MULTIPLE MYELOMA Research Foundation

Multiple Myeloma Precursor Conditions

April 5, 2023

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Tech Support

1-719-234-7952

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Resources

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

Submit your questions throughout the program!

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MMRF Research Initiatives

MULTIPLE MYELOMA Research Consortium

CoMMpass Study℠

MMRF CureCloud™

For more information, visit themmrf.org.

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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

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Overview of Multiple Myeloma Precursor Conditions

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

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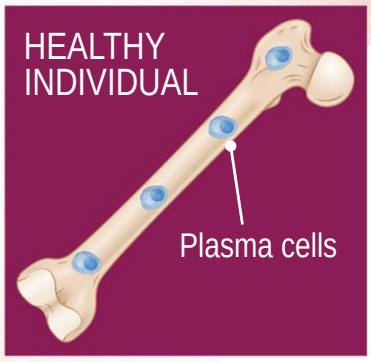

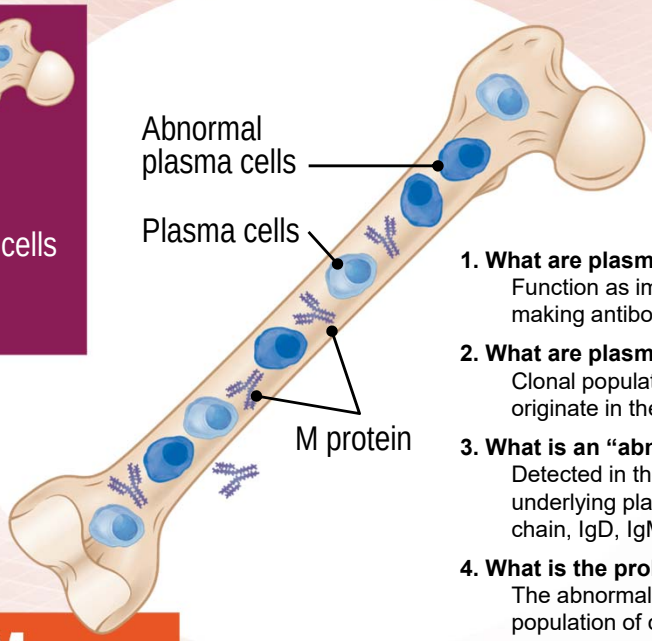

MGUS/SMM

FAQs

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.

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Plasma Cell Disorders: Classification

Updated IMWG criteria for diagnosis of multiple myeloma

MGUS

- M protein <3 g/dL
- Clonal plasma cells in bone marrow <10%
- No myeloma-defining events

Smoldering myeloma

- M protein ≥3 g/dL (serum) or ≥500 mg/24 hrs (urine)
- Clonal plasma cells in bone marrow ≥10% to 60%
- No myeloma-defining events

Multiple myeloma

- Underlying plasma cell proliferative disorder

AND

- 1 or more myeloma-defining events
- ≥1 CRAB* feature
- Clonal plasma cells in bone marrow ≥60%
- Serum free light chain ratio ≥100
- >1 MRI focal lesion

*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)

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

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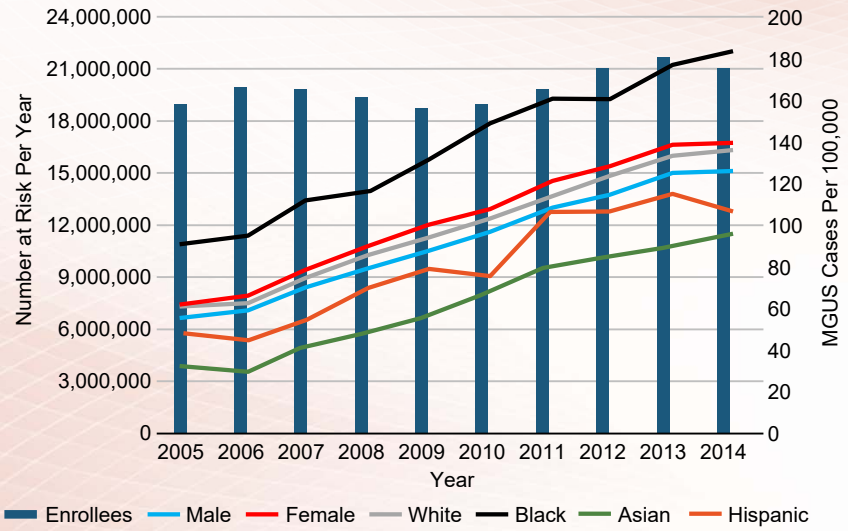
MGUS is a Very Common Condition



- 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

Go RS et al. *Leukemia.* 2016;30:1443.

