MULTIPLE MYELOMA Research Foundation

Opening Remarks

Mary DeRome, MS
MMRF

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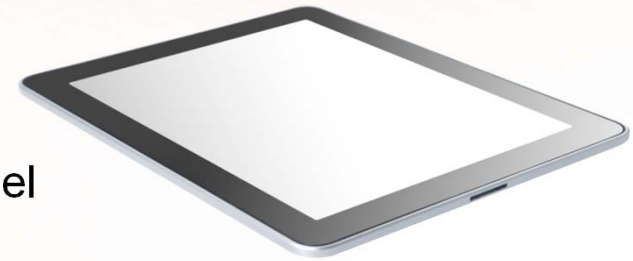
iPads

- To view the materials for this Summit, please log on to the iPad with your e-mail address
  - View slides
  - Answer questions
  - Take notes
  - Submit questions to panel
  - Program evaluation



Throughout the Summit, use the same e-mail address to log on to any iPad.

3

Program Faculty

Program Host

Ravi Vij, MD, MBA
Washington University School of Medicine
St. Louis, Missouri

Faculty

Craig Emmitt Cole, MD
Michigan State University
Karmanos Cancer Institute
Lansing, Michigan

Andrew D. Kin, MD
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan

Omar Nadeem, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

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Summit Agenda

Time (ET)	Topic	Speakers
9:00–9:15 AM	Introduction to the MMRF and Introduction to Washington University School of Medicine in St. Louis	Mary DeRome, MS Bettina F. Drake, PhD, MPH
9:15–9:25 AM	Welcome	Ravi Vij, MD, MBA
9:25–10:05 AM	The State of Myeloma Care and MM and Health Care Disparities	Craig Emmitt Cole, MD
10:05–10:35 AM	What's New in MGUS and Smoldering Multiple Myeloma?	Omar Nadeem, MD
10:35–11:05 AM	Newly Diagnosed Multiple Myeloma	Andrew D. Kin, MD
11:05–11:35 AM	Town Hall Q&A	Panel
11:35 AM–12:05 PM	CAR T-Cell Therapy and Bispecific Antibodies	Ravi Vij, MD, MBA
12:05–1:05 PM	Lunch and Patient Journey	Jerome Berry
1:05–1:35 PM	Town Hall Q&A	Panel
1:35 PM	Closing Remarks	Mary DeRome, MS

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MULTIPLE MYELOMA Research Foundation

MMRF Introduction

Mary DeRome, MS
MMRF

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The Work of the MMRF

The MMRF does three things in relentless pursuit of its mission to accelerate a cure for each and every myeloma patient.

1

We accelerate new treatments

Bringing next-generation therapies to patients faster

2

We drive precision medicine

Using data to deliver better answers and more precise treatments for patients

3

We empower patients

Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

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MMRF CoMMpass Study: Advancing Personalized Medicine Research

- Landmark study focusing on the genomics of myeloma
- Goals
  - Learn which patients respond best to which therapies
  - Identify new targets and new hypotheses
- Newly diagnosed patients will be followed for at least 8 years

All participants undergo a type of detailed genetic testing called *genomic sequencing.*

8

CoMMpass Is a Trial of Discovery

- CoMMpass data has
  - Provided the myeloma community with information on
    - Frequency of genetic abnormalities
    - How genetic abnormalities play a role in myeloma
      - Drive multiple myeloma cell growth and survival
      - Contribute to drug resistance
      - May predict which patients respond to which therapy
    - Genetic abnormalities that help refine risk assessment
  - Led to conception of the MyDRUG trial

All patients in CoMMpass had genomic sequencing from diagnosis to relapse. The resulting data provides detailed genetic profiles for every myeloma patient at every stage of their disease!

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MMRF CureCloud®

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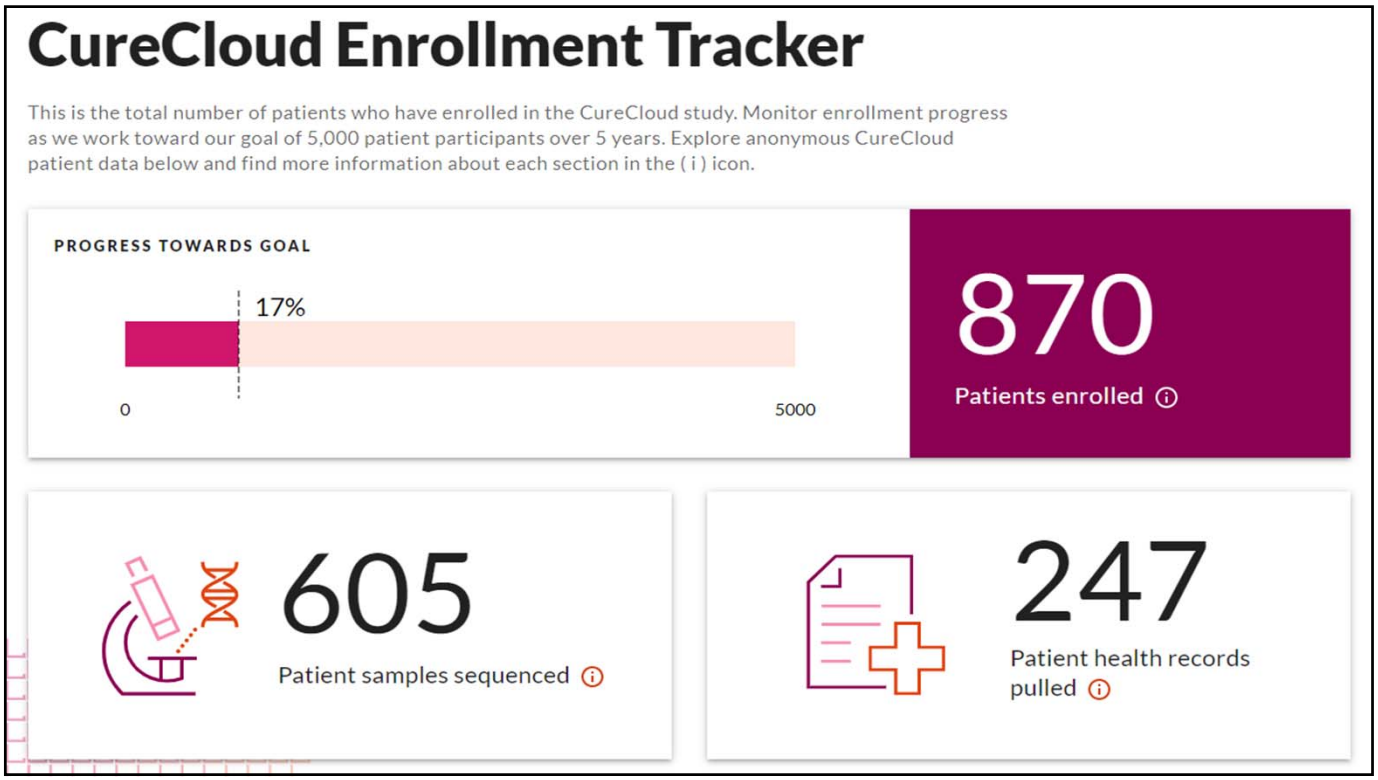
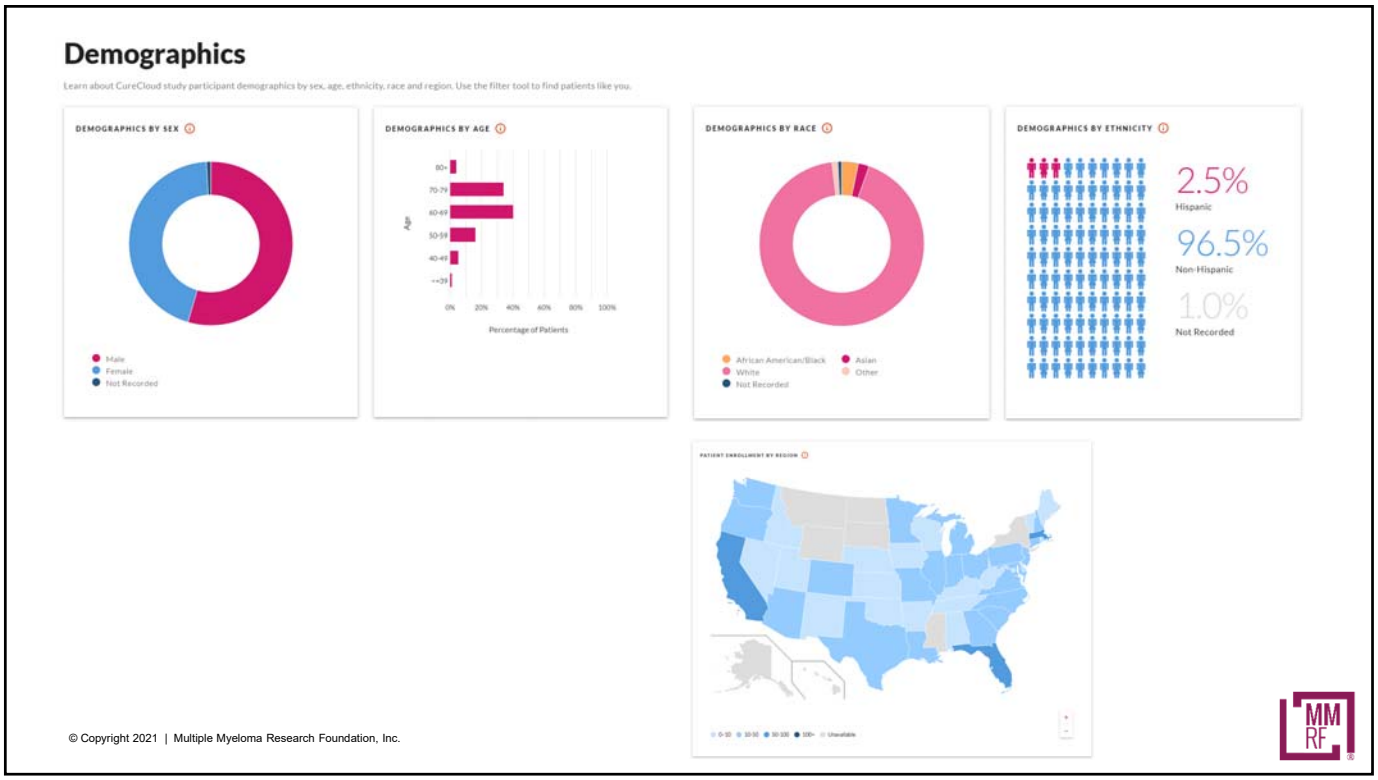

CureCloud Enrollment Tracker
This is the total number of patients who have enrolled in the CureCloud study. Monitor enrollment progress as we work toward our goal of 5,000 patient participants over 5 years. Explore anonymous CureCloud patient data below and find more information about each section in the (i) icon.
PROGRESS TOWARDS GOAL
17%
0
5000
870
Patients enrolled
605
Patient samples sequenced
247
Patient health records pulled

11


Demographics
Learn about CureCloud study participant demographics by sex, age, ethnicity, race and region. Use the filter tool to find patients like you.
DEMOGRAPHICS BY SEX
Male
Female
Not Recorded
DEMOGRAPHICS BY AGE
Age
Percentage of Patients
DEMOGRAPHICS BY RACE
African American/Black
Asian
White
Other
Not Recorded
DEMOGRAPHICS BY ETHNICITY
2.5%
Hispanic
96.5%
Non-Hispanic
1.0%
Not Recorded
PATIENT ENROLLMENT BY REGION
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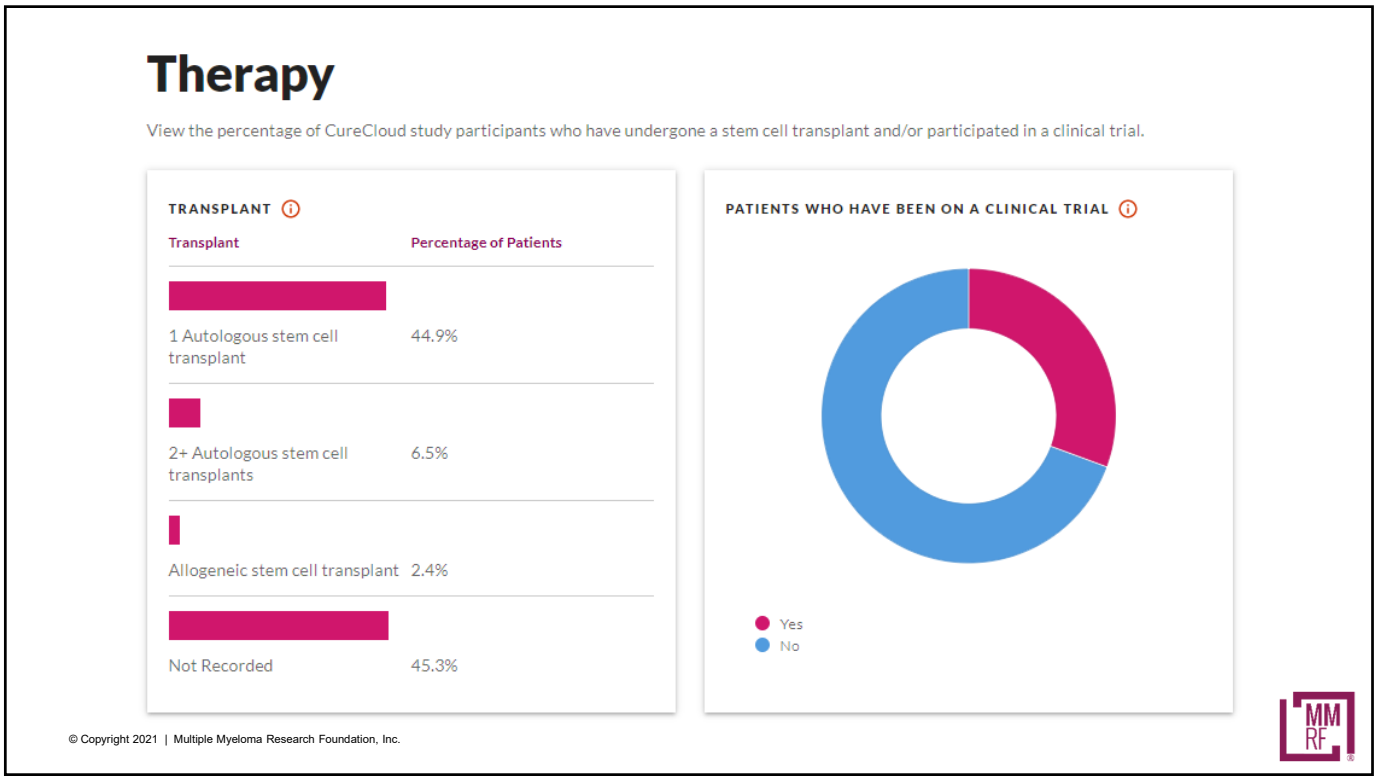
Therapy
View the percentage of CureCloud study participants who have undergone a stem cell transplant and/or participated in a clinical trial.
TRANSPLANT
Transplant
Percentage of Patients
1 Autologous stem cell transplant
44.9%
2+ Autologous stem cell transplants
6.5%
Allogeneic stem cell transplant
2.4%
Not Recorded
45.3%
PATIENTS WHO HAVE BEEN ON A CLINICAL TRIAL
Yes
No
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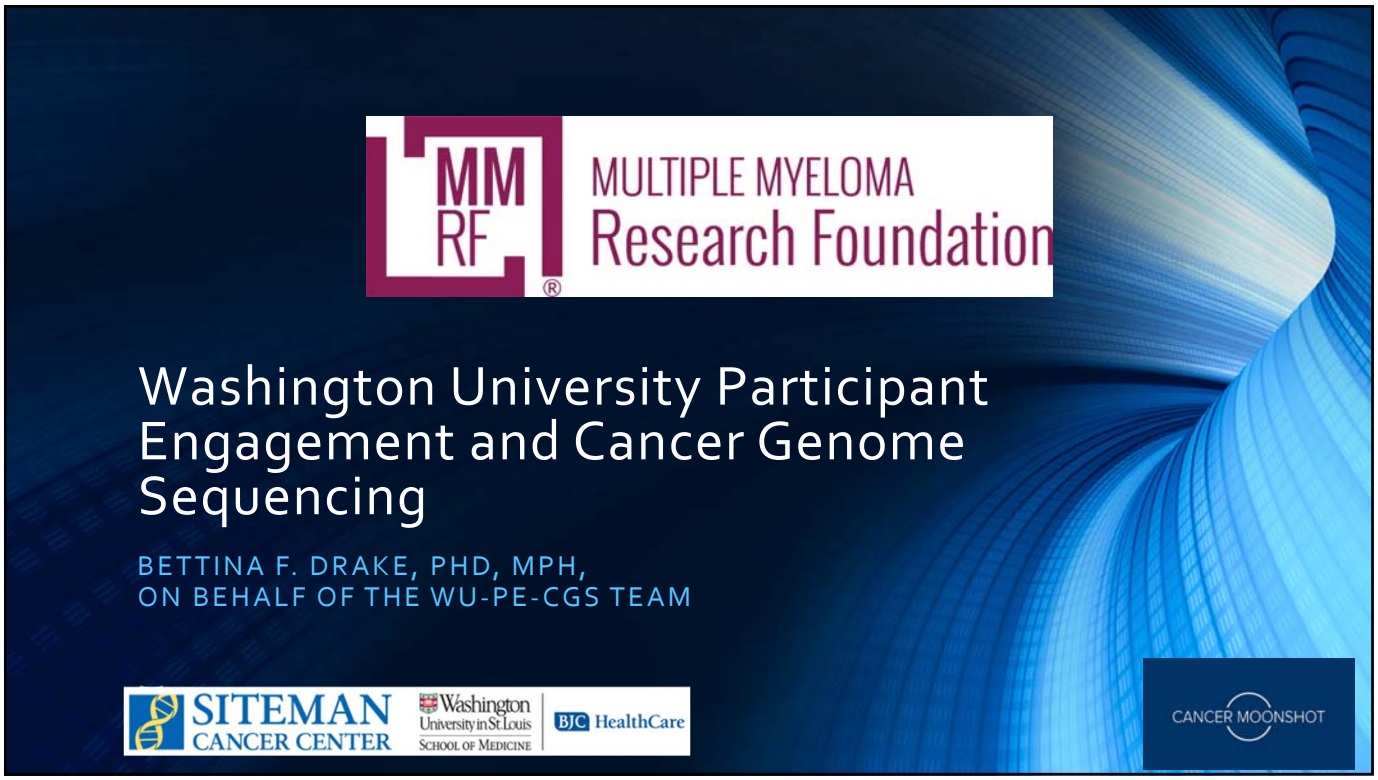
MULTIPLE MYELOMA
Research Foundation
Washington University Participant Engagement and Cancer Genome Sequencing
BETTINA F. DRAKE, PHD, MPH,
ON BEHALF OF THE WU-PE-CGS TEAM
SITEMAN CANCER CENTER
Washington University in St. Louis School of Medicine
BJC HealthCare
CANCER MOONSHOT

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2015 – Cancer Moonshot

ME SEARCH The New York Times

POLITICS

$1 Billion Planned for Cancer 'Moonshot'

By GARDINER HARRIS FEB. 1, 2016

Vice President Joseph R. Biden Jr., left, met with doctors at the Perelman School of Medicine and Abramson Cancer

CANCER MOONSHOT

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Why Did Moonshot Prioritize Participant Engagement in Rare Cancers?

