MULTIPLE MYELOMA Research Foundation

Opening Remarks

Mary DeRome, MS
MMRF

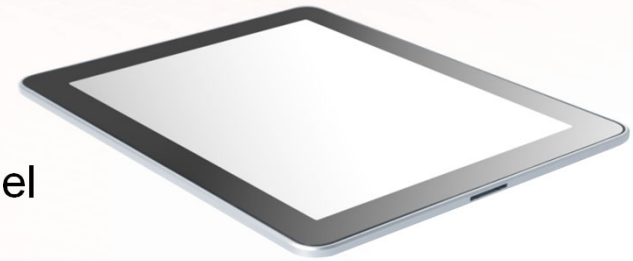
1

abbvie · Adaptive biotechnologies · AMGEN · Bristol Myers Squibb · CRISPR THERAPEUTICS · cure20 · 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

Clarence Adoo, MD
Medical Oncology and Hematology
Arizona Center for Cancer Care, Honor Health
Glendale, Arizona

P. Leif Bergsagel, MD
Mayo Clinic College of Medicine
Scottsdale, Arizona

William Brown
Arizona Myeloma Network
Scottsdale, Arizona

Suzanne Hyde, MSW, LCSW
Licensed Clinical Social Worker
Scottsdale, Arizona

Barbara Kavanagh, MSW
Arizona Myeloma Network
Glendale, Arizona

Jonathan Keats, PhD
Translational Genomics Research Institute
Phoenix, Arizona

Paul Long
Navajo Nation Healer and Health Disparities Liaison
Navajo Nation, Arizona

Sumit Madan, MD
Banner MD Anderson Cancer Center
Gilbert, Arizona

Joan Koerber-Walker
Arizona Bioindustry Association, Inc. (AzBio)
Chandler, Arizona

4

Summit Agenda

Time (MT)	Topic	Speakers
9:15 – 9:30 AM	Introduction to the MMRF	Mary DeRome, MS
9:30 – 9:45 AM	Welcome	Joan Koerber-Walker, CEO, AzBio
9:45 – 10:15 AM	Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy	P. Leif Bergsagel, MD
10:15 – 10:45 AM	High-Dose Chemotherapy and Stem Cell Transplantation, Maintenance Therapy, and Treatment Goals	Clarence Adoo, MD
10:45 – 11:00 AM	Break	
11:00 – 11:30 AM	Supportive Care	
11:30 AM – 12:00 PM	Personalized Medicine	Jonathan Keats, PhD
12:00 – 12:30 PM	Relapsed/Refractory Multiple Myeloma	Sumit Madan, MD
12:30 – 1:15 PM	Lunch	
1:15 – 1:30 PM	Patient and Caregiver Speakers	Moderator: Suzanne Hyde, MSW, LCSW
1:30 – 2:30 PM	Arizona Myeloma Network Virtual Cancer Caregiver's Education Program	William Brown Suzanne Hyde, MSW, LCSW
2:30 – 3:30 PM	Town Hall Q&A	Panel
3:30 – 3:45 PM	Closing Remarks	Barbara and Jack Kavanagh 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

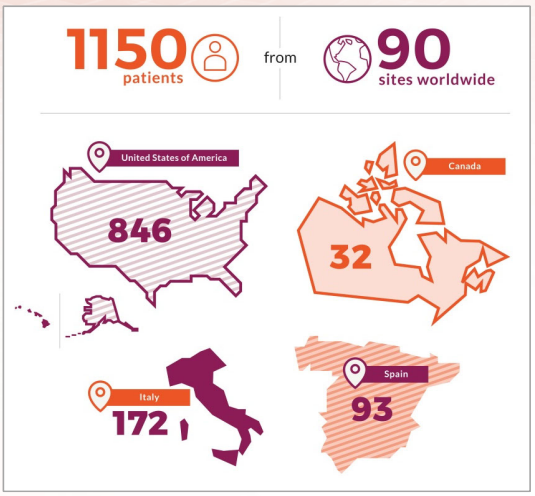
Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

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 are followed for at least 8 years

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



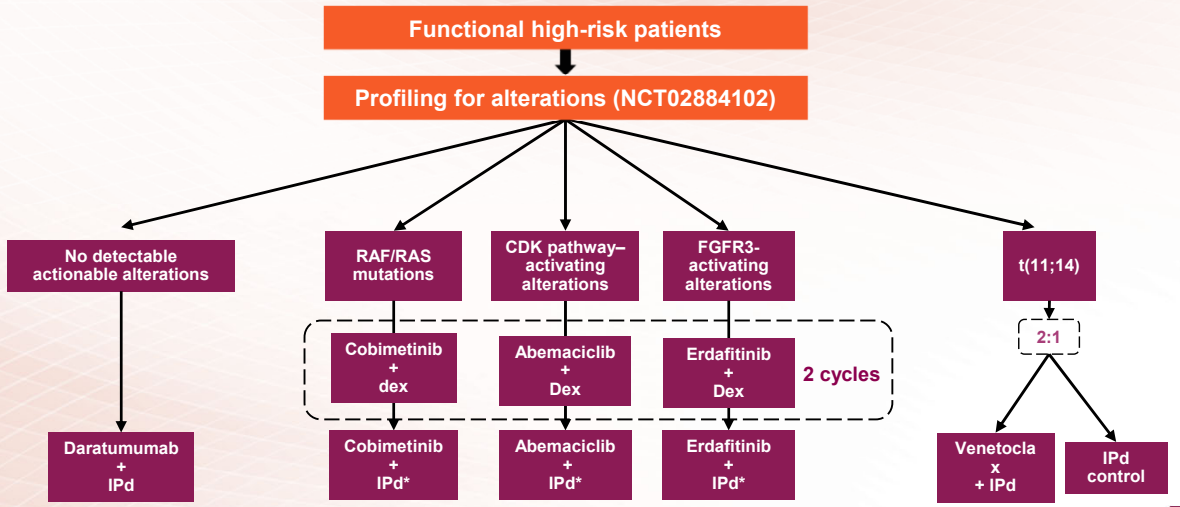
8

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 and CureCloud Research Study

9

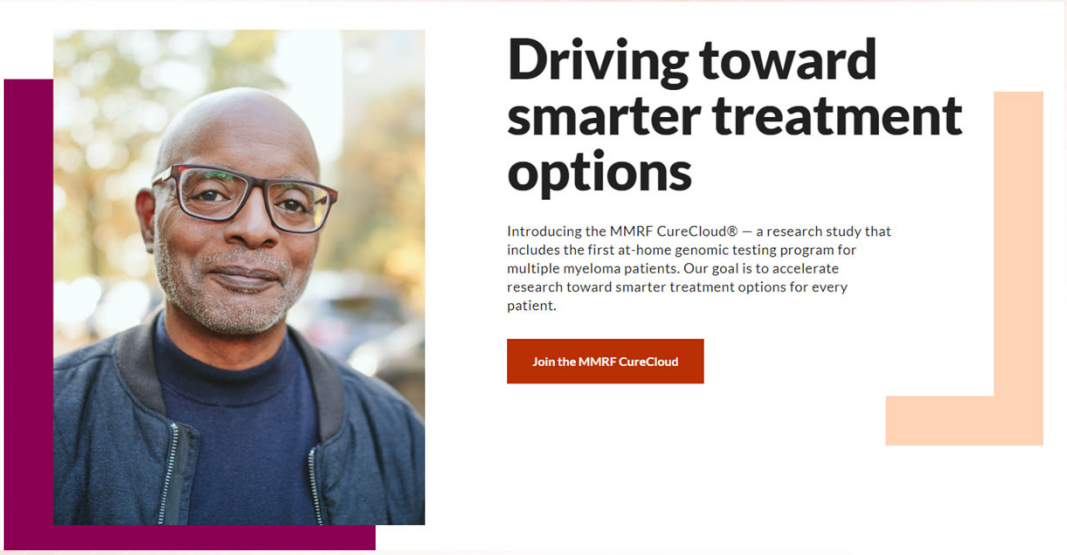
MyDRUG Trial



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

10

MMRF CureCloud



11

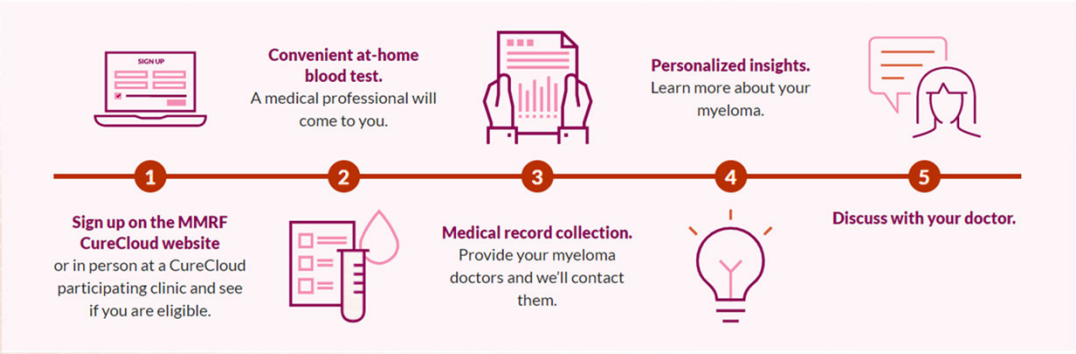
MMRF CureCloud
Recent Changes

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

12

MMRF CureCloud

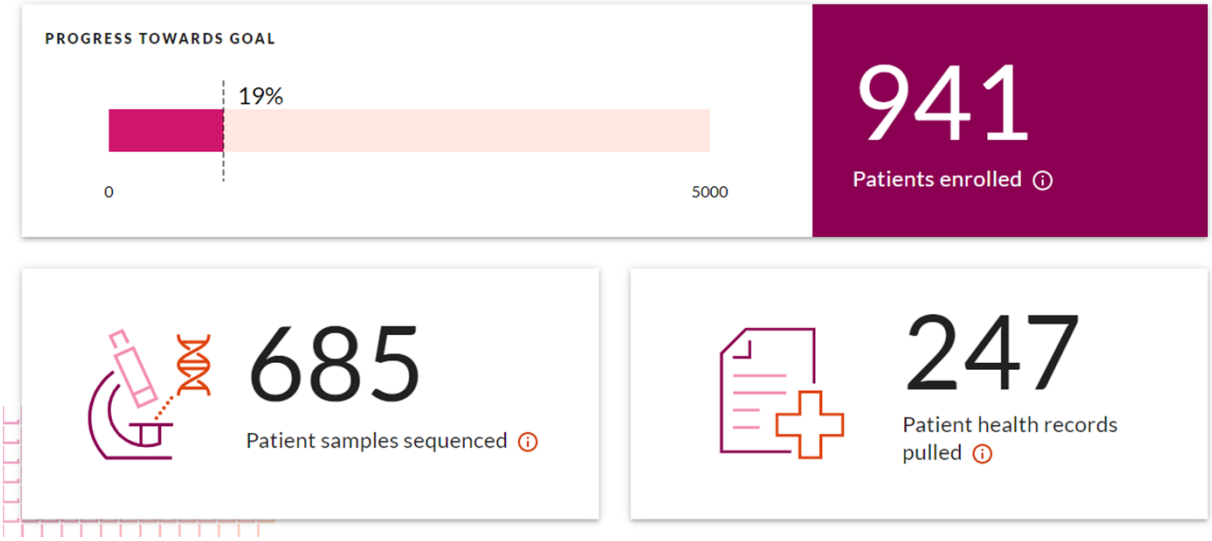
How Does the MMRF CureCloud® Work?



13

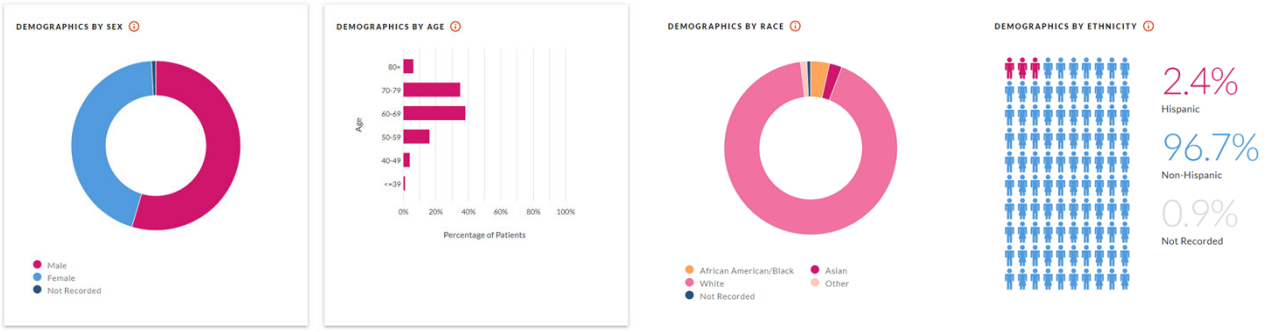
CureCloud Enrollment Tracker

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.



14

MMRF CureCloud Demographics



15

MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Welcome!

Joan Koerber-Walker
Arizona Bioindustry Association, Inc.
Chandler, Arizona

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

Is this your first Summit?

A. Yes
B. No

21

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.

22

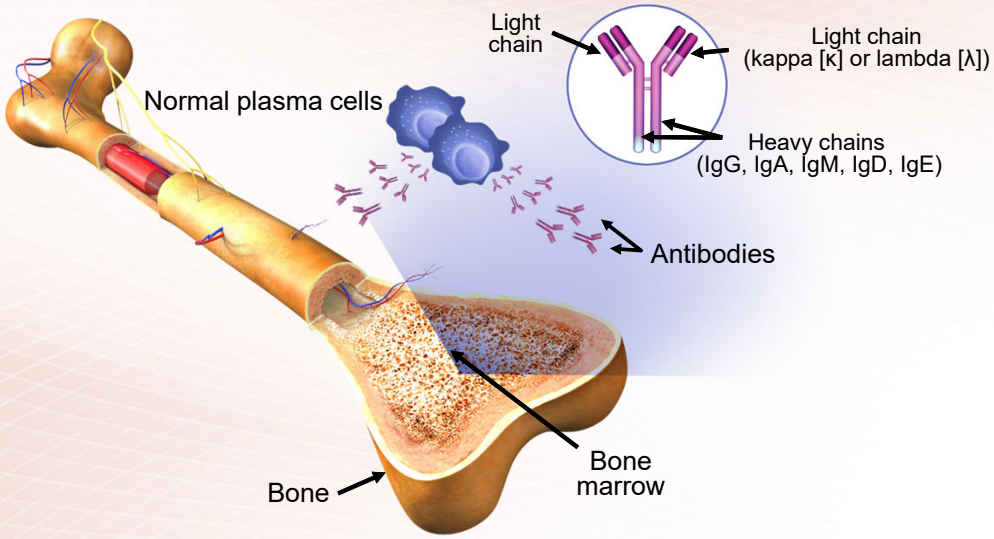
MULTIPLE MYELOMA Research Foundation

Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy

P. Leif Bergsagel, MD
Mayo Clinic College of Medicine
Scottsdale, Arizona

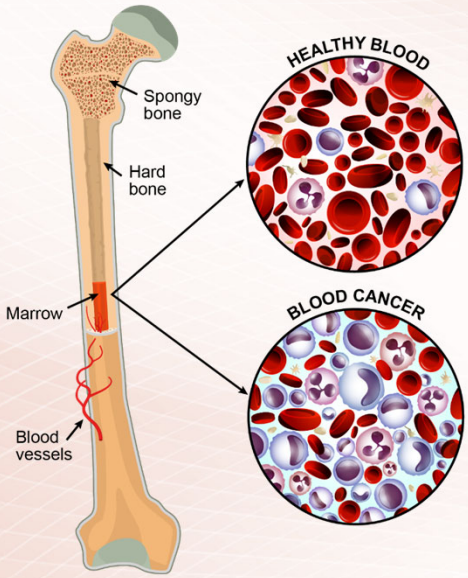
23

Normal Bone Marrow



24

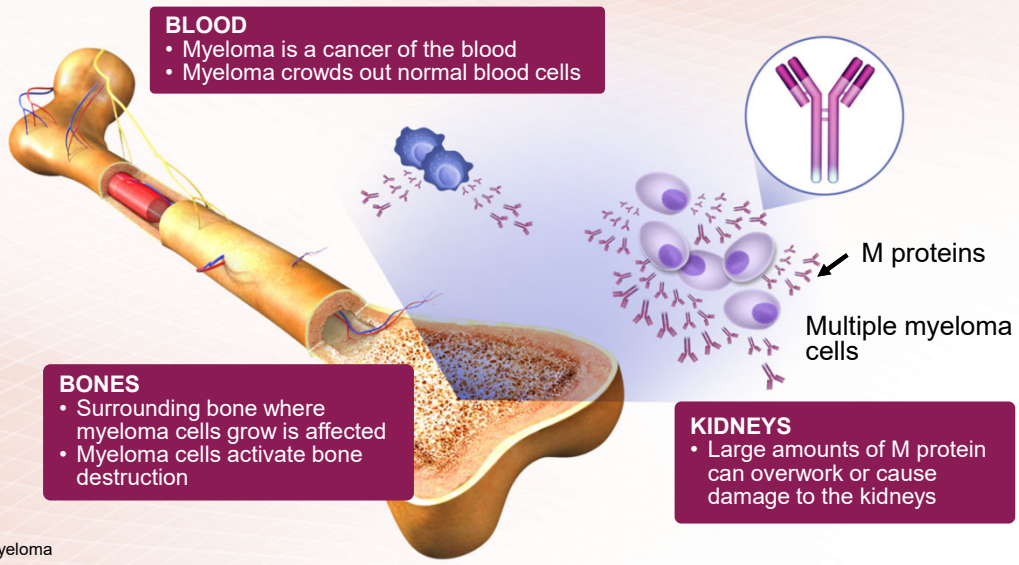
What is multiple myeloma?



