Precursor Conditions in Multiple Myeloma
July 10, 2024

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!
Delivering On Our Mission

The MMRF is committed to acting with urgency to ensure that patients have effective, more personalized treatments available when they need them and the resources necessary to increase their survival and improve their quality of life.

Accelerate the Development of Novel Therapies

Invest in companies with early-stage assets (Myeloma Investment Fund) and speed clinical trials through MMRC in patient populations with greatest unmet need (Horizon).

Driving More Personalized, Optimal Treatment Approaches

Deploy resources and funding to drive research focused in areas of high unmet need, generate hypotheses for clinical exploration (TRU and MAC) and make all MMRF-generated and/or supported data available to researchers (Virtual Lab).

Empower Patients and the Entire Community

Provide high-quality education to patients, caregivers, and healthcare providers, as well as access to nurse navigators with a strong focus on addressing the needs of traditionally underserved patients; fund Fellows and other initiatives to increase the number of BIPOC (especially Black) researchers and clinicians (Scholars).

Speakers

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

C. Ola Landgren, MD, PhD
Sylvester Comprehensive Cancer Center
University of Miami
Miami, Florida
Overview of Multiple Myeloma Precursor Conditions

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

The Multiple Myeloma Disease Spectrum

Almost all patients diagnosed with multiple myeloma have had a preceding phase of disease that is characterized by changes in the bone marrow.
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:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥1 CRAB feature</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥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

Risk of Progression to Myeloma From a Precursor Condition

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

Risk Assessment in Smoldering Myeloma: 2/20/20 Model to Identify High-Risk SMM Patients

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

Patients with two or more risk factors are considered high risk. This model does not include any biological or immune factors that may account for interpatient heterogeneity.

**Graph:**
- Low-risk group (no risk factors)
- Intermediate-risk group (1 risk factor)
- High-risk group (2–3 risk factors)

**Risk of progression at 2 Years**
- 44.2%
- 17.9%
- 6.2%

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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 20/20/20 model
Can we identify everyone who has a precursor condition?

Studies Focusing on Myeloma Precursor Conditions

Large ongoing precursor studies

- **Iceland**
  - Focus: role of population screening

- **United States and Canada**
  - Focus: racial disparities and familial aggregation

- **United States**
  - Focus: genomic markers of progression

TRANSFORMM study
**Prevalence of MGUS and SMM**

**iStopMM Study**
- Individuals 40 years of age or older in Iceland enrolled
- Screened for M protein and abnormal free light chain

**SMM**
- SMM prevalence is 0.53% in individuals 40 years or older
- One third of SMM patients have an intermediate or high risk* of progression to myeloma

**Key Observations**
- 3.9% of individuals screened have MGUS
  - (5% in individuals over 50 years of age)
- Risk categories*:
  - 43% low
  - 40.4% low-intermediate
  - 16.3% high-intermediate
  - 0.3% high.
- No evidence of MGUS progression following SARS-CoV-2 vaccination

*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.


**High Prevalence of Monoclonal Gammopathy in a Population at Risk**

**The PROMISE Study**
- Individuals age 40 or older screened*
- African Americans AND / OR
- Individuals of any race who have a parent, sibling, or child with:
  - Multiple myeloma, another blood cancer, OR one of these related conditions:
    - MGUS
    - Smoldering Multiple Myeloma
    - Waldenström Macroglobulinemia

**MGUS**
- 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.

*The PROMISE study and Mass General Brigham Biobank—detected by mass spectrometry.
HM, hematologic malignancy
Summary

Precursor conditions cause plasma cells in the bone marrow to grow faster than normal and produce monoclonal protein (M protein), which can be detected in the blood or urine.

These precursor conditions are known as either monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM).

MGUS is a common condition; prevalence increases with age.

People who have SMM have a higher risk of developing myeloma than those with MGUS.

Screening efforts are under way to improve identification of everyone with a precursor condition.