- There are understudied and rare cancers that affect underrepresented populations
- Goal: increase recruitment of these populations to research so we can learn more about the genetics of these cancers ➔improve future healthcare
- The project will mostly benefit future patients, but also may have some benefit to patients through return of results

CANCER MOONSHOT

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Aims

- Engage participants with continuous evaluation and research to study disparities in rare cancers
- Conduct comprehensive genomic testing and follow up participants long term
- Address cancer disparities by improving the ability for disadvantaged populations to benefit from genomic sequencing
- Share findings to broaden understanding of genomic characterizations of tumors

CANCER MOONSHOT

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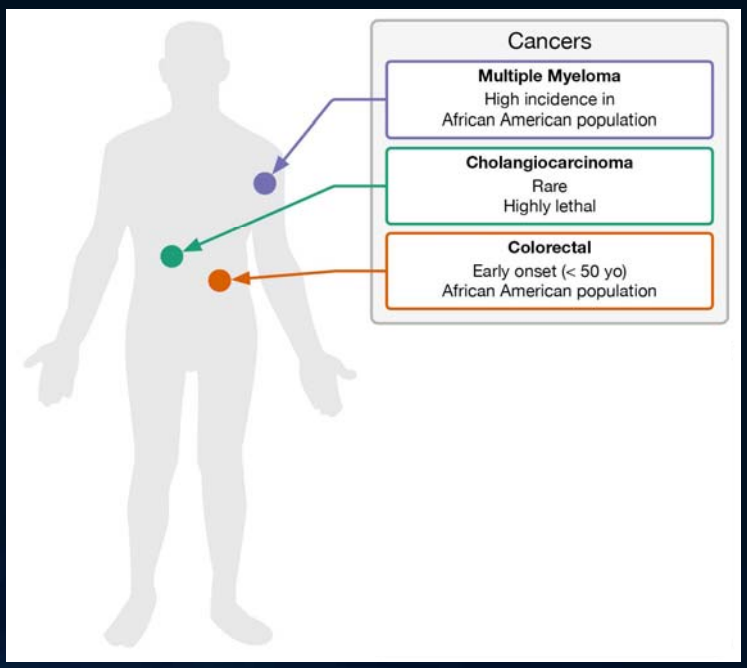

CANCER MOONSHOT

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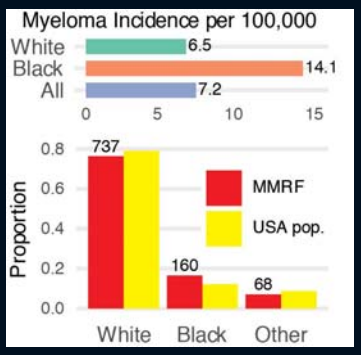
Multiple Myeloma in Black Americans

- Little is known about the genetic variability of multiple myeloma among Black Americans
- Progress is limited by underrepresentation of Black Americans in genomic research
- The ultimate goal is to improve treatment and care



CANCER MOONSHOT

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Leadership

Graham A. Colditz, MD, DrPH
- Public Health Sciences

Li Ding, PhD
- Cancer Genomics

Bettina Drake, PhD
- Public Health Sciences

Ryan Fields, MD
- Surgical Oncology

CANCER MOONSHOT

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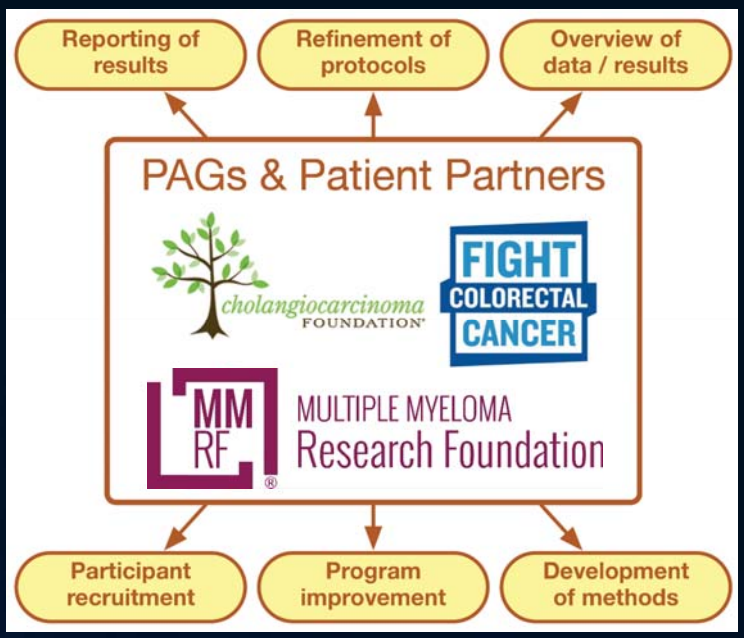

CANCER MOONSHOT

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How to Participate

- Complete 2 surveys over 6 months (online or by phone), interviews, and provide feedback
- Allow us to review your previous medical records and treatment
- Decide what results you want to receive
- No need for in-person visits, new biopsies, or procedures
- We will:
  - Use your previous biopsy or surgery specimens for genome sequencing
  - Share what we learn with you

CANCER MOONSHOT

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Contact Us

- Phone: (314) 273-2434
- Email: pecgs@wustl.edu
- Website: https://sites.wustl.edu/pecgs/

CANCER MOONSHOT

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Welcome!

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Question

Are you a...

A. Patient
B. Caregiver (family member or friend who helps patient manage his or her disease)
C. Other

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Question

At what stage is your myeloma? (If you are a caregiver, what is the stage of the patient's myeloma?)

A. Newly diagnosed
B. Relapsed/refractory
C. Remission: still on therapy
D. Remission: not on therapy
E. MGUS or smoldering myeloma not currently requiring treatment
F. Other
G. I don't know.

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Question

Have you had a stem cell transplant?

A. No, but I will soon!
B. No, but I am considering one (or my doctor is discussing with me).
C. No, my doctor tells me I am not a candidate.
D. Yes
E. Not applicable

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Question

Do you know if you had any molecular characterization performed on your tumor, such as FISH, cytogenetics, or sequencing?

A. No
B. Yes, I had FISH.
C. Yes, I had cytogenetics.
D. Yes, I had sequencing.
E. Yes, I had more than one of these tests performed.
F. I don't know.

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Question

Have you and your care team ever discussed the possibility of you joining a clinical trial that you are eligible for? (If you are a caregiver, do you know if joining a clinical trial has ever been discussed?)

A. Yes
B. No
C. I don't know.

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Question

Do you have access to reliable high-speed Internet (wifi) at your home?

A. Yes
B. No
C. I don't know.

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MULTIPLE MYELOMA Research Foundation

The State of Multiple Myeloma Care

Craig Emmitt Cole, MD
Michigan State University
Karmanos Cancer Institute
Lansing, Michigan

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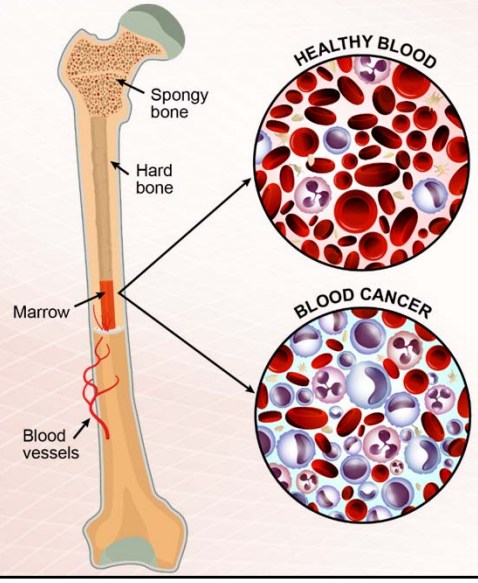
What is multiple myeloma?



- Multiple myeloma is a **blood cancer** that starts in the **bone marrow**, the place where all **blood cells** are produced
- Multiple myeloma is caused when a type of **white blood cell** called a **plasma cell** becomes cancerous and grows out of control

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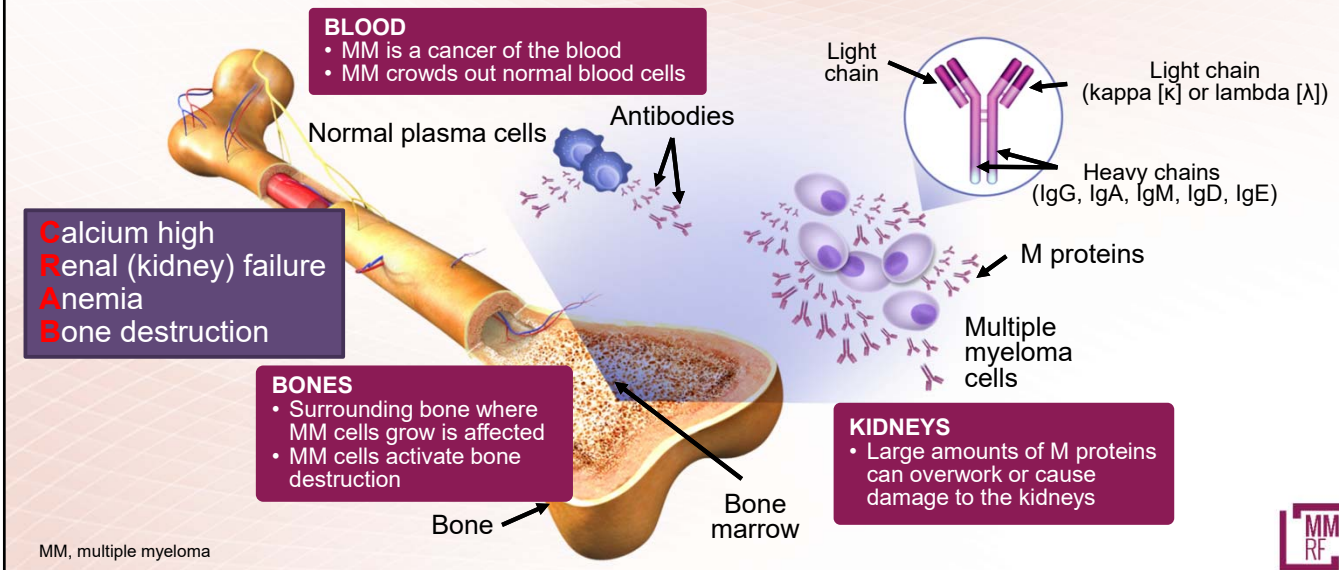
Multiple Myeloma Affects Your Bones, Blood, and Kidneys: CRAB



MM, multiple myeloma

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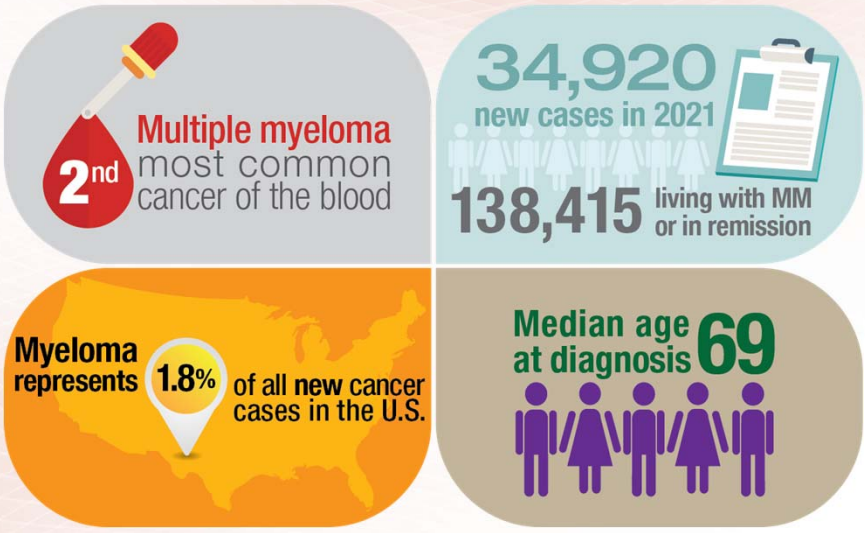
How common is multiple myeloma?



SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/mulmy.html

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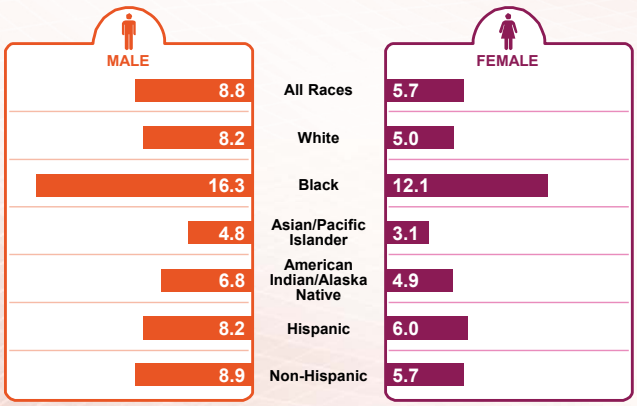
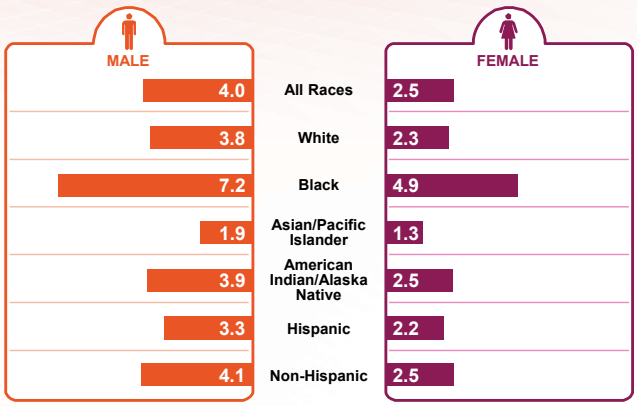
Multiple Myeloma Is Twice as Common—and Twice as Deadly—in Black Patients

Rate of new cases per 100,000 persons by race/ethnicity and sex



SEER 21 20144-2018, Age-Adjusted

Death rate per 100,000 persons by race/ethnicity and sex



U.S. 2015-2019, Age-Adjusted

SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/mulmy.html

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Demographic Risk Factors: Multiple Myeloma

- Older age
- Male sex
- Obesity
- Race
  - ↑ Blacks (2× Whites)
  - Ashkenazi Jews
  - Europe: Ireland
  - ↓ Asian

Family history risks

One first-degree relative with multiple myeloma

Relatives of multiple myeloma patients have more monoclonal gammopathy of undetermined significance (MGUS)

Schinasi LH et al. *Br J Haematol*. 2016;175:87. Blood Advances. 14 Nov 2017 x Vol 1, Number 24 DOI 10.1182/bloodadvances.2017007609.

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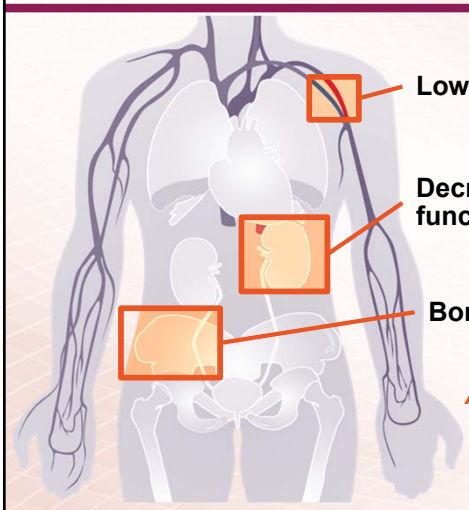
Effects of Myeloma and Common Symptoms



- **Low blood counts** → **Weakness, Fatigue, Infection**
- **Decreased kidney function** → **Weakness**
- **Bone damage** → **Bone pain**

About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.