- 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

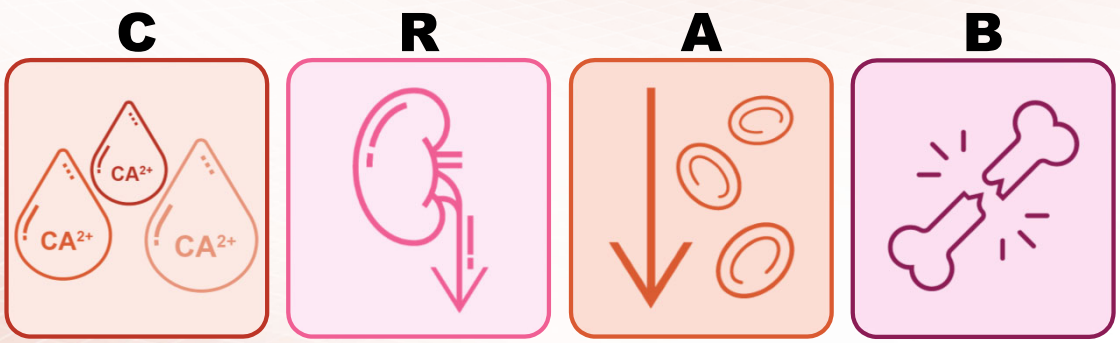


MM, multiple myeloma

26

Multiple Myeloma Affects Your Bones, Blood, and Kidneys

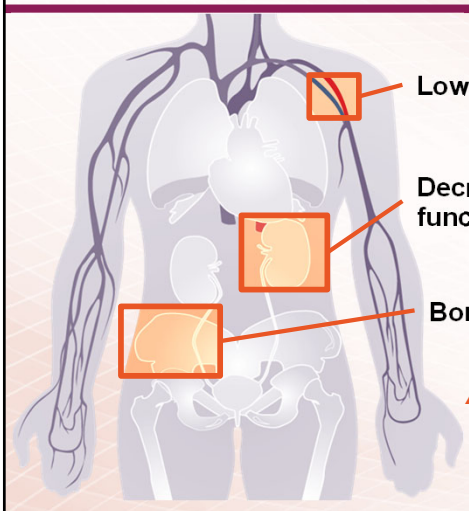
The clinical features that are characteristic of multiple myeloma



C	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

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

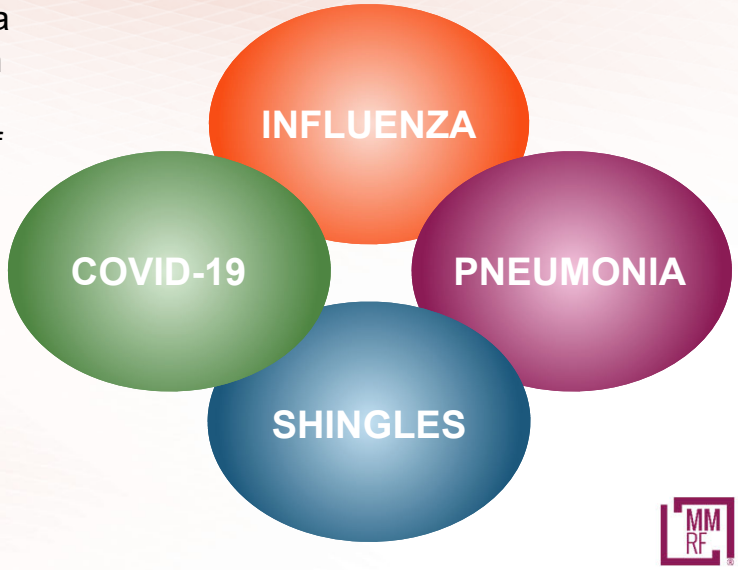
- Bone fractures

MMRF. Multiple myeloma symptoms, side effects, and complications. 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 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

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
- Complete metabolic panel
- Chemistries
  - Calcium
  - Creatinine
  - Lactate dehydrogenase
  - Beta-2 microglobulin
- **Serum protein electrophoresis with immunofixation electrophoresis (IFE)**
- **Serum free light chain assay**

Confirms the type of myeloma

Urine tests

- Urine protein electrophoresis 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

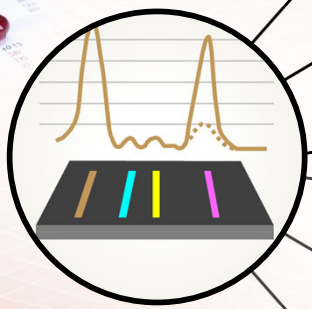
Assess changes in the bone structure and determine the number and size of tumors in the bone

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

33

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**

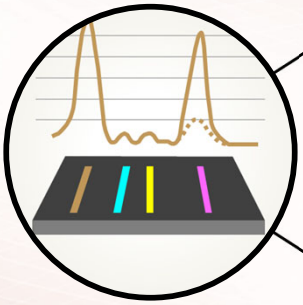
SFLC
- **Freelite test measures light chains (kappa or lambda)**

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

34

Learn Your Labs!
Urine Tests

Urine tests



UPEP

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

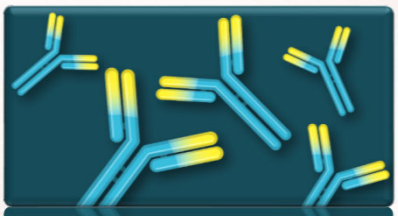
24-hr urine analysis

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

UPEP, urine protein electrophoresis

35

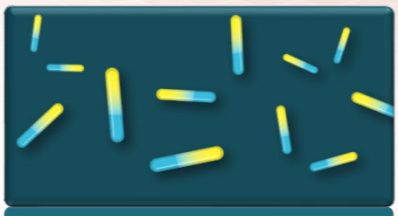
Types of Multiple Myeloma Based on Blood or Urine Tests



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

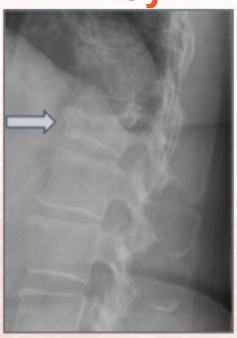
3%

36

Know Your Imaging Tests!

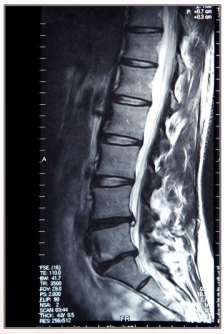
Assess changes in the bone structure and determine the number and size of tumors in the bone

X-ray

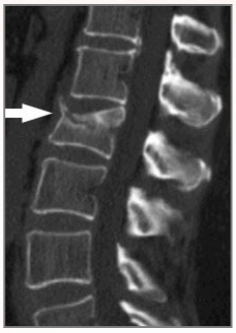


Conventional x-rays reveal lytic lesions, osteoporosis, or fractures in 75% of patients.

MRI



CT scan



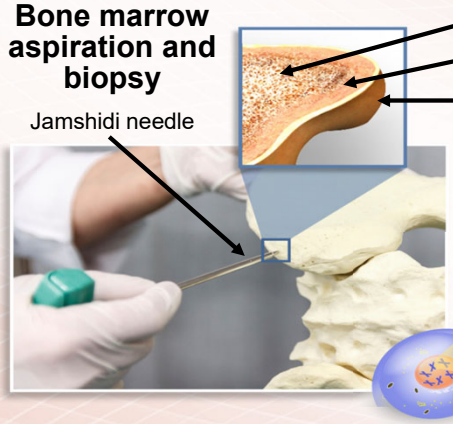
PET scan

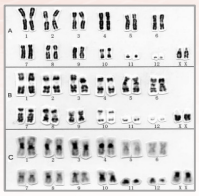
MRI and PET/CT appear to be more sensitive (85%) than skeletal x-rays for the detection of small lytic bone lesions.

37

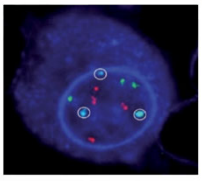
Know Your Bone Marrow Tests!

Bone marrow aspiration and biopsy

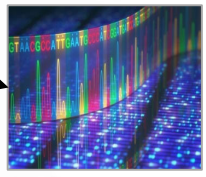




Karyotyping



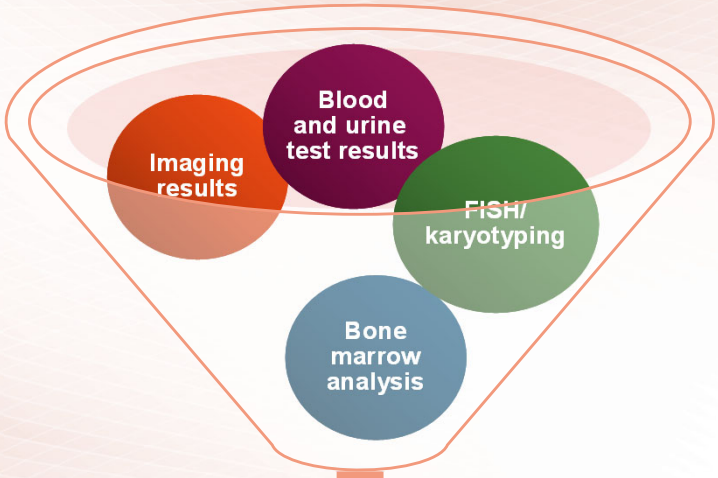
FISH (fluorescence in situ hybridization)



Genomic sequencing

38

Putting the Results Together



Staging, prognosis, and risk assessment

39

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
- R-ISS 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; GEP, gene-expression profiling

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.

40

Multiple Myeloma Prognosis and Risk

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

Standard risk

R-ISS Stage I

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

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

High risk

R-ISS Stage III

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

*High-risk chromosomal abnormality by FISH: del(17p) and/or t(4;14) and/or t(14;16)
β2M; beta-2 microglobulin; LDH, lactate dehydrogenase; FISH, fluorescent in situ hybridization

41

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.

42

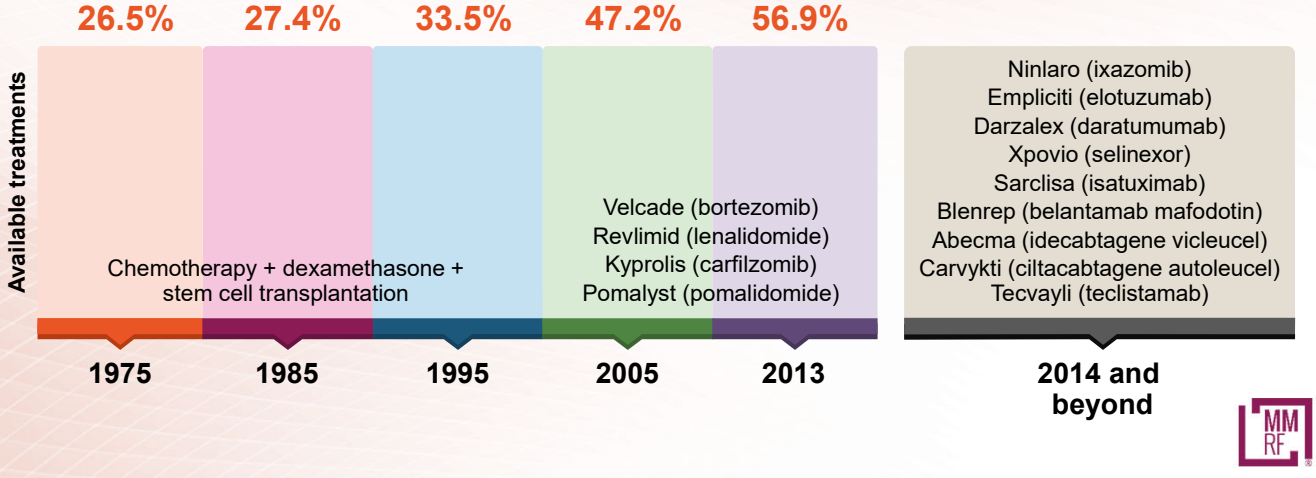
Getting the Right Treatment: Goals of Multiple Myeloma Therapy

- 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.

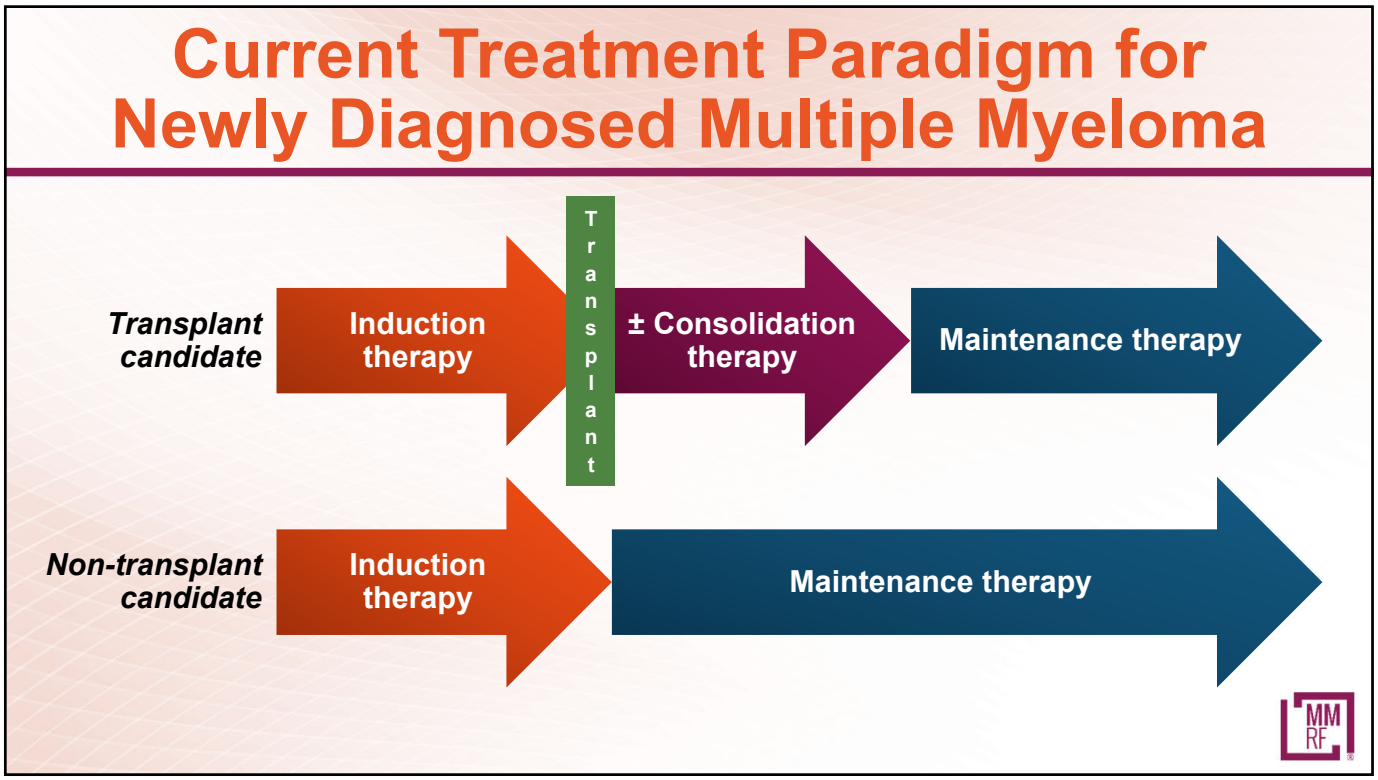
43

Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

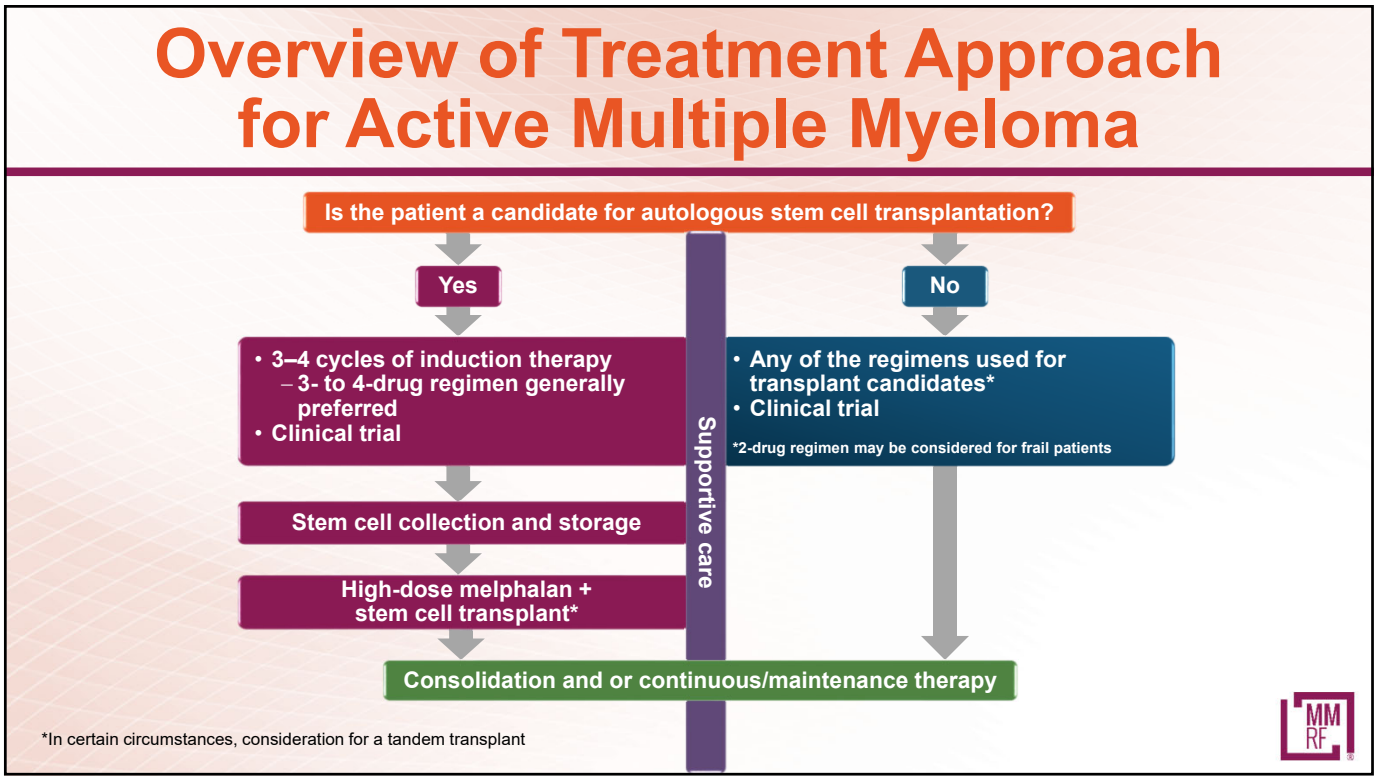
The percentage of people expected to survive 5 years or more after being diagnosed with myeloma



