MMRF Virtual *Expert Session*: Precursor Disease

August 18, 2021

**MODERATOR**

Mary DeRome

Multiple Myeloma Research Foundation
Norwalk, Connecticut

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Program Support

AbbVie  Bristol Myers Squibb
Cure  Karyopharm Therapeutics
Janssen  Pfizer

VIRTUAL EXHIBIT HALL
Speakers

Irene Ghobrial, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

Elisabet E. Manasanch, MD
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Virtual Expert Session Agenda

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<td>Overview of Multiple Myeloma Precursor Conditions</td>
<td>Elisabet E. Manasanch, MD</td>
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<td>11:40 AM–12:05 PM ET</td>
<td>Discussion/Questions and Answers</td>
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<td>Mary DeRome</td>
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Multiple Myeloma Research Foundation
CureCloud

MMRF Data-Generating Initiatives

The MMRF has already built several large genomic and clinical data sets.

- Multiple Myeloma Genomic Initiative: 200
- MMRF Molecular Profiling Protocol: 1,100
- Direct-to-Patient Registry: 5,000
- MMRF CureCloud®: 1,000
- CoMMpass
MMRF CureCloud® Build

Piloted in October 2019 with CLIA launch in July 2020.

Research Pilot in October 2019  CLIA Launch in July 2020

- Direct-to-Patient Enrollment
  - Enrollment via e-consent process
- Liquid Biopsy
  - Blood-based targeted gene-sequencing panel
- EHR Abstraction & Curation
  - Comprehensive EHR abstraction & curation
- Clinical Grade Report
  - Clinical grade sequencing report with trial matching
  - Patient-friendly report
- Data Visualizations
  - Patient-friendly and physician-facing visualizations

MMRF CureCloud®

It starts with you.
The MMRF CureCloud® is the first research study including at-home genomic testing for myeloma patients. As a participant, you receive free tests and resources that enable more productive and informed conversations with your multiple myeloma care team.

Genomic test
Get a free state-of-the-art genomics test, using the first liquid biopsy for multiple myeloma.

Personal report
Receive a free report on the genetic variations in your multiple myeloma cells.

Coming soon: Smarter treatment options
You and your care team can identify more informed treatment paths based on other patient data.

Join now — visit mmrfcurecloud.org or call 1-888-841-MMRF (6673)
CureCloud®

Personalized Reports

Personalized genomics reports designed to enhance doctor–patient communication.

MyGeneCounsel Report for Patients

DFCI Report for Physicians
Patient Resources

Provide personalized insights and actionable guidance to inform more precise treatment decision-making.

Mobile & Desktop Microsite

Personalized Dashboard

Patient Support

MMRF Patient Navigators are available to provide additional support; Facebook groups and Myeloma Mentors provide patients opportunities to connect with patients like them.

Patient Navigators

Facebook Groups

Myeloma Mentors
Thank you!

www.mmrfcurecloud.org

Discussion Topics

- Overview of multiple myeloma precursor conditions
- Preventing development of active myeloma
Overview of Multiple Myeloma Precursor Conditions

Elisabet Manasanch, MD
Monoclonal gammopathy of undetermined significance

MGUS → SMM → Multiple myeloma

Smoldering multiple myeloma

SMM: Current treatment plan is to observe only; ongoing question of best therapy to use as early intervention

Multiple Myeloma Disease Trajectory

MGUS
- M protein <3 g/dL
- No myeloma-defining events

1% risk of progression/year to multiple myeloma or related conditions

Smoldering myeloma
- M protein ≥3 g/dL (serum)
- ≥10% clonal plasma cells in bone marrow
- No myeloma-defining events

10% risk of progression/year to active myeloma

High-risk smoldering myeloma
- M protein ≥3 g/dL (serum)
- "Evolving type" ≥10% increase in M protein within 6 months

50% chance of progression/year to get active myeloma

Multiple myeloma
- Underlying plasma cell proliferative disorder
- AND ≥1 myeloma-defining events
- ≥1 CRAB* or SLiM feature†

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)

Overview of 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.

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**Smoldering Multiple Myeloma: Heterogeneous Disease**

![Graph showing the probability of progression over years since diagnosis for MGUS and Smoldering MM](image)

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

Phase 3 Trial of Revlimid-Dex vs Observation in High-Risk SMM

**Time to Progression**

- HR 0.24, 95% CI 0.14–0.41; P<0.0001

**Overall Survival**

- HR 0.43, 95% CI 0.21–0.92; P=0.024


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Revlimid vs Observation Alone in Patients With Smoldering MM

**Progression-Free Survival**

- Median follow up 35 months

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

Patients with two or more risk factors are considered high risk.

