MULTIPLE MYELOMA Research Foundation

Opening Remarks

Mary DeRome, MS
MMRF

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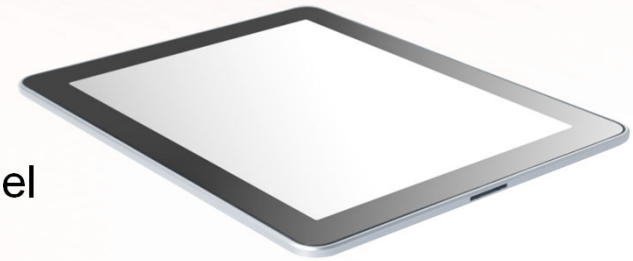
iPads

- 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.

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Program Faculty

Program Host

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Georgetown University School of Medicine
Washington, District of Columbia
John Theurer Cancer Center, Hackensack Meridian School of Medicine
Hackensack, New Jersey

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Hackensack University Medical Center
Hackensack, New Jersey

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Summit Agenda

Time (ET)	Topic	Speakers
9:00 – 9:10 AM	Introduction to the MMRF	Mary DeRome, MS
9:10 – 9:20 AM	Welcome	David H. Vesole, MD, PhD, FACP
9:20 – 10:00 AM	Myeloma 101 and Health Care Disparities in Multiple Myeloma	Kimberley Doucette, MD
10:00 – 10:30 AM	Treating Relapsed/Refractory Multiple Myeloma	Noa Biran, MD
10:30 – 11:00 AM	Town Hall Q&A	Panel
11:00 AM – 11:30 AM	CAR T-Cell Therapy and Bispecific Antibodies	David H. Vesole, MD, PhD, FACP
11:30 AM – 12:00 PM	Supportive Care	Susan M. Kumka, RN, MSN, APN Ann McNeill, RN, MSN, APN
12:00 – 1:00 PM	Lunch, Patient Journey	Lucretia Agee
1:00 – 1:30 PM	Town Hall Q&A	Panel
1:30 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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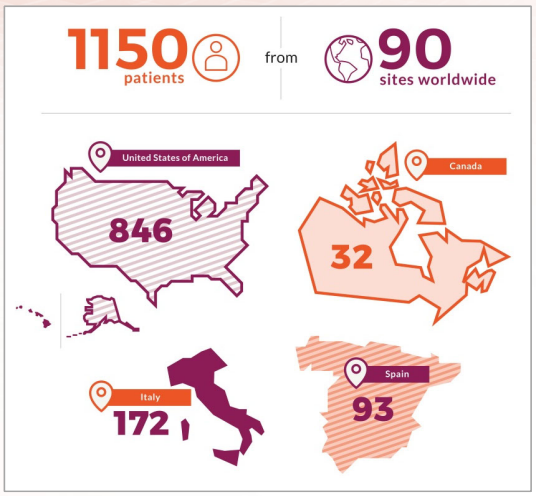
MMRF CoMMpass Study: Advancing Personalized Medicine Research

- 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 are followed for at least 8 years

All participants undergo a type of detailed DNA testing called *genomic sequencing* at diagnosis and each relapse.



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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 and CureCloud Research Study

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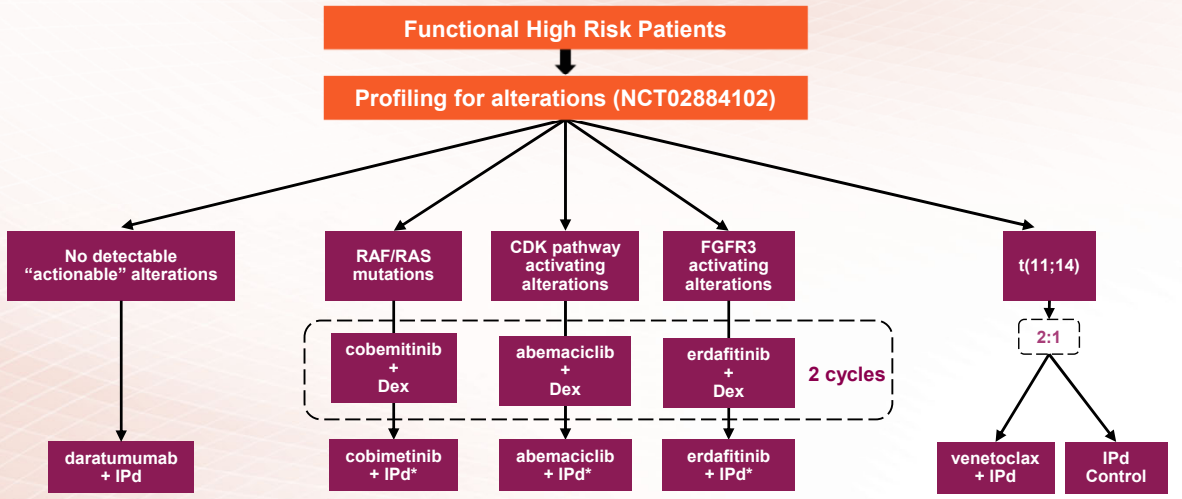
MyDRUG Trial



**Assess single agent activity after 2 cycles: After cycle 2, add backbone to single agent*

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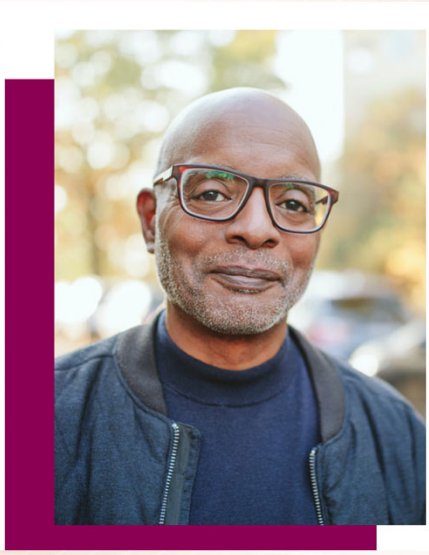
MMRF CureCloud



Driving toward smarter treatment options

Introducing the MMRF CureCloud® — a research study that includes the first at-home genomic testing program for multiple myeloma patients. Our goal is to accelerate research toward smarter treatment options for every patient.

Join the MMRF CureCloud

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MMRF CureCloud – Recent Changes

- A new and better assay is being developed to look at patient DNA data from myeloma cells in their blood sample – while this assay is being developed, patients who join will no longer be able to receive their DNA test results, but their DNA will still be analyzed, and the results placed in the CureCloud along with their clinical information
- Patients can still sign up for the CureCloud research study from home, but soon will be able to enroll at select clinical sites with help from site research staff – sites in preparation include UTSW, WashU, Hackensack, Emory, Ochsner, Karmanos, and the VA – by the end of 2023 we anticipate 15 sites will be approved for on-site enrollment
- For now, all patients will still provide their blood sample using an at-home blood draw
- Patients who live in New York may now enroll in CureCloud
- We anticipate that patients will be able to receive their DNA results from samples collected sometime in 2024

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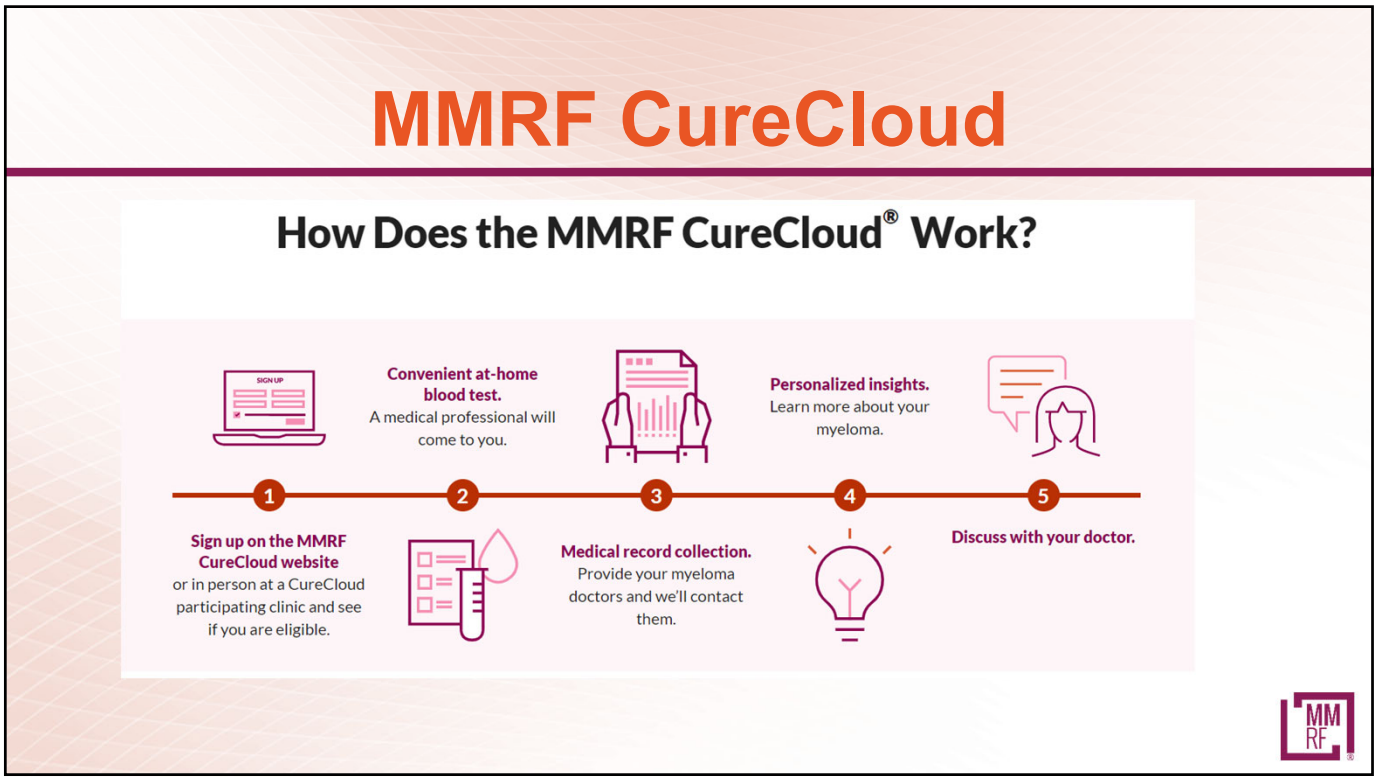
MMRF CureCloud
How Does the MMRF CureCloud® Work?
1
Sign up on the MMRF CureCloud website
or in person at a CureCloud participating clinic and see if you are eligible.
2
Convenient at-home blood test.
A medical professional will come to you.
3
Medical record collection.
Provide your myeloma doctors and we'll contact them.
4
Personalized insights.
Learn more about your myeloma.
5
Discuss with your doctor.

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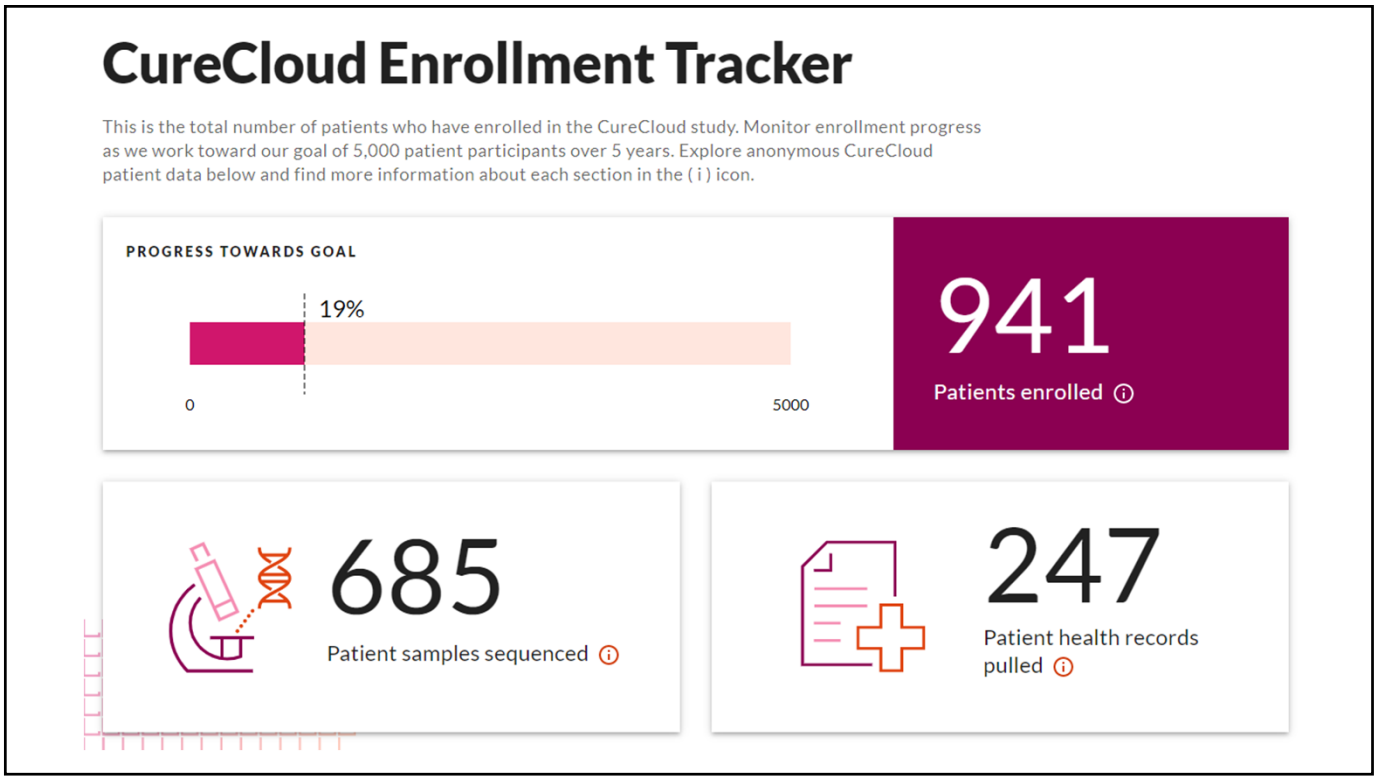
CureCloud Enrollment Tracker
This is the total number of patients who have enrolled in the CureCloud study. Monitor enrollment progress as we work toward our goal of 5,000 patient participants over 5 years. Explore anonymous CureCloud patient data below and find more information about each section in the (i) icon.
PROGRESS TOWARDS GOAL
19%
0
5000
941
Patients enrolled
685
Patient samples sequenced
247
Patient health records pulled

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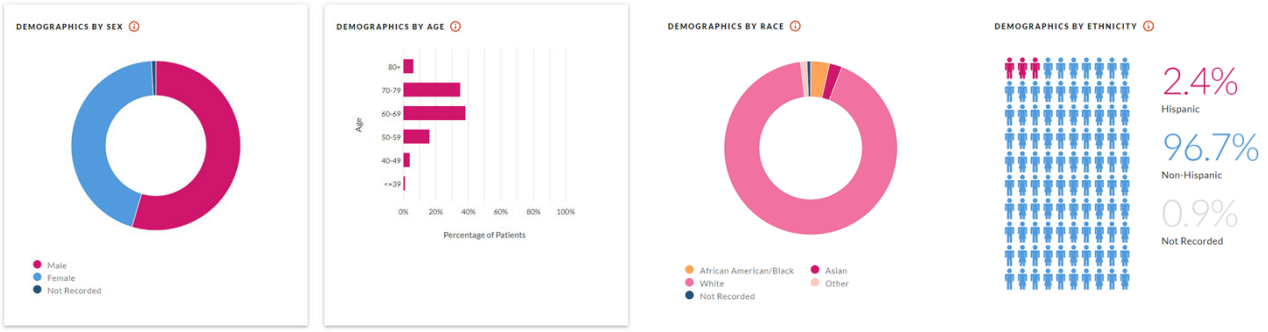
MMRF CureCloud Demographics



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MULTIPLE MYELOMA
Research Foundation

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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MULTIPLE MYELOMA Research Foundation

Myeloma 101 and Health Care Disparities in Multiple Myeloma

Kimberley Doucette, MD
MedStar Georgetown University Hospital
Georgetown Lombardi Comprehensive Cancer Center
Washington, District of Columbia

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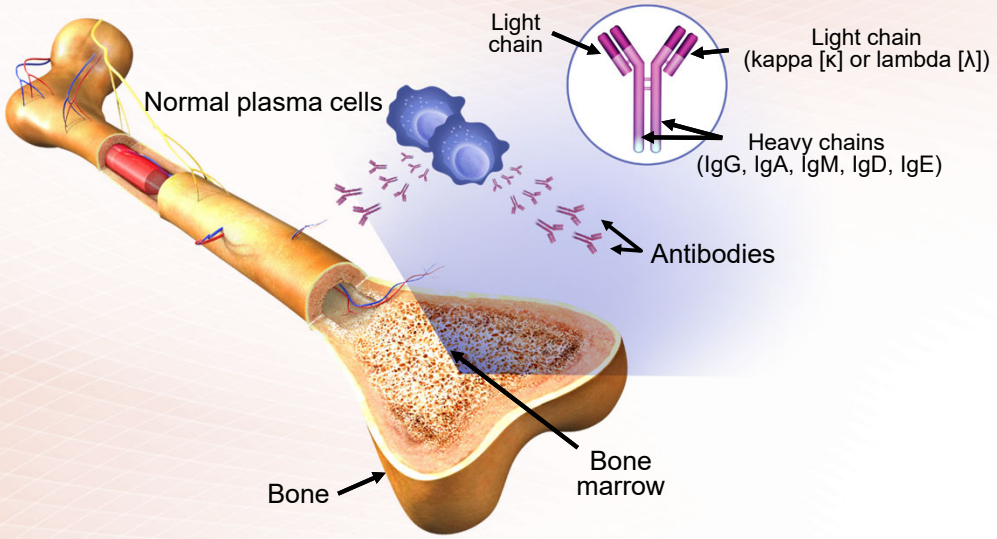
Normal Bone Marrow



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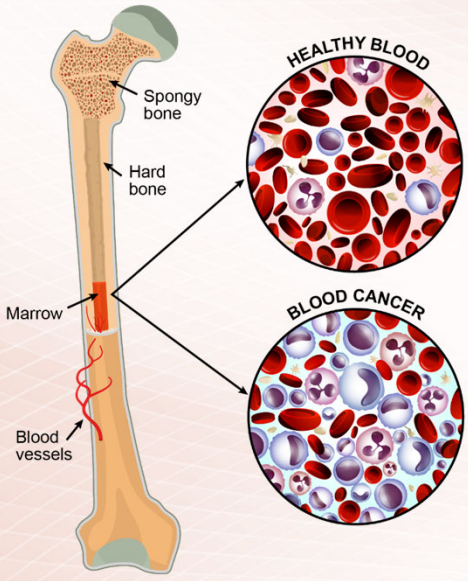
What is multiple myeloma?