Disease presentation and myeloma-related complications after myeloma diagnosis are different in patients by race

More common in Black patients

- Hypercalcemia
- Kidney dysfunction
  - Hemodialysis
- Anemia

Less common in Black patients

- Bone fractures

MMRF. Multiple myeloma symptoms, side effects, and complications. https://themmrf.org/multiple-myeloma/symptoms-side-effects-and-complications/. Campbell K. *Nurs Times*. 2014;110:12; Kyle R et al. *Mayo Clin Proc.* 2003;78:21; Ailawadhi S et al. *Cancer*. 2018;124:1710.

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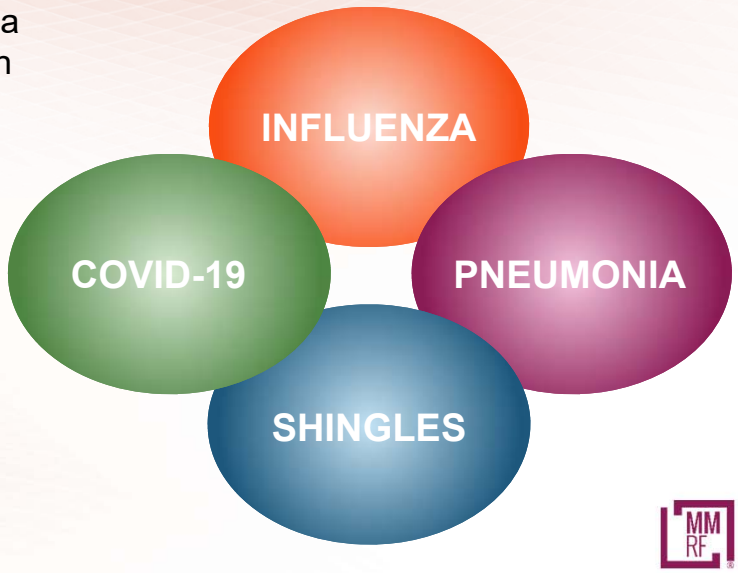
Infections and Vaccinations in Multiple Myeloma

- Risk of infection higher for myeloma patients than for general population
- Types of infections include
  - Bacterial: pneumonia (an infection of the lungs), bacteremia
  - Viral: varicella zoster (shingles), influenza, COVID
- Preventive strategies (prophylaxis) are recommended
  - Antibiotics
  - Growth factors
  - Vaccines/ pre-exposure antibodies
  - Other precautions: hand-washing, avoiding sick contacts



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Following the Proper Path Will Help Patients Obtain the Best Treatment and Results for Their Specific Type of Myeloma

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 decide on the best treatment plan and identify clinical trials that are right for you

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The Right Team

Connect with a myeloma specialist—a doctor who diagnoses and treats a high number of myeloma patients

Seek a second opinion at any point in your journey

Available resources

MMRF's online myeloma treatment locator: **themmrf.org/resources/find-a-treatment-center**

Contact the MMRF Patient Navigation Center: **themmrf.org/resources/patient-navigation-center**

1-888-841-MMRF (6673)

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The Right Tests

Common laboratory tests conducted

Blood tests

- Complete blood count (CBC)
- Complete metabolic panel (CMP)
- Chemistries
  - Calcium
  - Creatinine
  - Lactate dehydrogenase (LDH)
  - Beta-2 microglobulin
- **Serum protein electrophoresis (SPEP) with immunofixation electrophoresis (IFE)**
- **Serum free light chain assay (SFLC)**

Urine tests

- Urine protein electrophoresis (UPEP) with IFE
- 24-hour urine

Bone marrow biopsy

Conventional
- **Fluorescence in situ hybridization (FISH)**

New
- Genomic sequencing

Imaging tests

- X-ray
- **MRI**
- **Whole-body, low-dose CT scan**
- **PET scan**
- Metastatic bone survey

Assess changes in the bone structure and determine the number and size of tumors in the bone

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The Right Treatment

- Know the treatment options available to you based on your myeloma subtype at each stage of your disease
- Be aware of the pros and cons of each option
- Clearly communicate your treatment goals and concerns to the care team
- Find clinical trials that are right for you

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Therapeutic Options in Myeloma: The Current Landscape

IMiDs	Proteasome inhibitors	Chemotherapy anthracyclines	Chemotherapy alkylators	Steroids	Novel mechanisms of action	mAbs	Cellular therapy
Thalomid (thalidomide)	Velcade (bortezomib)	Adriamycin	Cytoxan (cyclophosphamide)	Dexamethasone	Farydak (panobinostat)	Empliciti (elotuzumab)	Abecma (idecabtagene vicleucel)
Revlimid (lenalidomide)	Kyprolis (carfilzomib)	Doxil (liposomal doxorubicin)	Bendamustine	Prednisone	XPOVIO (selinexor)	Darzalex (daratumumab)	Carvykti (ciltacabtagene autoleucel)
Pomalyst (pomalidomide)	Ninlaro (ixazomib)		Melphalan		Venclexta (venetoclax)*	Sarclisa (isatuximab)	
						Blenrep† (belantamab mafodotin)	

*Not yet FDA-approved for patients with multiple myeloma
†Antibody-drug conjugate

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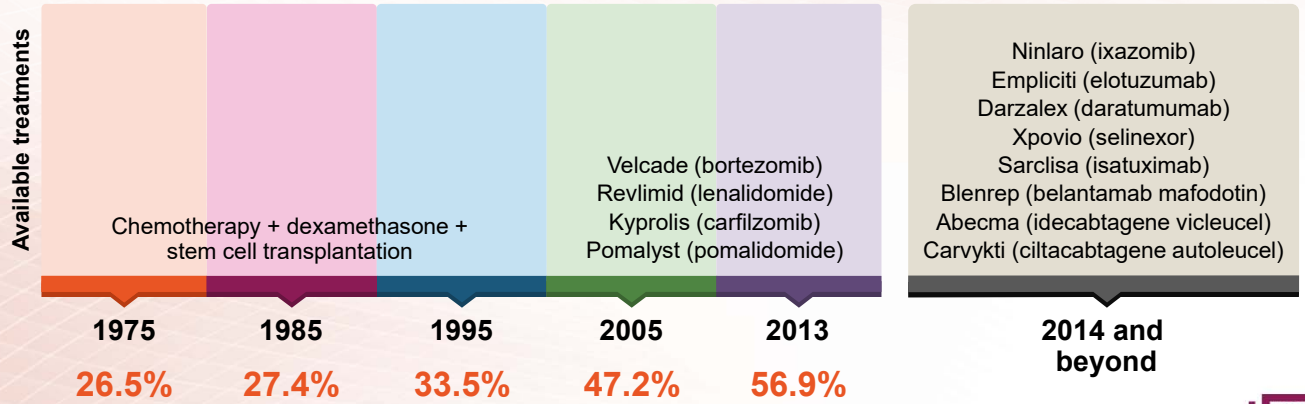
Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

The percentage of people expected to survive 5 years or more after being diagnosed with myeloma



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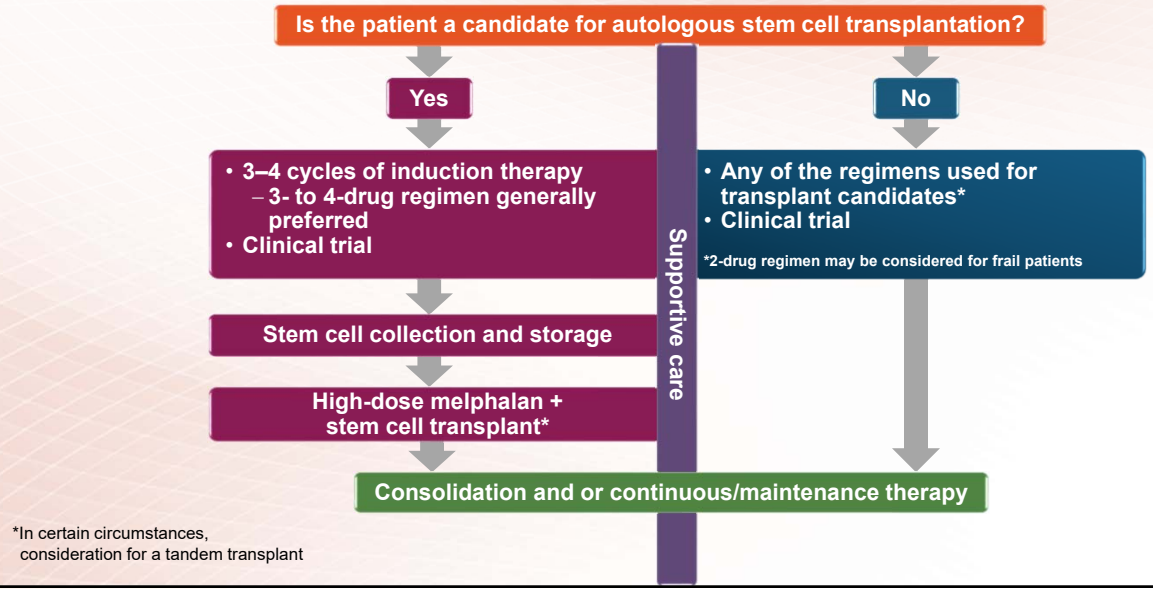
Overview of Treatment Approach for Active Multiple Myeloma



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Where is the myeloma field going?

- Staging with genomics and advanced imaging
- Higher efficacy using four-drug regimens
- Precision medicine and targeted therapies in subsets of patients—for example, t(11;14)
- Minimum Residual Disease (MRD)-driven therapy
- Minimize long-term toxicities since myeloma patients living (much) longer
- New drug classes and immunotherapies

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Summary

- Multiple myeloma is a rare blood cancer that can negatively affect the bones, kidneys, and the bone marrow, leading to lowered blood counts.
- Multiple myeloma compromises the immune system; therefore, infection prevention is key.
- Survival rates are improving because of new drugs and new combinations of drugs.
- Treatment paradigm will continue to change with the approval of additional novel agents.

Be an informed and empowered part of your health care team!

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Health Care Disparities in Multiple Myeloma

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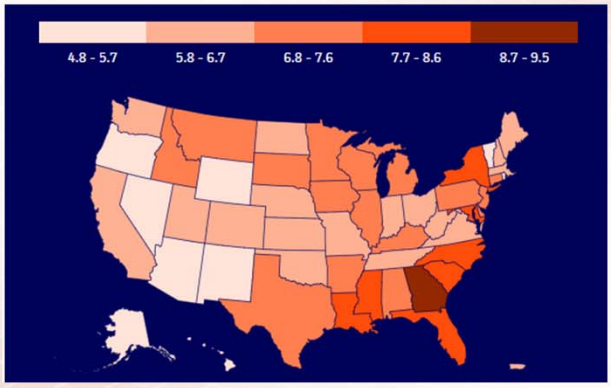
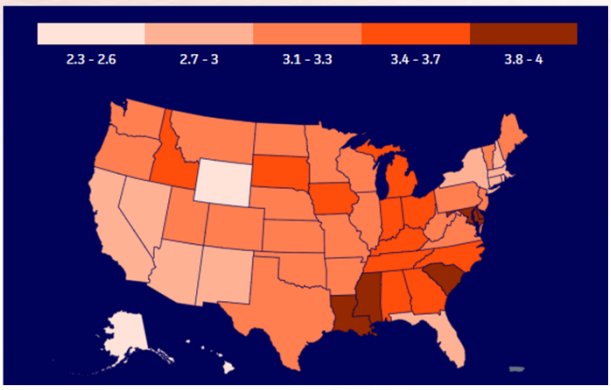
Incidence rates, 2014–2018
Myeloma, by state



Average annual rate per 100,000, age adjusted to the 2000 US standard population.

Data sources: North American Association of Central Cancer Registries (NAACCR), 2021

Death rates, 2015–2019
Myeloma, by state



Average annual rate per 100,000, age adjusted to the 2000 US standard population.

Data sources: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2021

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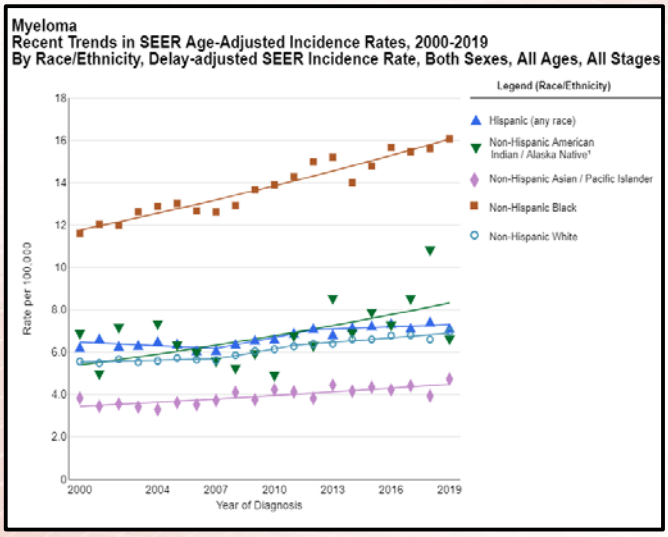
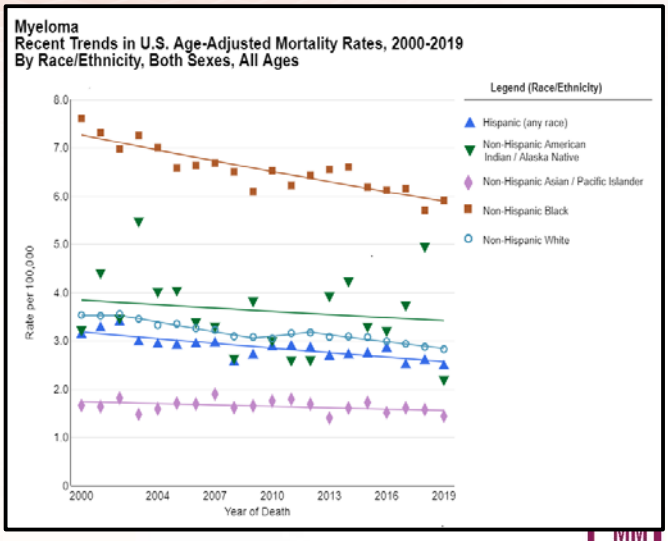
Multiple Myeloma
Incidence and Mortality by Race/ Ethncity





SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD,https://seer.cancer.gov/statistics-network/explorer/application.html

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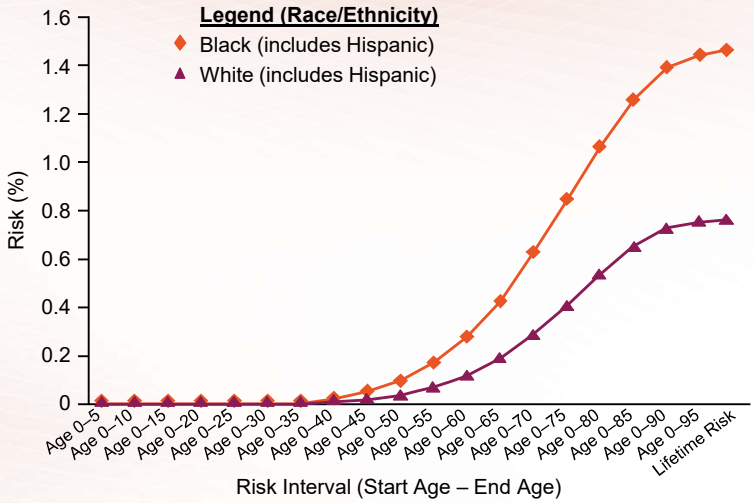
Risk of Myeloma Diagnosis Over Time

Black patients are diagnosed at an earlier age and have a twofold risk of being diagnosed with multiple myeloma



Data from National Cancer Institute
Surveillance, Epidemiology, and End Results Program (SEER)

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Multiple Myeloma in Black Patients

Demographics

- ↑ Myeloma prevalence (2× White patients)[1]
- Older adults have ↑ prevalence of the myeloma precursor condition MGUS[2]
- Younger[3-5]

Clinical factors

- ↑ Comorbidities[3,6]
- ↑ Incidence of all myeloma-defining events (for example, hypercalcemia, renal dysfunction, anemia, dialysis) except bone fractures[7]

Molecular (genetic) factors

- Significant differences in the frequency of certain chromosomal abnormalities:
  - High risk cytogenetics including del17p are seen less frequently[8]
  - Some other mutations seen more frequently but significance not known[9]

Treatment

- Significantly lower stem cell transplant utilization[7,9-13]

1. SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/statfacts/html/mulmy.html. **2.** El-Khoury H et al. *Blood*. 2021;138. Abstract 152. **3.** Blue B et al. *Br J Haematol*. 2017;176:322. **4.** Waxman AJ et al. *Blood*. 2010;116:5501. **5.** Ailawadhi S et al. *Blood Cancer J*. 2018;8:67. **6.** Schoen MW et al. *Blood*. 2019;134. Abstract 383. **7.** Ailawadhi S et al. *Cancer*. 2018;124:1710. **8.** Baker A et al. *Blood*. 2013;121:3147. **9.** Manojilovic Z et al. *PLoS Genet*. 2017;13:e1007087. **10.** Ailawadhi S et al. *Cancer Med*. 2017;6:2876. **11.** Fiala M et al. *Cancer*. 2017;123:1590. **12.** Costa LJ et al. *Biol Blood Marrow Transplant*. 2015;21:701. **13.** Vardell VA et al. *Blood*. 2019;134. Abstract 423.

