MULTIPLE MYELOMA Research Foundation

Opening Remarks

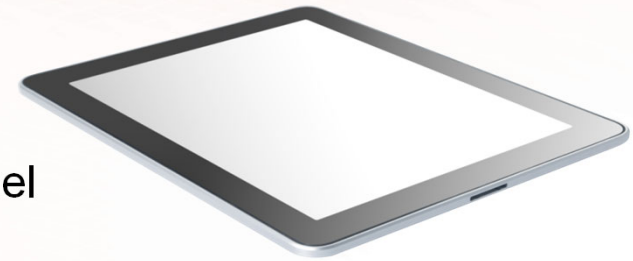
Veronica Bohorquez, MA
MMRF

1

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 Hosts

Benjamin A. Derman, MD
University of Chicago Medical Center
Chicago, Illinois

Andrzej J. Jakubowiak, MD, PhD
University of Chicago Medical Center
Chicago, Illinois

Faculty

Monique A. Hartley-Brown, MD, MMSc
Dana-Farber Cancer Institute
Boston, Massachusetts

Jing Christine Ye, MD, MSc
University of Michigan
Rogel Cancer Center
Ann Arbor, Michigan

4

Summit Agenda

Time (CT)	Topic	Speakers
9:00–9:10 AM	Introduction to the MMRF	Veronica Bohorquez, MA
9:10–9:20 AM	Welcome	Andrzej J. Jakubowiak, MD, PhD Benjamin A. Derman, MD
9:20–9:50 AM	Myeloma 101: Diagnosis, Prognosis, and Risk	Jing Christine Ye, MD
9:50–10:20 AM	Frontline Myeloma and The Emerging Role of MRD	Andrzej J. Jakubowiak, MD, PhD
10:20–10:50 AM	Treating Early Relapsed and Refractory Myeloma	Monique Hartley-Brown, MD
10:50–11:05 AM	Break	
11:05–11:35 AM	Emerging Treatment Options for Refractory Myeloma – CAR T, Immunotherapy, and Precision Medicine	Benjamin A. Derman, MD
11:35 AM–12:05 PM	Town Hall Q&A	Panel
12:05–1:05 PM	Lunch, Patient Journey	Louise Kraft
1:05–1:20 PM	Clinical Trials	Andrzej J. Jakubowiak, MD, PhD
1:20–1:50 PM	Town Hall Q&A	Panel
1:50 PM	Closing Remarks	Veronica Bohorquez, MA

5

MULTIPLE MYELOMA Research Foundation

MMRF Introduction

Veronica Bohorquez, MA
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

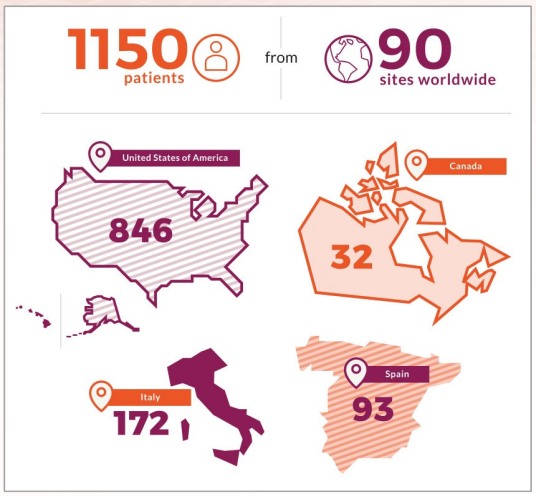
Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

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

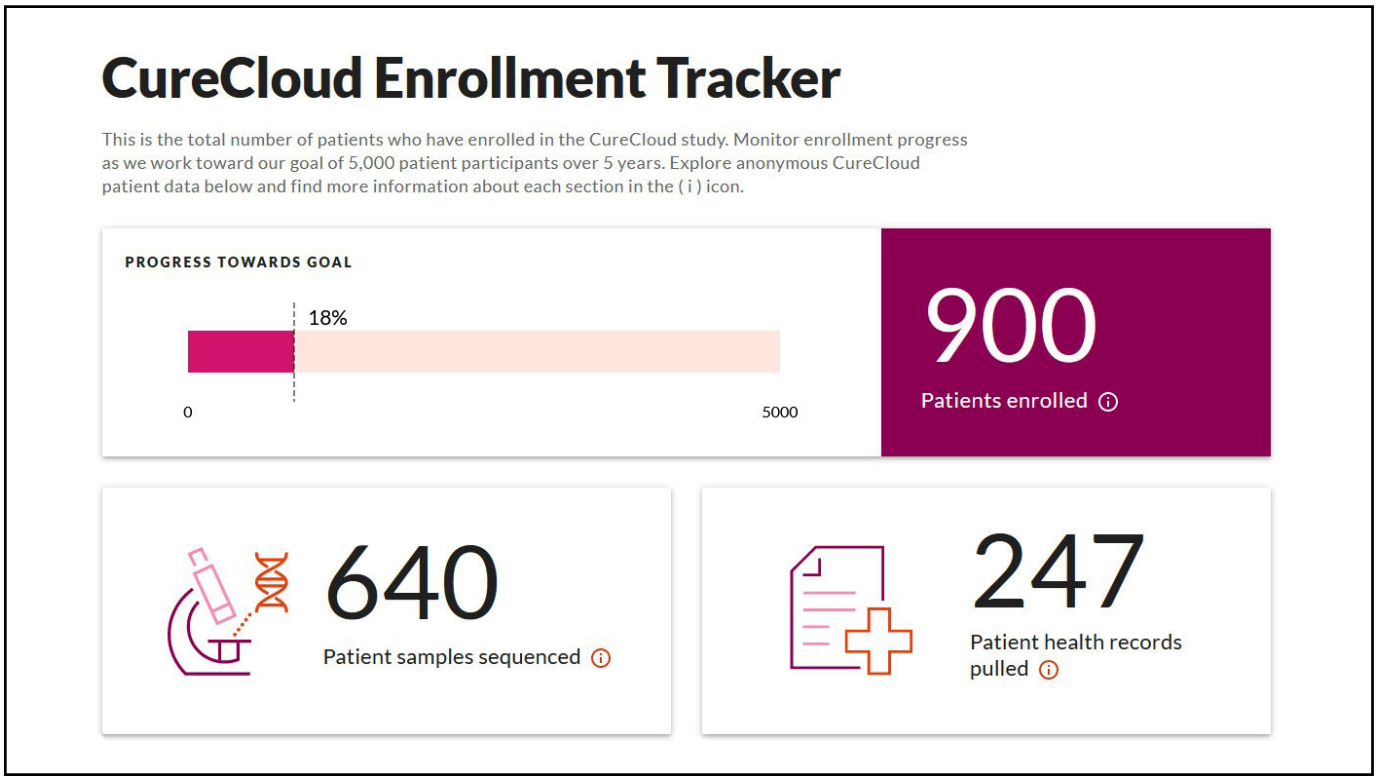
- CoMMpass data has
  - Provided the myeloma community with information on
    - Frequency of genetic abnormalities
    - How genetic abnormalities play a role in myeloma
      - Drive multiple myeloma cell growth and survival
      - Contribute to drug resistance
      - May predict which patients respond 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!

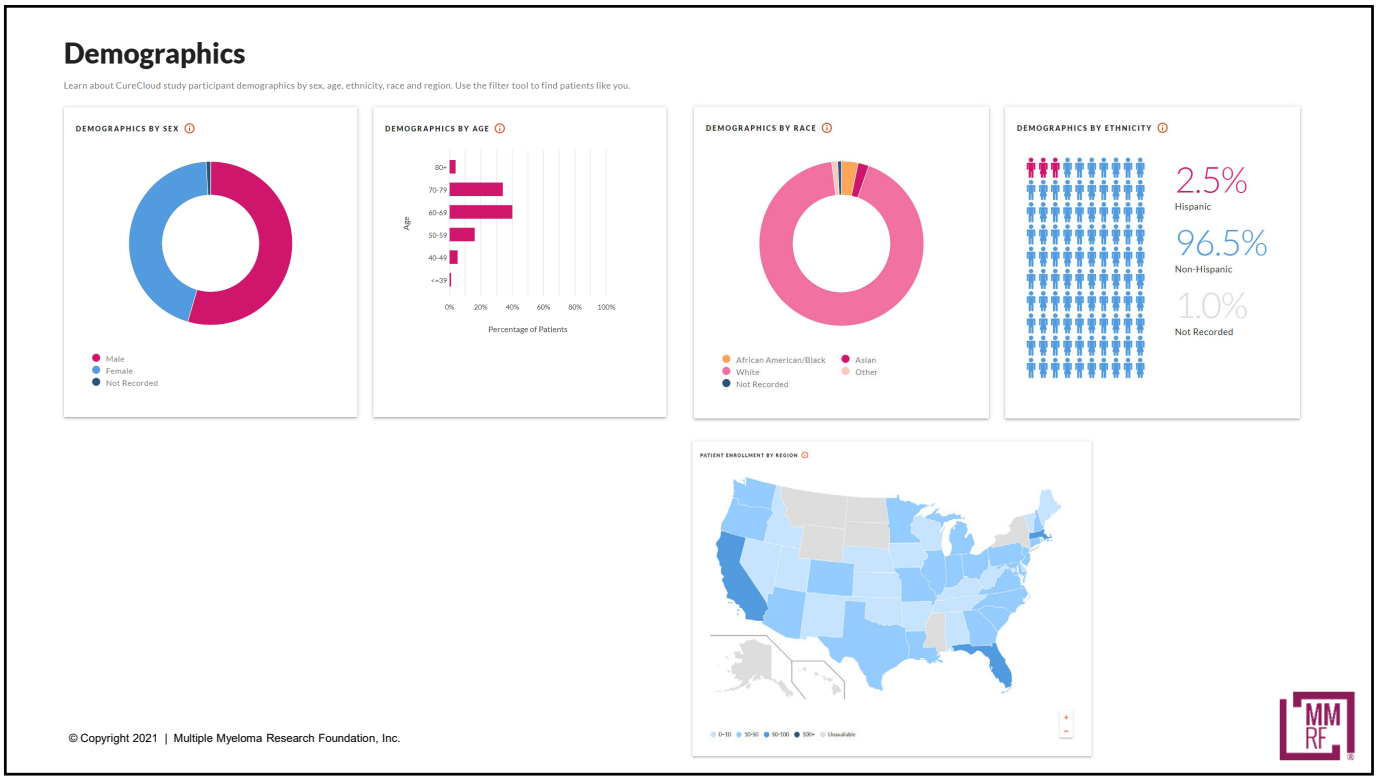
9

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
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12


Clinical
Explore clinical information from CureCloud study participants, including disease state, family history, staging information, years since diagnosis and subtype. Use the filter tool to see results relevant to the specifics of your multiple myeloma.
DISEASE STATE UPON ENROLLMENT
Smoldering Multiple Myeloma
Newly Diagnosed Multiple Myeloma
Relapsed Multiple Myeloma
Active Multiple Myeloma Not Otherwise Specified
FAMILY HISTORY OF ANY BLOOD CANCER
Yes
No
Not Recorded
FAMILY HISTORY OF MULTIPLE MYELOMA
Yes
No
Not Recorded
SUBTYPE: HEAVY CHAIN
Percentage of Patients
IgA
IgG
IgM
IgD
No Heavy Chain
Not Recorded
Subtype
SUBTYPE: LIGHT CHAIN
Percentage of Patients
Kappa
Lambda
No Light Chain
Not Recorded
Subtype
YEARS SINCE DIAGNOSIS
Percentage of Patients
0-2
3-5
6-9
10+
Years
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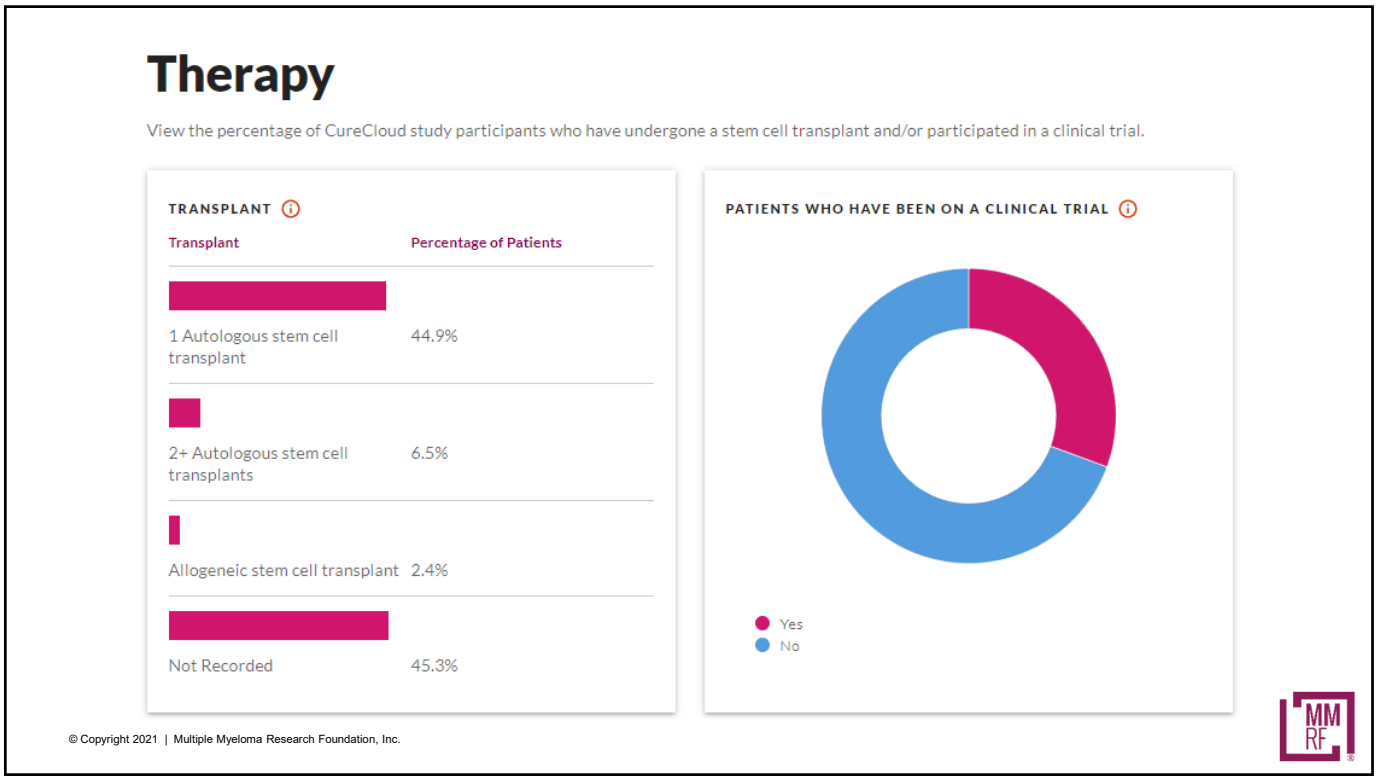
13