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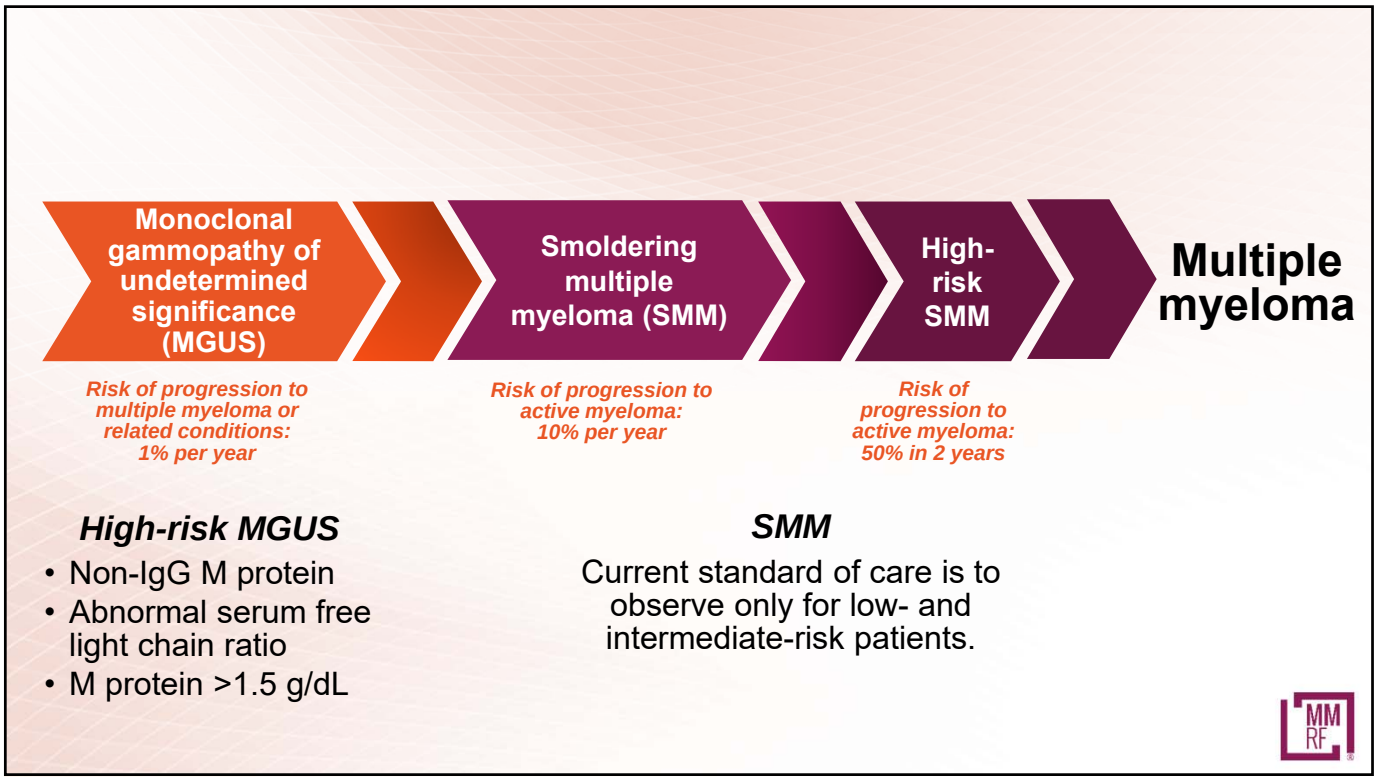
Monoclonal gammopathy of undetermined significance (MGUS)
Smoldering multiple myeloma (SMM)
High-risk SMM
Multiple myeloma
Risk of progression to multiple myeloma or related conditions: 1% per year
Risk of progression to active myeloma: 10% per year
Risk of progression to active myeloma: 50% in 2 years
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.

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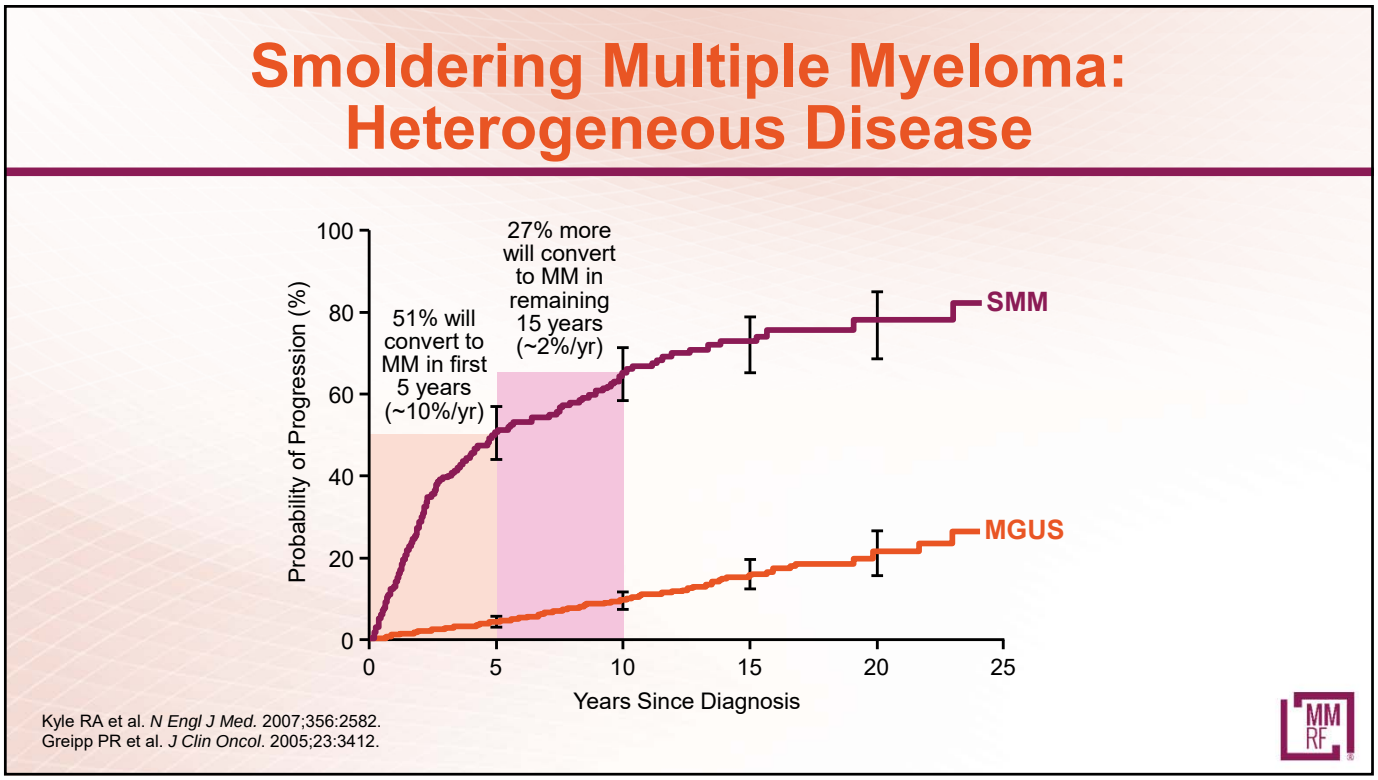
Smoldering Multiple Myeloma: Heterogeneous Disease
Probability of Progression (%)
100
80
60
40
20
0
0
5
10
15
20
25
Years Since Diagnosis
51% will convert to MM in first 5 years (~10%/yr)
27% more will convert to MM in remaining 15 years (~2%/yr)
SMM
MGUS
Kyle RA et al. N Engl J Med. 2007;356:2582.
Greipp PR et al. J Clin Oncol. 2005;23:3412.

