MULTIPLE MYELOMA Research Foundation

Opening Remarks

Mary DeRome, MS
MMRF

1

abbvie Bristol Myers Squibb™ cure® curetoday.com

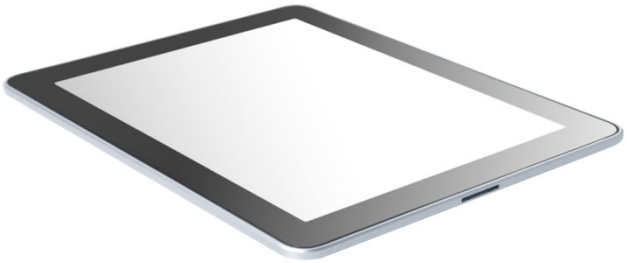
Genentech A Member of the Roche Group GSK Johnson&Johnson

Pfizer REGENERON SCIENCE TO MEDICINE® sanofi

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



Submit your questions throughout the program!

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

3

Program Faculty

Hearn Jay Cho, MD, PhD
MMRF
Norwalk, Connecticut
Icahn School of Medicine at Mount Sinai
New York, New York

Leora A. Giacoia, MS, FNP-BC, ACHPN
Icahn School of Medicine at Mount Sinai
New York, New York

Sundar Jagannath, MD
Icahn School of Medicine at Mount Sinai
New York, New York

Samir S. Parekh, MD
Icahn School of Medicine at Mount Sinai
New York, New York

Shambavi Richard, MD
Icahn School of Medicine at Mount Sinai
New York, New York

Joshua Richter, MD
Icahn School of Medicine at Mount Sinai
New York, New York

Cesar Rodriguez, MD
Icahn School of Medicine at Mount Sinai
New York, New York

Santiago Thibaud, MD
Icahn School of Medicine at Mount Sinai
New York, New York

4

Summit Agenda

Time (ET)	Topic	Speakers
9:00 – 9:15 AM	Introduction to MMRF	Mary DeRome, MS
9:15 – 9:30 AM	Welcome	Hearn Jay Cho, MD, PhD Sundar Jagannath, MD
9:30 – 9:45 AM	Multiple Myeloma Biology	Cesar Rodriguez, MD
9:45 – 10:00 AM	Treatment for Newly Diagnosed Multiple Myeloma	Joshua Richter, MD
10:00 – 10:15 AM	Autologous Stem Cell Transplant	Shambavi Richard, MD
10:15 – 10:30 AM	Town Hall Q&A	Speaker panel
10:30 – 10:45 AM	Break	
10:45 – 11:00 AM	Treatment for Relapsed/Refractory Multiple Myeloma	Santiago Thibaud, MD
11:00 – 11:15 AM	Personalized Medicine	Samir S. Parekh, MD
11:15 – 11:30 AM	Supportive Care	Leora A. Giacoia, MS, FNP-BC, ACHPN
11:30 – 11:45 AM	Town Hall Q&A	Speaker panel
11:45 AM – 12:15 PM	Lunch and Patient Speaker	Roger Rawlings
12:15 – 12:30 PM	Closing Remarks	Mary DeRome, MS, and Sundar Jagannath, MD

5

MULTIPLE MYELOMA Research Foundation

MMRF Introduction

Mary DeRome, MS and Hearn Jay Cho, MD, PhD
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

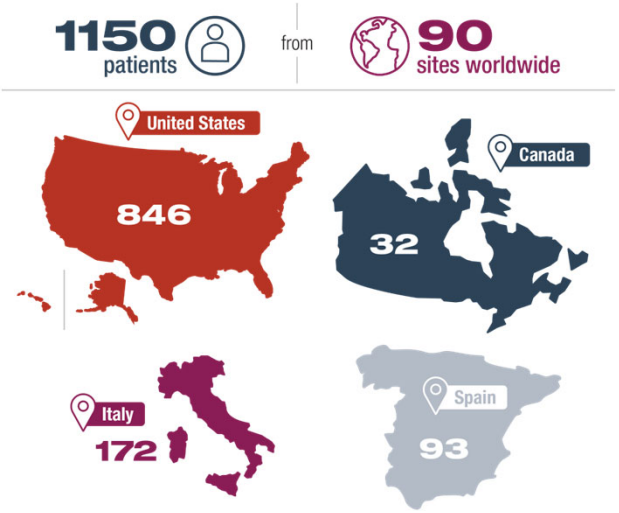
Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

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.



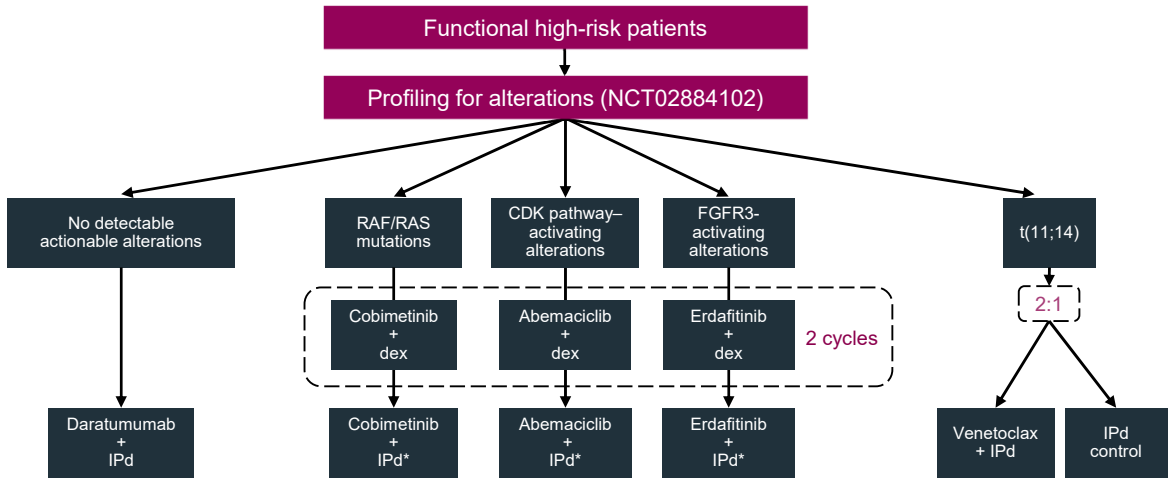
8

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

9

MyDRUG Trial



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

10

MMRF Research Initiatives

1. MMRF Myeloma Accelerator Challenge (MAC) Grants
   - Broad, multi-institutional research grants designed to advance clinical trial concepts in the areas of
     - High-risk newly diagnosed multiple myeloma (NDMM)
     - High-risk smoldering myeloma (SMM)
   - Each research network will be funded up to $7M over 3 years
2. MMRF Horizon Adaptive Platform Trials
   - Paired with MAC grants
   - Done in collaboration with 13 MMRC sites
   - Trials in relapsed/refractory myeloma, high-risk NDMM, high-risk SMM

For more information, visit themmrf.org

11

2023 Myeloma Accelerator Challenge Program Grant Recipients

Samir Parekh, MD

Transforming Treatment of High-Risk Myeloma

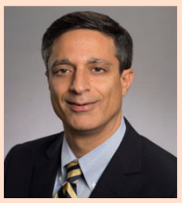
Network includes Tisch Cancer Center at Mt Sinai, Albert Einstein Medical College, Hackensack University Medical Center, Stanford University Medical Center, UCSF, Washington University of Saint Louis

Pieter Sonneveld, MD, PhD

A Systems Biology Approach to High-Risk Myeloma

Network includes Erasmus Medical Center, Rotterdam; Amsterdam University Medical Centers; Julius Maximilian University of Wurzburg; University of Turin; University of Salamanca

Each network will receive $7M over 3 years for a total $21M investment by the MMRF, meant to foster collaboration and advance compelling hypotheses that are ready for rapid testing in clinical trials.



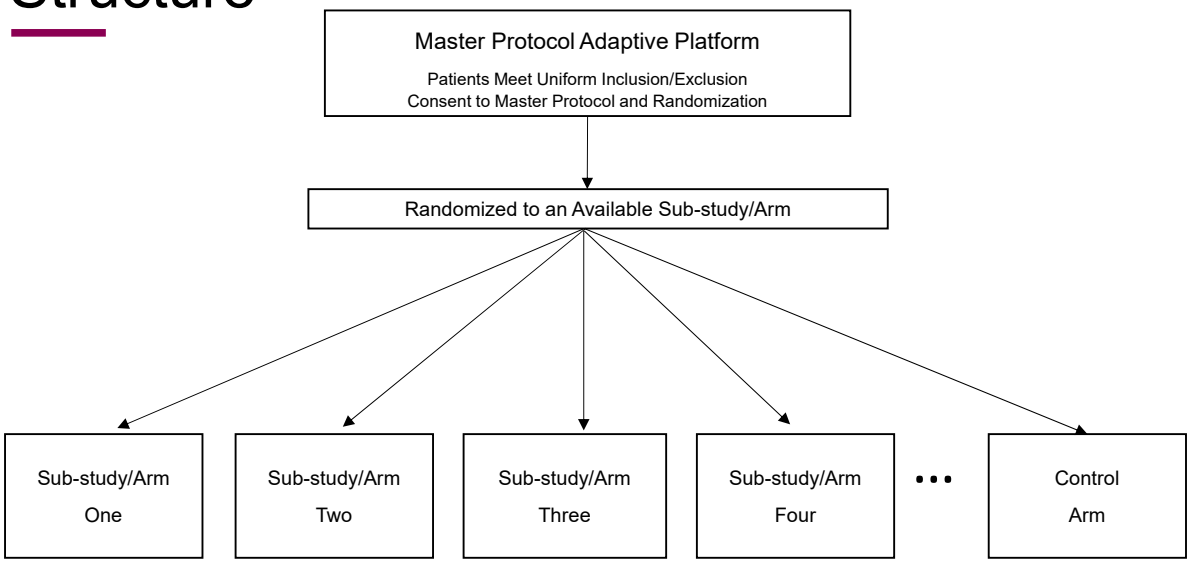
Sagar Lonial, MD

Clinical and Multi-Omics Platforms to Define High-Risk Smoldering Myeloma

Network includes Emory University, Atrium Health Levine Cancer Institute, Icahn School of Medicine at Mt. Sinai, Mass General Hospital, Mayo Clinic, MSKC Institute, Dana-Farber Cancer Institute

12

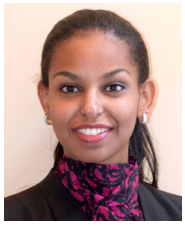
MMRC Horizon Adaptive Platform Trial Structure



13

MMRF 2023 Scholars Grant Awardees

Eden Biltibo
Vanderbilt University Medical Center



Grant Proposal:

Identifying Effective and Cost-Conscious Maintenance Daratumumab Dosing

Frequent hospital visits cost money and increases exposure to bad bugs. If we prove every 8-week daratumumab works as good, patients won't have to come to the hospital on a monthly basis.

Eden Biltibo, MD, MS is a Hematology/Oncology clinical fellow at Vanderbilt University Medical Center., who is passionate about developing strategies to bridge health care disparities in Multiple Myeloma care. She particularly focuses on the equitable utilization of immunotherapeutics in multiple myeloma and improving racial diversity of clinical trial participants in those trials.

Joselle Cook
Mayo Clinic, Rochester

Grant Proposal:

Prevalence Of MGUS Among Unique Populations Of Black People

For people who test positive for MGUS, we will perform DNA testing which will inform us about ancestral origins and will give information on genetic variations that we know are associated with MGUS and MM.

Joselle Cook, MBBS is an assistant professor and Hematology/Oncology Fellow at Mayo Rochester. Dr. Cook received her medical degree from University of the West Indies Faculty of Medical Sciences. She completed her residency and fellowship training in 2022.

14

MULTIPLE MYELOMA Research Foundation

Welcome!

15

Question

Are you a...

1. Patient
2. Caregiver (family member or friend who helps patient manage his or her disease)
3. Other

16

Question

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

1. Newly diagnosed
2. Relapsed/refractory
3. Remission: still on therapy
4. Remission: not on therapy
5. MGUS or smoldering myeloma not currently requiring treatment
6. Other
7. I don't know.

17

Question

Have you had a stem cell transplant?

1. No, but I will soon!
2. No, but I am considering one (or my doctor is discussing with me).
3. No, my doctor tells me I am not a candidate.
4. Yes
5. Not applicable

18

Question

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

1. No
2. Yes, I had FISH.
3. Yes, I had cytogenetics.
4. Yes, I had sequencing.
5. Yes, I had more than one of these tests performed.
6. I don't know.

19

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?)

1. Yes
2. No
3. I don't know.

20

MULTIPLE MYELOMA Research Foundation

Multiple Myeloma Biology

Cesar Rodriguez, MD
Icahn School of Medicine at Mount Sinai
New York, New York

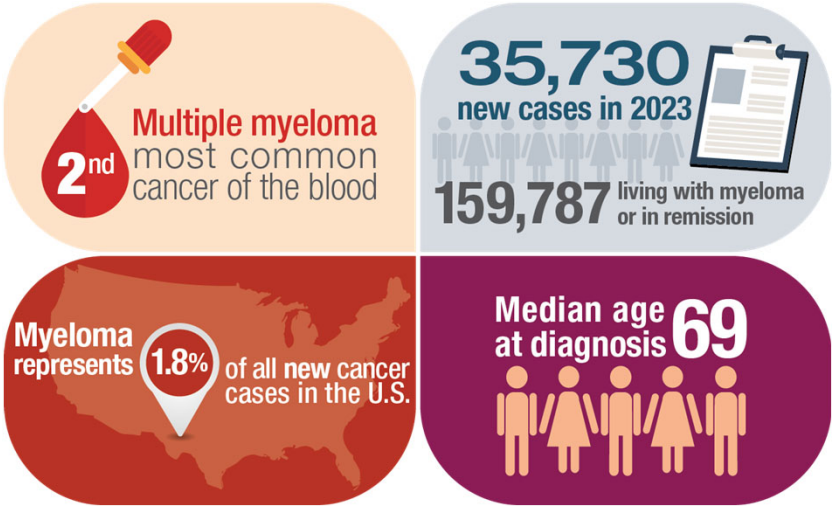
21

Disclosures

- *Research Support/PI:* Amgen, Celgene, ORIC, Janssen, BMS, Teneobio
- Employee: N/A
- *Consultant:* Amgen, Bristol Myers Squibb, Janssen, Karyopharm, Sanofi, Abbvie, Artiva
- Major Stockholder: N/A
- *Speakers Bureau:* BMS, Takeda
- Honoraria: N/A
- *Scientific Advisory Board:* BMS, Janssen, Sanofi, Abbvie, Artiva

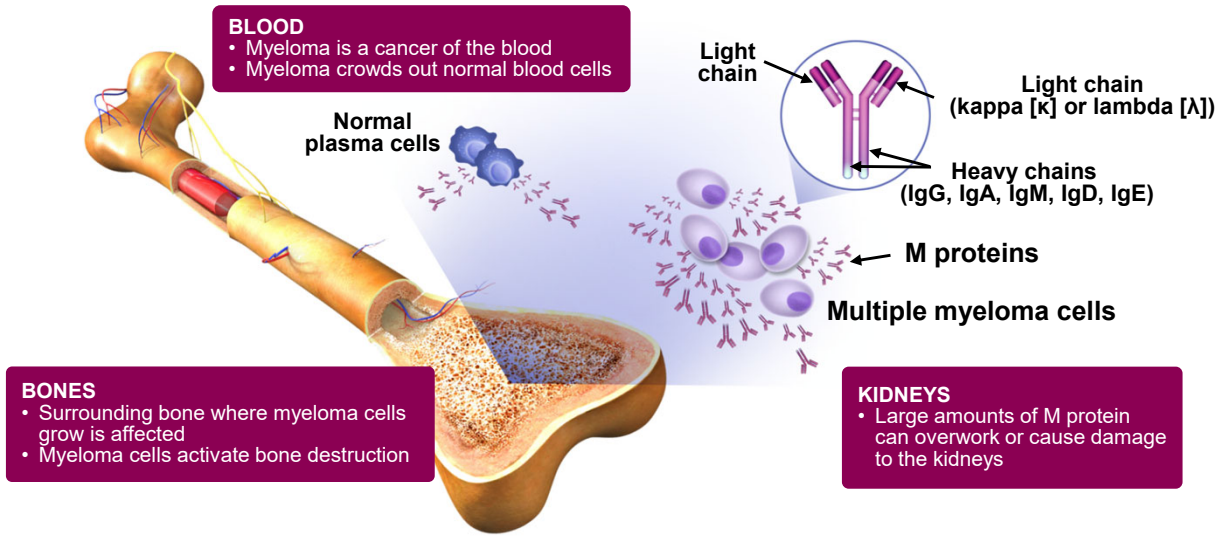
22

How common is multiple myeloma?