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Disparities in Care in Black Multiple Myeloma Patients

- Several studies have shown that the use of standard therapies tends to be significantly lower in Black patients
- However, with equal access to standard therapy, the outcome in Black patients is equal or superior to that of White patients

Treatment type	Use in black patients	Use in white patients	*P* value
Triplet therapy	**47%**	61%	.004
Stem cell transplantation	**30%**	40%	.034

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Reasons for Disparities in Outcomes for Black Americans With Multiple Myeloma and Other Cancers

- Less access to cancer screening services
- Structural racism
- Social determinants of health
- Shortage of African American physicians and lack of familiarity with black economic and social conditions
- Comorbid conditions
- Delayed onset of diagnosis and severity of disease at the time of diagnosis
- Lack of access to the same level of treatment as White patients
- Low enrollment in clinical trials

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Key Points

- **Despite disparities in incidence and outcomes of multiple myeloma among Black patients, evidence suggests that these disparities can be overcome.**
- **Ensure equal access to appropriate therapeutic options for Black patients.**
- **Increase awareness of these disparities and their solutions to patients, physicians, and the communities.**

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MULTIPLE MYELOMA Research Foundation

What's New in MGUS and Smoldering Multiple Myeloma?

Omar Nadeem, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

58

Plasma Cell Disorders: Classification

Updated IMWG criteria for diagnosis of multiple myeloma

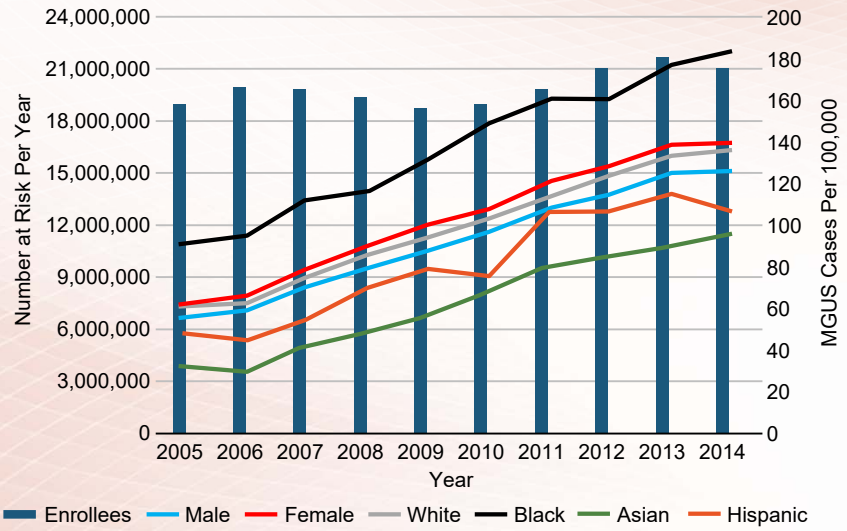
MGUS	Smoldering myeloma	Multiple myeloma
• M protein <3 g/dL • Clonal plasma cells in bone marrow <10% • No myeloma-defining events	• M protein ≥3 g/dL (serum) or ≥500 mg/24 hrs (urine) • Clonal plasma cells in bone marrow ≥10% to 60% • No myeloma-defining events	• Underlying plasma cell proliferative 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.

59

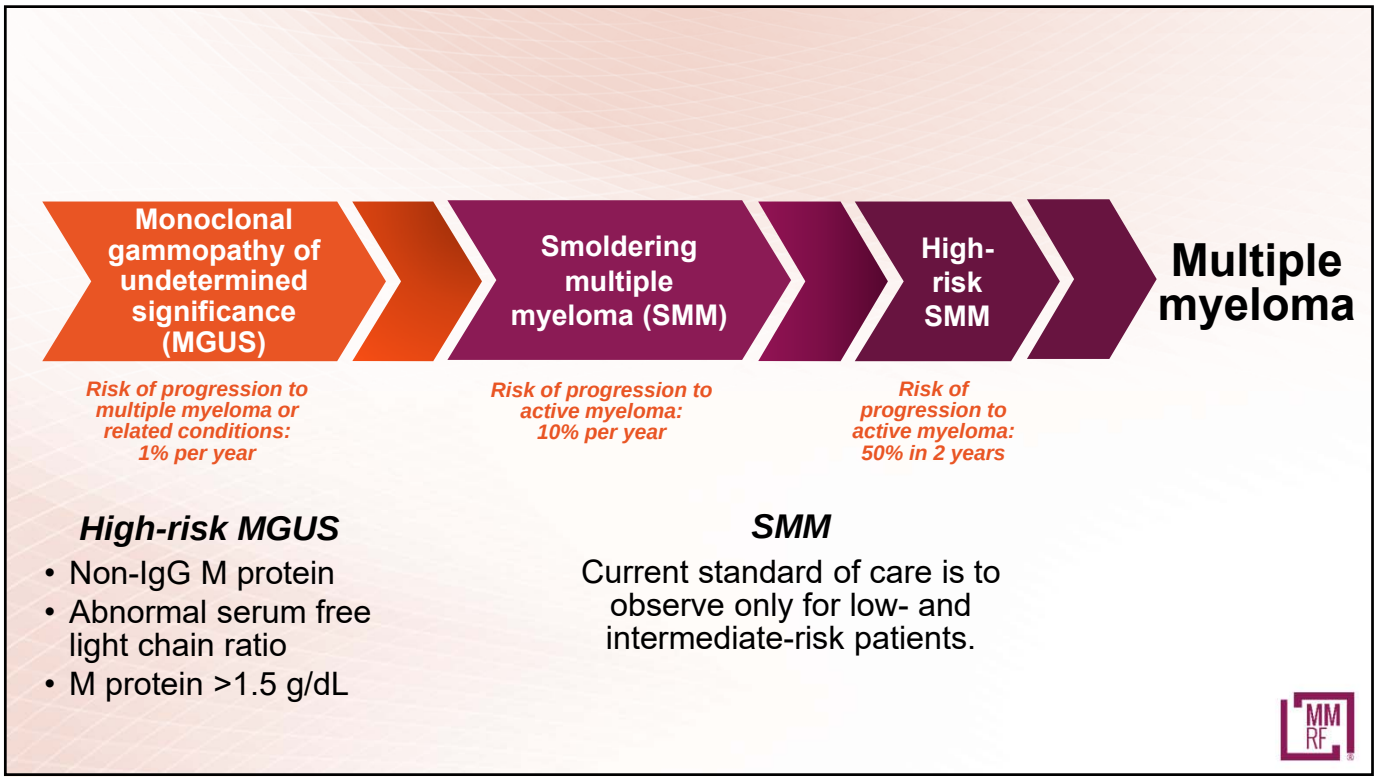
MGUS is a Very Common Condition



- 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.

60



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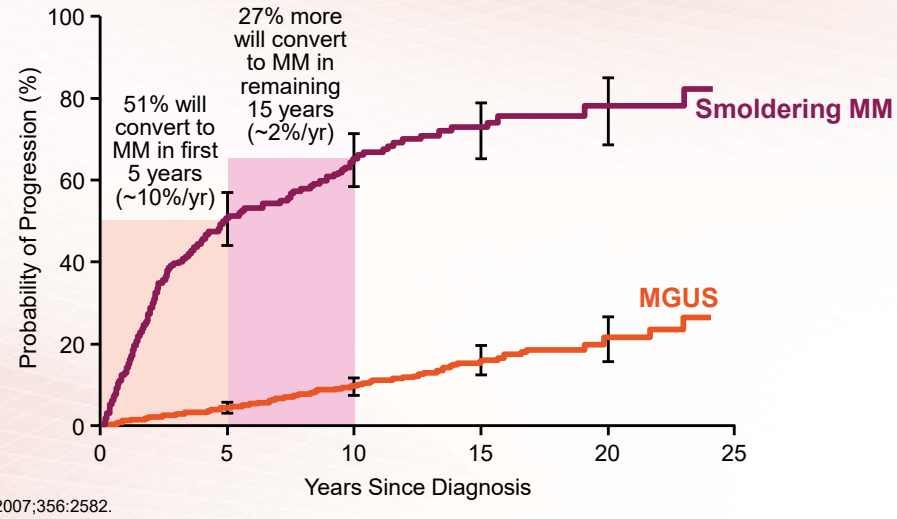
Smoldering Multiple Myeloma: Heterogeneous Disease

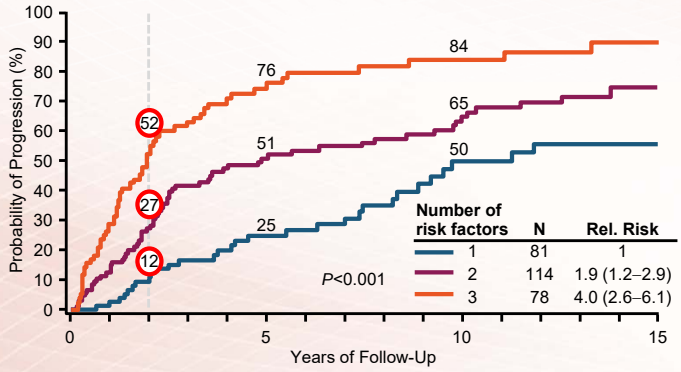


Kyle RA et al. *N Engl J Med.* 2007;356:2582.
Greipp PR et al. *J Clin Oncol.* 2005;23:3412.

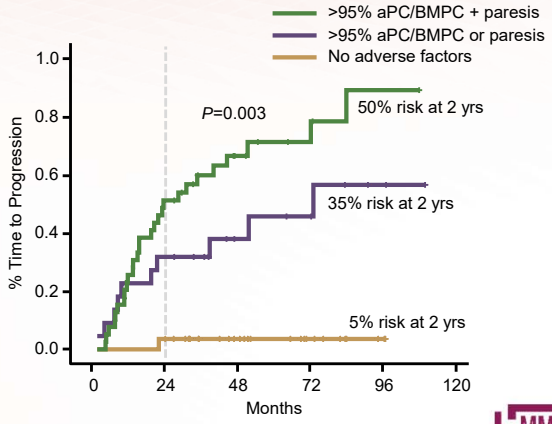
62

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.

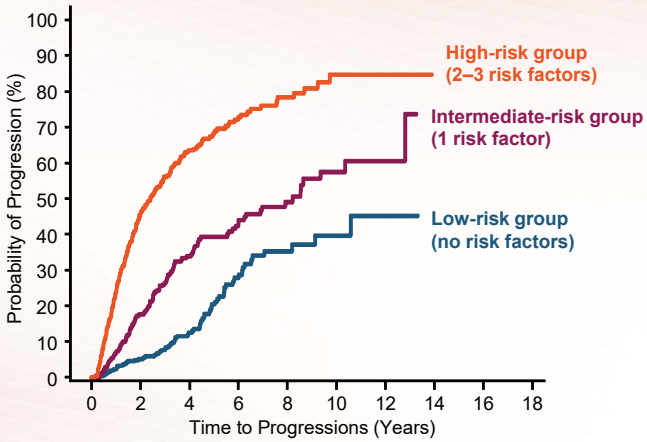
63

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	
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%

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 With 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

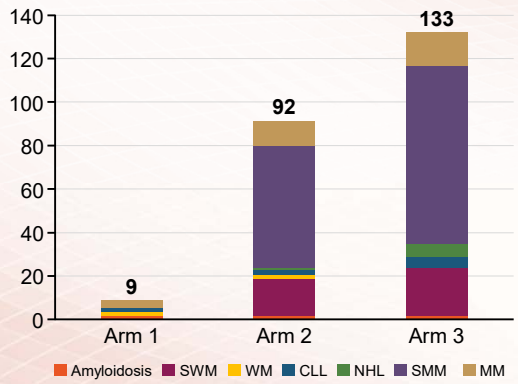
High prevalence of SMM has implications for future treatment policies and underlines the need for accurate risk stratification in SMM.

*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.

67

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.

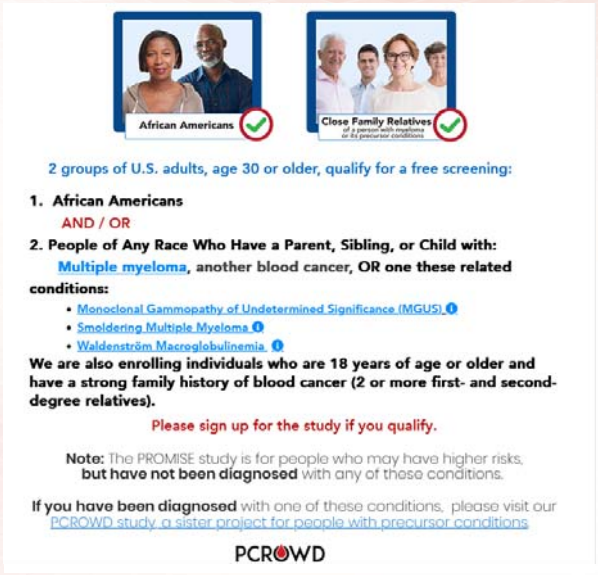
MGUS was *not* associated with COVID-19 susceptibility or COVID-19 severity.

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

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

68

Promise Study Eligibility Criteria



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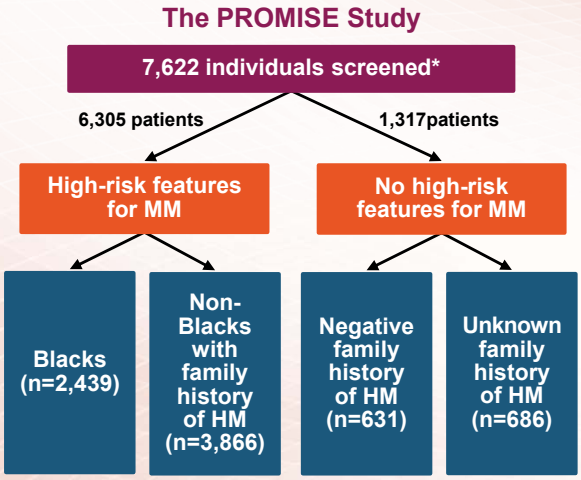
High Prevalence of Monoclonal Gammopathy in a Population at Risk



- 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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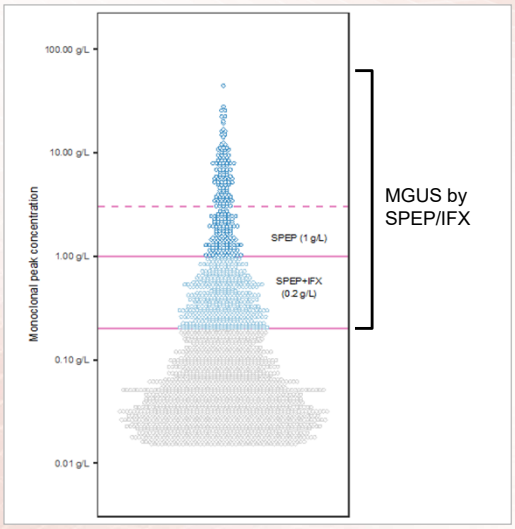
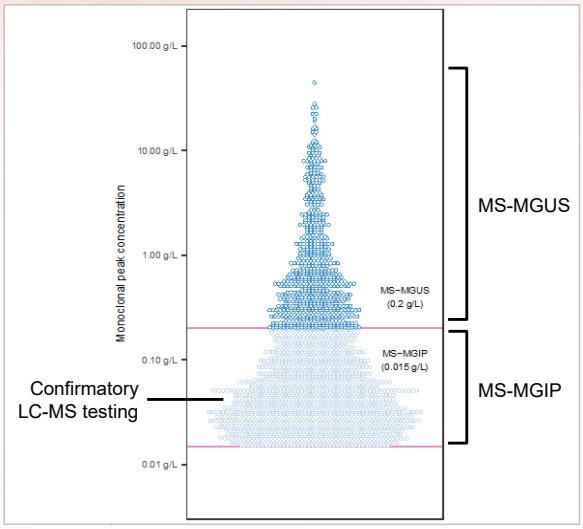
Defining Outcomes and Results





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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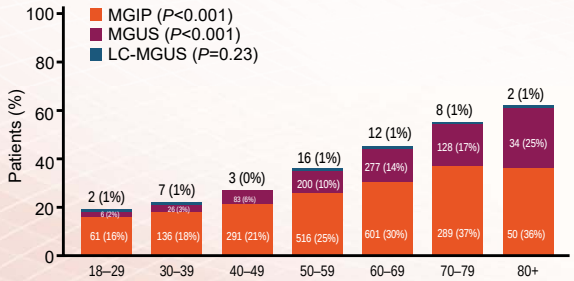
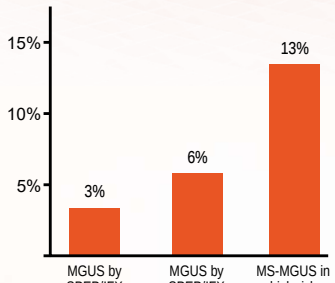
High Prevalence of Monoclonal Gammopathy in a Population at Risk

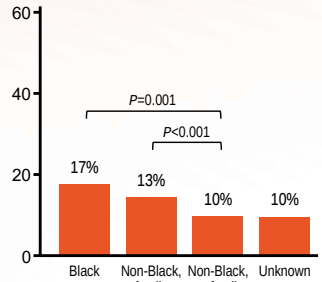
Rates of all monoclonal gammopathies* increase with age



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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Therapeutic Intervention for SMM

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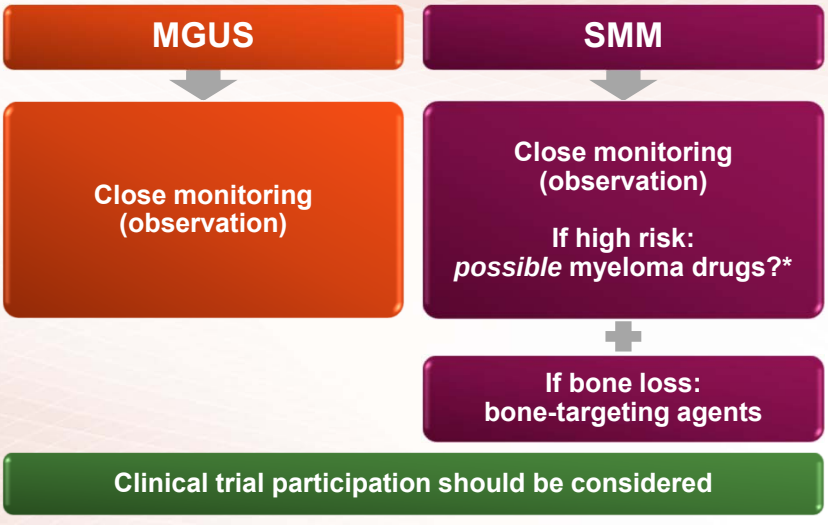
Overview of Treatment Approach



*Promising but only available as clinical trials.