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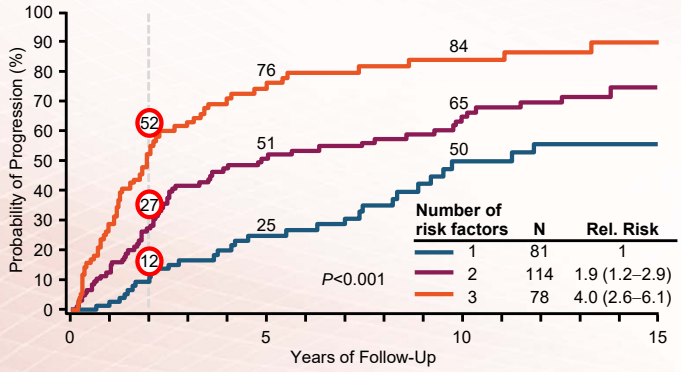
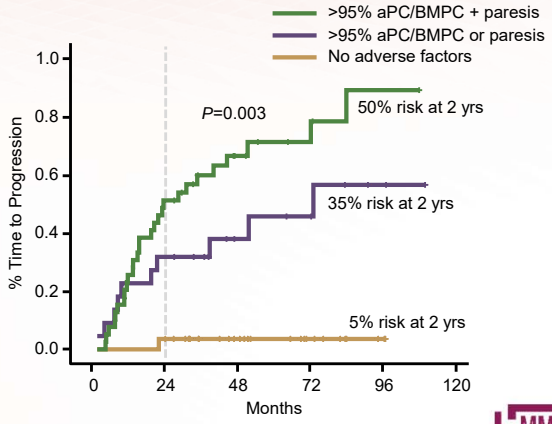
Risk Assessment in Smoldering Myeloma

Mayo risk model[1]
Plasma cell bone marrow infiltration, serum M-component level, and serum free light chain ratio



Spanish model[2]
Aberrant PCs by immunophenotype plus immunoparesis



1. Dispenzieri A et al. *Blood*. 2008;111:785.
2. Perez-Persona E et al. *Blood*. 2017;110:2586.

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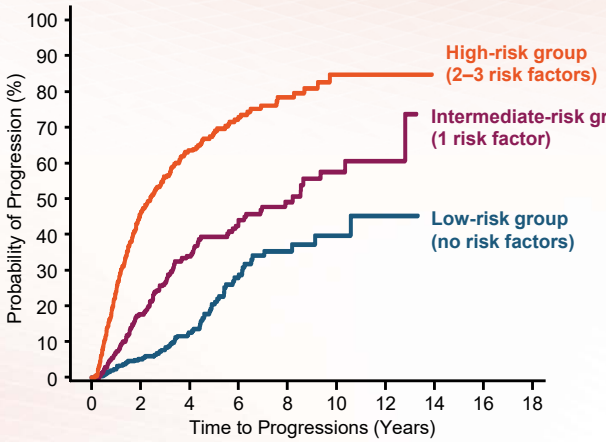
2/20/20 Model to Identify High-Risk SMM Patients

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.



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

Mateos MV et al. *Blood Cancer J*. 2020;10:102.

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Can we identify everyone who has a precursor condition?

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Identifying Patients Who Have Myeloma Precursor Conditions

Nationwide Screening Studies

Iceland

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

United States and Canada

THE PROMISE STUDY

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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.

*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.

Thorsteinsdottir S et al. *Blood*. 2021;138. Abstract 151.

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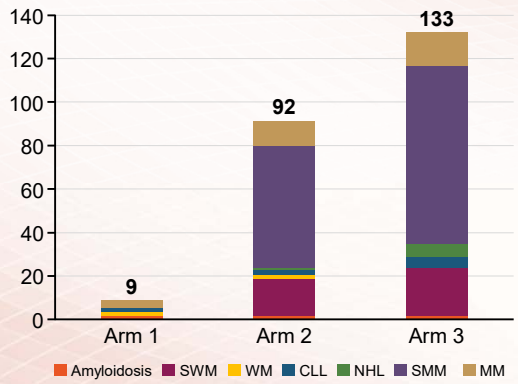
Additional iStopMM Study Findings



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

Kristinsson SY et al. *Blood*. 2021;138. Abstract 156.

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

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

Rögnvaldsson S et al. *Blood*. 2021;138. Abstract 154.