Genomics
Learn about the percentage of CureCloud study participants whose DNA tests identified cytogenetic abnormalities and/or genetic mutations.
CYTOGENETICS
Percentage of Patients
t(11;14)
t(14;16)
t(14;20)
t(4;14)
17p13
1p Loss
1q Gain
Genetics Mutations
GENETIC MUTATIONS
Genetic Mutations
NRAS
KRAS
FGFR3
BRAF
10%
30%
50%
70%
90%
Percentage of Patients
© 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
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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

Question

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

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

22

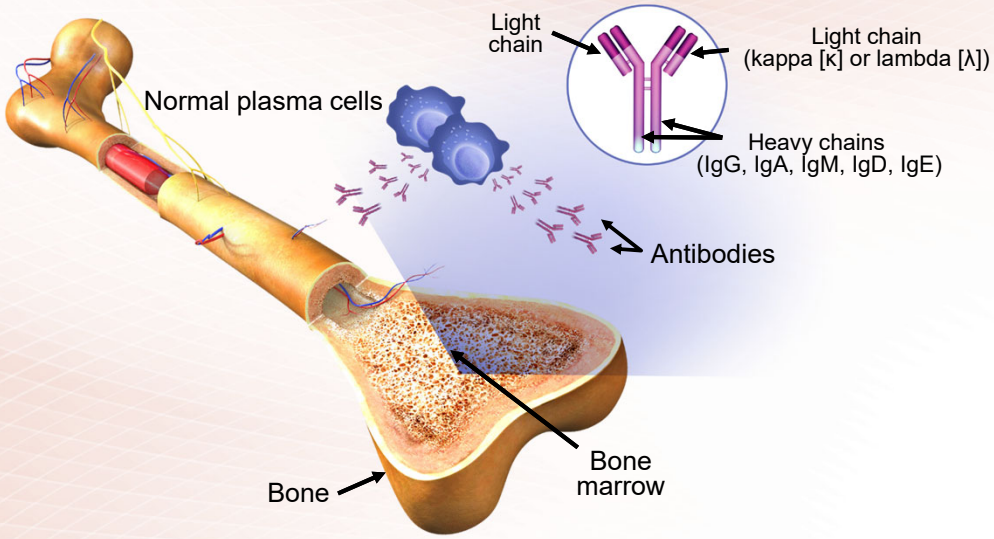
MULTIPLE MYELOMA Research Foundation

Myeloma 101: Diagnosis, Prognosis, and Risk

Jing Christine Ye, MD, MSc
University of Michigan, Rogel Cancer Center
Ann Arbor, Michigan

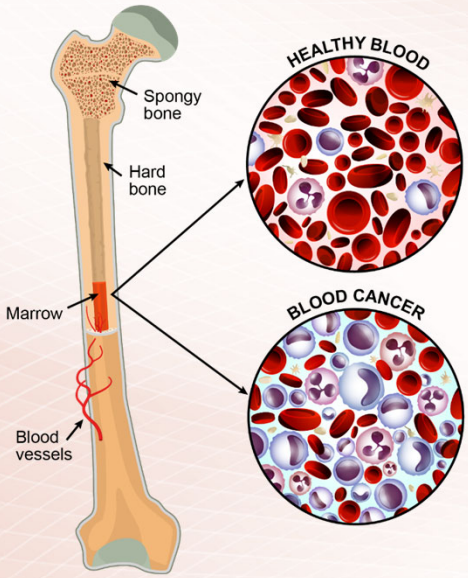
23

Normal Bone Marrow



24

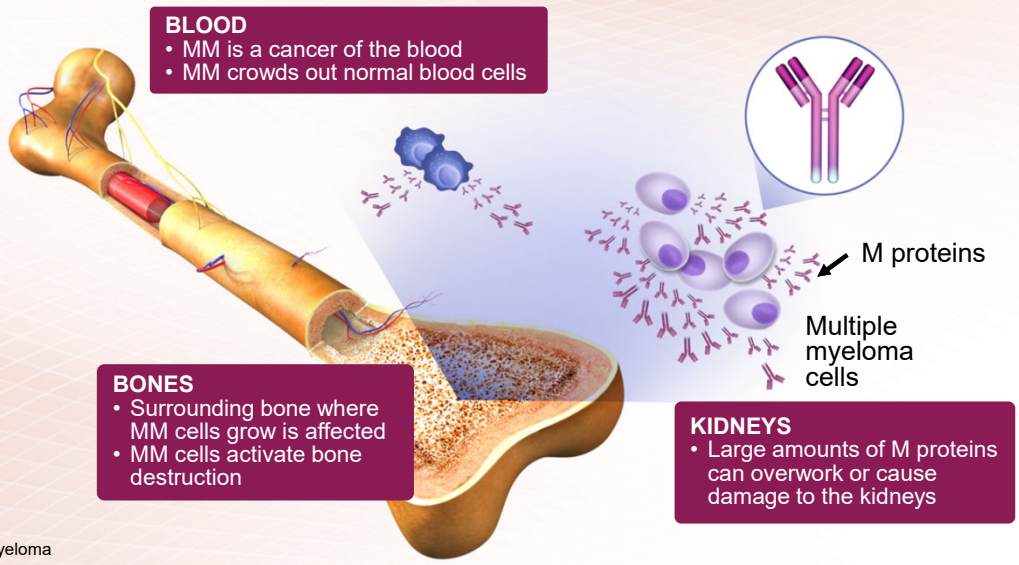
What is multiple myeloma?



- 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

25

Multiple Myeloma Affects Your Bones, Blood, and Kidneys



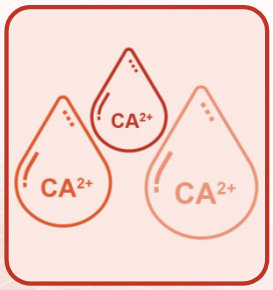
MM, multiple myeloma

26

Multiple Myeloma Affects Your Bones, Blood, and Kidneys

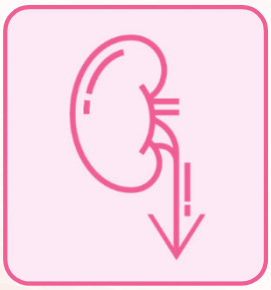
The clinical features that are characteristic of multiple myeloma

C



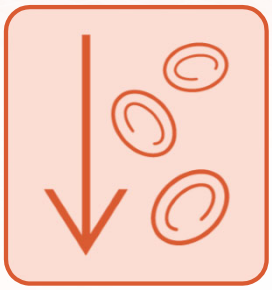
High levels of **c**alcium in the blood

R



Decreased kidney (**r**enal) function

A



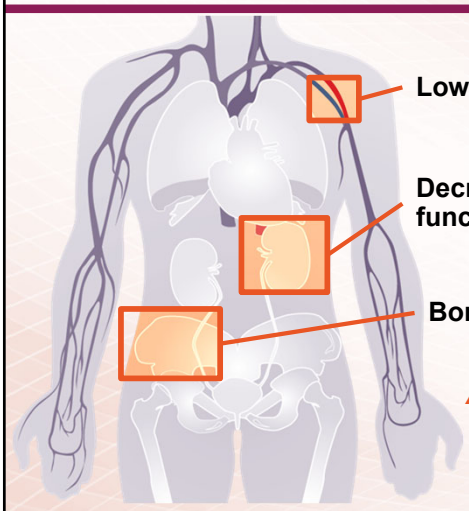
Low amount of red blood cells (**a**nemia)

B

Presence of **b**one damage

27

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

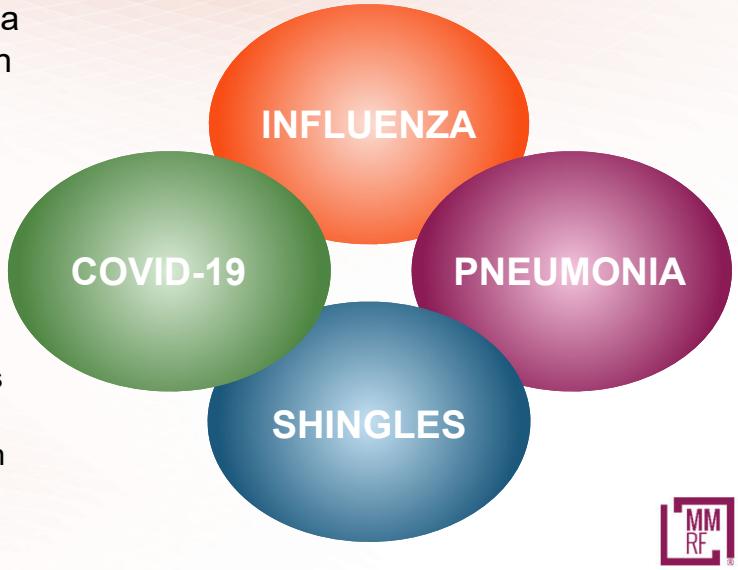
- Bone fractures

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.

28

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)



29

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.

30

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

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

Right Tests
Get the information, tests and precise diagnoses to make the right treatment decisions

Right Treatment
Work with your team to decide on the best treatment plan and identify clinical trials that are right for you

31

The Right Team

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

Seek a second opinion at any point in your journey

Available resources

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

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

1-888-841-MMRF (6673)

32

The Right Tests

Common laboratory tests conducted

Blood tests

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

Urine tests

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

Bone marrow biopsy

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

New
- Genomic sequencing

Imaging tests

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

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

33

Making the Diagnosis: The Right Tests

Common laboratory tests conducted

Blood and urine tests

- Confirms the type of myeloma

Bone marrow biopsy tests

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

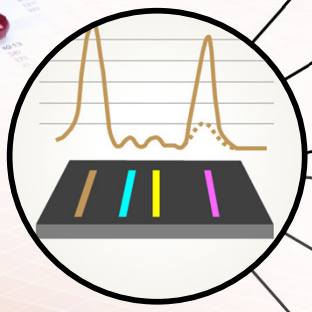
Imaging tests

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

34

Learn Your Labs in Blood!

Blood tests



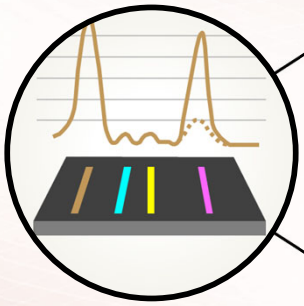
- **CBC** — Number of red blood cells, white blood cells, and platelets
- **CMP** — Measure levels of albumin, calcium, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and creatinine. Assess function of kidney, liver, and bone status and the extent of disease
- **B2M** — Determine the level of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

35

Learn Your Labs in Urine!

Urine tests

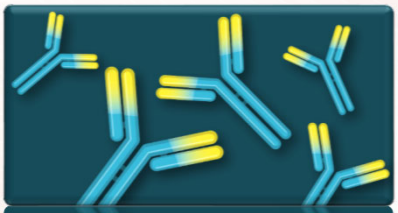


- **UPEP** — Detect Bence Jones proteins (otherwise known as myeloma light chains)
- **24-hr urine analysis** — Determine the presence and levels of M protein and Bence Jones protein

UPEP, urine protein electrophoresis

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

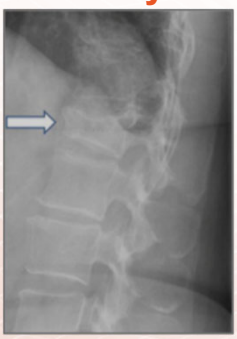
3%

37

Know Your Imaging Tests!

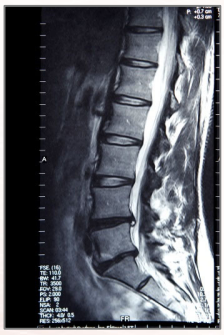
Assess changes in the bone structure and determine the number and size of tumors in the bone

X-ray

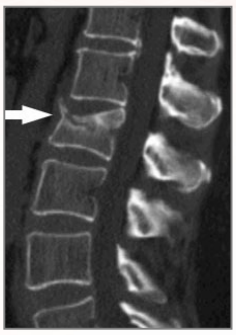


Conventional x-rays reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.