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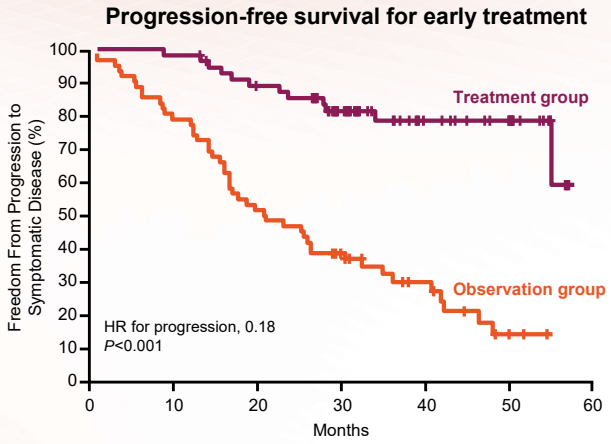
Early Therapeutic Intervention

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

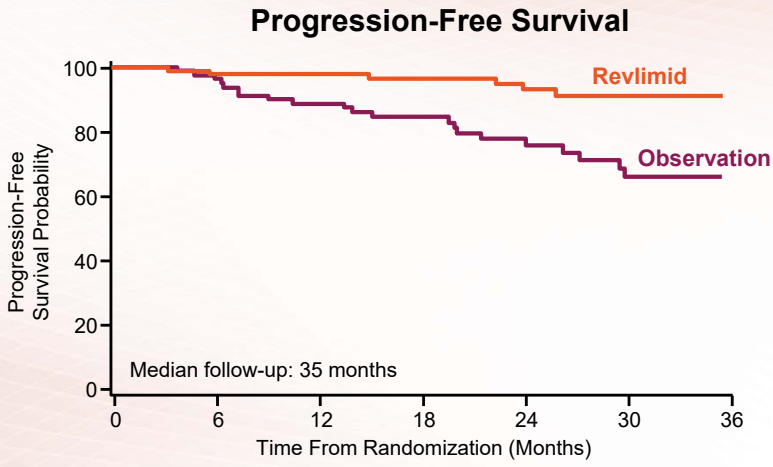
María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Albert Oriol, M.D., Felipe 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.



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

75

Revlimid vs Observation Alone in Patients With SMM



E3A06 Trial. Lonial S et al. *J Clin Oncol.* 2020;38:1126.

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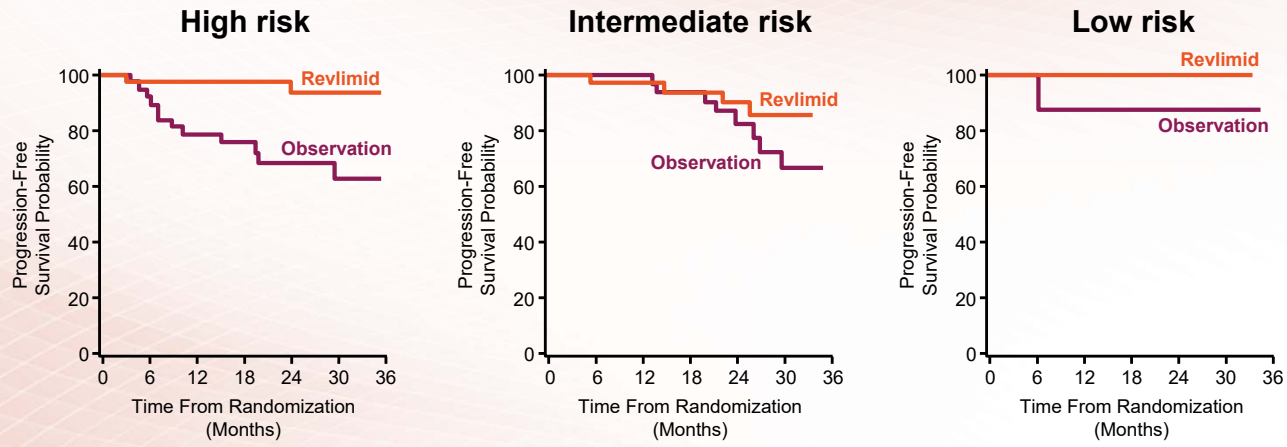
Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria



E3A06 Trial. Lonial S et al. *J Clin Oncol.* 2020;38:1126.

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Lessons Learned

- Early intervention improves PFS
- OS benefit seen in Spanish study
- Response rates of ~50% with lenalidomide alone leads to impressive PFS of >90% at 2 years
  - Does response matter as much in SMM?
- Many patients on observation also do quite well
  - How to identify them?
- Long-term therapy has toxicity implications and high rates of discontinuation

The Unknowns

- Would addition of a third (or fourth drug) in SMM lead to same benefit seen in NDMM?
  - Some high-risk patients with SMM are essentially MM patients
  - Deeper response should lead to better outcomes
- Is shorter but more intensified therapy better to limit long-term toxicity?
- What is the best intervention? Immunomodulatory drugs? Monoclonal antibodies? Proteasome inhibitors? Immunotherapy?

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Ongoing Clinical Studies for SMM 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
- Bispecifics
- Xgeva

SMM/MGUS

- PO Antibiotic trial (Emory)
- Predictors of progression (PROMISE study)
- Genomic and molecular predictors of progression (MD Anderson study)
- MMRF CureCloud
- Darzalex
- Metformin

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

Trials found at www.clinicaltrials.gov

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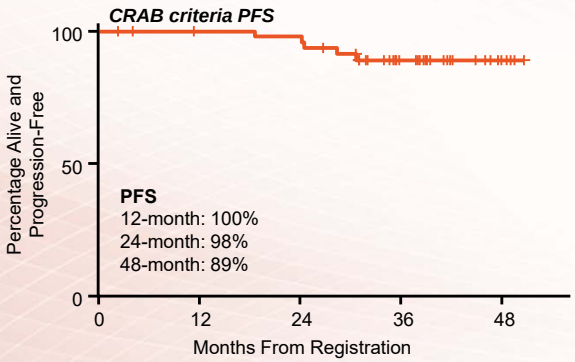
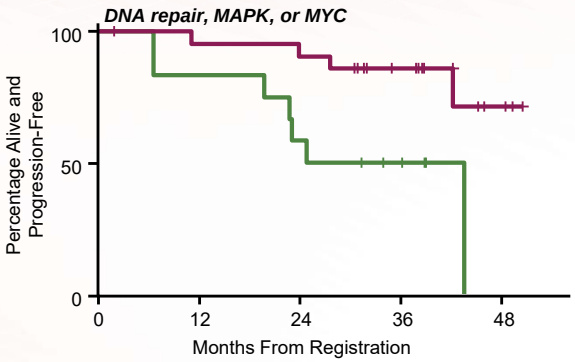
Precision Intervention With Empliciti in Smoldering Myeloma

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

PFS in All Patients



PFS by High-Risk Mutations



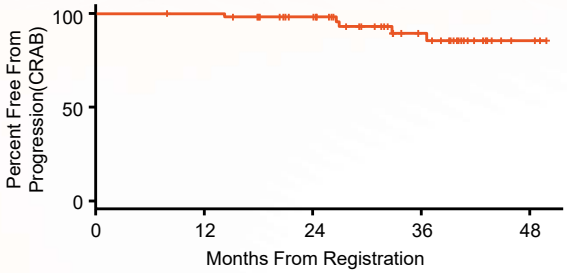
E-PRISM Trial. Liu C-J et al. *Blood.* 2018;132: Abstract 154.

80

Ninlaro, Revlimid + Dex for High-Risk SMM

- A novel approach that builds on PFS of RD vs observation for those with SMM, and NCT01217957 data showing efficacy and tolerability in the NDMM setting
- Ninlaro is a potent proteasome inhibitor that, when combined with RD, shows promising PFS with better tolerability than Velcade. This all-oral combination will further improve compliance and quality of life for participants with high-risk SMM who have risks of progression at 5 years of 51% for intermediate risk and 76% for high-risk individuals who have 1, 2, or 3 risk factors respectively.

Response	Total N=55 (%)
Overall response rate	50 (90.9)
Complete response	12 (21.8%)
Very good partial response	10 (18.2%)
Partial response	28 (50.9%)



Nadeem O et al. *Blood*. 2021;138. Abstract 2749.

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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 endpoint: Rate of confirmed sCR
Secondary objectives: Safety, PFS, OS, MRD negativity

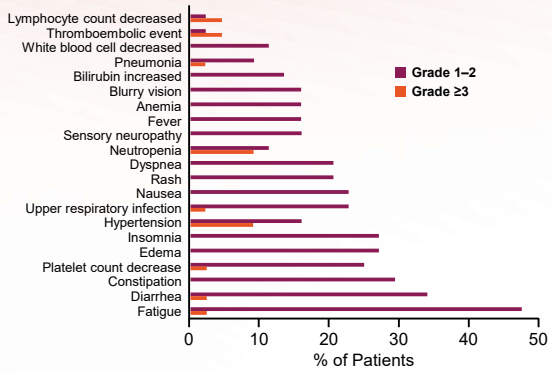
INDUCTION
(4-week cycles for 6 cycles)
- Carfilzomib (36 mg/m² twice weekly or 56 mg/m² weekly)
- Lenalidomide (25 mg daily for 3 weeks)
- Daratumumab (weekly for 8, every other week for 16 weeks)
- Dexamethasone 40 mg weekly

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 8 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

Toxicity profile



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

AE, adverse event; CR, complete response; 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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A Phase 2 Study of Darzalex, Velcade, Revlimid and Dexamethasone in High-Risk Smoldering Multiple Myeloma (B-PRISM)

High risk smoldering myeloma

Cycles 1-2	Cycles 3-6	Cycles 7-12	Cycles 13-24
Darzalex 1,800 mg SQ d1, 8, 15, 22 Velcade 1.3 mg/m² SQ d1, 8, 15 Revlimid 25 mg PO d1–21 Dexamethasone 20 mg weekly	Darzalex 1,800 mg SQ d1, 15 Velcade 1.3 mg/m² SQ d1, 8, 15 Revlimid 25 mg PO d1–21 Dexamethasone 20 mg weekly	Darzalex 1,800 mg SQ d1 Velcade 1.3 mg/m² SQ d1, 15 Revlimid 15 mg PO d1–21 Dexamethasone 20 mg d1, 15	D Darzalex 1,800 mg SQ d1 Velcade 1.3 mg/m² SQ d1, 15 Revlimid 15 mg PO d1–21 Dexamethasone 20 mg d1, 15

MRD → MRD → MRD

Primary end point
- MRD negativity rate at 2 years

Secondary end points
- Sustained MRD-negative disease assessed at 6 months, 1 year, and 2 years
- Progression-free survival to myeloma-defining events (SLIM-CRAB)
- Progression-free survival 2
- Duration of response
- Overall survival
- To assess safety

Inclusion criteria:
High-risk SMM defined as having one of the following two criteria:

1. High risk per "20-2-20" Criteria defined as presence of any two of the following:
- Serum M spike ≥2 gm/dL
- Involved to uninvolved free light chain (FLC) ratio ≥20
- Bone marrow PC% ≥20%

OR **total score** of 9 using the following scoring system:
- FLC ratio: >10–25 = 2, >25–40 = 3, >40 = 5
- Serum M Protein (g/dL): >1.5–3 = 3, >3 = 4
- BMPC%: >15–20 = 2, >20–30 = 3, >30–40 = 5, >40 = 6
- FISH abnormality t(4,14), t(14,16), 1q gain, or del13q = 2

2. Presence of ≥10% BMPC and at least one of the following:
Evolving pattern
- **Abnormal PC immunophenotype** (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotype. (Only IgG; IgA and IgM will be considered)
- **High-risk cytogenetics** defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain

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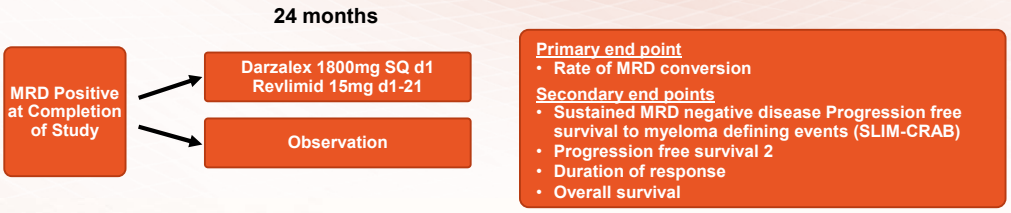
Phase 2 Study of Darzalex, Velcade, Revlimid, and Dexamethasone in High-Risk Smoldering Multiple Myeloma: Part 2



Randomization of MRD positive to observation vs 2 years of Darzalex/Revlimid. Primary end point MRD conversion to negative

ASCO 2022 Update

- **20 patients** have been enrolled with a median follow up of 6 months and median age of 58 years old (range 40-73).
- **Sixteen out of 20 (80%) patients met high risk criteria** per Mayo 2018 model with median plasmacytosis of 20%, median M protein value of 2.6 g/dl and median FLC ratio of 28.2.
- Seven patients had **high-risk FISH**: 5 with 1q duplication, 2 with t(4;14).
- **The overall response rate is 90**% with 40% PR, 25% VGPR and 25% CR. All patients have achieved at least a MR and **50% achieved VGPR or greater with responses deepening over time**. No patients have progressed on treatment.
- MRD was evaluable in 16 out of 20 and 8 patients have undergone MRD testing, with **MRD negativity rate of 50%** (4/8) and 25% (2/8) at thresholds of 10^{-5} and 10^{-6}, respectively.
- Most common grade 3 toxicities included neutropenia (15%), ALT increased (5%), thrombocytopenia (5%), hyperglycemia (5%), hypertension (5%), diarrhea (5%), syncope (5%). **No patients discontinued therapy due to toxicity.**
- Stem cells were successfully collected in all patients with mean stem cell yield of 5.78 x 10^6 CD34+/kg cells.

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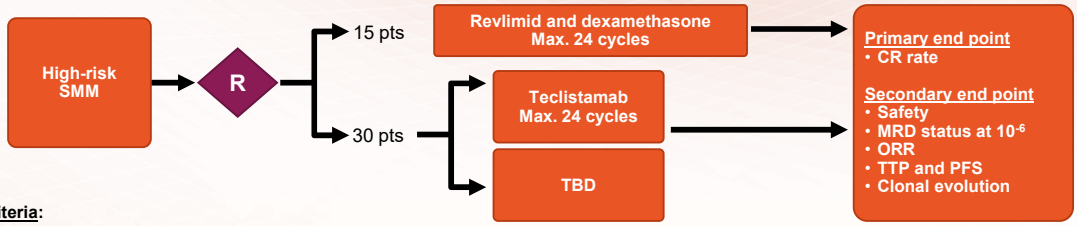
Immuno-PRISM (PRecision Intervention Smoldering Myeloma): A Randomized Phase 2 Platform Study of Select Immunotherapies for High-Risk Smoldering Myeloma



Inclusion criteria:

High-risk SMM defined as having one of the following two criteria:

1. High risk per "20-2-20" Criteria defined as presence of any two of the following:

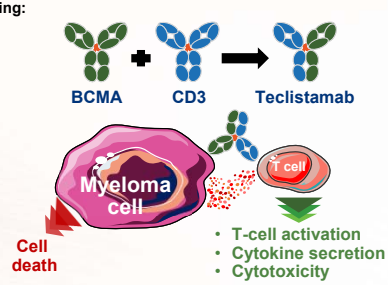
- Serum M spike ≥2 gm/dL
- Involved to uninvolved free light chain (FLC) ratio ≥20
- Bone marrow PC% ≥20%

OR **total score** of 9 using the following scoring system:

- FLC ratio: >10–25 = 2, >25–40 = 3, >40 = 5
- Serum M protein (g/dL): >1.5–3 = 3, >3 = 4
- BMPC%: >15–20 = 2, >20–30 = 3, >30–40 = 5, >40 = 6
- FISH abnormality t(4,14), t(14,16), 1q gain, or del13q = 2

2. Presence of ≥10% BMPC and at least one of the following:

- **Evolving pattern**
- **Abnormal PC immunophenotype** (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotype. (Only IgG; IgA and IgM will be considered)
- **High-risk cytogenetics** defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain



Teclistamab Dosing

Cycle 1
• Step-up dose: days 1 and 3
•Treatment Dose: days 8, 15, 22

Cycle 2:
•Teclistamab (subcutaneous): Days 1, 8, 15 and 22
•

Cycle 3-24
•Teclistamab (subcutaneous): Days 1 and 15

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

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Question

How much of the information presented was new to you?

A. All of it
B. More than half
C. Less than half
D. None of it
E. I don't know.

88

Question

Will you discuss any of this information further with your care team at your next office visit?

