



# Precursor Conditions in Multiple Myeloma

July 10, 2024

## Tech Support

1-719-234-7952

abbvie

**Adaptive**  
biotechnologies™

Advancing MRD measurement.  
Empowering patient care.

**Baxter**

 Bristol Myers Squibb™

**cure**®  
curetoday.com

**Genentech**  
A Member of the Roche Group

 **Kite**  
A GILEAD Company

 ARCELLX™

 **Pfizer**

**REGENERON**  
SCIENCE TO MEDICINE®

**sanofi**

3

## Resources

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

**Submit your questions  
throughout the program!**

4

# 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).

© Copyright 2021 | Multiple Myeloma Research Foundation, Inc.

# 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

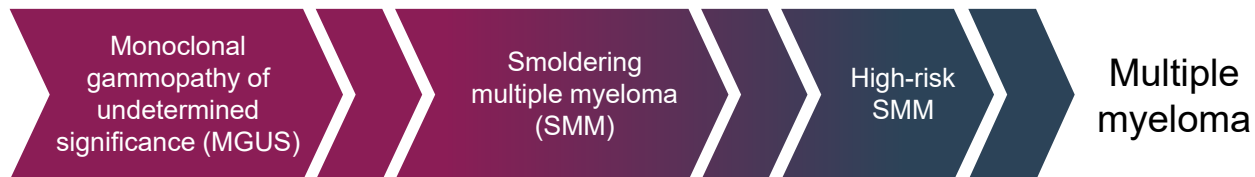
Emory University School of Medicine

Atlanta, Georgia

7

## 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.*



8

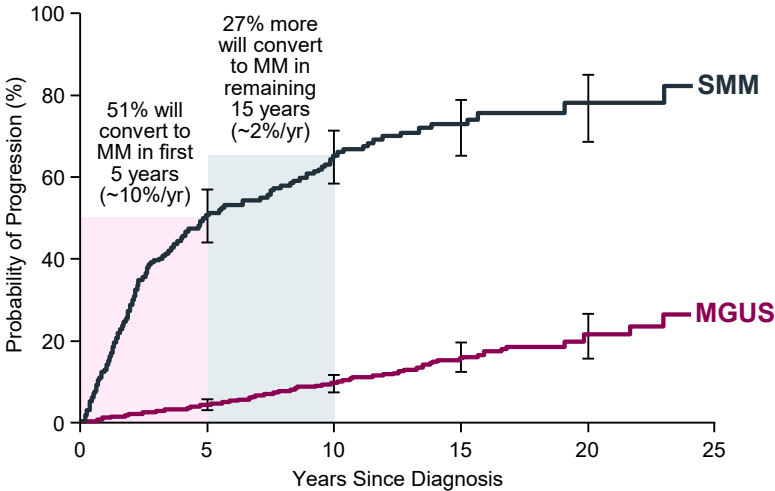
# Blood, Urine, Bone Marrow, and Imaging Tests Used to Identify MGUS, SMM, or Active Multiple Myeloma

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

\*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

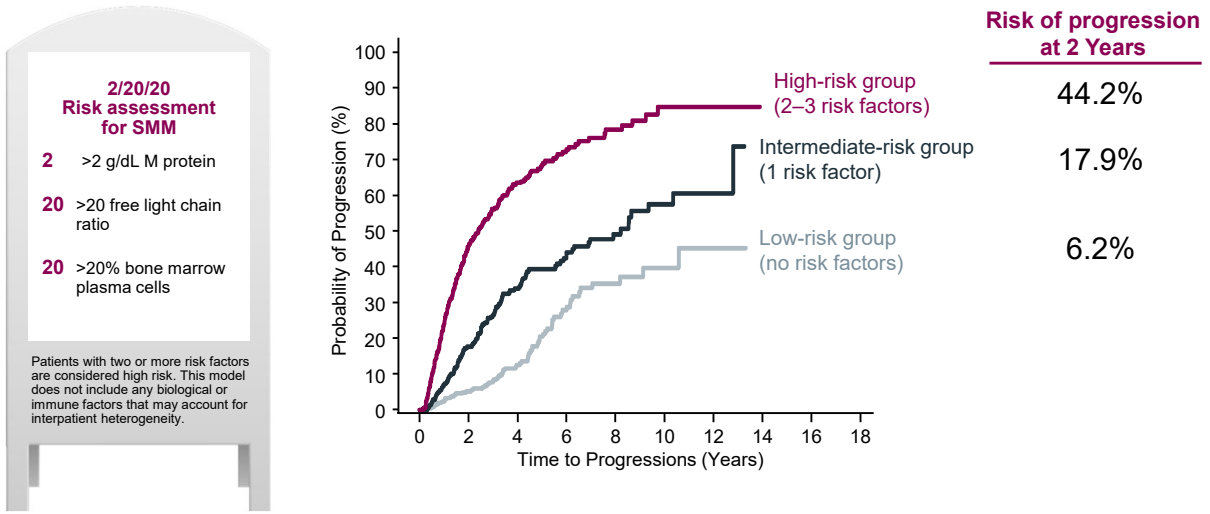
Rajkumar SV et al. *Lancet Oncol.* 2014;15:e538.