MRI



CT scan

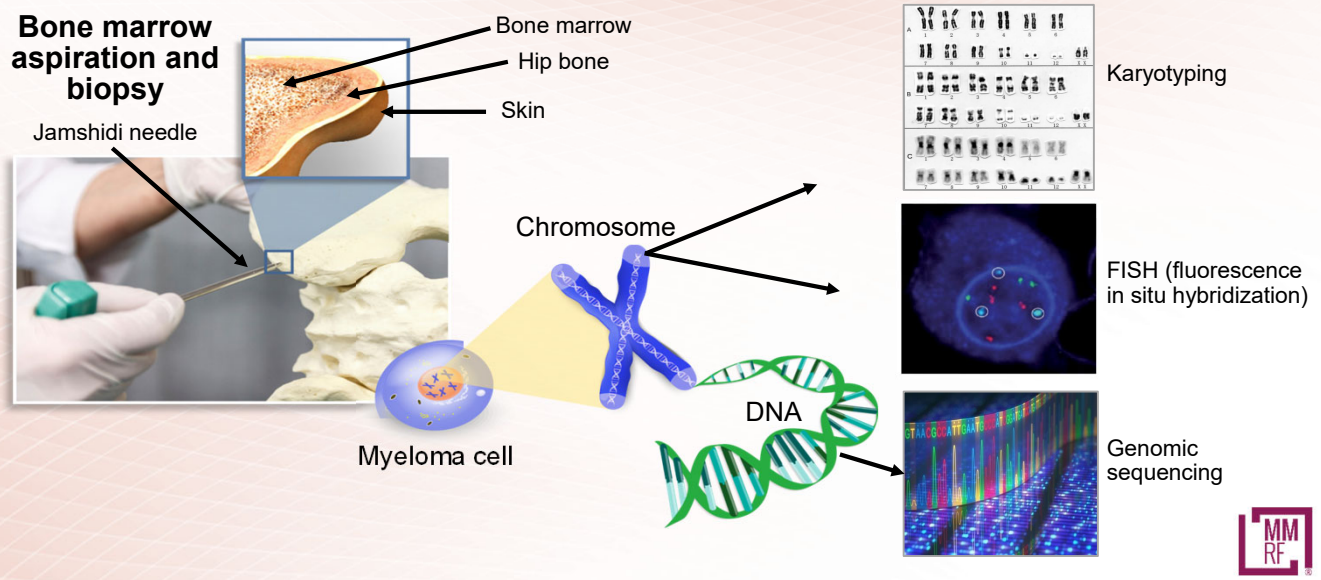


PET scan

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

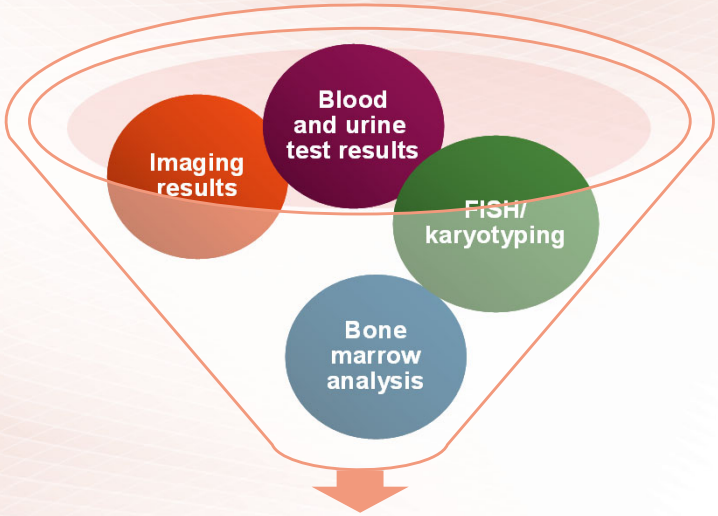
38

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	5-year overall survival (%)	5-year progression-free survival (%)
I	• Serum β2M level <3.5 mg/L • Serum albumin level ≥3.5 g/dL • No high-risk CA* • Normal LDH level	82	55
II	All other possible combinations	62	36
III	• Serum β2M level ≥5.5 mg/L • High-risk CA* or high LDH level	40	24

*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.

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

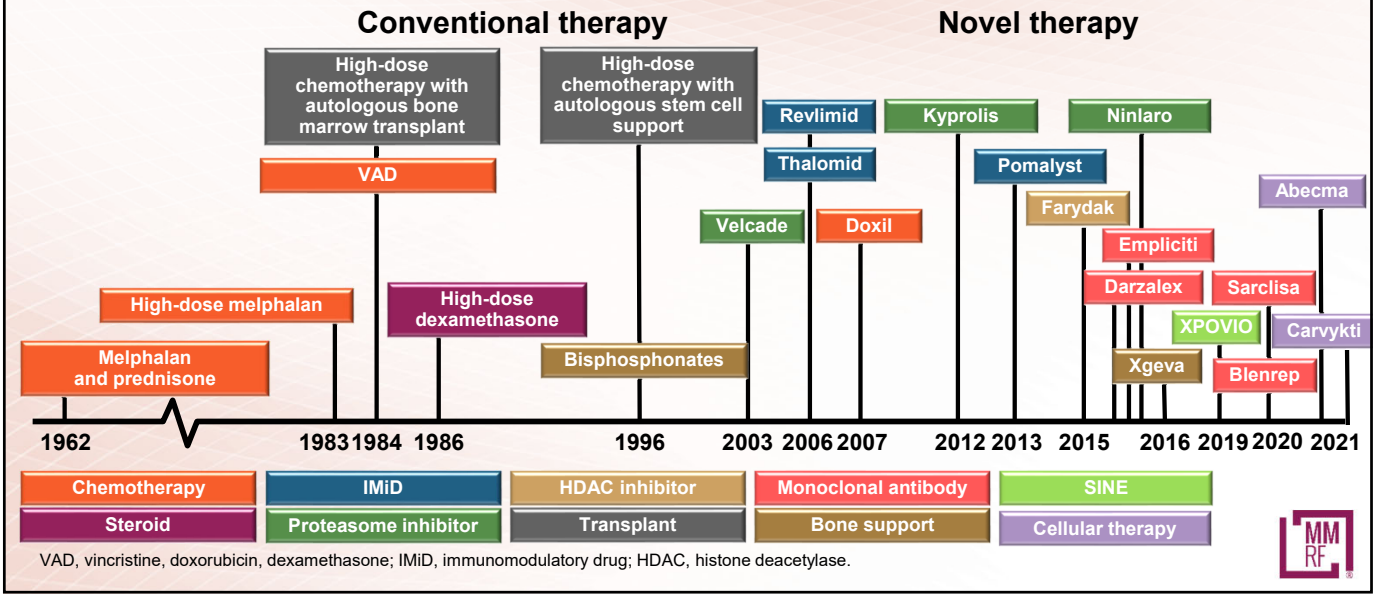
42

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

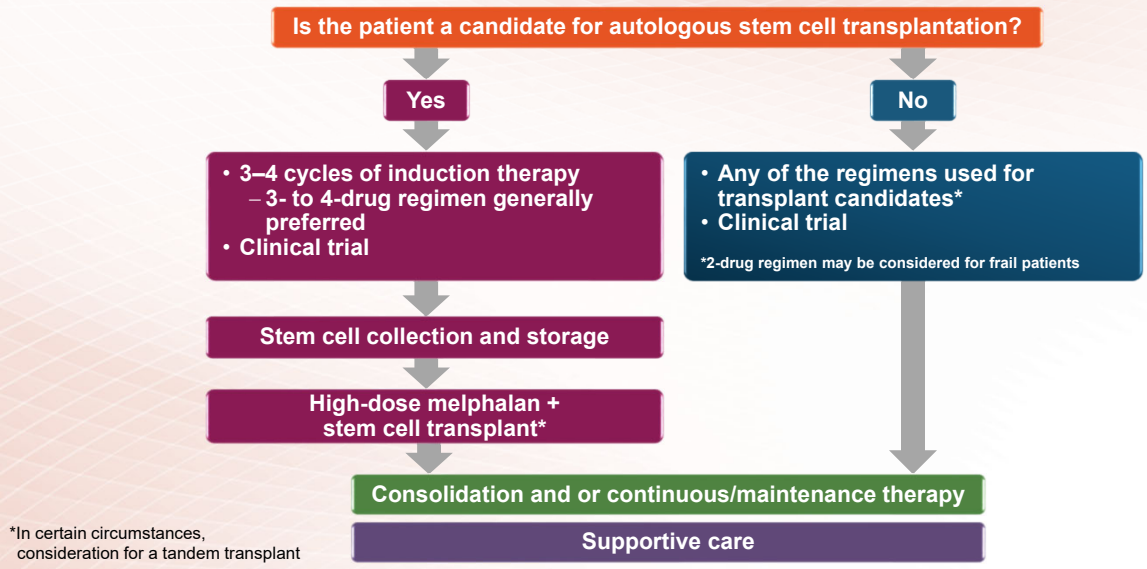
Evolution of Multiple Myeloma Treatment: 16 New Drugs Approved in ≤18 Years



VAD, vincristine, doxorubicin, dexamethasone; IMiD, immunomodulatory drug; HDAC, histone deacetylase.

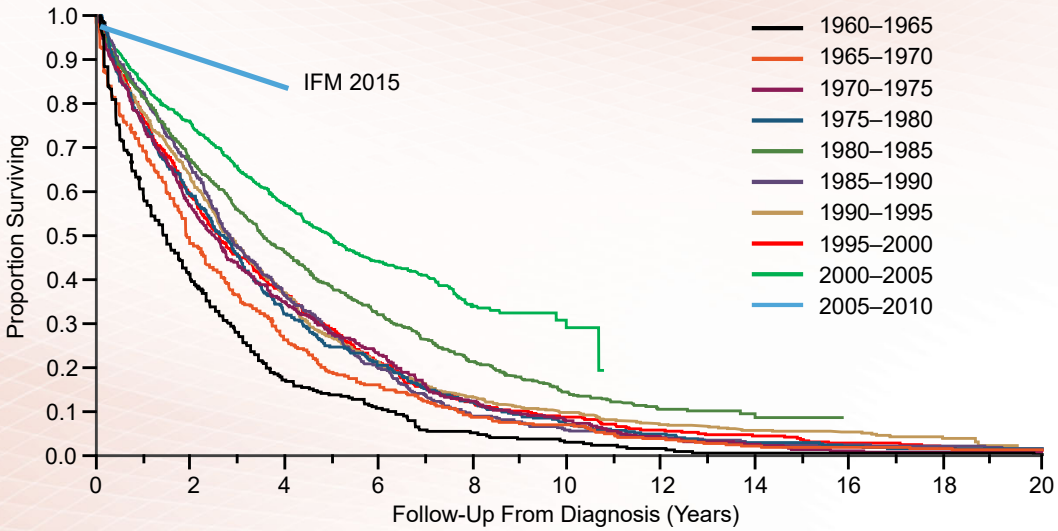
44

Overview of Treatment Approach for Active Multiple Myeloma



45

Current Drugs Have Improved Survival in MM



Adapted from Kumar SK et al. *Leukemia*. 2014;28:1122.

46

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.
- Myeloma patient survival has significantly increased.
- Knowledge is power: right team, right test, right treatment.

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

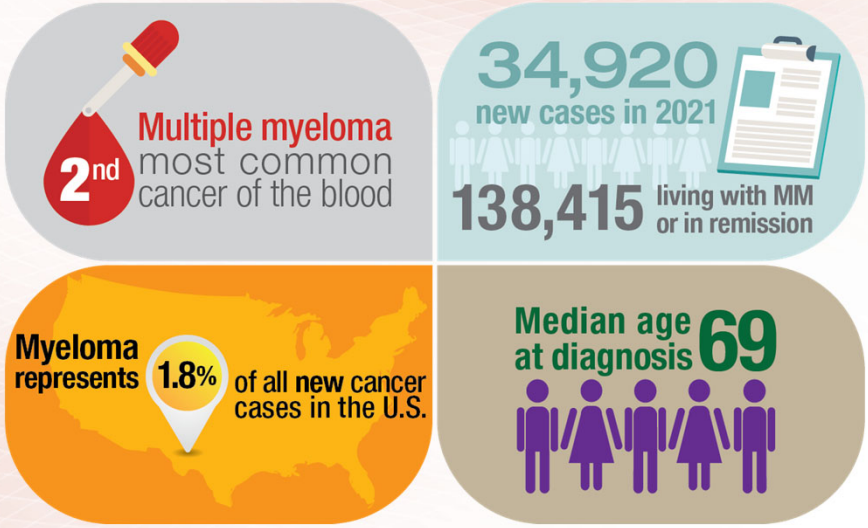
47

MULTIPLE MYELOMA Research Foundation

Health Care Disparities in Multiple Myeloma

48

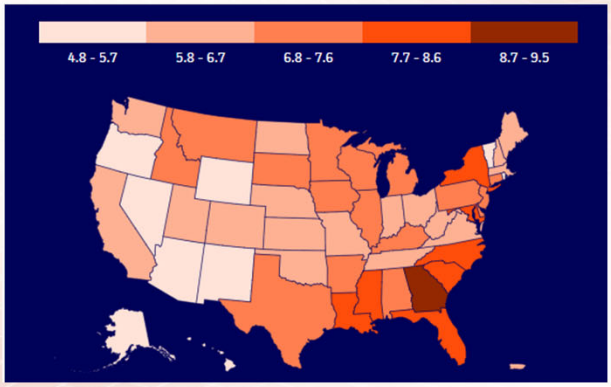
How common is multiple myeloma?



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

49

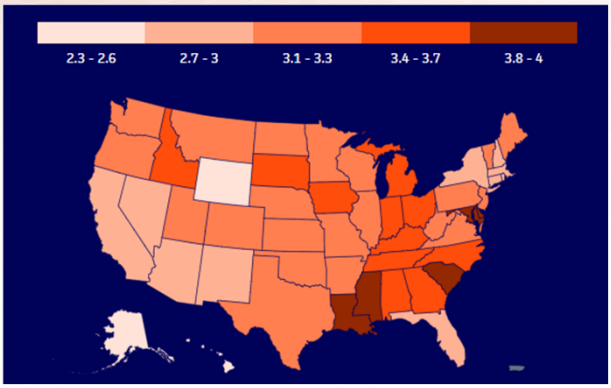
Incidence rates, 2014–2018
Myeloma, by state



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



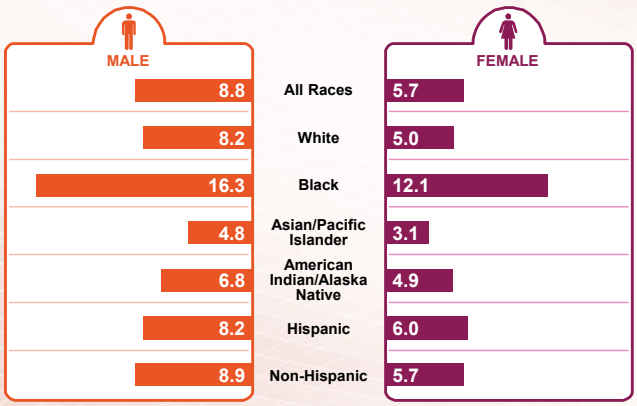
Average annual rate per 100,000, age adjusted to the 2000 US standard population.