- 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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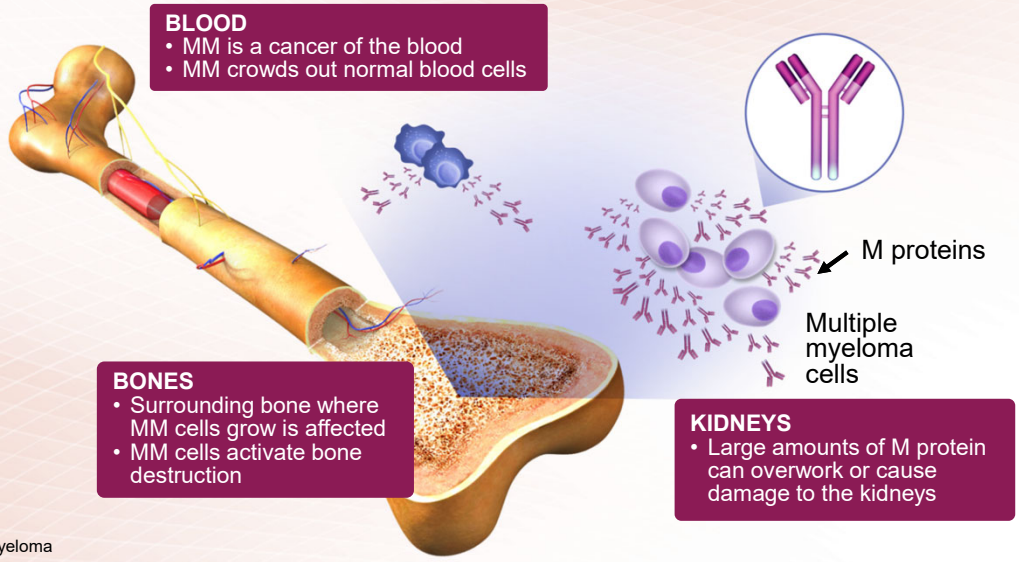
Multiple Myeloma Affects Your Bones, Blood, and Kidneys



MM, multiple myeloma

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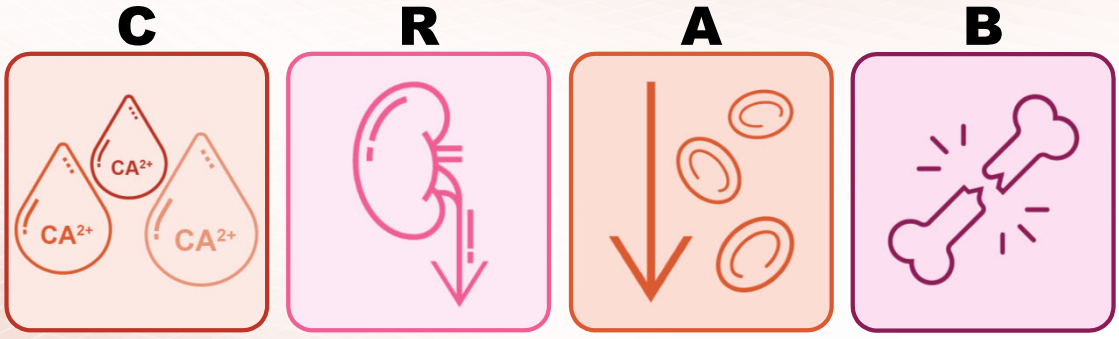
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

The clinical features that are characteristic of multiple myeloma



C — High levels of **c**alcium in the blood

R — Decreased kidney (**r**enal) function

A — Low amount of red blood cells (**a**nemia)

B — Presence of **b**one damage

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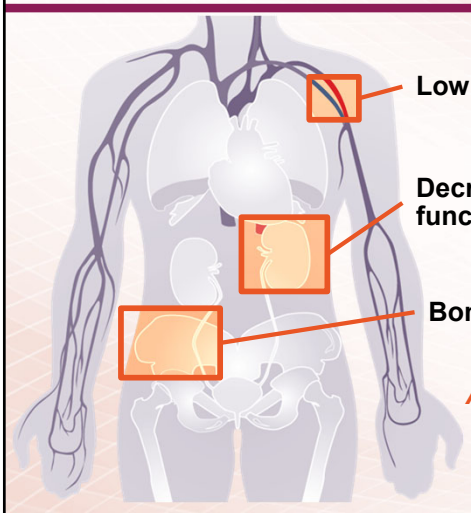
Effects of Myeloma and Common Symptoms



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. 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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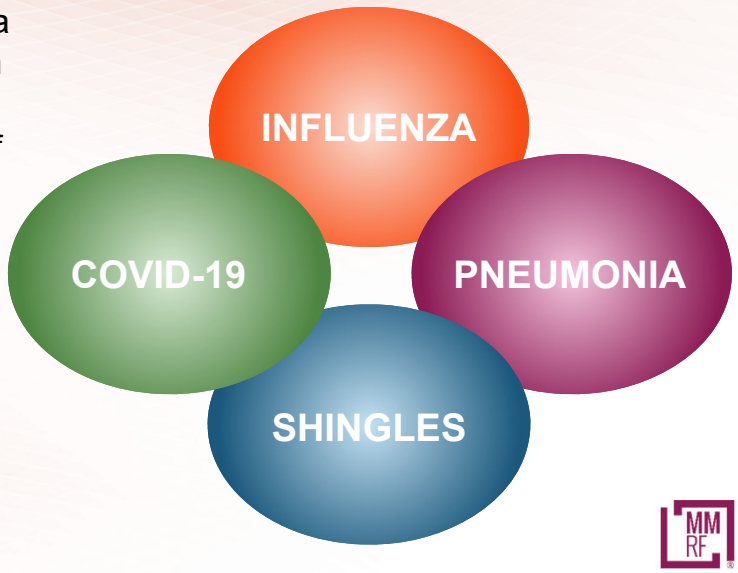
Infections and Vaccinations in Multiple Myeloma

- 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
  - Hand-washing, avoiding sick contacts
  - Vaccines/pre-exposure antibodies
  - Other precautions (antibiotics, growth factors)



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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.
Thordardottir M et al. *Blood Adv*. 2017;1:2186.

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Following the Proper Path Will Help Patients Get 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

Available resources

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

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

Seek a second opinion at any point in your journey

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)**

Confirms the type of myeloma

Urine tests

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

Bone marrow biopsy

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

New
- Genomic sequencing

Determines how advanced the myeloma is and identifies the myeloma subtype

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

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

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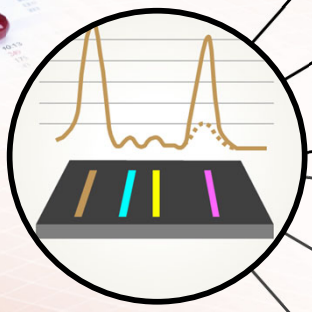
Learn Your Labs!
Blood Tests

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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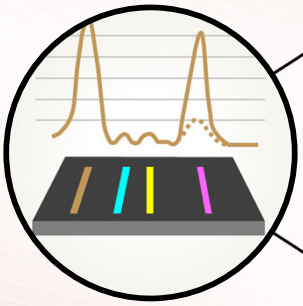
Learn Your Labs!
Urine Tests

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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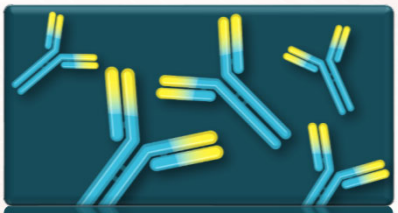
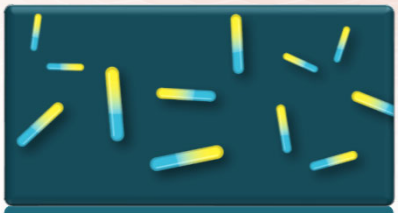
Types of Multiple Myeloma Based on Blood or Urine Tests



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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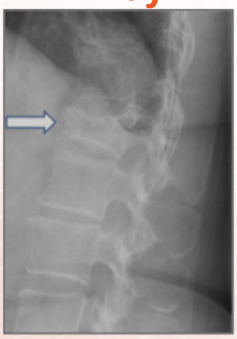
Know Your Imaging Tests!

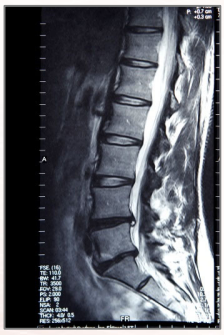
Assess changes in the bone structure and determine the number and size of tumors in the bone

X-ray

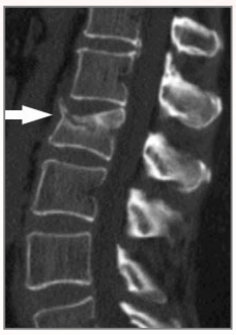


Conventional x-rays reveal lytic lesions, osteoporosis, or fractures in 75% of patients.

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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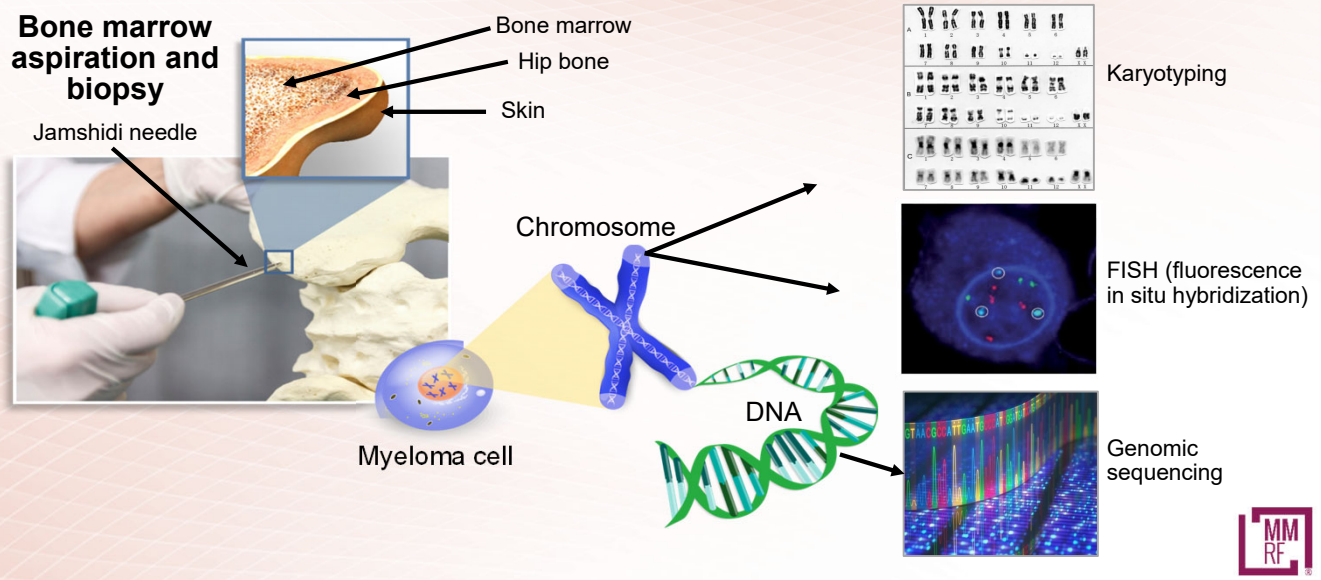
Know Your Bone Marrow Tests!



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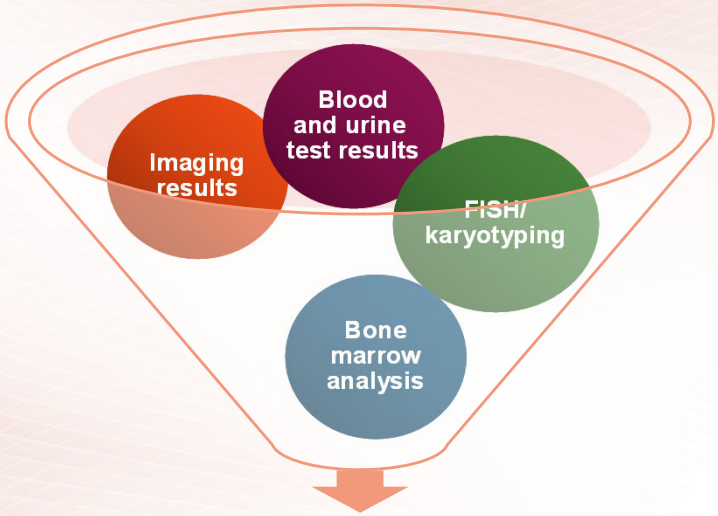
Putting the Results Together



Staging, prognosis, and risk assessment

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Multiple Myeloma Prognosis and Risk

Revised International Staging System (R-ISS)

R-ISS stage	Laboratory measurements
I	• Serum β2M level <3.5 mg/L • Serum albumin level ≥3.5 g/dL • No high-risk CA* • Normal LDH level
II	All other possible combinations
III	• Serum β2M level ≥5.5 mg/L • High-risk CA* or high LDH level

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

Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines

High risk
- High-risk genetic abnormalities
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High plasma cell S phase
- GEP: high-risk signature

Standard risk
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)

- ***Double-hit myeloma***: any two high-risk genetic abnormalities
- ***Triple-hit myeloma***: three or more high-risk genetic abnormalities

Currently cannot identify with great certainty all high-risk patients.

β2M; beta-2 microglobulin; LDH, lactate dehydrogenase

Greipp PR et al. *J Clin Oncol*. 2005;23:3412; Palumbo A et al. *J Clin Oncol*. 2015;33:2863; Mikhael JR et al. *Mayo Clin Proc*. 2013;88:360.

