacks (n=2,439)

Negative family history of HM (n=631)

Unknown family history of HM (n=686)

No high-risk features for myeloma

MGUS estimated in 13% to 17% of a high-risk screened population (rates increase with age).

Higher detection rates of free light chains by mass spectrometry than conventional methods.

Older adults who are Black or have a first-degree relative with a HM have an increased prevalence for MGUS.

Older individuals who are Black or have a first-degree relative with a HM may benefit from screening to allow for early detection and possible clinical intervention.

*The PROMISE study and Mass General Brigham Biobank—detected by mass spectrometry.

HM, hematologic malignancy


Defining Outcomes and Results

MGUS by SPEP/IFX

MS-MGUS

Confirmatory LC-MS testing

SPEP, serum protein electrophoresis; IFX, immunofixation; MS-MGUS, mass spectrometry-monoclonal gammopathy of undetermined significance; MS-MGIP, mass spectrometry-monoclonal gammopathies of indeterminate potential; LC-MS, light chain mass spectrometry
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**High Prevalence of Monoclonal Gammopathy in a Population at Risk**

Rates of all monoclonal gammopathies* increase with age

![Graph showing rates of all monoclonal gammopathies increase with age]

*Free light chains detected by mass spectrometry.

MGUS more prevalent in individuals older than 50 years at risk

![Graph showing higher rates of MGUS in Blacks or individuals with a family history of HM and older than 50 years at risk]

**Summary**

Precursor plasma cell disorders are characterized by the presence of abnormal clonal plasma cells without any end organ damage.

MGUS is a common condition; prevalence increases with age.

There is variable risk of progression from MGUS and SMM to overt myeloma; several risk models can help predict who is at risk of progression.

Screening efforts, particularly in high-risk populations, are under way.
Therapeutic Intervention for Myeloma Precursor Conditions

Sagar Lonial, MD
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

Preventing Evolution of Gammopathies to Prevent Myeloma

- Diet
- Lifestyle
- Microbiome

Antigen-mediated regulation in monoclonal gammopathy

Microbial/environmental triggers?

Nair S et al. JCI Insight. 2018;3:e98259.
Unpublished
SMM, to treat or not?

- Delaying symptomatic progression
- Maintain/increase quality of life by treating early
- Possibility of cure?

- Selection of resistant clone?
- Toxicity
- Costs of treatment
- Overtreatment

Overview of Current Treatment Approach

**MGUS**
- Close monitoring (observation)

**SMM**
- Close monitoring (observation)
- If high risk: possible myeloma drugs?*
- If bone loss: bone-targeting agents

Clinical trial participation should be considered

*Promising but only available as clinical trials.
2/20/20 Model to Identify High-Risk SMM Patients

- **2/20/20 Risk assessment for SMM**
  - 2 ≥2 g/dL M protein
  - 20 >20 free light chain ratio
  - 20 >20% bone marrow plasma cells

Model does not include any biological or immune factors that may account for interpatient heterogeneity.


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- 2 >2 g/dL M protein
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**Risk of progression at 2 Years**
- High-risk group (2-3 risk factors): 44.2%
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Approaches to SMM

- **Immunologic therapy** (prevention approach)
  - Len, Len/Dex, Dara

- **Intensive therapy** (curative intent)
  - IRD, KRD, ERD
  - CESAR, ASCENT

**Pros**
- Fewer side effects
- More likely to induce long-term effects

**Cons**
- Low OR
- Does not eliminate the clone

**Pros**
- High ORR
- Deep responses

**Cons**
- Toxicity similar to myeloma treatment
- May result in resistant clones
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Early Therapeutic Intervention

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D.,
Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D.,
Lucia López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D.,
Bruno Palis, Ph.D., Luis Palomer, M.D., Ph.D., Joan Bargay, M.D.,
Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D.,
Eduardo Olvarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D.,
Joan Bladé, M.D., Ph.D., Juan-José Lahuent, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

HR, hazard ratio

Progression-free survival for early treatment

QuiRedex Phase 3 Trial
Len-dex vs No Treatment in High-Risk SMM

Median follow-up (n=119): 75 mos

Early treatment with Rd significantly delayed the TTP to Myeloma with a benefit in OS

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**Revlimid vs Observation Alone in Patients With SMM**

![Graph showing Progression-Free Survival](image)

**Progression-Free Survival**

- **Revlimid**
- **Observation**

Median follow-up: 35 months


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**E3A06: Len vs Observation in Patients With Asymptomatic High-Risk SMM**

- **Treatment hazard ratio = 0.28 (95% CI, 0.12–0.63), P=0.0005**

![Graph showing PFS ITT](image)

**PFS ITT**

- 2yrs 93%
- 2yrs 76%
- 3yrs 91%
- 3yrs 66%

**Criteria:** PCBM ≥10% and sFLC ratio >8 or <0.125

**Mayo2008:** PCBM ≥10% + MC ≥ 3g/dL
**Mayo 2018:** 2/20/20

**Criteria:** PCBM ≥10% and sFLC ratio >8 or <0.125


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**Early treatment with R significantly prevented the progression to MM, especially in the high-risk subgroup.**

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**Key Points:**

- N=182, intermediate/high-risk SMM (BMPC% ≥10% and aberrant (FLC) ratio (<0.26 or >1.65)
- 1:1 randomization lenalidomide 25 mg day 1 to 21 in 28-day cycle vs observation
- Median FU 35 mnd, median time on len 23 cycles, len discontinued in 51% of patients

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**Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria**