44


Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma
Transplant candidate
Induction therapy
Transplant
± Consolidation therapy
Maintenance therapy
Non-transplant candidate
Induction therapy
Maintenance therapy

45


Overview of Treatment Approach for Active Multiple Myeloma
Is the patient a candidate for autologous stem cell transplantation?
Yes
No
• 3–4 cycles of induction therapy
– 3- to 4-drug regimen generally preferred
• Clinical trial
Stem cell collection and storage
High-dose melphalan + stem cell transplant*
Supportive care
• Any of the regimens used for transplant candidates*
• Clinical trial
*2-drug regimen may be considered for frail patients
Consolidation and or continuous/maintenance therapy
*In certain circumstances, consideration for a tandem transplant

46

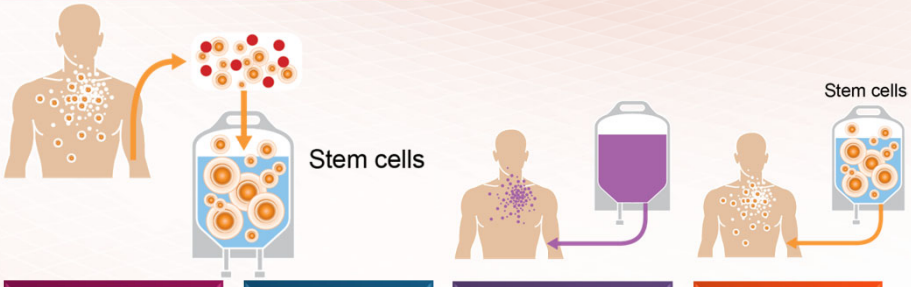
Induction Therapy Regimens

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

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

47

Autologous Stem Cell Transplantation



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

-2 to -3 weeks*

≥2 cycles

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

Melphalan
- Alkeran, Evomela

Day 0

Days +1 to +100†

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

48

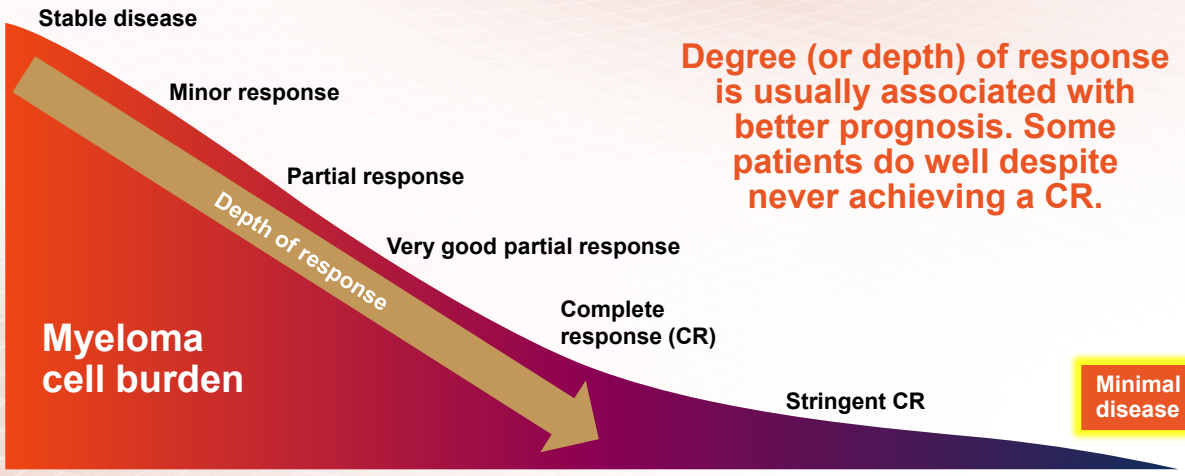
Continuous or Maintenance Therapy Options

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

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

49

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.

50

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

51

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!

52

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

53

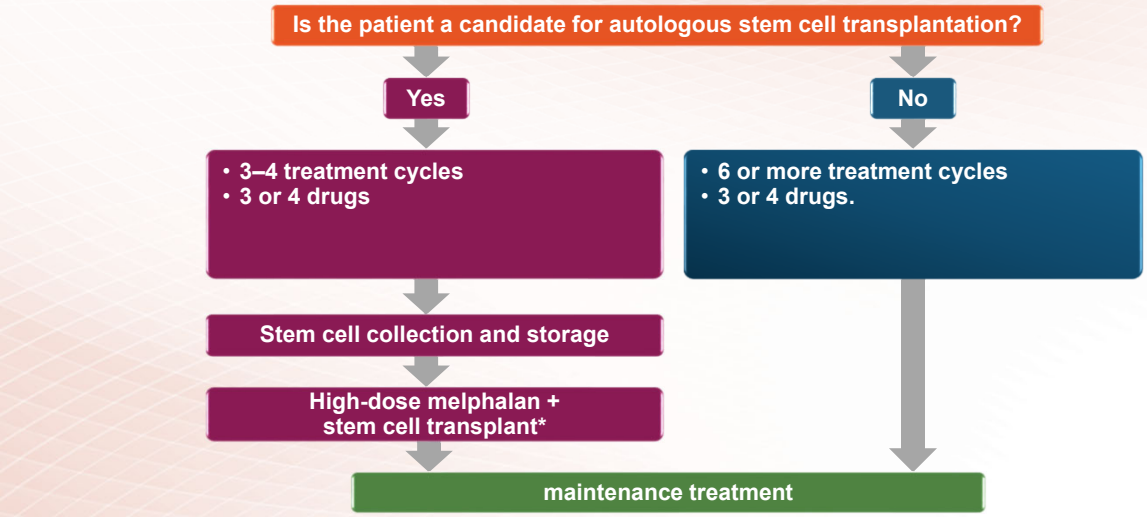
MULTIPLE MYELOMA Research Foundation

High-Dose Chemotherapy and Stem Cell Transplantation, Maintenance Therapy, and Treatment Goals

Clarence Adoo, MD
Arizona Center for Cancer Care
Honor Health
Glendale, Arizona

54

Overview of Treatment Approach for Active Multiple Myeloma



*In certain circumstances, consideration for a tandem transplant

55

High-Dose Chemotherapy and Stem Cell Transplantation

- Remission lasts longer
- Can be done early on or later (or both)
- Most patients will qualify,
  - including older patients,
  - patients with kidney disease
  - Insurance coverage.

56

What does transplant mean?

Understanding the basics of autologous stem cell transplantation

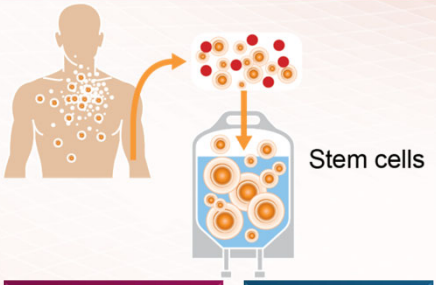
blood-forming cells collected from the patient's own blood
Stem cells are frozen and stored.

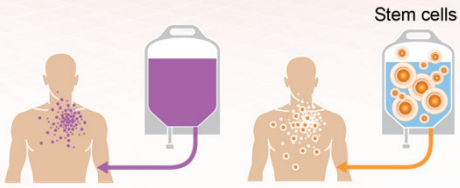
Patient gets high dose chemotherapy: melphalan.
most myeloma cells are destroyed
some normal cells (hair follicles, taste buds and blood cells)
are also temporarily destroyed.

The previously collected stem cells are given back by iv infusion.
Stem cells restore blood cells with fewer myeloma cells
Other cells like hair follicles and taste buds recover.

57

Autologous Stem Cell Transplantation





1. Induction therapy	2. Collection of stem cells from the bloodstream	3. Freezing of stem cells	4. High-dose chemotherapy	5. Thawing and infusion of stem cells	6. Recovery
≥2 cycles	Stem cell mobilization • Neupogen, Neulasta, Leukine, Cytoxan, Mozobil	-2 to -3 weeks*	Melphalan • Alkeran, Evomela	Day 0	Days +1 to +100†

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

58

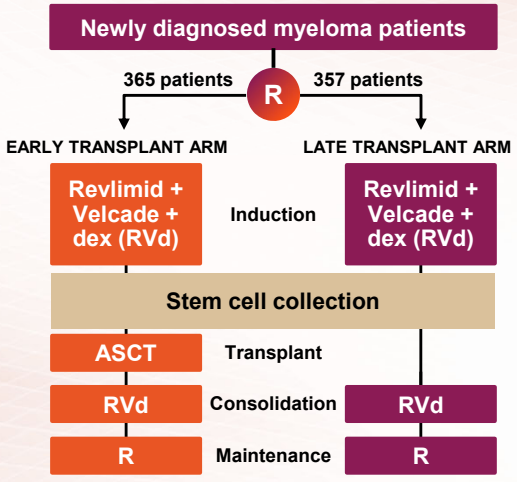
Side Effects of High-Dose Chemotherapy

Fatigue	Nausea & vomiting	Diarrhea	Mucositis	Low blood counts
• Expected • May last 1–3 months	• Symptoms much more manageable with newer anti-emetics • Try to prevent nausea	• May include stomach cramping • Encourage small amounts of food, more often • Avoid milk, milk products, high-fiber foods	• Pain, sores in mouth; sore throat • Pain meds, mouth swishes • Avoid tart, acidic, salty, spicy foods • Soft food better tolerated	• Low White blood cells count- risk for infection • Hemoglobin drop. Fatigue • Platelet count drop bleeding risk • Blood transfusion • Platelet transfusion • antibiotics • WBC and platelets recover in 2 weeks

59

Transplant or 3-drug treatment?

Comparative trial of Transplant vs continued 3 drug treatment: DETERMINATION Trial

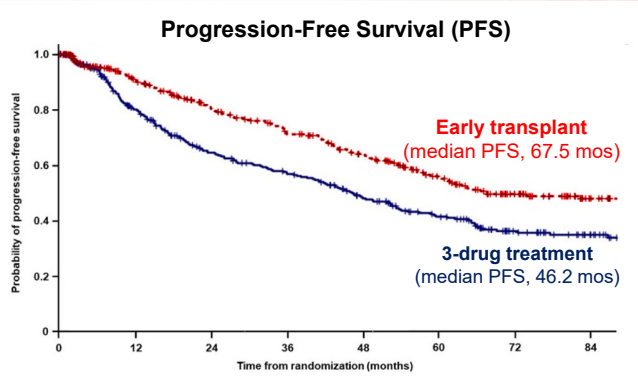


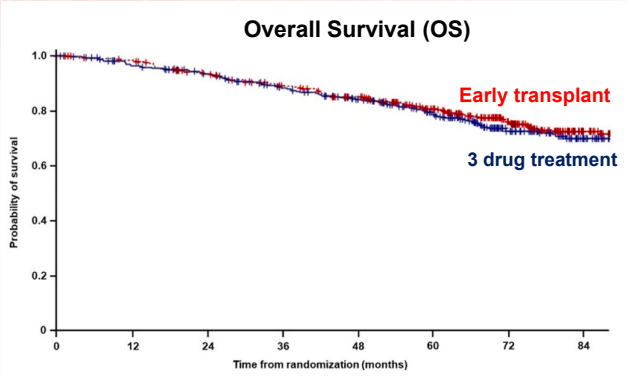
The study enrolled 19% Black myeloma patients.

Richardson PG et al. *N Engl J Med*. June 5, 2022 [Online ahead of print].

60

Comparative Study of Early Transplant vs continuation of Bortezomib, Lenalidomide and dexamethasone.





PFS for early transplant: 5 and one half years
PFS for 3 drug treatment: 4 years.

Length of overall survival was same.

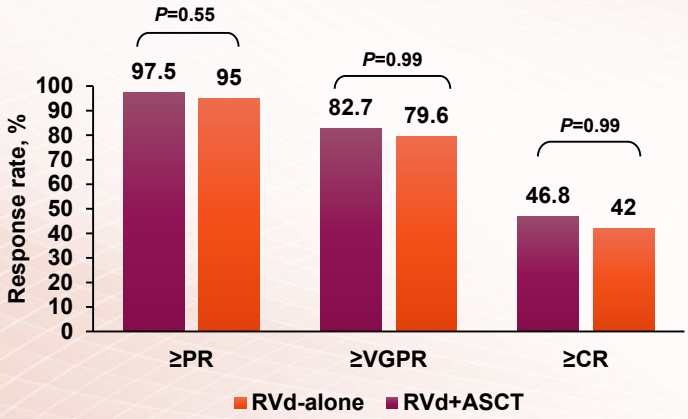
Transplant extended time to progression by 20 months

Richardson PG et al. *N Engl J Med*. June 5, 2022 [Online ahead of print].

61

Comparative Study of Transplantation in Patients With Newly Diagnosed Multiple Myeloma

Best Response to Treatment and Duration of Response



Duration of response	RVd alone (late transplant)	RVd + ASCT (early transplant)	*P* value
Median duration of ≥PR, months	38.9	56.4	0.003*
5-year duration of ≥CR, %	52.9	60.6	0.698

Richardson PG et al. *N Engl J Med*. June 5, 2022 [Online ahead of print].

62

Phase 3 Study of Early vs Late Autologous Stem Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma

Side effect, %	RVd-alone (N=357)	RVd+ASCT (N=365)
Any	78.2	94.2
Blood count problems	60.5	89.9
Fatal side effects	0.3	1.6 *
Very low white cell count	42.6	86.3
Low platelet count	19.9	82.7
Low white cell count	19.6	39.7
Anemia	18.2	29.6
Lymphopenia	9.0	10.1
Infections with low WBC	4.2	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mouth sores	0	5.2
Fatigue	2.8	6.0
Fever	2.0	5.2
Pneumonia	5.0	9.0
Low phosphate	9.5	8.2
numbness, tingling nerve	5.6	7.1

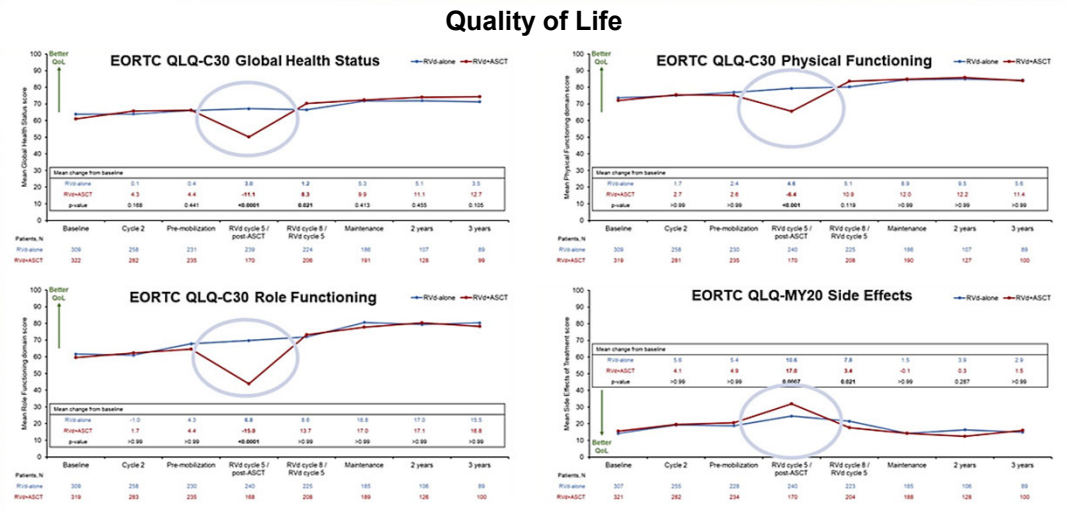
Severe side effects were more common with transplant.