A. Yes
B. No
C. Maybe
D. I don't know.
E. Not applicable

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MULTIPLE MYELOMA Research Foundation

Newly Diagnosed Multiple Myeloma

Andrew D. Kin, MD
Karmanos Cancer Institute
Wayne State University
Detroit, Michigan

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Multiple Myeloma Diagnosis

- Life-changing event
- Great strides in
  - Diagnostic and prognostic process
  - Availability of novel agents
- Treatment is for life

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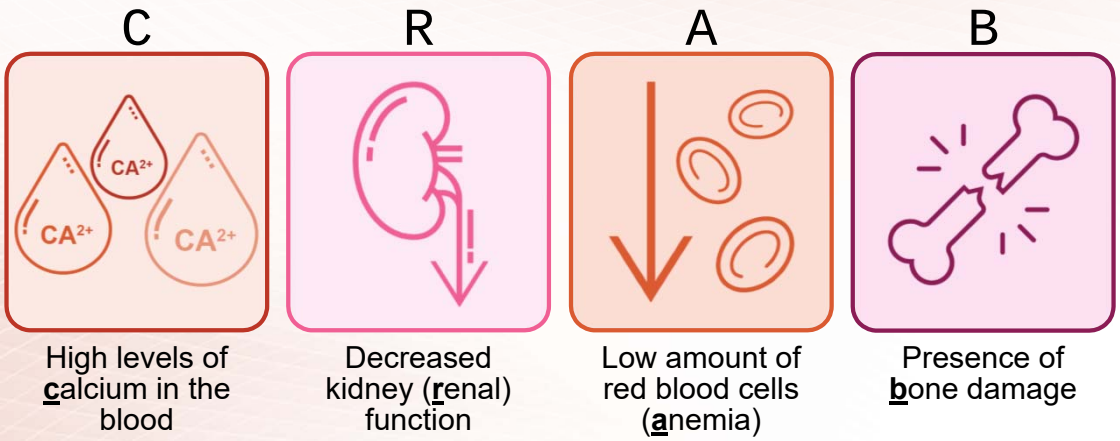
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

The clinical features that are characteristic of multiple myeloma



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Making the Diagnosis: The Right Tests

Common laboratory tests conducted

Blood and urine tests

- Confirms the type of myeloma

Bone marrow biopsy tests

- Determines how advanced the myeloma is and identifies the myeloma subtype

Imaging tests

- Detects the extent of bone disease and the presence of myeloma outside of the bone marrow

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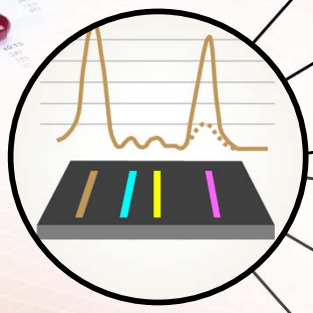
Learn Your Labs!

Blood tests



- **CBC** – Number of red blood cells, white blood cells, and platelets
- **CMP** – Measure levels of albumin, calcium, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and creatinine. Assess function of kidney, liver, and bone status and the extent of disease
- **B2M** – Determine the level of a protein that indicates the presence/extent of MM and kidney function
- **SPEP** – Detect the presence and level of M protein
- **IFE** – Identify the type of abnormal antibody proteins
- **SFLC** – Freelite test measures light chains (kappa or lambda)

CBC, complete blood count; CMP, complete metabolic panel; B2M; beta-2 microglobulin; SPEP, serum protein electrophoresis; IFE, immunofixation electrophoresis; SFLC, serum free light chain assay

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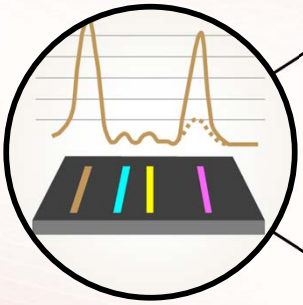
Learn Your Labs!

Urine tests



UPEP

- Detect Bence Jones proteins (otherwise known as myeloma light chains)

24-hr urine analysis

- Determine the presence and levels of M protein and Bence Jones protein

UPEP, urine protein electrophoresis

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Types of Multiple Myeloma Based on Blood or Urine Tests

Intact M protein

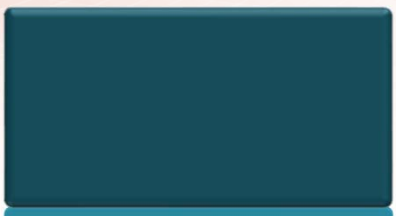
- Named for the type of immunoglobulin and light chain pair; for example, IgG kappa (κ) or IgG lambda (λ)

80%

Light chain only

- Also known as Bence Jones protein
- Renal failure more common in light chain multiple myeloma

20%



Non-secretory

- No M protein present

3%

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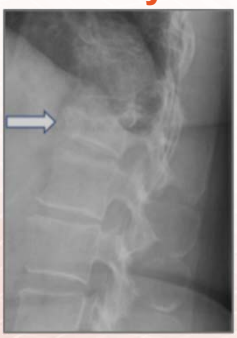
Know Your Imaging Tests!

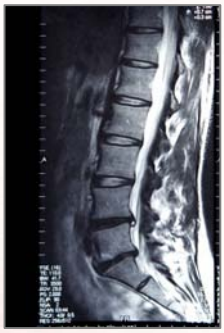
Assess changes in the bone structure and determine the number and size of tumors in the bone

X-ray

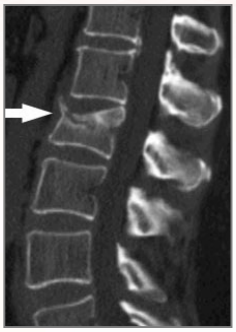


Conventional x-rays reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.

MRI



CT scan



PET scan

MRI and PET/CT appear to be more sensitive (85%) than skeletal x-rays for the detection of small lytic bone lesions.

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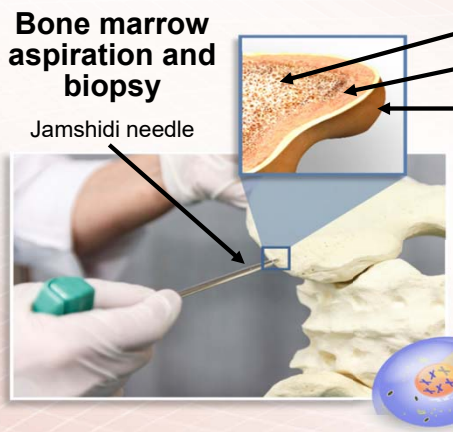
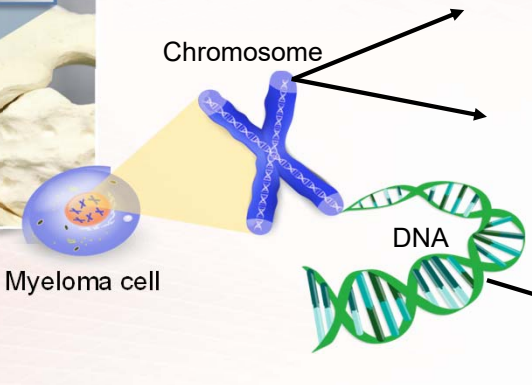
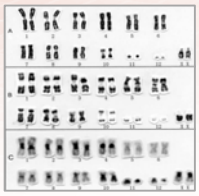
Know Your Bone Marrow Tests!

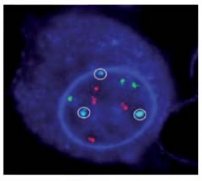
Bone marrow aspiration and biopsy



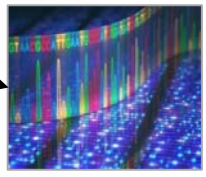




Karyotyping



FISH (fluorescence in situ hybridization)



Genomic sequencing

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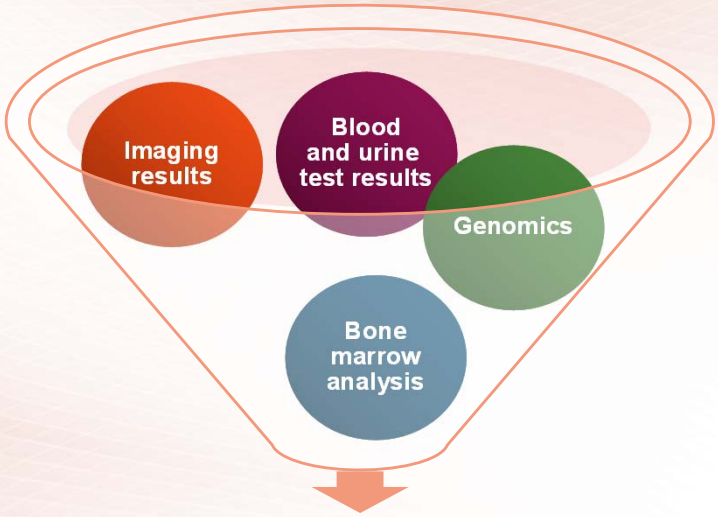
Putting the Results Together



Staging, prognosis, and risk assessment

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Multiple Myeloma Prognosis and Risk

Many blood test and bone marrow biopsy test results can determine a patient's risk for myeloma that is aggressive (high risk) or not (standard risk) based on the revised-International Staging System (R-ISS)

Standard risk

R-ISS Stage I

- Serum β2M level <3.5 mg/L
- Serum albumin level ≥3.5 g/dL
- No high-risk chromosomal abnormality*
- Normal LDH level

All other possible combinations of the test results means that a patient is **R-ISS stage II**

High risk

R-ISS Stage III

- Serum β2M level ≥5.5 mg/L
- High-risk chromosomal abnormality* or high LDH level

*High-risk chromosomal abnormality by FISH: del(17p) and/or t(4;14) and/or t(14;16)

β2M; beta-2 microglobulin; LDH, lactate dehydrogenase; FISH, fluorescent in situ hybridization

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Getting the Right Treatment: Goals of Multiple Myeloma Therapy

- Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible
- Eliminate myeloma cells from the bone marrow (as measured via minimal residual disease [MRD] testing)
- Improve quality of life with as few treatment side effects as possible
- Provide the longest possible period of response before first relapse
- Prolong overall survival

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Overview of Treatment Approach for Active Multiple Myeloma

Is the patient a candidate for autologous stem cell transplantation?

Yes

- 3–4 cycles of induction therapy
  - 3- to 4-drug regimen generally preferred
- Clinical trial

Stem cell collection and storage

High-dose melphalan + stem cell transplant

No

- Any of the regimens used for transplant candidates*
- Clinical trial

*2-drug regimen may be considered for frail patients

Consolidation and or continuous/maintenance therapy

Supportive care

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Induction Therapy Regimens

	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid-Velcade-dex (RVd)*	• Kyprolis-Revlimid-dex (KRd) • Ninlaro-Revlimid-dex (IRd) • Darzalex-Revlimid-Velcade-dex (D-RVd)	• Velcade-Cytoxan-dex (VCd) • Kyprolis-Cytoxan-dex (KCd) • Ninlaro-Cytoxan-dex (ICd) • Revlimid-Cytoxan-dex (RCd) • Velcade-Thalomid-dex (VTd)* • Velcade-Doxil-dex (VDd) • Darzalex-Velcade-Revlimid-dex (D-VRd) • Darzalex-Kyprolis-Revlimid-dex (D-KRd) • Darzalex-Cytoxan-Velcade-dex (D-VCd) • Darzalex-Velcade-Thalomid-dex (D-VTd) • VTD-PACE
Transplant ineligible	• Revlimid-Velcade-dex (RVd)* • Darzalex-Revlimid-dex (DRd)*	• Kyprolis-Revlimid-dex (KRd) • Ninlaro-Revlimid-dex (IRd) • Darzalex-Velcade-melphalan-prednisone (D-VMP)* • Darzalex-Cytoxan-Velcade-dex (D-VCd)	• Velcade-dex (Vd) • Revlimid-dex (Rd)* • Velcade-Cytoxan-dex (VCd) • Revlimid-Cytoxan-dex (RCd) • Kyprolis-Cytoxan-dex (KCd) • Revlimid-Velcade-dex (RVd)-lite

*Category 1 recommendation. Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
National Comprehensive Cancer Network Guidelines Version 1.2022. Multiple Myeloma.

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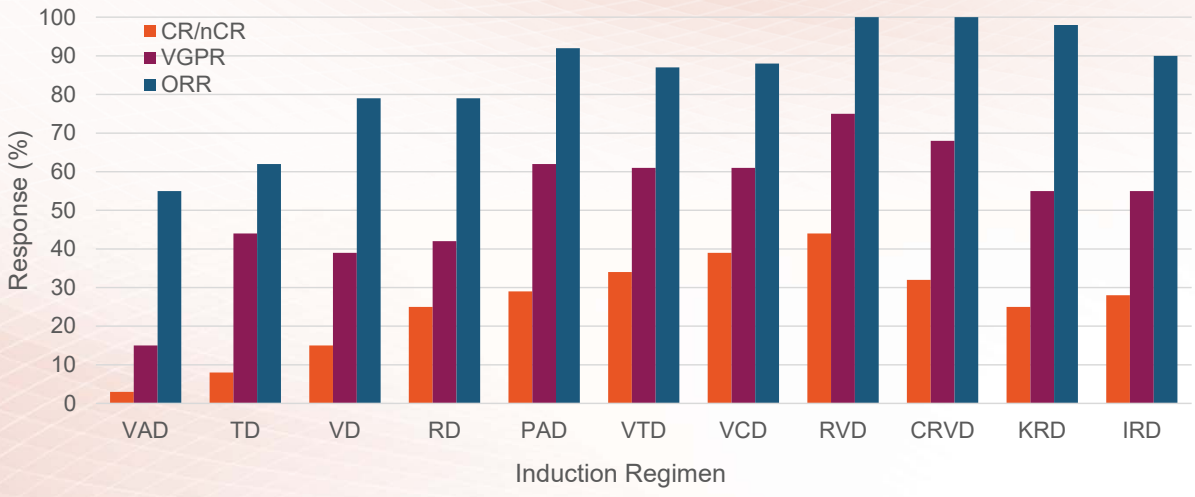
Induction Choices



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What does transplant mean?

Understanding the basics of autologous stem cell transplantation

Hematopoietic, or blood-forming, cells are stimulated to move to the bloodstream and are collected from the patient.

The patient receives high-dose melphalan chemotherapy to eradicate myeloma cells in the blood and bone marrow.

Because melphalan also reduces the normal cells in the bone marrow, causing immunosuppression, a stem cell transplant (or re-infusion) with the previously collected cells is the next step to replenish the bone marrow.

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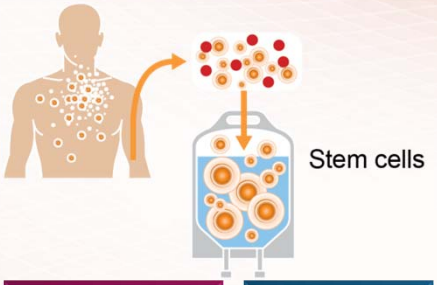
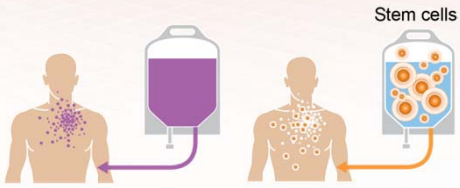
Autologous Stem Cell Transplantation





1. Induction therapy
2. Collection of stem cells from the bloodstream
3. Freezing of stem cells
4. High-dose chemotherapy
5. Thawing and infusion of stem cells
6. Recovery

-2 to -3 weeks*

Day 0

Days +1 to +100†

~4–6 cycles

Stem cell mobilization
- Neupogen, Neulasta, Leukine, Cytoxan, Mozobil

Melphalan
- Alkeran, Evomela

*The weeks leading up to the transplant; †The days after the transplant.

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What is maintenance therapy?

- A prolonged, and often low-dose, treatment given to myeloma patients after their initial therapy (or transplant)
- To prevent disease progression for as long as possible while maintaining favorable quality of life
- To eliminate minimal residual disease (MRD) or maintain the absence of MRD, reduce the risk of relapse, and prolong survival

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Continuous or Maintenance Therapy Options

	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid*	• Ninlaro* • Velcade	• Velcade-Revlimid ± dex
Transplant ineligible	• Revlimid*	• Ninlaro* • Velcade	• Velcade-Revlimid

Additional agents under investigation: Darzalex, Empliciti, Kyprolis

*Category 1 recommendation. Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
National Comprehensive Cancer Network Guidelines Version 1.2022. Multiple Myeloma.

