MULTIPLE MYELOMA Research Foundation

Opening Remarks

Mary DeRome, MS
MMRF

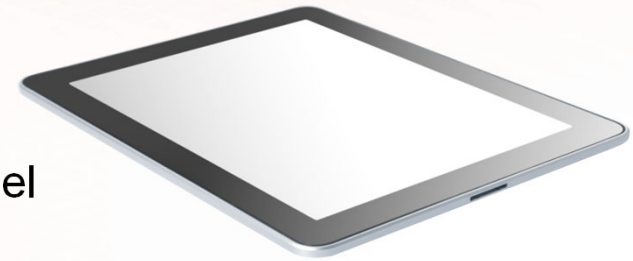
1

abbvie · Adaptive biotechnologies · AMGEN · Bristol Myers Squibb · CRISPR THERAPEUTICS · cure · Genentech A Member of the Roche Group · GSK · janssen · Karyopharm Therapeutics · Pfizer · REGENERON SCIENCE TO MEDICINE · sanofi · Takeda ONCOLOGY

2

iPads

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



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

3

Program Faculty

Program Host

Jesus G. Berdeja, MD
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

Faculty

Elizabeth O'Donnell, MD
Dana-Farber Cancer Institute
Harvard University
Boston, Massachusetts

Joshua Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

4

Summit Agenda

Time (CT)	Topic	Speakers
9:00 – 9:15 AM	Introduction to the MMRF	Mary DeRome, MS
9:15 – 9:25 AM	Welcome	Jesus G. Berdeja, MD
9:25 – 10:00 AM	Myeloma 101 and Health Care Disparities in Multiple Myeloma	Joshua Richter, MD
10:00 – 10:30 AM	Treating Relapsed/Refractory Multiple Myeloma	Elizabeth O'Donnell, MD
10:30 – 11:30 AM	Town Hall Q&A	Panel
11:30 AM – 12:00 PM	CAR T-Cell Therapy and Bispecific Antibodies	Jesus G. Berdeja, MD
12:00 – 1:00 PM	Lunch, Patient Journey	Michael Crossland
1:00 – 1:30 PM	Town Hall Q&A	Panel
1:30 PM	Closing Remarks	Mary DeRome, MS

5

MULTIPLE MYELOMA Research Foundation

MMRF Introduction

Mary DeRome, MS
MMRF

6

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

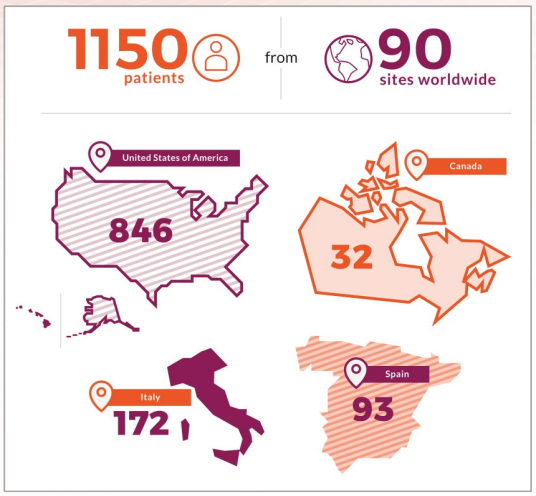
Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

7

MMRF CoMMpass Study: Advancing Personalized Medicine Research

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

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



8

CoMMpass Is a Trial of Discovery

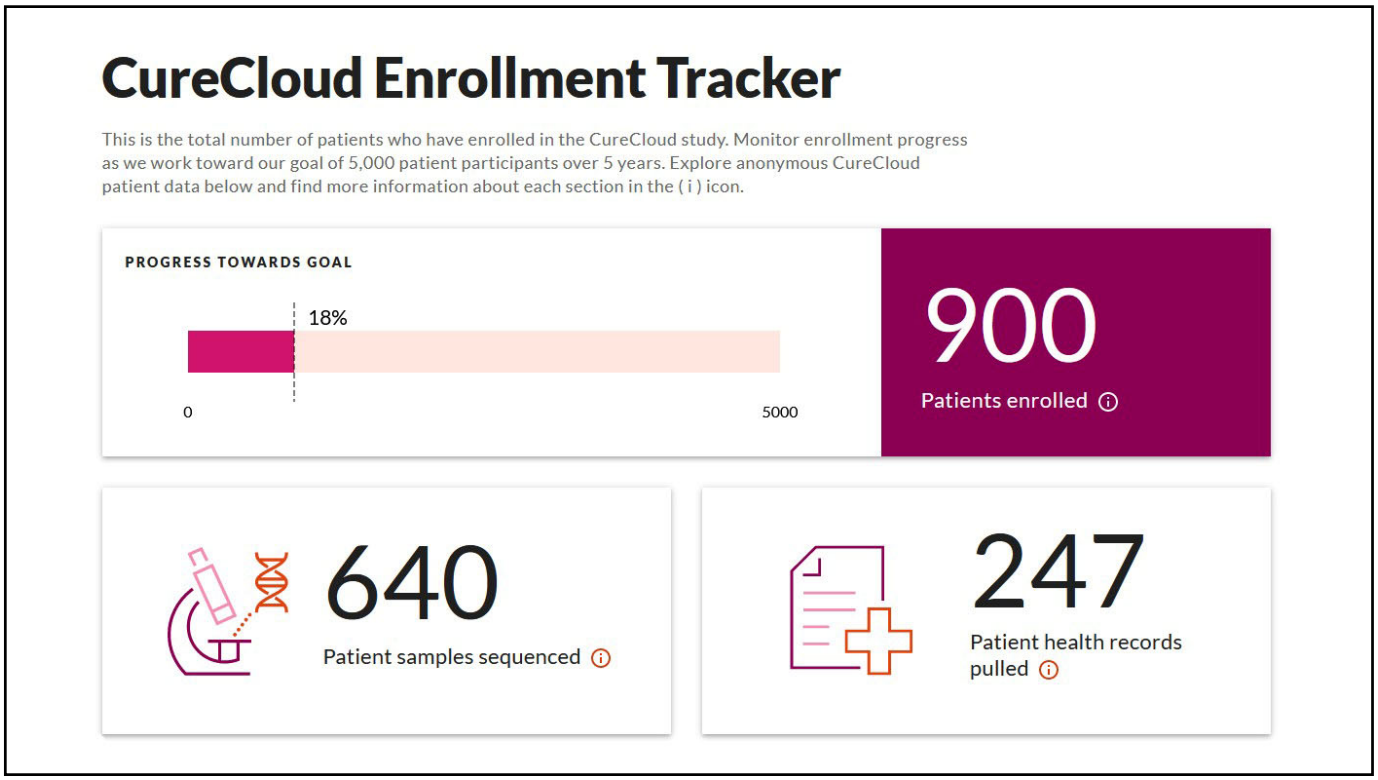
- CoMMpass data has
  - Provided the myeloma community with information on
    - Frequency of genetic abnormalities
    - How genetic abnormalities play a role in myeloma
      - Drive multiple myeloma cell growth and survival
      - Contribute to drug resistance
      - May predict which patients respond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

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

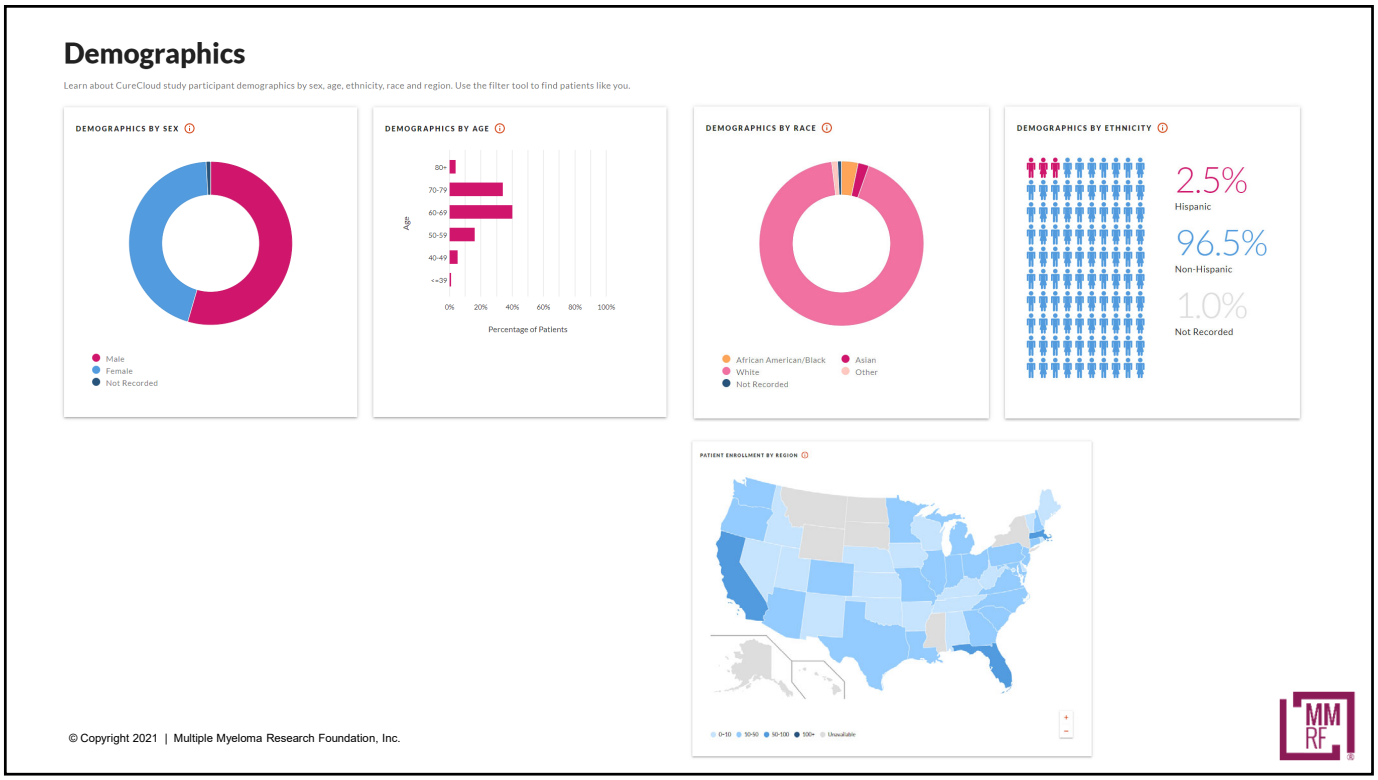
9

MMRF CureCloud

10


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
18%
0
5000
900
Patients enrolled
640
Patient samples sequenced
247
Patient health records pulled

11


Demographics
Learn about CureCloud study participant demographics by sex, age, ethnicity, race and region. Use the filter tool to find patients like you.
DEMOGRAPHICS BY SEX
Male
Female
Not Recorded
DEMOGRAPHICS BY AGE
80+
70-79
60-69
50-59
40-49
<=39
Age
0%
20%
40%
60%
80%
100%
Percentage of Patients
DEMOGRAPHICS BY RACE
African American/Black
Asian
White
Other
Not Recorded
DEMOGRAPHICS BY ETHNICITY
2.5%
Hispanic
96.5%
Non-Hispanic
1.0%
Not Recorded
PATIENT ENROLLMENT BY REGION
© Copyright 2021 | Multiple Myeloma Research Foundation, Inc.