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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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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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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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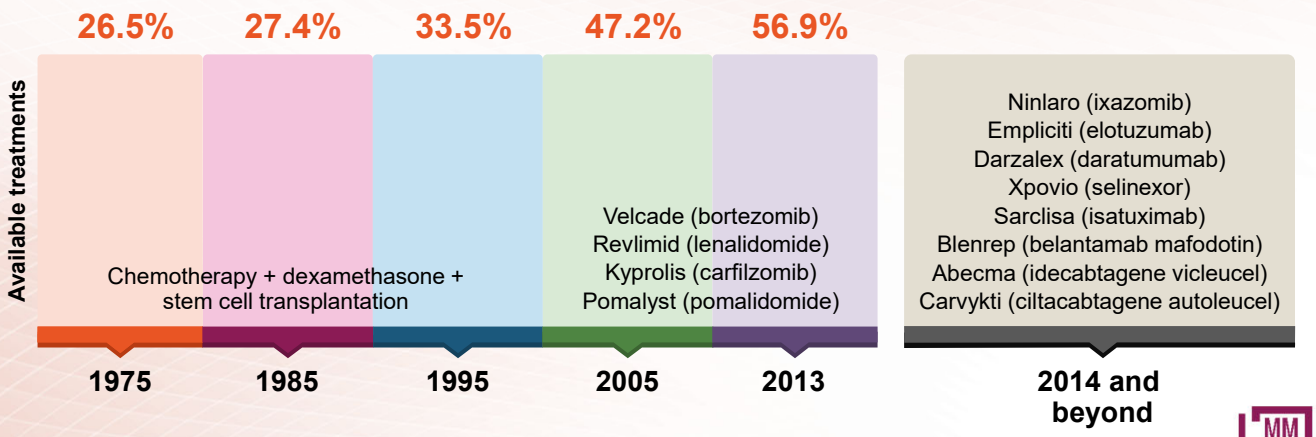
Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

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



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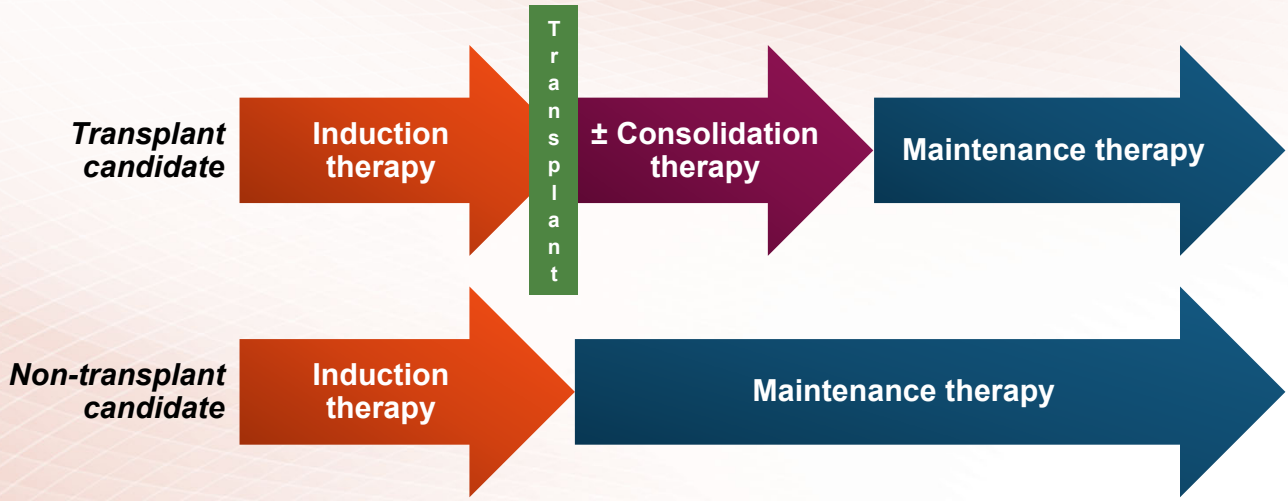
Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma



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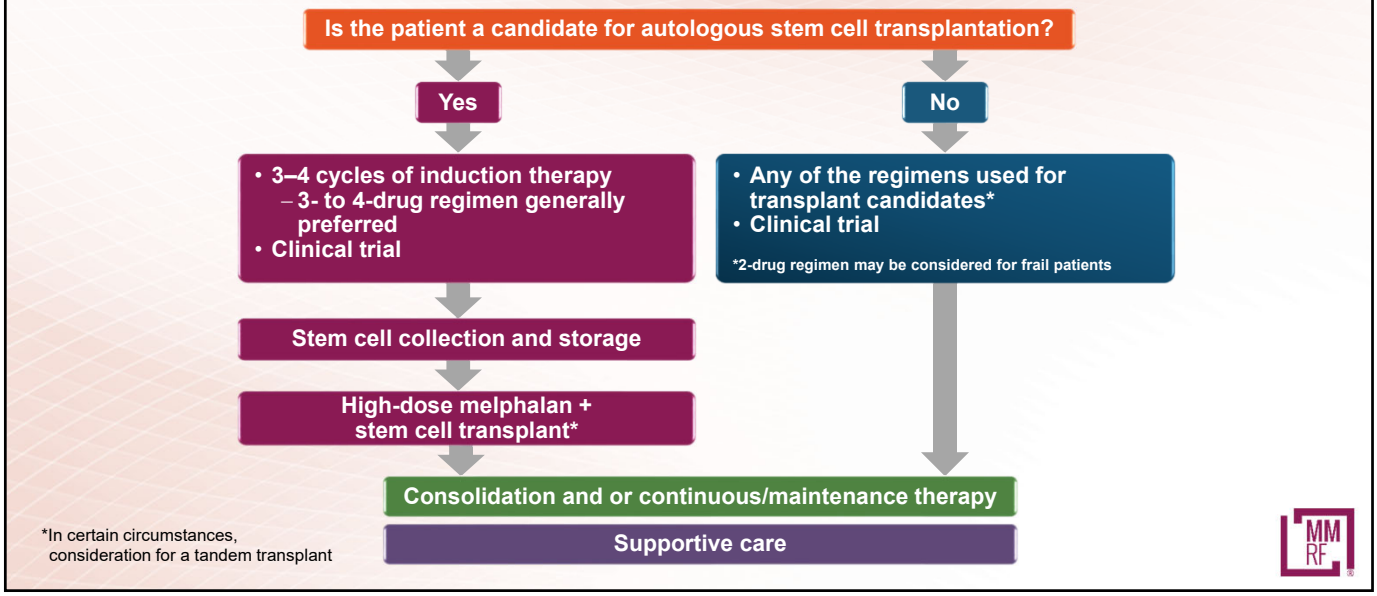
Overview of Treatment Approach for Active Multiple Myeloma



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Induction Therapy Regimens

	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid-Velcade-dex (RVd)* • Kyprolis-Revlimid-dex (KRd)	• Darzalex-Revlimid-Velcade-dex (D-RVd)	• Velcade-Thalomid-dex (VTd)* • Velcade-Cytoxan-dex (VCd) • Velcade-Doxil-dex (VDd) • Kyprolis-Cytoxan-dex (KCd) • Revlimid-Cytoxan-dex (RCd) • Darzalex-Velcade-Thalomid-dex (D-VTd) • Darzalex-Kyprolis-Revlimid-dex (D-KRd) • Darzalex-Cytoxan-Velcade-dex (D-VCd) • Ninlaro-Revlimid-dex (IRd) • Ninlaro-Cytoxan-dex (ICd) • 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 on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
National Comprehensive Cancer Network Guidelines Version 3.2023. Multiple Myeloma.

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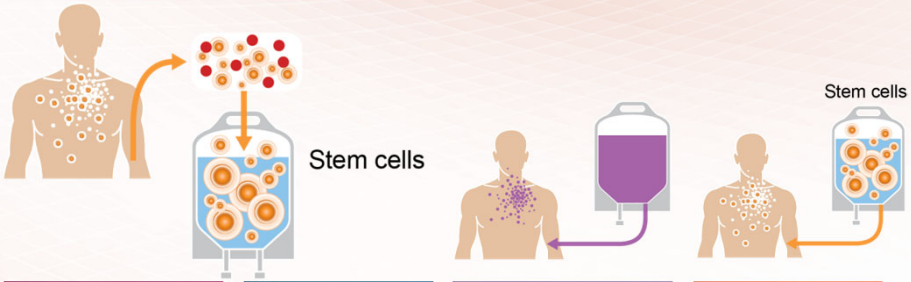
Autologous Stem Cell Transplantation



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 cycles	Stem cell mobilization • Neupogen, Neulasta, Leukine, Cytoxan, Mozobil	-2 to -3 weeks*	Melphalan • Alkeran, Evomela	Day 0	Days +1 to +100†

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

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Continuous or Maintenance Therapy Options

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

*Category 1 recommendation. Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
National Comprehensive Cancer Network Guidelines Version 3.2023. Multiple Myeloma.

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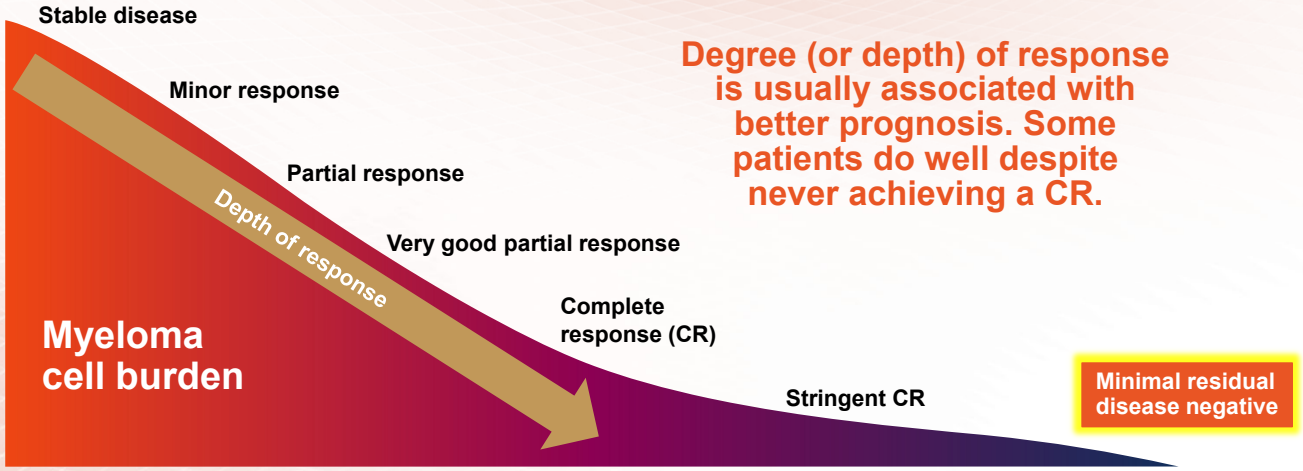
Measuring Response to Therapy



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.

49

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)
- 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.
- The prognosis of multiple myeloma depends on the genetic makeup of myeloma cell chromosomes; R-ISS is used for staging in multiple myeloma.
- Survival rates are improving because of new drugs and new combinations of drugs.
- The treatment paradigm will continue to change with the approval of additional novel agents.
- Knowledge is power: right team, right test, right treatment.

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

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MULTIPLE MYELOMA Research Foundation

Health Care Disparities in Multiple Myeloma

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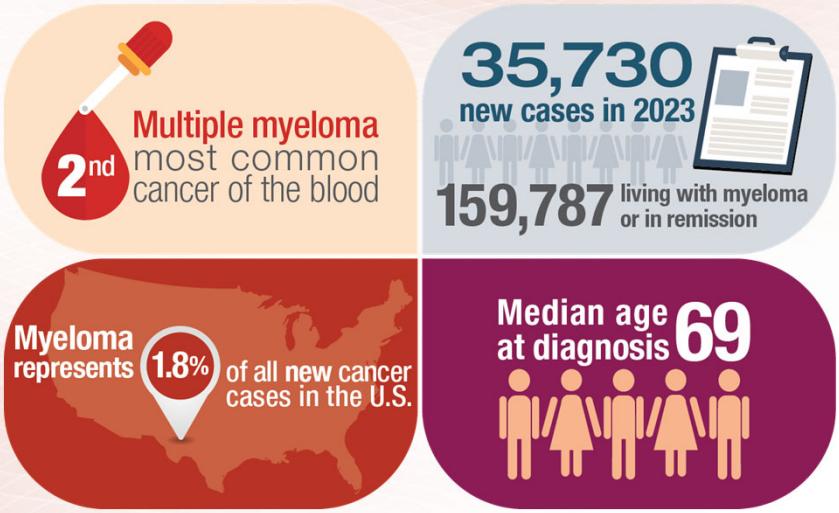
How common is multiple myeloma?



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

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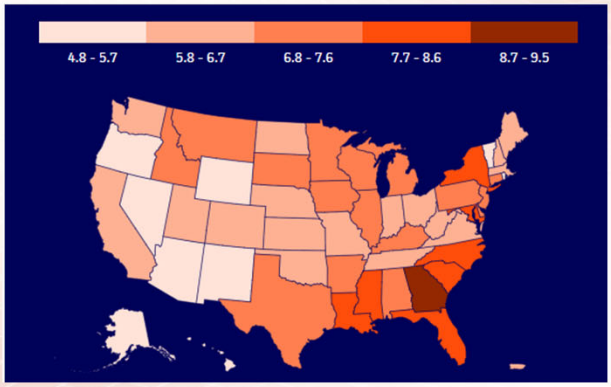
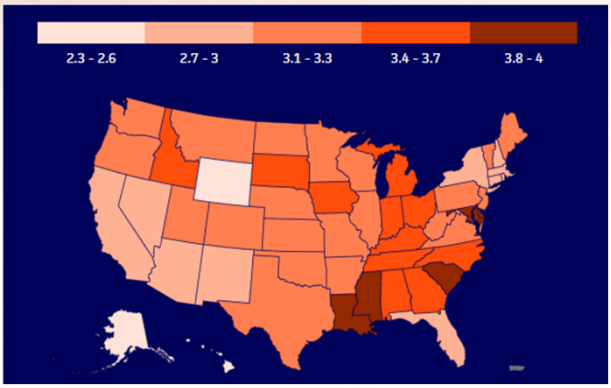
Incidence rates, 2014–2018
Myeloma, by state



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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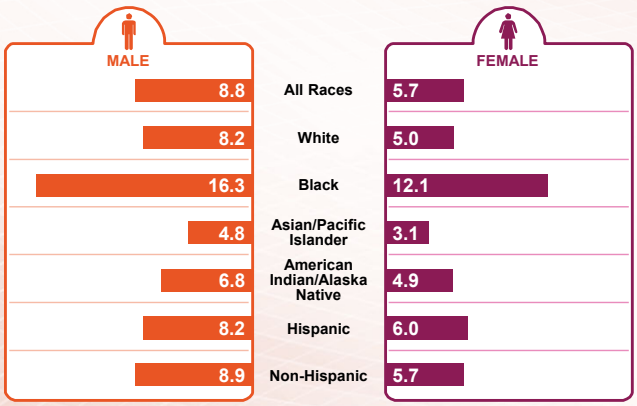
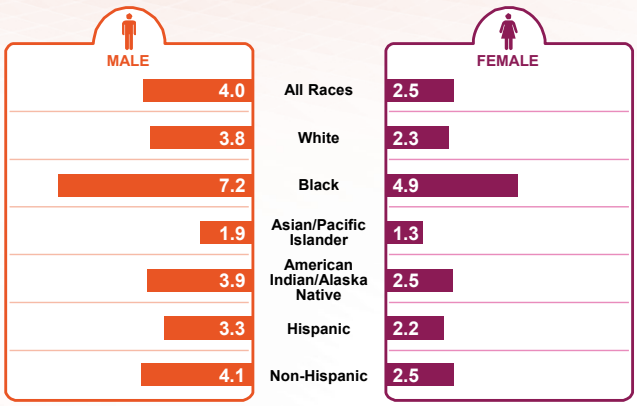
Multiple Myeloma Is Twice as Common in Black Patients

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, seer.cancer.gov/statfacts/html/mulmy.html

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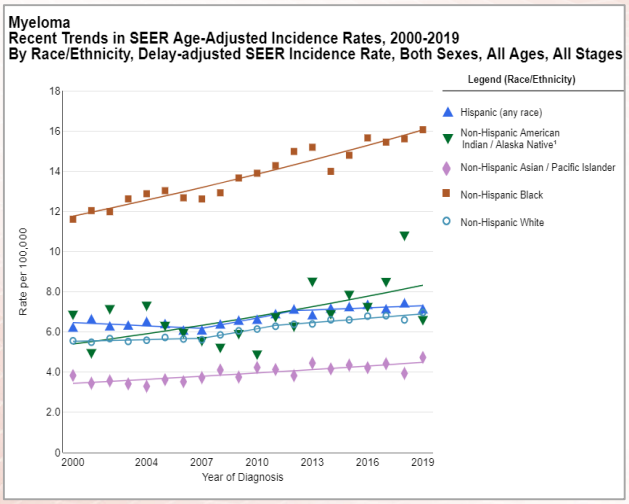
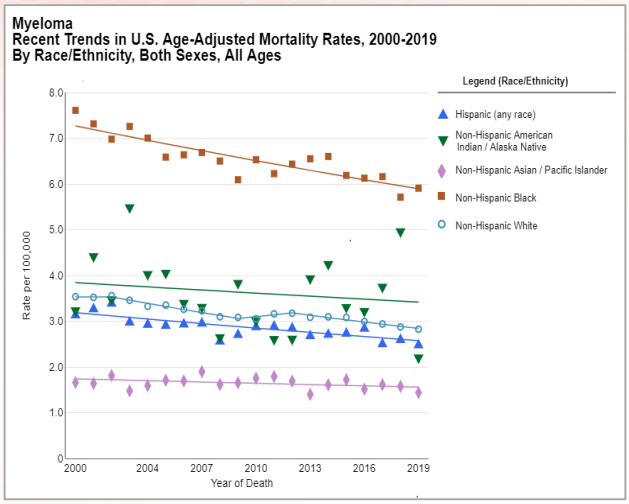
Multiple Myeloma Incidence and Mortality by Race/Ethnicity





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

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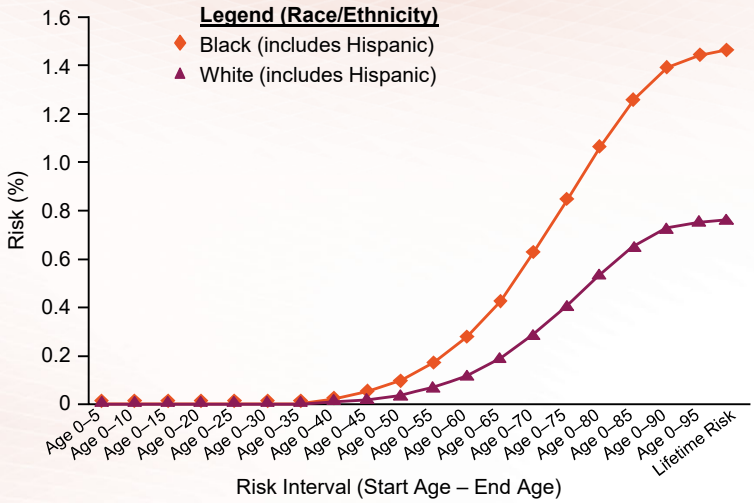
Risk of Myeloma Diagnosis by Age

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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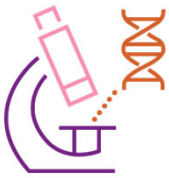
Multiple Myeloma in Black Patients

Demographics

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

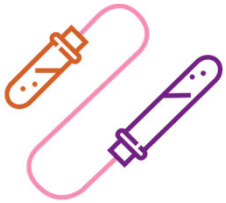
Clinical factors

- ↑ 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. 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 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%	0.004
Stem cell transplantation	**30%**	40%	0.034

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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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Please take a moment to answer two questions about this presentation.