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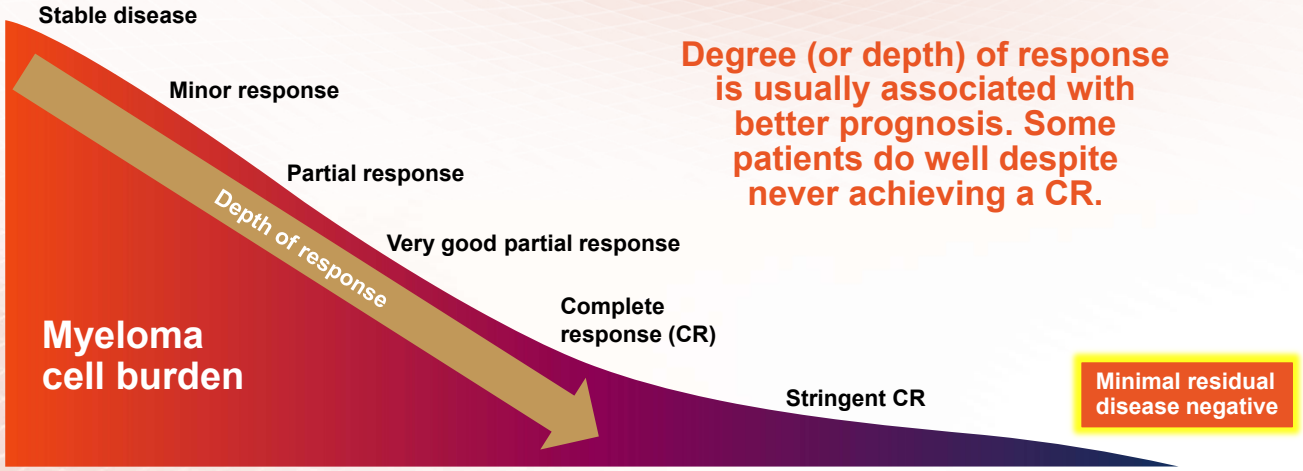
Measuring Response to Therapy



Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

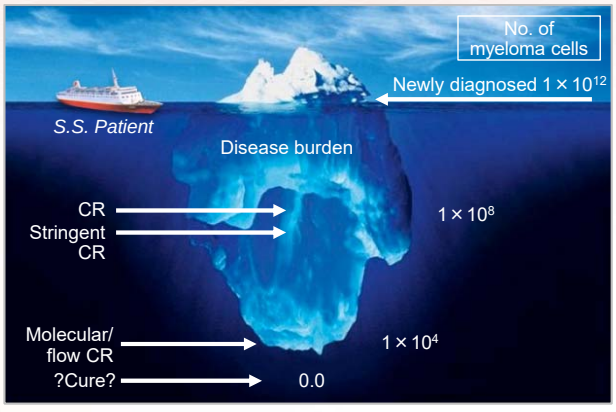
ClonoSEQ is an FDA-approved next-generation sequencing (NGS) test to measure MRD in MM patients

Palumbo A et al. *J Clin Oncol.* 2014;32:587.
Kumar S et al. *Lancet Oncol.* 2016;17:e328.

109

What is minimal residual disease (MRD)?

- With new and more effective treatments, more patients achieve complete response (CR)
- However, achieving a CR does not necessarily mean that all myeloma cells are gone
- Routine blood tests are not sensitive enough to detect these remaining cells



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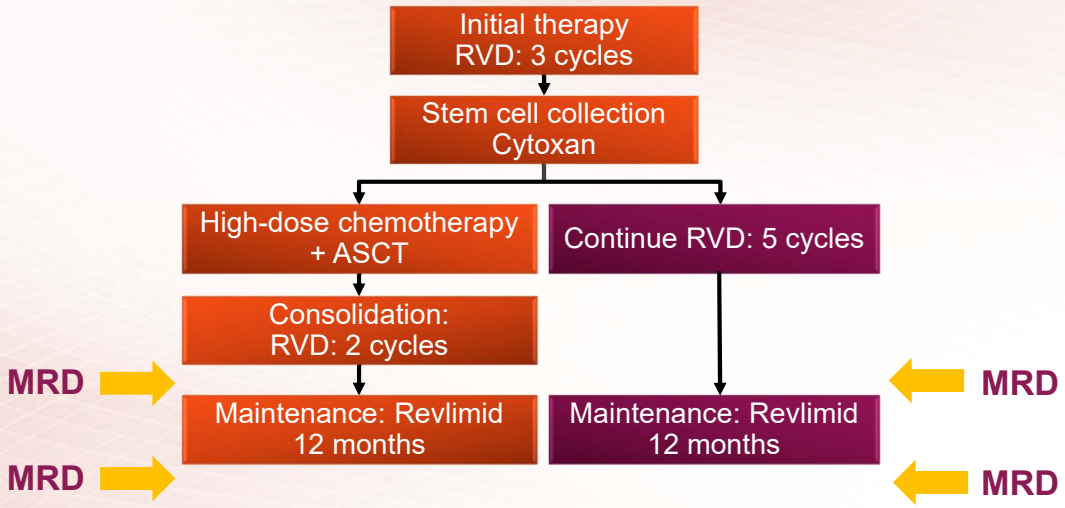
Why is it important to achieve MRD negativity?



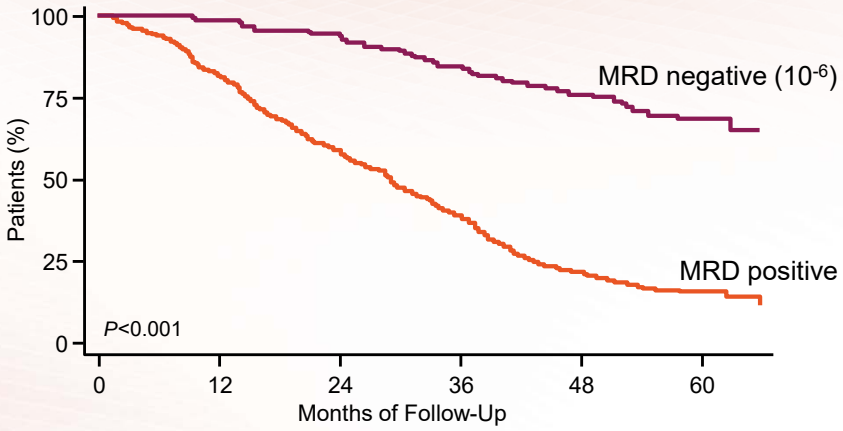
RVD, Revlimid, Velcade, dexamethasone; Cytoxan, cyclophosphamide

Determination Trial (IFM 2009). Avet-Loiseau H et al. *Blood*. 2017;130: Abstract 435.

111

Why is it important to achieve MRD negativity?

Patients who achieve MRD negativity following treatment experience longer remission than those who are still MRD positive after treatment



Perrot A et al. *Blood*. 2018;132:2456.

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MRD-Negativity Achieved by Various Regimens

	Combination therapy	ASCT	MRD-negativity
Triplet regimen[1,2]	KRd 8 cycles	Yes	58%
	KRd 12 cycles	No	54%
	VRd ×6 cycles	Yes	20%
Quadruplet regimens[2,3]	VRd-daratumumab ×6 cycles	Yes	51%
	KRd-daratumumab ×8 cycles	No	71%

1. Gay F et al. *J Clin Oncol*. 2019;37: Abstract 8002; 2. Voorhees PM et al. *Blood*. 2020;136:936; 3. Landgren O et al. *JAMA Oncol*. 2021;7:862

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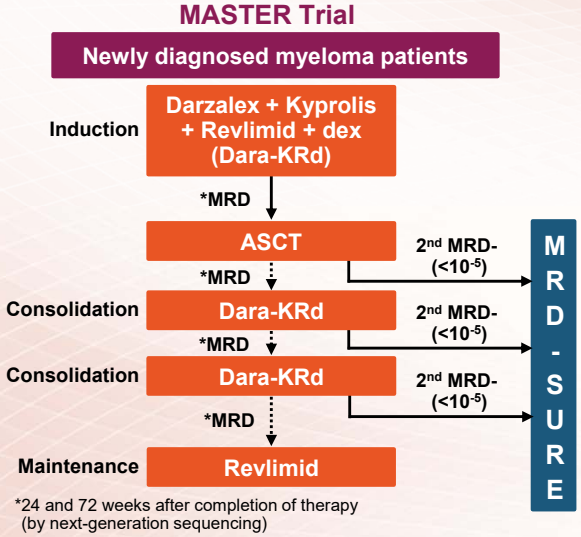
MRD Response-Adapted Consolidation and Treatment Cessation



- 80% of patients achieved MRD negativity (at <1 × 10^{-5}) and 66% achieved MRD negativity at <1 × 10^{-6}.
- 86% of patients achieved a CR or better.
- Responses deepened with each phase of treatment—and were similar in patients with zero, one, or two or more high-risk genetic abnormalities.
- ASCT increased the rates of MRD negativity following induction therapy, benefitting patients with highest-risk disease features.

Nearly all patients with no or only one high-risk genetic abnormality and confirmed MRD negativity had no disease progression or MRD resurgence since stopping treatment.

Treatment-free observation and MRD surveillance*

Costa LJ et al. *Blood*. 2021;138. Abstract 481; Costa LJ et al. *J Clin Oncol*. 2021; Dec 13 [epub ahead of print].

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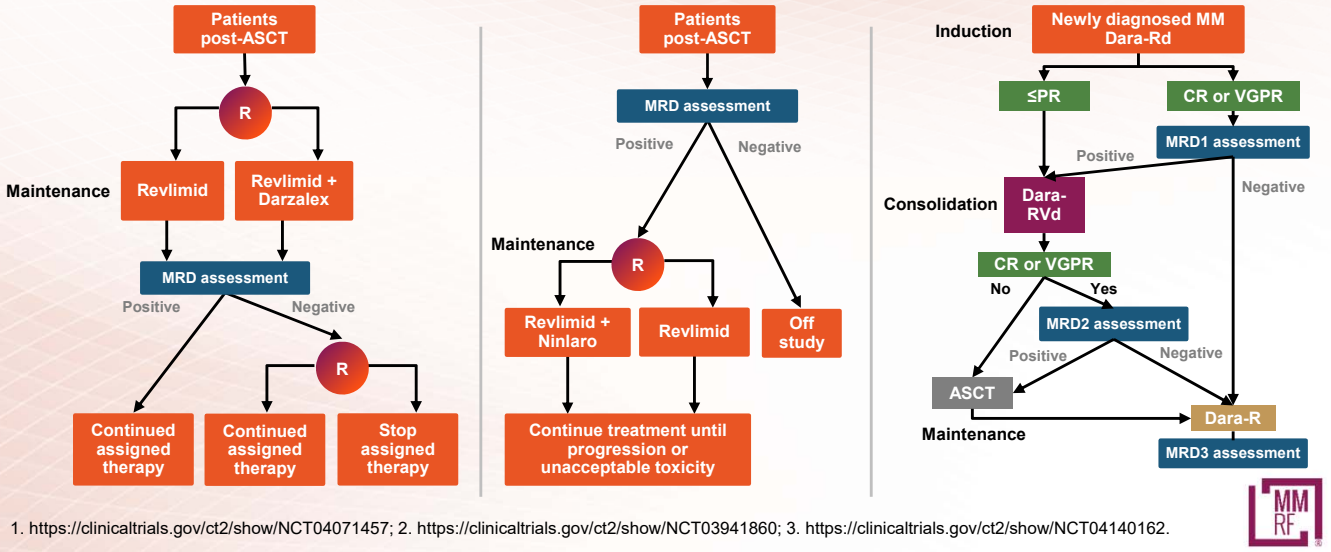
Ongoing Studies Using MRD Results to Direct Therapy



1. https://clinicaltrials.gov/ct2/show/NCT04071457; 2. https://clinicaltrials.gov/ct2/show/NCT03941860; 3. https://clinicaltrials.gov/ct2/show/NCT04140162.

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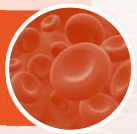
Main Body Systems Affected by Myeloma Treatment

Blood

- Myeloma patients are at increased risk of developing blood clots
- Several myeloma drugs are associated with an increased risk of deep vein thrombosis (DVT)



CNS

- Peripheral neuropathy is a condition that affects the nerves, resulting in pain, tingling, burning sensations, and numbness in the hands and feet
- Peripheral neuropathy may be caused by multiple myeloma or its treatments

Cardio-vascular

- Cardiovascular side effects (including high blood pressure or congestive heart failure) can occur with some multiple myeloma drugs

Gastro-intestinal

- Commonly used multiple myeloma drugs may cause a variety of gastrointestinal problems, such as constipation, diarrhea, and nausea/vomiting

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Side Effects of Steroids (dexamethasone)

Insomnia	Fluid retention	Mood changes	Dyspepsia–heartburn	Elevation in glucose
				
• Healthy sleep habits • Timing • Medication to assist with sleeping as needed	• Monitor for swelling of extremities and “puffy” face • Monitor weight changes/gain • Reduce dose	• Irritable, anxiety, difficulty concentrating • Severe cases → depression, euphoria	• Dietary modifications (spicy, acidic foods) • Avoid NSAIDs • Acid-blocking medications • Take steroid with food; use enteric-coated aspirin with food	• Monitor glucose and refer/treat as needed

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Summary

- **Blood and bone marrow tests give us key insights into the biology of your myeloma, and the genetic information we obtain from the bone marrow biopsy can provide prognostic information and help guide the optimal drug choice.**
- **ASCT remains the standard of care for frontline therapy of myeloma for patients who are eligible; its safety has been established and it induces long remissions.**
- **MRD is the deepest response after myeloma treatment, including bone marrow MRD and imaging MRD. NGF and NGS are the two most commonly used marrow MRD tests. MRD has been associated with longer progression-free and overall survival to predict lower risk of progression.**
- **The body of evidence from phase 3 trials indicates that maintenance (or “continuous”) therapy improves PFS and likely OS and should be given until progression. Most patients who are thought to be Revlimid responsive and able to tolerate the side effects should receive maintenance.**

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Question

How much of the information presented was new to you?

A. All of it
B. More than half
C. Less than half
D. None of it
E. I don't know.

119

Question

Will you discuss any of this information further with your care team at your next office visit?

A. Yes
B. No
C. Maybe
D. I don't know
E. Not applicable

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Town Hall Questions & Answers

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MULTIPLE MYELOMA Research Foundation

CAR T-Cell Therapy and Bispecific Antibodies

Ravi Vij, MD, MBA
Washington University School of Medicine
St. Louis, Missouri

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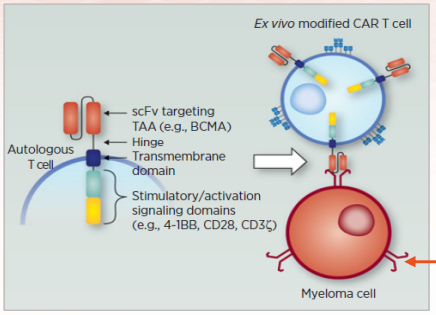
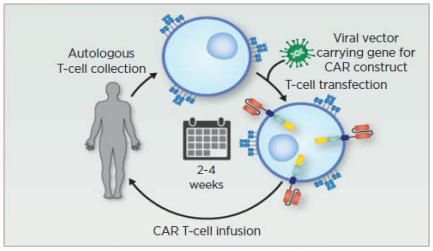
CAR T-Cell Therapy

- Genetically modified T cells designed to recognize specific proteins on MM cells
- CAR T cells are activated once in contact with the MM cell and can destroy the MM cell
- CAR T cells can persist for long periods of time in the body
- CAR T cells are created from a patient's own blood cells, but the technology is evolving to develop "off-the-shelf" varieties



B-cell maturation antigen (BCMA)



Examples:
- Abecma (ide-cel)
- Carvykti (cilta-cel)
- CT103A
- Gamma secretase inhibitor followed by CAR T-cells

CAR, chimeric antigen receptor; MM, multiple myeloma
Cohen A et al. *Clin Cancer Res.* 2020;26:1541.

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CAR T-Cell Therapy Patient Journey

Apheresis 1	**1 day**	**Immune cells from the patient are collected**
(Manufacturing) Patients return home 2	**4–6 weeks**	**Standard of care therapy is permitted until CAR T cells are ready for infusion**
Lymphodepletion (chemotherapy) 3	**3 days**	**Fludarabine and Cytoxan are used to create "immunologic space" to CAR T cells to expand**
Infusion 4	**2 weeks**	
Follow up 5	**Within 2 weeks**	

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Two CAR T-Cell Therapies Approved!

Drug	Formulation	Approval
Abecma (idecabtagene vicleucel)*	300 to 460 × 10^6 genetically modified autologous CAR T cells in one or more infusion bags	• For **relapsed/refractory** myeloma (after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb)
Carvykti (ciltacabtagene autoleucel)†	0.5 to 1.0 × 10^6 genetically modified autologous CAR T cells/kg of body weight	• For **relapsed/refractory** myeloma (after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb)

IMiD, immunomodulatory agent; PI, proteasome inhibitor; mAb, monoclonal antibody

*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
†Black box warning: cytokine release syndrome; neurologic toxicities; Parkinsonism and Guillain-Barré syndrome; HLH/MAS; prolonged cytopenia

Abecma and Carvykti are available only through a restricted distribution program

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Triple-Class Refractory

- For patients with relapsed or refractory multiple myeloma who have received treatment with—and did not respond satisfactorily to, or progressed while on treatment with—the three main classes of drugs currently used to treat myeloma are...