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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

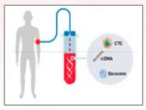
Genetics and genomics
Viktor Adalsteinsson, Gad Getz, Irene Ghobrial

Epidemiology
Tim Rebbeck, Lorelei Mucci, Catherine Marinac

Bone marrow niche
Ivan Borrello, Irene Ghobrial

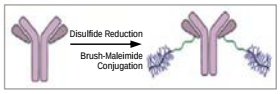
Imaging and therapeutics
Jeremiah Johnson, Irene Ghobrial

Develop novel **biomarkers for diagnosis**



Establish new **risk stratification** tools

Generate new tools to **prevent disease progression**



BROAD INSTITUTE · MIT · JOHNS HOPKINS MEDICINE · HARVARD SCHOOL OF PUBLIC HEALTH · STAND UP TO CANCER · MMRF

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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 Gammopathy of Undetermined Significance (MGUS)
- Smoldering Multiple Myeloma
- Waldenström 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, a sister project for people with precursor conditions

PCROWD

MMRF

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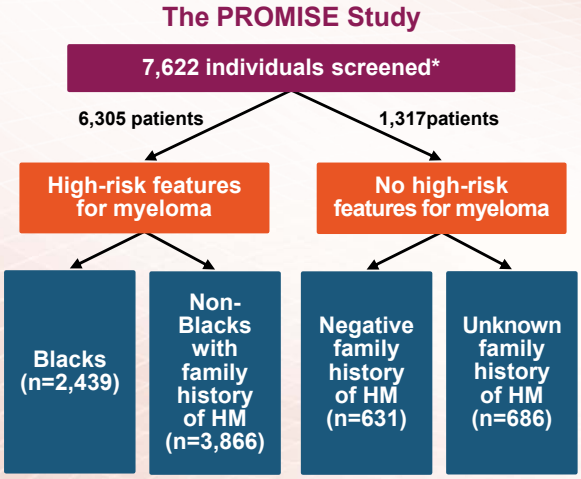
High Prevalence of Monoclonal Gammopathy in a Population at Risk



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

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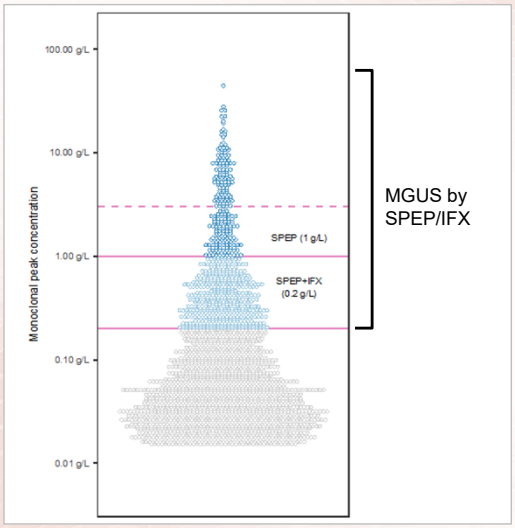
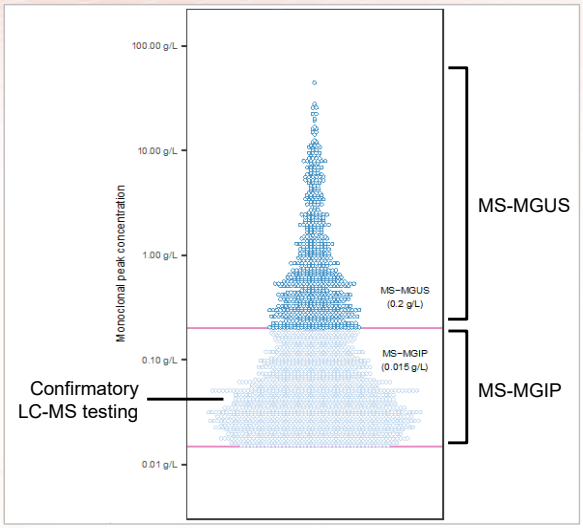
Defining Outcomes and Results





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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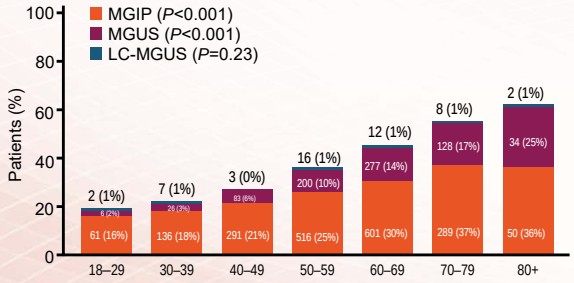
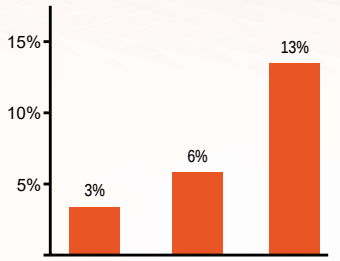
High Prevalence of Monoclonal Gammopathy in a Population at Risk

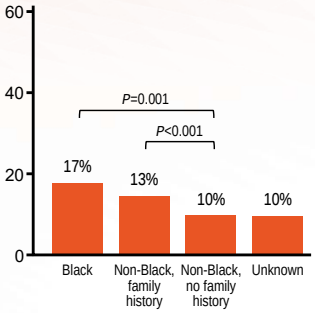
Rates of all monoclonal gammopathies* increase with age



MGUS more prevalent in individuals older than 50 years at risk



Higher rates of MGUS* in Blacks or individuals with a family history of HM and older than 50 years at risk



*Free light chains detected by mass spectrometry.