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MULTIPLE MYELOMA Research Foundation

Treating Relapsed/Refractory Multiple Myeloma

Noa Biran, MD
John Theurer Cancer Center
Hackensack University Medical Center
Hackensack, New Jersey

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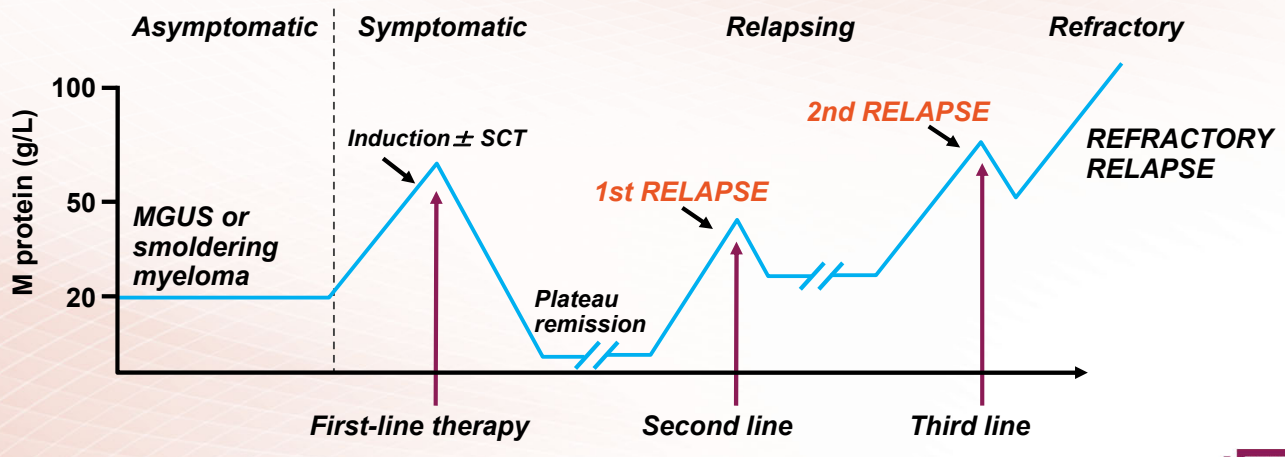
Multiple Myeloma Is a Marathon, Not a Sprint



Adapted from Borrello I. *Leuk Res*. 2012;36 Suppl 1:S3.

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Definitions: What is relapsed/refractory disease and a line of therapy?

- ***Relapsed:*** recurrence (reappearance of disease) after a response to therapy
- ***Refractory:*** progression despite ongoing therapy
- ***Progression:*** change in M protein/light chain values
- ***Line of therapy:*** change in treatment due to either progression of disease or unmanageable side effects
  - **Note:** initial (or induction) therapy + stem cell transplant + consolidation/ maintenance therapy = 1 line of therapy

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Biochemical Relapse or Clinical Relapse

Biochemical

- Patients with asymptomatic rise in blood or urine M protein, free light chains, or plasma cells

→ **Timing of therapy initiation/escalation dependent on many factors**

Clinical

- Based on direct indicators of increasing disease and/or end-organ dysfunction

→ **Requires immediate initiation/escalation of therapy**

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Choosing Therapy for First or Second Relapse

Choices are broadest and guided by

- Disease biology
- Nature of relapse
- Patient preference

Factors to consider

- Prior autologous stem cell transplant
- Prior therapies
- Aggressiveness of relapse
- Comorbidities
- Psychosocial issues
- Access to care

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Options for Relapsed/Refractory Disease Continue to Increase

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

*Not yet FDA-approved for patients with multiple myeloma; †Withdrawn from the US market in 2021; ‡Antibody-drug conjugate, withdrawn from the US market in 2022; §Bispecific antibody

New formulations, new dosing, and new combinations, too!

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Three Drugs Withdrawn From US Market
What happened?

All drugs were granted accelerated approval by the FDA which requires further clinical studies to verify a drug's clinical benefit.

Withdrawn 2021

Farydak (panobinostat)

- The required clinical studies were not completed within the FDA-specified timeframe

Pepaxto (melflufen)

- The phase 3 OCEAN study compared Pepaxto-dex with Pomalyst-dex in patients with relapsed/refractory myeloma
  - Overall survival with Pepaxto-dex was not improved versus Pomalyst-dex which didn't pass the regulatory hurdles to confirm the accelerated approval in the US

Withdrawn 2022*

Blenrep (belantamab mafodotin)

- Results from the confirmatory phase 3 DREAMM-3 study that compared Blenrep with Pomalyst-dex in patients with relapsed/refractory myeloma after at least two prior lines of therapy showed that progression-free survival with Blenrep was not improved versus Pomalyst-dex
- The DREAMM clinical study program is continuing as a path forward for approval with two ongoing phase 3 studies (DREAMM-7 and DREAMM-8) testing Blenrep in combinations in an earlier treatment setting for patients who have tried at least one prior line of therapy
  - Results are anticipated in the first half of 2023

*Marketing of Blenrep continues in other countries where it has been approved.

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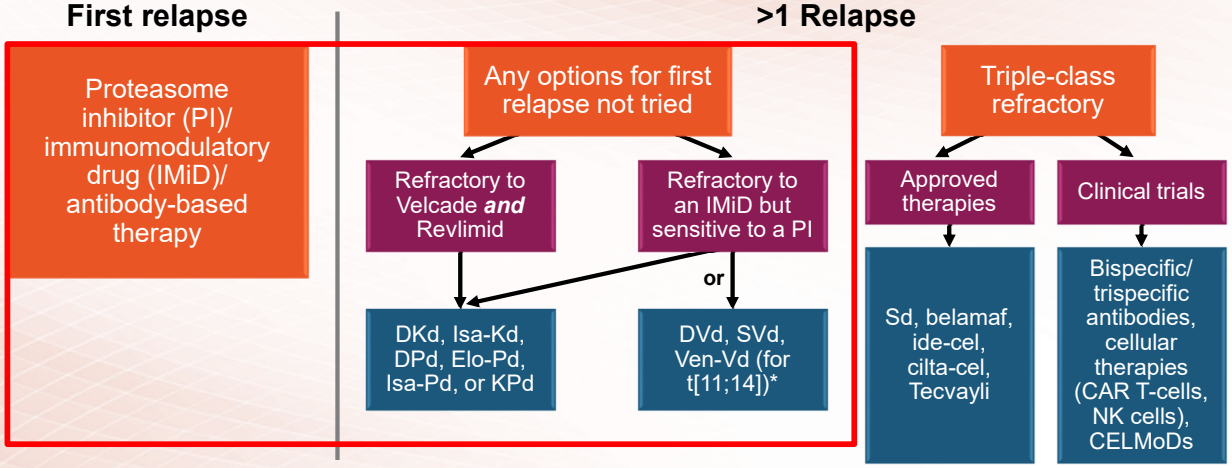
Treatment Approach



D, daratumumab (Darzalex); K, carfilzomib (Kyprolis); d, dexamethasone; Isa, isatuximab (Sarclisa); P, pomalidomide (Pomalyst); Elo, elotuzumab (Empliciti); V, bortezomib (Velcade); S, selinexor (Xpovio); Ven, venetoclax (Venclexta); belamaf, belantamab mafodotin (Blenrep); ide-cel, idecabtagene vicleucel (Abecma); cilta-cel, ciltacabtagene autoleucel (Carvykti);

*Not yet approved for use in myeloma patients.

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Triplet Regimens for Early Relapse

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Currently Available Naked Monoclonal Antibodies for One to Three Prior Lines of Therapy

Drug	Formulation		Approval
Darzalex (daratumumab)		SC once a week for first 8 weeks, then every 2 weeks for 4 months, then monthly	• For **relapsed/refractory** myeloma as a single agent and as a triplet with Revlimid or Velcade or Kyprolis or Pomalyst plus dexamethasone
Empliciti (elotuzumab)		IV once a week for first 8 weeks, then every 2 weeks (or every 4 weeks with pom)	• For **relapsed/refractory** myeloma as a triplet with Revlimid or Pomalyst and dexamethasone
Sarclisa (isatuximab)		IV once a week for first 4 weeks, then every 2 weeks	• For **relapsed/refractory** myeloma as a triplet with Pomalyst or Kyprolis and dexamethasone

IV, intravenous; SC, subcutaneous

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Currently Available Agents for One to Three Prior Lines of Therapy

Drug	Formulation		Approval
Velcade (bortezomib)		• IV infusion • SC injection	• For **relapsed/refractory** myeloma
Kyprolis (carfilzomib)		• IV infusion • Weekly dosing	• For **relapsed/refractory** myeloma as a single agent, as a doublet with dexamethasone, and as a triplet with Revlimid or Darzalex plus dexamethasone
Ninlaro (ixazomib)		Once-weekly pill	• For **relapsed/refractory** myeloma as a triplet with Revlimid and dexamethasone
Revlimid (lenalidomide)*		Once-daily pill	• For **relapsed/refractory** myeloma in combination with dexamethasone
Pomalyst (pomalidomide)*		Once-daily pill	• For **relapsed/refractory** myeloma in combination with dexamethasone
XPOVIO (selinexor)		Once-weekly pill	• For **relapsed/refractory** myeloma as a triplet with Velcade and dexamethasone

*Black box warnings: embryo-fetal toxicity; hematologic toxicity (Revlimid); venous and arterial thromboembolism

IV, intravenous; SC, subcutaneous

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Monoclonal Antibody–Based Regimens for Early Relapse: Darzalex

	POLLUX	CASTOR	CANDOR	APOLLO
Regimens compared	• Darzalex-Revlimid-dex (DRd) vs Rd	• Darzalex-Velcade-dex (DVd) vs Vd	• Darzalex-Kyprolis-dex (DKd) vs Kd	• Darzalex-Pomalyst-dex (DPd) vs Pd
Median progression-free survival favored	• DRd: 45 vs 18 months	• DVd: 17 vs 7 months	• DKd: 29 vs 15 months	• DPd: 12 vs 7 months
Clinical consider-ations	• Consider for relapses from Revlimid or Velcade maintenance • DRd associated with more upper respiratory infections, low blood white blood cell counts, and diarrhea	• Consider for patients who are Revlimid-refractory without significant neuropathy • DVd associated with more low blood cell counts	• Consider for younger, fit patients who are double-refractory to Revlimid and Velcade • DKd associated with more respiratory infections • Sever side effects (possibly fatal) in intermediate fit patients 65 and older	• Consider in patients who are double-refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro) • Severe low white blood cell counts

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Monoclonal Antibody–Based Regimens for Early Relapse: Sarclisa and Empliciti

	ELOQUENT-2	ELOQUENT-3	ICARIA-MM	IKEMA
Regimens compared	• Empliciti-Revlimid-dex vs Rd	• Empliciti-Pomalyst-dex vs Pd	• Sarclisa-Pomalyst-dex vs Pd	• Sarclisa-Kyprolis-dex vs Kd
Median progression-free survival favored	• Empliciti-Rd: 19 vs 15 months	• Empliciti-Pd: 10 vs 5 mos	• Sarclisa-Pd: 12 vs 7 mos	• Sarclisa-Kd: 42 vs 21 mos
Clinical consider-ations	• Consider for non-Revlimid refractory, frailer patients • Overall survival benefit with Empliciti-Rd • Empliciti-Rd associated with more infections	• Consider for patients refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro)	• Consider for patients refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro) • Sarclisa-Pd associated with severe low white blood cell counts, more dose reductions, upper respiratory infections, and diarrhea	• Consider for patients refractory to Revlimid and Velcade • Sarclisa-Kd associated with higher MRD negativity rates • Sarclisa-Kd associated with severe respiratory infections

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Proteasome Inhibitor– and Immunomodulatory Drug–Based Regimens for Early Relapse

	OPTIMISMM	ASPIRE	TOURMALINE-MM1	BOSTON
Regimens compared	• Velcade-Pomalyst-dex (VPd) vs Vd	• Kyprolis-Revlimid-dex (KRd) vs Rd	• Ninlaro-Rd (IRd) vs Rd	• XPOVIO-Velcade-dex (XPO-Vd) vs Vd
Median progression-free survival favored	• VPd: 11 vs 7 months	• KRd: 26 vs 17 months	• IRd: 21 vs 15 months	• XPO-Vd: 14 vs 9 months
Clinical considerations	• Consider for relapse on Revlimid • VPd associated with more low blood counts, infections, and neuropathy than Pd	• KRd associated with more upper respiratory infections and high blood pressure than Rd	• IRd an oral regimen • Gastrointestinal toxicities and rashes • Lower incidence of peripheral neuropathy	• XPO-Vd associated with low platelet counts and fatigue with triplet, but less neuropathy than the Vd

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Important Considerations for Use of Monoclonal Antibodies

Darzalex

- **Infusion reactions**
  - Less with SC use
- Risk of **shingles**
  - Use appropriate vaccination
- Increased risk of **hypogamma-globulinemia** and upper respiratory infections
  - Bactrim prophylaxis
  - IVIG support

Empliciti

- **Infusion reactions**
- Risk of **shingles**
  - Use appropriate vaccination

Sarclisa

- **Infusion reactions**
- Risk of **shingles**
  - Use appropriate vaccination

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Important Considerations for Use of Proteasome Inhibitors

Velcade

- Risk of **peripheral neuropathy (PN;** numbness, tingling, burning sensations and/or pain due to nerve damage)
  - Avoid in patients with severe existing PN
  - Reduced with subcutaneous once-weekly dosing
- High risk of **shingles**
  - Use appropriate vaccination
- No dose adjustment for kidney issues; adjust for liver issues

Kyprolis

- Less **PN** than Velcade
- High risk of **shingles**
  - Use appropriate vaccination
- Monitor for **heart, lung, and kidney side effects**
  - Use with caution in older patients with cardiovascular risk factors
- High blood pressure
- No dose adjustment for kidney issues; adjust for liver issues

Ninlaro

- Less **PN** than Velcade
- High risk of **shingles**
  - Use appropriate vaccination
- Monitor for rashes and **gastrointestinal (GI)** side effects
  - GI effects occur early
- Needs to be taken at least 1 hour before or 2 hours after a meal

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Important Considerations for Use of Immunomodulatory Drugs

Revlimid*

- **Rash**
  - Consider antihistamines
- **Diarrhea**
  - Consider bile acid sequestrants
- Risk of **blood clots**
- Risk of second primary **malignancies**
- Dose adjustment based on kidney function

Pomalyst*

- **Low blood counts**
- Less **rash** than Revlimid
- Risk of second primary **malignancies**
- Risk of **blood clots**

*Black box warning

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Important Considerations for Use of XPOVIO

Gastrointestinal

Begin prophylactic anti-nausea medications.
Consult with your doctor if nausea, vomiting, or diarrhea occur or persist.

Low sodium (hyponatremia)

Maintain fluid intake.
Salt tabs

Fatigue

Stay hydrated and active.

Low blood counts (cytopenias)

Report signs of bleeding right away.
Report signs of fatigue or shortness of breath.

Chari A et al. *Clin Lymphoma Myeloma Leuk*. 2021;21:e975.

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Update From the 2022 American Society of Hematology (ASH) Meeting

Sarclisa After Early or Late Relapse

IKEMA Study

Patients with relapsed/refractory myeloma who received 1–3 prior therapies, no prior therapy with Kyprolis and not refractory to prior anti-CD38 antibody

179 patients — **R** — **123 patients**

Sarclisa-Kd | **Kd**

Data evaluated according to patients who experienced an early* versus late† relapse.