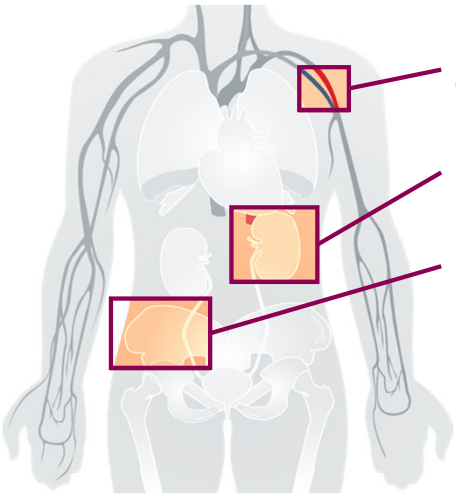
23

Multiple Myeloma Affects Your Bones, Blood, and Kidneys



24

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

25

Demographic Risk Factors: Multiple Myeloma

- Older age
- Male sex
- Obesity
- Race: 2× incidence in African Americans

Family history

- One first-degree relative with multiple myeloma
- Relatives of multiple myeloma patients have more monoclonal gammopathy of undetermined significance (MGUS)
- Current recommendation is to *not* screen families

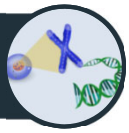
Schinasi LH et al. *Br J Haematol*. 2016;175:87. Thordardottir M et al. *Blood Adv*. 2017;1:2186.

26

The Right Tests: Common Tests Conducted in Myeloma Patients

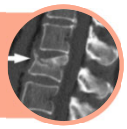
Blood tests
Urine tests

- Confirms the type of myeloma or precursor condition



Bone marrow biopsy

- Confirms diagnosis of myeloma
- Determines how advanced the myeloma or precursor condition is

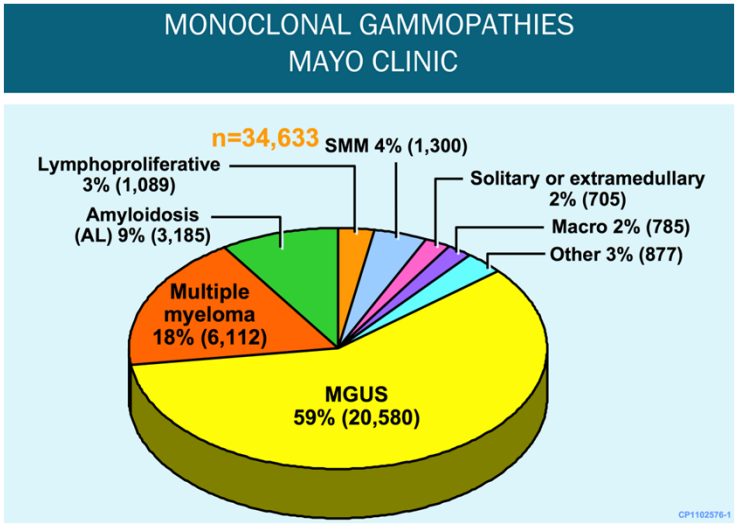


Imaging tests

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

27

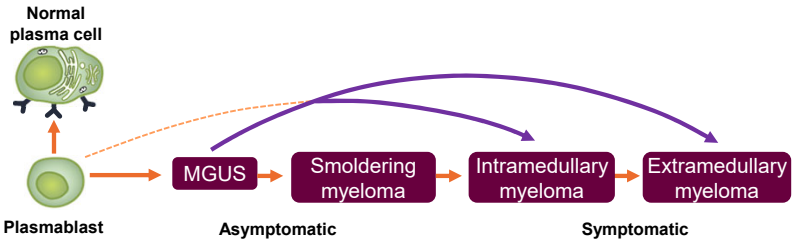
Not All M Spikes Are Myeloma!



Medical oncology best practices. 2012.

28

Type of Disorder Has the Potential to Evolve



MGUS

- M protein <3 g/dL
- Clonal plasma cells in bone marrow <10%
- No myeloma-defining events

Smoldering myeloma

- M protein ≥3 g/dL (serum) or ≥500 mg/24 hrs (urine)
- Clonal plasma cells in bone marrow ≥10% to 60%
- No myeloma-defining events

Multiple myeloma

- Underlying plasma cell proliferative disorder

AND

- ≥1 myeloma-defining event
- ≥1 CRAB feature
- Clonal plasma cells in bone marrow ≥60%
- Serum free light chain ratio ≥100
- >1 MRI focal lesion

Rajkumar SV et al. *Lancet Oncol*. 2014;15:e538.

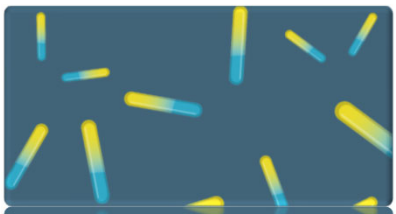
29

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%

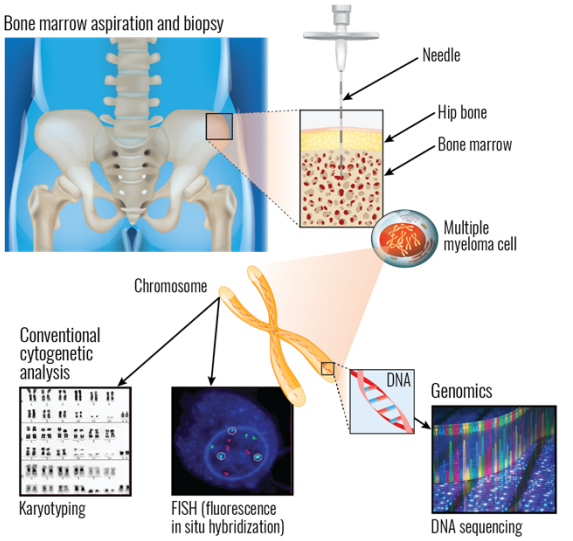
Non-secretory

- No M protein present

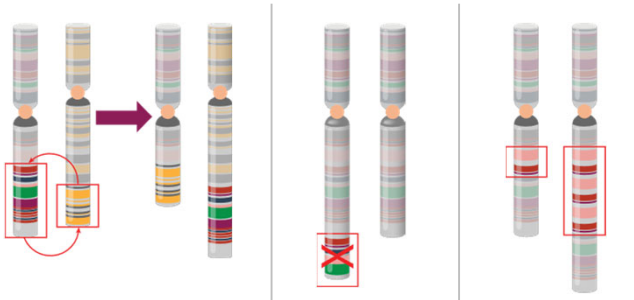
3%

30

Know Your Bone Marrow Tests!



Types of chromosomal abnormalities



Translocation | **Deletion** | **Gain or amplification**

31

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

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

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

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.

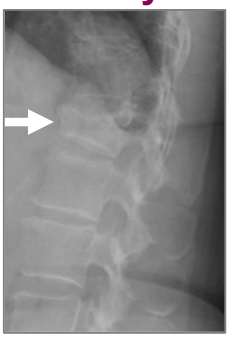
Currently cannot identify with great certainty all high-risk patients.

32

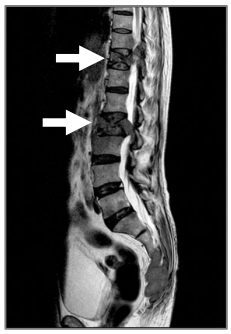
Know Your Imaging Tests!

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

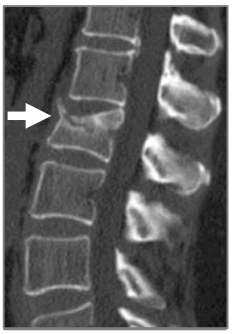
X-ray



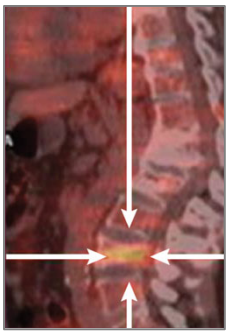
MRI



CT scan

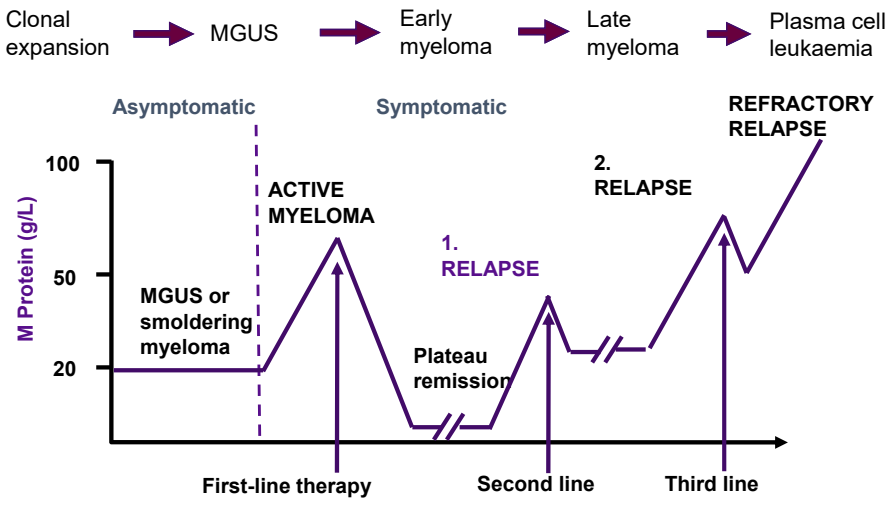


PET scan



33

Natural History of MM After Treatment



34

Summary

- Multiple myeloma is a rare blood cancer that can negatively affect the bones, kidneys, and bone marrow, leading to lowered blood counts.
- The prognosis of multiple myeloma depends on the genetic makeup of the myeloma cell and its chromosomes; R-ISS is used for staging in multiple myeloma.
- Knowledge is power: right team, right test, right treatment.

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

35

MULTIPLE MYELOMA Research Foundation

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

36

MULTIPLE MYELOMA Research Foundation

Treatment for Newly Diagnosed Multiple Myeloma

Joshua Richter, MD, FACP
Icahn School of Medicine at Mount Sinai
New York, New York

37

Disclosures

- *Consultant/advisor:* Janssen, BMS, Pfizer, Karyopharm, Sanofi, Takeda, Genentech, AbbVie, Regeneron, Forus, Menarini/Stemline, Antengene
- *Speakers Bureau:* Janssen, BMS, Sanofi, Adaptive Biotechnologies

38

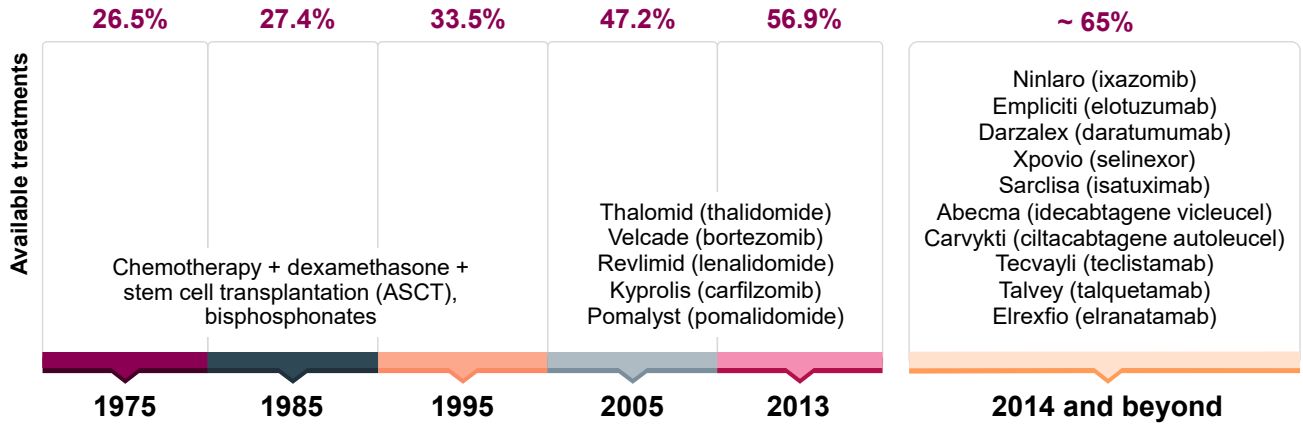
Getting the Right Treatment: Goals of Multiple Myeloma Therapy

- 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.

39

Myeloma Survival Has Improved Over Time, Mainly Due to Novel Agents and Immune Therapies (including mAbs)

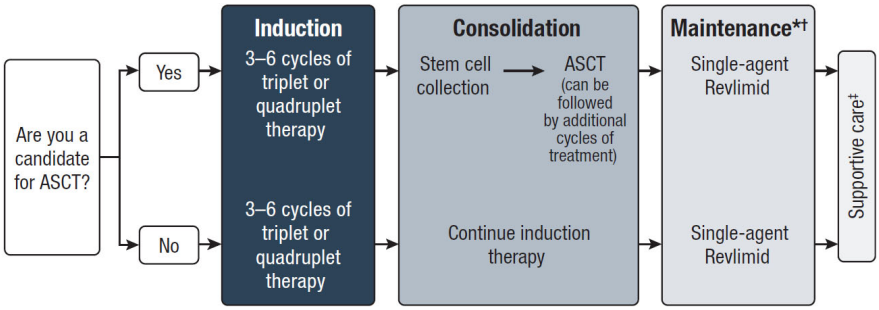
The percentage of people expected to survive 5 years or more after being diagnosed with myeloma has dramatically improved in the last 20 years



mAbs, monoclonal antibodies

40

Overview of Treatment Approach for Active Multiple Myeloma



*If you have high-risk markers, additional agents may be given with Revlimid; if you cannot tolerate Revlimid, another treatment (for example, a proteasome inhibitor) may be given.

†In the U.S., maintenance is typically given until progression, but studies are evaluating stopping treatments for patients with deep responses. If you have little or no evidence of disease but are experiencing side effects, discuss with your doctor whether to continue until progression. Dose adjustments are also options.

‡**Supportive care** is given throughout treatment.

41

Induction Therapy Regimens

	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid-Velcade-dex (RVd)* • Kyprolis-Revlimid-dex (KRd)	• Darzalex-Revlimid-Velcade-dex (D-RVd)	• Velcade-Cytoxan-dex (VCd) • Velcade-Doxil-dex (VDd) • Kyprolis-Cytoxan-dex (KCd) • Darzalex-Velcade-Thalomid-dex (D-VTd) • Darzalex-Kyprolis-Revlimid-dex (D-KRd) • Darzalex-Cytoxan-Velcade-dex (D-VCd) • Sarclisa-Revlimid-Velcade-dex • VTD-PACE
Transplant ineligible	• Revlimid-Velcade-dex (RVd)* • Darzalex-Revlimid-dex (DRd)*	• Kyprolis-Revlimid-dex (KRd) • 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

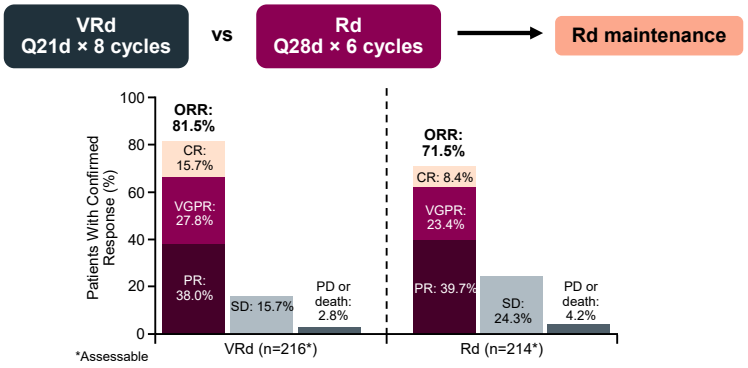
*Category 1 recommendation. Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2024. Multiple Myeloma.