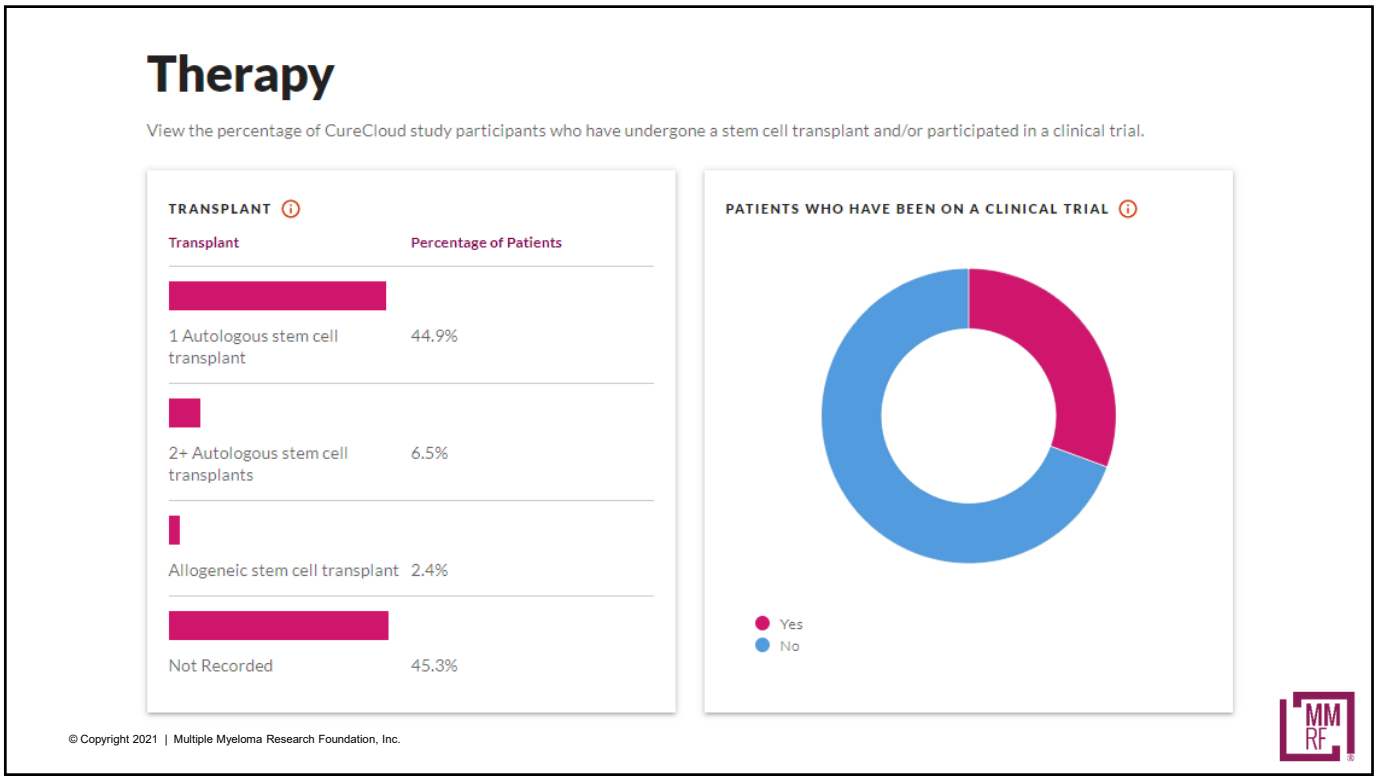
12

© Copyright 2021 | Multiple Myeloma Research Foundation, Inc.

13

© Copyright 2021 | Multiple Myeloma Research Foundation, Inc.

14


Therapy
View the percentage of CureCloud study participants who have undergone a stem cell transplant and/or participated in a clinical trial.
TRANSPLANT
Transplant
Percentage of Patients
1 Autologous stem cell transplant
44.9%
2+ Autologous stem cell transplants
6.5%
Allogeneic stem cell transplant
2.4%
Not Recorded
45.3%
PATIENTS WHO HAVE BEEN ON A CLINICAL TRIAL
Yes
No
© Copyright 2021 | Multiple Myeloma Research Foundation, Inc.

15


MULTIPLE MYELOMA
Research Foundation
Welcome!

16

Question

Are you a...

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

17

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.

18

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

19

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.

20

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.

21

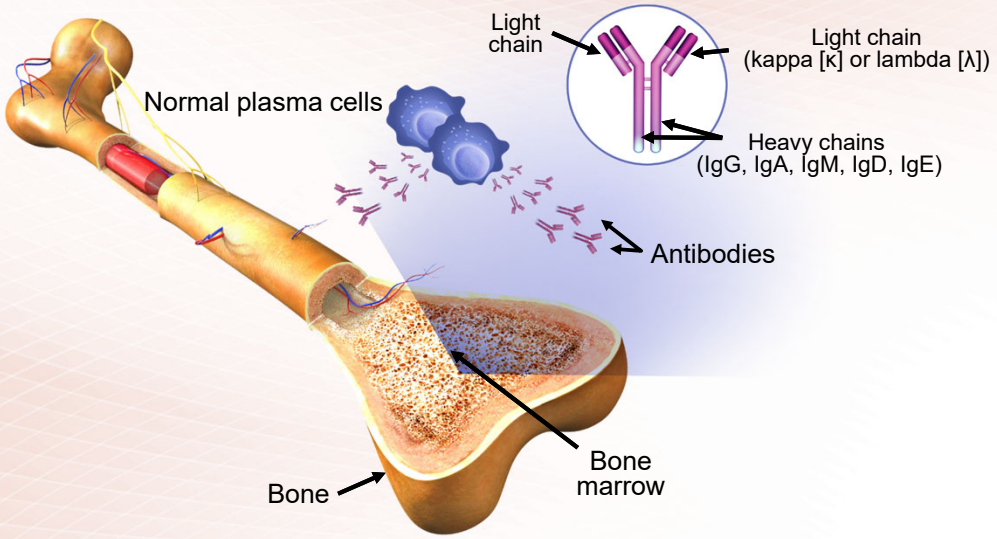
MULTIPLE MYELOMA Research Foundation

Myeloma 101 and Health Care Disparities in Multiple Myeloma

Joshua Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

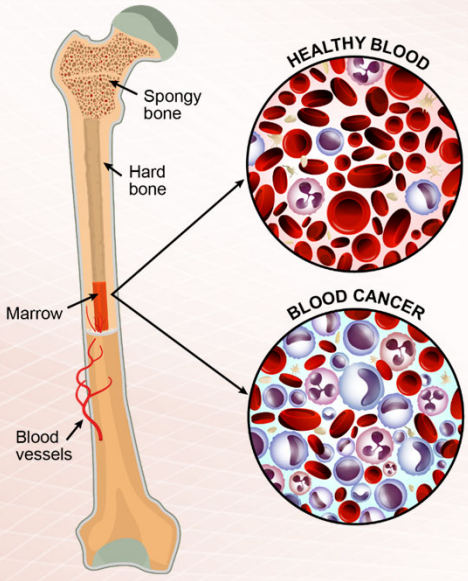
22

Normal Bone Marrow



23

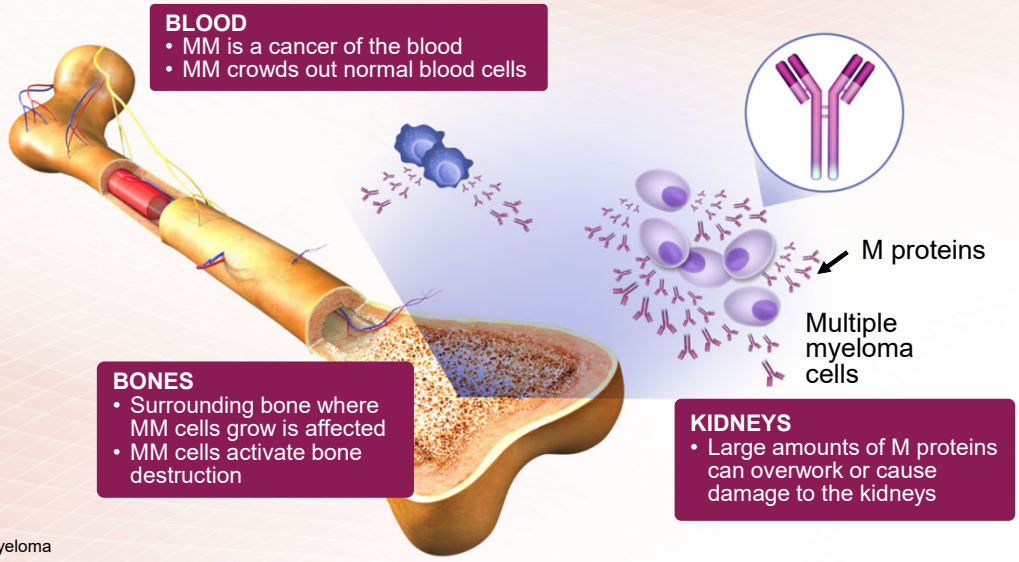
What is multiple myeloma?



- 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

24

Multiple Myeloma Affects Your Bones, Blood, and Kidneys

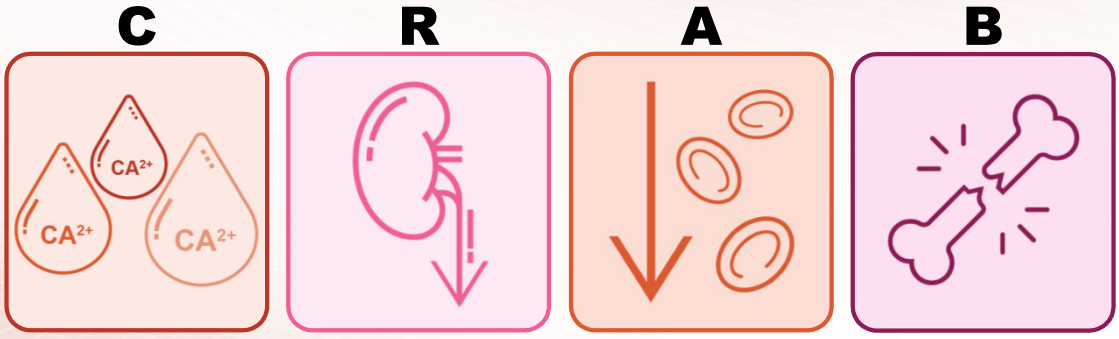


MM, multiple myeloma

25

Multiple Myeloma Affects Your Bones, Blood, and Kidneys

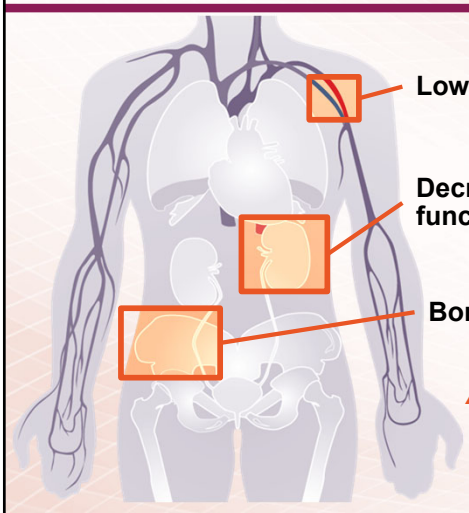
The clinical features that are characteristic of multiple myeloma