Proteasome inhibitors	Immunomodulatory drugs	Anti-CD38 monoclonal antibodies
• Velcade (bortezomib) • Kyprolis (carfilzomib) • Ninlaro (ixazomib)	• Revlimid (lenalidomide) • Pomalyst (pomalidomide)	• Darzalex (daratumumab) • Sarclisa (isatuximab)

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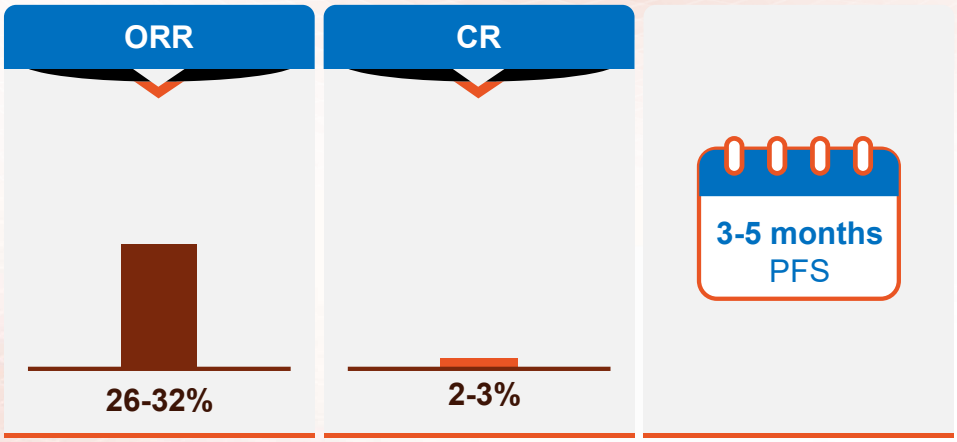
Outcomes for Later-line Triple Class-Exposed Patients With RRMM



Exposed to an immunomodulatory imide drug, proteasome inhibitor, and CD38 monoclonal antibody

Source: American Cancer Society, Pomalyst & Darzalex labels; BMSene materials; https://www.ascopost.com/issues/august-25-2019/selinexor-in-relapsed-or-refractory-multiple-myeloma/ https://www.ncbi.nlm.nih.gov/pubmed/30858549;

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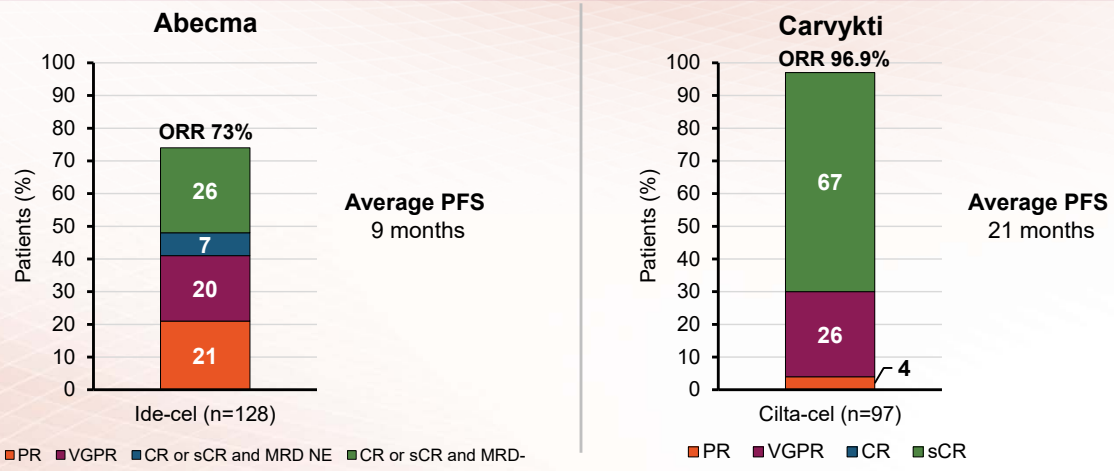
Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma



ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; PFS, progression-free survival

KarMMa Trial. Munshi NC et al. *N Engl J Med*. 2021;384:705.
CARTITUDE-1 Trial. Berdeja JG et al. *Lancet*. 2021;398:314.

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CAR-T: Expected Toxicities

Cytokine release syndrome (CRS)

Neurotoxicity (ICANS)

Cytopenias

Infections

	CRS	ICANS
Onset	1–9 days after CAR T-cell infusion	2–9 days after CAR T-cell infusion
Duration	5–11 days	3–17 days
Symptoms	• Fever • Difficulty breathing • Dizziness • Nausea • Headache • Rapid heartbeat • Low blood pressure	• Headache • Confusion • Language disturbance • Seizures • Delirium • Cerebral edema
Management	• Actemra (tocilizumab) • Corticosteroids • Supportive care	• Antiseizure medications • Corticosteroids

*Based on the ASTCT consensus; †Based on vasopressor; ‡For adults and children >12 years; §For children ≤12 years; ǁOnly when concurrent with CRS

Xiao X et al. Mechanisms of cytokine release syndrome and neurotoxicity of CAR T-cell therapy and associated prevention and management strategies. *J Exp Clin Cancer Res.* 2021;40(1):367. Article licensed under a Creative Commons Attribution 4.0 International License; Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625; Shah N et al. *J Immunother Cancer*. 2020;8:e000734.

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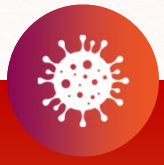
CAR T-Cell Therapy Themes: Myeloma



All patients were very heavily pretreated, at least six prior therapies. Many patients on the trials were considered *triple-class refractory.*

All have similar side effects, causing cytokine release syndrome (CRS), confusion, and low blood counts.

Most patients respond well to treatment, but the duration of response is 9–21 months depending on the CAR T-cell.

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Transplant vs CAR T Cells

Cellular therapies	CAR T-cell therapy	Autologous stem cell transplantation
Patient's cells collected	Yes	Yes
Types of cells collected	T cells*	Stem cells†
Collected cells are genetically engineered in a lab	Yes	No
Patient given chemotherapy before cells are infused back into patient	Yes, lymphodepleting therapy	Yes, melphalan
When in the course of myeloma is this *usually* done?	After multiple relapses	As part of initial treatment
Side effects of treatment	Cytokine release syndrome; confusion	Fatigue, nausea, diarrhea

*An immune cell that is the 'business end' of the system, in charge of maintaining order and removing cells.
†Precursor cells that give rise to many types of blood cells. We actually collect CD34+ve cells.

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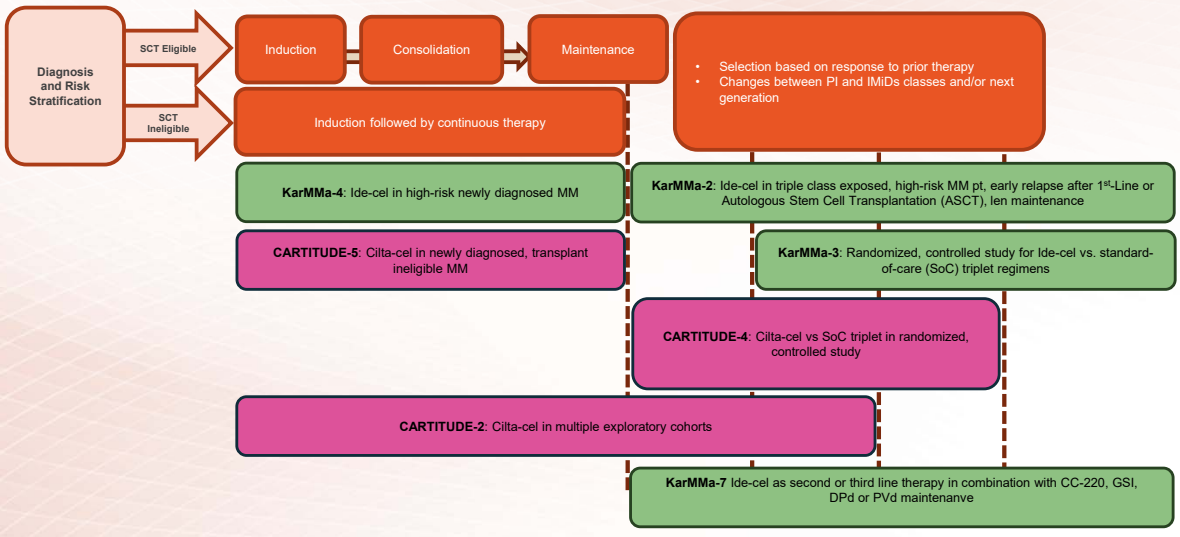
Moving CAR-T Upfront



*Graphic adapted from ASCO 2021 Discussion Session – Created and presented by Yi Lin, MD, PhD – Mayo Clinic

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Key Points

- **CAR T are very active even in heavily pre-treated patients.**
- **Side effects of CAR T-cells include cytokine release syndrome (CRS), confusion, and low blood counts, all of which are treatable.**
- **Two CAR T-cell therapies are approved for use in relapsed/refractory myeloma—Abecma (ide-cel) and Carvykti (cilta-cel)**
- **Abecma and Carvykti are only the first-generation CAR T cells and target the same protein. Different CARs and different targets are on the way.**

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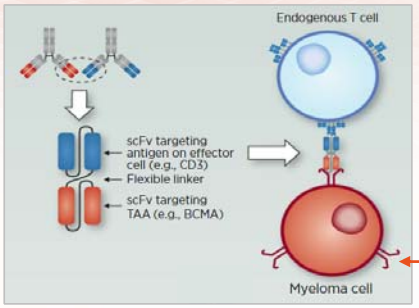
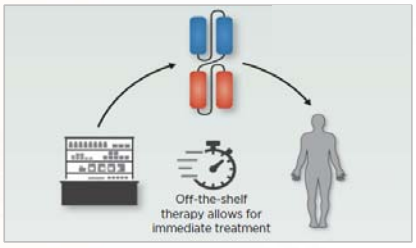
Bispecific Antibodies

- Bispecific antibodies are also referred to as dual specific antibodies, bifunctional antibodies, or T-cell engaging antibody
- Bispecific antibodies can target 2 cell surface molecules at the same time (one on the myeloma cell and one on a T cell)
- Many different bispecific antibodies are in clinical development; none are approved for use in myeloma
- Availability is off-the-shelf allowing for immediate treatment



BCMA, GPRC5D, or FcRH5



Examples:
- Elranatamab
- Teclistamab
- TNB-303B (ABBV-383)
- REGN5458
- Cevostamab
- Talquetamab

Cohen A et al. *Clin Cancer Res.* 2020;26:1541.

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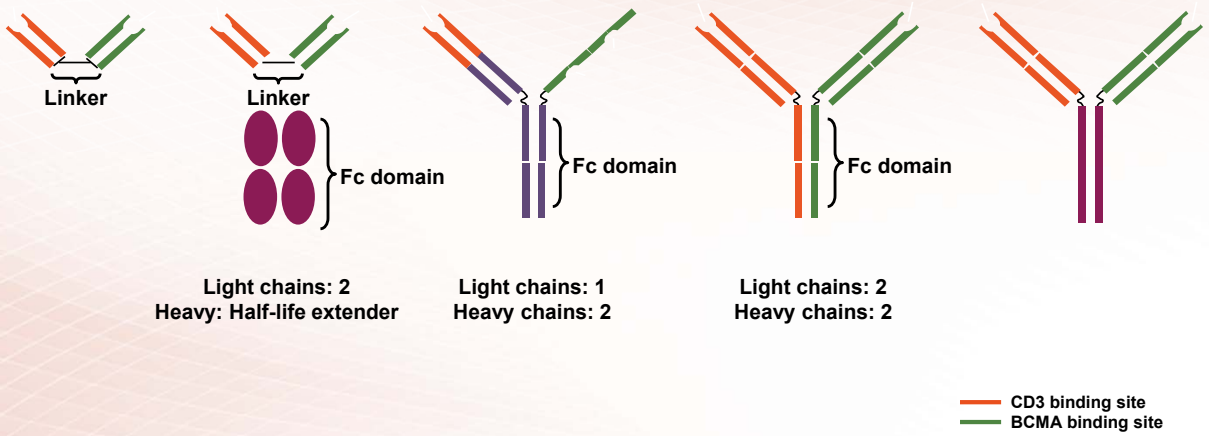
There are Different Types of Bispecific T-Cell Engagers/Antibodies



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Bispecific Antibodies: >20% Activity

Myeloma Cell Target	Bispecific Agent	Patients Responding*
BCMA	Teclistamab	65%
BCMA	REGN5458	73%
BCMA	Elranatamab	73%
BCMA	TNB383B	79%
BCMA	CC93269	89%
BCMA	AMG701	83%
GPCR5	Talquetamab	70%
FCRH5	Cevostamab	55%

*Based on a recent sampling

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Bispecific Antibodies on the Horizon

Study	MagnetisMM-1 (Phase 1)	MajesTEC-1 (Phase 1/2)	Phase 1	Phase 1	Phase 1	MonumenTAL-1 (Phase 1)
Agent	**Elranatamab[1]**	**Teclistamab[2]**	**TNB-383B (ABBV-383)[3]**	**REGN5458[4]**	**Cevostamab[5]**	**Talquetamab[6]**
Targets	**BCMA × CD3**	**BCMA × CD3**	**BCMA × CD3**	**BCMA × CD3**	**FcRH5 × CD3**	**GPRC5D × CD3**
No. patients	55	165	118	73	161	55 at 2 RP2D
Median no. prior therapies	6 (2–15)	5 (2–14)	5 (1–15)	5 (2–17)	6 (2–18)	6 (2–17)
Efficacy						
Overall response rate (%)	69	62	81 (≥40 mg)	75 (200–800 mg)	56.7 (132–198 mg)	69
Complete response or better (%)	30	29	39	16	8	16
Median duration of response (mos)	Not reported	Not reached	Not reported	Not reached	11.5	Not reached
Median progression-free survival (mos)	Not reported	59% at 9 mos	Not reported	Not reported	Not reported	Not reported
Safety						
CRS, all grades (G3/4), %	87 (0)	72 (1)	54 (3)	38 (0)	80 (1.2)	75 (5)
Neurotoxicity, all grades (G3/4), %	Not reported	13 (0)	Not reported	4 (0)	14 (1)	Not reported

RP2D, recommended phase 2 dose

1. Sebag M et al. *Blood.* 2021;138. Abstract 895; **2.** Moreau P et al. *Blood*. 2021;138. Abstract 896; **3.** Kumar SK et al. *Blood.* 2021;138. Abstract 900;
4. Zonder JA et al. *Blood.* 2021;138. Abstract 160; **5.** Trudel S et al. *Blood.* 2021;138. Abstract 157; **6.** Krishnan AY et al. *Blood.* 2021;138. Abstract 158.

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Bispecific Antibodies: Expected Toxicities

- Cytokine release syndrome (CRS)
- Neurotoxicity (ICANS)
  - Usually occurs within first 1–2 weeks
  - Frequency (all grade and grade 3–5) higher with CAR T
- Cytopenias
- Target unique: cytokeratin change/rash
- Infections
  - Incidence for bispecifics at RP2D not yet known
  - Viruses: CMV, EBV
  - PCP/PJP
  - Ongoing discussions regarding prophylactic measures
    - IVIG
    - Anti-infectives

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Similarities and Differences Between CAR T-Cell Therapy and Bispecific Antibodies

	CAR T cell therapy	Bispecific antibody
Approved product	Abecma, Carvykti	None (several in phase 2)
Efficacy	++++	+++
How given	One-and-done	IV or SC, weekly or q2 weeks until progression
Where given	Academic medical centers	Academic medical centers**
Notable adverse events	CRS and neurotoxicity	CRS and neurotoxicity
Cytokine release syndrome	+++	++
Neurotoxicity	++	+
Availability	Wait time for manufacturing	Off-the-shelf, close monitoring for CRS and neurotoxicity

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Key Points

- **Bispecific antibodies represent a new wave of myeloma treatments that are highly active even in heavily pre-treated patients.**
- **Bispecific antibodies represent an "off-the-shelf" immunotherapy.**
- **Similar to CAR T-cell therapy, toxicities of bispecific antibodies mainly consist of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and low blood counts, all of which are treatable.**
- **Several different bispecific antibodies are under clinical evaluation.**

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Question

How much of the information presented was new to you?

A. All of it
B. More than half
C. Less than half
D. None of it
E. I don't know.

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Question

Will you discuss any of this information further with your care team at your next office visit?

A. Yes
B. No
C. Maybe
D. I don't know.
E. Not applicable

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MULTIPLE MYELOMA Research Foundation

Patient Experience

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Town Hall Questions & Answers

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Thank you!

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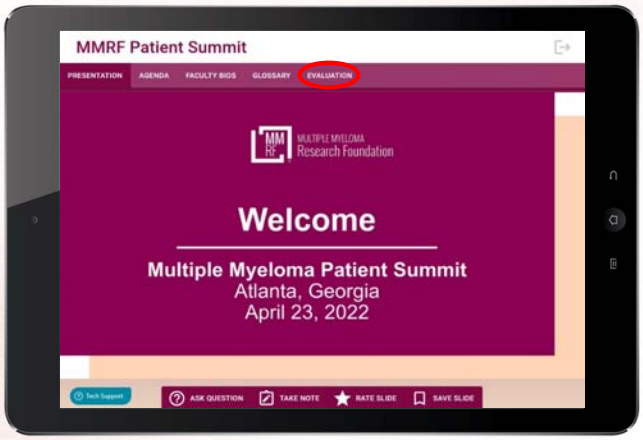
Don't Forget!

Complete your evaluation
Leave the iPad at your seat



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Upcoming Patient Education Events
Save the Date

Topic	Date and Time (ET)	Speakers
Facebook Live FAQs on Precursor Conditions	Wednesday, September 7 at 2:30 PM	C. Ola Landgren, MD, PhD Dennis Verducci, MSN, RN, NP-BC, OCN
Patient Summit (live and online)	Saturday, September 10 9:00 AM – 2:00 PM Chicago, Illinois	Andrzej Jakubowiak, MD—Host Benjamin Derman, MD—Host
Patient Summit (live and online)	Saturday, October 22 9:00 AM – 2:00 PM Nashville, Tennessee	Jesus Berdeja, MD—Host

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

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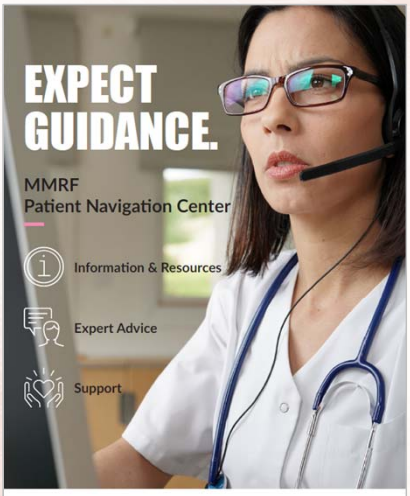
MMRF Patient Resources



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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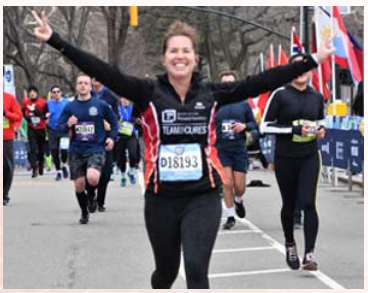
MMRF Events

**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: https://themmrf.org/get-involved/mmrf-events/

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