	Early Relapse		Late Relapse	
	Sarclisa-Kd	Kd	Sarclisa-Kd	Kd
Median progression-free survival (months)	24.7	17.2	42.7	21.9
Overall response rate (%)	82	82.6	90.4	86.1
≥VGPR rate (%)	67.2	52.2	76	58.3
MRD negativity rate (%)	24.6	15.2	37.5	16.7
MRD-negative CR rate (%)	18	10.9	30.8	13.9

Regardless of early or late relapse, RRMM patients benefit from the use of isa-Kd with respect to depth of response and prolonged PFS.

*<12 months from initiation of most recent line of therapy (for patients who had ≥2 lines of therapy); <18 months (for patients who had 1 prior line of therapy) and <12 months from ASCT
†≥12 months from initiation of most recent line of therapy (for patients who had ≥2 lines of therapy; ≥18 months for patients who had 1 prior line of therapy)

Facon T et al. *Blood*. 2022;140. Abstract 753.

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Treatment Approach

First relapse

Proteasome inhibitor/ immunomodulatory drug/antibody-based therapy

>1 Relapse

Any options for first relapse not tried

- Refractory to Velcade ***and*** Revlimid → DKd, Isa-Kd, DPd, Elo-Pd, Isa-Pd, or KPd
- Refractory to an IMiD, but sensitive to a PI → DVd, SVd, Ven-Vd (for t[11;14])*

or

Triple-class refractory

- Approved therapies → Sd, belamaf, ide-cel, cilta-cel, Tecvayli
- Clinical trials → Bispecific/ trispecific antibodies, CAR T cells, CELMoDs

D, daratumumab (Darzalex); K, carfilzomib (Kyprolis); d, dexamethasone; Isa, isatuximab (Sarclisa); P, pomalidomide (Pomalyst); Elo, elotuzumab (Empliciti); V, bortezomib (Velcade); S, selinexor (Xpovio); Ven, venetoclax (Venclexta); belamaf, belantamab mafodotin (Blenrep); ide-cel, idecabtagene vicleucel (Abecma); cilta-cel, ciltacabtagene autoleucel (Carvykti)

*Not yet approved for use in myeloma patients.

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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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Currently Available Drugs for Triple-Class Refractory Myeloma

Class	Drug	Formulation	Approval
Nuclear export inhibitor	XPOVIO (selinexor)	Twice-weekly pill	• For **relapsed/refractory** myeloma in combination with dexamethasone (after at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 mAb
Chimeric antigen receptor (CAR) T cell	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
CAR T cell	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
Bispecific antibody	Tecvayli (teclistamab)‡	Step-up dosing§ the first week then once weekly thereafter by subcutaneous injection	• For **relapsed/ refractory** myeloma (after 4 or more prior lines of therapy, including an IMiD, a PI, 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; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
‡Black box warning: cytokine release syndrome; neurologic toxicities
§Patients are hospitalized for 48 hours after administration of all step-up doses.

Abecma, Carvykti, and Tecvayli are available only through a restricted distribution program.

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XPOVIO + Dexamethasone in Relapsed/Refractory Myeloma

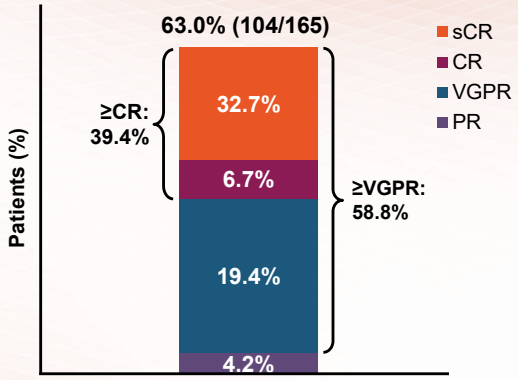
	No. patients with ≥PR (%)[1]
Total	32 (26)
Previous therapies to which the disease was refractory, n (%)	
Velcade, Kyprolis, Revlimid, Pomalyst, and Darzalex	21 (25)
Kyprolis, Revlimid, Pomalyst, and Darzalex	26 (26)
Velcade, Kyprolis, Pomalyst, and Darzalex	25 (27)
Kyprolis, Pomalyst, and Darzalex	31 (26)

Additional analyses showed clinical benefit with XPOVIO regardless of patient age and kidney function.[2,3]

1. STORM Trial. Chari A et al. *N Engl J Med*. 2019;381:727. **2.** Gavriatopoulou M et al. Presented at the 17th International Myeloma Workshop; September 12-15, 2019. Abstract FP-110. **3.** Vogl DT et al. Presented at the 17th International Myeloma Workshop; September 12-15, 2019. Abstract FP-111.

85

Now Approved: Tecvayli, the First Bispecific Antibody!



Median duration of response 18.4 months

Moreau P et al. *N Engl J Med*. 2022;387:495.

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Emerging Treatment Options

- Cereblon E3 ligase modulators (CELMoDs)
- Immunocytokines
- More bispecific antibodies (BCMA, GCPR5D, Fc5H targets)
- More chimeric antigen receptor (CAR) T-cell therapies

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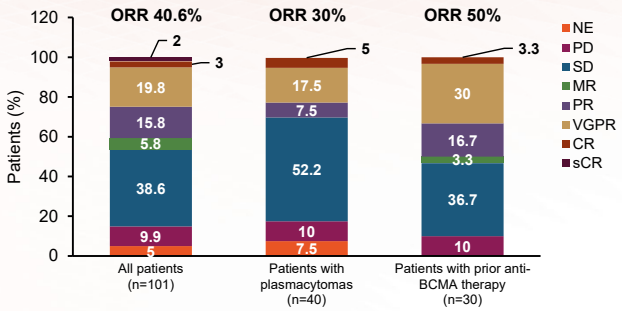
Mezigdomide: A Cereblon E3 Ligase Modulator (CELMoD)

CELMoDs are related to the immunomodulatory drugs (IMiDs) but are more potent and may overcome resistance to IMiDs

A phase 1/2 study of mezigdomide combined with dex in relapsed/refractory patients

101 patients—who had received at least 6 prior lines of therapy and 100% were triple-class refractory (one third were previously exposed to anti-BCMA therapy—received treatment with mezigdomide-dex

Phase 3 trials of iberdomide and mezigdomide are under way.



Most Hematologic Frequent Adverse Events, %	Grade 3	Grade 4
Neutropenia	21.8	53.5
Anemia	34.7	1.0
Thrombocytopenia	13.9	13.9
Febrile neutropenia	12.9	2.0

Most Frequent Non-Hematologic Adverse Events, %	Grade 3	Grade 4
Infections	28.7	5.9
Pneumonia	12.9	3.0
COVID-19	6.9	0

Richardson PG et al. *Blood*. 2022;140. Abstract 568.

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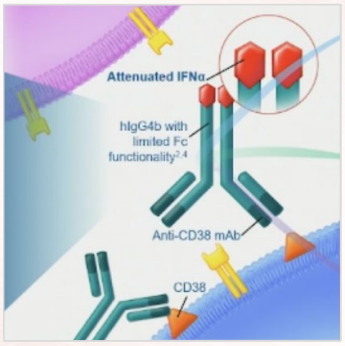
Modakafusp Alfa: An Immunocytokine

Modakafusp alfa is an antibody that is fused to the cytokine interferon-alpha and that can bind to CD38 on myeloma cells



100 patients who had a median of 7 prior lines of therapy were treated with different doses of modakafusp (19% had prior CAR T-cell therapy and 14% prior T-cell engagers).

Overall response rate was 43% in patients receiving 1.5 mg/kg dose every 4 weeks (n=30); 27% of anti-BCMA exposed patients responded.

Immunocytokines are engineered to deliver cytokines (a protein produced by immune cells) that can prevent myeloma cells from dividing and help boost myeloma-fighting immune cells

Vogl DT et al. *Blood*. 2022;140. Abstract 565.

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Summary

- **We now have many different options for relapsed myeloma depending on patient and myeloma factors at relapse.**
- **Therapy choices will depend on teamwork between physician, patient, and caregivers and are based on many decision points.**
- **Combinations of proteasome inhibitors with either immunomodulatory drugs or selinexor improve progression-free survival.**
- **We have three different monoclonal antibodies that improve progression-free survival when added to other standard therapies without significantly increasing side effects.**
- **In general, three-drug combinations are going to work better than two drugs.**
- **Many other exciting immunotherapy options are in trials and look very promising.**

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Please take a moment to answer two questions about this presentation.

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Town Hall Questions & Answers

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MULTIPLE MYELOMA Research Foundation

CAR T-Cell Therapy and Bispecific Antibodies

David H. Vesole, MD, PhD
MedStar Georgetown University Hospital
Georgetown University School of Medicine
Washington, District of Columbia
John Theurer Cancer Center, Hackensack Meridian School of Medicine
Hackensack, New Jersey

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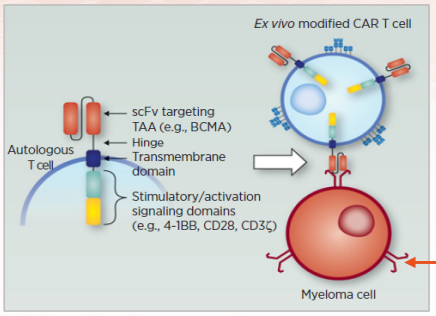
CAR T-Cell Therapy

- 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



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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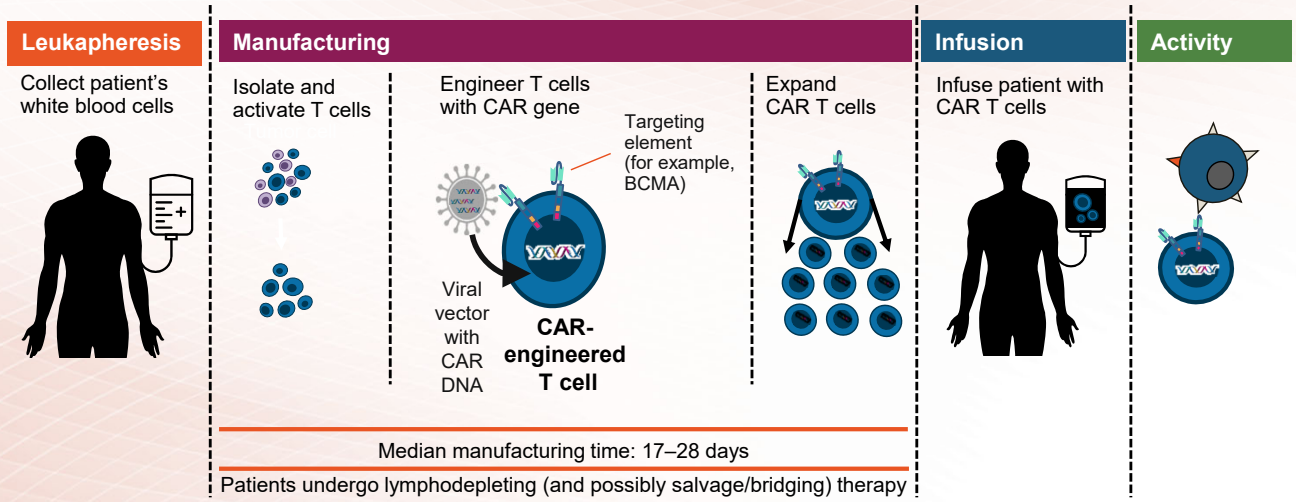
Autologous CAR T-Cell Therapy: Underlying Principles



Majors B et al. Presented at EHA; June 16, 2018. Abstract PS1156. Lim WA, June CH. *Cell.* 2017;168:724. Sadelain M et al. *Nat Rev Cancer.* 2003;3:35. Brentjens RJ et al. *Nat Med.* 2003;9:279. Park JH et al. Presented at ASH 2015; December 7, 2015. Abstract 682.

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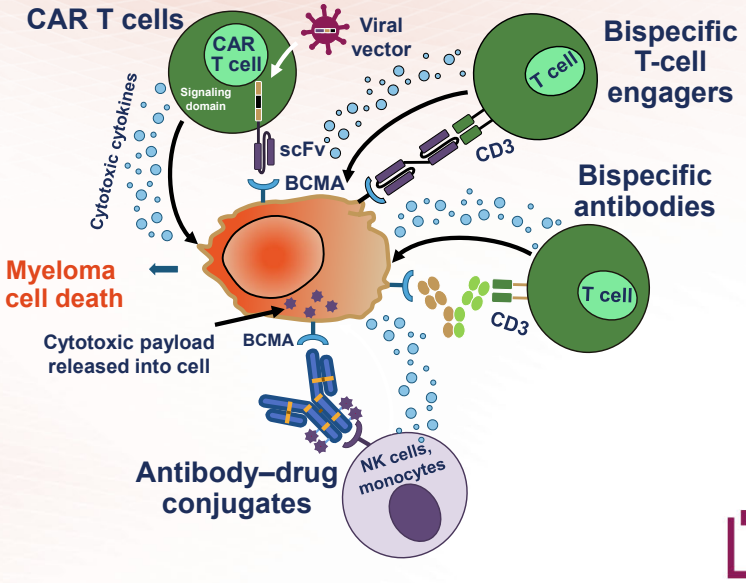
BCMA in Multiple Myeloma

- Expressed on late memory B cells committed to plasma cell (PC) differentiation and PCs
- BCMA plays a role in survival of long-lived PCs
- γ-secretase cleaves BCMA from the cell surface, yielding soluble BCMA



Cho S et al. *Front Immunol.* 2018;10:1821.

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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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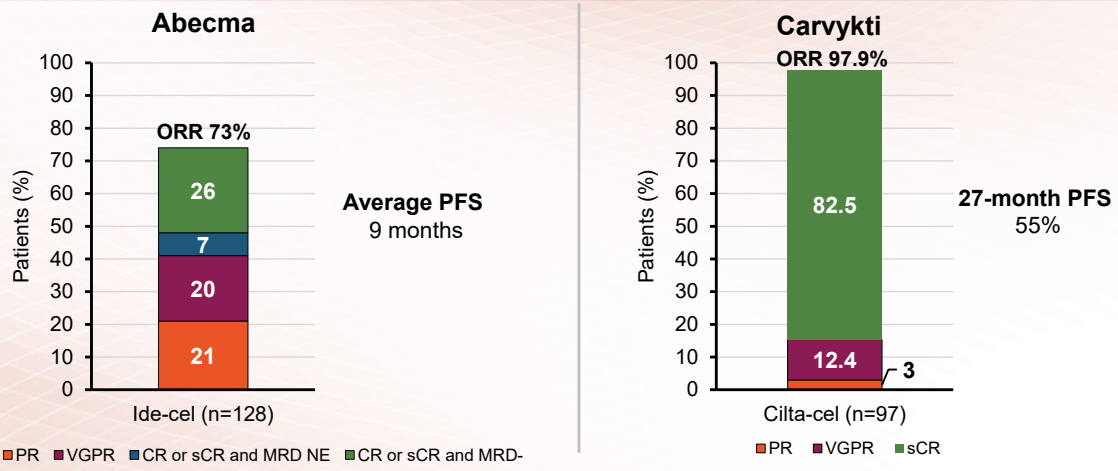
Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma



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; Martin T et al. *J Clin Oncol*. June 4, 2022 [Epub ahead of print].

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Future Directions for Abecma and Carvykti in Myeloma

Studies in Earlier Stage of Disease

Study	Agent	Phase	Patient Populations/ Study Design
KarMMa-2	Abecma	2	Multiple cohorts, including early relapse
CARTITUDE-2	Carvykti	2	Multiple cohorts, including early relapse
KarMMa-3	Abecma	3	Abecma vs SoC in patients with 2-4 prior lines
CARTITUDE-4	Carvykti	3	Carvykti vs SoC in patients with 1-3 prior lines*

*Carvykti met PFS end point in relapsed/lenalidomide-refractory multiple myeloma: January 27, 2023.