HM, hematologic malignancy; MGUS, monoclonal gammopathy of undetermined significance; MGIP, monoclonal gammopathies of indeterminate potential; LC, light chain; SPEP, serum protein electrophoresis; IFX, immunofixation; MS, mass spectrometry; MGBB, Mass General Brigham Biobank

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

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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.**

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Therapeutic Intervention for Myeloma Precursor Conditions

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

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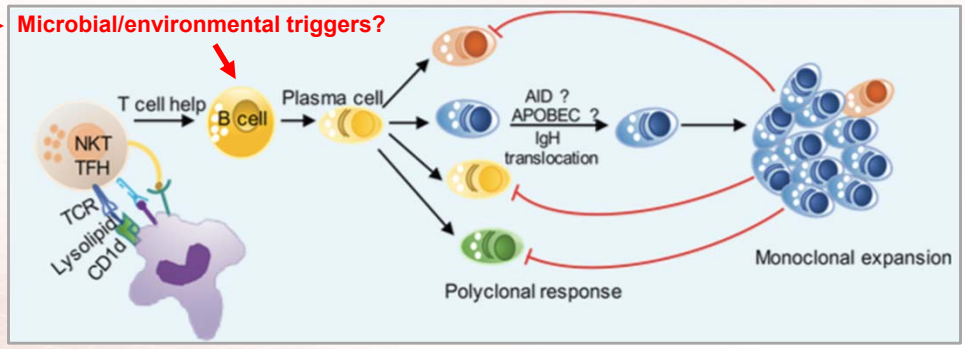
Preventing Evolution of Gammopathies to Prevent Myeloma

- Diet
- Lifestyle
- Microbiome

Antigen-mediated regulation in monoclonal gammopathy



Nair S et al. *JCI Insight*. 2018;3:e98259.
Unpublished

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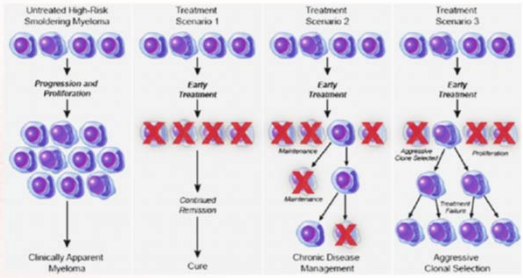
SMM, to treat or not?

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

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



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Overview of Current Treatment Approach

MGUS	SMM
Close monitoring (observation)	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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2/20/20 Risk assessment for SMM

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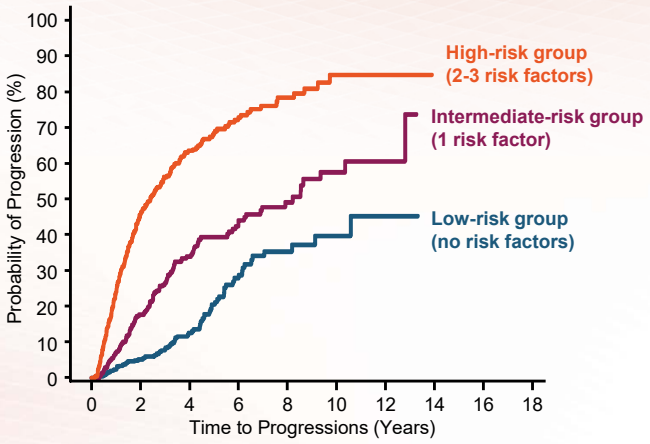
- **20** >20% bone marrow plasma cells

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



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

Mateos MV et al. *Blood Cancer J.* 2020;10:102.

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Approaches to SMM

Immunologic therapy
(prevention approach)

Intensive therapy
(curative intent)

Len, Len/Dex, Dara — **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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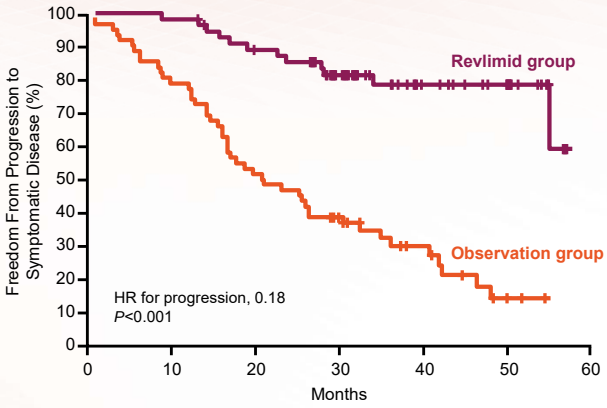
Early Therapeutic Intervention

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., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, 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 Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

Progression-free survival for early treatment



HR, hazard ratio
Mateos MV et al. *N Engl J Med.* 2013;369:438.

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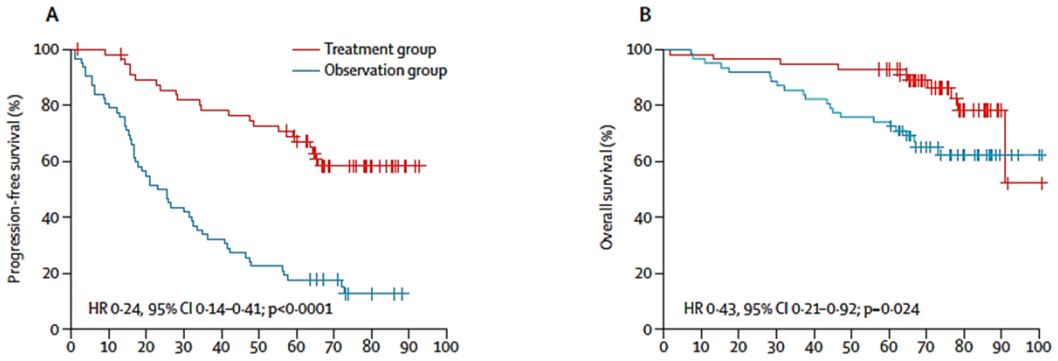
QuiRedex Phase 3 Trial
Len-dex vs No Treatment in High-Risk SMM

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



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

Mateos MV et al. *N Engl J Med.* 2013.
Mateos MV et al. *Lancet Oncol.* 2016.