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

50

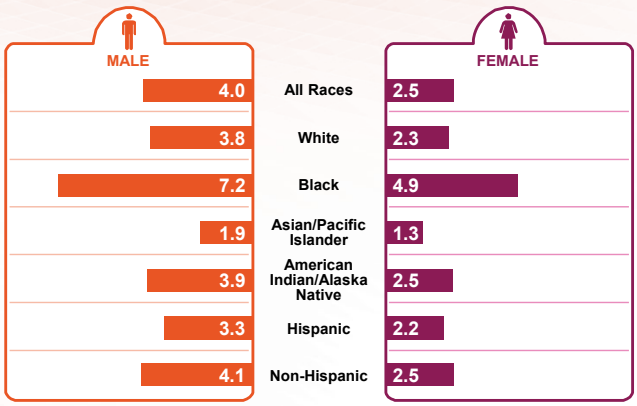
Multiple Myeloma Is Twice as Common in Black Patients

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

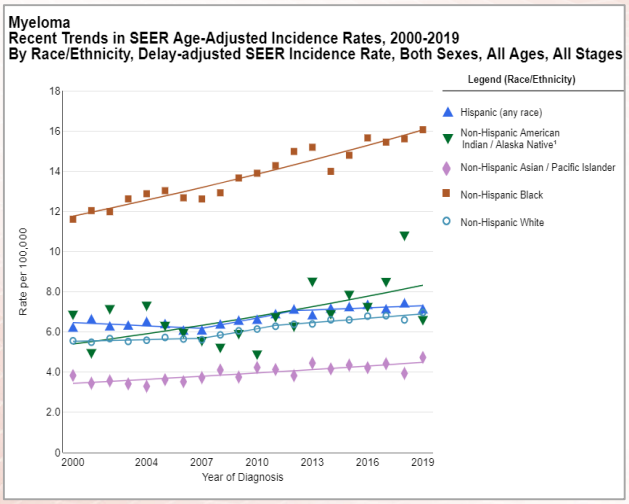


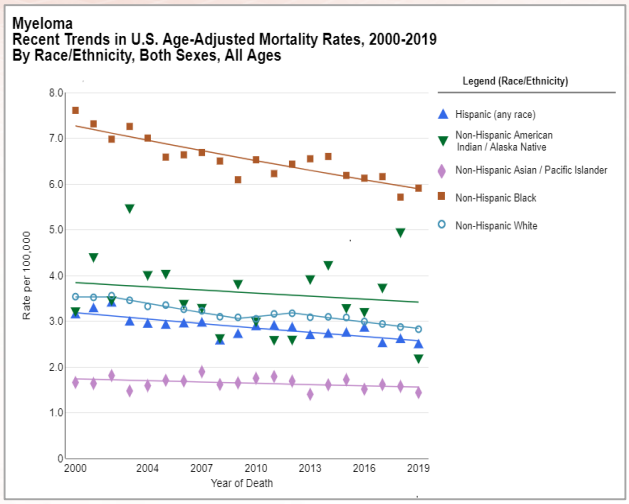
U.S. 2015-2019, Age-Adjusted

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

51

Multiple Myeloma Incidence and Mortality by Race/Ethnicity



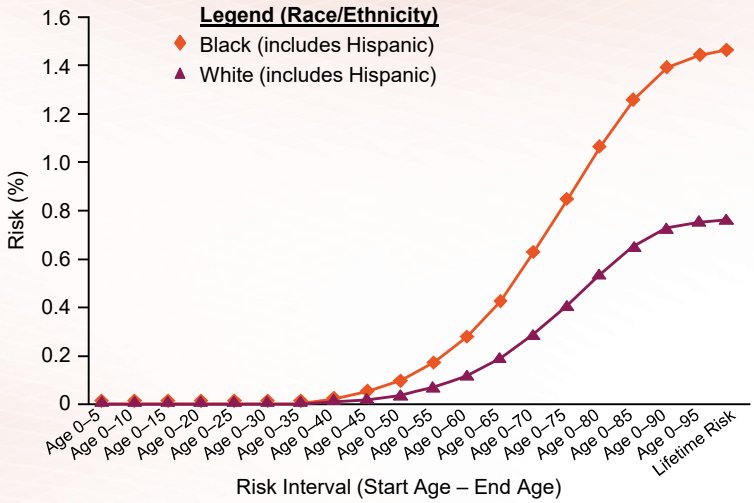


SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD. https://seer.cancer.gov/statistics-network/explorer/application.html

52

Risk of Myeloma Diagnosis Over Time

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



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

53

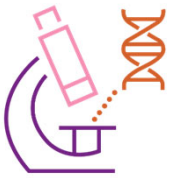
Multiple Myeloma in Black Patients

Demographics

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

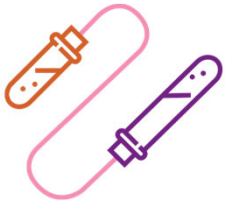
Clinical factors

- ↑ 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.

54

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%	.004
Stem cell transplantation	**30%**	40%	.034

55

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

56

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.**

57

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

58

MULTIPLE MYELOMA Research Foundation

Frontline Myeloma and the Emerging Role of MRD

Andrzej J. Jakubowiak, MD, PhD
University of Chicago Medical Center
Chicago, Illinois

59

Multiple Myeloma Diagnosis

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

60

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

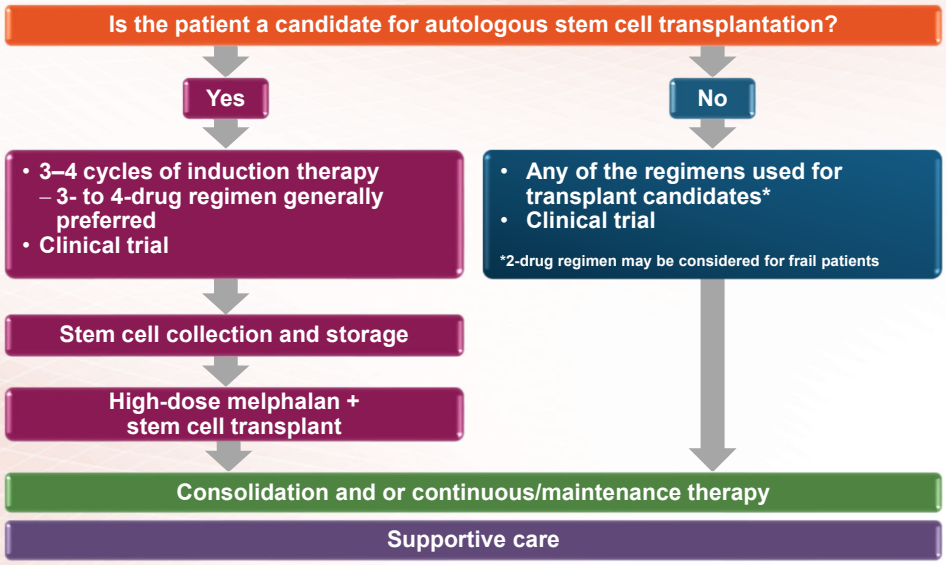
61

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

62

Overview of Treatment Approach for Active Multiple Myeloma



63

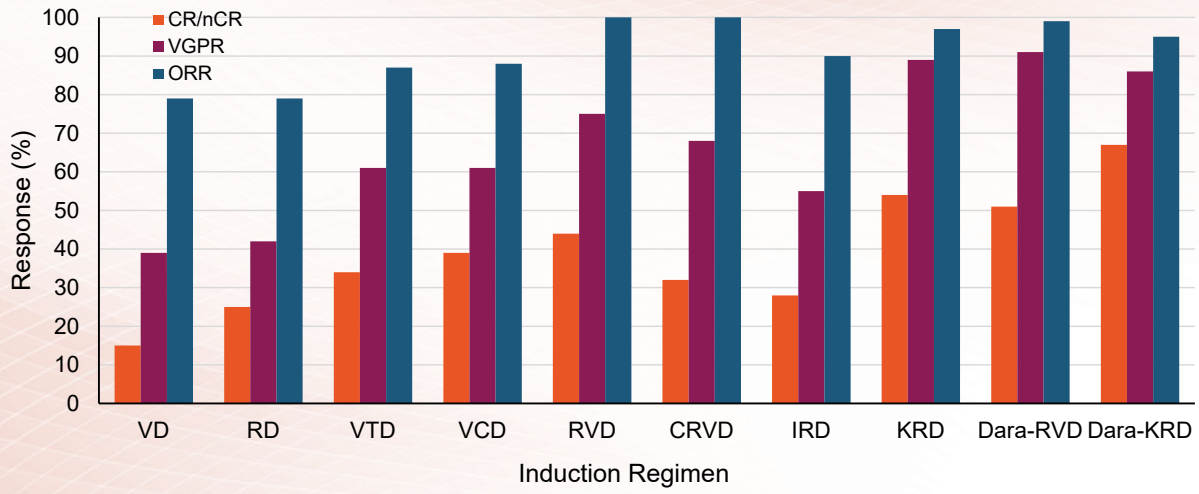
Induction Therapy Regimens

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

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

64

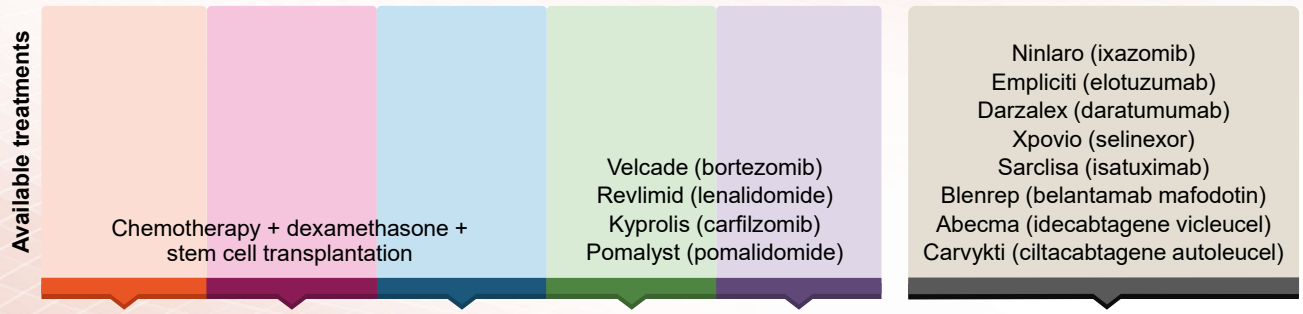
Induction Choices



65

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



66

Main Body Systems Affected by Myeloma Treatment

Blood

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

CNS

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

Cardio-vascular

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

Gastro-intestinal

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

67

Side Effects of Steroids (dexamethasone)

Insomnia

- Healthy sleep habits
- Timing
- Medication to assist with sleeping as needed

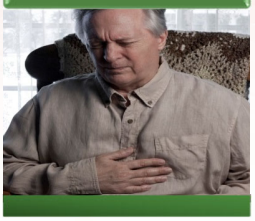
Fluid retention

- Monitor for swelling of extremities and "puffy" face
- Monitor weight changes/gain
- Reduce dose

Mood changes

- Irritable, anxiety, difficulty concentrating
- Severe cases → depression, euphoria

Dyspepsia–heartburn



- Dietary modifications (spicy, acidic foods)
- Avoid NSAIDs
- Acid-blocking medications
- Take steroid with food; use enteric-coated aspirin with food

Elevation in glucose

- Monitor glucose and refer/treat as needed

68

What does transplant mean?

Understanding the basics of autologous stem cell transplantation

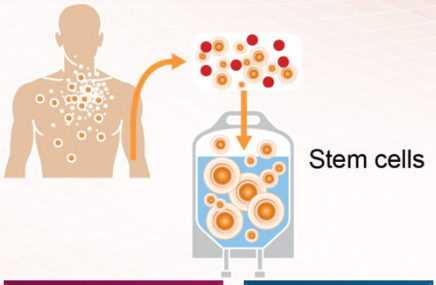
Hematopoietic, or blood-forming, cells are stimulated to move to the bloodstream and are collected from the patient.

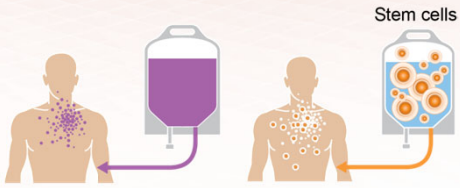
The patient receives high-dose melphalan chemotherapy to eradicate myeloma cells in the blood and bone marrow.

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

69

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	-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.

70

What is maintenance therapy?

A prolonged, and often low-dose, treatment given to myeloma patients after their initial therapy (or transplant)

To prevent disease progression for as long as possible while maintaining favorable quality of life

To eliminate minimal residual disease (MRD) or maintain the absence of MRD, reduce the risk of relapse, and prolong survival

71

Continuous or Maintenance Therapy Options

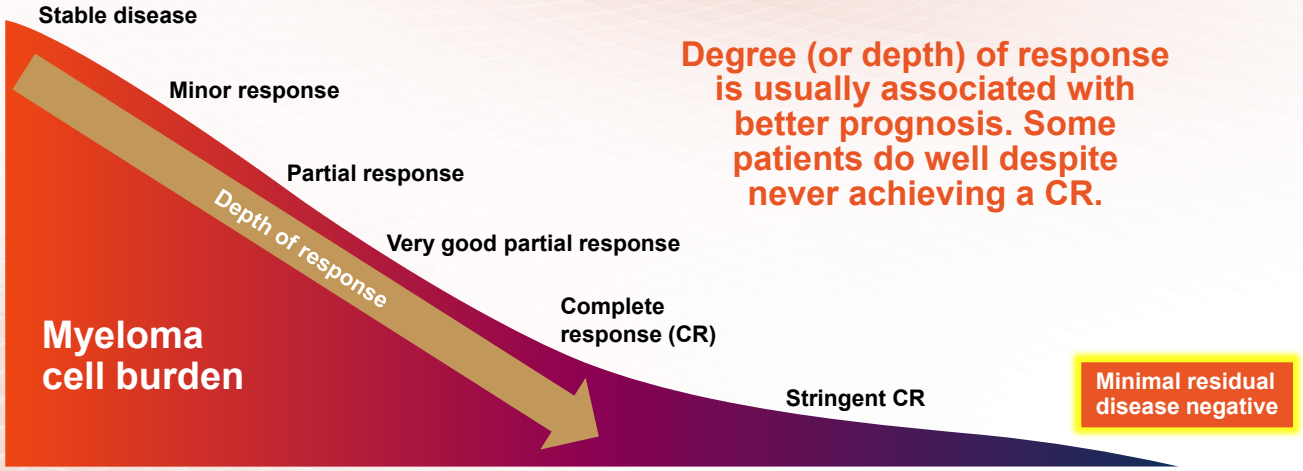
	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid*	• Ninlaro* • Velcade	• Velcade-Revlimid ± dex
Transplant ineligible	• Revlimid*	• Ninlaro* • Velcade	• Velcade-Revlimid

Additional agents under investigation: Darzalex, Empliciti, Kyprolis

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

72

Measuring Response to Therapy



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

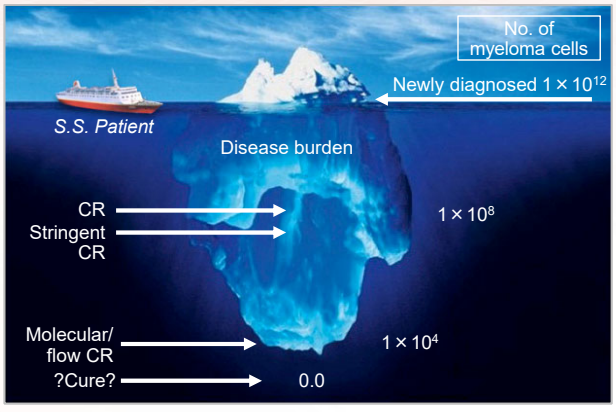
ClonoSEQ is an FDA-approved next-generation sequencing (NGS) test to measure MRD in MM patients

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

73

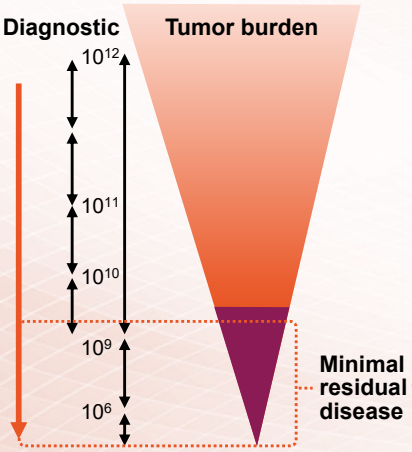
What is minimal residual disease (MRD)?