Therapeutic Intervention for Myeloma Precursor Conditions

C. Ola Landgren, MD, PhD
Sylvester Comprehensive Cancer Center
University of Miami
Miami, Florida
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

- Low Risk SMM
- High Risk SMM

- Close monitoring (observation)
- Consider clinical trial, or close monitoring (SOC)

Close Monitoring & Observation Recommendations for MGUS

- **Observation remains the standard of care for patients with MGUS**
- Low risk MGUS patients (M protein < 1.5 g/dL and normal FLC ratio) should be followed with serum M protein in 6 months, and if stable can be followed every 2–3 years
- Intermediate-risk or high-risk MGUS (M protein > 1.5 g/dL and IgA or IgM protein type, or an abnormal FLC ratio should also have a bone marrow aspiration and bone marrow biopsy


Close Monitoring & Observation Recommendations for Low Risk SMM

- **Observation remains the standard of care for patients with low risk SMM by the 20-2-20 criteria**
- Every 3–4 months patients should be monitored for:
  - Serum M protein
  - Serum FLC levels
  - Complete blood count
  - Serum calcium
  - Serum creatinine
- The interval for follow-up can be reduced to once every 6 months after the first 5 years

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Approaches to SMM Treatment: Only in the Context of a Clinical Study

Low-efficacy therapy (control approach)

- R, Rd, Dara

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

Cons
- Low ORR
- Does not eliminate the clone

High-efficacy therapy (curative intent)

- IRd, KRd, ERd, KRd + transplant, Dara-KRd, Bispecific mAbs

Pros
- High ORR
- Deep responses

Cons
- Toxicity similar to myeloma treatment
- May result in resistant clones

Dara, Darzalex (daratumumab); d, dexamethasone; E, Eluxefio (elotuzumab); I, Ninlaro (ixazomib); R, Revlimid (Lenalidomide)

One or Two-Drug Treatment Strategies for High-Risk SMM Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revlimid-dexamethasone vs observation¹</td>
<td>After 12.5 years of follow up, treatment with Rd extended time to progression (TTP) to multiple myeloma by 7 years²</td>
</tr>
<tr>
<td>Revlimid vs observation³</td>
<td>Early treatment with R significantly prevented the progression to MM, especially in the high-risk subgroup.</td>
</tr>
<tr>
<td>Darzalex monotherapy⁴,⁵</td>
<td>After 7 years of follow up, overall survival was: 88% in short treatment group 90% in intermediate treatment group 89% in long treatment group</td>
</tr>
<tr>
<td>Short: 8 weeks Intermediate: 20 weeks Long: 20 weeks + optional extension</td>
<td></td>
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</tbody>
</table>

Phase 2 Trial of Darzalex for Intermediate- and High-Risk SMM Patients

- **Centaurus Study** assessed Darzalex treatment in intermediate- and high-risk SMM patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Short</th>
<th>Intermediate</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>D once a week for 1 cycle</td>
<td>D once a week for 1 cycle then every other week for 19 cycles + optional extension</td>
<td>D once a week for 1 cycle then every other week for 2 cycles then every other month for 13 cycles + optional extension</td>
<td></td>
</tr>
</tbody>
</table>

| Median PFS including extension (months) | 74 | 84 | Not reached |
| 84-month OS rate (%) | 88 | 90 | 81 |
| Overall response rate (%) | 38 | 54 | 59 |
| Median duration of response (months) | 73 | 83 | Not reached |

Landgren O et al. Leukemia. 2020;34:1840.

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Three or Four-Drug Combination Strategies for High-Risk SMM Patients

<table>
<thead>
<tr>
<th>NCI Study¹</th>
<th>GEM-CESAR²</th>
<th>ASCENT³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
<td>Kryprolis + Revlimid + dex (KRd)</td>
<td>KRd + stem cell transplant</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Revlimid</td>
<td>Revlimid</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>The 8-year probability of being free from progression to myeloma was 91%</td>
<td>At 70 months, 94% of patients have not progressed to multiple myeloma</td>
</tr>
</tbody>
</table>

Discordance Between Risk Scores for SMM and Patterns of Progression

LRM, PETHEMA, Mayo2018, Mayo2008, and IMWG2014 are five different clinical risk scores which have been published in the literature.

Here, when patients were assessed by all five risk scores, all but one patient were both high-risk (black) and non-high-risk (grey) at the same time. Progressors were high-risk by 1/5 (20%) to 5/5 (100%) scores.