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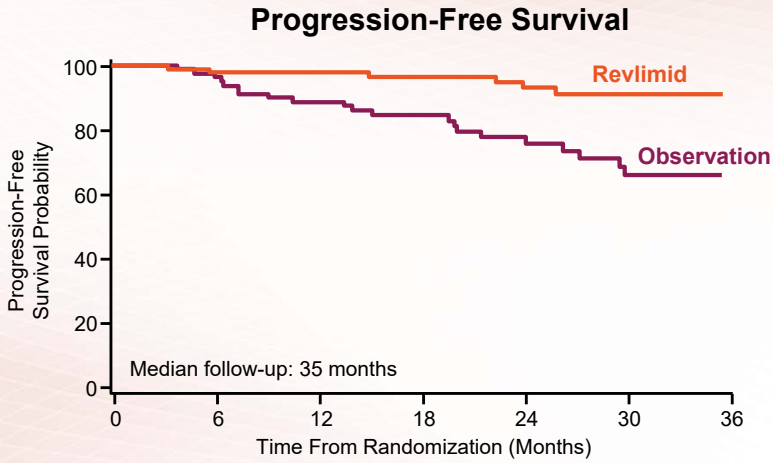
Revlimid vs Observation Alone in Patients With SMM



Lonial S et al. *J Clin Oncol.* 2020;38:1126.

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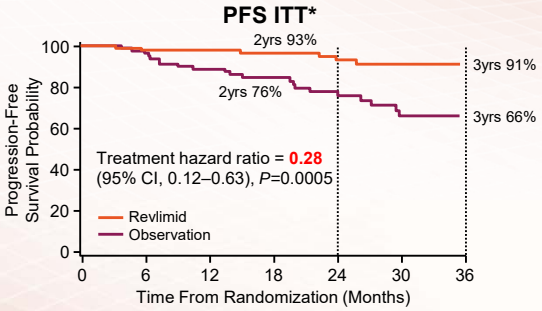
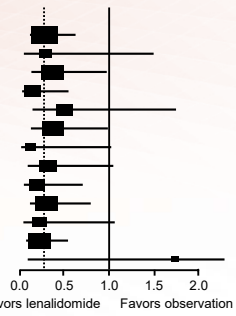
E3A06: Len vs Observation in Patients With Asymptomatic High-Risk SMM



Group	n	HR	95% ci
All patients	182	0.28	(0.12, 0.62)
Mayo 2008 risk high	29	0.29	(0.06, 1.49)
Mayo 2008 risk intermediate	104	0.37	(0.14, 0.97)
Mayo 2018 risk high	56	0.09	(0.02, 0.44)
Mayo 2018 risk intermediate	68	0.52	(0.15, 1.85)
Age <70	135	0.37	(0.14, 0.98)
Age ≥70	47	0.13	(0.02, 1.01)
Male	88	0.32	(0.10, 1.03)
Female	94	0.20	(0.06, 0.70)
ECOG PS 0	134	0.30	(0.12, 0.79)
ECOG PS 1–2	48	0.22	(0.05, 1.05)
White	140	0.22	(0.09, 0.54)
Black	31	1.73	(0.10, 30.76)



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

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

- 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

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

Lonial S et al. *J Clin Oncol.* 2019;38:1126.

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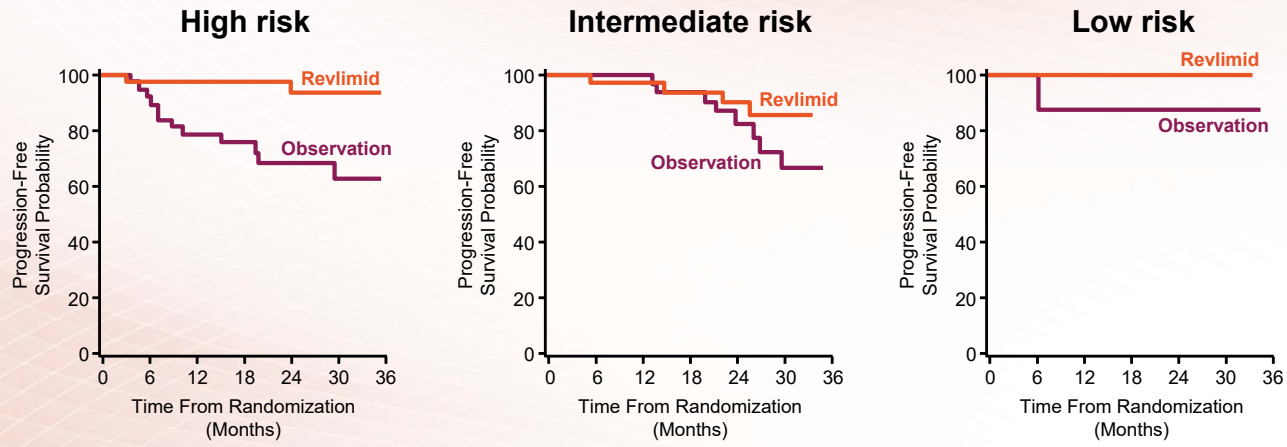
Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria



Lonial S et al. *J Clin Oncol.* 2020;38:1126.

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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)
- Iberdomide ± dex
- Darzalex + Revlimid + Velcade + dex (PRISM Trial)
- Sarclisa alone or + Revlimid
- Metformin
- Revlimid + dex ± Kyprolis
- Darzalex + Kyprolis + dex
- Blenrep
- Vaccines: PVX-410, DKK1, custom-made
- Xgeva

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

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GEM-CESAR: Multicenter, Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex

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

Courtesy of MV Mateos.