# Risk of Progression to Myeloma From a Precursor Condition



Kyle RA et al. *N Engl J Med.* 2007;356:2582.  
Greipp PR et al. *J Clin Oncol.* 2005;23:3412.

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



11

## 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

Cowan A et al. *Lancet Haematol.* 2023;10:e203.

12

# Can we identify everyone who has a precursor condition?

13

## Studies Focusing on Myeloma Precursor Conditions

### Large ongoing precursor studies

**Iceland**



**iStopMM**  
Iceland Screens,  
Treats or Prevents  
Multiple Myeloma

Focus: role of population screening

**United States and Canada**



**THE PROMISE STUDY**

Focus: racial disparities and familial aggregation

**United States**



**TRANSFORMM**  
study

Focus: genomic markers of progression

14

## 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<sup>1</sup>

- 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

### MGUS<sup>2-4</sup>

- 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; and 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.

1. Thorsteinsdottir S et al. *Blood*. 2021;138. Abstract 151. 2. Love TJ et al. *Blood*. 2022;140. Abstract 103. 3. Palmason R et al. *Blood*. 2022;140. Abstract 105. 4. Eythorsson E et al. *Blood*. 2022;140. Abstract 107.

15

## 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 these related conditions:
    - MGUS
    - Smoldering Multiple Myeloma
    - Waldenström Macroglobulinemia

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

El-Khoury H et al. *Blood*. 2021;138. Abstract 152.

16



## 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

17



## Therapeutic Intervention for Myeloma Precursor Conditions

***C. Ola Landgren, MD, PhD***

Sylvester Comprehensive Cancer Center  
University of Miami  
Miami, Florida

18

## SMM, to treat or not?

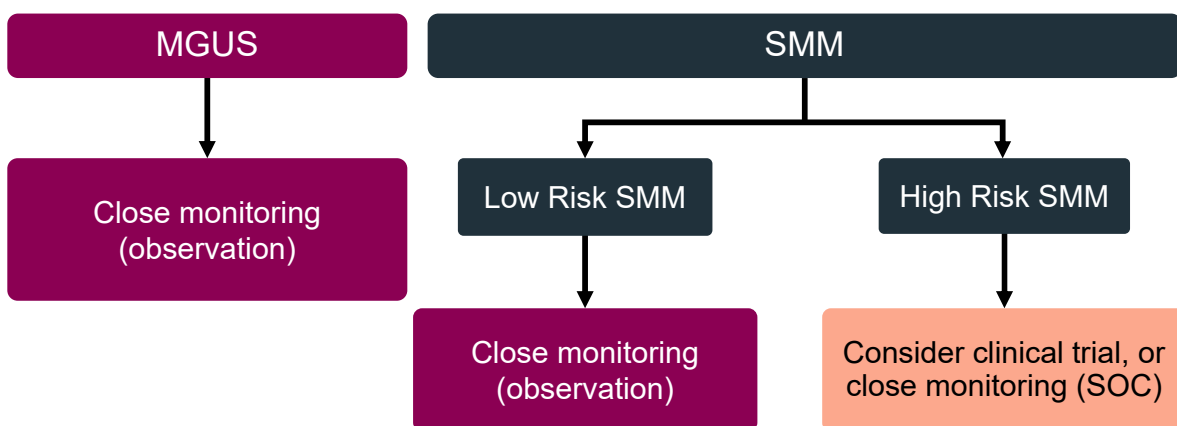
- Delaying symptomatic progression
- Maintain/increase quality of life by treating early
- Possibility of cure?