C	R	A	B
High levels of **c**alcium in the blood	Decreased kidney (**r**enal) function	Low amount of red blood cells (**a**nemia)	Presence of **b**one damage

26

Effects of Myeloma and Common Symptoms



Low blood counts → • **Weakness** • **Fatigue** • **Infection**

Decreased kidney function → **Weakness**

Bone damage → **Bone pain**

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

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

More common in Black patients

- Hypercalcemia
- Kidney dysfunction
  - Hemodialysis
- Anemia

Less common in Black patients

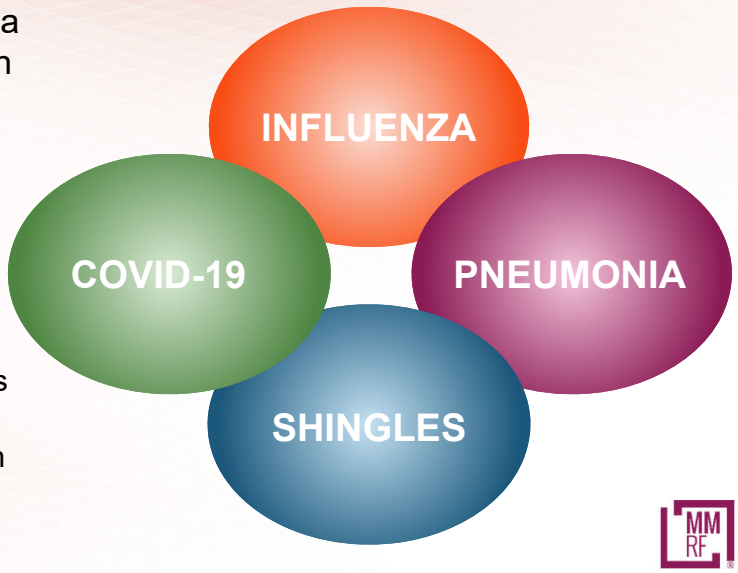
- Bone fractures

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

27

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)



28

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.

29

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

30

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)

31

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

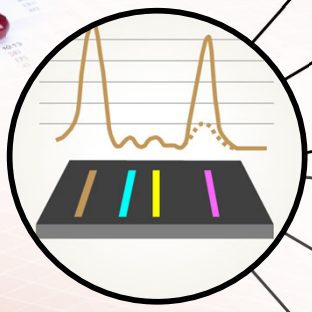
Assess changes in the bone structure and determine the number and size of tumors in the bone

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

32

Learn Your Labs!
Blood Tests

Blood tests



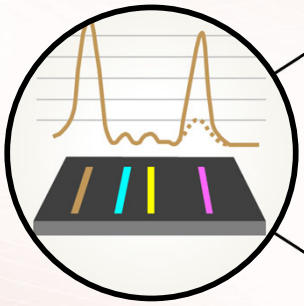
- **CBC** — Number of red blood cells, white blood cells, and platelets
- **CMP** — Measure levels of albumin, calcium, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and creatinine. Assess function of kidney, liver, and bone status and the extent of disease
- **B2M** — Determine the level of 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

33

Learn Your Labs!
Urine Tests

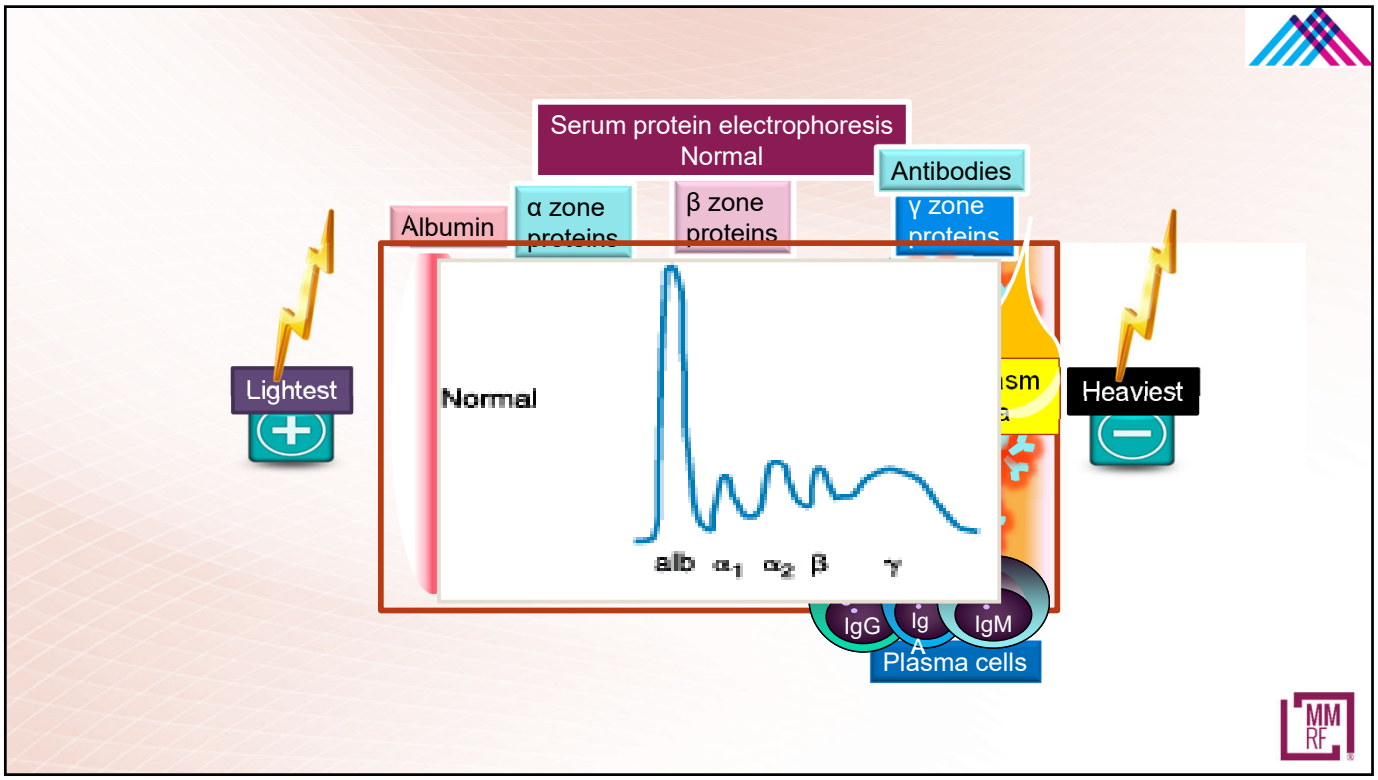
Urine tests



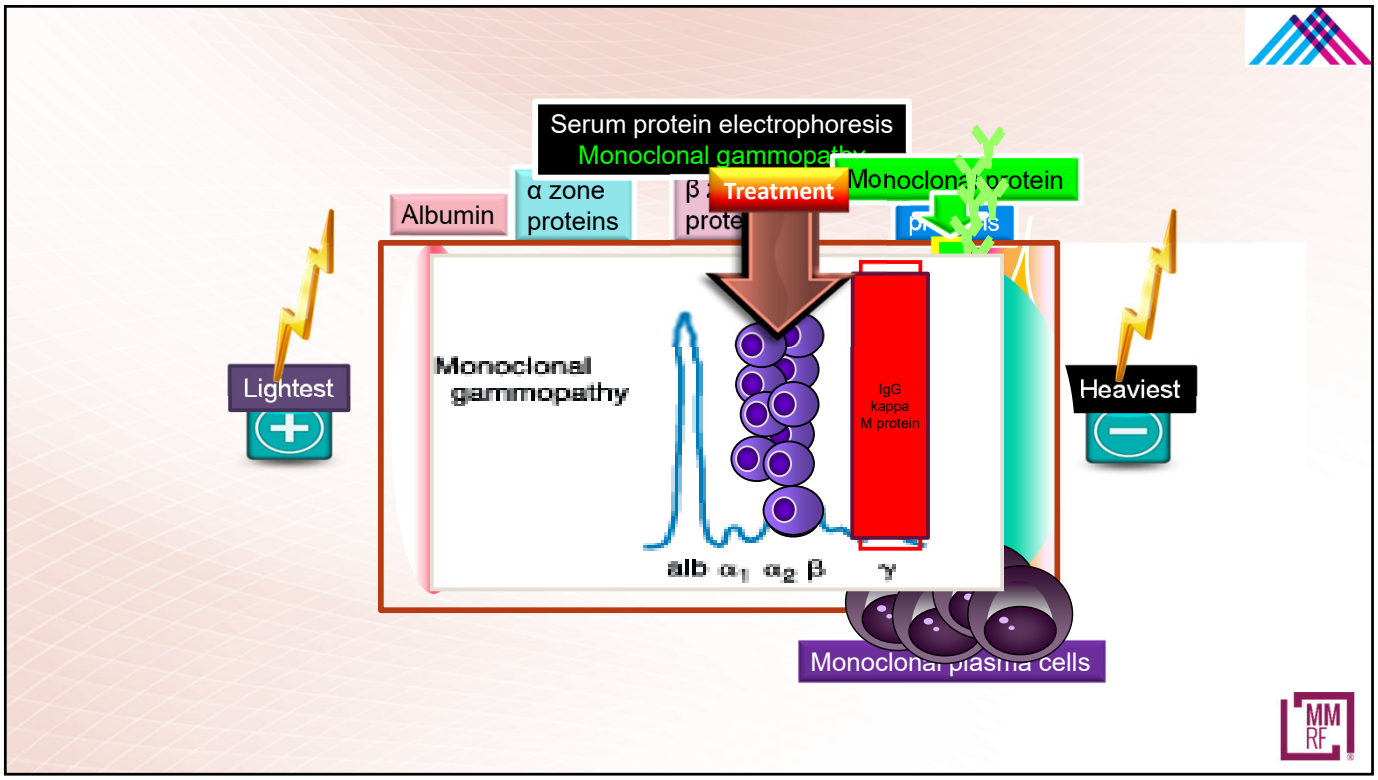
- **UPEP** — Detect Bence Jones proteins (otherwise known as myeloma light chains)
- **24-hr urine analysis** — Determine the presence and levels of M protein and Bence Jones protein

UPEP, urine protein electrophoresis

34

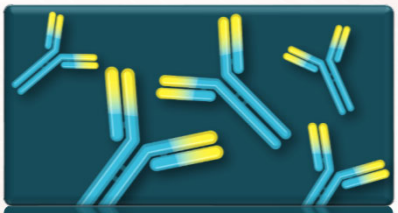

Serum protein electrophoresis
Normal
Antibodies
Albumin
α zone proteins
β zone proteins
γ zone proteins
Lightest
Heaviest
Normal
alb α1 α2 β γ
IgG
IgA
IgM
Plasma cells

35


Serum protein electrophoresis
Monoclonal gammopathy
Treatment
Albumin
α zone proteins
Lightest
Heaviest
Monoclonal gammopathy
IgG kappa M protein
alb α1 α2 β γ
Monoclonal plasma cells

36

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

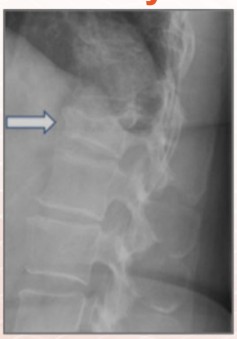
3%

37

Know Your Imaging Tests!