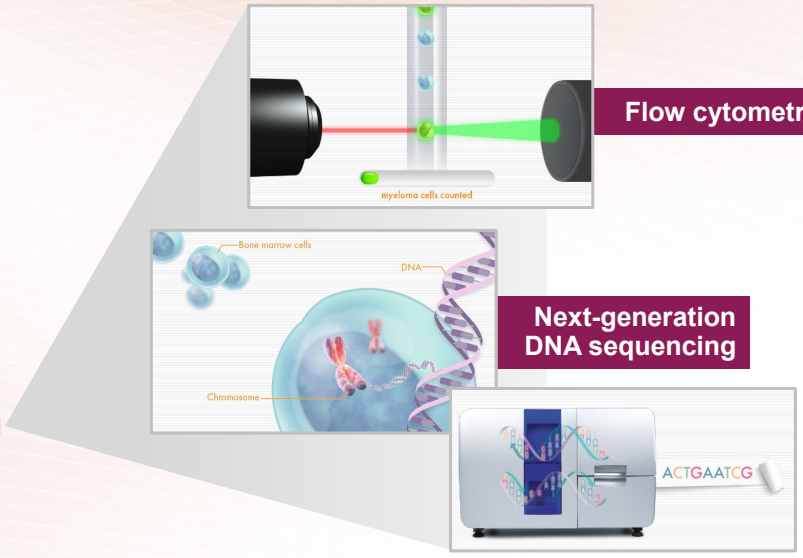
- With new and more effective treatments, more patients achieve complete response (CR)
- However, achieving a CR does not necessarily mean that all myeloma cells are gone
- Routine blood tests are not sensitive enough to detect these remaining cells



74

How is MRD measured?





75

Key Terms for MRD

MRD positive or MRD positivity (MRD+)

- Myeloma cells are still detectable

MRD negative or MRD negativity (MRD-)

- Myeloma cells are not detected

Level of sensitivity can be different depending on methodology used: next-generation sequencing (NGS) or next-generation flow cytometry (NGF).

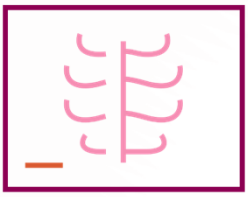
76

Comprehensive Response Assessment

Right now, measurement of MRD depends on counting cells in bone marrow samples

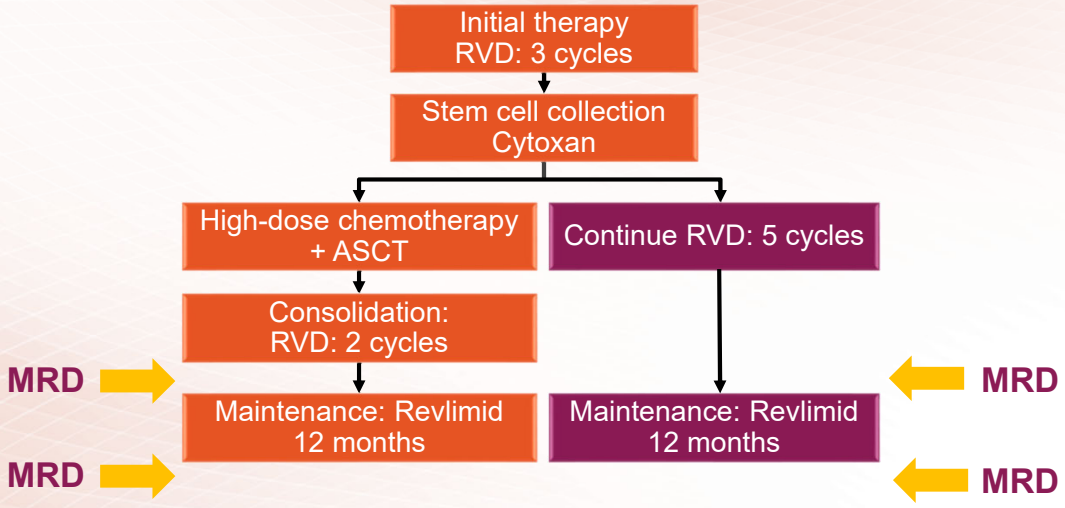
What about other areas of the body?

Imaging (with PET/CT scan) is also required to detect residual disease outside of the bone marrow



77

Why is it important to achieve MRD negativity?



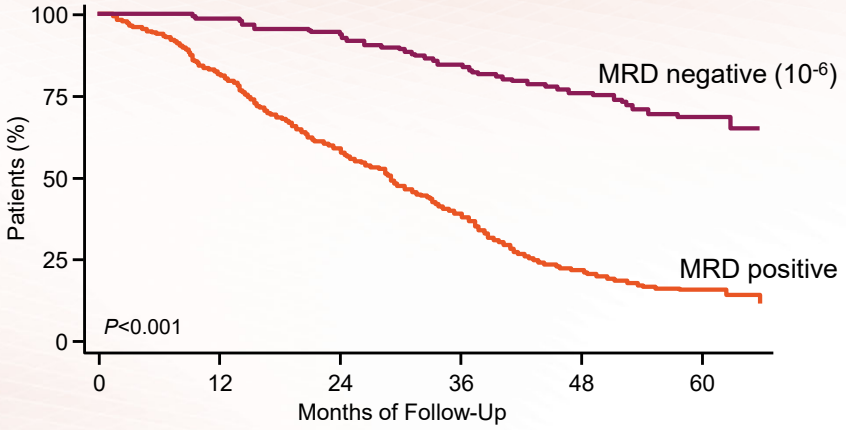
RVD, Revlimid, Velcade, dexamethasone; Cytoxan, cyclophosphamide

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

78

Why is it important to achieve MRD negativity?

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



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

79

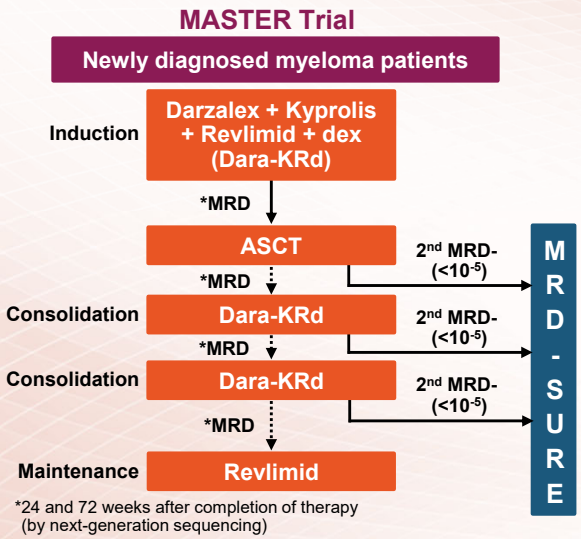
MRD-Negativity Achieved by Various Regimens

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

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

80

MRD Response-Adapted Consolidation and Treatment Cessation



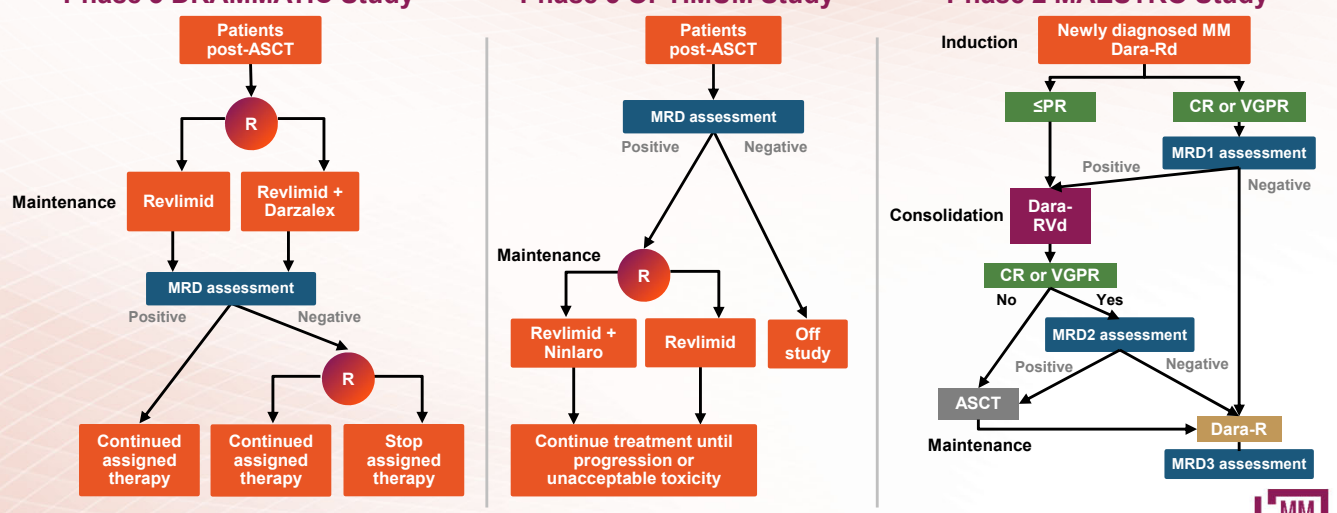
- 80% of patients achieved MRD negativity (at <1 × 10^{-5}) and 66% achieved MRD negativity at <1 × 10^{-6}.
- 86% of patients achieved a CR or better.
- Responses deepened with each phase of treatment—and were similar in patients with zero, one, or two or more high-risk genetic abnormalities.
- ASCT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

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

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

81

Ongoing Studies Using MRD Results to Direct Therapy

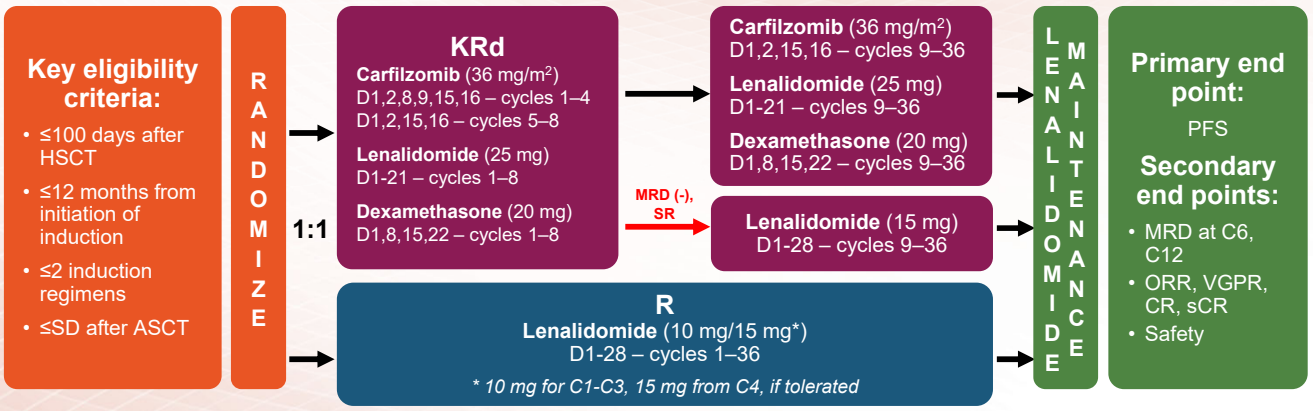


1. https://clinicaltrials.gov/ct2/show/NCT04071457; **2.** https://clinicaltrials.gov/ct2/show/NCT03941860; **3.** https://clinicaltrials.gov/ct2/show/NCT04140162.

82

International Myeloma Society

Study Design: Multicenter, Randomized, Open-Label, Phase 3 Study



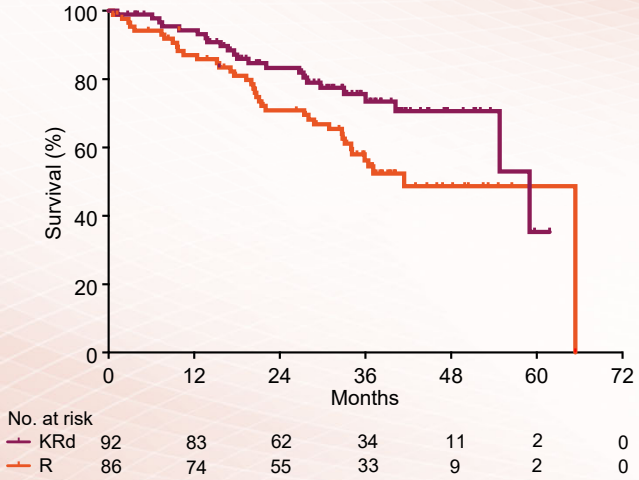
Stratification factors:
- Post-ASCT response (≥VGPR vs <VGPR)
- Standard (SR) vs high risk (HR) cytogenetics
- Location of site (US vs Poland)

KRd patients with SR cytogenetics and IMWG MRD negativity[1] after C6 converted to R alone after C8

83

International Myeloma Society

Progression-Free Survival



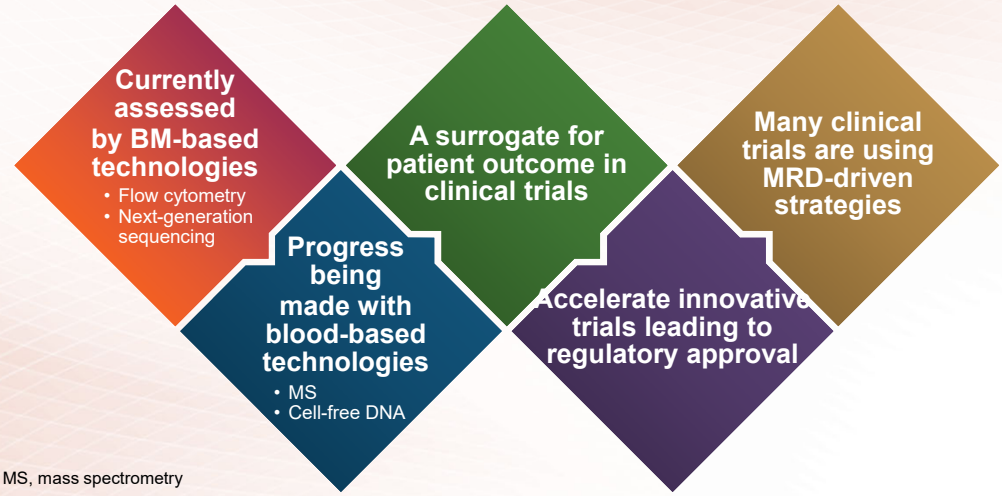
After median follow-up of 33.8 months there were **61 PFS events:**
- **23 in the KRd arm**
- **38 in the R arm**

Median PFS
- **KRd 59.0 months** (95% CI 52.5–NR)
- **R 41.1 months** (95% CI 33.4–65.4)
- **HR 0.56 (95% CI 0.34–0.93); *P*=0.026**

This analysis was at 63% of 96 expected events for primary analysis, for which the *P* value criterion for significance (*P*=0.05) was not adjusted for the interim nature of the comparison. The primary analysis will conducted at 4-year follow-up of last patient enrolled.