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



19

## Overview of Current Treatment Approach



Rajkumar SV et al. *Blood Cancer J.* 2022;129.

20

## 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

Kyle RA et al. *Leukemia*. 2010;129.

21

## 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

Rajkumar SV et al. *Blood Cancer J*. 2022;129.

22

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

**Low-efficacy therapy**  
(control approach)

**High-efficacy therapy**  
(curative intent)



R, Rd, Dara

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

**Pros**

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

**Cons**

- Low ORR
- Does not eliminate the clone

**Pros**

- High ORR
- Deep responses

**Cons**

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

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

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

Treatment	Results
Revlimid-dexamethasone vs observation <sup>1</sup>	After 12.5 years of follow up, treatment with Rd extended time to progression (TTP) to multiple myeloma by 7 years <sup>2</sup>
Revlimid vs observation <sup>3</sup>	Early treatment with R significantly prevented the progression to MM, especially in the high-risk subgroup.
Darzalex monotherapy <sup>4,5</sup> Short: 8 weeks Intermediate: 20 weeks Long: 20 weeks + optional extension	After 7 years of follow up, overall survival was: 88% in short treatment group 90% in intermediate treatment group 89% in long treatment group

1. Mateos MV et al. *N Engl J Med.* 2013;369:438; 2. Mateos MV, et al. *Eur J Cancer.* 2022;174:243; 3. Lonial S et al. *J Clin Oncol.* 2019;38:1126; 4. Landgren O et al. *Leukemia.* 2020;34:1840; 5. Landgren O et al. *Blood.* 2023. Abstract 210.

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

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

	Short	Intermediate	Long
Treatment	D once a week for 1 cycle	D once a week for 1 cycle then every other month for 19 cycles + optional extension	D once a week for 1 cycle then every other week for 2 cycles then every month for 4 cycles then every other month for 13 cycles + optional extension
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.  
Landgren O et al. *Blood*. 2023. Abstract 210.

25

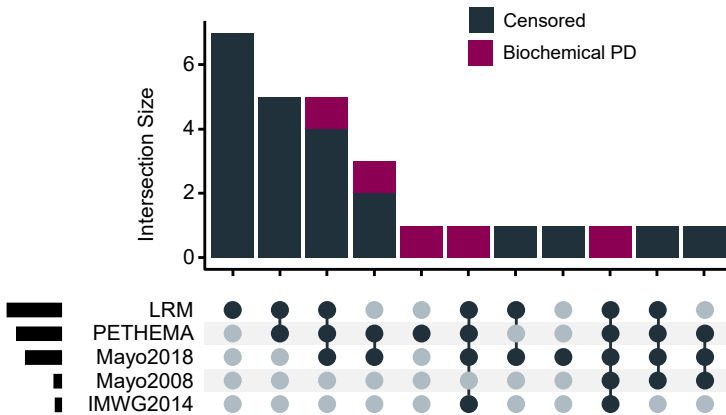
## Three or Four-Drug Combination Strategies for High-Risk SMM Patients

	NCI Study <sup>1</sup>	GEM-CESAR <sup>2</sup>	ASCENT <sup>3</sup>
Induction	Kyprolis + Revlimid + dex (KRd)	KRd + stem cell transplant	Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)
Maintenance	Revlimid	Revlimid	Dara-R
Results	The 8-year probability of being free from progression to myeloma was 91%	At 70 months, 94% of patients have not progressed to multiple myeloma	90% of patients were progression-free at 3 years

1. Kazandjian D, et al. *JAMA Oncology*. 2021;7:1678; 2. Mateos MV et al. *Blood*. 2022;140. Abstract 118; 3. Kumar SK et al. *Blood*. 2022;140. Abstract 757.