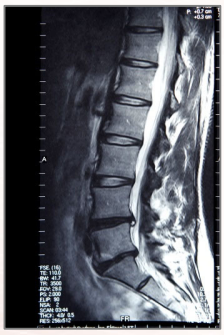
Assess changes in the bone structure and determine the number and size of tumors in the bone

X-ray

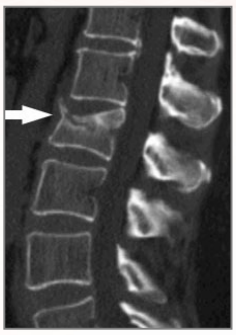


Conventional x-rays reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.

MRI



CT scan

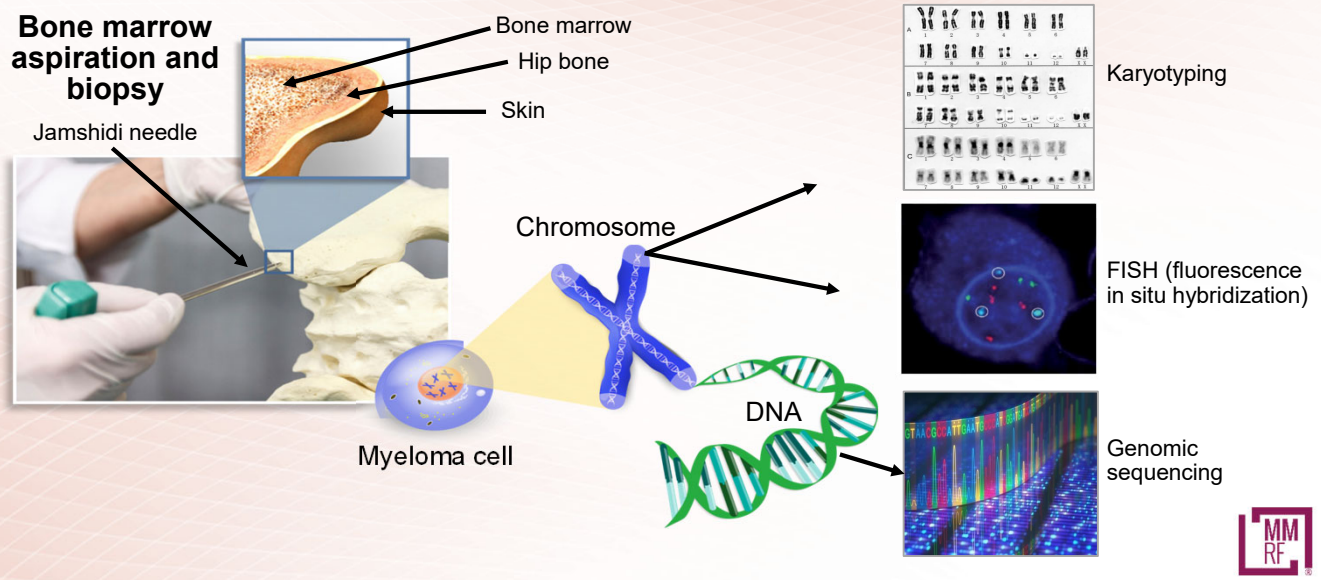


PET scan

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

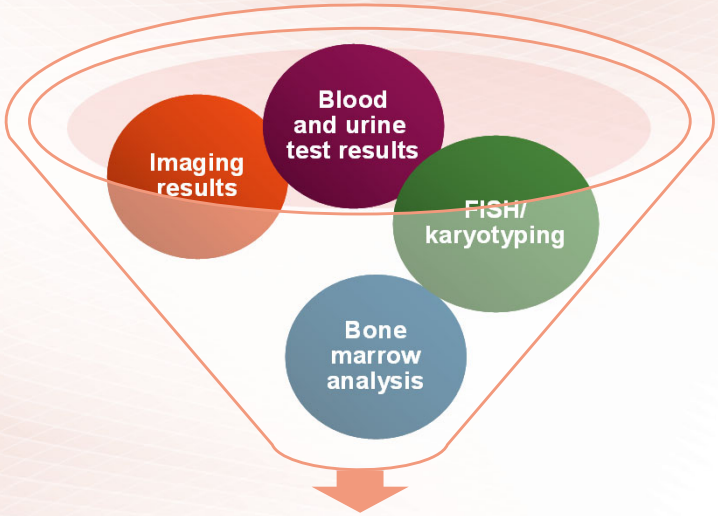
38

Know Your Bone Marrow Tests!



39

Putting the Results Together



Staging, prognosis, and risk assessment

40

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

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

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

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.

41

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

- 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

- 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

42

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

43

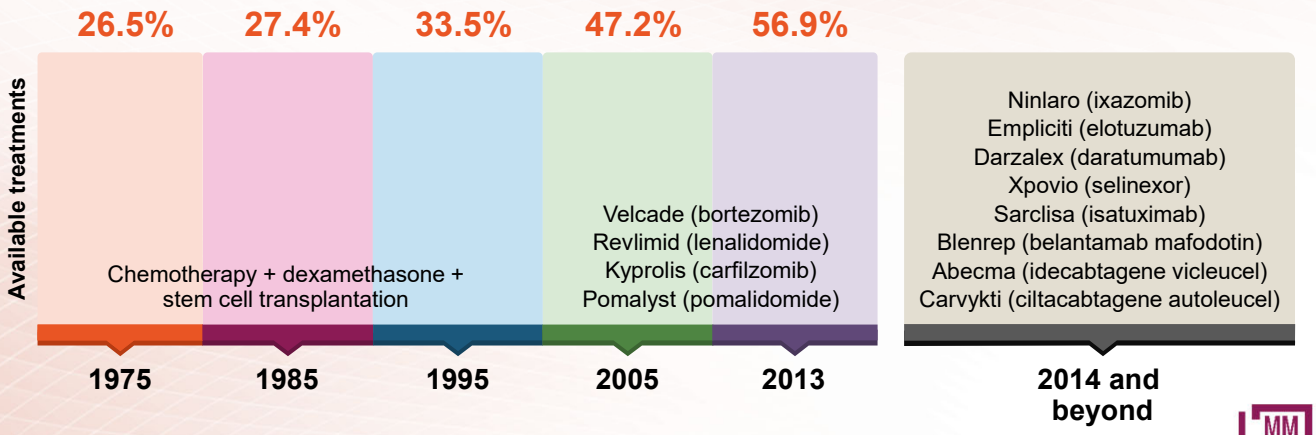
Getting the Right Treatment: Goals of Multiple Myeloma Therapy

- 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

44

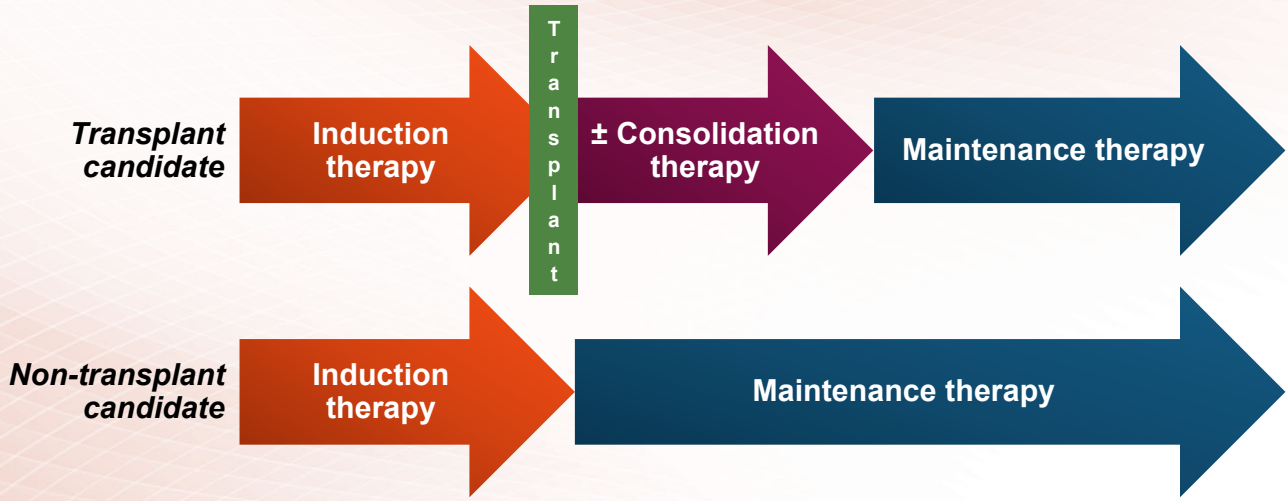
Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

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



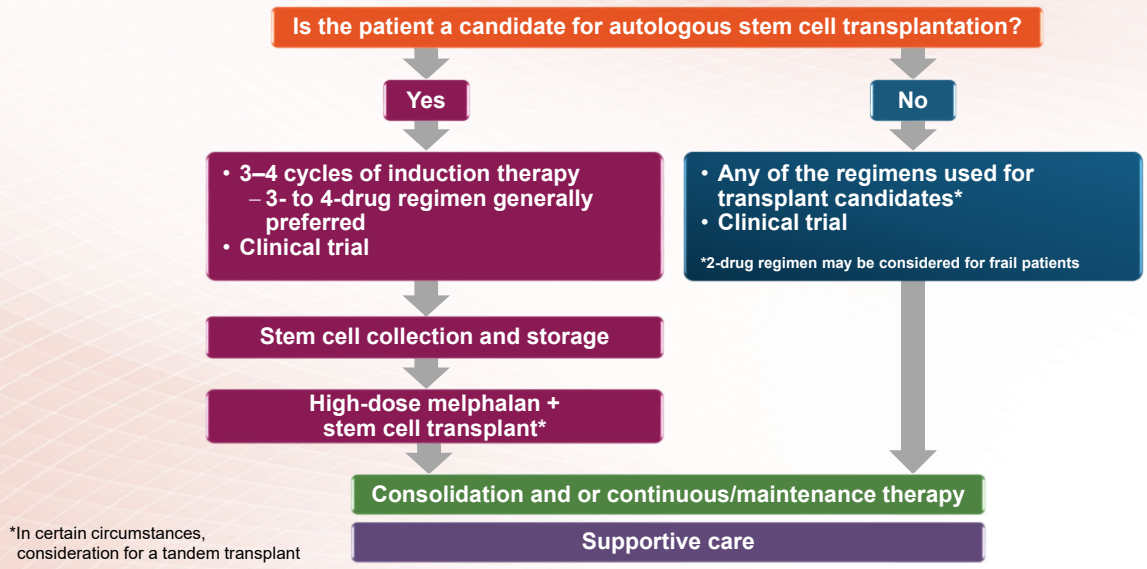
45

Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma



46

Overview of Treatment Approach for Active Multiple Myeloma



*In certain circumstances, consideration for a tandem transplant

47

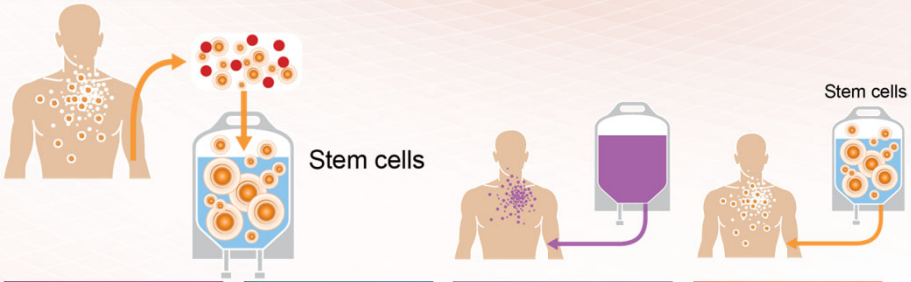
Induction Therapy Regimens

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

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

48

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
~4–6 cycles	Stem cell mobilization • Neupogen, Neulasta, Leukine, Cytoxan, Mozobil		Melphalan • Alkeran, Evomela	Day 0	Days +1 to +100†