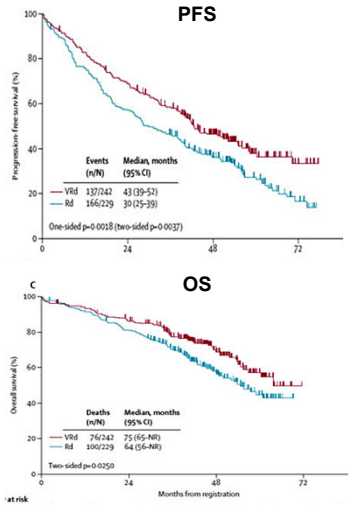
42

Phase 3 SWOG S0777 Trial
Bortezomib + Lenalidomide + dex (VRd) vs Lenalidomide + dex (Rd) and Rd Maintenance

Newly diagnosed myeloma (transplant eligible and non-eligible patients)



	VRD	Rd	Hazard ratio (95% CI)
Median PFS, months	43	30	0.712 (0.560 - 0.906)
Median OS, months	75	64	0.709 (0.516 - 0.973)



ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD progressive disease; CI, confidence interval; PFS, progression-free survival; OS, overall survival

Durie B et al. ASH 2015. Abstract 25. Durie B et al. *Lancet.* 2017;389;519.

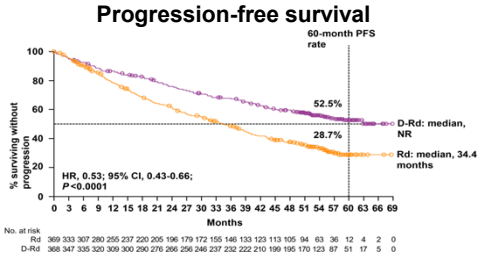
43

MAIA: Updated Efficacy Results

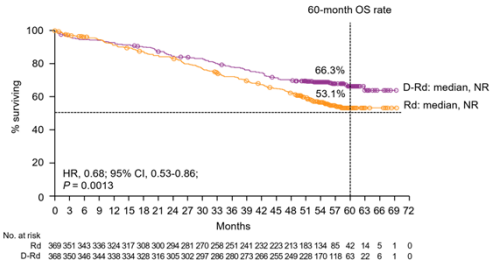
- Phase 3 Study of lenalidomide and dex ± daratumumab
- Median duration of follow-up: 56.2 mos

Response	DRd	Rd
ORR	92.9%	81.3%
PR	13.6%	28.2%
VGPR	31.8%	28.2%
CR	17.1%	12.5%
sCR	30.4%	12.5%
≥VGPR	79.3%	53.1%
MRD- (10^{-5})	31%	10%

Progression-free survival



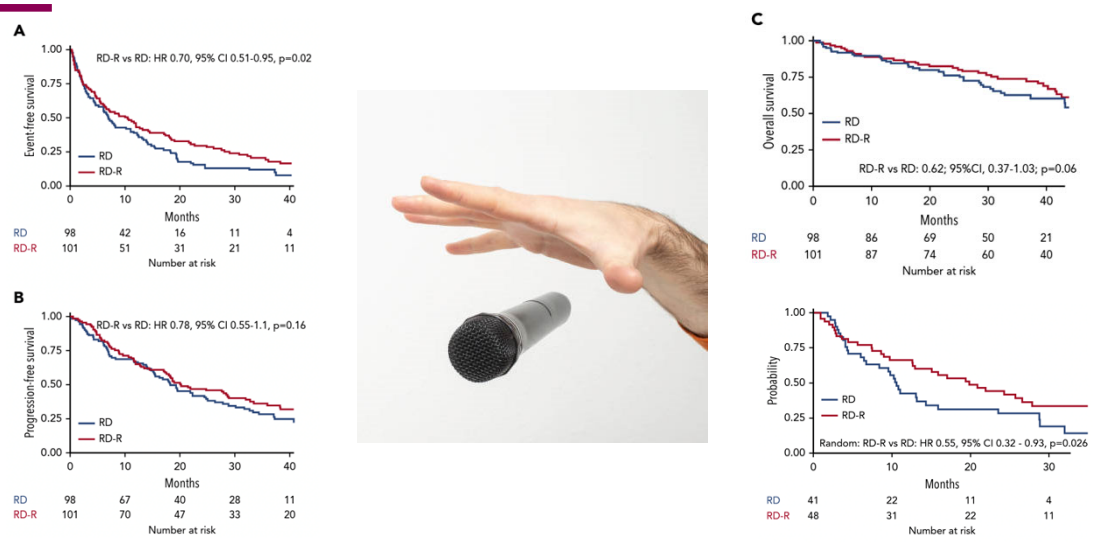
Overall survival



Facon T et al. *Lancet Oncol.* 2021;22:1582. Facon T et al. *N Engl J Med.* 2019;380:2104.

44

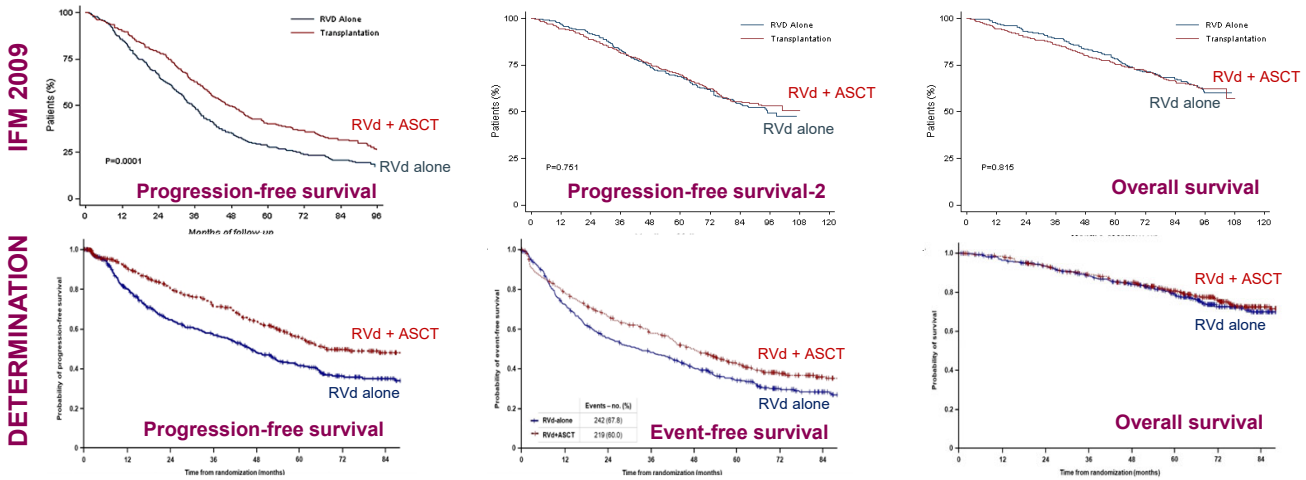
Drop the Dex



Larocca A et al. *Blood*. 2021;137:3027.

45

What is the role of ASCT in the current age of modern induction regimens?

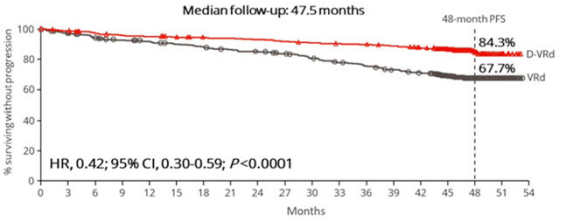


Perrot A et al. *Blood*. 2020. Abstract 143.
Richardson et al. *N Engl J Med*. 2022;387:132.

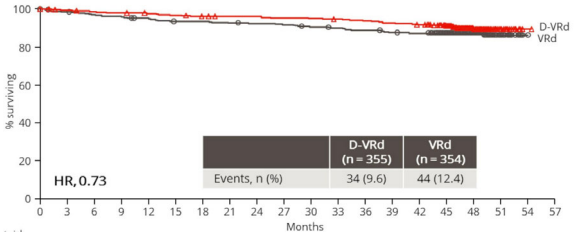
46

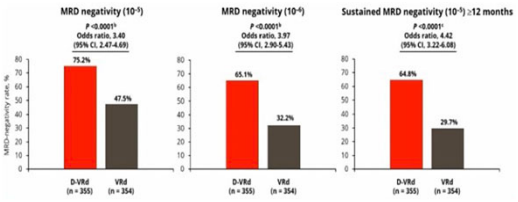
Phase 3 Study of Darzalex + Velcade + Revlimid + Dex vs Velcade + Revlimid + Dex in NDMM

PFS



OS





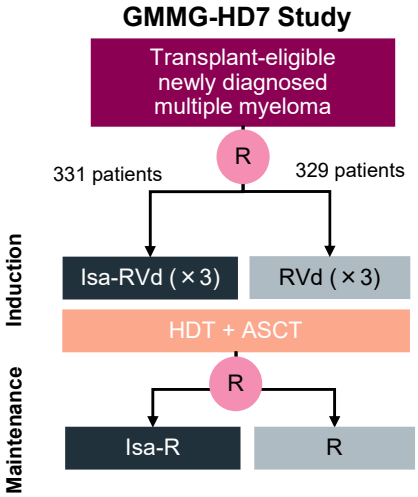
Event, n (%)*	D-VRd (n = 351) Any grade	D-VRd (n = 351) Grade 3 or 4	VRd (n = 347) Any grade	VRd (n = 347) Grade 3 or 4
HEMATOLOGIC				
Neutropenia	**243 (69.2)**	**218 (62.1)**	**204 (58.8)**	**177 (51.0)**
Thrombocytopenia	**170 (48.4)**	**102 (29.1)**	**119 (34.3)**	**60 (17.3)**
Anemia	78 (22.2)	21 (6.0)	72 (20.7)	22 (6.3)
Febrile neutropenia	34 (9.7)	33 (9.4)	38 (11.0)	35 (10.1)
NON-HEMATOLOGIC				
Diarrhea	214 (61.0)	37 (10.5)	188 (54.2)	27 (7.8)
Peripheral sensory neuropathy	**188 (53.6)**	**15 (4.3)**	**179 (51.6)**	**14 (4.0)**
Constipation	119 (33.9)	8 (2.3)	118 (34.0)	6 (1.7)
Pyrexia	111 (31.6)	8 (2.3)	109 (31.4)	9 (2.6)
Insomnia	95 (27.1)	8 (2.3)	61 (17.6)	6 (1.7)
Asthenia	94 (26.8)	12 (3.4)	89 (25.6)	9 (2.6)
Cough	85 (24.2)	1 (0.3)	51 (14.7)	0
Fatigue	84 (23.9)	10 (2.8)	92 (26.5)	18 (5.2)
Rash	82 (23.4)	9 (2.6)	94 (27.1)	17 (4.9)
Back pain	80 (22.8)	2 (0.6)	66 (19.0)	1 (0.3)
Peripheral edema	72 (20.5)	4 (1.1)	74 (21.3)	1 (0.3)
Nausea	71 (20.2)	2 (0.6)	58 (16.7)	2 (0.6)
Infections	**305 (86.9)**	**124 (35.3)**	**266 (76.7)**	**95 (27.4)**
COVID-19	123 (35.0)	12 (3.4)	83 (23.9)	4 (1.2)
Upper respiratory tract infection	111 (31.6)	2 (0.6)	87 (25.1)	6 (1.7)
Pneumonia	64 (18.2)	37 (10.5)	38 (11.0)	21 (6.1)

NDMM, newly diagnosed multiple myeloma

PERSEUS Study. Sonneveld P et al. *N Engl J Med*. December 12, 2023 [Online ahead of print].

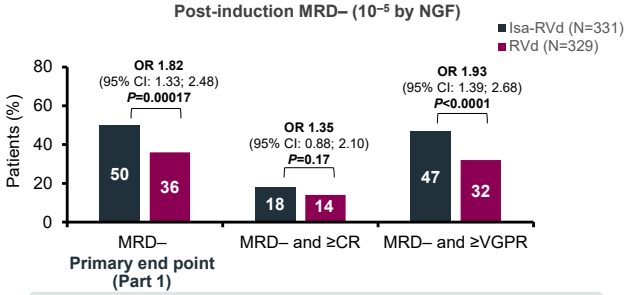
47

Investigational Phase 3 With RVd Backbone



Baseline characteristics	Isa-RVd (n=331)	RVd (n=329)
Median (IQR) age, years	59 (54–64)	60 (54–65)
R-ISS Stage I/II/III, %	23/66/8	30/56/8
HRCAs: ≥1 of: del(17p), t(4;14), or t(14;16) (%)	18	20

Post-induction MRD– (10^{-5} by NGF)



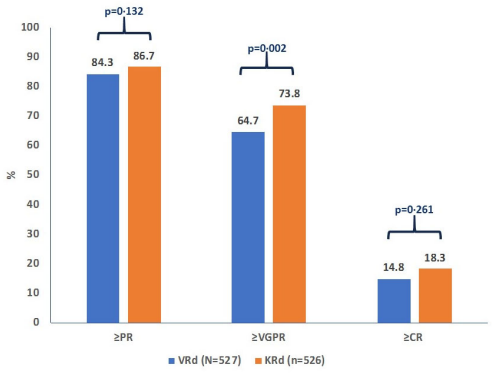
There was no impact on SC mobilization with the addition of Isa to RVd.

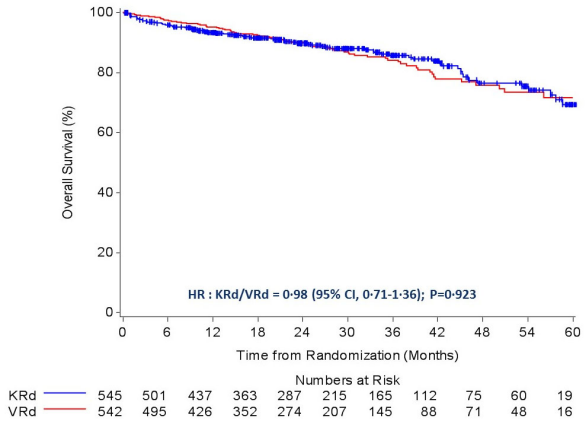
HDT, high-dose therapy; HRCA, high-risk chromosomal abnormalities; R-ISS, Revised International Staging System; OR, odds ratio

Goldschmidt H et al. *Lancet Haematol*. 2022;9:e810.

48

KRd vs VRd Superior >VGPR But Comparable PFS and OS



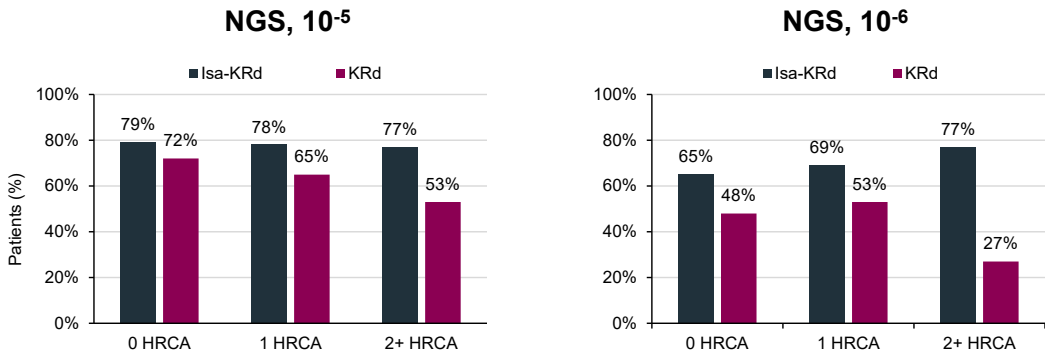


Kumar SK et al. *Lancet Oncol*. 2020;21(10):1317.

49

Investigational Phase 3 Study of Isatuximab + KRd vs KRd in Transplant-Eligible NDMM

Post-consolidation MRD negativity by NGS
Subgroup analysis by cytogenetic risk



1 HRCA was defined as the presence of one of the following high-risk cytogenetic abnormalities: del(17p13.1), t(4;14) (p16.3;q32.3), t(14;16) (q32.3;q23), gain(1q21), or amp(1q21); 2+ HRCA was defined as the presence of at least two high-risk cytogenetic abnormalities.

NGS, next-generation sequencing

IsKia/EMN24 Study. Gay F et al. *Blood*. 2023;142. Abstract 4.