*Includes one death related to ASCT

Richardson PG et al. *J Clin Oncol.* 2022;40. Abstract LBA4. Richardson PG et al. *N Engl J Med.* June 5, 2022 [Online ahead of print].

63

Autologous Stem Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma



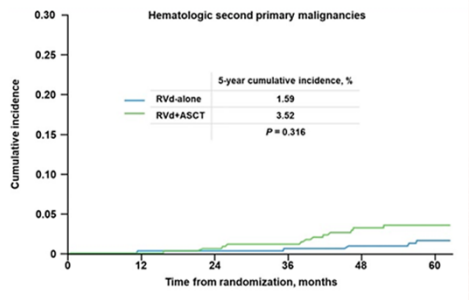
Richardson PG et al. *J Clin Oncol.* 2022;40. Abstract LBA4. Richardson PG et al. *N Engl J Med.* June 5, 2022 [Online ahead of print].

64

Phase 3 Study of Early vs Late Autologous Stem Cell Transplantation in Patients With Newly Diagnosed Multiple Myeloma

Second Cancers

- 5-year cumulative incidence of SPMs (RVd-alone vs RVd+ASCT):
  - All: 9.7% vs 10.8%
  - Invasive: 4.9% vs 6.5%
  - Hematologic: 1.59% vs 3.52%



Another cancer, %	RVd-alone (N=357)	Transplant RVd+ASCT (N=365)
Any	10.4	10.7
Any invasive SPM	5.3	6.8
Any hematologic SPM	2.5	3.6
ALL, n	7	3
AML/MDS, n	0*	10*
CLL/CML, n	2	0
Any solid tumor SPM	3.4	3.3
Any non-invasive solid tumor SPM	0	0.5
Any non-melanoma skin cancer	5.9	4.1

SPM, second primary malignancy

*P=0.002

Richardson PG et al. *J Clin Oncol.* 2022;40. Abstract LBA4. Richardson PG et al. *N Engl J Med*. June 5, 2022 [Online ahead of print].

65

Subsequent Therapy and Rate of ASCT in RVD-Alone Arm (Late ASCT)

Subsequent therapy in patients off protocol therapy, %	RVd-alone (N=279) Late Transplant	RVd+ASCT (N=276) Early Transplant
Any treatment*	79.6	69.6
Subsequent therapy	**n=222**	**n=192**
Any immunomodulatory drug	55.9	58.3
Pomalyst (pomalidomide)	30.2	29.2
Revlimid (lenalidomide)	25.7	29.2
Any proteasome inhibitor	55.9	50.0
Velcade (bortezomib)	27.5	25.5
Kyprolis (carfilzomib)	21.2	16.7
Ixazomib	8.1	7.8
Marizomib	0	0.5
Any monoclonal antibody	16.2	27.6
Darzalex (daratumumab)	11.3	21.4
Empliciti (elotuzumab)	4.5	6.3
Sarclisa (isatuximab)	0.5	0

*Including IMiDs, PIs, mAbs, HDACi (panobinostat), ASCT, chemotherapy, RT, steroids, other

Only 28.0% of RVd-alone (late transplant) patients had received ASCT at any time following end of study treatment

Richardson PG et al. *J Clin Oncol.* 2022;40. Abstract LBA4. Richardson PG et al. *N Engl J Med*. June 5, 2022 [Online ahead of print].

66

Early vs Delayed Transplant Pros and Cons

Pros

Early ASCT

- Youngest you are going to be
- Healthiest you are going to be
- Allows for fewer cycles of initial treatment
- Deeper and more durable response

Delayed ASCT

- Conserve quality of life in the early part of disease journey
- PFS may be shorter with delayed (vs early) hematopoietic cell transplantation (HCT), but OS is the same
- Better drugs or treatments could be available later on

Cons

Early ASCT

- 20% of patients still relapse within 2 years
- 1% risk of serious life-threatening complications
- 3 months of full clinical recovery
- No proven impact on overall survival

Delayed ASCT

- 60%–70% of patients will relapse and may need it as salvage
- Not all patients relapsing are able to undergo salvage HCT
- May need longer duration of chemotherapy to replace its effects

67

What is maintenance therapy?

A prolonged, and often low-dose, treatment given to myeloma patients after achieving a desired response to initial therapy

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

To deepen responses by reducing minimal residual disease (MRD) or maintaining the response achieved, reduce the risk of relapse, and prolong survival

68

Successful Maintenance Therapy Must...

1. Be convenient
2. Be safe and well tolerated long term
3. Not interfere with the use of other future treatments
   Not obscure disease measurement

69

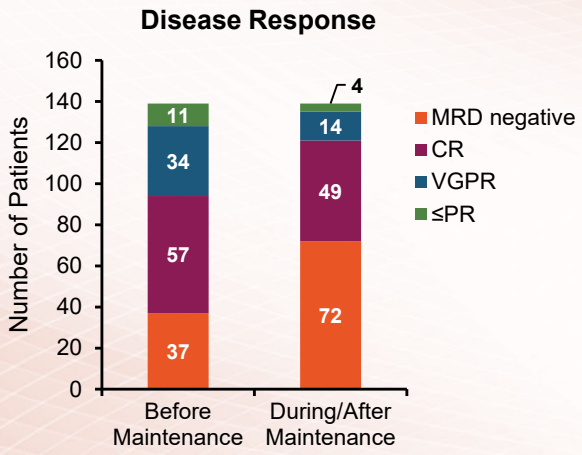
Continuous or Maintenance Therapy Options

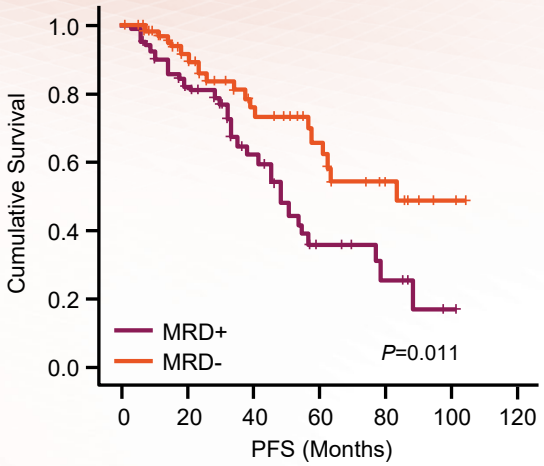
	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid*	• Velcade • Darzalex • Ninlaro	• Velcade-Revlimid ± dex • Kyprolis-Revlimid
Transplant ineligible	• Revlimid*	• Velcade • Ninlaro	• Velcade-Revlimid

*Category 1 recommendation. Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
National Comprehensive Cancer Network Guidelines Version 2.2023. Multiple Myeloma.

70

Revlimid Maintenance Therapy: Improves Depth of Response





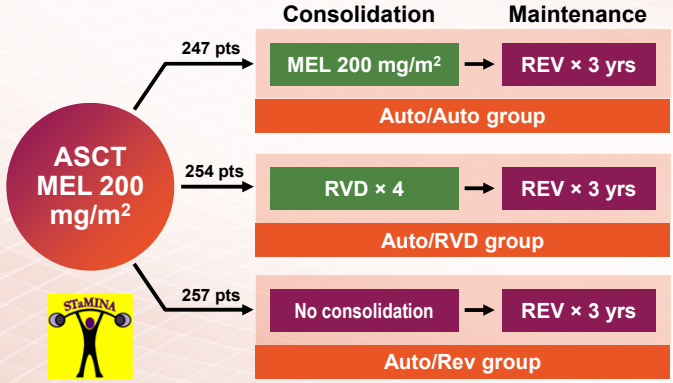
At maximal response during or after maintenance treatment with Revlimid

Alonso R et al. *Blood Adv*. 2020;4:2163.

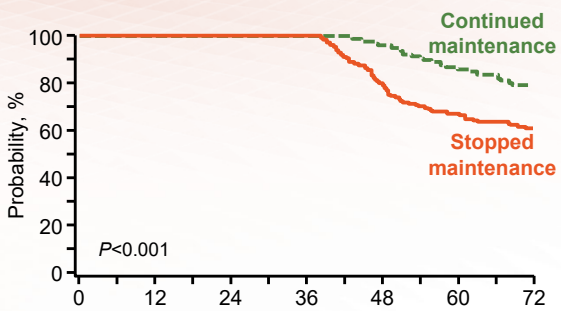
71

Revlimid Maintenance Duration

STAMINA Trial (BMT-CTN0702)



There was no difference in PFS or OS between the 3 groups



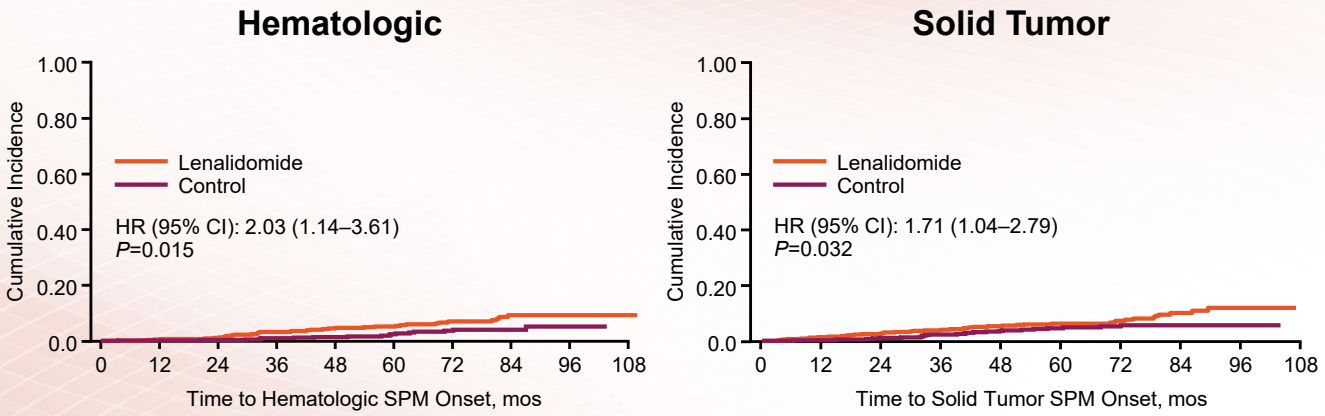
Discontinuation of Revlimid @ 3 years did not impact overall second primary malignancies (SPM) rates @ 6 years

Discontinuation of Revlimid maintenance at 3 years is not recommended because of the increased risk of disease progression

MEL, melphalan; RVD, Revlimid-Velcade-dex; REV, Revlimid
STAMINA Trial. Stadtmauer EA et al. *J Clin Oncol*. 2019;37:589; Hari P et al. *J Clin Oncol*. 2020;38. Abstract 8506.

72

Revlimid Maintenance: Cumulative Incidence of Second Primary Malignancies



McCarthy PL et al. *J Clin Oncol*. 2017;35:3279.

73

Minimal Residual Disease Negativity as a Multiple Myeloma Treatment Goal

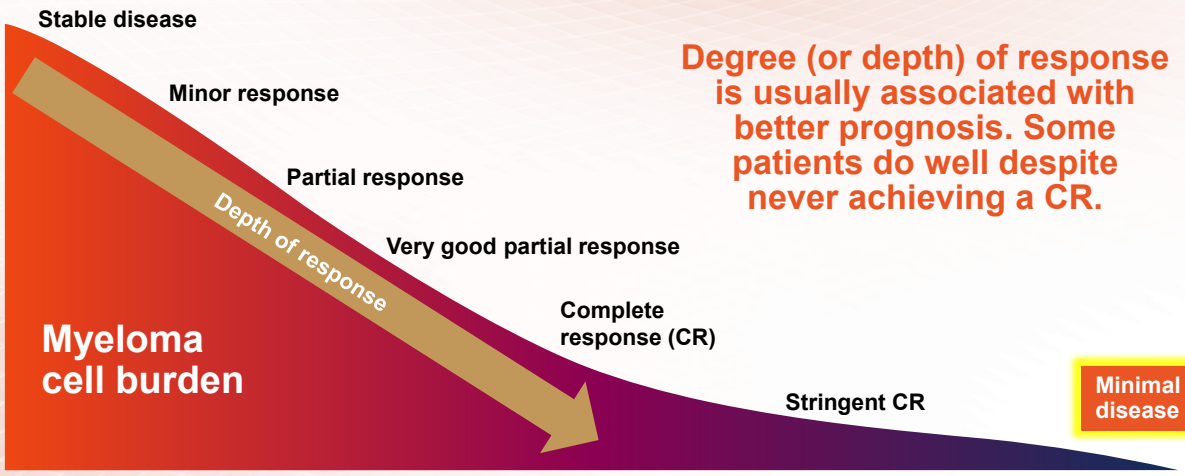
74

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

75

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.

76

What is MRD?

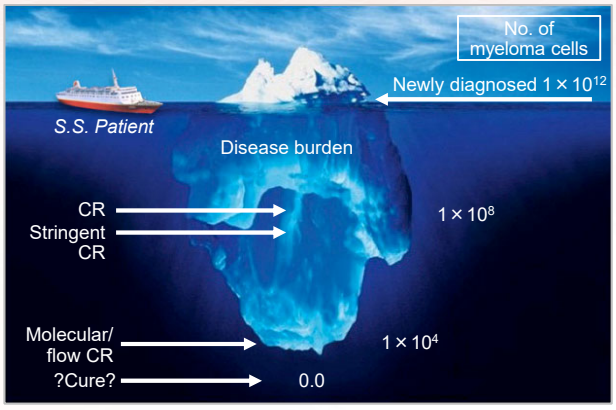
The presence of small amounts of myeloma cells in the body after treatment

MRD tests can detect at least 1 cell in 100,000

77

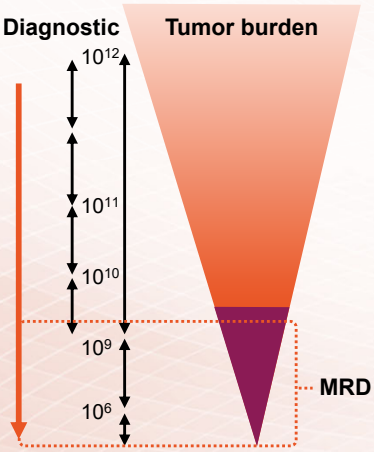
Why do we need to MRD?

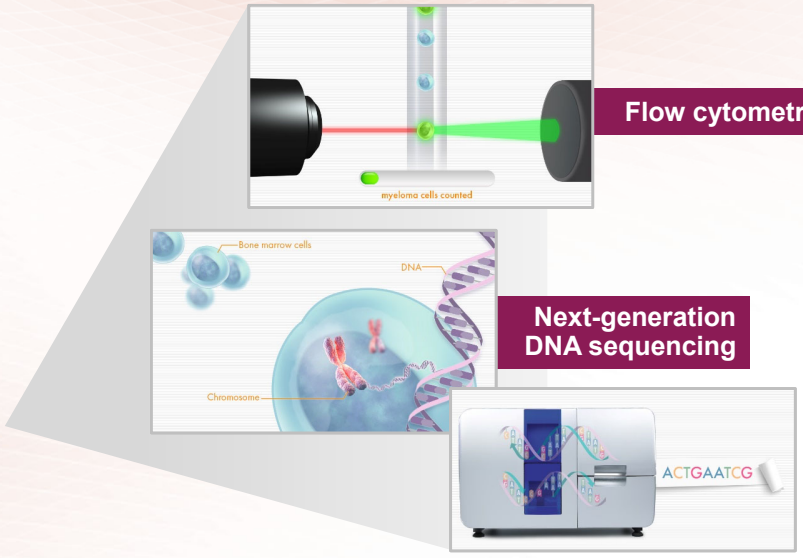
- With new and more effective treatments, more patients achieve CR
- However, achieving a CR does not necessarily mean that all myeloma cells are gone
- Routine blood tests are not sensitive enough to detect these remaining cells



78

How is MRD measured?