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

Risk assessment for SMM

- **2** >2 g/dL protein
- **20** >20 free light chain ratio
- **20** >20% bone marrow plasma cells

Progression by Risk Group

<table>
<thead>
<tr>
<th>Risk of Progression at 2 Years</th>
<th>Low-risk group (no risk factors)</th>
<th>Intermediate-risk group (1 risk factor)</th>
<th>High-risk group (2-3 risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of Progression (%)</td>
<td>6.2%</td>
<td>17.9%</td>
<td>44.2%</td>
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</table>

Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria

High risk

Intermediate risk

Low risk


Ongoing Clinical Studies for SMM Patients

Phases 1–3 or Observational

SMM patients at high risk of disease progression

- Xgeva
- Ninlaro + Revlimid + dex
- Darzalex (sc)
- Kyprolis + Revlimid + dex
- Revlimid + dex ± Kyprolis
- Kyprolis + Revlimid + Darzalex + dex (ASCENT trial)
- Revlimid + dex ± Darzalex
- Empliciti + Revlimid + dex (E-PRISM Trial)
- Vaccines: PVX-410, DKK1, custom-made
- Sarcisla

SMM/MGUS

- Predictors of progression (PROMISE study)
- Genomic and molecular predictors of progression (MD Anderson study)
- Darzalex
- Rifaximin
- DKK1 (dendritic cell) vaccine
- Neo-antigen personalized vaccine

Ask your doctor about whether you are a candidate for a clinical trial.
Phase 2 Trial of Sarclisa in SMM Patients

Sarclisa is a monoclonal antibody that binds to CD38 on myeloma cells

- 62.5% of patients responded to treatment
  - Comparable response rate to a recent phase 3 trial of Revlimid in a similar patient population (50%)

Similar binding site of Darzalex

- 20% of patients experienced grade 3 side effects and no grade 4
  - No patients discontinued the trial due to side effects

Phase 2 study of Sarclisa in 24 patients with SMM (majority were considered high risk by 2/20/20 model)

- Treatment decreased patients’ worries about cancer.

Analysis is ongoing.

Extensive Changes of the Immune Microenvironment Are Associated With Progression From Precursor Stages to MM

Prospective Observational Study Design

Changes in immune cell populations and their function have been described as early as MGUS

- 2015–2019 → 100 eligible patients were included in the analysis
  - 41 MGUS and 59 SMM
  - Median follow-up 24 months (12–48 months)

Study goal: Characterize immune dysregulation in MM precursor disease and describe changes in evolution to MM

BM, bone marrow; PC, plasma cell
17% of SMM patients progressed to active myeloma

Higher risk of progression may be associated with increasing mutation rates in patients

Gene-expression features of both the tumor and the immune system may be used to predict risk of progression

Patients that progressed had different genes upregulated or downregulated when compared to non-progressors at baseline

Significant changes in the immune cell composition included changes in CD8 T cells, dendritic cells, NK cells, and macrophages of progressors vs non-progressors at baseline

Key Points

The classic description of SMM having an ~10% chance per year of progression to symptomatic disease is too broad a characterization of a heterogeneous group.

Genetic changes and mutations in the myeloma together with clinical factors can best predict progression to myeloma.

Genetic and mutation analysis is not yet widely available.

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.
Questions & Answers

Preventing Development of Active Myeloma

Irene Ghobrial, MD
Modifying current risk models using genomics to significantly improve the accuracy of identifying those at highest risk of progressing to MM.

Why is “precision prevention” and early detection important? And why now?

Historically, most efforts in this area have been focused on environmental causes of cancer and developing therapeutics to treat cancer.

Advances in molecular biology (for example, genomics) enable us to better understand, predict, prevent, and detect cancers and achieve better outcomes for patients.
Detecting Multiple Myeloma Precursor Conditions

**Monoclonal Gammopathy of Undetermined Significance (MGUS)**

**Smoldering Multiple Myeloma (SMM)**

- 3% of the general population at age 50 have 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

![Graph showing the number of MGUS cases per 100,000 individuals](image)

**Changing the Multiple Myeloma Diagnosis**

**Specific Aims**

**Aim 1. The PROMISE Study**

- Screen 50,000 high-risk individuals
- Screen negative 47,000
- Screen positive 3,000
- Prospective follow-up