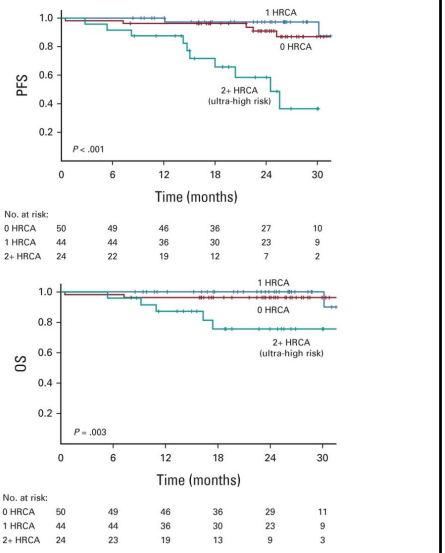
50

MASTER: MRD Response-Adapted Therapy Using a Dara-KRd Platform

- 4 cycles of Dara-KRd → ASCT → 4 cycles of Dara-KRd → 4 cycles of Dara-KRd → Len maintenance
- MRD assessment after completion of each cassette of therapy
- Transition to observation with 2 consecutive MRD-negative readouts at 10^{-5}

	All patients		0 HRCA* abnormality		1 HRCA abnormality		≥2 HRCA abnormalities	
Treatment phase	**MRD-10^{-5}**	**MRD-10^{-6}**	**MRD-10^{-5}**	**MRD-10^{-6}**	**MRD-10^{-5}**	**MRD-10^{-6}**	**MRD-10^{-5}**	**MRD-10^{-6}**
Post induction	38%	24%	40%	30%	41%	25%	29%	8%
Post SCT	65%	48%	60%	44%	73%	59%	63%	38%
Post MRD-directed consolidation	80%	66%	78%	64%	82%	73%	79%	58%

*HRCAs: gain or amp 1q21, del(17p), t(4;14), t(14;16), t(14;20)



Costa L et al. *J Clin Oncol*. 2022;40:2901.

51

Continuous or Maintenance Therapy

Successful maintenance therapy must...

- Be convenient
- Be safe and well tolerated long term
- Not interfere with the use of other future treatments

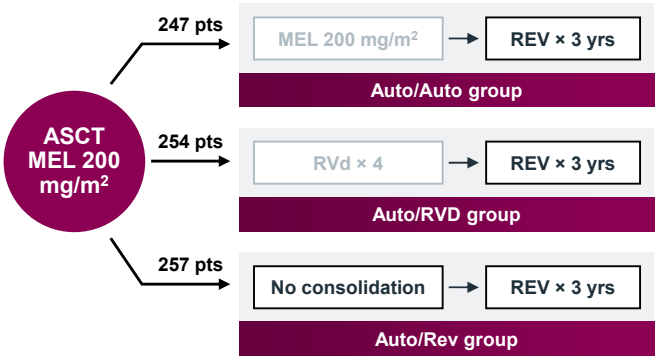
	Preferred	Recommended	Certain circumstances
Transplant eligible	• Revlimid*	• Velcade	• Velcade-Revlimid • Kyprolis-Revlimid • Darzalex ± Revlimid • Ninlaro
Transplant ineligible	• Revlimid*	• Velcade	• Velcade-Revlimid • Ninlaro

*Category 1 recommendation. Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
National Comprehensive Cancer Network Guidelines Version 4.2023. Multiple Myeloma.

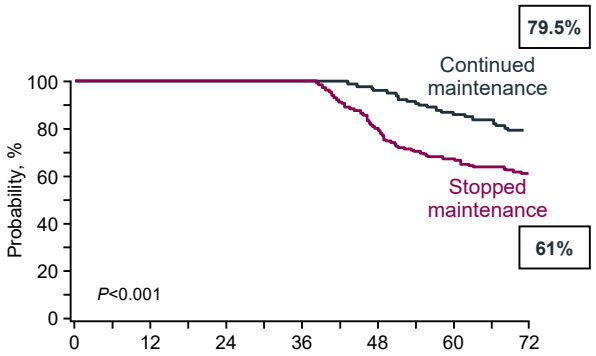
52

Revlimid Maintenance Duration

STAMINA Trial (BMT-CTN0702)



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



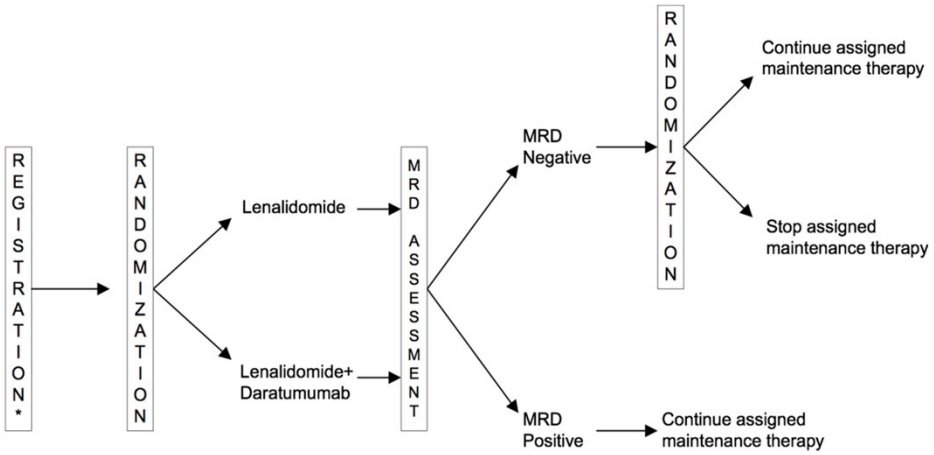
Discontinuation of Revlimid maintenance at 3 years is not recommended because of the increased risk of disease progression.

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.

53

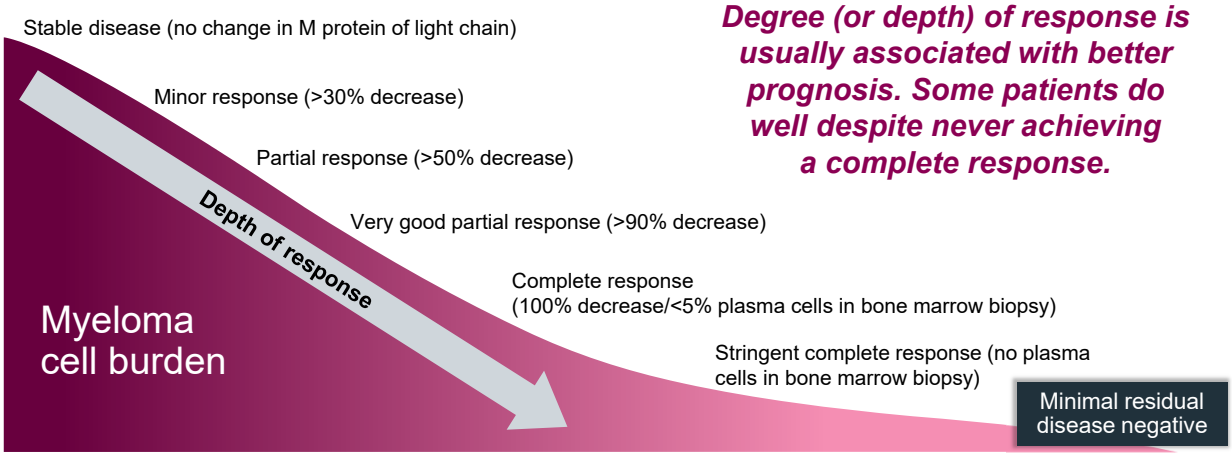
Phase III Study of Daratumumab/rhuph20 (nsc- 810307) + Lenalidomide or Lenalidomide as Post-Autologous Stem Cell Transplant Maintenance Therapy in Patients With Multiple Myeloma (mm) Using Minimal Residual Disease To Direct Therapy Duration (DRAMMATIC study): SWOG s1803



Krishnan A et al. *Blood*. 2020;136 (Supplement 1):21.

54

Measuring Response to Therapy



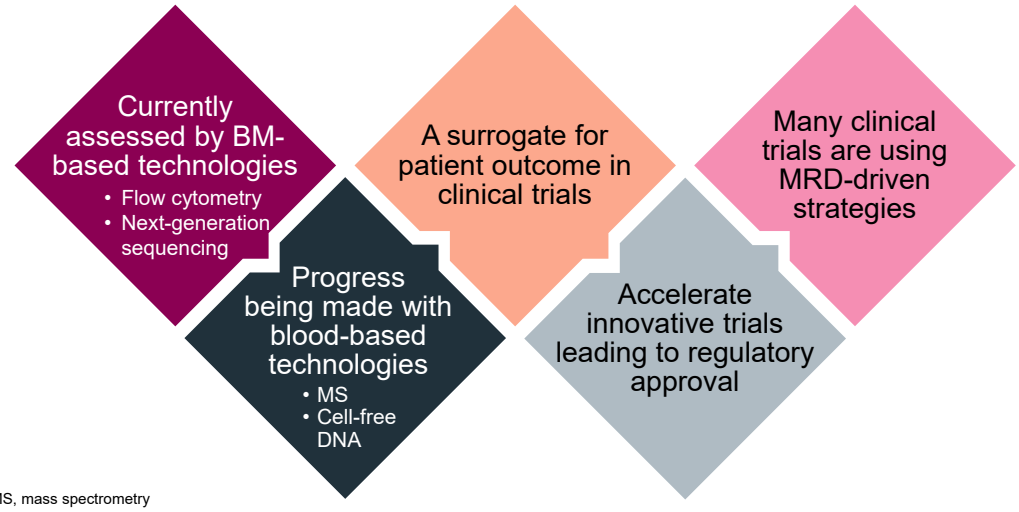
Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a complete response.

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

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

55

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.

56

Summary

- Survival rates are improving because of new drugs and new combinations of drugs, including immune therapies and especially monoclonal antibodies.
- The body of evidence from phase 3 trials indicates that maintenance therapy improves PFS and likely OS.
- 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 is also useful as an end point in clinical trials helping to expedite new drug approval in myeloma.
- The treatment paradigm will continue to change with the approval of additional novel agents.

57

MULTIPLE MYELOMA Research Foundation

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

58

MULTIPLE MYELOMA Research Foundation

Autologous Stem Cell Transplantation

Shambavi Richard, MD
Icahn School of Medicine at Mount Sinai
New York, New York

59

Disclosures

- Honoraria received – Janssen, BMS
- Steering Committee– Gracell Biotechnologies
- Research support – Janssen, BMS, C4 Therapeutics, Gracell Biotechnologies, Heidelberg Pharma

60

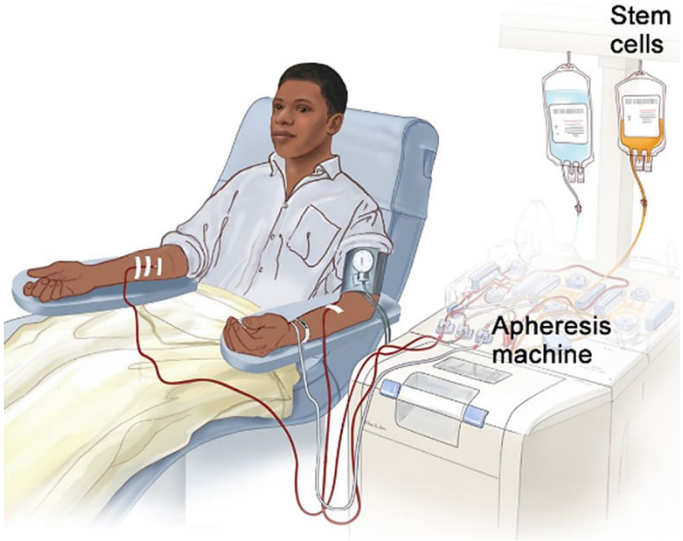
What does transplant mean?

Understanding the basics of autologous stem cell transplantation

- Blood-forming stem cells are 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 (hair follicles and taste buds) recover.

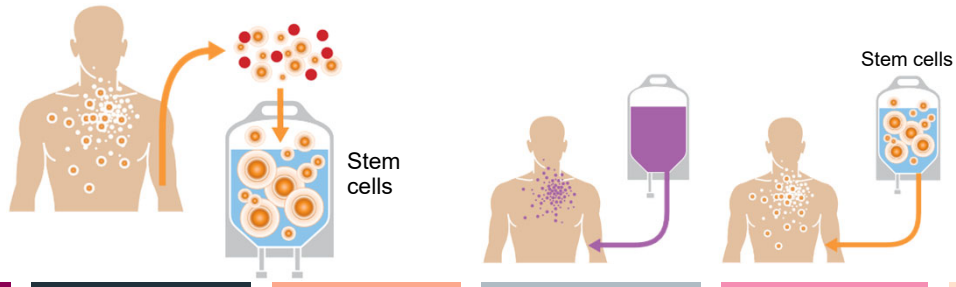
61

Stem Cell Harvest



62

Autologous Stem Cell Transplantation (ASCT)



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. Bone marrow recovery
~3 to 6 cycles	Stem cell mobilization • Neupogen, Neulasta, Leukine, Cytoxan, Mozobil	-2 to -3 weeks*	Melphalan • Alkeran, Evomela	Day 0	Days +1 to +100†

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

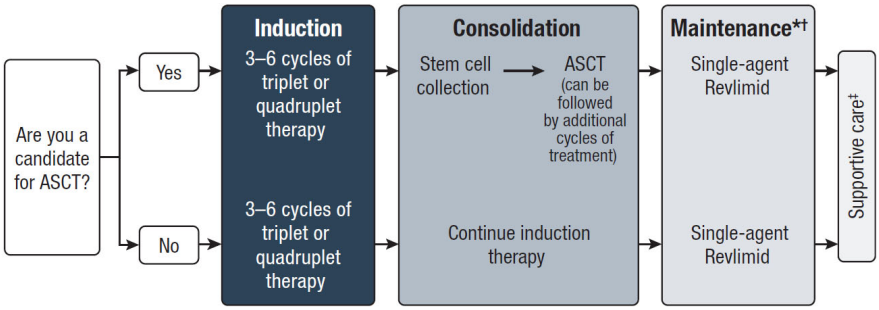
63

Side Effects of High-Dose Chemotherapy

Fatigue	Nausea, vomiting, and diarrhea	Mucositis	Low blood counts	Hair loss
• 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 cell count (risk for infection) • Hemoglobin drop (fatigue) • Platelet count drop (bleeding risk) • Blood transfusion • Platelet transfusion • Antibiotics • White blood cells and platelets recover in 2 weeks	

64

Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma



*If you have high-risk markers, additional agents may be given with Revlimid; if you cannot tolerate Revlimid, another treatment (for example, a proteasome inhibitor) may be given.

†In the U.S., maintenance is typically given until progression, but studies are evaluating stopping treatments for patients with deep responses. If you have little or no evidence of disease but are experiencing side effects, discuss with your doctor whether to continue until progression. Dose adjustments are also options.

‡**Supportive care** is given throughout treatment.

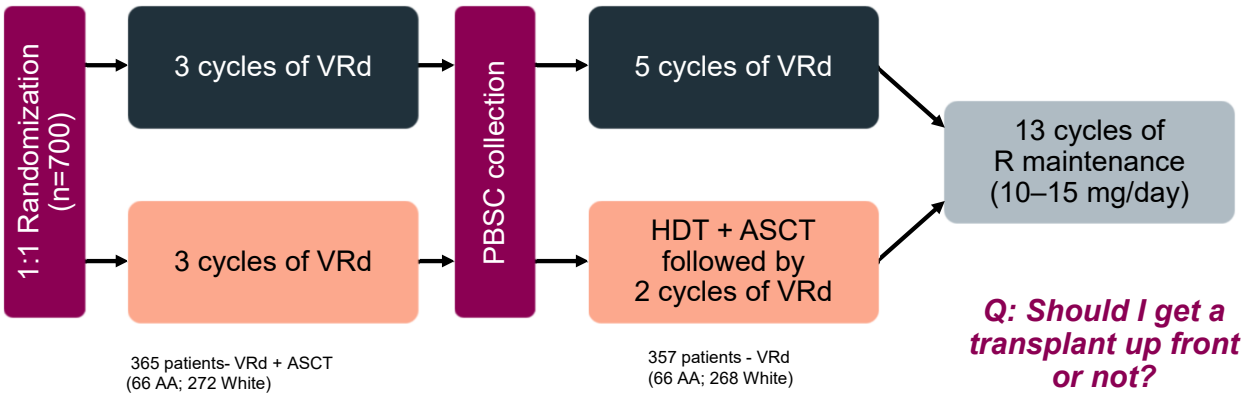
65

High-Dose Chemotherapy and Stem Cell Transplantation

- Remission lasts longer
- Can be done early on or later (or both)
- Some patients will not qualify
  - Older/frail patients
  - Comorbidities
- Dose-reduced melphalan
  - Age >75
  - Kidney disease

66

IFM 2009/DETERMINATION Phase 3 Study

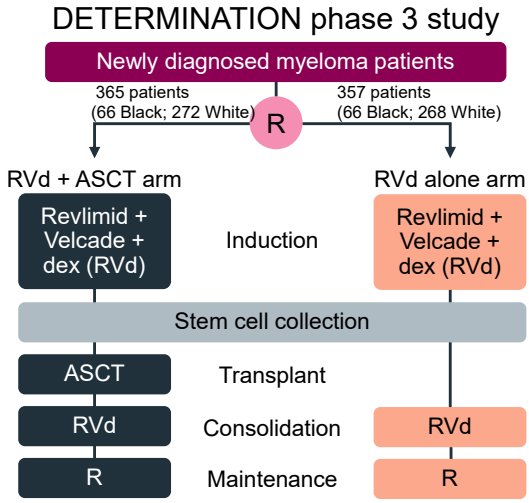


Q: Should I get a transplant up front or not?