79

Comprehensive Response Assessment

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

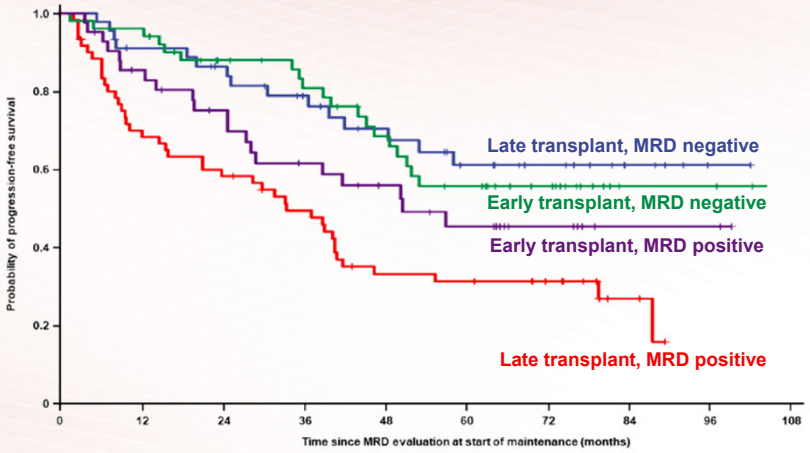
What about other areas of the body?

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

80

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.



MRD by next-generation sequencing (sensitivity 1 × 10^{-5})
Determination Study. Richardson PG et al. *N Engl J Med*. 2022;387:132.

81

Patients Who Achieve MRD Negativity Following Treatment Live Longer Than Those Who Are MRD Positive

Key points from 14 studies analyzed*

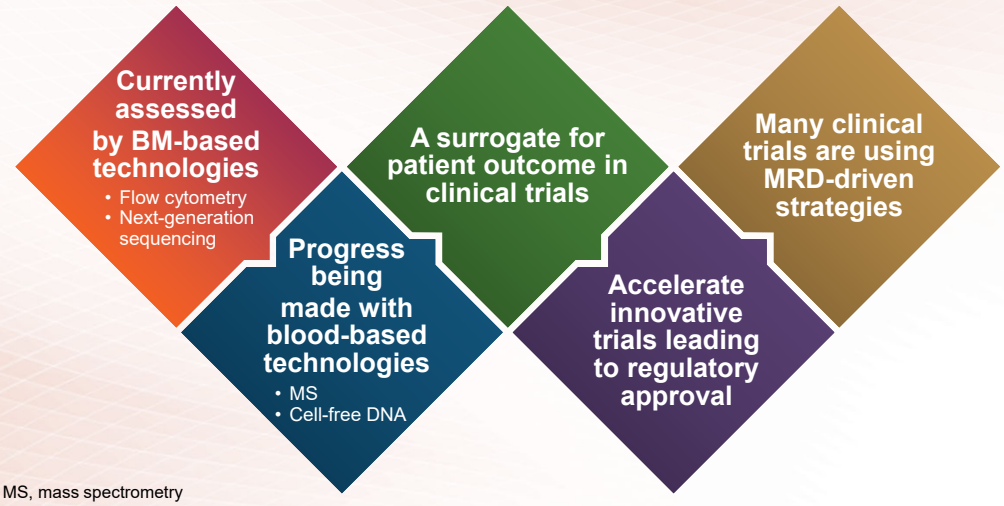
- Being MRD negative is correlated with longer progression-free and overall survival.
- MRD negativity may not (?) carry the same weight in patients with standard-risk vs high-risk disease.

*5 trials included stem cell transplantation/10 studies included maintenance

Munshi NC et al. *JAMA Oncol*. 2017;3:28.

82

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.

83

Summary

Autologous Stem Cell Transplantation

- **ASCT remains the standard of care for frontline therapy of myeloma; its safety has been established and it induces long remissions.**

Continuous or Maintenance Therapy

- **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 should receive maintenance who are thought to be Revlimid responsive and able to tolerate the side effects.**
- **For patients who are unable to tolerate Revlimid there are other agents such as Ninlaro, Kyprolis, and Darzalex that are effective, but they are not yet FDA-approved for use as maintenance. Several clinical trials are under way.**

Minimal Residual Disease

- **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. Blood-based MRD is in exploration.**
- **MRD has been associated with longer progression-free and overall survival to predict lower risk of progression. Modern combination therapies show increasingly higher MRD negativity rate.**
- **MRD response–directed therapy has been applied in more and more clinical trials to explore how to guide treatment decisions in myeloma.**
- **MRD is also useful as an end point in clinical trials helping to expedite new drug approval in myeloma.**

84

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

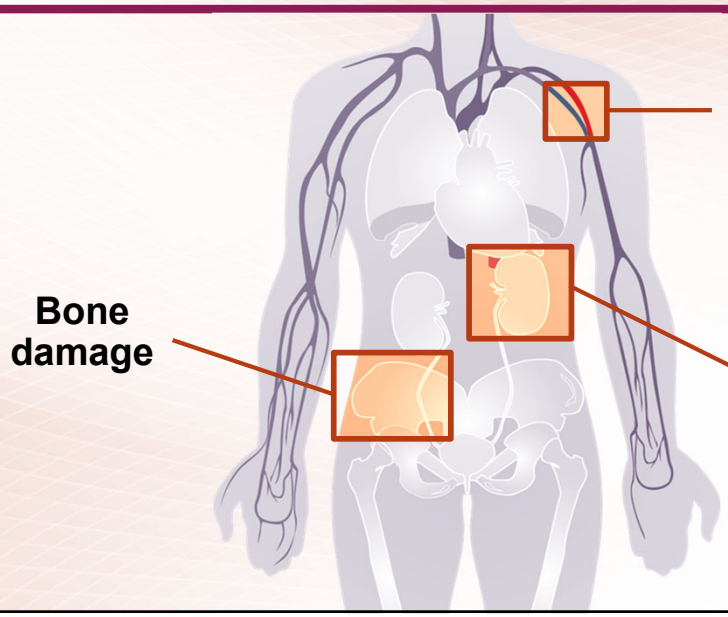
85

MULTIPLE MYELOMA Research Foundation

Supportive Care

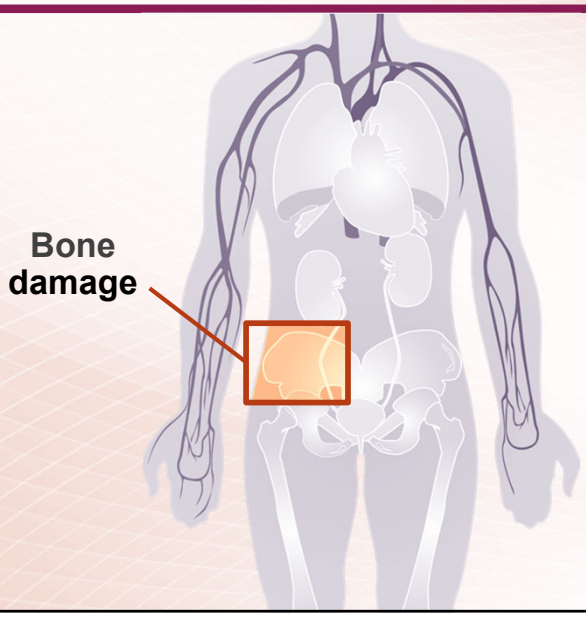
86

Effects of Myeloma

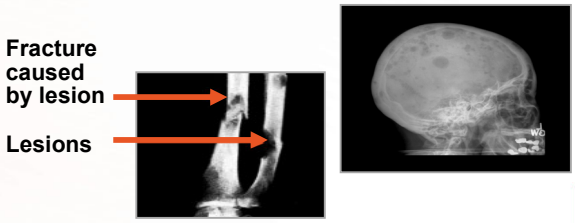


87

Effects of Myeloma: Bone Disease

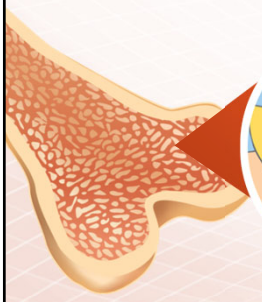


- Occurs in 85% of patients
- Weakened bone due to lesions or “holes”
- Increased levels of calcium in the blood (hypercalcemia)
- Leads to
  - Pathologic fractures
  - Spinal cord compression/collapse
  - Bone pain



88

Bone Strengthening Agents for Myeloma Bone Disease



How they work
- Prevent bone disease from getting worse

Benefits
- Decrease pain and reduce skeletal-related fractures

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

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

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

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

89

Recommendations for Reducing the Risk of ONJ

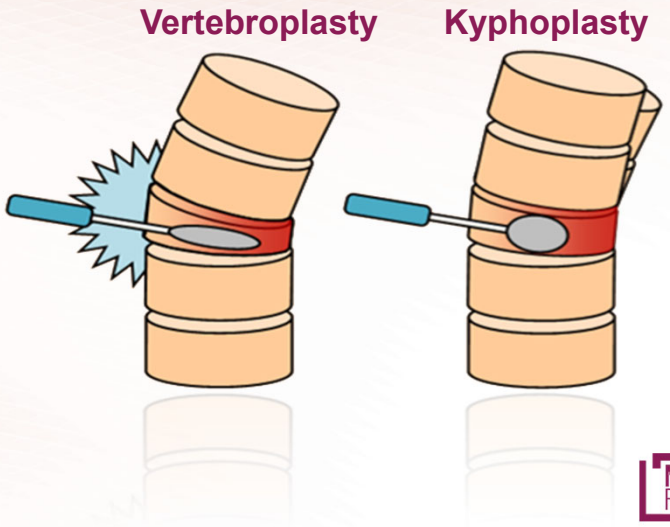
- Complete major dental work before beginning treatment for bone disease
- Practice good oral hygiene
- Schedule regular dental visits
- Let your dentist know that you are receiving treatment for bone disease
- Keep your doctor informed of dental issues/need for dental work
- Be attentive! ONJ seems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

ONJ, osteonecrosis of the jaw

90

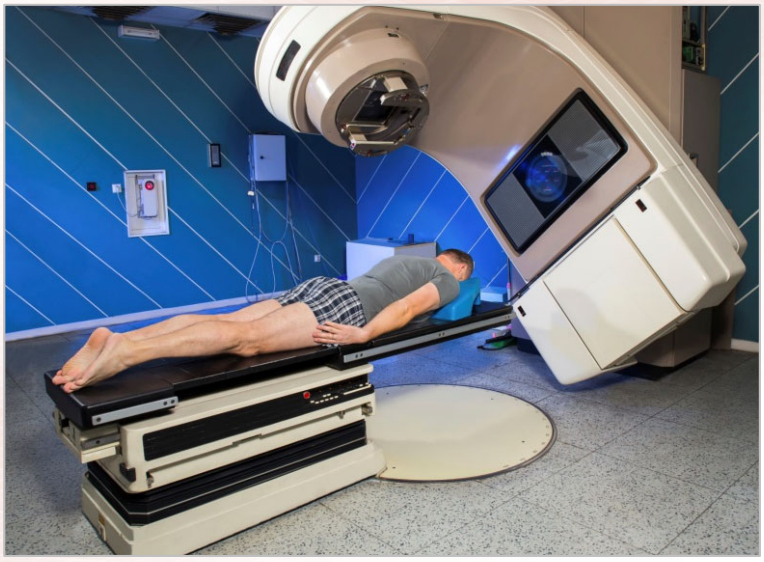
Orthopedic Procedures to Stabilize the Spine

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



91

Radiation Therapy for Pain Management



92

Pain Management Medications

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

93

Effects of Myeloma: Low Blood Counts

Low red blood cells (anemia)

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

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

Low white blood cells (leukopenia)

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

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

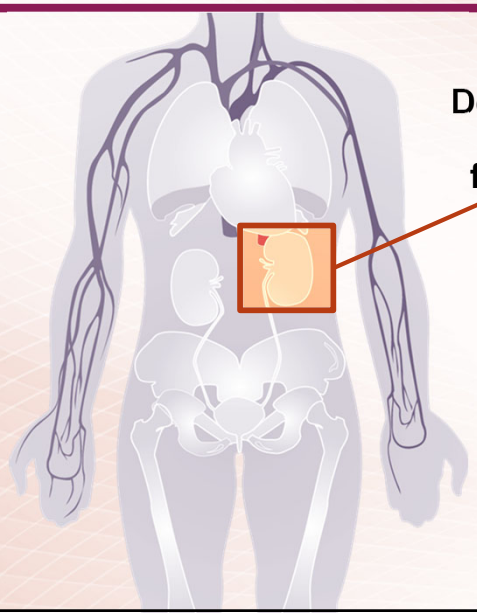
Low platelets (thrombocytopenia)

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

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

94

Effects of Myeloma: Decreased Kidney Function



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

95

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)

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

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

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

96

Class: Immunomodulatory Drugs Side Effects and Management

Revlimid*

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

Pomalyst*

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

Management

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

*Black box warning.
GI, gastrointestinal

97

Class: Proteasome Inhibitors Side Effects and Management

Velcade

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

Kyprolis

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

Ninlaro

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

Management

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

*Do not take any supplements without consulting with your doctor.
PN, peripheral neuropathy; GI, gastrointestinal

98

Class: Monoclonal Antibodies Side Effects and Management

Empliciti

- Low blood counts
- Infusion reactions

Darzalex*/Sarclisa

- Infusion reactions
- Fatigue
- Upper respiratory tract infection

*Now approved as subcutaneous injection with fewer side effects.

Management

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

99

XPOVIO: Selective Inhibitor of Nuclear Export Side Effects and Management

Gastrointestinal

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

Low sodium (hyponatremia)

Maintain fluid intake

Fatigue

Stay hydrated and active

Low blood counts (cytopenias)

Report signs of bleeding right away

Report signs of fatigue or shortness of breath

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

100

Bispecific Antibodies

Tecvayli

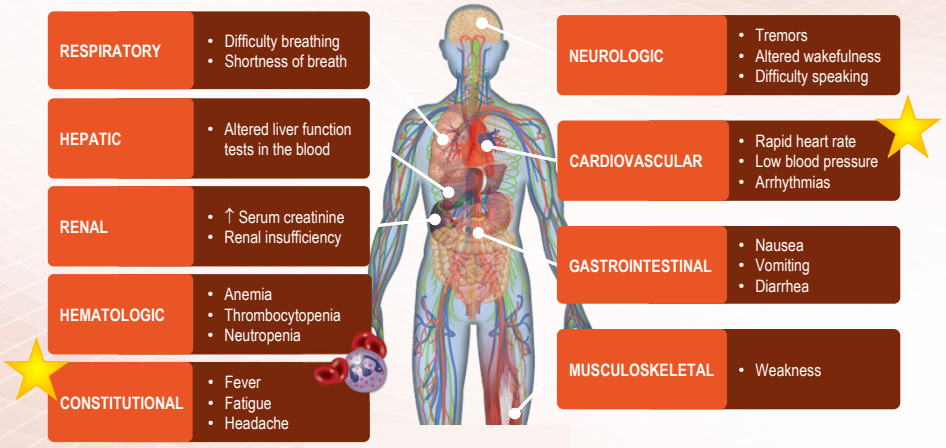
- Cytokine release syndrome
- Injection-related reactions
- Injection-site reaction
- Infections
- Neutropenia
- Anemia
- Thrombocytopenia

Management

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

101

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



Mitigation and monitoring for CRS

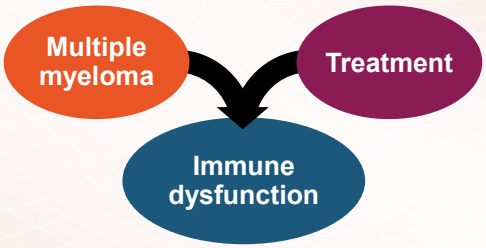
- Step-up dosing with hospitalization for monitoring
- Frequent vital signs
- Rule out infection
- Laboratory monitoring
- Early intervention with tocilizumab

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

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

102

Infection Can be Serious for Patients With Myeloma



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

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

General infection-prevention tips

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

As recommended by your health care team

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

103

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

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

104

Infection Prevention

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

105

Side Effects of Steroids (Dexamethasone)

Insomnia

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

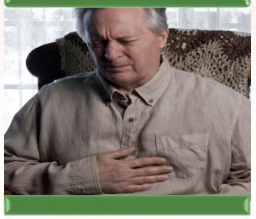
Fluid retention

- 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

106

Symptom Management
Constipation

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

107

Symptom Management
Acid Reflux/Heartburn

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

A few ways to treat

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

108

Symptom Management
Insomnia

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

109

Marijuana

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

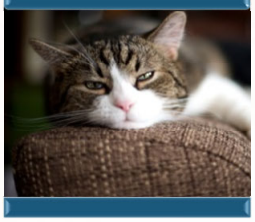
110

Daily Living

Proper nutrition

Exercise

Rest



Social contacts

111

Taking Care of Yourself

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

112

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

113

MULTIPLE MYELOMA Research Foundation

Personalized Medicine

Jonathan Keats, PhD
Translational Genomics Research Institute
Phoenix, Arizona

114

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?
Personalized medicine

115

Treatment of Multiple Myeloma

Where are we now?