Studies in Frontline Setting

Study	Agent	Phase	Patient Populations/ Study Design
KarMMa-4	Abecma	1	High-risk, newly diagnosed MM
CARTITUDE-5	Carvykti	3	VRd → Carvykti vs VRd → Rd in newly diagnosed, transplant-ineligible patients
CARTITUDE-6	Carvykti	3	Trial of DVRd → Carvykti vs DVRd → ASCT in newly diagnosed MM

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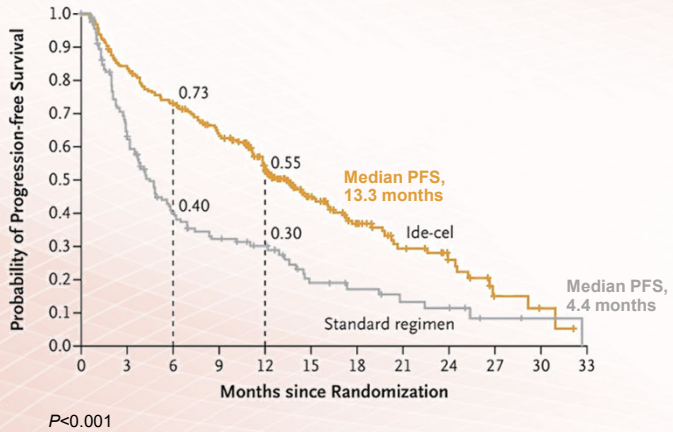
Abecma or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Progression-Free Survival



P<0.001

Treatment Response

	Abecma (n=254)	Standard regimen (n=132)
Overall response (%)*	71	42
Complete response (%)	39	5
Best overall response (%)		
Stringent complete response	35	5
Complete response	3	1
Very good partial response	22	10
Partial response	11	27
Minimal response	2	7
Stable disease	12	36
Progressive disease	9	8
Median duration of response (mos)	14.8	9.7

**P*<0.001

Rodriguez-Otero P et al. *N Engl J Med.* 2023 Feb 10. Online ahead of print.

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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; ‖Only when concurrent with CRS

ICANS, immune effector cell-associated neurotoxicity syndrome

Xiao X et al. *J Exp Clin Cancer Res.* 2021;40(1):367. 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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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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BCMA CAR T-Cell Therapies: Summary

	CARTITUDE-1[1] Carvykti Phase 1	KarMMa[2] Abecma Phase 2	CRB-402[3] bb21217 Phase 1	LUMMICAR-2[4] CT053 Phase 1b	PRIME[5] BCMA-101 Phase 1/2	GC012F[6] Dual CAR T-Cell BCMA + CD19
Patients, n	97	128	72	20	98	19
Median prior regimens, n	6	6	6	5	7	5
Triple refractory, %	87.6	84	64	85	--	--
CAR T-cell therapy dose	0.75×10^6 ($0.5–1.0 \times 10^6$)	450×10^6 ($150–450 \times 10^6$)	150, 300, 450×10^6	1.5–1.8/ $2.5\text{-}3.0 \times 10^8$	$0.75–15 \times 10^6$	$1.0–3.0 \times 10^5$
ORR, %	97.9	73	69/81*	94	57.1§	94.7
CR/sCR, %	82.5	33	36/41*	25	21.4§	84.2
CRS (all grades), %	94.8	84	75	77/83‡	28	95
CRS (grade ≥3), %	5.4	4	4†	0/0‡	0	11
Neurotoxicity (all grades), %	20.6	18	15	15/17‡	7	0
Neurotoxicity (grade ≥3), %	10.3	4	4	8/0‡	2	0

*After manufacturing change. †Two grade 5 events: 1 on Day 15 with grade 3 NT and 1 on Day 6 with afib and cardiac arrest. ‡Data for each dosing cohort.
§ORR for patients receiving CAR T-cells manufactured using nanoplasmid technology (n=28).

1. Martin. ASH 2021. Abstract 549. **2.** Anderson. ASCO 2021. Abstract 8016. **3.** Raje. ASH 2021. Abstract 548.
4. Kumar. ASH 2020. Abstract 133. **5.** Costello. ASH 2021. Abstract 3858. **6.** Jiang. ASCO 2021. Abstract 8014.

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GPRC5D-Targeted CAR T Cells for Myeloma

Clinical Responses in All Patients With or Without Previous BCMA-Directed Therapies

Response	All Patients		Previous BCMA Therapies		No Previous BCMA Therapies	
	All Dose Levels (n=17)	25–150 × 10^6 CAR T Cells (n=12)	All Dose Levels (n=10)	25–150 × 10^6 CAR T Cells (n=6)	All Dose Levels (n=7)	25–150 × 10^6 CAR T Cells (n=6)
Partial response or better (%)	71	58	70	50	71	67
Very good partial response or better (%)	59	42	60	33	57	50
Complete response or better (%)	35	25	40	33	29	17
Negativity for MRD in bone marrow* (%)	47	50	30	33	71	67

*By flow cytometry ($\times 10^5$)

Mailankody S et al. *N Engl J Med.* 2022.387:1196.

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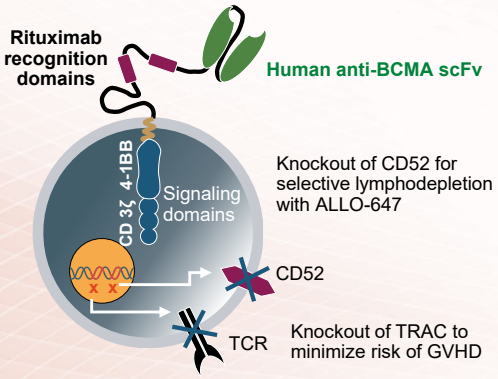
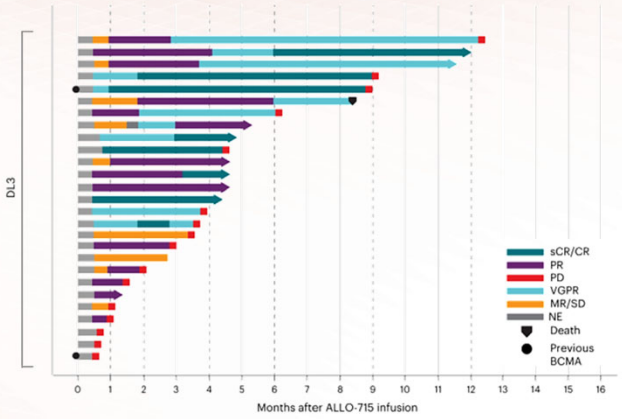
ALLO-715, An Allogeneic Anti-BCMA CAR T-Cell Product

- Gene editing specifically designed to:
  - Reduce risk of graft-vs-host disease
  - Allow the use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells while simultaneously protecting donor cells



Phase 1 UNIVERSAL trial interim results



Mailankody S et al. Presented at ASH 2021. Abstract 651. Mailankody S et al. *Nat Med*. 2023;29:422.

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What's next for CAR T-cell therapy?

	BMS-986354[1]	FasT CAR-T GC012F[2]	BMS-986393[3]
Features	• Targets BCMA with a shortened manufacturing time through the NEXT-T process	• Targets BCMA *and* CD19 • Manufacturing process that takes as little as 24 hours	• Targets GPRC5D
Trial Details	• Phase 1 trial of 55 patients with RRMM with a median of 5 prior lines of therapy	• Phase 1 trial of 13 newly diagnosed high-risk MM patients ineligible for stem cell transplant	• Phase 1 trial of 17 heavily pretreated patients with RRMM, including those who relapsed from BCMA CAR-T therapy
Clinical Results	• CRS occurred in 80% of patients with only 1 patient experiencing ≥G3. • Neurotoxicity occurred in 10.9% of patients (one grade 4). • Overall response rate was 98.1% with 57.4% achieving ≥VGPR (29.6% ≥CR).	• 100% of patients achieved ≥VGPR (69% sCR) • All patients achieved MRD negativity (by EuroFlow). • CRS observed in 23% of patients (all low grade).	• Neutropenia and thrombocytopenia most frequent grade 3/4 adverse events • Additional adverse events include skin- and nail-related; dysgeusia/dysphagia; CRS; ICANS • 86% evaluable patients responded including 7 of 11 patients treated with prior BMCA-targeted treatment

1. Costa LJM et al. *Blood*. 2022;140. Abstract 566. **2.** Du J et al. *Blood*. 2022;140. Abstract 366. **3.** Bal S et al. *Blood*. 2022;140. Abstract 364.

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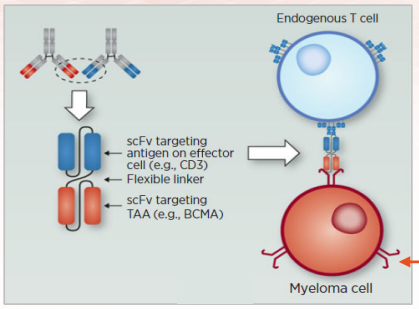
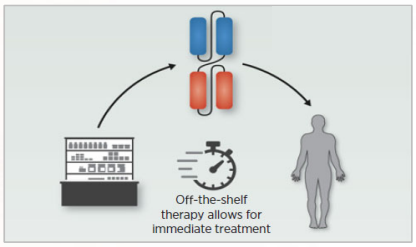
Bispecific Antibodies

- Bispecific antibodies are also referred to as *dual specific antibodies, bifunctional antibodies,* or *T-cell engaging antibodies*
- Bispecific antibodies can target two 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)
- Linvoseltamab
- Alnuctamab
- Cevostamab
- Talquetamab

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

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Bispecific Antibody Agents

Bispecific Antibody	Target (on MM cell × T cell)
Tecvayli (teclistamab)	BCMA × CD3
Elranatamab	BCMA × CD3
Linvoseltamab	BCMA × CD3
Alnuctamab	BCMA × CD3
ABBV-383	BCMA × CD3
Talquetamab	GPRC5D × CD3
Forimtamig (RG6234)	GPRC5D × CD3
Cevostamab	FcRH5 × CD3

GPRC5D, G protein-coupled receptor family C group 5 member D

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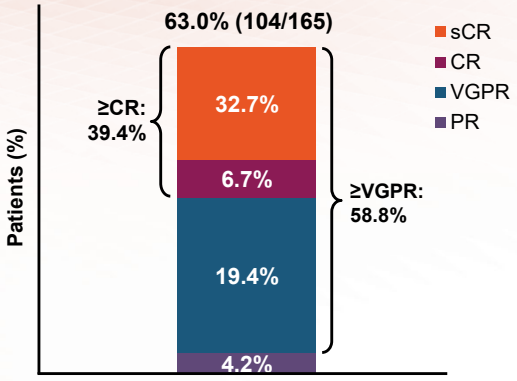
Now Approved: Tecvayli, the First Bispecific Antibody

Drug	Formulation	Approval
Tecvayli (teclistamab)*	Step-up dosing† the first week then once weekly thereafter by subcutaneous injection	• For **relapsed/ refractory** myeloma (after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb)

IMiD, immunomodulatory agent; PI, proteasome inhibitor; mAb, monoclonal antibody
*Black box warning: cytokine release syndrome; neurologic toxicities
†Patients are hospitalized for 48 hours after administration of all step-up doses.
Tecvayli is available only through a restricted distribution program.

	All patients (n=165)
MRD negative (10-5), %	
All treated	26.7
MRD evaluable	81.5
MRD negativity with ≥CR (%)	46.2

	All patients (n=165)
Median time to first response (mos)	1.2
Median time to best response (mos)	3.8



Median duration of response 18.4 months

Moreau P et al. *N Engl J Med*. 2022;387:495. Nooka A et al. ASCO 2022. Abstract 8007.

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Tecvayli Side Effects

Side Effects

- Cytokine release syndrome
- Injection-related reactions
- Injection-site reaction
- Infections
- Neutropenia
- Anemia
- Thrombocytopenia
- Neurotoxicity

Side Effect Management

- Available only through a Risk Evaluation and Mitigation Strategies (REMS) due to the risk of cytokine release syndrome
- Patients will receive step-up dosing and will be monitored in an inpatient setting
- Cytokine release syndrome is managed in the same fashion as CAR T
- Injection reactions are managed with oral antihistamines and topical steroids
- Infection prevention!
- COVID precautions

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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	Tecvayli
Efficacy	++++	+++
How given	One-and-done	IV or SC, weekly to every 3 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
Advantages	• Personalized • Targeted immunocytotoxicity • Single infusion (“one and done”) • Potentially persistent	• Off the shelf • Targeted immunocytotoxicity • No lymphodepletion • Minimal steroids
Disadvantages	• FACT-accredited center required (hospitalization likely required) • CRS and neurotoxicity; requires ICU and neurology services • Dependent on T-cell health (manufacturing failures) • Requires significant social support; caregiver required • $$$$	• Initial hospitalization required • CRS and neurotoxicity possible • Dependent on T-cell health (T-cell exhaustion) • Requires continuous administration • $$$

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Updates from the 2022 American Society of Hematology Meeting

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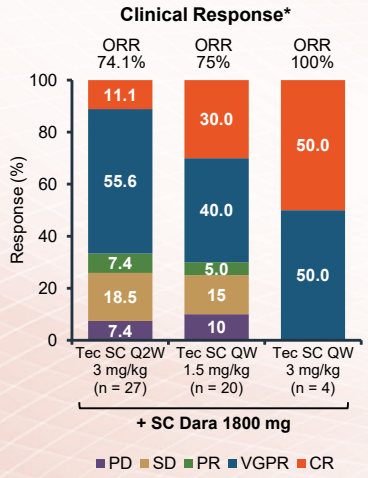
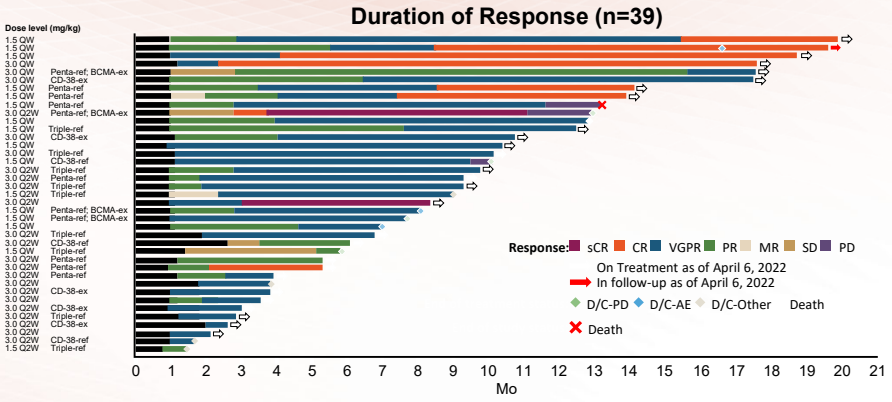
TRIMM-2: Response With Teclistamab + Daratumumab in Relapsed/Refractory MM





- Responses were durable and deepened over time
- At median follow-up of 8.6 mo (range: 0.3-19.6), 66.7% of responders were alive and continuing on treatment

*Response evaluable patients.

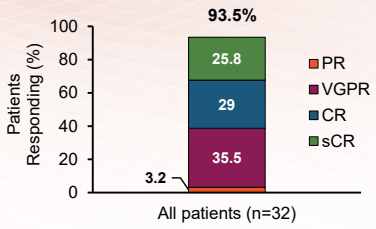
Rodriguez-Otero. EHA 2022. Abstract S188.

113

Tecvayli in Combination With Darzalex and Revlimid

Phase 1b study (MajesTEC-2) in RRMM with 1–3 prior lines of therapy (including an IMiD and a PI)

32 patients—who had received at least 2 prior lines of therapy—received treatment with the triplet with Tecvayli at 2 different doses (0.72 mg/kg and 1.5 mg/kg) subcutaneously



Most frequent non-hematologic adverse events, %	Any grade	Grade 3/4
CRS	81.3	0
Fatigue	46.9	6.3
Infections (≥1)	90.6	37.5
COVID-19	37.5	12.5
Upper respiratory	31.3	0
Pneumonia	25	15.6
COVID pneumonia	12.5	3.1
Sepsis	9.4	9.4
Pneumonia pseudomonal	6.3	6.3
CMV	6.3	6.3

IMiD, immunomodulatory drug; PI, proteasome inhibitor

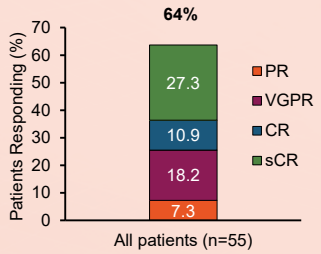
Searl E et al. *Blood*. 2022;140. Abstract 160.

114

Elranatamab in Patients With Relapsed/Refractory Multiple Myeloma

Updated Efficacy and Safety Results with Elranatamab (MagnetisMM-1 Study)[1]

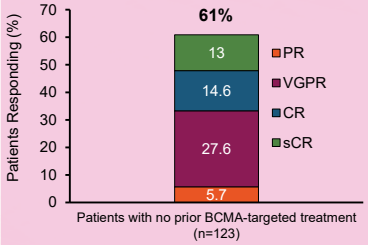
Phase 1 study in RRMM
(91% triple-class refractory)



Median duration of response 17.1 months.

MagnetisMM-3 Study of Elranatamab[2]

Phase 2 study in RRMM refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody—no prior BMCA-targeted treatment



Elranatamab to be investigated alone and in combination with other drugs in phase 3 studies.

Data from this trial was recently used to submit a Biologics License Application to the U.S. Food and Drug Administration for the treatment of patients with relapsed or refractory multiple myeloma.