VRd, Velcade (bortezomib) + Revlimid (lenalidomide) + dexamethasone; PBSC, peripheral blood stem cells; HDT, high-dose therapy; ASCT, autologous stem cell transplant; R, Revlimid

67

Is transplant still required in newly diagnosed myeloma?



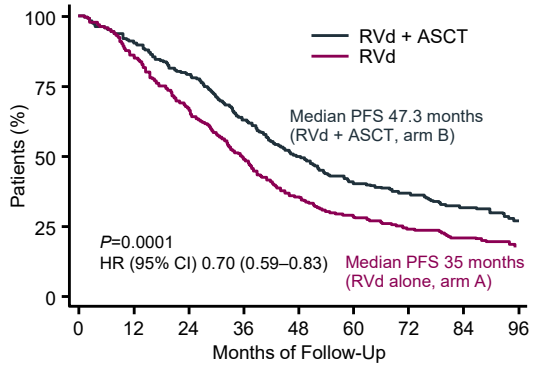
Q: Should I get a transplant up front or not?

Richardson PG et al. *N Engl J Med*. 2022;387:132.

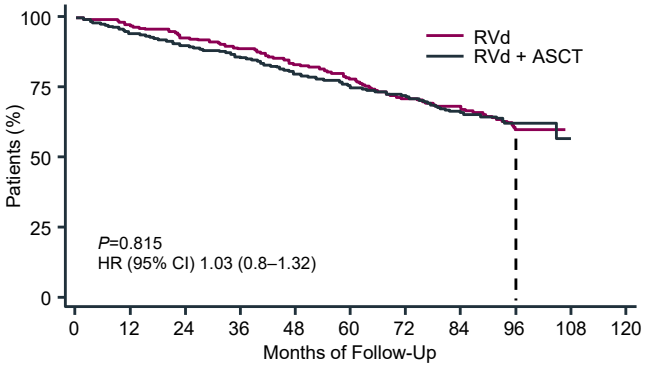
68

IFM 2009: ASH 2020 Updated Results

Updated PFS (primary end point)



Median follow-up: 93 months



30% reduction in the risk of progression or death in patients receiving transplant

- 8-year OS 62.2% for RVd-ASCT and 60.2% for RVd alone (60% alive in both arms after 8 years)

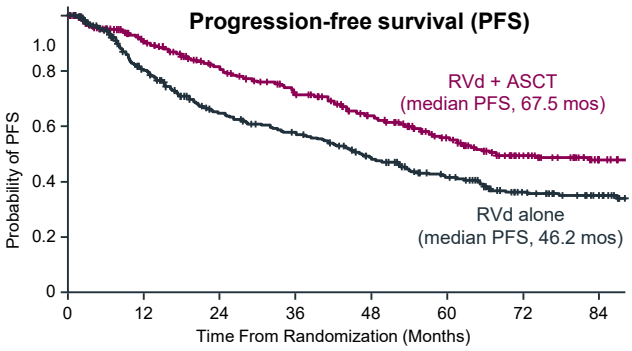
PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

Perrot A et al. *Blood*. 2020. 136. Abstract 39.

69

Phase 3 Study of ASCT for NDMM: Survival Analysis

Progression-free survival (PFS)

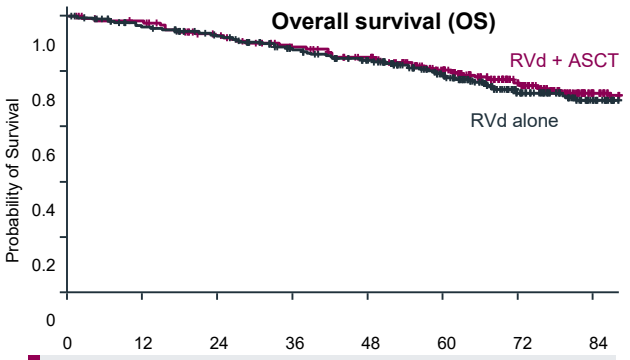


Primary end point
- PFS for RVd + ASCT: approximately 5.5 years
- PFS for RVd alone: approximately 4 years

Transplant extended time to progression by 20 months

Risk of progression or death 53% higher in RVd alone group

Overall survival (OS)



Length of OS: no difference (with a median follow-up time of 76 months).

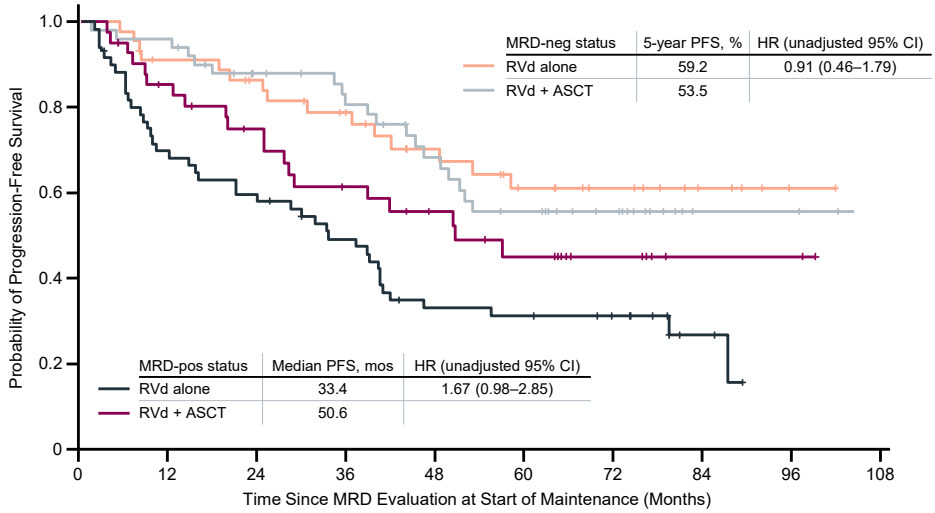
- High risk PFS 17.1 vs 55.5 mo PFS (n=66 vs 66); HR 1.99

NDMM, newly diagnosed multiple myeloma

Richardson PG et al. *N Engl J Med*. 2022;387:132.

70

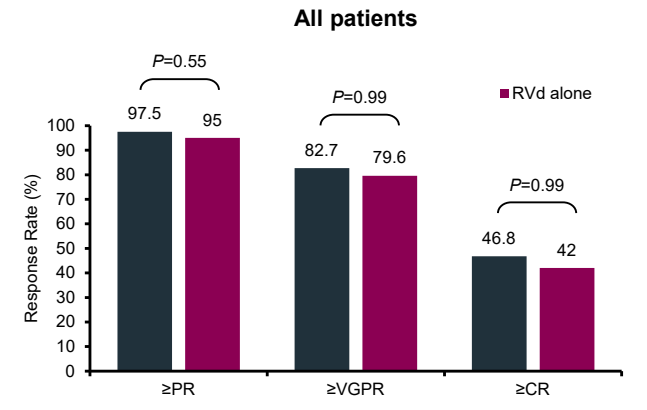
Phase 3 Study of ASCT for NDMM: Survival Analysis by MRD Status



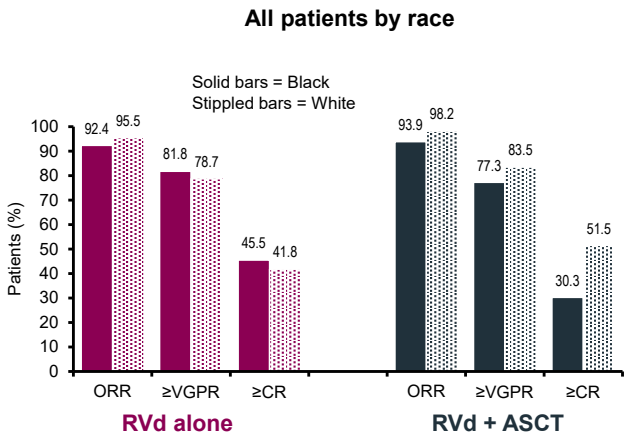
Richardson PG et al. *N Engl J Med*. 2022;387:132.

71

Phase 3 Study of ASCT for NDMM: Best Response to Treatment and Duration of Response



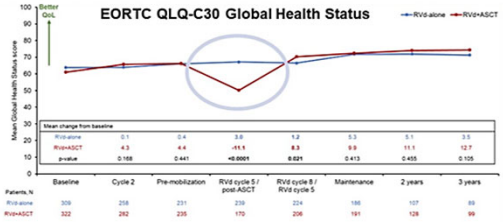
Median duration of response was 38.9 mo in RVd vs 56.4 mo in ASCT group

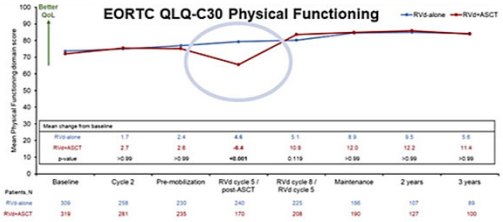


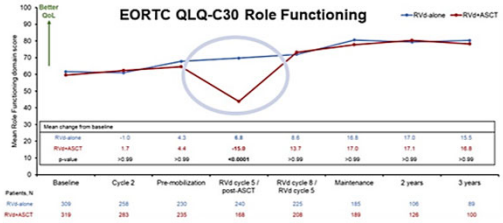
Richardson PG et al. *N Engl J Med*. 2022;387:132.
Houde CA et al. *Blood*. 2023;142. Abstract 4762.

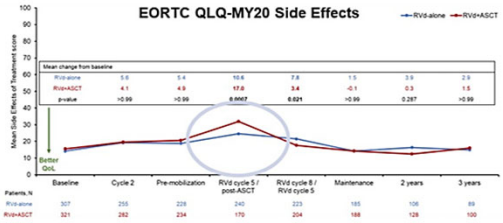
72

Phase 3 Study of ASCT for NDMM: Quality of Life









Richardson PG et al. *J Clin Oncol*. 2022;40. Abstract LBA4.
Richardson PG et al. *N Engl J Med*. 2022;387:132.

73

Phase 3 Study of ASCT for NDMM: 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 immunomodulatory drugs (IMiDs), protease inhibitors (PIs), monoclonal antibodies (mAbs), HDACi (panobinostat), ASCT, chemotherapy, radiation therapy (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*. 2022;387:132.

74

Early vs Late Transplant
Pros and Cons

Pros

Early ASCT
- Deeper and more durable response
- Youngest/healthiest you are going to be
- Allows for fewer cycles of induction treatment

Late ASCT
- PFS may be shorter, but currently appears OS is the same
- Fewer side effects without high-dose chemotherapy
- Conserve quality of life in the early part of disease journey

Cons

Early ASCT
- No proven impact on overall survival
- 20% of patients still relapse within 2 years
- More side effects, including a small risk of serious life-threatening complications
- 3 months to full clinical recovery

Late ASCT
- Need more cycles of induction
- May need next treatment sooner, including (late) transplant
- Not all patients relapsing are able to undergo salvage ASCT

75

Early vs Late ASCT Summary

- ASCT is a standard of care for frontline therapy of myeloma.
- ASCT safety has been established, and it induces long progression-free survival.
- Decision of ASCT should be individualized in every patient and deserves a thorough discussion between the patient and provider.
- Emerging data suggests patients with an extremely good response (that is, complete response and ideally minimal residual disease negative) to induction therapy may have a long PFS. Studies are ongoing to determine whether these patients require ASCT.

76

MULTIPLE MYELOMA Research Foundation

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

77

MULTIPLE MYELOMA Research Foundation

Questions?

78

MULTIPLE MYELOMA Research Foundation

Treatment for Relapsed/Refractory Multiple Myeloma

Santiago Thibaud, MD
Icahn School of Medicine at Mount Sinai
New York, New York

79

Disclosures

- Santiago Thibaud, MD, has no relevant financial information to disclose.

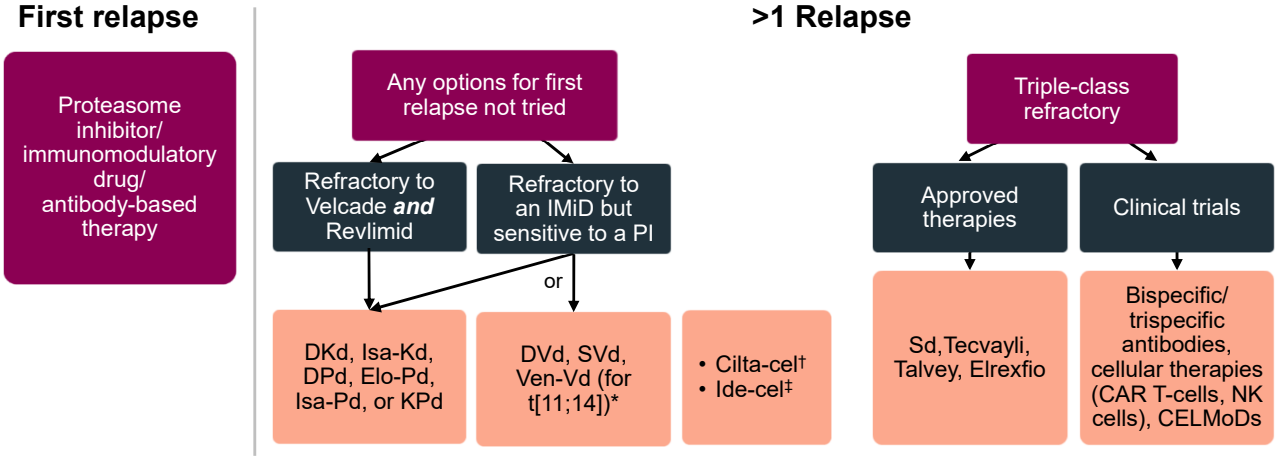
80

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:*** increase 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

81

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); ide-cel, idecabtagene vicleucel (Abecma); cilta-cel, ciltacabtagene autoleucel (Carvykti)

*Not approved for use in myeloma patients; †At least 1 prior line of therapy, including a PI and an IMiD, and are refractory to Revlimid; ‡After two or more prior lines of therapy including an IMiD, a PI, and an anti-CD38 monoclonal antibody.

82

Currently Available 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

83

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

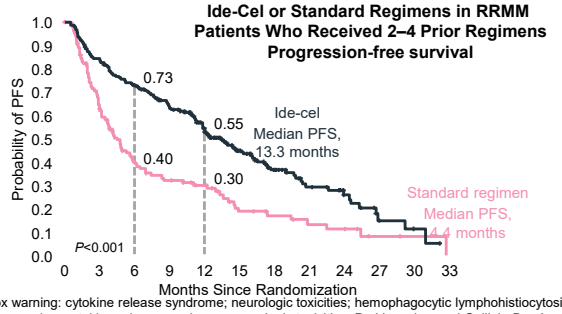
*Black box warnings: embryo-fetal toxicity; hematologic toxicity (Revlimid); venous and arterial thromboembolism

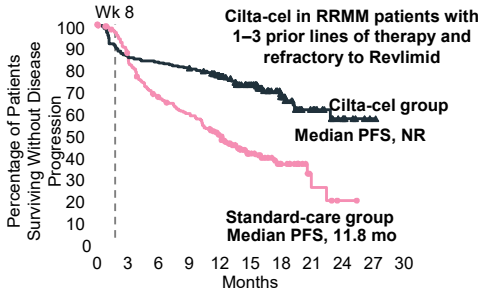
IV, intravenous; SC, subcutaneous

84

Currently Available Agents for One to Three Prior Lines of Therapy

Class	Drug	Formulation
Chimeric antigen receptor (CAR) T cell	Abecma (idecabtagene vicleucel)*	300 to 510 × 10^6 genetically modified autologous CAR T cells in one or more infusion bags
CAR T cell	Carvykti (ciltacabtagene autoleucel)†	0.5 to 1.0 × 10^6 genetically modified autologous CAR T cells/kg of body weight

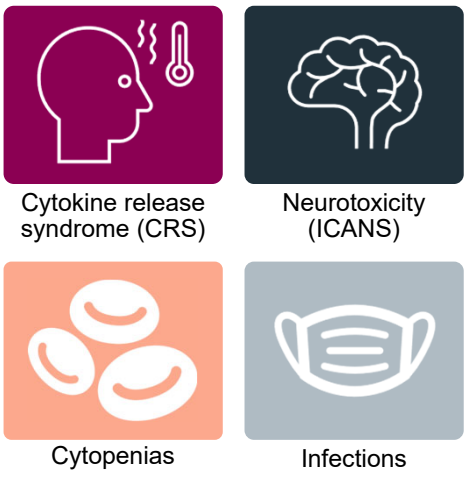




*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
†Black box warning: cytokine release syndrome; neurologic toxicities; Parkinsonism and Guillain-Barré syndrome; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
Abecma, Carvykti, Tecvayli, Talvey, and Elrexfio are available only through a restricted distribution program.