-2 to -3 weeks*

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

49

Continuous or Maintenance Therapy Options

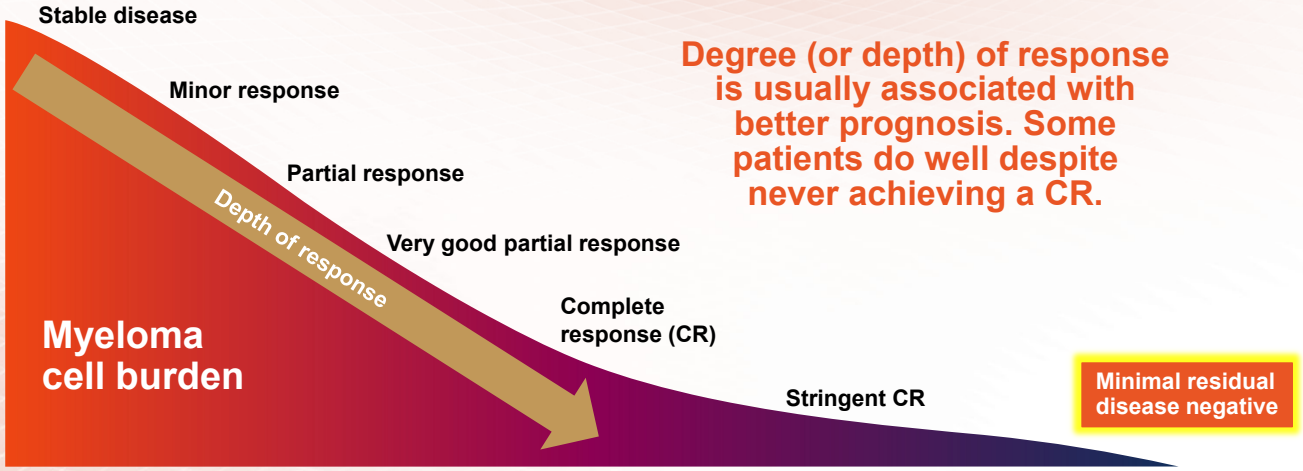
	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid*	• Ninlaro* • Velcade	• Velcade-Revlimid ± dex
Transplant ineligible	• Revlimid*	• Ninlaro* • Velcade	• Velcade-Revlimid

Additional agents under investigation: Darzalex, Empliciti, Kyprolis

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

50

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.

51

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

52

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!

53

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

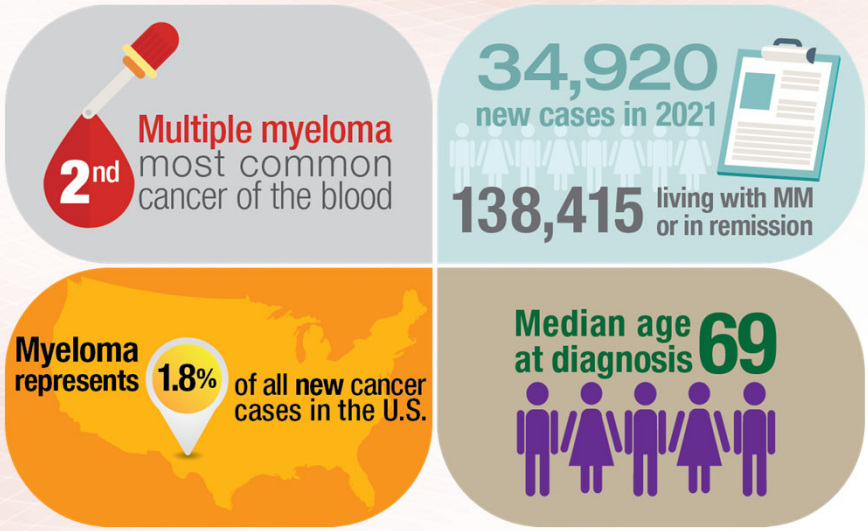
54

MULTIPLE MYELOMA Research Foundation

Health Care Disparities in Multiple Myeloma

55

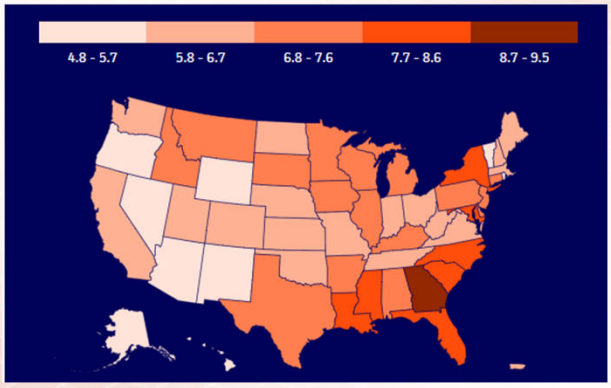
How common is multiple myeloma?



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

56

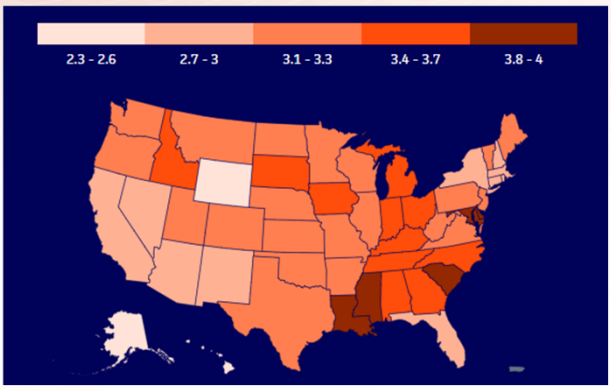
Incidence rates, 2014–2018
Myeloma, by state



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



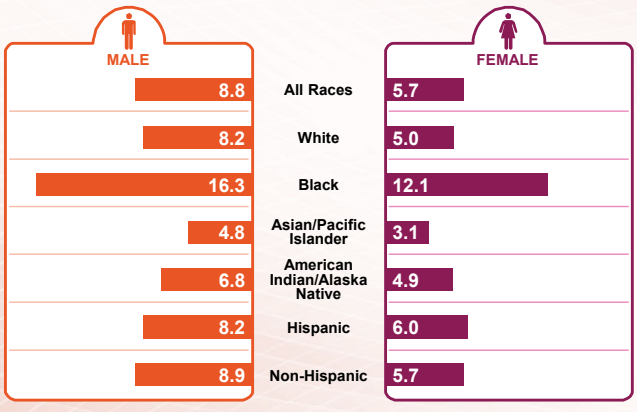
Average annual rate per 100,000, age adjusted to the 2000 US standard population.

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

57

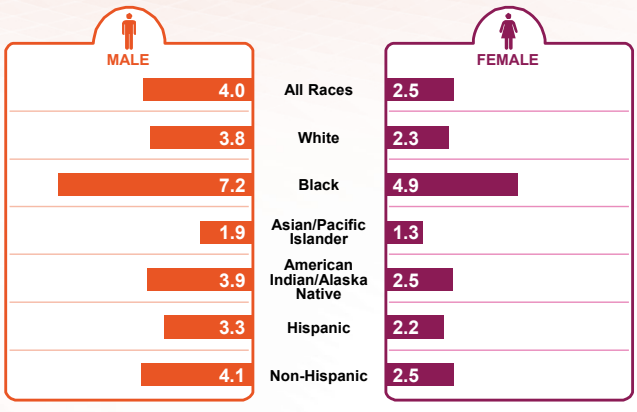
Multiple Myeloma Is Twice as Common in Black Patients

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

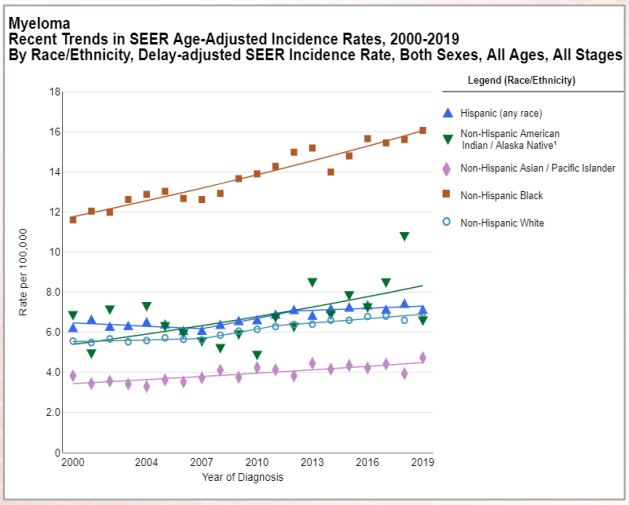


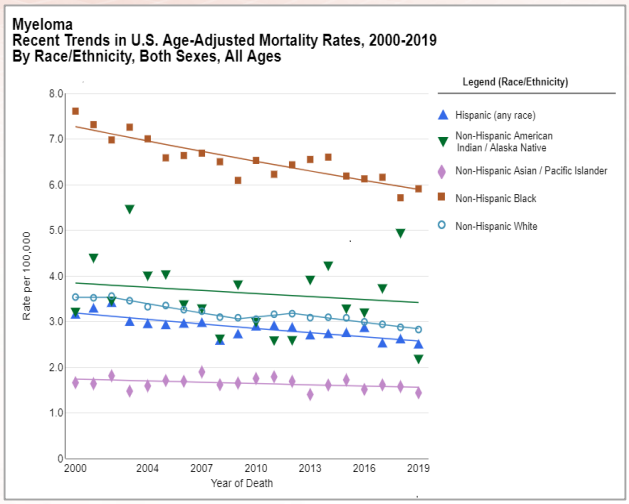
U.S. 2015-2019, Age-Adjusted

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

58

Multiple Myeloma Incidence and Mortality by Race/Ethnicity



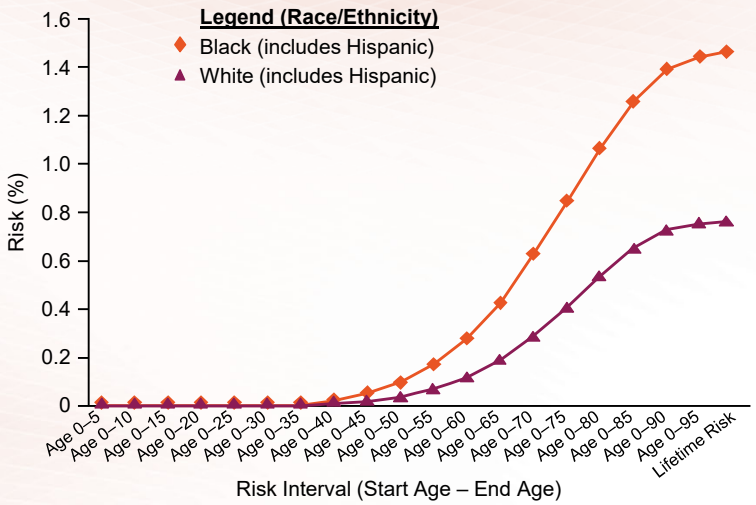


SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/statistics-network/explorer/application.html