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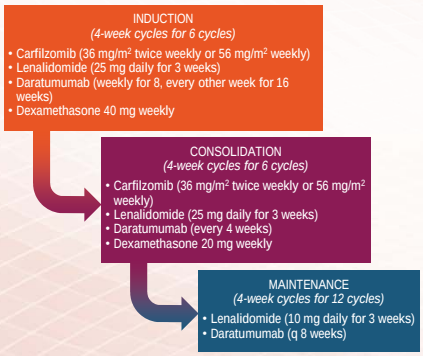
ASCENT: KRd-D

Study design

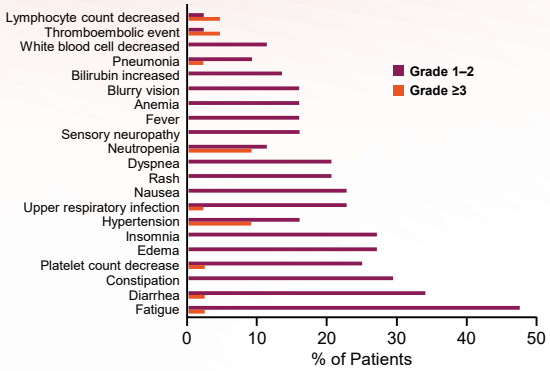


Primary end point: Rate of confirmed sCR
Secondary objectives: Safety, PFS, OS, MRD negativity

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

Toxicity profile



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
Kumar SK et al. *Blood*. 2020;136. Abstract 2285.

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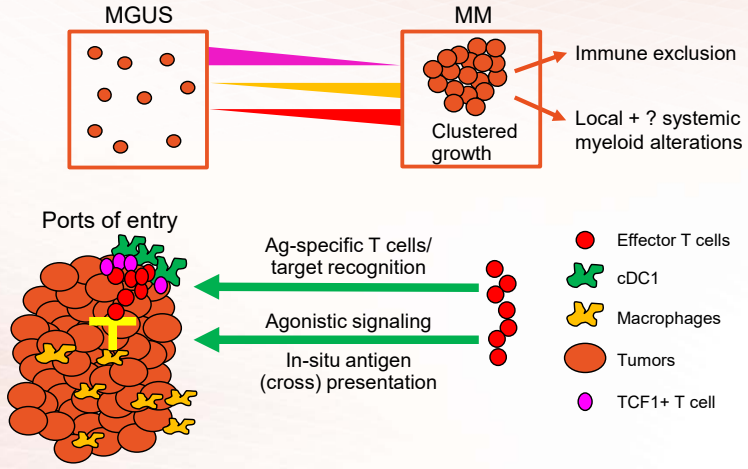
Is the malignant evolution in myeloma more like solid tumors and real estate? Location, location, location!

Spatial regulation of immune infiltration and tumor growth in malignant transformation



Robinson, Villa …Dhodapkar. Under review

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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 <u>which patients</u> can benefit the most from early treatment and what is the best treatment to offer early.**

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Recent Updates

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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 20/2/20 model

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

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Questions & Answers

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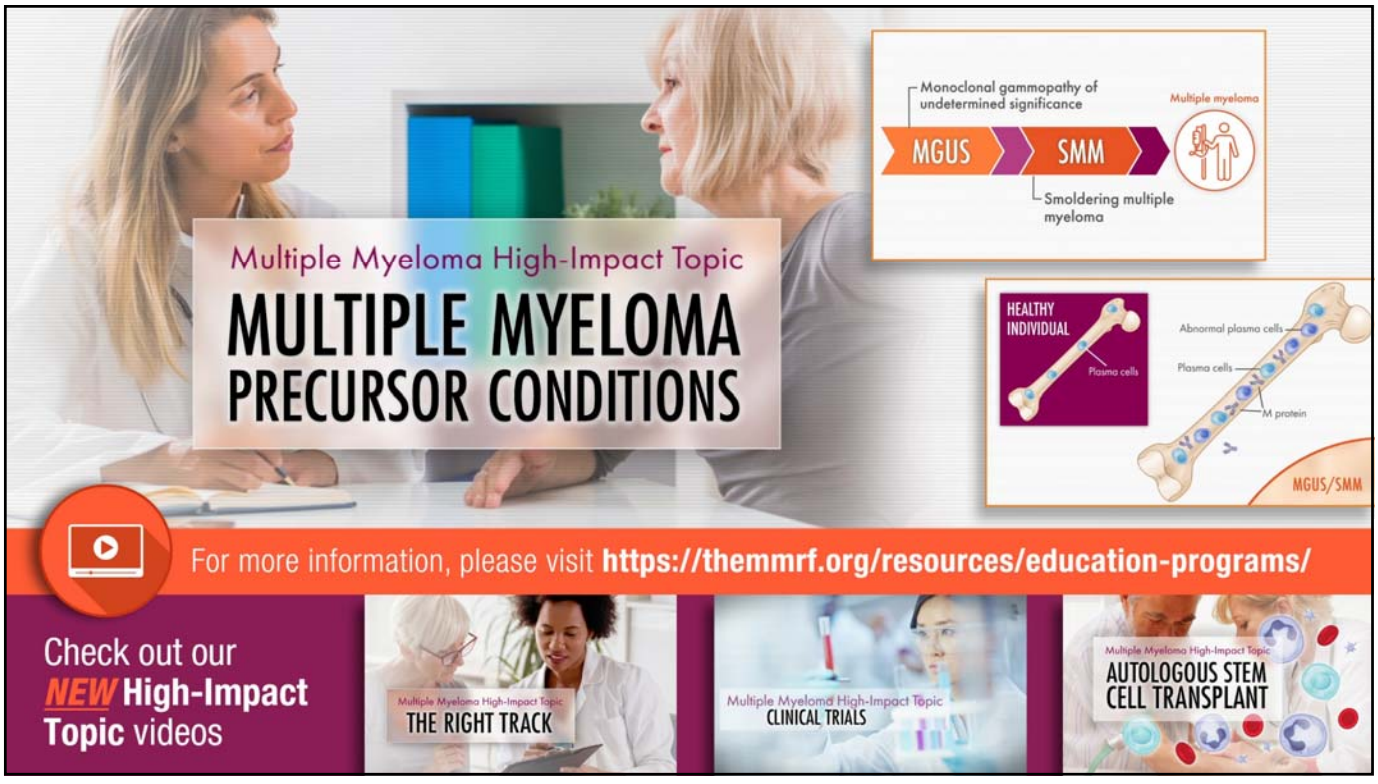