85

CAR T: Expected Toxicities



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

*Based on the ASTCT consensus; †Based on vasopressor; ‡For adults and children >12 years; §For children ≤12 years; ‖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.

86

Ongoing Clinical Studies With Ide-Cel and Cilta-Cel

Ide-Cel Studies

- KarMMa-2
  - Phase 2 study in RRMM and high-risk myeloma (relapse early after induction)
- KarMMa-4
  - Phase 1 study in newly diagnosed high-risk myeloma

Cilta-Cel Studies

- CARTITUDE-2
  - Phase 2 study in RRMM and high-risk myeloma (relapse early after induction)
    - Arm D: len/dex after CAR
    - Arm E: dara-RVd induction, CAR then dara-R consolidation
- CARTITUDE-6
  - Phase 3 study in NDMM
  - Replaces transplant with CAR-T

87

Triple-Class Refractory

- 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

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

88

Currently Available Drugs for Triple-Class Refractory Myeloma

Class	Drug	Formulation		Approval
Nuclear export inhibitor	XPOVIO (selinexor)		Twice-weekly pill	• For **relapsed/refractory** myeloma in combination with dexamethasone (after at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 IMiDs, and an anti-CD38 mAb

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.

89

Currently Available Drugs for Triple-Class Refractory Myeloma

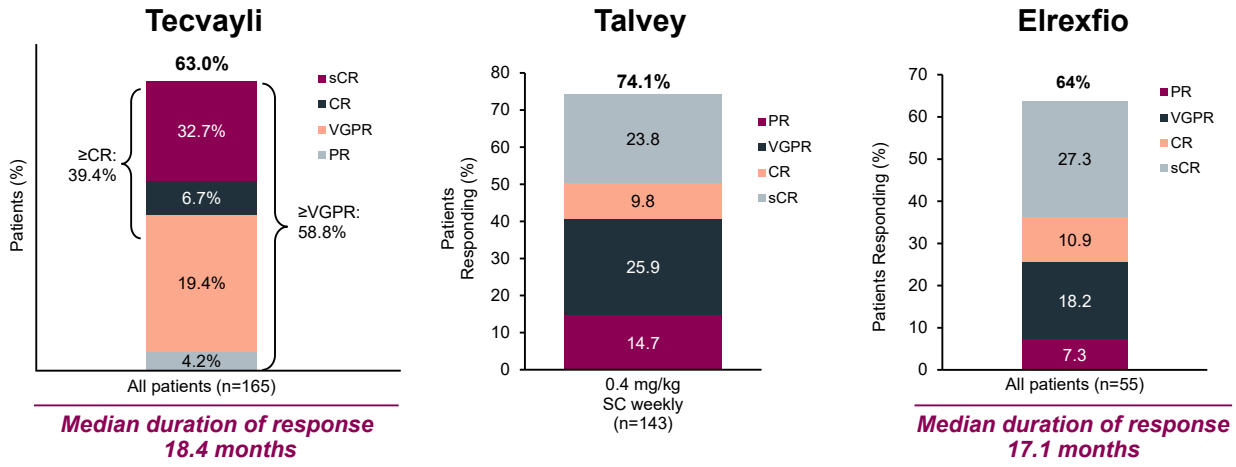
Class	Drug	Formulation	
Bispecific antibody	Tecvayli (teclistamab)*‡		Step-up dosing† the first week then once weekly thereafter by subcutaneous injection
Bispecific antibody	Talvey (talquetamab)*‡		Step-up dosing† the first week then once weekly thereafter by subcutaneous injection
Bispecific antibody	Elrexfio (elranatamab)*		Step-up dosing‡ the first week then once weekly thereafter by subcutaneous injection

And, CAR T-cell therapies: Abecma, Carvykti

*Black box warning: cytokine release syndrome; neurologic toxicities
†Patients are hospitalized for 48 hours after administration of all step-up doses.
‡Patients are hospitalized for 48 hours after administration first step-up dose and for 24 hours after second step-up dose.
Abecma, Carvykti, Tecvayli, Talvey, and Elrexfio are available only through a restricted distribution program.

90

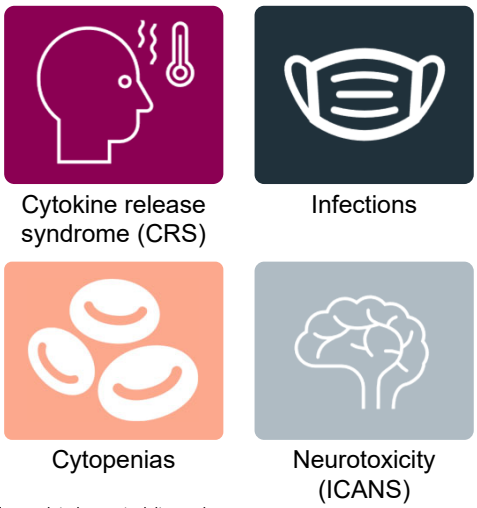
Now Approved: Three Bispecific Antibodies!



MajesTEC-1 Study. Moreau P et al. *N Engl J Med*. 2022;387:495.
Chari A et al. *N Engl J Med*. 2022;387:2232.
Schinke CD et al. *J Clin Oncol*. 2023;41. Abstract 8036.

91

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



Off-target effects (with GPRC5D-targeted agents)

Cytokeratin changes/rash
Dysgeusia

ICANS, immune effector cell-associated neurotoxicity syndrome

92

GPRC5D-Associated Side Effects

Affected area	Symptoms and effects	Management
Skin	Rash, skin peeling	Relatively benign, not painful, self-limiting, and manageable with emollients
Nails	Nail thinning and loss	Mostly aesthetic but take time to resolve
Oral	Difficulty swallowing, dry mouth, taste changes	Can lead to weight loss; have longer duration and can affect quality of life. Most successfully managed with dose modification. Supportive measures may be used (eg, NaCl mouth rinse, artificial saliva spray, diet modification)

Myeloma patients respond well to treatment, and GPRC5D-associated side effects improve over time, becoming more tolerable; notable reduction in side effects is seen with dose modification

Catamero D et al. *Clin Lymphoma Myeloma Leuk*. 2023;23. Abstract NSP-03.

93

Bispecific Antibodies Under Investigation

Bispecific antibody	Target (on MM cell × T cell)	Status
Tecvayli (teclistamab)	BCMA × CD3	Approved for use in myeloma patients
Elrexfio (elranatamab)	BCMA × CD3	Approved for use in myeloma patients
Linvoseltamab	BCMA × CD3	Clinical studies
Alnuctamab	BCMA × CD3	Clinical studies
ABBV-383	BCMA × CD3	Clinical studies
Talvey (talquetamab)	GPRC5D × CD3	Approved for use in myeloma patients
Forimtamig (RG6234)	GPRC5D × CD3	Clinical studies
Cevostamab	FcRH5 × CD3	Clinical studies

BCMA

- Highly expressed only on the surface of plasma cells
- Myeloma patients have significantly higher serum BCMA levels than healthy individuals

GPRC5D

- Highly expressed on myeloma cells in the bone marrow
- Lowly expressed on hair follicles but not on other healthy cells
- Expression on myeloma cells is independent of BCMA

FcRH5

- Selectively expressed on B cells and plasma cells

CD3: a T-cell receptor

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

94

Summary

- We now have many different options for relapsed myeloma depending on patient and myeloma factors at relapse.
- Therapy choices will depend on teamwork between physician, patient, and caregivers and are based on many decision points.
- Combinations of proteasome inhibitors with either immunomodulatory drugs or selinexor improve PFS.
- We have three different monoclonal antibodies that improve PFS 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 with unprecedented response rates and durations of response.

95

MULTIPLE MYELOMA Research Foundation

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

96

MULTIPLE MYELOMA Research Foundation

Personalized Medicine

Samir S. Parekh, MD
Icahn School of Medicine at Mount Sinai
New York, New York

97

Disclosures

- Dr. Parekh discloses consulting relationships with Grail and research support from Amgen, Celgene/BMS Corporation, and Caribou

98

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

99

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 are needed to address high-risk patients

What we need

- Evolving definitions of high-risk beyond historic markers such as translocation 4;14 and 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

100

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

101

An Example of the Importance of Personalized Medicine

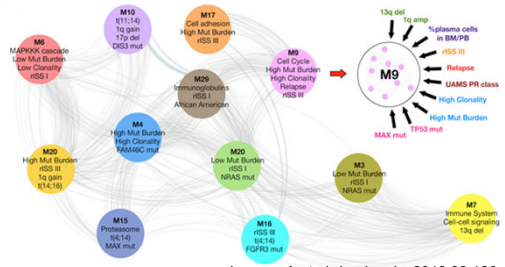
	CoMMpassMMRF2172 	CoMMpassMMRF2250 
Age	72	71
Ethnicity	Caucasian	Caucasian
ISS stage	II	II
Baseline treatment	VRD	VRD
Cytogenetics	t(4;14), del13	t(4;14), del13
Time of progression	11 months	36 months
Overall survival	1.6 years	6.3 years
Other genetic events	**1q21, del17p + TP53 mut**	No 1q21, no 17p or TP53 mut

102

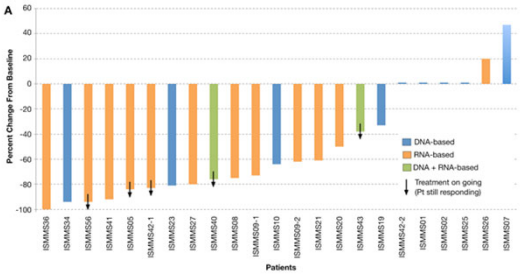
Multiple Myeloma Genomics/Precision Medicine at Sinai

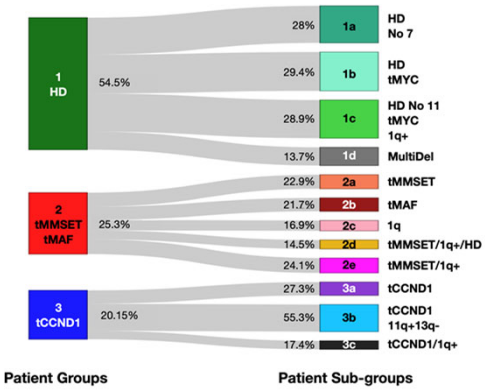
Alessandro Lagana, PhD

Joel Dudley, PhD



Lagana A et al. *Leukemia*. 2018;32:120.





Bhalla S et al. *Sci Adv*. 2021;7:eabg9551.

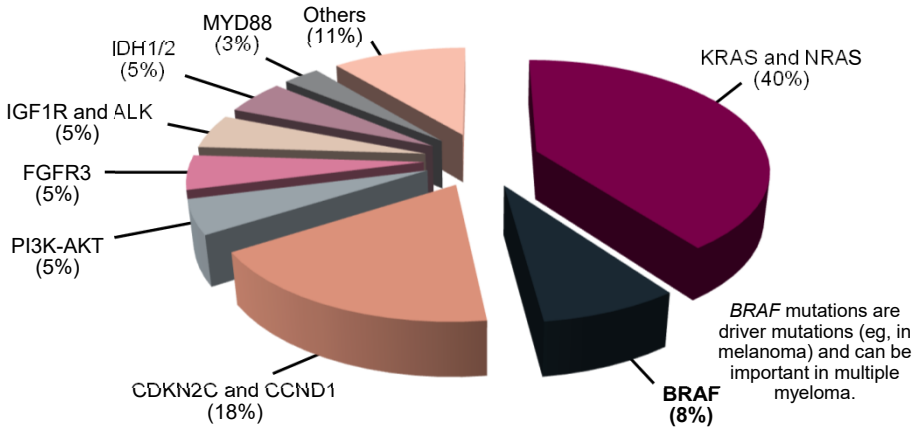
Lagana A et al. *JCO Precis Oncol*. 2018;2018:PO.18.00019.

103

Actionable Alterations in Multiple Myeloma

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

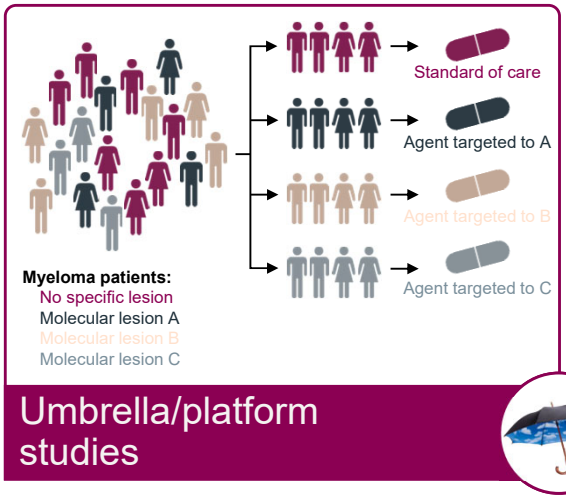
Precision medicine efforts have identified molecular alterations for which there are drugs in the clinic.

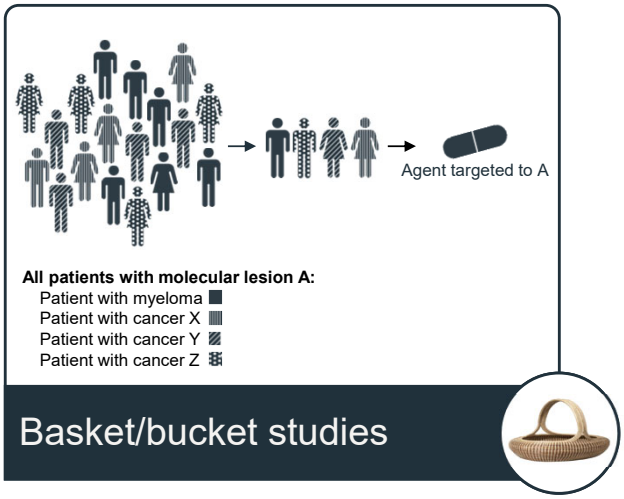


BRAF mutations are driver mutations (eg, in melanoma) and can be important in multiple myeloma.

104

Innovative Study Designs: Shaping the Future of Cancer Research Toward Personalized Medicine

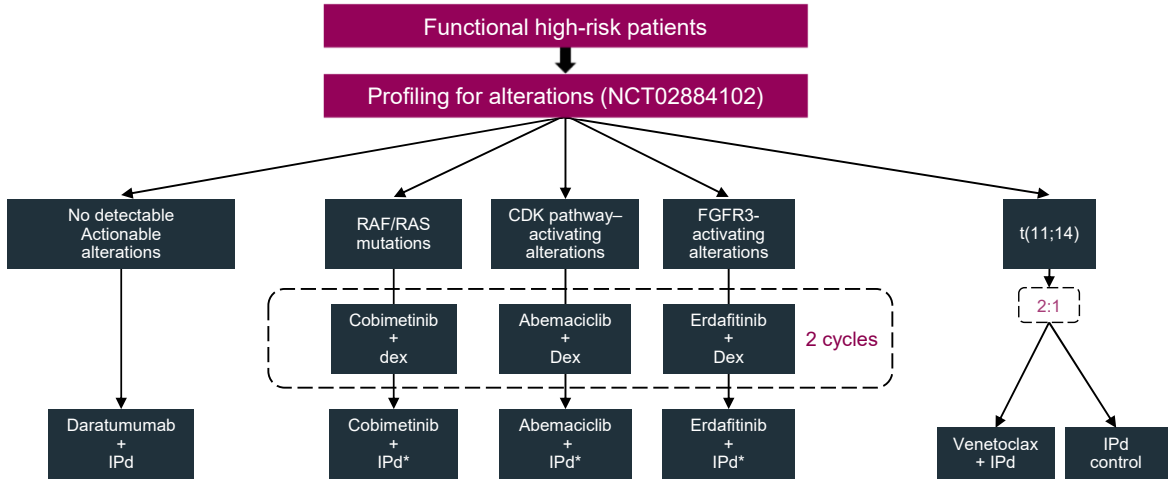




Pawlyn C, Davies F. *Blood*. 2019;133:660.