59

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



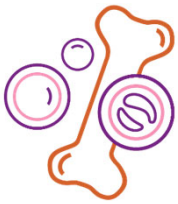
Data from National Cancer Institute
Surveillance, Epidemiology, and End Results Program (SEER)

60

Multiple Myeloma in Black Patients

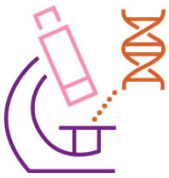
Demographics

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



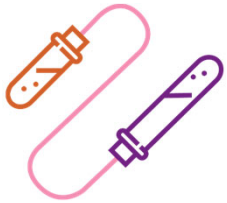
Clinical factors

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



Molecular (genetic) factors

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



Treatment

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

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

61

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

62

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

63

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**

64

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

65

Town Hall Questions & Answers

66

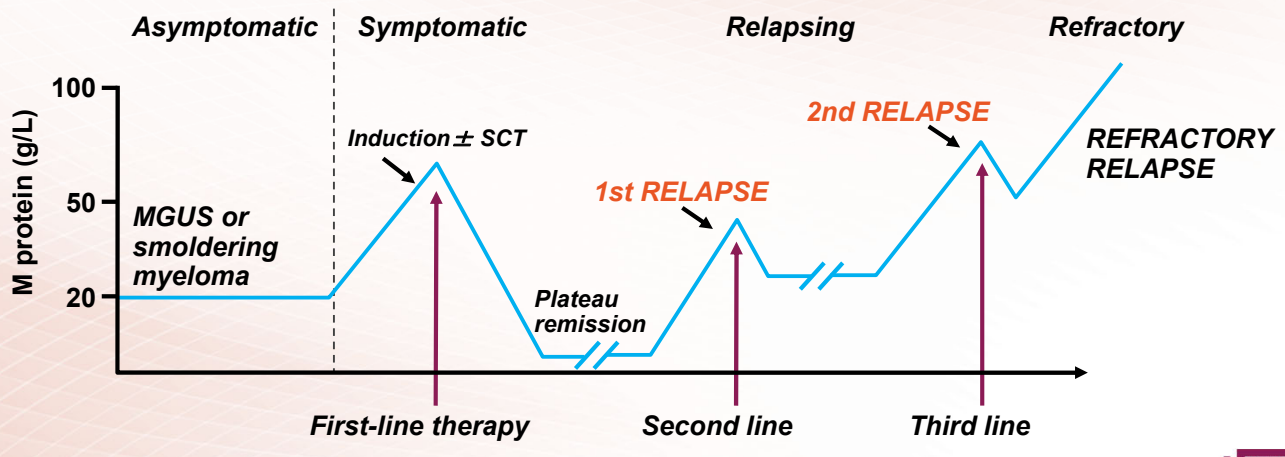
MULTIPLE MYELOMA Research Foundation

Treating Relapsed/Refractory Multiple Myeloma

Elizabeth O'Donnell, MD
Harvard University
Dana-Farber Cancer Institute
Boston, Massachusetts

67

Multiple Myeloma Is a Marathon, Not a Sprint



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

68

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

69

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**

70

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

71

Options for Relapsed/Refractory Disease Continue to Increase

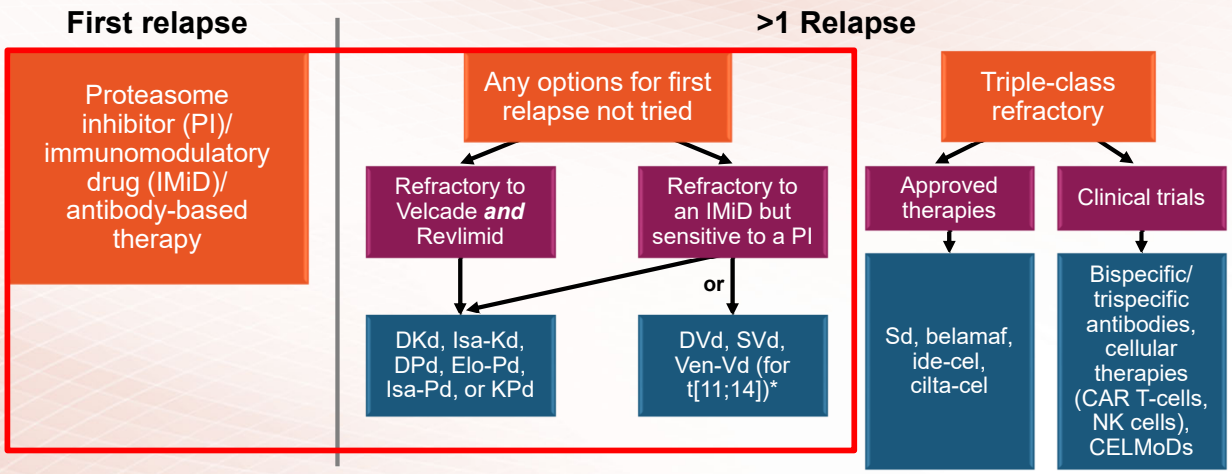
IMiDs	Proteasome inhibitors	Chemotherapy anthracyclines	Chemotherapy alkylators	Steroids	Novel mechanisms of action	Monoclonal antibodies	Cellular therapy
Thalomid (thalidomide)	Velcade (bortezomib)	Adriamycin	Cytoxan (cyclophosphamide)	Dexamethasone	XPOVIO (selinexor)	Empliciti (elotuzumab)	Abecma (idecabtagene 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)‡	

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

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

72

Treatment Approach

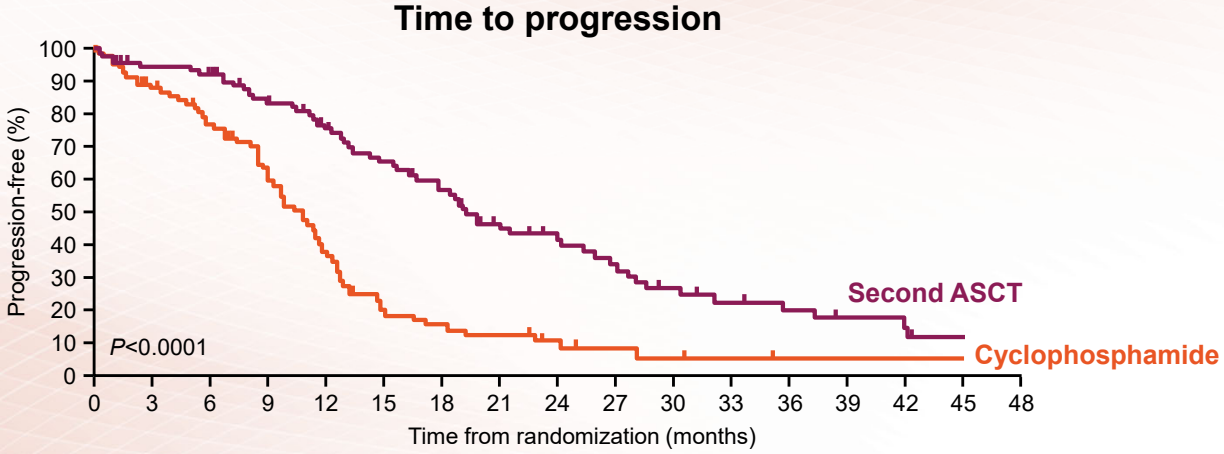


D, daratumumab (Darzalex); K, carfilzomib (Kyprolis); d, dexamethasone; Isa, isatuximab (Sarclisa); P, pomalidomide (Pomalyst); Elo, elotuzumab (Empliciti); V, bortezomib (Velcade); S, selinexor (Xpovio); Ven, venetoclax (Venclexta); belamaf, belantamab mafodotin (Blenrep); ide-cel, idecabtagene vicleucel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

*Not yet approved for use in myeloma patients

73

Second ASCT an Option for Early Relapse



Cook G et al. *Lancet Oncol*. 2014;15:874.

74

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

75

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

76

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

77

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

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

78

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

79

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. Manuscript under preparation.

80

Monoclonal Antibody–Based Regimens at Relapse

81

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

82

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

83

Important Considerations for Use of Darzalex

Darzalex

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

84

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: 36 vs 19 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

85

Important Considerations for Use of Monoclonal Antibodies

Empliciti

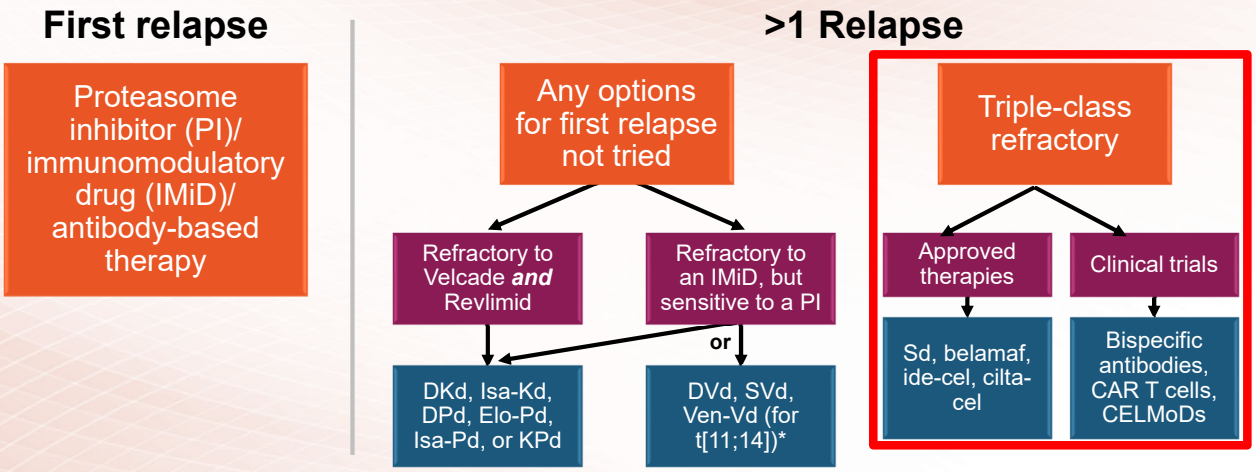
- **Infusion reactions**
- Risk of **shingles**
  - Use appropriate vaccination

Sarclisa

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

86

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

87

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)

88

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
Antibody-drug conjugate	Blenrep (belantamab mafodotin)*	2.5 mg/kg IV over approximately 30 minutes once every 3 weeks	• For **relapsed/refractory** myeloma (after at least 4 prior therapies including an anti-CD38 mAb, a PI, and an IMiD
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

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

*Black box warning: changes in the corneal epithelium resulting in changes in vision; Blenrep is available only through a restricted distribution program
†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
Abecma and Carvykti are available only through a restricted distribution program

89

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)

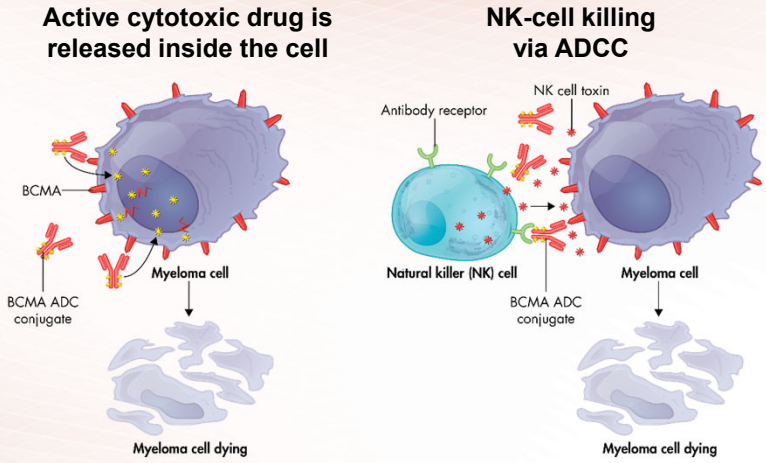
Additional analyses showed clinical benefit with XPOVIO regardless of patient age and kidney function.[2,3]

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.