IMiD, immunomodulatory drug; PI, proteasome inhibitor

1. Raje N et al. *Blood*. 2022;140. Abstract 158. **2.** Bahlis NJ et al. *Blood*. 2022;140. Abstract 159.

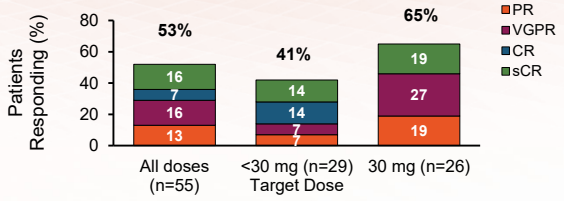
115

Phase 1 Study of Alnuctamab in Patients With Relapsed/Refractory Multiple Myeloma

Intravenous Formulation Results

	IV Alnuctamab (n=70)
Median follow up (months)	8.0
Overall response rate (%)	39
Median duration of response (months)	33.6
Responses ongoing (%)	48
Median progression-free survival (months)	
All patients	3.1
Responders	36.4
Nonresponders	1.7

Subcutaneous Formulation Results



Most frequent adverse events, %	Any grade	Grade 3/4
Hematologic		
Anemia	38	25
Neutropenia	37	32
Thrombocytopenia	24	9
Non-hematologic		
CRS	53	0
Infections	34	9
ICANS	3	0
ALT increase	12	6

Wong SW et al. *Blood*. 2022;140. Abstract 162.

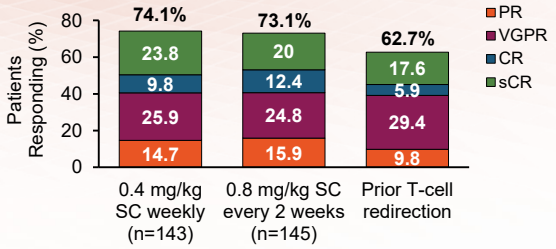
116

Talquetamab in Patients With Relapsed/Refractory Multiple Myeloma

Phase 1/2 study (MonumenTAL-1) in RRMM

288 patients—with no prior T-cell redirecting therapies—received treatment with talquetamab at 2 different doses (0.4 mg/kg every week and 0.8 mg/kg every other week) subcutaneously.

Data from this trial was recently used to submit a Biologics License Application to the US Food and Drug Administration for the treatment of patients with relapsed or refractory multiple myeloma.



	0.4 mg/kg		0.8 mg/kg	
Most frequent adverse events, %	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Hematologic				
Anemia	44.8	31.5	39.3	24.8
Neutropenia	34.3	30.8	28.3	22.1
Lymphopenia	28	25.9	26.2	25.5
Thrombocytopenia	27.3	20.3	26.9	16.6
Infections	57.3	16.8	50.3	11.7

IMiD, immunomodulatory drug; PI, proteasome inhibitor

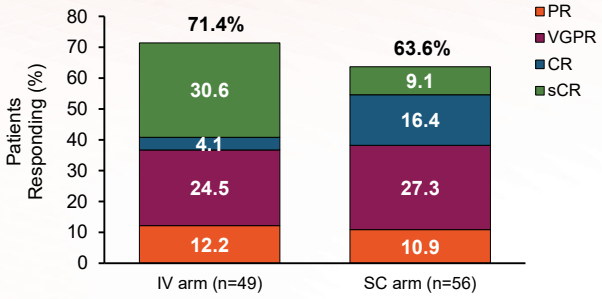
Chari A et al. *Blood*. 2022;140. Abstract 157.

117

Forimtamig (RG6234) in Patients With Relapsed/Refractory Multiple Myeloma

Phase 1 study in RRMM

105 patients received treatment with RG6234 in 2 different formulations (intravenous and subcutaneous)

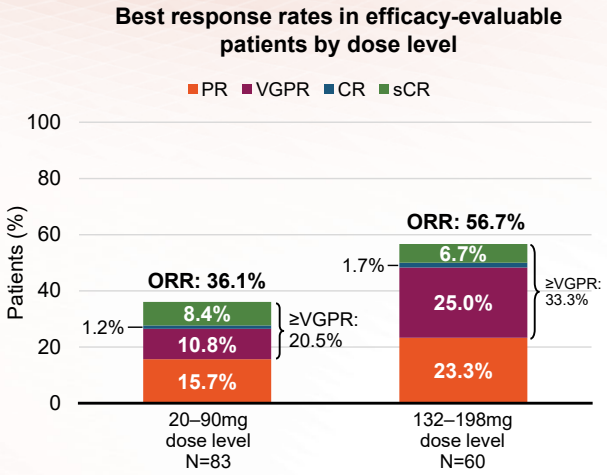


Carlo-Stella C A et al. *Blood*. 2022;140. Abstract 161.

118

Cevostamab (Targets FcRH5)

- Fc receptor-homolog 5 (FcRH5)
  - Expressed exclusively in B-cell lineage (myeloma cells > normal B cells)
  - Near ubiquitous expression on myeloma cells
- Cevostamab bispecific antibody
  - Targets membrane-proximal domain of FcRH5 on myeloma cells and epsilon domain of CD3 on T cells
  - Dual binding results in T-cell directed killing of myeloma cells



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Expected Toxicities With T-Cell Activating Therapies (CAR T and Bispecific Antibodies)

Cytokine release syndrome (CRS)

Infections

- Viruses: CMV, EBV
- PCP/PJP
- Ongoing discussions regarding prophylactic measures
  - IVIG
  - Anti-infectives

Cytopenias

Neurotoxicity (ICANS)

- Usually occurs within first 1–2 weeks
- Frequency (all grade and grade 3–5) higher with CAR T

Off target effects (with GPRC5D targeted agents)

Cytokeratin changes/rash
Dysgeusia

ICANS, immune effector cell-associated neurotoxicity syndrome; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PCP/PJP, pneumocystis pneumonia/pneumocystis jiroveci pneumonia

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Pretreatment With Tocilizumab Reduces Incidence and Severity of Cytokine Release Syndrome

Cevostamab is an FcRH5-targeted bispecific antibody under investigation in patients with RRMM

An ongoing phase 1 study evaluating the use of tocilizumab (an IL-6 antibody) prior to the first dose of cevostamab. A single 8 mg/kg dose of tocilizumab was administered to 28 patients 2 hours prior to cevostamab

35.7% of patients receiving tocilizumab experienced CRS compared to 90.9% of patients who didn't receive tocilizumab.

Grade 3 CRS was observed in only one patient in each group and no G4/5.

The frequency of neutropenia was higher for patients receiving tocilizumab compared with those who didn't (64.3% vs 38.6% G3/4).

No impact on response was observed with tocilizumab pretreatment.

Trudel S et al. *Blood*. 2022;140. Abstract 567.

121

BCMA-Targeted Bispecific Agents: Summary

	MajesTEC-1[1] Teclistamab Phase 1/2	MagnetisMM-1 Elrantamab[2] Phase 1	REGN-5458[3] Phase 1/2	AMG-701[4] (Pavurutamab) Phase 1b	ABBV-383[5] (TNB-383B) Phase 1
Patients, n	165	55	73	85	118
Median prior regimens, n	5	6	5	6	5
Dosing	SC weekly (RP2D)	SC weekly	Q2 wk after W16	IV weekly	IV Q3 wk
ORR, %	62.0	70	51 (75 at high dose)	26	53–81 in cohorts
CR/sCR, %	28.7	30	43 (16 at high dose)	9.7	13–39 in cohorts
CRS (all grades), %	71.5	87.3 (↓ with priming and pre-meds)	38	65	54
CRS (grade ≥3), %	0.6	0	0	9	3
Neurotoxicity (all grades), %	12.7	—	4	—	5.1
Neurotoxicity (grade ≥3), %	0	—	0	—	—
Notes	9-mo PFS: 58.5%	22% received prior BCMA-targeted tx			Allowed for CrCl 30

1. Moreau. ASH 2021. Abstract 896. **2.** Sebag. ASH 2021. Abstract 895. **3.** Zonder. ASH 2021. Abstract 160.
4. Harrison. ASH 2020. Abstract 181. **5.** Kumar. ASH 2021. Abstract 900.

122

Key Points

- CAR T and bispecific antibodies are very active even in heavily pre-treated patients.
- Side effects of CAR T cells and bispecific antibodies include cytokine release syndrome, confusion, and low blood counts, all of which are treatable.
- Abecma and Carvykti are only the first-generation CAR T cells and target the same protein. Different CAR Ts and different targets are on the way.
- Bispecific antibodies represent an "off-the-shelf" immunotherapy; Tecvayli was approved in October 2022.
- Several additional bispecific antibodies are under clinical evaluation.

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Please take a moment to answer two questions about this presentation.

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MULTIPLE MYELOMA Research Foundation

Supportive Care

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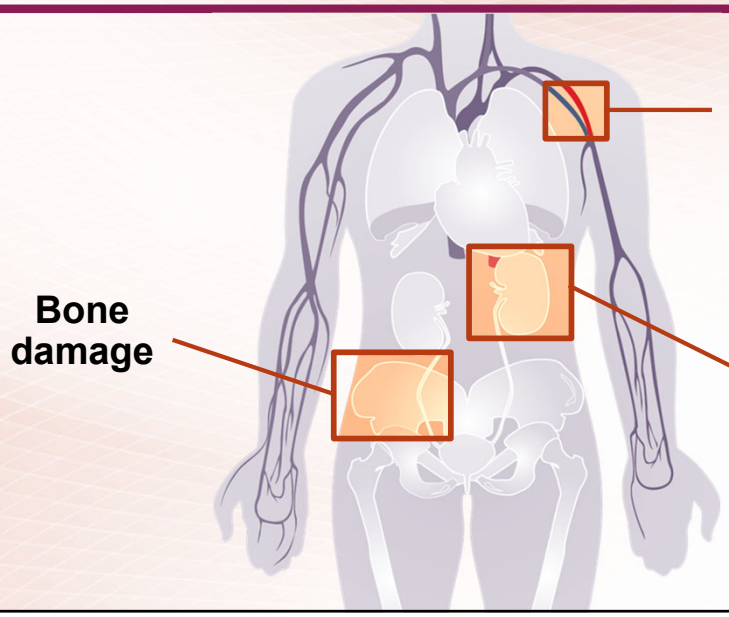
Effects of Myeloma



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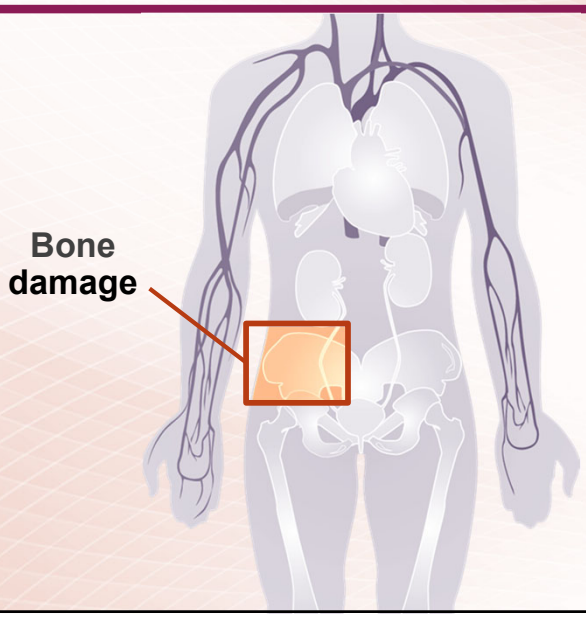
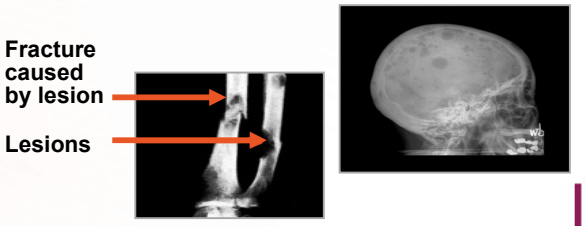
Effects of Myeloma: Bone Disease



- Occurs in 85% of patients
- Weakened bone due to lesions or "holes"
- Increased levels of calcium in the blood (hypercalcemia)
- Leads to
  - Pathologic fractures
  - Spinal cord compression/collapse
  - Bone pain



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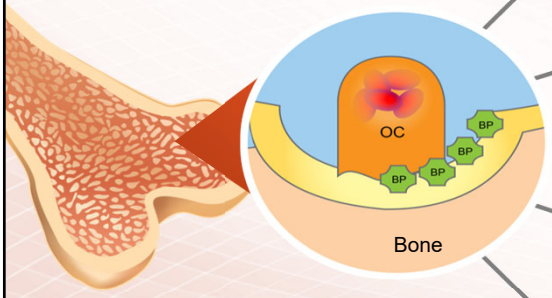
Bone Strengthening Agents for Myeloma Bone Disease



How they work
- Prevent bone disease from getting worse

Benefits
- Decrease pain and reduce skeletal-related fractures

Medication types
- Zometa (zoledronic acid): 15-minute infusion
- Aredia (pamidronate): 2-hour infusion
- Xgeva (denosumab): injection

Dosing
- Zometa/Aredia: IV infusion in doctor's office every 3–4 weeks
- Xgeva: injection once every 4 weeks

Side effects
- Fracture of the femur
- Osteonecrosis of the jaw (ONJ)

OC, osteoclast (inhibited, halting bone breakdown); BP, bisphosphonate

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Recommendations for Reducing the Risk of ONJ

- Complete major dental work before beginning treatment for bone disease
- Practice good oral hygiene
- Schedule regular dental visits
- Let your dentist know that you are receiving treatment for bone disease
- Keep your doctor informed of dental issues/need for dental work
- Be attentive! ONJ seems to be related to the length of time patients are on treatment for bone disease

ONJ, osteonecrosis of the jaw

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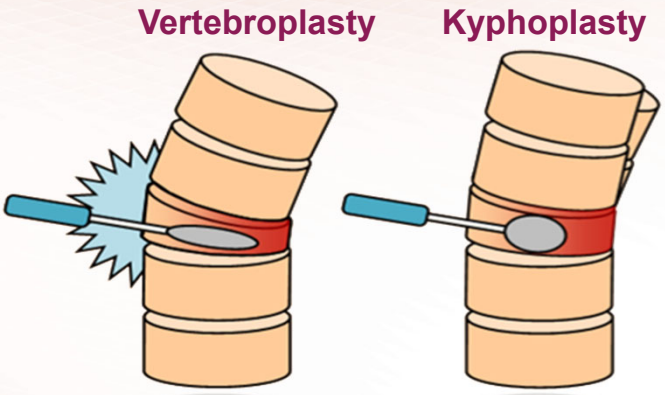
Orthopedic Procedures to Stabilize the Spine

- Minimally invasive procedures
- Can be performed without hospitalization
- Small incision
- Cement filler stabilizes bone
- Potential for relatively rapid symptom relief (approximately 1 month with kyphoplasty)



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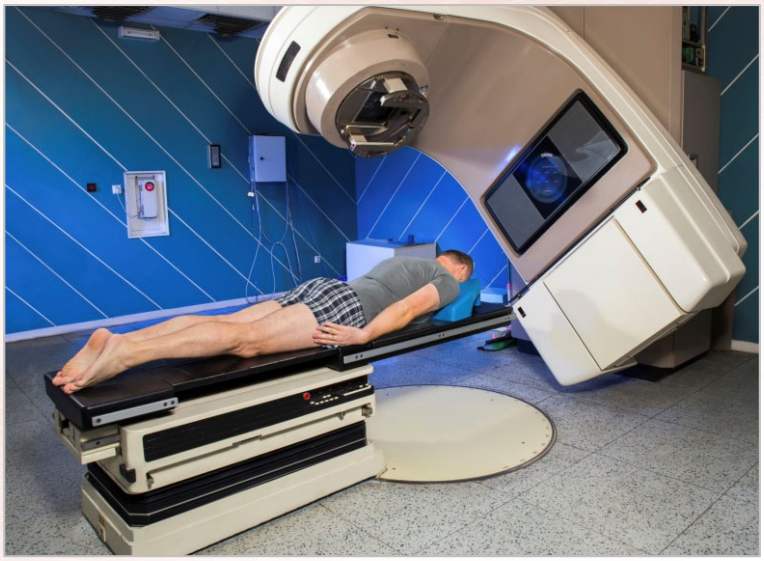
Radiation Therapy for Pain Management



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Pain Management Medications

Acetaminophen (Tylenol)	NSAIDs (nonsteroidal anti-inflammatory drugs)	Opioids	Corticosteroids (dexamethasone, prednisone)	Gabapentin
Will not hurt your kidneys; high dosage can hurt your liver	Prefer to avoid with MM due to increased risk of kidney injury	Will not hurt kidneys, liver, stomach; potential for constipation, sedation, confusion, dependence, addiction	Will not hurt kidneys; can raise blood sugar; short- and long-term effects	

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Effects of Myeloma: Low Blood Counts

Low red blood cells (anemia)

- Symptoms
  - Fatigue; depression/mood changes; difficulty breathing; rapid heartbeat; dizziness
- Other causes
  - Low levels of iron, folate, and vitamin B12

Treatment: Identify and treat causes other than myeloma; supplements; medications to increase number of red blood cells; blood transfusions

Low white blood cells (leukopenia)

- Symptoms
  - Fatigue; frequent infections
- Other causes
  - Radiotherapy
  - Infection