- **High risk**
  - Revlimid
  - Observation

- **Intermediate risk**
  - Revlimid
  - Observation

- **Low risk**
  - Revlimid
  - Observation


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**Ongoing Clinical Studies for SMM/MGUS Patients**

**Phases 1–3 or Observational**

- **SMM patients at high risk of disease progression**
  - Revlimid + dex ± Darzalex
  - Ninlaro + Revlimid + dex
  - Darzalex (sc)
  - Kyprolis + Revlimid + dex
  - Empliciti + Revlimid + dex (E-PRISM Trial)
  - Leflunomide
  - Ninlaro + dex
  - Pembrolizumab
  - Kyprolis + Revlimid + Darzalex + dex (ASCENT trial)

- **SMM/MGUS**
  - PO antibiotic trial (Emory)
  - Predictors of progression (PROMISE study)
  - Genomic and molecular predictors of progression (MD Anderson study)
  - MMRF CureCloud
  - Darzalex

Ask your doctor about whether you are a candidate for a clinical trial.

Trials found at www.clinicaltrials.gov
### GEM-CESAR: Multicenter, Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex

**High-risk** SMM patients

<table>
<thead>
<tr>
<th>Response category</th>
<th>Induction (n=90)</th>
<th>HDT-ASCT (n=83)</th>
<th>Consolidation (n=81)</th>
<th>High risk (n=54)</th>
<th>Ultra-high risk (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n(%)</td>
<td>85 (94%)</td>
<td>82 (99%)</td>
<td>81 (100%)</td>
<td>54 (100%)</td>
<td>27 (100%)</td>
</tr>
<tr>
<td>≥CR</td>
<td>37 (41%)</td>
<td>53 (64%)</td>
<td>61 (76%)</td>
<td>41 (76%)</td>
<td>20 (74%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>35 (39%)</td>
<td>18 (22%)</td>
<td>15 (19%)</td>
<td>10 (19%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>PR</td>
<td>13 (14%)</td>
<td>11 (13%)</td>
<td>5 (6%)</td>
<td>2 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>2 (3%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MRD negative</td>
<td>27 (30%)</td>
<td>47 (56%)</td>
<td>51 (63%)</td>
<td>36 (67%)</td>
<td>15 (56%)</td>
</tr>
</tbody>
</table>

Courtesy of MV Mateos.

### ASCENT: KRd-D

#### Study design

- **Induction** (4-week cycles for 6 cycles)
  - Carfilzomib (36 mg/m² twice weekly or 56 mg/m² weekly)
  - Lenalidomide (25 mg daily for 3 weeks)
  - Daratumumab (weekly for 8, every other week for 16 weeks)
  - Dexamethasone 40 mg weekly

- **Consolidation** (4-week cycles for 6 cycles)
  - Carfilzomib (36 mg/m² twice weekly or 56 mg/m² weekly)
  - Lenalidomide (25 mg daily for 3 weeks)
  - Daratumumab (every 4 weeks)
  - Dexamethasone 20 mg weekly

- **Maintenance** (4-week cycles for 12 cycles)
  - Lenalidomide (10 mg daily for 3 weeks)
  - Daratumumab (q 4 weeks)

Results to date:
- 54 patients accrued
- Median patient age 63 years
- 6% have completed maintenance, 56% consolidation, 80% induction, and 17% in induction phase
- ≥1 patient needed a dose modification
- ≥ grade 3 AE seen in 43% of patients

#### Primary end point: Rate of confirmed sCR
Secondary objectives: Safety, PFS, OS, MRD negativity

#### Toxicity profile

- Lymphocyte count decreased
- Thromboembolic event
- White blood cell decreased
- Neutropenia
- Diaphoresis
- Nausea
- Upper respiratory infection
- Hypertension
- Insomnia
- Platelet count decreased
- Constipation
- Diarrhea
- Fatigue

Quadruplet regimen KRd-D is well tolerated in high-risk SMM.

AE, adverse event; KRd-D, carfilzomib, lenalidomide, dexamethasone, daratumumab; MRD, minimal residual disease; sCR, stringent complete response

Summary

- Smoldering myeloma carries a variable risk of progression to overt myeloma.
- Several criteria to identify patients at high risk for progression
- Growing data for benefit with early intervention
- Patients with SMM should be offered treatment on clinical trials.
- Participation in observational/interventional studies is key to finding out which patients can benefit the most from early treatment and what is the best treatment to offer early.
Recent Updates

Personalized Progression Prediction in Patients With MGUS or SMM (PANGEA)

A new model to assess risk of progression using accessible, time-varying biomarkers

Biomarkers tested include monoclonal protein concentration, free light chain ratio, age, creatinine concentration, and bone marrow plasma cell percentage + hemoglobin trajectories

Improves prediction of progression from SMM to multiple myeloma compared with the 20/2/20 model

Questions & Answers
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.
MMRF Events

Our events are returning live and in-person, and there are so many ways to get involved. Most have a virtual option, too. Join us today!

FIND AN EVENT AND JOIN US: themmrf.org/get-involved/mmrf-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>Facebook Live: FAQs on BCMA-targeted Bispecific Antibody Therapy</td>
<td>Friday, April 14 1:00 – 2:00 PM</td>
<td>Saad Usmani, MD Anna Howard, RN</td>
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<tr>
<td>Virtual Patient Summit</td>
<td>Saturday, April 29 9:00 – 3:00 PM</td>
<td>Ajai Chari, MD Jonathan Kaufman, MD Ola Landgren, MD, PhD Hans Lee, MD Robert Orlowski, MD Christine Jing Ye, MD</td>
</tr>
</tbody>
</table>

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