84

MRD Is Important for Clinical Care and New Drug Registration

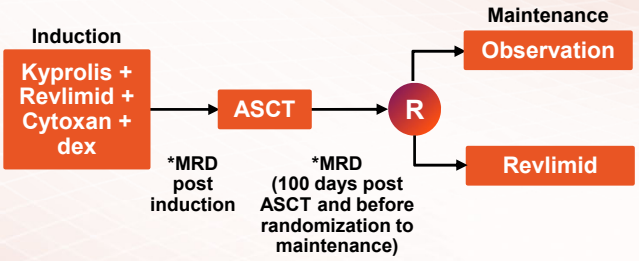


BM, bone marrow; MS, mass spectrometry

Anderson KC et al. *Clin Cancer Res*. 2021;27:5195.
Costa LJ et al. *Leukemia*. 2021;35:18.

85

Potential Blood-Based MRD Testing: Mass Spectrometry



MRD is currently measured using a bone marrow sample; myeloma cells are detected using one of two methodologies: (1) flow cytometry or (2) next-generation sequencing.

Mass spectrometry (MS) is being evaluated as a method to detect free light chains (FLCs) in the blood as a potentially more sensitive test to detect MRD in patients after therapy.

MS positivity was associated with patients having a shorter time until disease progression compared to being MS negative.

In patients who achieved a CR or sCR, 16% to 34% were MS positive following induction, ASCT, or prior to maintenance; these patients also had a shorter time until disease progression compared to being MS negative and in CR/sCR.

Some patients who were MRD negative* and also MS positive also had a shorter time until disease progression compared to being MRD negative and MS negative.

MS may provide a useful alternative to bone marrow testing to detect MRD in patients and may even help to identify patients at increased risk of early relapse if they are MRD negative but MS positive during maintenance therapy.

*By flow cytometry at a sensitivity of 4×10^{-5}

Giles HV et al. *Blood*. 2021;138. Abstract 820; Derman BA et al. *Blood Cancer J*. 2021;11:19.

86

Where is the myeloma field going?

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

87

Summary

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

88

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

89

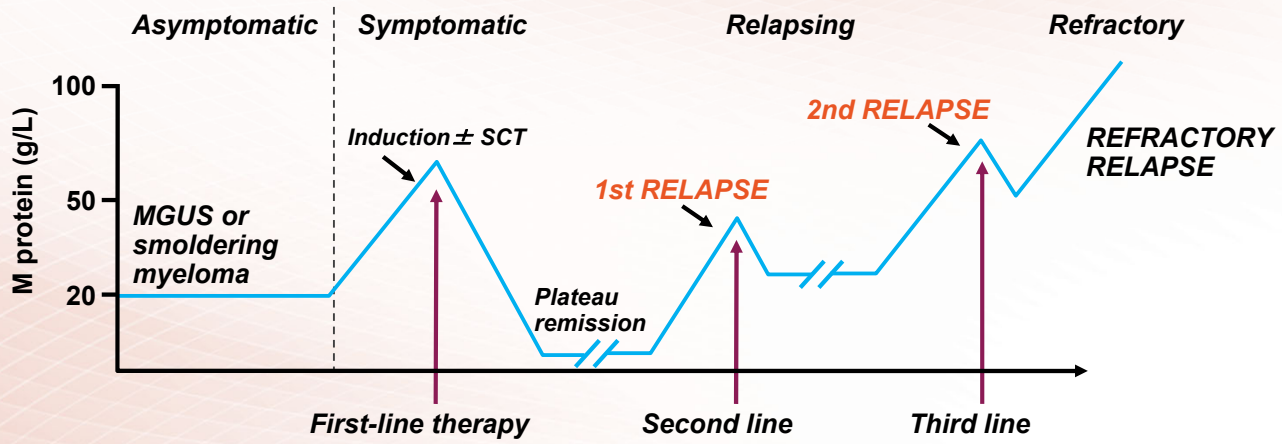
MULTIPLE MYELOMA Research Foundation

Treating Early Relapsed and Refractory Myeloma

Monique Hartley-Brown, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

90

Multiple Myeloma Is a Marathon, Not a Sprint



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

91

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

92

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 numerous factors**

Clinical

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

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

93

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

94

Options for Relapsed/Refractory Disease Continue to Increase

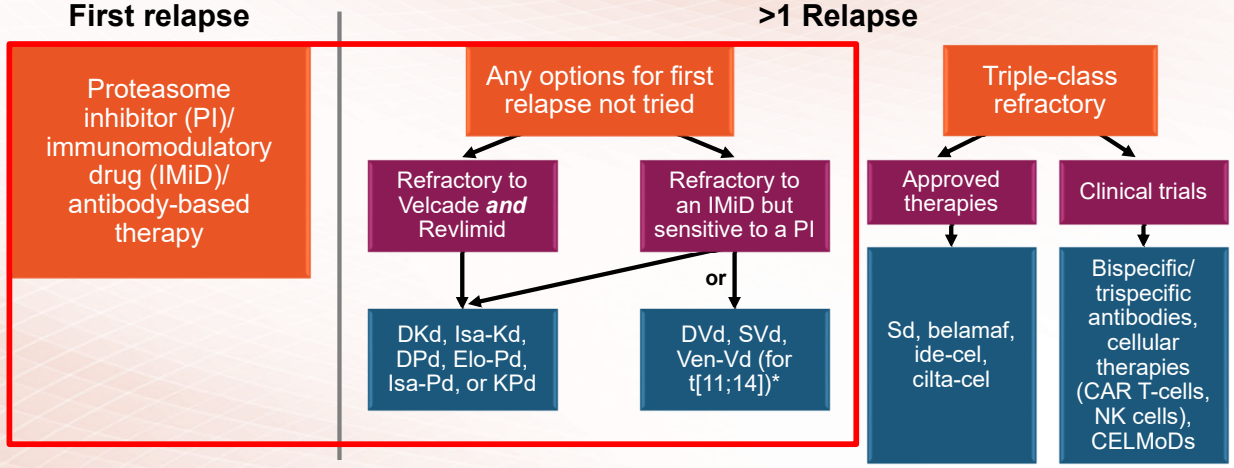
IMiDs	Proteasome inhibitors	Chemotherapy anthracyclines	Chemotherapy alkylators	Steroids	Novel mechanisms of action	mAbs	Cellular therapy
Thalomid (thalidomide)	Velcade (bortezomib)	Adriamycin	Cytoxan (cyclophosphamide)	Dexamethasone	XPOVIO (selinexor)	Empliciti (elotuzumab)	Abecma (idecabtagene vicleucel)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

95

Treatment Approach

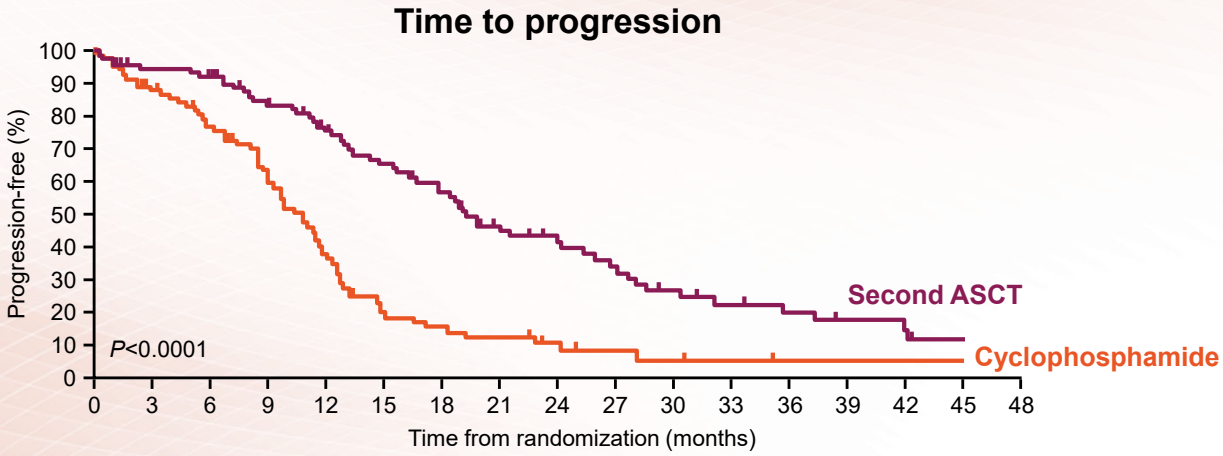


D, daratumumab (Darzalex); K, carfilzomib (Kyprolis); d, dexamethasone; Isa, isatuximab (Sarclisa); P, pomalidomide (Pomalyst); Elo, elotuzumab (Empliciti); V, bortezomib (Velcade); S, selinexor (Xpovio); Ven, venetoclax (Venclexta); belamaf, belantamab mafodotin (Blenrep); ide-cel, idecabtagene vicleucel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

*Not yet approved for use in myeloma patients

96

Second ASCT an Option for Early Relapse



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

97

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

98

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

99

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

100

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; but 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; but 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.

101

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.

102

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.

103

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

104

Monoclonal Antibody–Based Regimens at Relapse

105

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

Drug	Formulation		Approval
Darzalex (daratumumab)		IV once a week for first 8 weeks; then every 2 weeks for 4 months, then monthly • The first prescribed dose may be split over 2 consecutive days • SC administration also available	• 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

106

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

107

Important Considerations for Use of Darzalex

Darzalex

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

108

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

109

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

	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: Not reached vs 19 mos

110

Important Considerations for Use of Monoclonal Antibodies

Empliciti

- Lower rate of **infusion reactions** than Darzalex or Sarclisa
- Risk of **shingles**
  - Use appropriate vaccination

Sarclisa

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

111

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: Not reached 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

112

Current and Emerging Therapies for Relapsed/Refractory Multiple Myeloma

Current therapies

Antibody-drug conjugates

- Blenrep
- Targets BCMA
- A monoclonal antibody conjugated by a protease-resistant linked to a microtubule-disrupting agent

Chimeric antigen receptor (CAR) T cells

- Abecma and Carvykti
- Targets BCMA
- Genetically modified autologous T cells that attack myeloma cells

Emerging therapies

Bispecific antibodies

- Teclistamab, elranatamab, and others
- Targets BCMA 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

113

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 and patient and caregivers and are based on multiple 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.**

114

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

115

MULTIPLE MYELOMA Research Foundation

CAR T-Cell Therapy and Bispecific Emerging Treatment Options for Refractory Myeloma: CAR T, Immunotherapy, and Precision Medicine

Benjamin A. Derman, MD
University of Chicago Medical Center
Chicago, Illinois

116

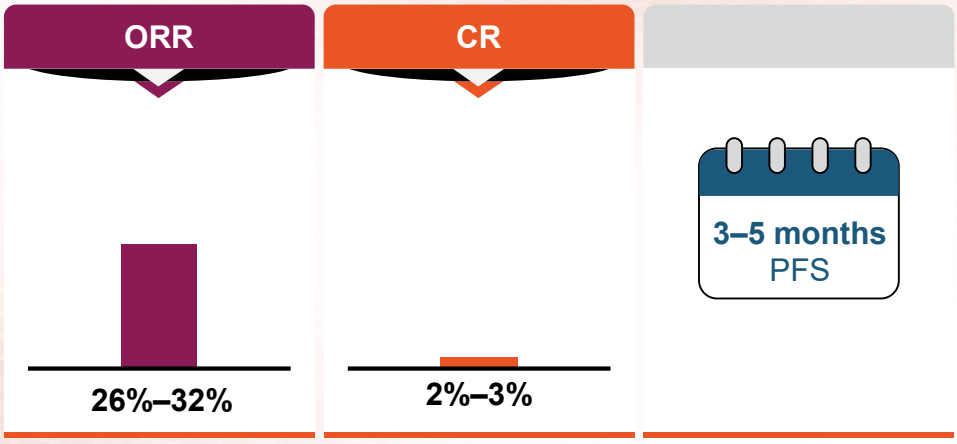
Triple-Class Refractory

- 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)

117

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



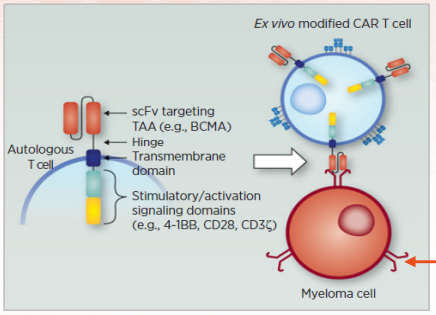
Exposed to an immunomodulatory imide drug, proteasome inhibitor, and CD38 monoclonal antibody

Source: Gandhi UH et al. *Leukemia.* 2019;33(9):2266. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6820050/

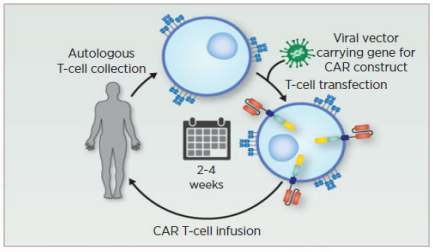
118

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.