**Aim 2. Genomic Characteristics of MGUS/SMM**

- Viktor Adalsteinsson
- Irene Ghobrial
- Benjamin Ebert
- Gaddy Getz

**Aim 3. Race/Obesity on Precursor Progression**

- Lorelei Mucci
- Tim Rebbeck
- Catherine Marinac

**Aim 4. MGUS/SMM Permissive Microenvironment**

- Ivan Borrello
- Irene Ghobrial

**Aim 5. Imaging /Therapeutics For Detection/Interception**

- Jeremiah Johnson
- Irene Ghobrial

**Develop novel biomarkers for diagnosis**

**Establish advanced risk stratification**

**Generate new tools to prevent precursor progression**
The PROMISE Study
Accomplishments Since Most Recent Meeting With Review Committee

- Registered: 2,772
  These participants each have a personalized PROMISE Dashboard
- Consented: 2,287
  Our team sends weekly emails to remind participants to finish filling out their forms
- Sent Blood Kit: 2,287
  Kits are sent out in batches every other week to consented participants
- Sent Blood Samples: 1,329
  60% of the kits that have been sent out have returned with samples for testing
- Screened Positive: 164
  13.3% of screened participants are positive for a precursor condition

2 groups of U.S. adults, age 45-75, 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
   - One of these related conditions:
     - Monoclonal Gammopathy of Undetermined Significance (MGUS)
     - Smoldering Multiple Myeloma
     - Waldenström’s Macroglobulinemia

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 PROMISE study for those affected with precursor conditions.

www.enroll.promisestudy.org/
The PROMISE Study
Predicting Progression of Developing Myeloma in a High-Risk Screened Population

Screening individuals of African descent
• The PROMISE Study has, as of today, enrolled 15% individuals of African descent
• 13% of screened POSITIVE PROMISE participants identify as being of African descent

New CPOP Clinic
(Center for Prevention of Progression of Blood Cancers)

FEATURES

Aim and scope of clinic: To actively study patients with precursor hematological malignancies and define mechanisms/therapies that prevent progression

Goal: Have DFCI be the center of excellence for early precursor hematological conditions
• Physical clinic
• Multidisciplinary
  – DFCI HM & BWH Hematology clinical staff, Medical Genetics, BWH Cardiology
• Integration of research and clinical care
Defining Disease Progression Through Genomic Profiling

- Bone marrow samples from 203 SMM patients were analyzed to
  - Determine the genetic and molecular profiles that underlie disease progression
  - Improve risk stratification by identifying those at highest risk of progression compared to conventional risk assessment

<table>
<thead>
<tr>
<th>Genetic Profile</th>
<th>Time to Progression (months)</th>
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<tbody>
<tr>
<td></td>
<td>SMM Pts With</td>
</tr>
<tr>
<td>MYC abnormality</td>
<td>8.4</td>
</tr>
<tr>
<td>MAPK pathway mutations</td>
<td>15</td>
</tr>
<tr>
<td>DNA repair mutations</td>
<td>19</td>
</tr>
<tr>
<td>≥1 DNA repair mutation</td>
<td>1.2 yrs</td>
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Can intervention prevent progression in multiple myeloma?

Screen with mammogram → Early-stage breast cancer → Treat as early as possible → CURE

Just a blood test! (SPEP) → MGUS and SMM → Watch and wait until end organ damage → NO CURE

Multiple myeloma

Precision Intervention With Empliciti in Smoldering Myeloma

Phase 2 Trial of Combination of Empliciti, Revlimid, and Dexamethasone in High-Risk Smoldering Multiple Myeloma (With Whole-Genome Sequencing of Patient Samples)

Questions & Answers

Program Support

- abbvie
- Bristol Myers Squibb
- cure®
- Karyopharm Therapeutics
- janssen
- Pfizer
COVID-19 Resources

Coronavirus (COVID-19) & Multiple Myeloma

Our Chief Medical Officer, Hsuan Chu, addresses important questions for multiple myeloma patients


MMRF Patient Resources

MMRF Patient Navigation Center

 Expect Guidance.

MMRF Patient Navigation Center

THE RIGHT TRACK™

Get on the right track for you
The MMRF’s Right Track program puts you on the path to the best results for you.

Right Tests
Get the information, tests, and answers you need to make the best treatment decisions.

Right Treatments
Work with our team to create the best treatment plan and identify clinical trials that are right for you.

Contact the Patient Navigation Center Today

Landing for guidance? We’re here to help.
Monday – Friday 9am – 5pm EST
Phone: 540-430-1468 (US) / 0800 1234 5678 (Global)

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Research Foundation
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

**Autologous Stem Cell Transplantation for Multiple Myeloma**
Wednesday, September 22, 2021, 2:00 PM–3:00 PM ET

*Sergio A. Giralt, MD*
Memorial Sloan Kettering Cancer Center
New York, New York

*Amrita Y. Krishnan, MD*
City of Hope Medical Center
Duarte, California

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