Treatment: Medications to stimulate production of white blood cells; antibiotics; antifungal medications; infection prevention

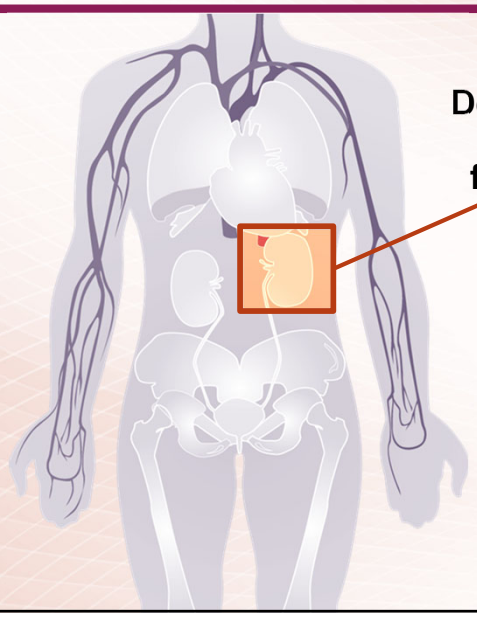
Low platelets (thrombocytopenia)

- Symptoms
  - Easy or excessive bruising; superficial bleeding into the skin; prolonged bleeding from cuts; bleeding from the gums or nose; blood in urine or stool
- Other causes
- Viral infection (hep B or C); immune thrombocytopenia; medications

Treatment: Identify and treat causes other than myeloma; platelet transfusion; hold anticoagulation

133

Effects of Myeloma: Decreased Kidney Function



- Detection
  - Decreased amount of urine
  - Increase in creatinine and other proteins
- Other causes beside myeloma
  - Hypertension
  - Diabetes
  - Some medications
- Treatment
  - Fluids
  - Avoid nonsteroidal anti-inflammatory drugs such as Aleve, Advil/Motrin
  - Plasmapheresis
  - Treat other causes
  - Dialysis (severe)

134

Main Body Systems Affected by Myeloma Treatment

Blood

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

Central Nervous System

- 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 MM or its treatments

Cardio-vascular

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

Gastro-intestinal

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

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Class: Immunomodulatory Drugs Side Effects and Management

Revlimid*

- Potential for blood clots
- Reduced blood counts
- Rash
- Fatigue
- Muscle pain or muscle cramping
- Diarrhea
- Small chance of second new cancers when given with melphalan

Pomalyst*

- Fatigue and weakness
- Reduced blood counts
- GI effects
- Shortness of breath
- Upper respiratory infection
- Back pain
- Fever
- Blood clots
- Mental fogginess

Management

- Blood thinners
- Tonic water/increased fluid intake for cramps
- GI toxicity: avoid dairy; fibers (Metamucil); Imodium; colestipol; cholestyramine; dose reduction
- Sleep hygiene, regular exercise, dose reduction for fatigue

*Black box warning.
GI, gastrointestinal

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Class: Proteasome Inhibitors Side Effects and Management

Velcade

- PN (numbness, tingling, burning sensations and/or pain due to nerve damage)
- Low platelets
- GI problems: nausea, diarrhea, vomiting, loss of appetite
- Fatigue
- Rash

Kyprolis

- Fatigue
- Anemia
- Nausea
- Low platelets
- Shortness of breath
- Diarrhea
- Fever
- Hypertension
- Cardiac toxicity

Ninlaro

- Diarrhea
- Constipation
- Low platelets
- PN
- Nausea
- Peripheral edema
- Vomiting
- Back pain

Management

- PN occurs less often when subcutaneous or once weekly dosing is used for Velcade
- Other PN prevention:
  - Vitamins and other supplements*
  - Certain medications such as gabapentin, pregabalin, duloxetine, opioids
  - Acupuncture
  - Physical therapy
- Shingles-prevention pills
- Blood thinners

*Do not take any supplements without consulting with your doctor.

PN, peripheral neuropathy; GI, gastrointestinal

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Class: Monoclonal Antibodies Side Effects and Management

Empliciti

- Low blood counts
- Infusion reactions

Darzalex*/Sarclisa

- Infusion reactions
- Fatigue
- Upper respiratory tract infection

*Now approved as subcutaneous injection with fewer side effects.

Management

- Premedication in anticipation of infusion reactions
- Post-infusion medications (Darzalex)

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XPOVIO: Selective Inhibitor of Nuclear Export Side Effects and Management

Gastrointestinal

Consult with your doctor if nausea, vomiting, or diarrhea occur or persist. Begin prophylactic anti-nausea medications

Low sodium (hyponatremia)

Maintain fluid intake

Fatigue

Stay hydrated and active

Low blood counts (cytopenias)

Report signs of bleeding right away

Report signs of fatigue or shortness of breath

Chari A et al. *Clin Lymphoma Myeloma Leuk*. 2021;21:e975.

139

Bispecific Antibodies

Tecvayli

- Cytokine release syndrome
- Injection-related reactions
- Injection-site reaction
- Infections
- Neutropenia
- Anemia
- Thrombocytopenia

Management

- Available only through a Risk Evaluation and Mitigation Strategies (REMS) due to the risk of cytokine release syndrome
- Patients will receive step-up dosing and will be monitored in an inpatient setting
- Cytokine release syndrome is managed in the same fashion as CAR T
- Injection reactions are managed with oral antihistamines and topical steroids
- Infection prevention!
- COVID precautions

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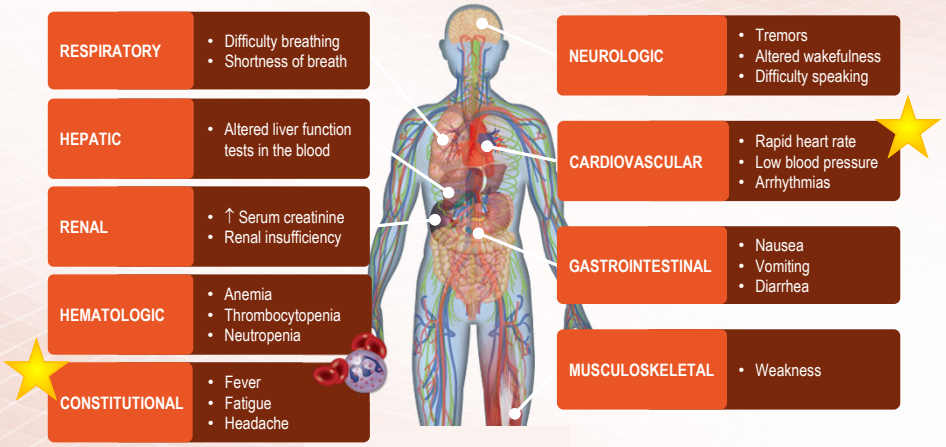
CRS With Bispecifics Severity Is Typically Mild: Early Recognition and Treatment Is Key



Mitigation and monitoring for cytokine release syndrome (CRS)

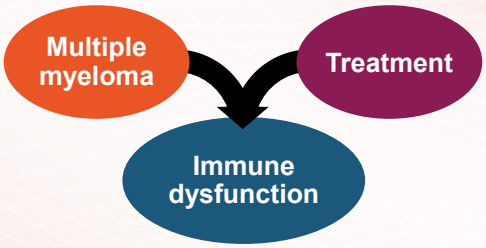
- Step-up dosing with hospitalization for monitoring
- Frequent vital signs
- Rule out infection
- Laboratory monitoring
- Early intervention with tocilizumab

ALP, alkaline phosphatase; CPK, creatine phosphokinase; CRP, C-reactive protein; CRS, cytokine release syndrome; LDH, lactate dehydrogenase; O_2, oxygen; TLS, tumor lysis syndrome.

Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265. June CH, et al. *Science*. 2018;359:1361. Brudno JN, Kochenderfer JN. *Blood*. 2016;127(26):3321. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019:34:45. Shimabukuro-Vornhagen et al. *J Immunother Cancer*. 2018;6:56. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625.

141

Infection Can be Serious for Patients With Myeloma



7–10–fold increased risk of bacterial and viral infections for people with myeloma

Report fever of more than 100.4°F, shaking chills even without fever, dizziness, shortness of breath, low blood pressure to HCP as directed.

General infection-prevention tips

- Good personal hygiene (skin, oral)
- Environmental control (wash hands, avoid crowds and sick people, etc)
- Growth factor (Neupogen [filgrastim])
- Immunizations (NO live vaccines)
- Medications (antibacterial, antiviral)

As recommended by your health care team

Brigle K et al. *Clin J Oncol Nurs*. 2017;21(5)suppl:60. Faiman B et al; IMF Nurse Leadership Board. *Clin J Oncol Nurs*. 2011;15(Suppl):66. Miceli TS et al. *Clin J Oncol Nursing*. 2011;15(4):9. ASH Website. COVID-19 Resources. www.hematology.org/covid-19/covid-19-and-multiple-myeloma

142

BCMA-Targeted Therapies Are Associated With an Increased Risk of Infections

- Both viral and bacterial
  - Up to 1/3 of patients in clinical trials have serious infections (requiring IV antibodies or hospitalization)
- Increased risk of serious COVID complications despite history of vaccination
  - Antibody levels
  - Immediate treatment once diagnosed nirmatrelvir with ritonavir (Paxlovid)
    - Start as soon as possible; must begin within 5 days of when symptoms start
  - Oral prophylactic antimicrobials

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Infection Prevention

- Avoid crowds
- Ensure handwashing, hygiene
- Growth factor (for example, filgrastim)
- IVIG for hypogammaglobulinemia
  - Know your healthy IgG level
- Immunizations (No live vaccines)
  - COVID-19 vaccination + booster(s)
  - Pneumococcal 20-valent conjugate vaccine
  - Seasonal inactivated influenza vaccine (×2 or high-dose)
  - Shingles vaccine: zoster vaccine recombinant, adjuvanted
- COVID-19 prevention
  - Antibody levels
  - Tixagevimab co-packaged with cilgavimab

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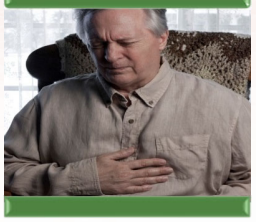
Side Effects of Steroids (Dexamethasone)

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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Symptom Management
Constipation

- Stimulant laxatives
  - Mild: senna/sennoside (Senokot)
    - 1–2 pills twice a day
  - More potent: bisacodyl (Dulcolax)
- Osmotic laxatives
  - Gentle, pulls water into the intestine
    - Lactulose
    - Miralax
- Bulking agents
  - Soluble fiber: psyllium (Metamucil)

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Symptom Management
Acid Reflux/Heartburn

- Our stomachs make a powerful acid to digest food, hydrochloric acid
- Hydrochloric acid can also digest our stomach lining → leads to gastritis and ulcers

A few ways to treat

1. Decrease the amount of acid the stomach is making
   a. Zantac, Pepcid
   b. Prilosec, Prevacid, Protonix, Nexium
2. Absorb excess acid: Tums, Maalox, Mylanta
3. Coat stomach: Carafate
4. Avoid late night eating

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Symptom Management
Insomnia

- Causes: anxiety, stress, meds—dexamethasone
- Sleep hygiene
  - Routine: go to bed, wake up at routine times
  - Exercise
  - No TV or screens when trying to sleep
  - Relaxation training; meditation/yoga/Reiki
  - Counseling support
- Medications: useful but all have drawbacks
  - Lorazepam (Ativan)
  - Zolpidem (Ambien)
  - Diphenhydramine (Benadryl)

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Marijuana

- Claims and hype: advocates and detractors
  - Promoted as relieving pain and muscle spasm, improving appetite, decreasing nausea, helping anxiety and insomnia, *and even curing cancer*
- Laws vary by state
- Marijuana contains 100 **cannabinoids**, most notably **THC** and **CBD**
- Sativex contains equal parts THC and CBD
  - Available in Great Britain and Canada
  - Double-blind trial in 2015: effective but no more effective than placebo for cancer pain; not available in U.S.
- Bottom line: Marijuana has been shown to have modest benefits in symptom management; claims of dramatic results are anecdotal and have not been proven

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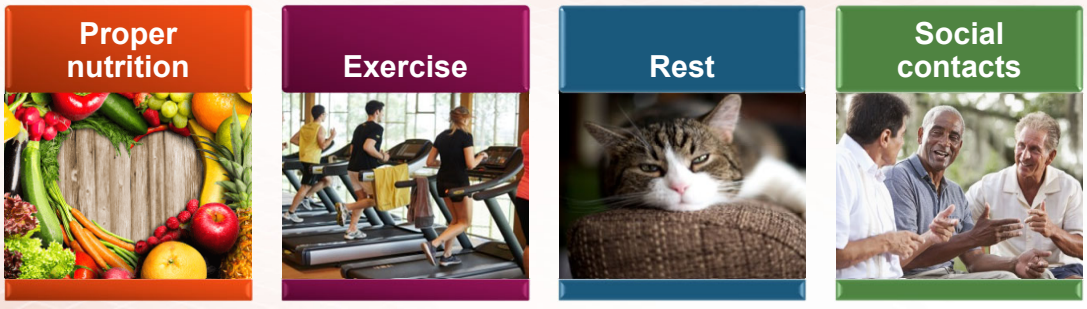
Daily Living



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Taking Care of Yourself

- Talk to your provider about side effects… there is usually a way to make treatment tolerable.
- Pay attention to your own needs and don't be afraid to ask for help.
- Learn more about multiple myeloma.
- Look for the positive.

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Please take a moment to answer two questions about this presentation.

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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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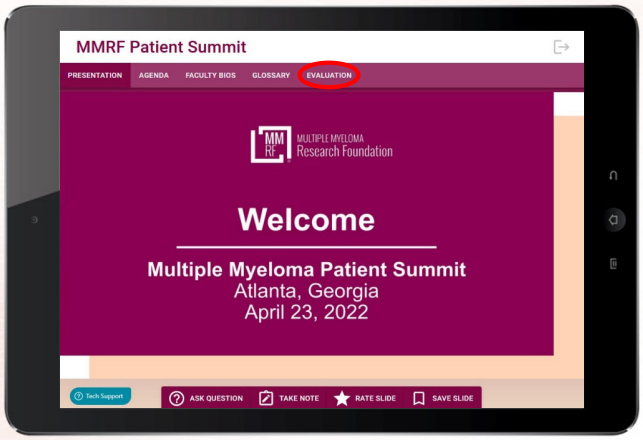
Don't Forget!

Complete your evaluation
Leave the iPad at your seat



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Upcoming Patient Education Events
Save the Date

Topic	Date and Time	Speakers
Facebook Live: FAQs on Newly Diagnosed Multiple Myeloma	Tuesday, March 14 3:00 PM – 4:00 PM (ET)	Gurbakhash Kaur, MD Sonia Patel, MSN, AGACNP-BC, APRN, AOCNP
Webinar: BCMA-Targeted Bispecific Antibody Therapy	Tuesday, March 21 4:00 PM – 5:00 PM (ET)	Jesus G. Berdeja, MD Amrita Y. Krishnan, MD
Patient Summit Scottsdale, AZ *In collaboration with Arizona Myeloma Network*	Saturday, March 25 9:00 AM to 3:45 PM MT	Leif Bergsagel, MD Clarence Adoo, MD Jonathan Keats, PhD Sumit Madan, MD Suzanne Hyde, MSW, LCSW Barbara Kavanagh, MSW, LCSW Joan Koerber-Walker William Brown
Facebook Live: FAQs on Relapsed/Refractory Multiple Myeloma	Tuesday, March 28 2:00 PM – 3:00 PM (ET)	Brandon Blue, MD Dana Spiak, RN
Webinar: Multiple Myeloma Precursor Conditions	Wednesday, April 5 2:30 PM – 3:30 PM (ET)	Sagar Lonial, MD Omar Nadeem, MD

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

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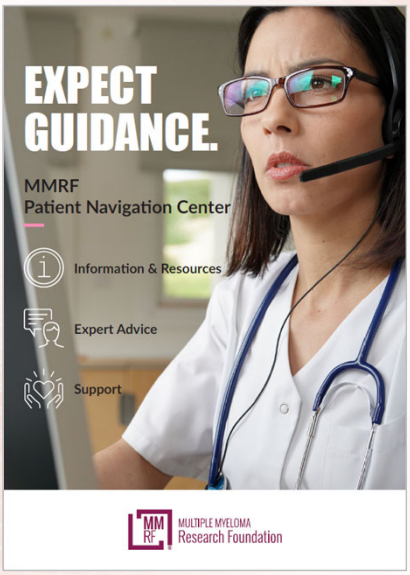
MMRF Patient Resources



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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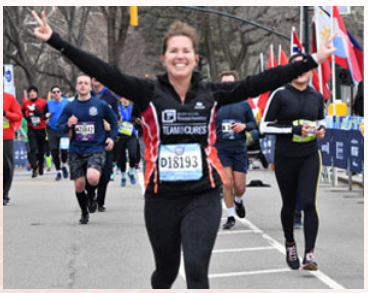
MMRF Events

**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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