119

CAR T-Cell Therapy Patient Journey

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

120

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

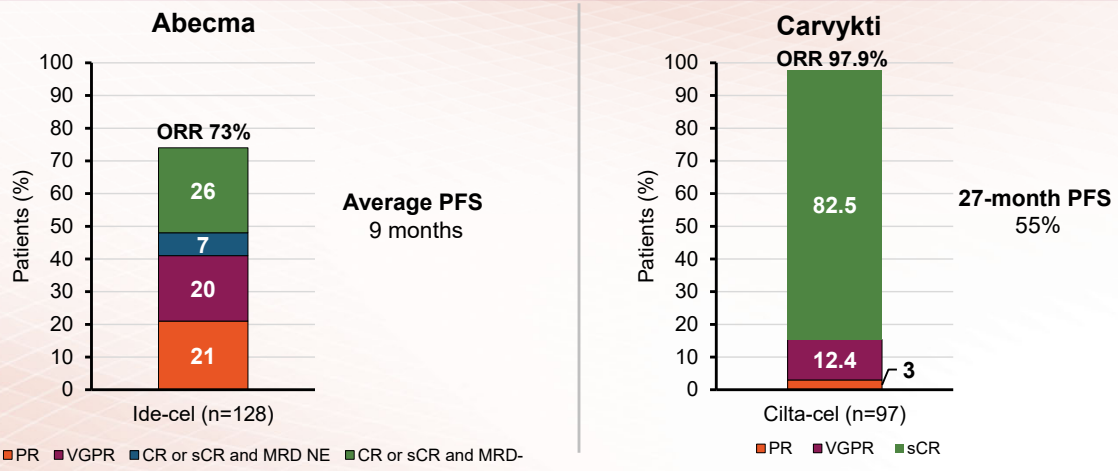
*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia

†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

121

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.

122

One Product Better Than Another?

The "simple" answers

- We don't know
- With limited availability at limited number of centers, ***availability may be the best ability***.
- Waiting for cells to be manufactured has challenges, no matter the product

The more complicated answers

- Trials with CAR T-cell therapy select for patients who ***CAN wait*** for cells to be manufactured (= less aggressive disease)
- Patients enrolled in the studies with the different products are ***different*** – and results might look different
- Clinical trials are looking at "*off-the-shelf*" options or ***quicker turnaround***.

123

CAR-T: Expected Toxicities

Cytokine release syndrome (CRS)

Neurotoxicity (ICANS)

Cytopenias

Infections

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

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

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

124

CAR T-Cell Therapy Themes: Myeloma

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

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

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

125

Transplant vs CAR T Cells

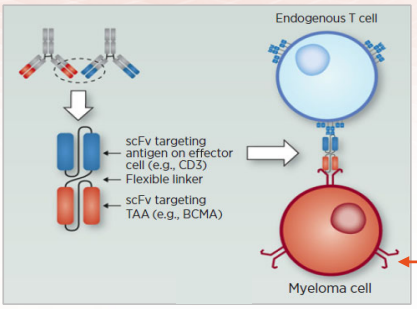
Cellular therapies	CAR T-cell therapy	Autologous stem cell transplantation
Patient's cells collected	Yes	Yes
Types of cells collected	T cells*	Stem cells†
Collected cells are genetically engineered in a lab	Yes	No
Patient given chemotherapy before cells are infused back into patient	Yes, lymphodepleting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

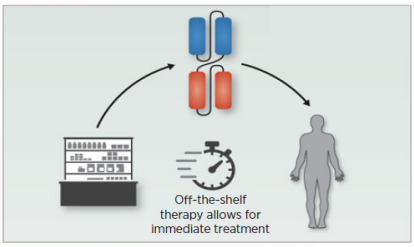
126

Bispecific Antibodies

- Bispecific antibodies are also referred to as dual specific antibodies, bifunctional antibodies, or T-cell engaging antibody
- 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

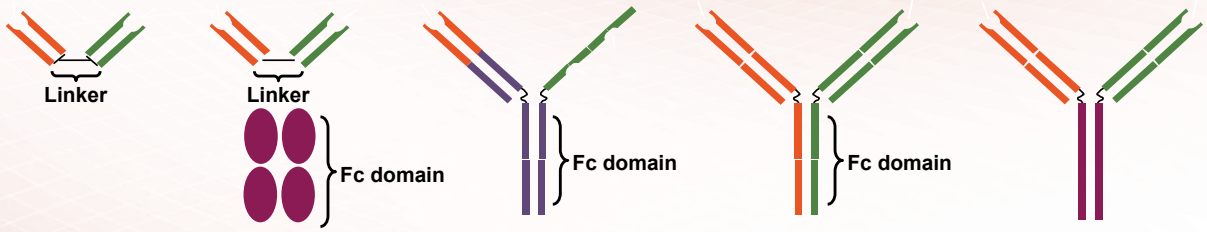


Examples:
- Elranatamab
- Teclistamab
- TNB-303B (ABBV-383)
- REGN5458
- Cevostamab
- Talquetamab

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

127

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

128

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

129

Bispecific Antibodies: Expected Toxicities

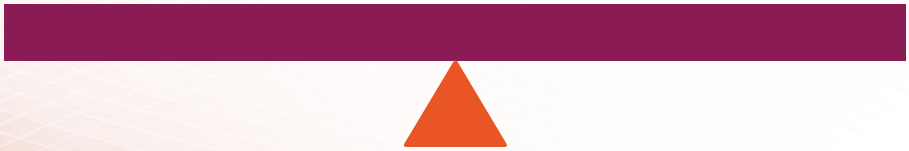
- Cytokine release syndrome (CRS)
- Neurotoxicity (ICANS)
  - Usually occurs within first 1–2 weeks
  - Frequency (all grade and grade 3–5) higher with CAR T
- Cytopenias
- Target unique: cytokeratin change/rash
- Infections
  - Incidence for bispecifics at RP2D not yet known
  - Viruses: CMV, EBV
 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

130

Bispecific Antibodies: Pros/Cons

- High rates of response
- Off-the-shelf
- Can be given as outpatient

- % responses < CAR T
- Must be given continually
- Must be started inpatient
- Infections!



131

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

132

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 CARs and different targets are on the way.**
- **Bispecific antibodies represent an "off-the-shelf" immunotherapy.**
- **Several different bispecific antibodies are under clinical evaluation.**

133

Options on the Horizon

Clinical phase	Novel agents	
	Precision medicine	Novel mechanisms of action†
Phase 3	Venetoclax*	
Phase 1, 2	Abemaciclib* Cobimetinib* Dabrafenib Enasidenib* Erdafitinib* Idasanutlin Trametinib Vemurafenib	AMG-176 AMG-232 APG-2575 Azacitidine CFT7455 Citarinostat COM902 CYT-0851 Disulfiram Duvelisib

*Being studied in the MyDRUG trial; †More agents can be found at www.clinicaltrials.gov

134

Multiple Myeloma Is Not Just One Disease!

Multiple myeloma is a heterogeneous disease even within cytogenetically defined molecular subtypes.

In the future, the goal is to go beyond a one-size-fits-all approach.

How do we customize treatment?
Precision medicine

135

An Example of the Importance of Personalized Medicine

	CoMMpassMMRF2172	CoMMpassMMRF2250
Age	72	71
Ethnicity	Caucasian	Caucasian
ISS stage	II	II
Baseline treatment	VRD	VRD
Cytogenetics	t(4;14), del13, del17p	t(4;14), del13, del17p
Time of progression	1 month	>18 months

136

An Example of the Importance of Personalized Medicine

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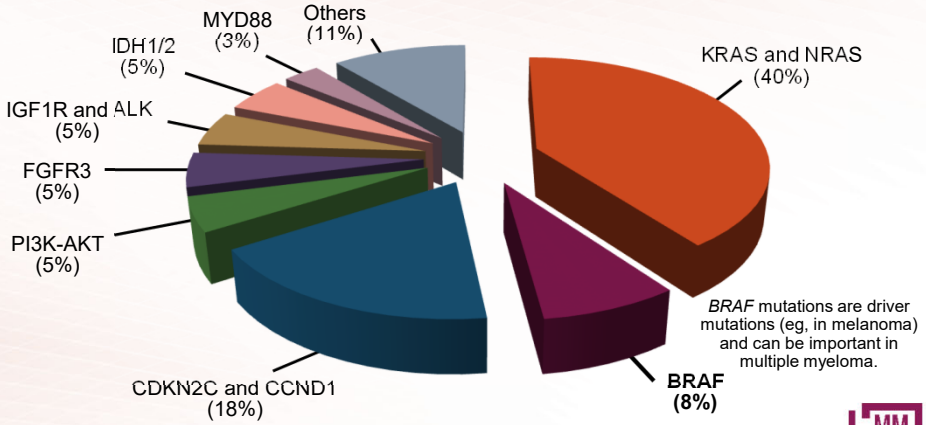
Ethnicity	Caucasian	Caucasian
ISS stage	II	II
Baseline treatment	VRD	VRD
Cytogenetics	t(4;14), del13, del17p	t(4;14), del13, del17p
Time of progression	1 month	>18 months
p53 status	Mutated	Wild-type

137

Actionable Alterations in MM

These alterations may be the Achilles' heel of myeloma cells.

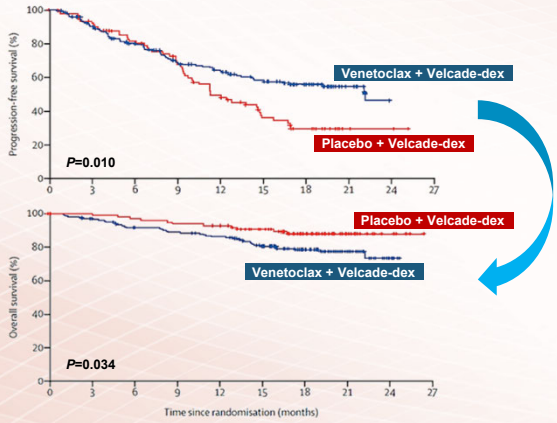
Precision medicine efforts have identified molecular alterations for which there are drugs in the clinic



138

Venetoclax and t(11;14)

Venetoclax is a Bcl-2 inhibitor



Venetoclax especially active in t(11;14) or *BCL2*^{high} multiple myeloma

The BELLINI Trial. Kumar SK et al. *Lancet Oncol*. 2020;21:1630.

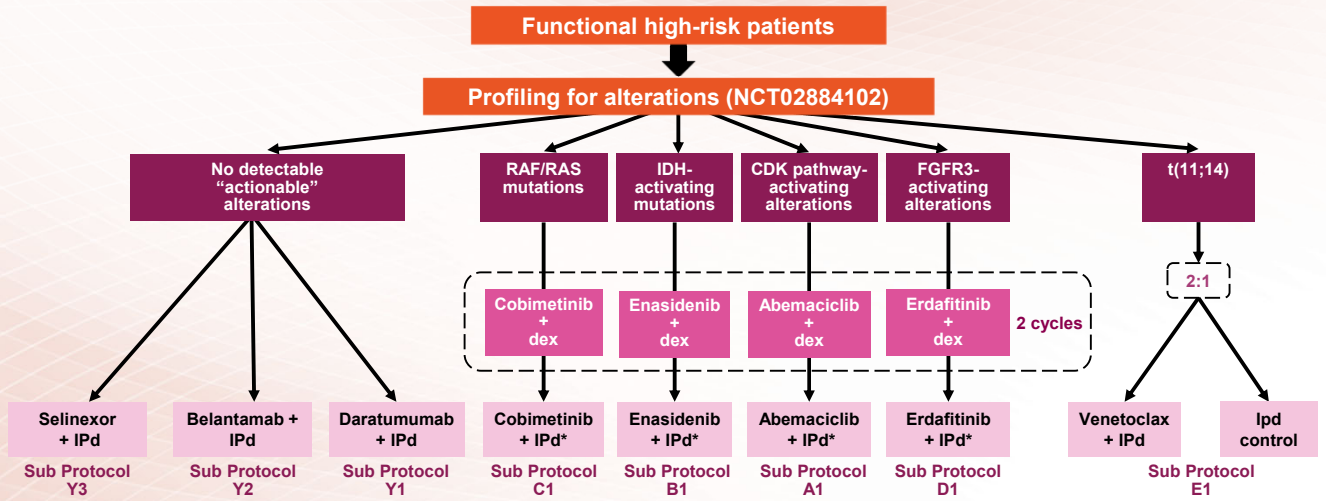
A phase 1b/2 study of MEK inhibition ± Bcl-2 (venetoclax) and PD-L1 Inhibition in patients with relapsed/refractory multiple myeloma

- 49 patients treated with COTELLIC (cobimetinib) alone or in combination with Venclexta (venetoclax) ± TECENTRIQ (atezolizumab)
- 51% had *RAS* mutations; 31% had high PD-L1 expression
- Overall response rates
  - 0% for COTELLIC alone
  - 27% for COTELLIC and Venclexta; **50% in t(11;14) patients**
  - 29% for COTELLIC, Venclexta, and TECENTRIQ; **100% t(11;14) patients**
- Common side effects included diarrhea, nausea, low blood counts, increase in blood creatine phosphokinase, and rash
- Serious side effects included low blood counts and pneumonia

Schjesvold F et al. *Blood*. 2020;136. Abstract 295.

139

MMRF MyDRUG (NCT03732703) *Treatment Arms*



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

IPD, Ninlaro (ixazomib), Pomalyst (pomalidomide), d, dexamethasone

140

Precision Medicine in Myeloma: MyDRUG (NCT03732703)

Case study: Man, age 59

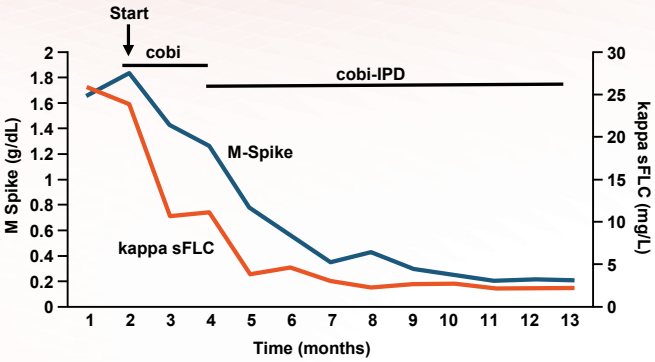
Treatments

1st Line
- VRd/KRd induction, ASCT, Rev maintenance
- Best response: CR
- Progressed in 30 months (22 months post-ASCT/maint.)