105

MyDRUG Study



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

106

Personalized 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.)

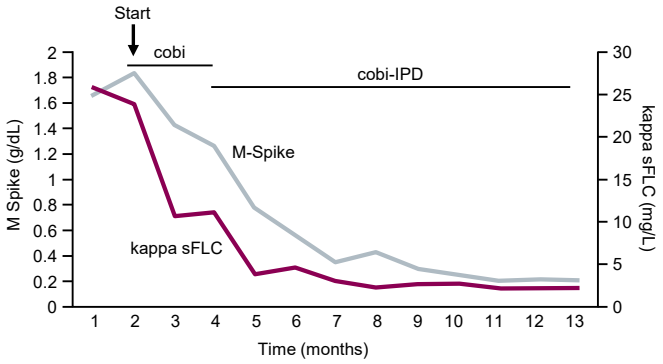
2nd Line

- 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

107

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

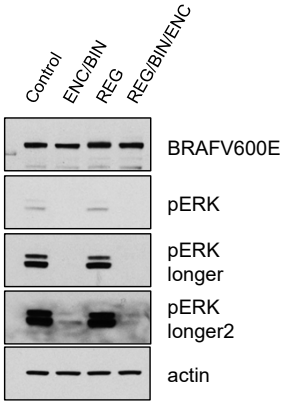
*Being studied in the MyDRUG trial

108

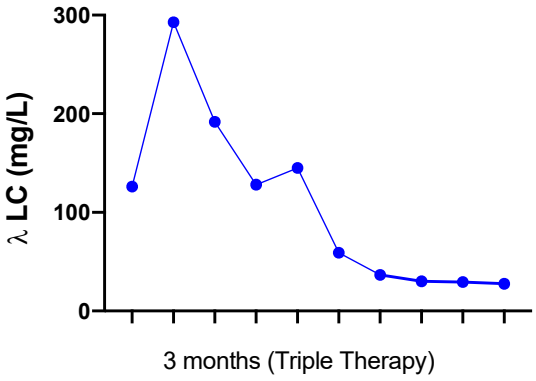
64-Year-Old With Relapsed Myeloma After CAR T With BRAF V600E

Muhammad Elnaggar, MD, PhD

Sarita Agte, MD



48-hour treatment
Encorafenib: 50 nM
Binimetinib: 250 nM
Regorafenib: 1 μM



Phase 2 clinical trial (R01 funded) in 2022 to include other genomic guided drugs (for example, Selinexor).

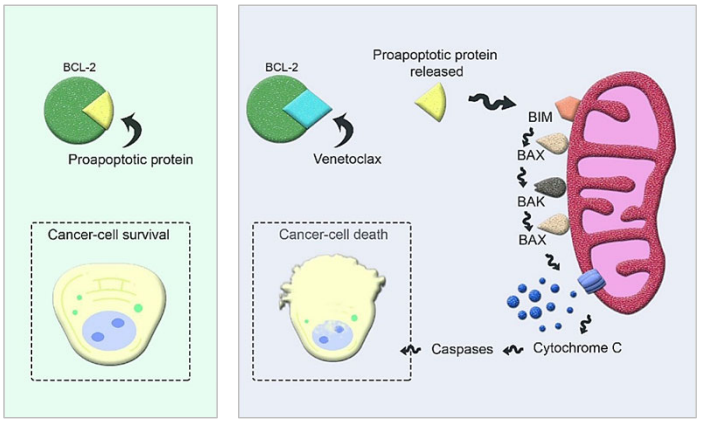
Elnaggar M et al. *J Hematol Oncol*. 2022;15:109.

109

Venetoclax and t(11;14)

Venetoclax is a Bcl-2 inhibitor

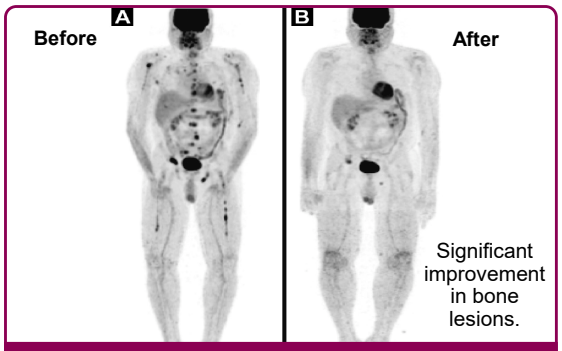
- BCL2 inhibitor
- Induces cancer cell death
- t(11;14) multiple myeloma → ↑BCL2 and ↓MCL1
- t(11;14): first predictive marker in multiple myeloma, indicating susceptibility to BCL2 inhibition



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

110

BRAF and MEK



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

- 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

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

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

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

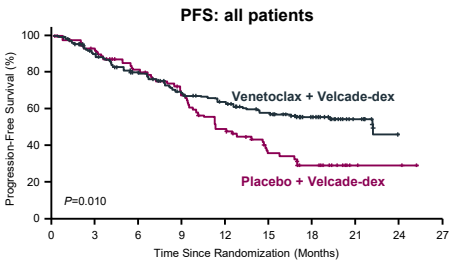
111

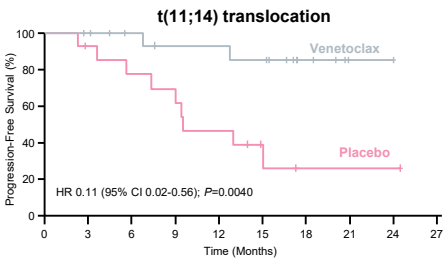
Venetoclax and t(11;14)

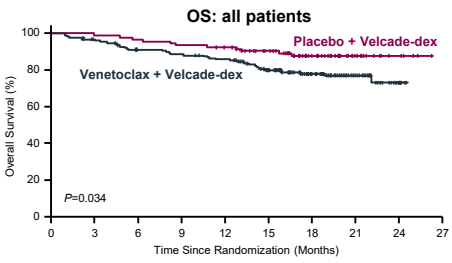
Venetoclax bortezomib dex vs placebo bortezomib dex;
1–3 prior lines

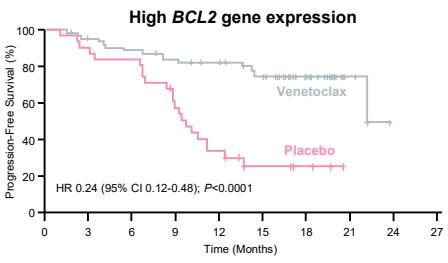
Median follow up 18.7 m mPFS
22.4 m venetoclax
11.5 m placebo

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









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

112

Next-Generation BCL-2 Inhibitors

Lisaftoclax[1]

30 patients

- 22 RRMM, lisaftoclax + pom-dex
- 3 RRMM, lisaftoclax + dara-Rd
- 5 RR AL, lisaftoclax + pom-dex
- Median 4 prior lines of therapy
- 18 patients triple-class exposed

Safety

- TRAEs: neutropenia 16.7%, nausea 16.7%
- Grade ≥3 TRAEs: neutropenia 10%

ORR, lisaftoclax + pom-dex in RRMM: 67%

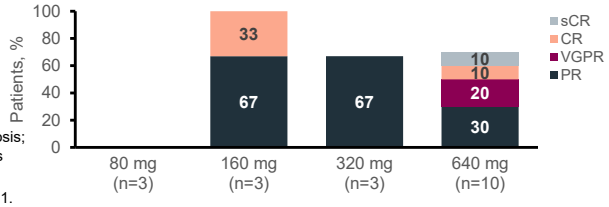
Sonrotoclax[2]

19 patients

- Median age 68 years
- 21% R-ISS III; 16% high-risk cytogenetics
- Median 4 prior lines of therapy
- All patients received prior IMiD and prior PI

Safety

- Hematologic AEs 21%, infections 32%
- Grade ≥3 AEs 26%, SAEs 11%



RRMM, relapsed/refractory multiple myeloma; RR AL, relapsed/refractory amyloid light chain amyloidosis; TRAE, treatment-related adverse event; ORR, overall response rate; AE, adverse event; SAE, serious adverse event

1. Ailawadhi S et al. *Blood*. 2023;142. Abstract 2016. **2.** Quach H et al. *Blood*. 2023;142. Abstract 1011.

113

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

114

Personalized 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 studies to provide bone marrow and peripheral blood is paramount.
- Personalized medicine provides the right treatment at the right time for each myeloma patient.

115

MULTIPLE MYELOMA Research Foundation

Supportive Care

Leora A. Giacoia, MS, FNP-BC, ACHPN
Mount Sinai Hospital
New York, NY

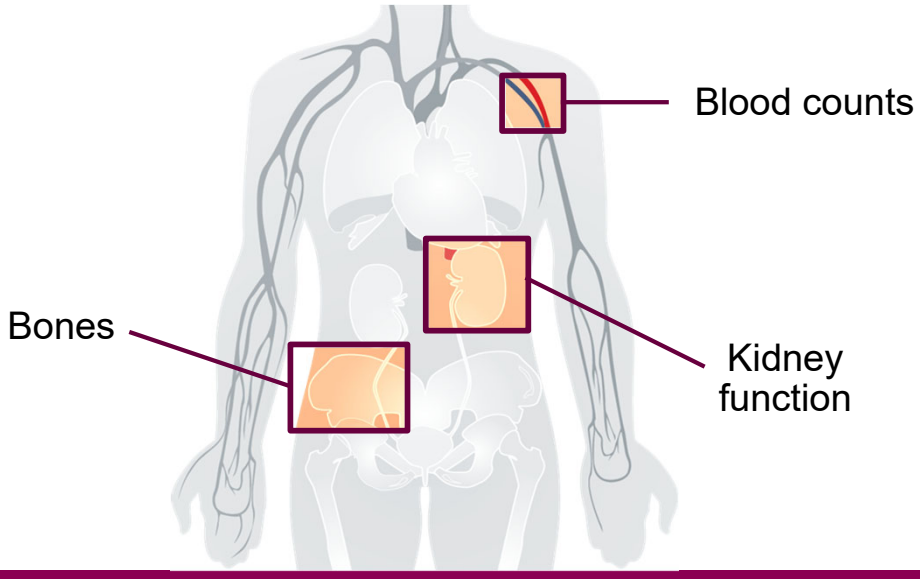
116

Disclosures

- Leora A. Giacoia, MS, FNP-BC, ACHPN, has no relevant financial information to disclose.

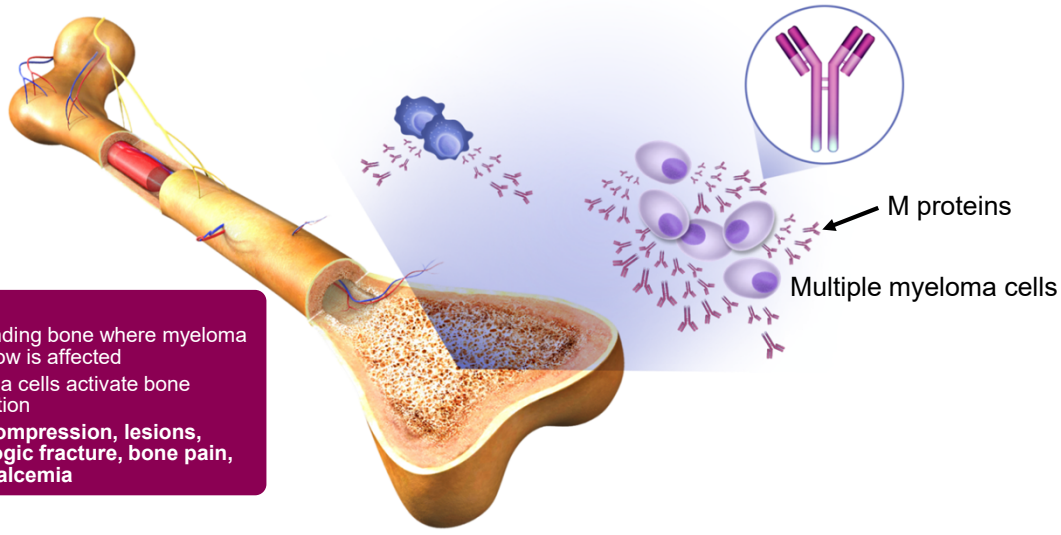
117

Myeloma Affects Your…



118

Multiple Myeloma Affects Your…
Bones

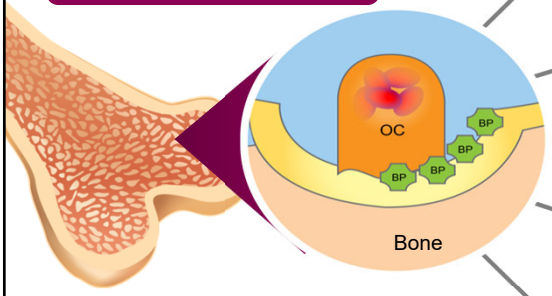


BONES
- Surrounding bone where myeloma cells grow is affected
- Myeloma cells activate bone destruction
- **Cord compression, lesions, pathologic fracture, bone pain, hypercalcemia**

119

Medications for Myeloma Bone Disease

Recommendation
- Vitamin D 600–1,000 IU daily
- Calcium 1,000–1,200 mg daily
- Monitor renal function



How they work
- Prevent bone disease from getting worse

Benefits
- Decrease pain and reduce skeletal-related fractures

Medication types
- Zometa* (zoledronic acid): 30-minute infusion
- Aredia* (pamidronate): 2-hour infusion
- Xgeva (denosumab): injection

Dosing
- Zometa: IV over 15 min every 3–4 weeks
- Aredia: IV over 2 hours every 3–4 weeks
- Xgeva: injection once every 4 weeks

Side effects
- Reduced kidney function
- Fracture of the femur
- Osteonecrosis of the jaw (ONJ)†

*Dose adjust for renal function
OC, osteoclast (inhibited, halting bone breakdown); BP, bisphosphonate

120

Recommendations for Reducing the Risk of ONJ and Infection

- Complete major dental work before beginning treatment for bone disease
- Practice good oral hygiene
- Schedule regular dental visits/antibiotic prophylaxis
- 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

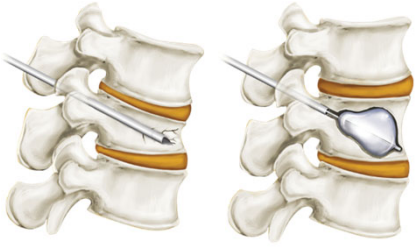
ONJ, osteonecrosis of the jaw

121

Procedures for Bone Pain Radiation and Surgical Intervention

- 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)

Vertebroplasty **Kyphoplasty**



- Destroys myeloma cells
- Stops bone destruction
- Pain control
- Targeted and localized therapy
- Can affect bone marrow function
- Can affect adjacent tissues