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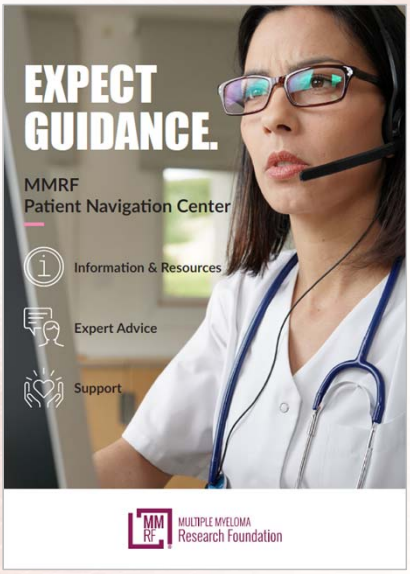
MMRF Patient Resources



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 Hartmann, RN-BSN
- Erin Mensching, 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.

Right Team
Access experts and centers that have extensive experience treating multiple myeloma.

Right Tests
Get the information, tests, and precise diagnoses 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 – 7:00PM ET

Phone: 1-888-841-MMRF (6673) Online: TheMMRF.org/PatientNavigationCenter

Email: patientnavigator@themmrf.org

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Myeloma Mentors®

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.

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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!

Endurance Events

5K Walk/Run Events

Independent Events

FIND AN EVENT AND JOIN US: themmrf.org/get-involved/mmrf-events/

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Upcoming Patient Education Events

Save the Date

Topic	Date and Time (ET)	Speakers
Facebook Live: FAQs on BCMA-targeted Bispecific Antibody Therapy	Friday, April 14 1:00 – 2:00 PM	Saad Usmani, MD Anna Howard, RN
Virtual Patient Summit	Saturday, April 29 9:00 – 3:00 PM	Ajai Chari, MD Jonathan Kaufman, MD Ola Landgren, MD, PhD Hans Lee, MD Robert Orlowski, MD Christine Jing Ye, MD

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

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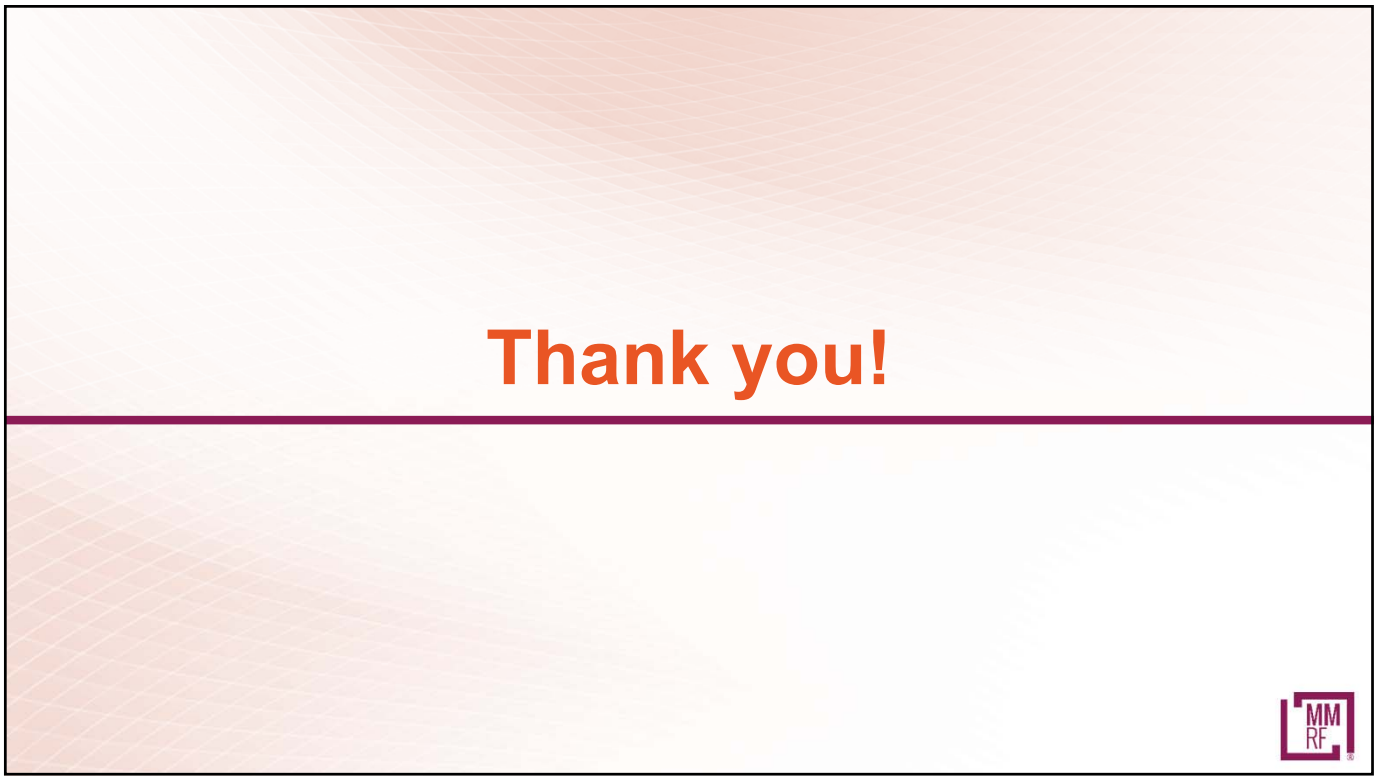
Thank you!
MM RF

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