2nd Line
- EPd
- Best response: MR
- Progressed in 4 months

3rd Line
- MyDrug – C1

Response on MyDrug



Genomics
- Hyperdiploid, del13q, del1p, Myc ampl.
- NRAS Q61H, 56% allelic fraction

141

Precision Medicine Summary

- **Efforts are under way to better understand the nature of the disease and to provide patients with a more personalized approach to treatment.**
- **Genomic sequencing and data from myeloma patients are key to identifying subtype: our goal is to help individualize treatment for better outcomes.**
- **Continue to ask whether genetic mutation analysis is conducted by your doctor.**
- **Discuss with your doctor what genomic subtype of myeloma you have and what impact that may have on your treatment.**
- **Precision medicine provides the right treatment at the right time for each myeloma patient.**

142

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

143

Town Hall Questions & Answers

144

MULTIPLE MYELOMA Research Foundation

Patient Experience

145

MULTIPLE MYELOMA Research Foundation

Clinical Trials

Andrzej J. Jakubowiak, MD, PhD
University of Chicago Medical Center
Chicago, Illinois

146

Goal of Clinical Trials: Making Progress Against Myeloma

Participants in clinical trials receive specific treatments according to the research plan or protocol created by the investigators to determine the safety and efficacy of the treatment.

Develop treatments and strategies to potentially lengthen lives
- **Improve the way we use currently available drugs and regimens**
- **Develop new medications**

Increase the understanding of the disease
- **Identify rational selection of existing drugs**

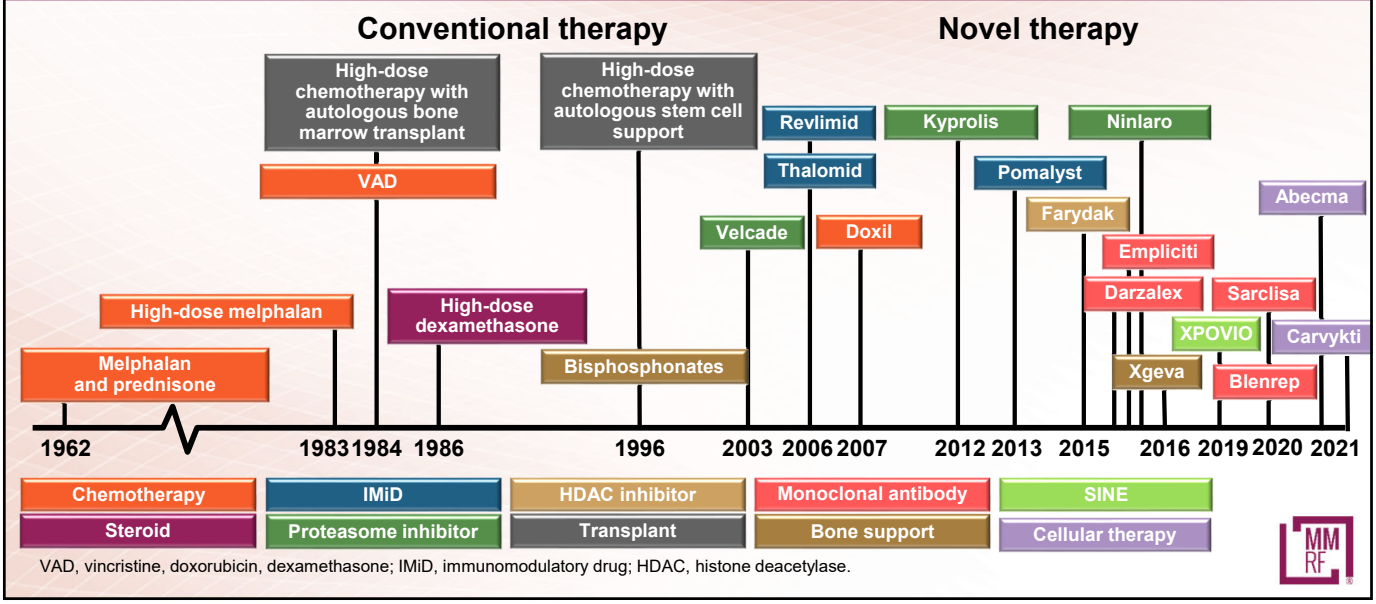
147

Impact of Clinical Trials in Myeloma: Dramatic Improvements in Survival in <10 Years

- Survival rates have nearly doubled; further improvements expected in near future.
- 15 new drugs approved since 2003.
- Many new drugs being studied in clinical trials.
- Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine.

148

Evolution of Multiple Myeloma Treatment: 16 New Drugs Approved in ≤18 Years



VAD, vincristine, doxorubicin, dexamethasone; IMiD, immunomodulatory drug; HDAC, histone deacetylase.

149

Conventional Trial Design

150

New Drug Development

STEP 1
Identify a target for therapy in the laboratory

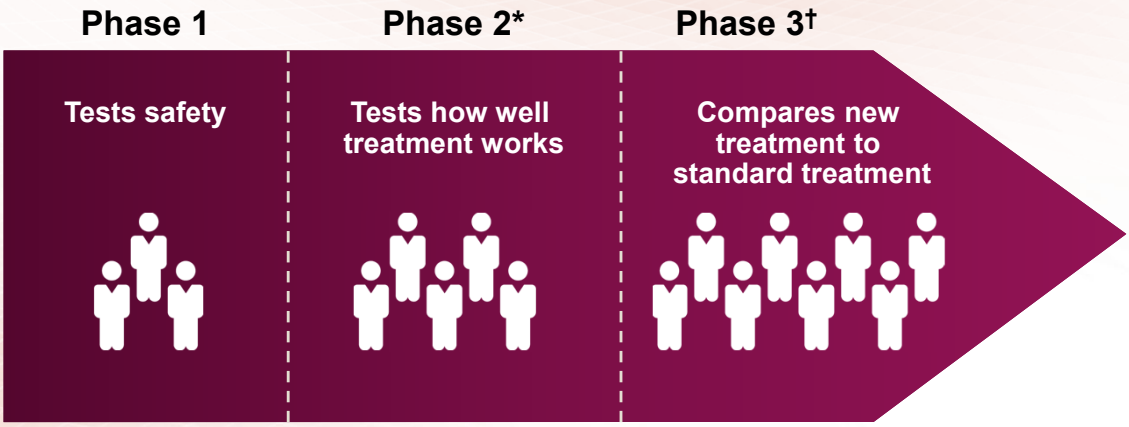
STEP 2
Confirm the anti-cancer activity in laboratory and animal studies

STEP 3
Clinical trials (human studies) to determine safety, dosing, and effectiveness

The whole process costs millions of dollars and years of effort!

151

Conventional Clinical Trial Types



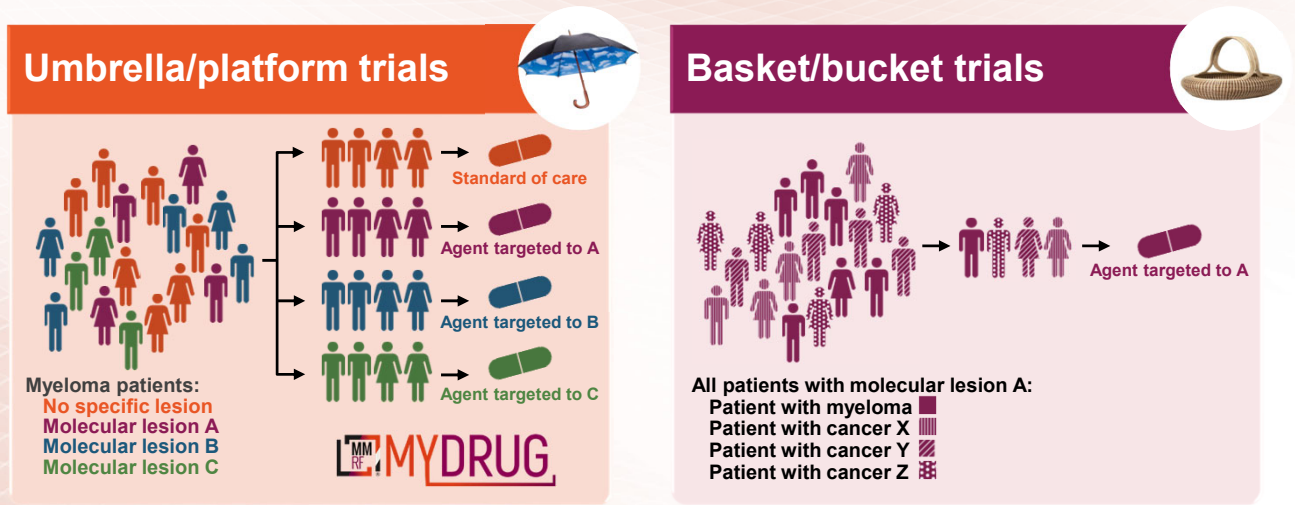
*When no standard treatment is available, FDA may approve drugs based on trial results
†Conducted to receive FDA approval of new drugs, in most cases

152

Innovative Trial Design

153

Innovative Trial Designs: Guiding the Future of Cancer Research Toward Precision Medicine



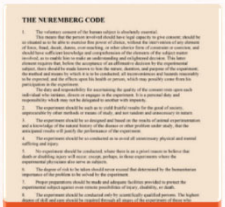
Pawlyn C, Davies F. *Blood*. 2019;133:660.

154

Participation in a Clinical Trial

155

Will I be treated like a guinea pig?



The Nuremberg Code

The Declaration of Helsinki

The Belmont Report

Ethics Committees and Research Boards

Three influential documents

156

Benefits of Clinical Trials

- You will have normal standard of care in terms of office visits, lab work, etc
- You may even have additional care and investigation as a part of the clinical trial
- You will generally see your health care providers and will also have a research coordinator involved in your care
- You will likely even have a higher standard of care than normal!

157

Considering Entering Clinical Trials

- Find a clinical trial
  - Contact an MMRF Patient Navigator at 1-888-841-6673 or visit themmrf.org/resources/clinical-trial-finder/
  - Ask your treating hematologist/oncologist about any available trials
  - Check with any academic medical centers close to your home
- Talk to your doctor about your eligibility
- Meet with the research nurse to learn more
- Carefully review the informed consent paperwork

158

Key Points

- Myeloma survival rates have nearly doubled; further improvements are expected.
- 15 new drugs approved since 2003.
- The drive of research and clinical trials has brought us to where we are.
- Clinical trials are available for patients at all stages of myeloma, including those who have precursor conditions, those who are newly diagnosed, and those who have received previous treatments and whose myeloma has relapsed.
- No one is expected to be a guinea pig; research and clinical trials are under very tight supervision and standards.
- Open, clear communication between the physician and the patient is essential.

159

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

160

Town Hall Questions & Answers

161

Thank you!

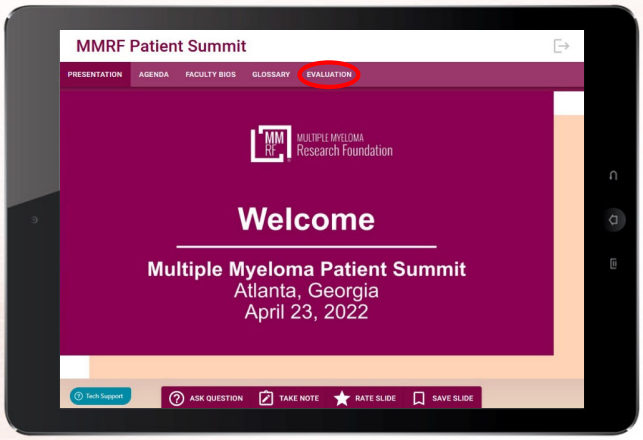
162

Adaptive biotechnologies
AMGEN
Bristol Myers Squibb
CRISPR THERAPEUTICS
cure20
Genentech
A Member of the Roche Group
GSK
janssen
Karyopharm Therapeutics
sanofi
Takeda ONCOLOGY

163

Don't Forget!

Complete your evaluation
Leave the iPad at your seat



164

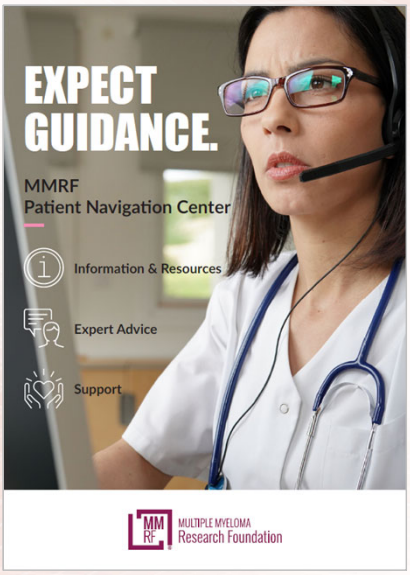
Upcoming Patient Education Events
Save the Date

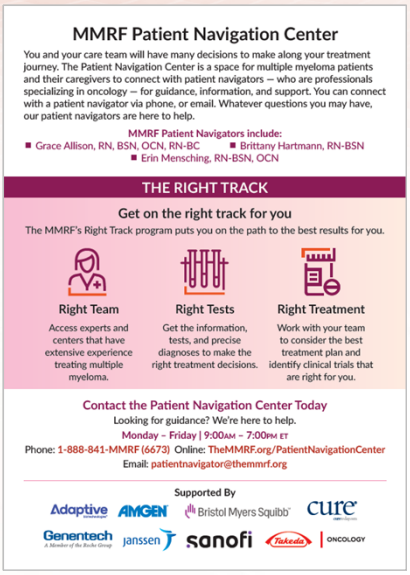
Topic	Date and Time (CT)	Speakers
Patient Summit (live and online)	Saturday, October 22 9:00 AM – 2:00 PM Nashville, Tennessee	Jesus Berdeja, MD—Host
Patient Summit (live and online)	Saturday, December 9 9:00 AM – 2:00 PM New Orleans, Louisiana	Laura Finn, MD—Host

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

165

MMRF Patient Resources





166

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.

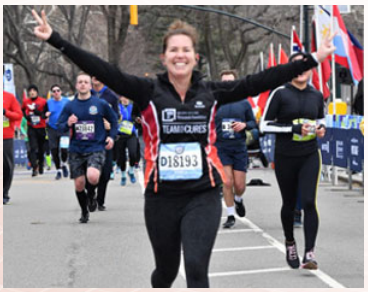
Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.

167

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/

168