- Standard induction with proteasome inhibitors and IMiDs, consolidation with ASCT, and maintenance therapy have benefited the majority of multiple myeloma patients
- A subset of myeloma patients still have poor outcome with standard therapy
- Personalized medicine approaches needed to address high-risk patients

What We Need

- Evolving definitions of high-risk, beyond historic markers such as translocation 4;14, deletion of chromosome 17p
- Advanced molecular diagnostics are key to revealing individual targets and therapies
- Immunotherapies are emerging as promising new weapons in the fight against multiple myeloma

IMiDs, immunomodulatory drugs; ASCT, autologous stem cell transplantation

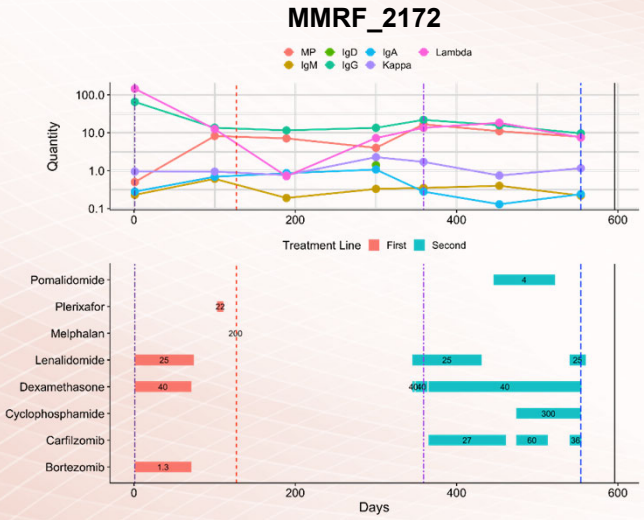
116

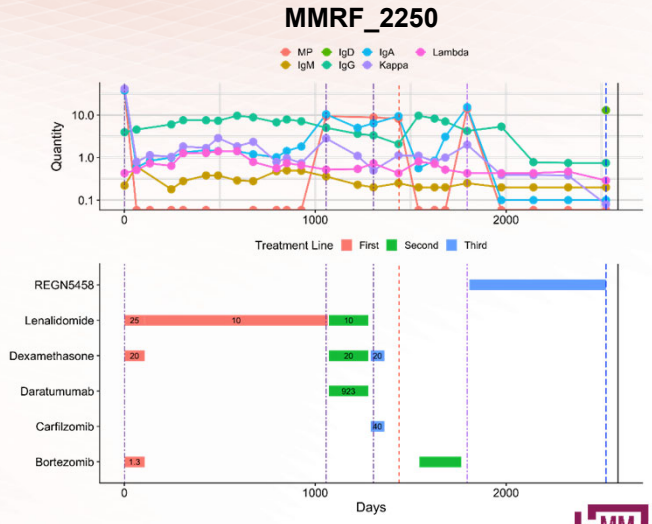
An Example of the Importance of Personalized Medicine

	CoMMpassMMRF2172	CoMMpassMMRF2250
Age	72	71
Ethnicity	Caucasian	Caucasian
ISS stage	II	II
Baseline treatment	VRD	VRD
Cytogenetics	t(4;14), del13	t(4;14), del13
Time of progression	11 months	36 months
Overall Survival	1.6 years	6.3 years

117

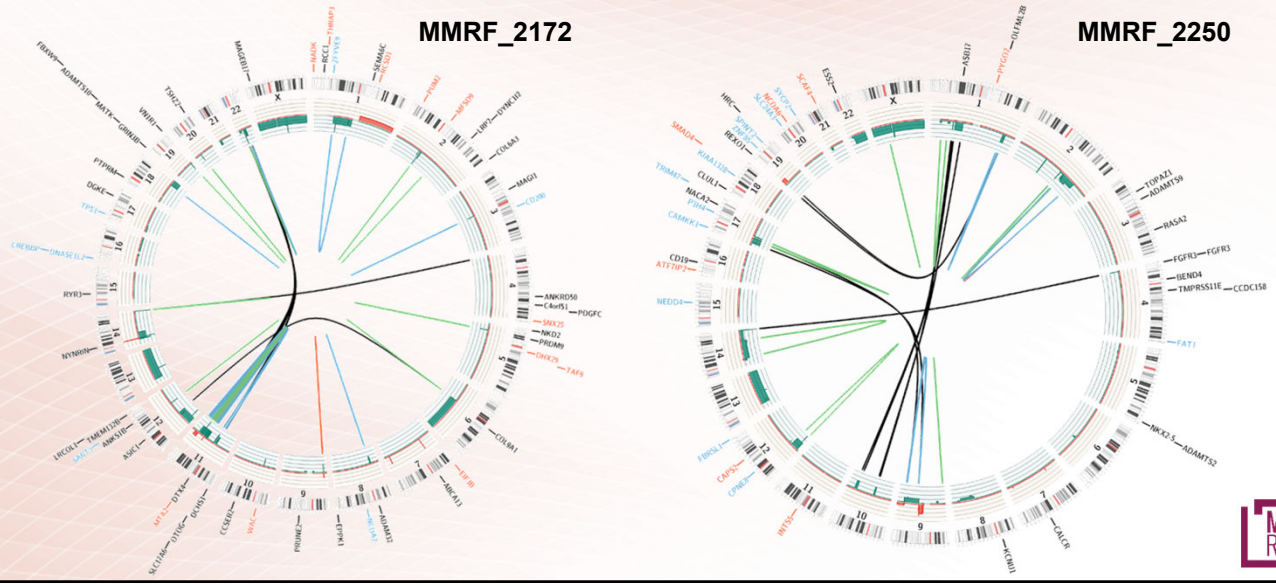
How did their clinical courses compare?





118

How do the patients' tumors compare?



119

An Example of the Importance of Personalized Medicine

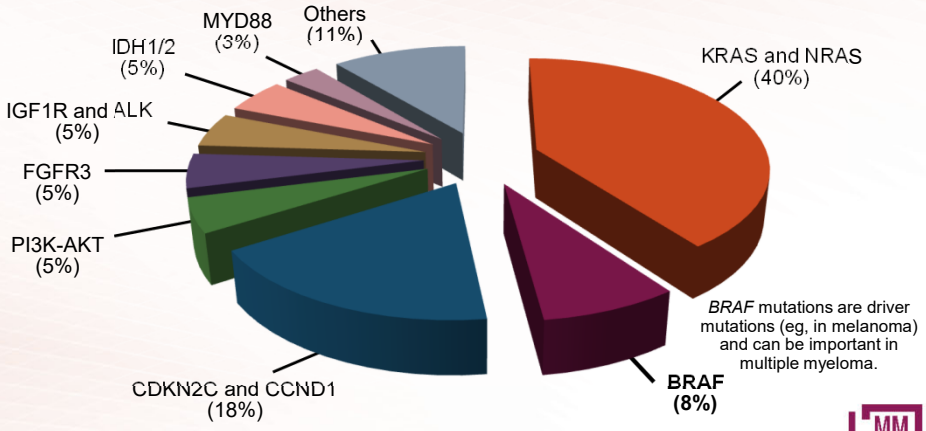
	CoMMpass MMRF2172	CoMMpass MMRF2250
Age	72	71
Ethnicity	Caucasian	Caucasian
ISS stage	II	II
Baseline treatment	VRD	VRD
Cytogenetics	t(4;14), del13	t(4;14), del13
Time of progression	11 months	36 months
Overall Survival	1.6 years	6.3 years
Other Genetic Events	**1q21, del17p + TP53 mut**	No 1q21, No 17p or TP53 mut

120

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



BRAF mutations are driver mutations (eg, in melanoma) and can be important in multiple myeloma.

121

Personalized Medicine Agents Under Clinical Investigation

Clinical phase	Novel agents Personalized medicine
Phase 3	Venetoclax*
Phase 1, 2	Abemaciclib* Cobimetinib* Dabrafenib Enasidenib Erdafitinib* Idasanutlin Trametinib Vemurafenib

*Being studied in the MyDRUG trial

122

BRAF and MEK

PET CT before and after 2 months of vemurafenib (a BRAF inhibitor) treatment in patient with *BRAF V600E* mutation

Sharman JP et al. *Clin Lymphoma Myeloma Leuk*. 2014;14:e161.

A phase 2 study evaluating combined BRAF and MEK inhibition in relapsed/refractory multiple myeloma patients with activating *BRAF V600E* mutations

- 12 patients treated with
  - BRAFTOVI (encorafenib)
  - MEKTOVI (binimetinib)
- 83% of patients responded to treatment
- Common side effects included blurred vision, macular edema, cramps, arthralgia, diarrhea, rash, and decreased left ventricular function
- Serious side effects included low blood counts and hypertension

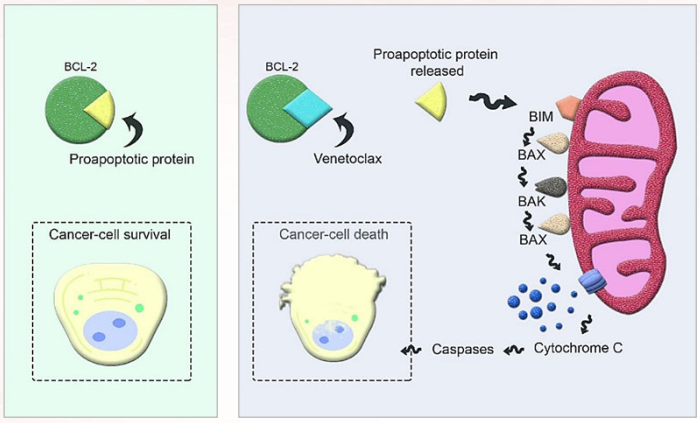
GMMG-Birma Trial. Raab MS et al. *Blood*. 2020;136. Abstract 294.

123

Venetoclax and t(11;14)

Venetoclax is a Bcl-2 inhibitor

- BCL2 inhibitor
- Induces cancer cell death
- t(11;14) multiple myeloma → ↑BCL2 and ↓MCL1
- t(11;14): first predictive marker in multiple myeloma, indicating susceptibility to BCL2 inhibition



Ehsan H et al. *J Hematol*. 2021;10:89.

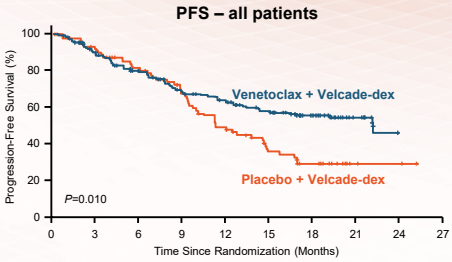
124

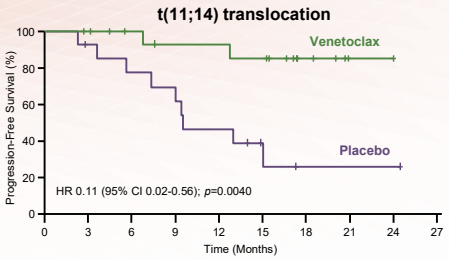
Venetoclax and t(11;14)

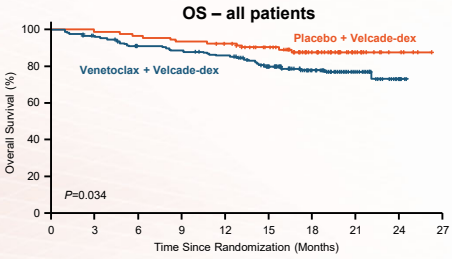
Venetoclax bortezomib dex vs placebo bortezomib dex;
1–3 prior lines

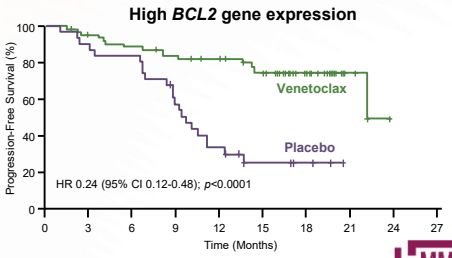
Median follow up 18.7 m mPFS
22.4 m venetoclax
11.5 m placebo

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







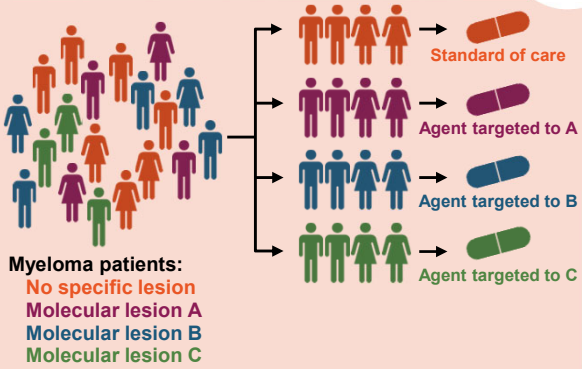


The BELLINI Trial. Kumar SK et al. *Lancet Oncol*. 2020;21:1630.

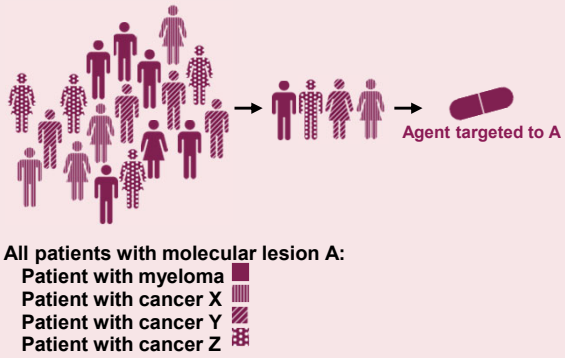
125

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

Umbrella/platform trials



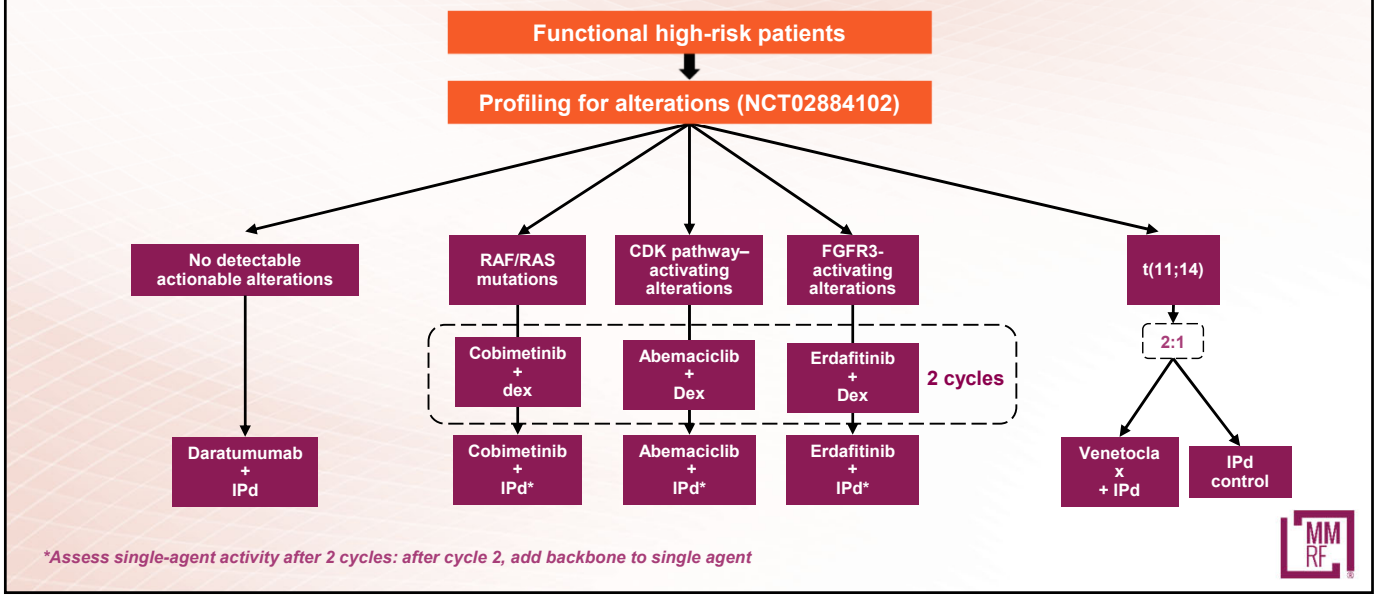
Basket/bucket trials



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

126

MyDRUG Trial



127

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.)