122

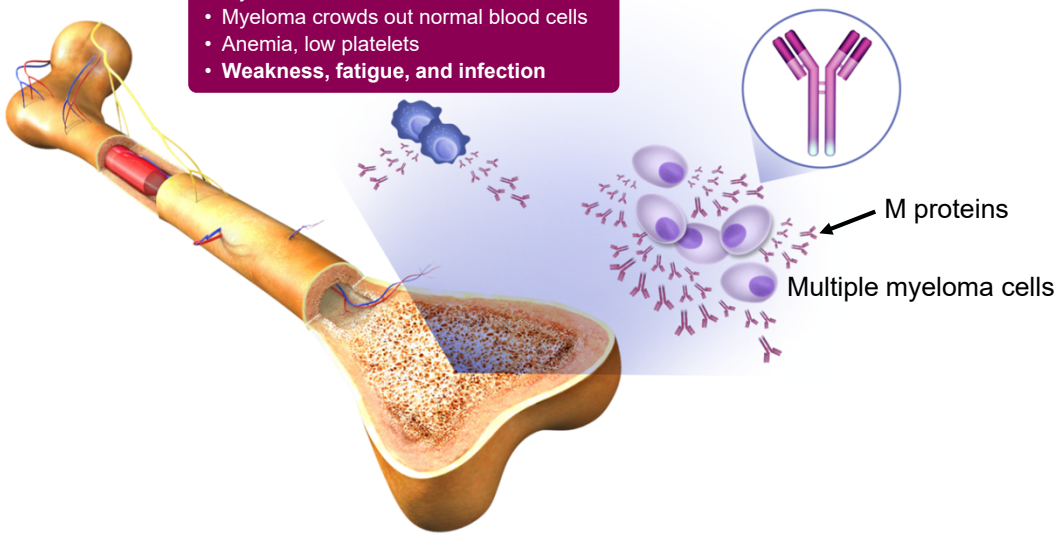
Pain Management Medications

Acetaminophen (Tylenol)	NSAIDs (nonsteroidal anti-inflammatory drugs)	Opioids	Corticosteroids (dexamethasone, prednisone)	GABA analogues (gabapentin and Lyrica)
High dosage can hurt your liver; caution with elevated liver function tests (LFTs)	**Prefer to avoid with multiple myeloma due to increased risk of kidney injury** **Topical NSAIDS may be acceptable on case by case basis**	Potential for constipation, sedation, confusion, physiologic dependence	Has myeloma-fighting effects. Can raise blood sugar and cause insomnia; short- and long-term effects	For use of neuropathic pain. Potential for drowsiness and dizziness

123

Multiple Myeloma Affects Your…
Blood

BLOOD
- Myeloma is a cancer of the blood
- Myeloma crowds out normal blood cells
- Anemia, low platelets
- **Weakness, fatigue, and infection**



124

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

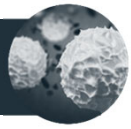
Treatment: Identify and treat causes other than myeloma; supplements; medications to increase number of red blood cells; blood transfusions

Low 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

Low white blood cells (leukopenia)

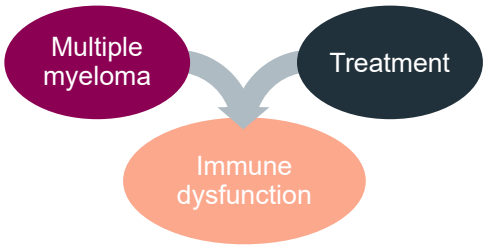


- Symptoms
  - Fatigue; frequent infections
- Other causes
  - Radiotherapy
  - Infection

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

125

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.

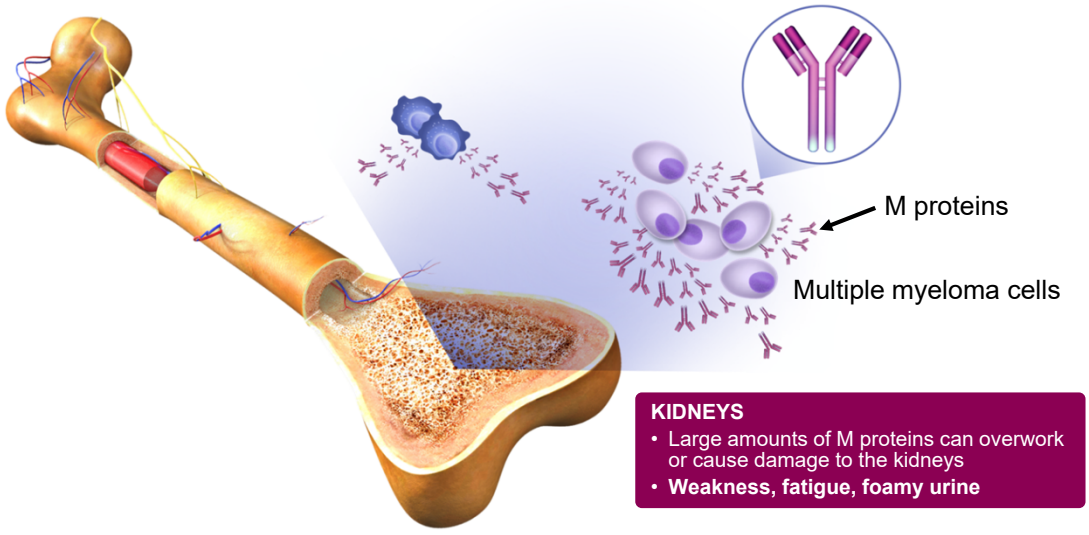
General infection-prevention tips

- Good personal hygiene (skin, oral)
- Environmental control (wash hands, avoid crowds and sick people, etc)
- Growth factor (Neupogen, Neulasta)
- IV gamma globulin infusion (Gamunex)
  - 4-hour infusion every 4 weeks IV
- Immunizations
  - COVID-19 vaccination + booster(s)
  - Pneumococcal 20-valent conjugate vaccine
  - Seasonal inactivated influenza vaccine
  - Shingles vaccine: zoster vaccine recombinant, adjuvanted
- Prophylactic medications (antibacterial, antiviral)
  - Valacyclovir/acyclovir
  - Hepatitis B virus nucleoside reverse transcriptase inhibitors
  - Bactrim, Mepron, or dapsone

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. https://www.hematology.org/covid-19/covid-19-and-multiple-myeloma

126

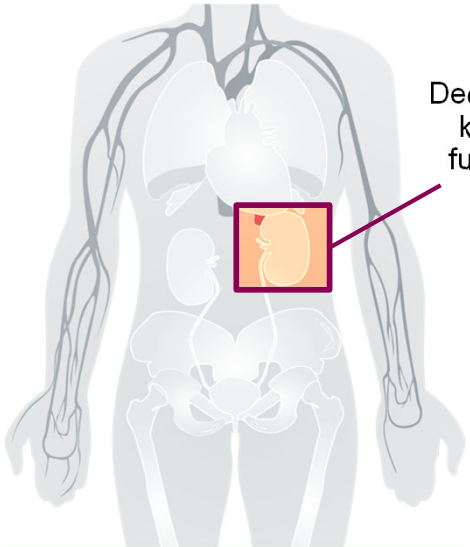
Multiple Myeloma Affects Your...
Kidneys



KIDNEYS
- Large amounts of M proteins can overwork or cause damage to the kidneys
- **Weakness, fatigue, foamy urine**

127

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 nephrotoxic substances
    - Nonsteroidal anti-inflammatory drugs (NSAIDs) such as Aleve, Advil/Motrin
    - CT contrast
  - Plasmapheresis
  - Treat other causes
  - Dialysis (severe)

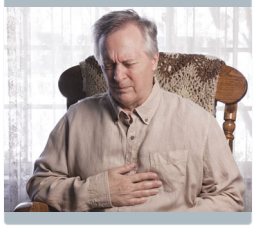
128

Side Effects and Management of Myeloma Therapies

Immunomodulatory medications	Proteasome inhibitors	Monoclonal antibodies
Revlimid, Pomalyst	Velcade, Kyprolis, Ninlaro	Darzalex/Sarclisa, Empliciti
• Fatigue and weakness • Blood clots • GI effects: diarrhea • Muscle cramping and back pain • Drug rash • Shortness of breath • Upper respiratory infections • Mental fogginess • Birth defects	• **Peripheral neuropathy** • Low platelets • GI problems • Styes • Fatigue • Rash • Hypertension • Cardiac toxicity • Shortness of breath • Back pain	• Infusion reactions • Fatigue • Low platelets • Hepatitis B reactivation • Upper respiratory tract infections
Management Blood thinners for potential clots; tonic water/hydration for cramps; avoid dairy; fiber Imodium; cholestyramine for GI toxicities; sleep hygiene, regular exercise, dose reduction for fatigue	**Management** Dose or frequency decrease, vitamins and supplements, gabapentin, pregabalin, duloxetine, opioids, acupuncture, anticoagulants, antivirals, stop meds if needed	**Management** Premedication in anticipation of infusion reactions, post-infusion medications (dex), antivirals

129

Side Effects of Steroids (Dexamethasone)

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

130

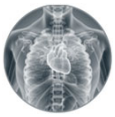
Bispecific Antibodies

Tecvayli, Talvey, Elrexfio

- Tecvayli (teclistamab) and Elrexfio (elranatamab)
  - BCMA target: CRS, neurotoxicities/ICANS, infections, decreased blood counts, injection-related reactions
- Talvey (talquetamab)
  - GPRC5D target: CRS, neurotoxicities/ICANS, neutropenia, hypogammaglobulinemia, taste changes, oral and skin effects, nail changes

Management

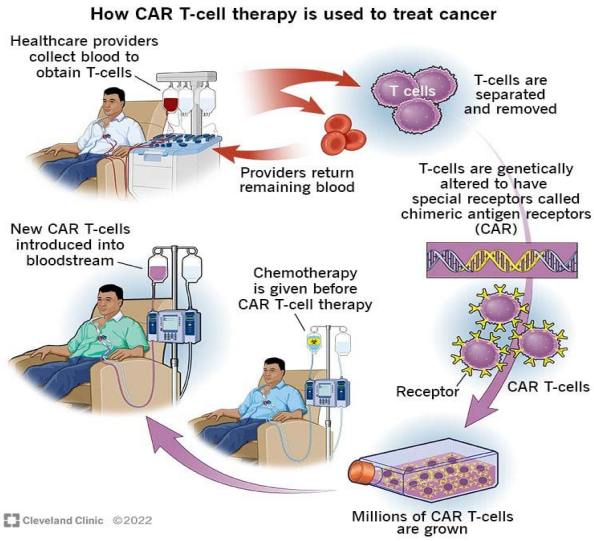
- Patients receive step-up dosing and are monitored in an inpatient setting
- CRS is managed with tocilizumab
- Neurological toxicities managed with anakinra and/or steroids
- Supportive care (oral, skin, and nail care)
- Injection reactions are managed with oral antihistamines and topical steroids
- Infection prevention!



131

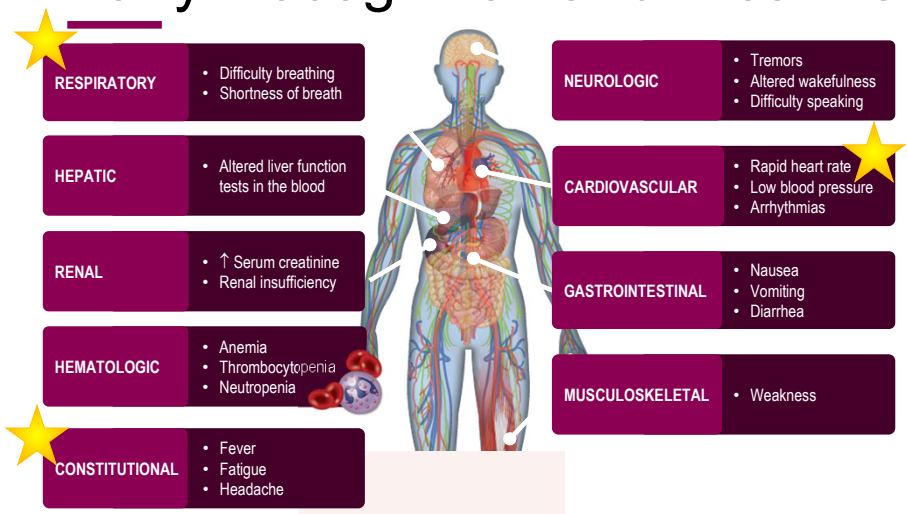
Chimeric Antigen Receptor T Cell (CAR T)

- Cytokine release syndrome (CRS)
- Neurotoxicity/ICANS
  - Caregiver role
- Low blood counts
- Infection risk
  - Prophylactic medications
    - Levaquin
    - Mepron
    - Bactrim



132

CRS With Bispecifics and CAR T: 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***

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 A et al. *J Immunother Cancer*. 2018;6:56. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625.

133

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.

134

MULTIPLE MYELOMA Research Foundation

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

135

MULTIPLE MYELOMA Research Foundation

Questions?

136

MULTIPLE MYELOMA Research Foundation

Patient Experience

Roger Rawlings

137

MULTIPLE MYELOMA Research Foundation

Thank you!

138

abbvie Bristol Myers Squibb™ cure curetoday.com

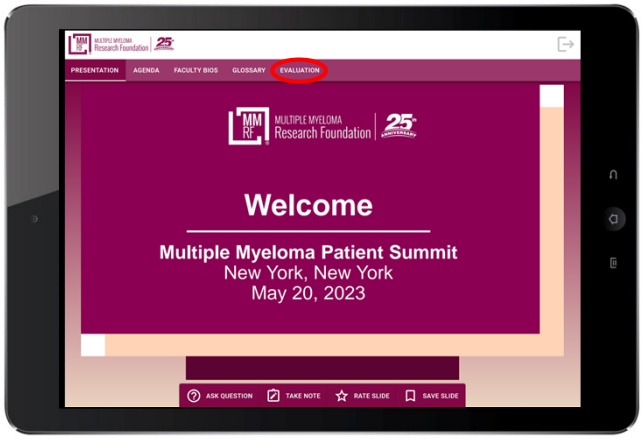
Genentech A Member of the Roche Group GSK Johnson&Johnson

Pfizer REGENERON SCIENCE TO MEDICINE® sanofi

139

Don't Forget!

Complete your evaluation
Leave the iPad at your seat



140

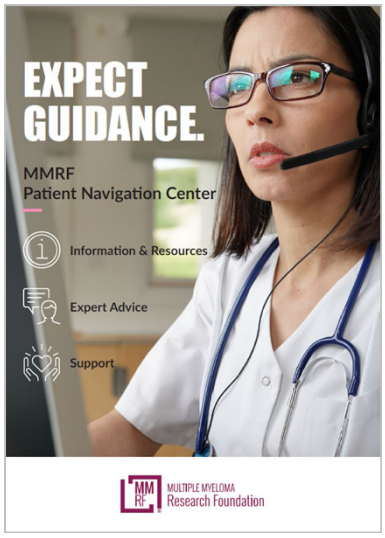
Upcoming Patient Education Events
Save the Date

Topic	Date and Time (ET)	Speakers
Autologous Stem Cell Transplantation FAQs *Livestream*	Monday, May 6, 2024 4:00 PM	Amrita Krishnan, MD Cherry Lou Rudge, NP-C Todd Kennedy
Understanding Your Lab Report *Webinar*	Monday, May 13, 2024 3:30 PM	Craig Emmitt Cole, MD Amy Blake, NP-C
Understanding Lab Report FAQs *Livestream*	Friday, June 7, 2024 3:00 PM	Joshua Richter, MD Michelle Lyn, NP
Patient Summit *Hybrid*	Saturday, August 17, 2024 Los Angeles, California	Amrita Krishnan, MD—Host

For more information or to register,
visit **themmrf.org/educational-resources**

141

MMRF Patient Resources



142

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.

143

Join the MMRF Community!

National Walk/Run Program

Atlanta | 10.26.24
Boston | 10.12.24
Chicago | 9.8.24
Dallas | 11.16.24
Houston | 11.23.24
Los Angeles | 8.17.24
National Virtual | 12.14.24
New York City | 10.5.24
Philadelphia | 10.19.24
San Francisco | 8.24.24
Scottsdale | 12.7.24
Southeast Michigan | TBD
Tampa | TBD
Twin Cities | 9.14.24
Washington, D.C. | 9.28.24

Other MMRF Event Programs

Moving Mountains for Multiple Myeloma

Half and Full Marathons

Bike/Road to Victories

Create Your Own Fundraiser

144

Need help with travel to a clinical study?

- The MMRF has partnered with the Lazarex Cancer Foundation to help provide more equitable access to clinical studies for multiple myeloma patients
- This partnership is one facet of the MMRF's commitment to improve diversity and representation in myeloma clinical trials
- MMRF has provided $100,000 over 2 years to Lazarex to fund travel, lodging, and food for patients (and a travel companion) so that they can participate in clinical studies that are appropriate for them
- Patients are funded according to income guidelines and will be reimbursed for allowed expenses
- For more information on this program and to be connected with Lazarex, call our Patient Navigation Center at 1-888-841-6673

It's About Living
Lazarex
CANCER FOUNDATION

145

MM RF MULTIPLE MYELOMA Research Foundation

Mount Sinai

Multiple Myeloma Patient and Caregiver Summit
New York, New York
May 4, 2024

146