Genomic Patterns of SMM vs. Multiple Myeloma

- Genomically, most smoldering myeloma patients’ disease biology is simple (vs newly diagnosed myeloma)
- Recurrent patterns of genomic lesions in those with resistance to early intervention

Summary

- Single arm study data show benefit with early intervention.
- Patients with high-risk 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. To identify molecular markers of progression vs stable disease.
**Patient Education Programs 2024**

**Multi-channel offerings**

- Patient Summits
- Patient Webinars
- Myeloma Matters Podcasts
- FB Livestreams
- Conference Highlights
- Nursing Fireside Chats
- The MMRF Patient Toolkit
- High Impact Topic Videos
- Fast Facts in Myeloma
- Infographics

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**MMRF Patient Resources**

**Expect Guidance.**

**MMRF Patient Navigation Center**

- Information & Resources
- Expert Advice
- Support

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**The Right Track**

Get on the right track for you.

**Right Team**

- Medical experts and caregivers that focus on active and personalized treatment, multiple options.

**Right Tests**

- Errors in information, facts, and prior decisions to make the right treatment decisions.

**Right Treatment**

- Work with your team to consider the best treatment plan and identify clinical trials that are right for you.

Contact the Patient Navigation Center Today

Looking for guidance? We’re here to help.

Monday – Friday | 9:00AM – 5:00PM

Phone: 1-888-64-MMRF (646-6737) Online: TheMMRF.org/PatientNavigationCenter

Email: patientservice@themmrf.org

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Supported by:

- [Other Supporters]

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**PATIENT SUMMIT**

Seattle, WA

Saturday, October 12, 2024

In-person: 8:00 AM – 12:30 PM PT

Online: 9:00 AM – 12:00 PM PT

This event can be attended in-person, if you can.
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 myeloma 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.

Join the MMRF Community!

**National Walk/Run Program**
- Atlanta | 10.26.24
- Boston | 10.12.24
- Chicago | 9.8.24
- Dallas | 11.16.24
- Detroit | 9.21.24
- Houston | 11.23.24
- Los Angeles | 8.17.24
- National Virtual | 12.14.24

**Other MMRF Event Programs**
- New York City | 10.5.24
- Philadelphia | 10.19.24
- San Francisco | 8.24.24
- Scottsdale | 12.7.24
- Tampa | 11.2.24
- Washington D.C. | 9.28.24

Moving Mountains for Multiple Myeloma
Half and Full Marathons
Bike/Road to Victories
Create Your Own Fundraiser
Upcoming Patient Education Events

Save the Date

<table>
<thead>
<tr>
<th>Program</th>
<th>Date and Time</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managing Side Effects in Multiple Myeloma</td>
<td>Tuesday, August 13, 2024</td>
<td>Donna D. Catamero, ANP-BC, Leora A. Giacoia, MS, FNP-BC</td>
</tr>
<tr>
<td>Patient Webinar</td>
<td>2:00 PM ET</td>
<td></td>
</tr>
<tr>
<td>Precursor Conditions Livestream</td>
<td>Wednesday, July 31, 2024</td>
<td>Benjamin T. Diamond, MD</td>
</tr>
<tr>
<td></td>
<td>3:00 PM ET</td>
<td>Stephanie Mompoint, APRN</td>
</tr>
<tr>
<td>Expert Session on IMS Highlights</td>
<td>Wednesday, October 9, 2024</td>
<td>Nikhil Munshi, MD</td>
</tr>
<tr>
<td></td>
<td>10:00 AM ET</td>
<td></td>
</tr>
<tr>
<td>MMRF Patient Summit Hybrid Event in collaboration with the Fred Hutchinson Cancer Center</td>
<td>Saturday, October 12, 2024</td>
<td>Andrew J. Cowan, MD, Kara Cicero, MD, MPH, Andrew Portuguese, MD</td>
</tr>
<tr>
<td></td>
<td>8:00 AM – 12:30 PM PT</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Need help with travel to a clinical study?

- The MMRF has partnered with the Lazarex Cancer Foundation to expand access to clinical trials
- Funding is available for travel, lodging, and food for patients (and a travel companion)
- Patients are funded according to income guidelines and will be reimbursed for allowed expenses
- For more information on this program, call our Patient Navigation Center at 1-888-841-6673
Thank you!