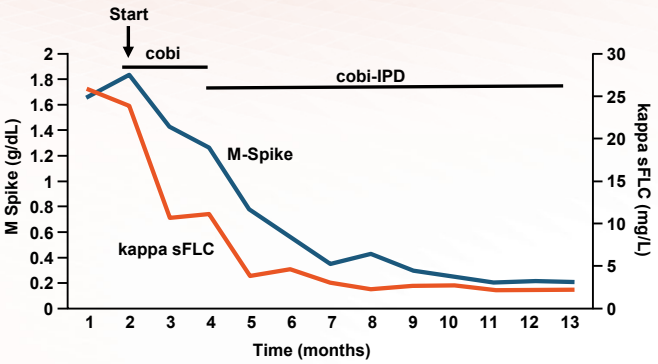
2nd Line

- EPd
- Best response: MR
- Progressed in 4 months

3rd Line

- MyDRUG

Response on MyDRUG



Genomics

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

128

The Road Ahead

- Comprehensive translational and clinical research to find the best combinations of targeted and immune therapies for each group of myeloma patient
- Deliver on the promise of personalized medicine for every patient

129

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.**
- **Participation in clinical trials to provide bone marrow and peripheral blood is paramount.**
- **Personalized medicine provides the right treatment at the right time for each myeloma patient.**

130

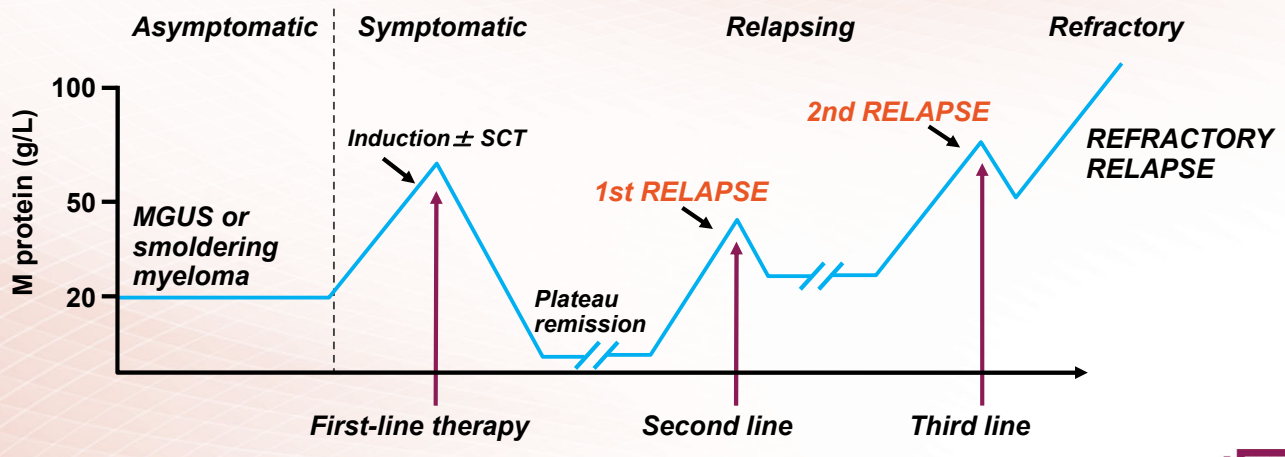
MULTIPLE MYELOMA Research Foundation

Relapsed/Refractory Multiple Myeloma

Sumit Madan, MD
Banner MD Anderson Cancer Center
Gilbert, Arizona

131

Multiple Myeloma Is a Marathon, Not a Sprint



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

132

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

133

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**

134

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

135

Options for Relapsed/Refractory Disease Continue to Increase

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

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

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

136

Three Drugs Withdrawn From US Market
What happened?

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

Withdrawn 2021

Farydak (panobinostat)

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

Pepaxto (melflufen)

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

Withdrawn 2022*

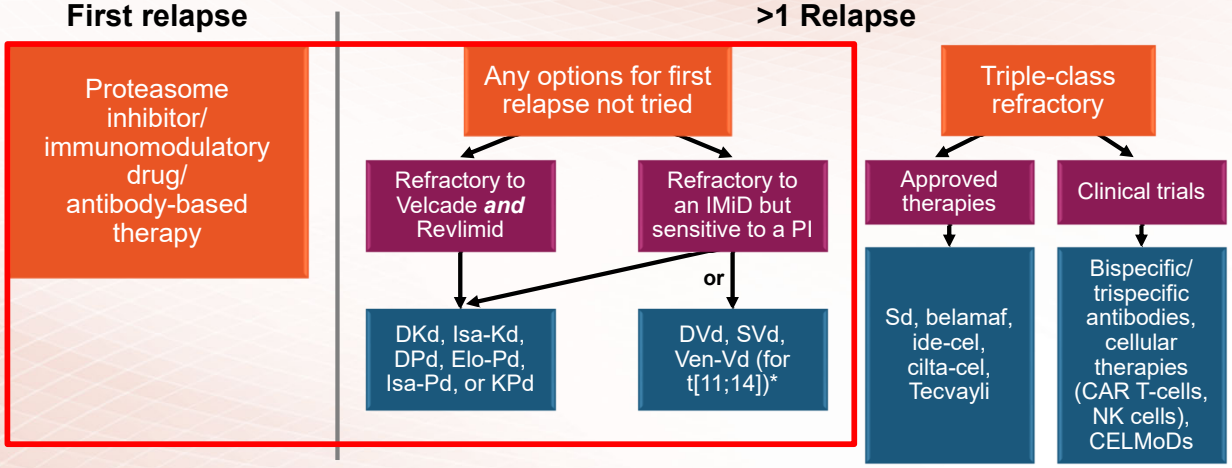
Blenrep (belantamab mafodotin)

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

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

137

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.

138

Triplet Regimens for Early Relapse

139

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

140

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

141

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

142

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

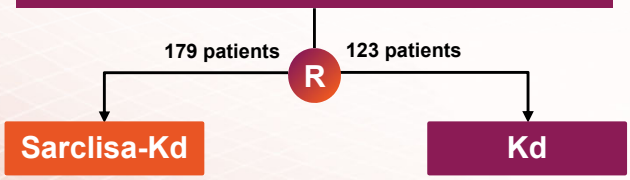
	ELOQUENT-2	ELOQUENT-3	ICARIA-MM	IKEMA
Regimens compared	• Empliciti-Revlimid-dex vs Rd	• Empliciti-Pomalyst-dex vs Pd	• Sarclisa-Pomalyst-dex vs Pd	• Sarclisa-Kyprolis-dex vs Kd
Median progression-free survival favored	• Empliciti-Rd: 19 vs 15 months	• Empliciti-Pd: 10 vs 5 mos	• Sarclisa-Pd: 12 vs 7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

143

Update From the 2022 American Society of Hematology (ASH) Meeting
Sarclisa After Early or Late Relapse

IKEMA Study

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



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

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

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

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

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

144

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

145

Important Considerations for Use of Monoclonal Antibodies

Darzalex

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

Empliciti

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

Sarclisa

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

SC, subcutaneous; IVIG, intravenous immunoglobulin

146

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

147

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

148

Important Considerations for Use of XPOVIO

Gastrointestinal

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

Low sodium (hyponatremia)

Maintain fluid intake.
Salt tabs

Fatigue

Stay hydrated and active.

Low blood counts (cytopenias)

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

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

149

Treatment Approach

First relapse

Proteasome inhibitor/ immunomodulatory drug/antibody-based therapy

>1 Relapse

Any options for first relapse not tried

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

or

Triple-class refractory

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

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

*Not yet approved for use in myeloma patients.

150

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)

151

Currently Available Drugs for Triple-Class Refractory Myeloma

Class	Drug	Formulation	Approval
Nuclear export inhibitor	XPOVIO (selinexor)	Twice-weekly pill	• For **relapsed/refractory** myeloma in combination with dexamethasone (after at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 mAb
Chimeric antigen receptor (CAR) T cell	Abecma (idecabtagene vicleucel)*	300 to 460 × 10^6 genetically modified autologous CAR T cells in one or more infusion bags	• For **relapsed/refractory** myeloma (after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb
CAR T cell	Carvykti (ciltacabtagene autoleucel)†	0.5 to 1.0 × 10^6 genetically modified autologous CAR T cells/kg of body weight	• For **relapsed/refractory** myeloma (after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb
Bispecific antibody	Tecvayli (teclistamab)‡	Step-up dosing§ the first week then once weekly thereafter by subcutaneous injection	• For **relapsed/ refractory** myeloma (after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb)

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

*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
†Black box warning: cytokine release syndrome; neurologic toxicities; Parkinsonism and Guillain-Barré syndrome; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
‡Black box warning: cytokine release syndrome; neurologic toxicities
§Patients are hospitalized for 48 hours after administration of all step-up doses.

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

152

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)

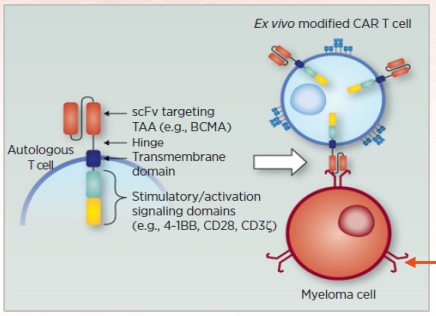
Additional analyses showed clinical benefit with XPOVIO regardless of patient age and kidney function.[2,3]

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.

153

CAR T-Cell Therapy

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

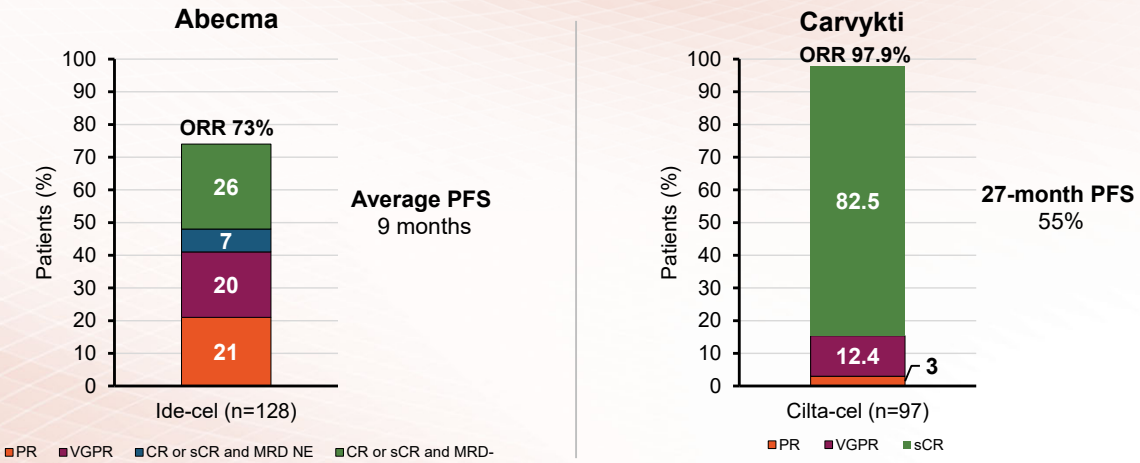


Examples:
- Abecma (ide-cel)
- Carvykti (cilta-cel)
- CT103A
- Gamma secretase inhibitor followed by CAR T-cells

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

154

Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma



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

KarMMa Trial. Munshi NC et al. *N Engl J Med*. 2021;384:705.
CARTITUDE-1 Trial. Berdeja JG et al. *Lancet*. 2021;398:314; Martin T et al. *J Clin Oncol*. June 4, 2022 [Epub ahead of print].

155

CAR T: Expected Toxicities

Cytokine release syndrome (CRS)

Neurotoxicity (ICANS)

Cytopenias

Infections

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

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

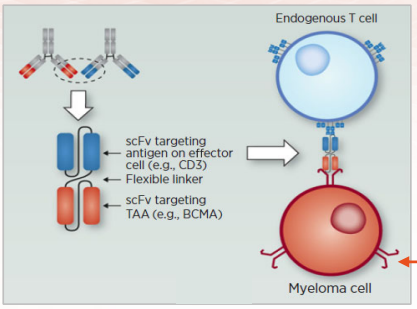
ICANS, immune effector cell-associated neurotoxicity syndrome

Xiao X et al. *J Exp Clin Cancer Res*. 2021;40(1):367. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625;
Shah N et al. *J Immunother Cancer*. 2020;8:e000734.

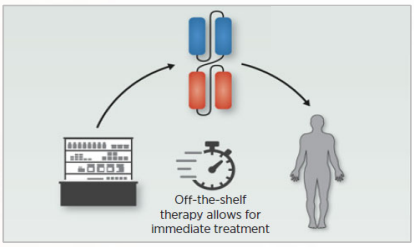
156

Bispecific Antibodies

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



BCMA, GPRC5D, or FcRH5

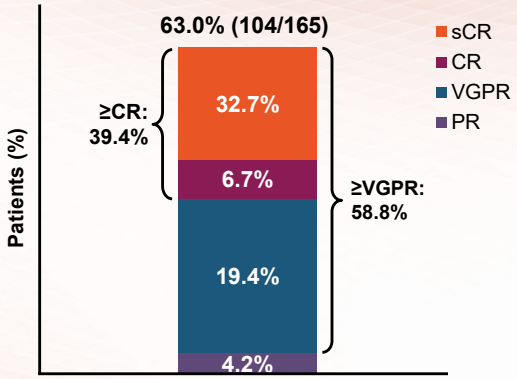


Examples:
- Elranatamab
- Teclistamab
- TNB-303B (ABBV-383)
- Linvoseltamab
- Alnuctamab
- Cevostamab
- Talquetamab

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

157

Now Approved: Tecvayli, the First Bispecific Antibody!



Median duration of response 18.4 months

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

158

Tecvayli Side Effects

Side Effects

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

Side Effect Management

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

159

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

	CAR T-cell therapy	Bispecific antibody
Approved product	Abecma, Carvykti	Tecvayli
Efficacy	++++	+++
How given	One-and-done	IV or SC, weekly to every 3 weeks until progression
Where given	Academic medical centers	Academic medical centers
Notable adverse events	CRS and neurotoxicity	CRS and neurotoxicity
Cytokine release syndrome	+++	++
Neurotoxicity	++	+
Availability	Wait time for manufacturing	Off-the-shelf, close monitoring for CRS and neurotoxicity
Advantages	• Personalized • Targeted immunocytotoxicity • Single infusion (“one and done”) • Potentially persistent	• Off the shelf • Targeted immunocytotoxicity • No lymphodepletion • Minimal steroids
Disadvantages	• FACT-accredited center required (hospitalization likely required) • CRS and neurotoxicity; requires ICU and neurology services • Dependent on T-cell health (manufacturing failures) • Requires significant social support; caregiver required • $$$$	• Initial hospitalization required • CRS and neurotoxicity possible • Dependent on T-cell health (T-cell exhaustion) • Requires continuous administration • $$$

160

Emerging Treatment Options

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

161

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.
- CAR T and bispecific antibodies are very active even in heavily pre-treated patients. Many other exciting immunotherapy options are in trials and look very promising.

162

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

163

CancerCaregivers Of America

A Cancer Patient and Caregiver's Journey

Cancer Caregiving: Its challenges and celebrations.
An intimate conversation with the England Family

Objective

A look at a cancer caregiving experience and the importance of enhancing the skills and knowledge of the cancer caregivers.

164

CancerCaregivers Of America

Cancer Caregivers of America

Cancer Caregivers Education Platform

Online Training, Resources, and a Cancer Care Community

165

CancerCaregivers Of America

HOW DID WE GET HERE?

Our Journey

Jack Kavanagh diagnosed with Multiple Myeloma **(1991)** → Arizona Multiple Myeloma Network Non-profit created **(2004)** → Cancer Caregivers AZ, Cancer Caregivers Education Program created **(2014)** → **WELCOME** Cancer Caregivers of America, Online Cancer Caregivers Education Platform Launch **(2023)**

166

CancerCaregivers Of America

Cancer Caregivers Education
The NEED

167

CancerCaregivers Of America

Today we *LAUNCH!!!*

Online Cancer Caregivers Education Platform

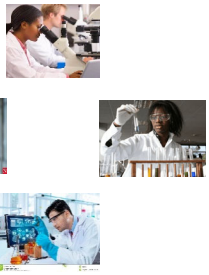
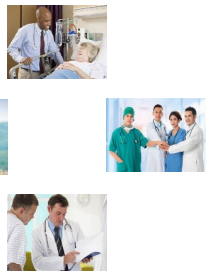
Available in the U.S. and Canada

168

CancerCaregivers Of America

CANCER HEALTH CARE CONTINUUM, today

GAP

Dedicated Scientist and Researchers	Committed Doctors and Nurses	Faithful Cancer Caregivers
		
Knowledgeable and Skillful	**Knowledgeable and Skillful**	**Little Knowledge and little or no Skills**

169

CancerCaregivers Of America

Cancer Caregivers are a vital part of the cancer care continuum.

OUR VISION is that they are Knowledgeable and skillful cancer caregivers.

Dedicated Scientist and Researchers	Committed Doctors and Nurses	Faithful Cancer Caregivers
		
Knowledgeable and Skillful	Knowledgeable and Skillful	Knowledgeable and Skillful

170

CancerCaregivers Of America

What is the Online Cancer Caregivers Education Platform?

Online Cancer Caregivers Education Platform includes, online Education/Training, Resources, and a Cancer Care Community
The program also has the option to provide **In-Person Training Sessions**

The program is designed for **ALL CANCERS** and **CANCER CAREGIVERS**

The program focuses on **INCREASING** your **KNOWLEDGE** and **BUILDING** your cancer caregiving **SKILLS**

The program is developed using actual Cancer Caregivers and Patients knowledge and experiences

The program is designed with a **360°** view of what the cancer caregiver and patient will experience.
The psychological, physical, social, emotional, financial and the many other circumstances that will arise on your journey.