90

Blenrep: Antibody-Drug Conjugate (ADC)

ADCs can selectively target and deliver drugs to myeloma cells.



ADCC, antibody-dependent cellular cytotoxicity; BCMA, B-cell maturation antigen
Figure adapted from Cho S-F et al. *Front Immunol*. 2018;9:1821. Trudel S et al. *Lancet Oncol*. 2018;19:1641.

91

Blenrep First ADC Approved in MM

DREAMM-2 Study	Blenrep (2.5 mg/kg)	Blenrep (3.4 mg/kg)
N	97	99
Median no. lines of therapy, n (range)	7 (3–21)	6 (3–21)
Overall response rate (%)	31	34
Median progression-free survival (mos)	2.9	4.9
Median overall survival (mos)	Not reached	Not reached

DREAM-2 Study. Lonial S et al. *Lancet Oncol*. 2020;21:207.

92

Currently Available ADC
Side Effects

Blenrep

- Thrombocytopenia
- Keratopathy
- Decrease visual acuity
- Nausea
- Blurred vision
- Fever
- Infusion-related reactions
- Fatigue

Management

- Available only through a Risk Evaluation and Mitigation Strategies (REMS) due to the risk of ocular toxicity
- Patients receive ophthalmic examinations at baseline (within 3 weeks prior to the first dose), prior to each dose, and promptly for worsening symptoms
- Patients are advised to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion and continuing until end of treatment
- Patients should also avoid use of contact lenses unless directed by an ophthalmologist

93

Emerging Therapies for Relapsed/Refractory Multiple Myeloma

Bispecific antibodies

- Teclistamab, elranatamab, talquetamab, cevostamab, and others
- Targets BCMA, GPRC5D, or FcRH5 on myeloma cells and CD3 on T cells
- Redirects T cells to myeloma cells

Cereblon E3 ligase modulators (CELMoDs)

- Iberdomide
- Targets cereblon
- Enhances tumoricidal and immune-stimulatory effects compared with immunomodulatory agents

Small molecule inhibitors

- Venetoclax
- Targets Bcl-2
- Induces multiple myeloma cell apoptosis

94

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.

95

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

96

MULTIPLE MYELOMA Research Foundation

CAR T-Cell Therapy and Bispecific Antibodies

Jesus G. Berdeja, MD
Sarah Cannon Research Institute
Tennessee Oncology
Nashville, Tennessee

97

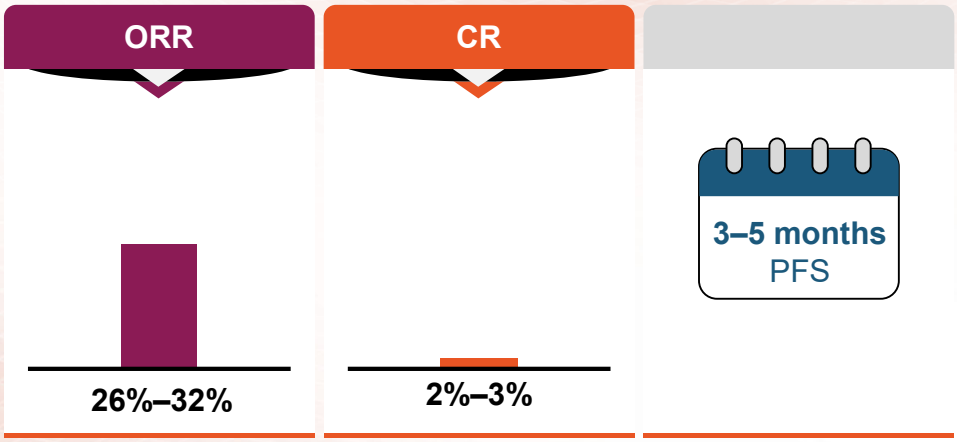
Triple-Class Refractory

- 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)

98

Where We've Been: Outcomes for Later-Line Triple Class-Exposed Patients With RRMM



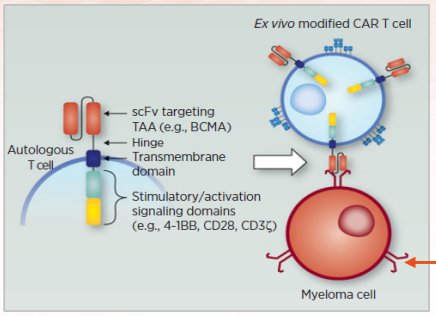
Exposed to an immunomodulatory imide drug, proteasome inhibitor, and CD38 monoclonal antibody

Gandhi UH et al. *Leukemia.* 2019;33(9):2266.

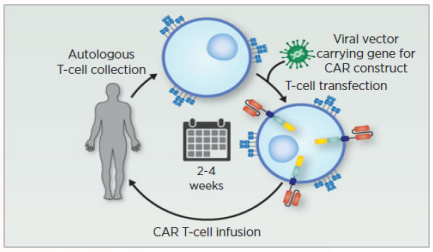
99

Where We're Going: CAR T-Cell Therapy

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



B-cell maturation antigen (BCMA)



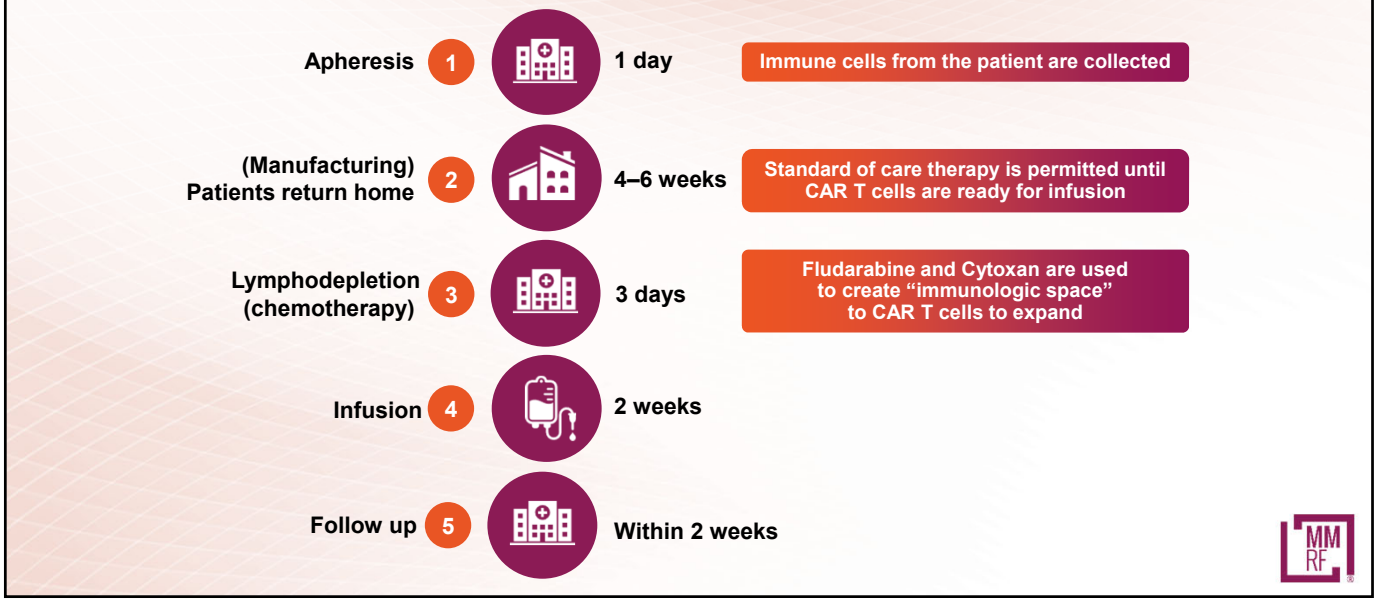
Examples:
- Abecma (ide-cel)
- Carvykti (cilta-cel)
- CT103A
- Gamma secretase inhibitor followed by CAR T-cells

CAR, chimeric antigen receptor; MM, multiple myeloma

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

100

CAR T-Cell Therapy Patient Journey



101

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

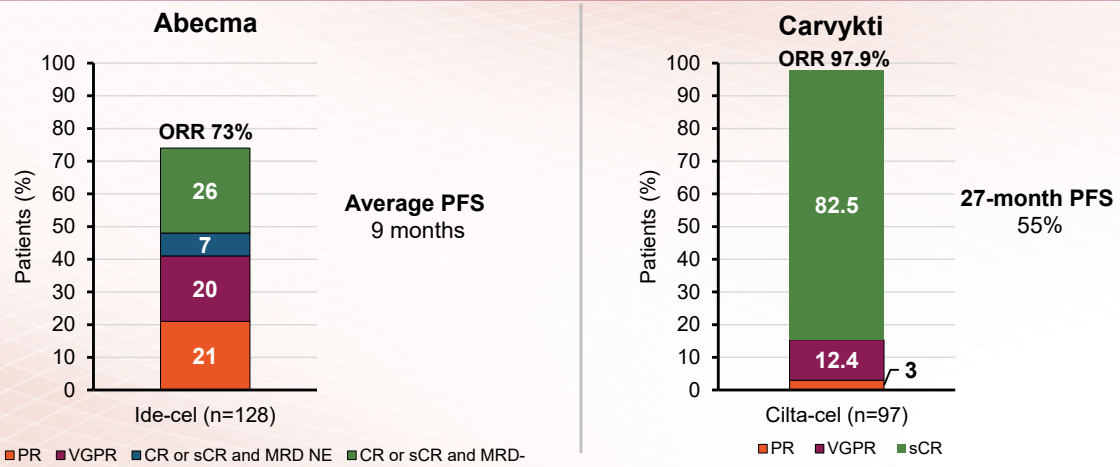
*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia

†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.

102

Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma

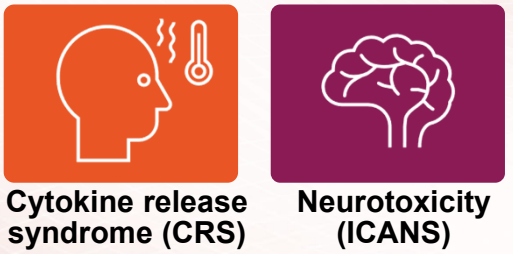


ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; PFS, progression-free survival

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. *JCO* 2022.

103

CAR T: Expected Toxicities



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

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

Xiao X et al. *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.

104

CAR T-Cell Therapy Themes: Myeloma

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

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

Most patients respond well to treatment and responses are durable; unfortunately, most patients eventually progress.