26

# Discordance Between Risk Scores for SMM and Patterns of Progression



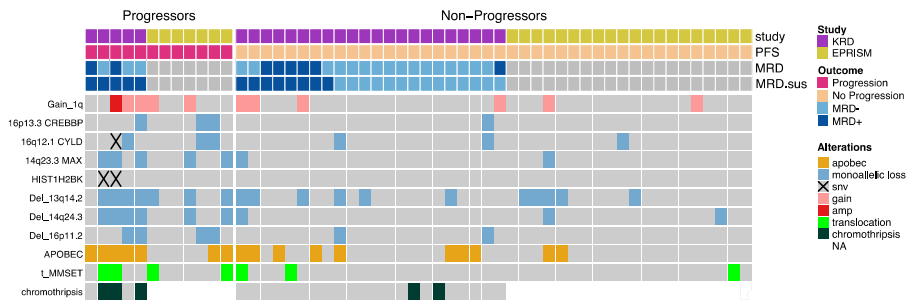
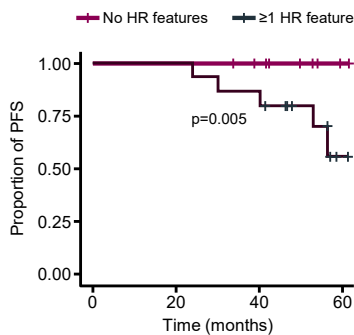
LRM, PETHEMA, Mayo2018, Mayo2008, and IMWG2014 are five different clinical risk scores which have been published in the literature.

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.

Kazandjian D, et al. JAMA Oncology. 2021;7:1678.

27

# 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

Kazandjian D, et al. Clin Cancer Res. 2024 Apr 23

28

## 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.

29



## Questions & Answers

30

**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

© Copyright 2021 | Multiple Myeloma Research Foundation, Inc.

The collage features several key pieces of patient education content:

- Multiple Myeloma Personalized Medicine: What You Need to Know** infographic.
- Clinical Studies in Multiple Myeloma: What You Need to Know** infographic.
- Bone Health and Multiple Myeloma: What You Need to Know** infographic.
- PATIENT SUMMIT** poster for Seattle, WA on Saturday, October 12, 2024.
- SAVE THE DATE: 8/13 Patient Webinar** poster for "Managing Side Effects in Multiple Myeloma" on Tuesday, August 13th at 2:00 PM ET.
- MYELOMA matters** logo.
- MULTIPLE MYELOMA TREATMENT OVERVIEW** graphic.
- AUTOLOGOUS STEM CELL TRANSPLANT** and **LEARN YOUR LABS** high-impact topic graphics.

**MMRF Patient Resources**

**EXPECT GUIDANCE.**  
 MMRF Patient Navigation Center

- Information & Resources
- Expert Advice
- Support

MULTIPLE MYELOMA Research Foundation

**MMRF Patient Navigation Center**

You and your care team will have many decisions to make along your treatment journey. The Patient Navigation Center is a space for multiple myeloma patients and their caregivers to connect with patient navigators – who are professionals specializing in oncology – for guidance, information, and support. You can connect with a patient navigator via phone, or email. Whatever questions you may have, our patient navigators are here to help.

MMRF Patient Navigators include:  
 ■ Grace Allison, RN, BSN, OCN, RN-BC ■ Brittany Hurtmann, RN-BSN  
 ■ Erin Mensing, RN-BSN, OCN

**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.

 <b>Right Team</b> Access experts and centers that have extensive experience treating multiple myeloma.	 <b>Right Tests</b> Get the information, tests, and precise diagnoses to make the right treatment decisions.	 <b>Right Treatment</b> 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 – 7:00pm ET  
 Phone: 1-888-841-MMRF (6673) | Online: TheMMRF.org/PatientNavigationCenter  
 Email: patientnavigator@themmrff.org

Supported By

Adaptive AMGEN Bristol Myers Squibb cure  
 Genentech janssen sanofi Takeda ONCOLOGY





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
New York City | 10.5.24
Philadelphia | 10.19.24
San Francisco | 8.24.24
Scottsdale | 12.7.24
Tampa | 11.2.24
Twin Cities | 9.14.24
Washington D.C. | 9.28.24



Other MMRF Event Programs

- Moving Mountains for Multiple Myeloma (with mountain icon)
Half and Full Marathons (with t-shirt icon)
Bike/Road to Victories (with bicycle icon)
Create Your Own Fundraiser (with balloons icon)



# Upcoming Patient Education Events

## Save the Date

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

For more information or to register,  
visit [themmrf.org/educational-resources](https://themmrf.org/educational-resources)



## Resources

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

37

## 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



38



Thank you!