171

CancerCaregivers Of America

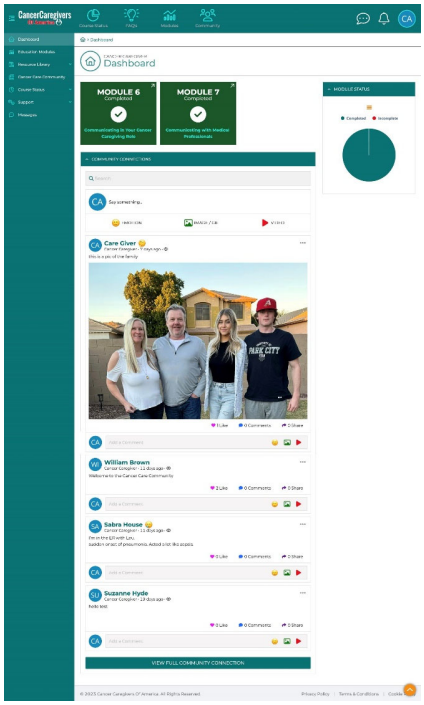
Online Cancer Caregivers Education Program Assets

Program Assets	Cancer Caregivers/Patients	Cancer Care Professionals
1 Cancer Caregivers Online Training	8 Education modules	Interactive and engaging Pre/post assessments
	Interactive and engaging Pre/Post assessments	4 Education modules
	Data collection Certificate of completion	CME/CEU available 2023/24
2 Cancer Care Resource Library	Only cancer related resources Clinical trials, finance support, etc.	Not Available
	Additional videos, links , documents from the program and other sources	
3 Cancer Care Community	National cancer caregiver's network where you can share information in a closed network	Not Available
	Share resources and more in a supportive environment	
4 Cancer Caregivers In-person Training	Same benefits / access as Online Training	Available

Cancer Care Professional's Education Modules will be available 9/1/23

172

Online Cancer Caregivers Education Platform



173

Online Cancer Caregivers Education Platform

CancerCaregivers Of America

Cancer Caregivers Education Training Modules (8)

Cancer Caregivers Education Program Introduction

Program Overview

- Navigating through the platform
- Benefits
- What you can expect

Module 1

Who You Are as A Cancer Caregiver

- Understand what it means to assume responsibilities of being a Cancer Caregiver
- Know the common frustrations
- Understand resilience

Module 2

Circle of Responsibilities

- Understand the scope of work
- Understand the amount of time you spend cancer caregiving
- Learn how to build your Cancer Care Team
- Learn how to effectively plan caregiving work

Module 3

Managing Stress In The Cancer Caregiving Role

- Understand what stress is
- Learn how to recognize your stress triggers
- Build your self care plan to manage stress

Module 4

Cancer Caregiving Survivorship

- Understand what cancer survivorship is
- How the impacts of cancer caregiving affects you
- Learn how to manage your overall well-being as a cancer caregiver

Module 5

Communications with Family in your Cancer Caregiving Role

- Learn the types of communication needs and challenges in your cancer caregiving role
- Provide you with tools to enhance your communication skills

Module 6

Communications with Medical Professionals

- Build your skills to effectively communicate with your Medical Care Professionals
- Learn how to be organized to get the most out of time spent with Medical care professionals

Module 7

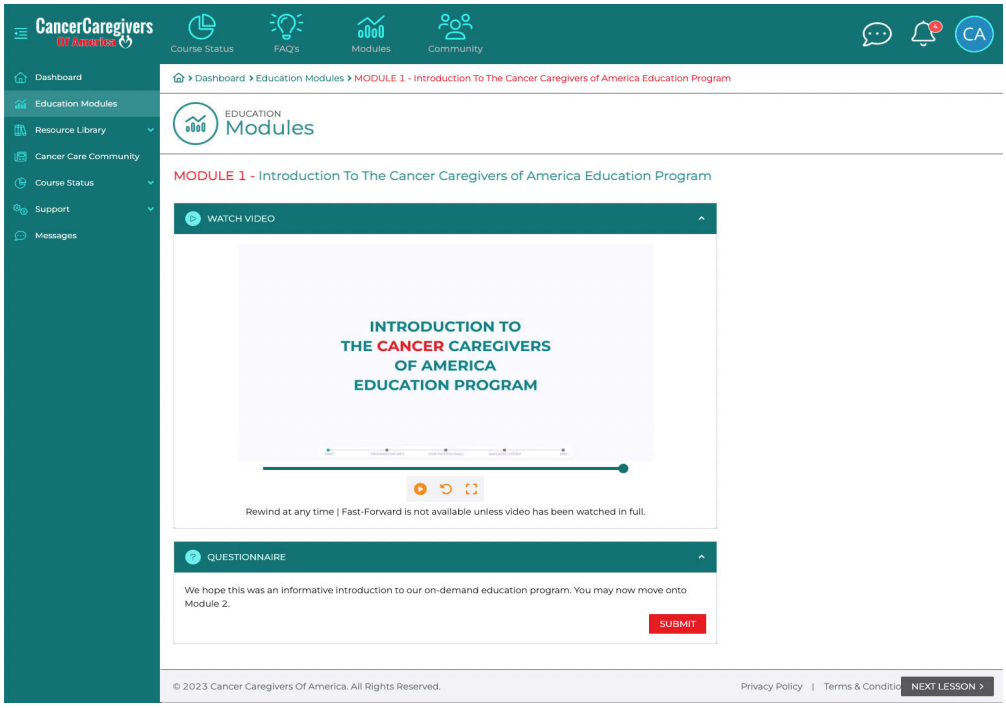
Navigating the Healthcare System

- Understand the many functions involved with delivering care and support for your l oved one.
- Learn strategies that will enhance your ability to navigate the healthcare system

Module 8

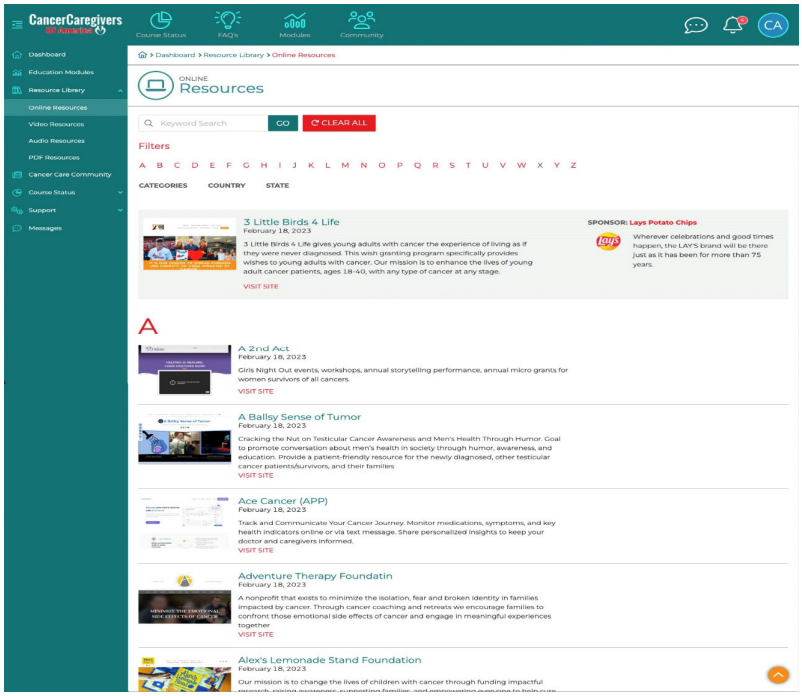
174

Online Cancer Caregivers Education Platform



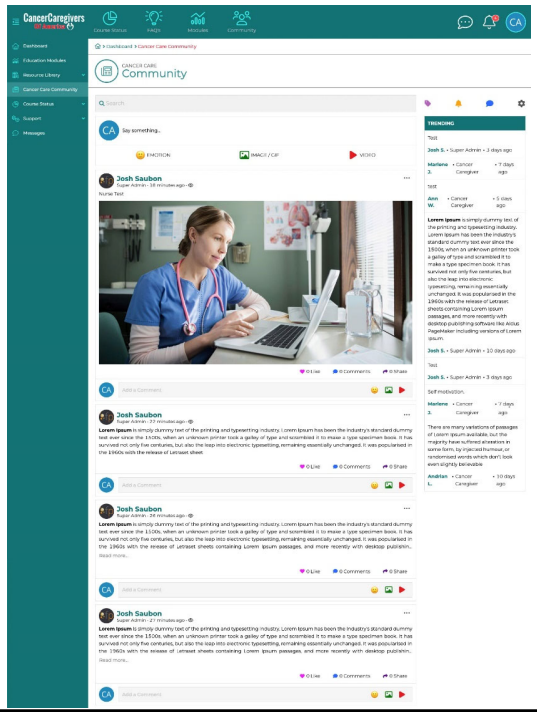
175

Online Cancer Caregivers Education Platform



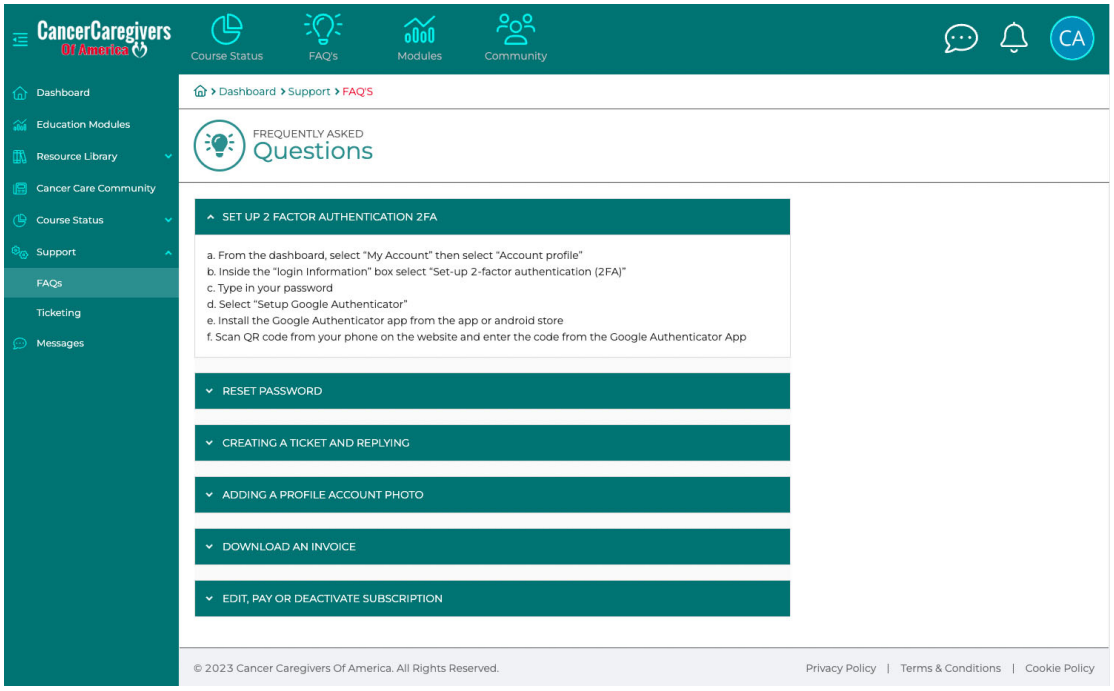
176

Online Cancer Caregivers Education Platform



177

Online Cancer Caregivers Education Platform



178

CancerCaregivers Of America

Online Cancer Caregivers Education Platform

Introduction to the Online Cancer Caregivers Education Program - Module 1

179

CancerCaregivers Of America

In Summary

Cancer Caregivers Education Program was developed with Cancer Patients and Cancer Caregivers input and guidance

Cancer Caregivers Education Platform Assets

Cancer Caregivers Online Education/Training

Cancer Care Resource Library

Cancer Care Community

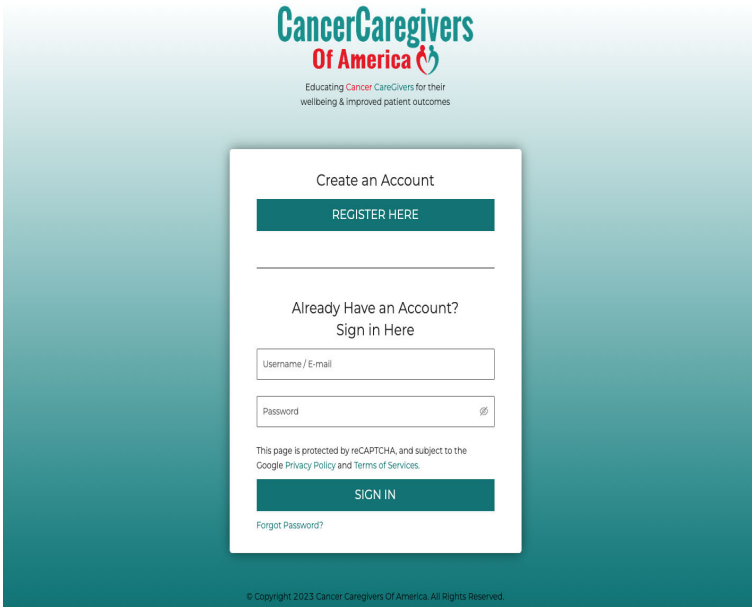
The program is designed with a 360° view of what the cancer caregiver and patient will experience. The psychological, physical, social, emotional, financial and the many other circumstance that will arise on your journey.

Our Mission is to educate, build skills, provide resources that will improve quality of life, treatment, and healthcare outcomes for the cancer patient, caregivers, and family.

180

CancerCaregivers Of America

Online Cancer Caregivers Education Platform



A Gift for YOU

We are giving away 100 free, 1-year subscriptions

The code is only good through midnight Monday March 27, 2023

CODE: CCEP!

Directions:
Go to Cancer Caregivers of America Website;
https://cancercaregiversofamerica.com/
Register for the Cancer Caregivers Education Program using promotion code: CCEP!

Start taking advantage of the Cancer Caregivers Education Platform right away

181

CancerCaregivers Of America

Online Cancer Caregivers Education Platform

Available in the U.S. and Canada

We are officially **LAUNCHED!!!**

182

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

183

Town Hall Questions & Answers

184

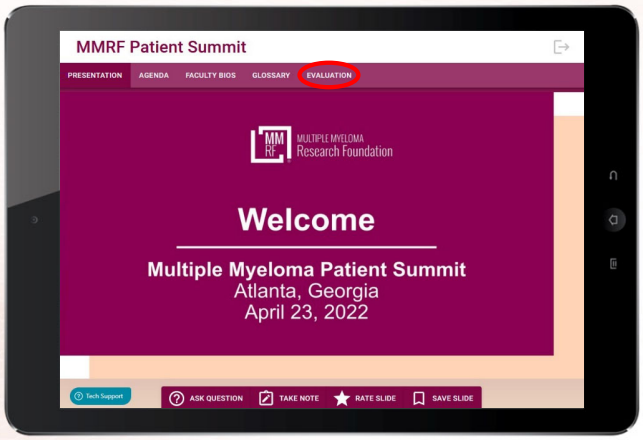
Thank you!

185

186

Don't Forget!

Complete your evaluation
Leave the iPad at your seat



187

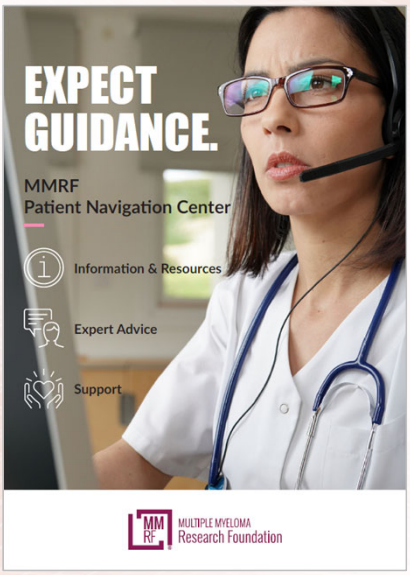
Upcoming Patient Education Events
Save the Date

Topic	Date and Time	Speakers
Facebook Live: FAQs on Relapsed/Refractory Multiple Myeloma	Tuesday, March 28 2:00 PM – 3:00 PM (ET)	Brandon Blue, MD Dana Spiak, RN
Webinar: Multiple Myeloma Precursor Conditions	Wednesday, April 5 2:30 PM – 3:30 PM (ET)	Sagar Lonial, MD Omar Nadeem, MD

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

188

MMRF Patient Resources



MMRF Patient Navigation Center

You and your care team will have many decisions to make along your treatment journey. The Patient Navigation Center is a space for multiple myeloma patients and their caregivers to connect with patient navigators — who are professionals specializing in oncology — for guidance, information, and support. You can connect with a patient navigator via phone, or email. Whatever questions you may have, our patient navigators are here to help.

MMRF Patient Navigators include:
- Grace Allison, RN, BSN, OCN, RN-BC
- Brittany Hartmann, RN-BSN
- Erin Mensching, RN-BSN, OCN

THE RIGHT TRACK

Get on the right track for you

The MMRF's Right Track program puts you on the path to the best results for you.

Right Team	Right Tests	Right Treatment
Access experts and centers that have extensive experience treating multiple myeloma.	Get the information, tests, and precise diagnoses to make the right treatment decisions.	Work with your team to consider the best treatment plan and identify clinical trials that are right for you.

Contact the Patient Navigation Center Today

Looking for guidance? We're here to help.

Monday – Friday | 9:00AM – 7:00PM ET

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

Email: patientnavigator@themmrf.org

Supported By

Adaptive · AMGEN · Bristol Myers Squibb · cure · Genentech · janssen · sanofi · Takeda ONCOLOGY

189

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.

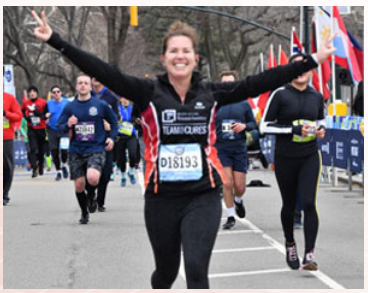
Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.

190

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/

191