105

Transplant vs CAR T Cells

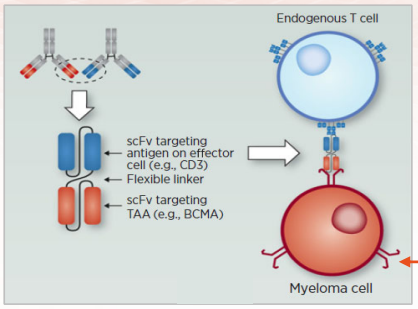
Cellular therapies	CAR T-cell therapy	Autologous stem cell transplantation
Patient's cells collected	Yes	Yes
Types of cells collected	T cells*	Stem cells†
Collected cells are genetically engineered in a lab	Yes	No
Patient given chemotherapy before cells are infused back into patient	Yes, lymphodepleting 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.

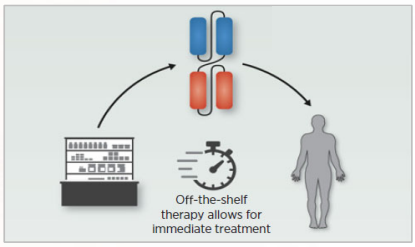
106

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

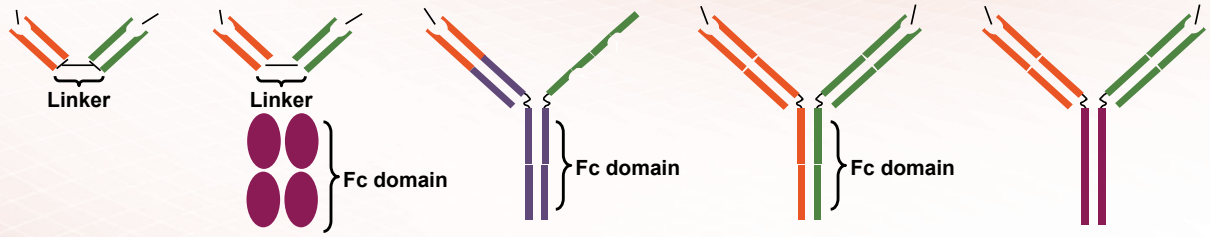


Examples:
- Elranatamab
- Teclistamab
- TNB-303B (ABBV-383)
- REGN5458
- Cevostamab
- Talquetamab

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

107

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



Light chains: 2
Heavy: Half-life extender

Light chains: 1
Heavy chains: 2

Light chains: 2
Heavy chains: 2

CD3 binding site
BCMA binding site

108

Bispecific Antibodies: >20% Activity

Myeloma cell target	Bispecific agent	Patients responding*
BCMA	Teclistamab	65%
BCMA	REGN5458	73%
BCMA	Elranatamab	73%
BCMA	TNB383B	60%
BCMA	CC93269	89%
BCMA	AMG701	83%
GPCR5	Talquetamab	70%
FCRH5	Cevostamab	55%

*Based on a recent sampling

109

Bispecific Antibodies: Expected Toxicities

- Cytokine release syndrome (CRS)
- Neurotoxicity (ICANS)
  - Usually occurs within first 1–2 weeks
  - Frequency (all grade and grade 3–5) higher with CAR T
- Cytopenias
- Target unique
  - For example, rash, taste disturbance seen with GPRC5D, but not with BCMA
- Infections
  - Incidence for bispecifics at RP2D not yet known
  - Viruses: CMV, EBV
  - PCP/PJP
  - Ongoing discussions regarding prophylactic measures
    - IVIG
    - Anti-infectives

110

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

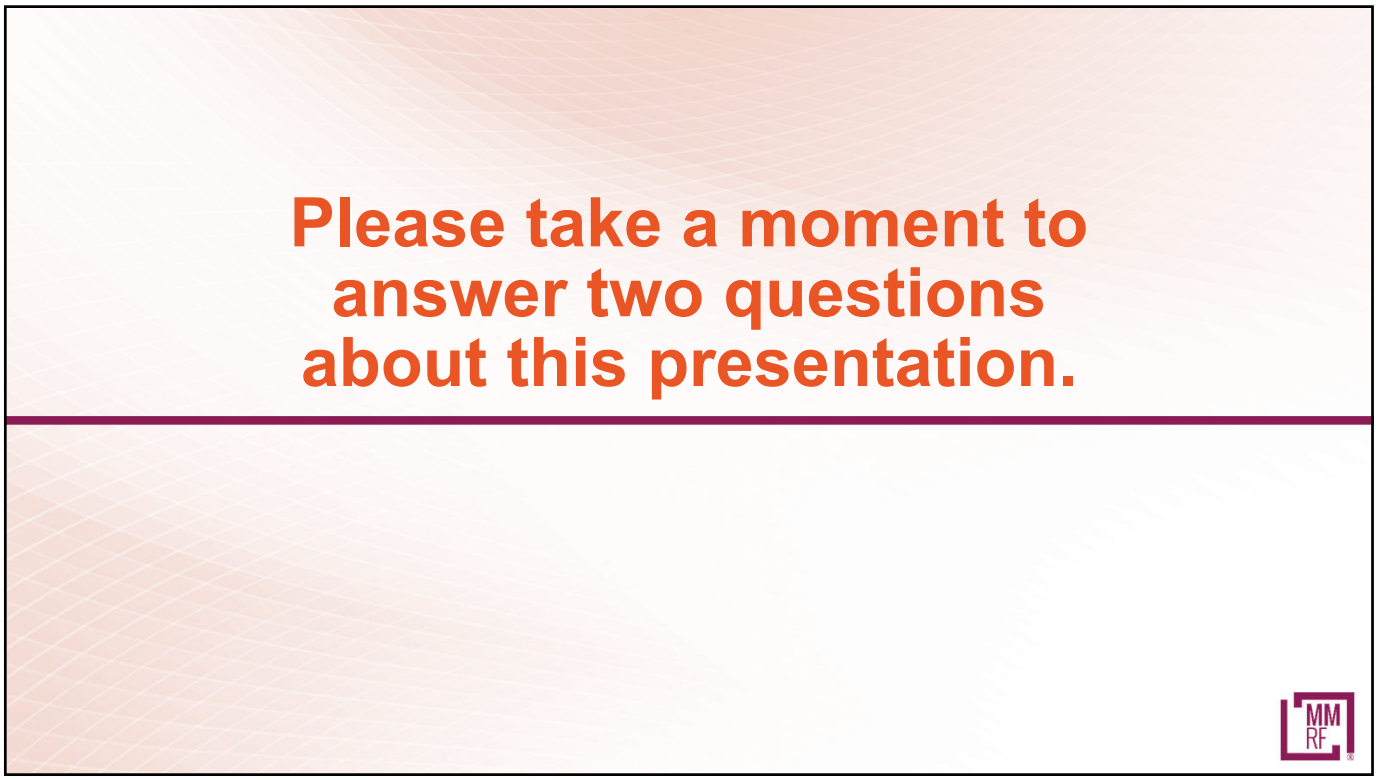
	CAR T cell therapy	Bispecific antibody
Approved product	Abecma, Carvykti	None (several in phase 2)
Efficacy	++++	+++
How given	One-and-done	IV or SC, weekly to every 3 weeks until progression
Where given	Academic medical centers	Academic medical centers**
Notable adverse events	CRS and neurotoxicity	CRS and neurotoxicity
Cytokine release syndrome	+++	++
Neurotoxicity	++	+
Availability	Wait time for manufacturing	Off-the-shelf, close monitoring for CRS and neurotoxicity

111

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 (CRS), 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.**
- **Several different bispecific antibodies are under clinical evaluation.**

112


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

113


MULTIPLE MYELOMA
Research Foundation
Patient Experience

114

Town Hall Questions & Answers

115

Thank you!

116

abbvie Adaptive biotechnologies AMGEN Bristol Myers Squibb™

CRISPR THERAPEUTICS cure20TH anniversary Genentech A Member of the Roche Group GSK

janssen Karyopharm® Therapeutics Pfizer

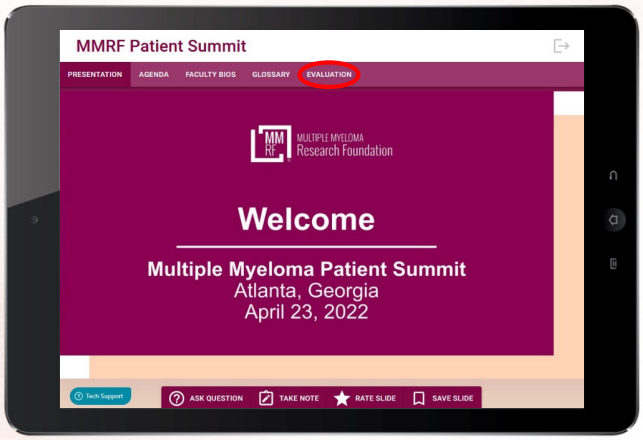
REGENERON SCIENCE TO MEDICINE® sanofi Takeda ONCOLOGY

MM RF

117

Don't Forget!

Complete your evaluation
Leave the iPad at your seat



MM RF

118

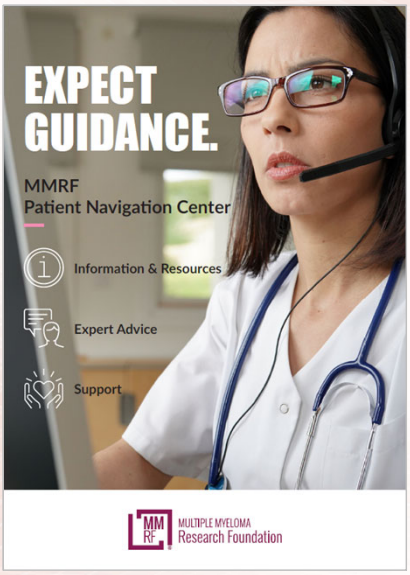
Upcoming Patient Education Events
Save the Date

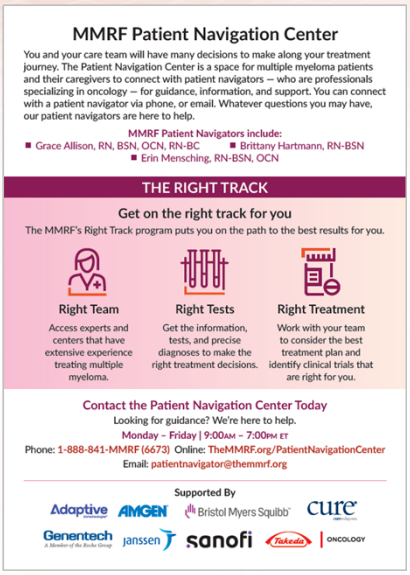
Topic	Date and Time	Speakers
Patient Summit (live and online)	Saturday, November 5 9:00 AM – 2:00 PM (ET) Washington, DC	David Vesole, MD, PhD—Host Kenneth Shain, MD, PhD Edward Stadtmauer, MD
Patient Summit (live and online)	Friday, December 9 12:00 PM – 4:30 PM (CT) New Orleans, Louisiana	Laura Finn, MD—Host Ambuga R. Badari, MD Amrita Y. Krishnan, MD Suzanne Lentzsch, MD, PhD Paul G. Richardson, MD A. Keith Stewart, MBChB

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

119

MMRF Patient Resources





120

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.

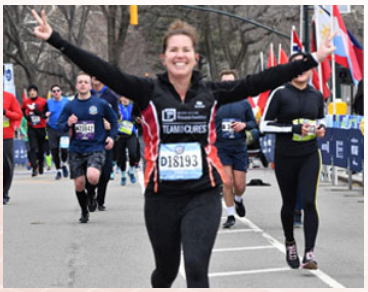
Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.

121

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/

122