MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Opening Remarks

Mary DeRome, MS
MMRF

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Advancing MRD measurement. Empowering patient care.

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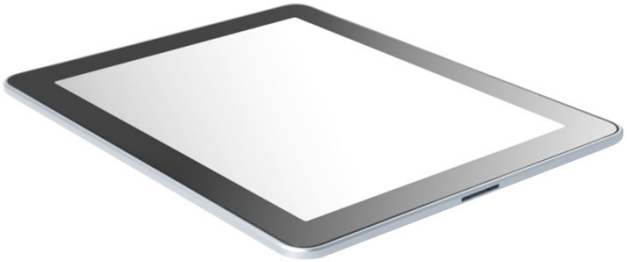
iPads

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



Submit your questions throughout the program!

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

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Program Faculty

Faith E. Davies, MBBCh, MD
Perlmutter Cancer Center at New York University Langone Health
NYU Grossman School of Medicine
New York, New York

Justina A. Kiernan, MPS, PA-C
Memorial Sloan Kettering Cancer Center
New York, New York

Neha Korde, MD
Memorial Sloan Kettering Cancer Center
New York, New York

Sham Mailankody, MBBS
Memorial Sloan Kettering Cancer Center
New York, New York

Gunjan L. Shah, MD
Memorial Sloan Kettering Cancer Center
New York, New York

Saad Z. Usmani, MD, MBA
Memorial Sloan Kettering Cancer Center
New York, New York

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

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Summit Agenda

Time (ET)	Topic	Speakers
9:30 – 9:45 AM	Welcome	Saad Z. Usmani, MD, MBA
9:45 – 10:15 AM	Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy	David H. Vesole, MD, PhD
10:15 – 10:45 AM	High-Dose Chemotherapy and Stem Cell Transplantation, Maintenance Therapy, and Treatment Goals	Faith E. Davies, MBBCh, MD
10:45 – 11:00 AM	Break	
11:00 – 11:30 AM	Relapsed/Refractory Multiple Myeloma	Sham Mailankody, MBBS
11:30 AM – 12:00 PM	Immunotherapy	Saad Z. Usmani, MD, MBA
12:00 – 12:30 PM	Supportive Care	Justina A. Kiernan, MPS, PA-C
12:30 – 1:15 PM	Lunch	
1:15 – 1:30 PM	Patient Speaker	Gail Goode
1:30 – 1:45 PM	Hot Topic 1: Minimal (Measurable) Residual Disease	Neha Korde, MD
1:45 – 2:00 PM	Hot Topic 2: Clinical Studies	Gunjan L. Shah, MD
2:00 – 2:15 PM	Hot Topic 3: High-Risk Disease	Sham Mailankody, MBBS
2:15 – 3:15 PM	Town Hall Q&A	Panel
3:15 – 3:30 PM	Closing Remarks	Mary DeRome, MS

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MMRF Introduction

Mary DeRome, MS
MMRF

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The Work of the MMRF

The MMRF does three things in relentless pursuit of its mission to accelerate a cure for each and every myeloma patient.

1

We accelerate new treatments

Bringing next-generation therapies to patients faster

2

We drive precision medicine

Using data to deliver better answers and more precise treatments for patients

3

We empower patients

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

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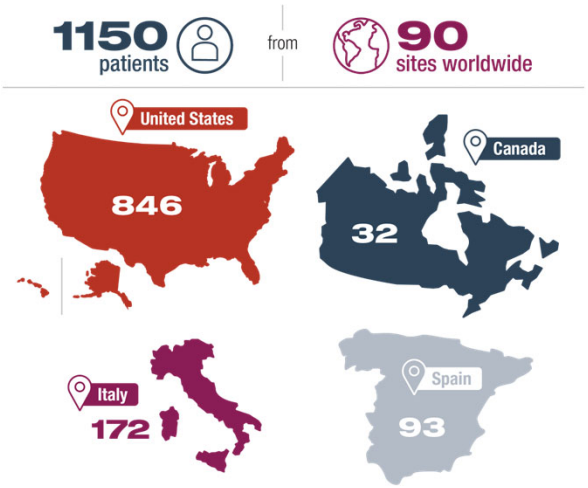
MMRF CoMMpass Study: Advancing Personalized Medicine Research

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

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



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CoMMpass Is a Trial of Discovery

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

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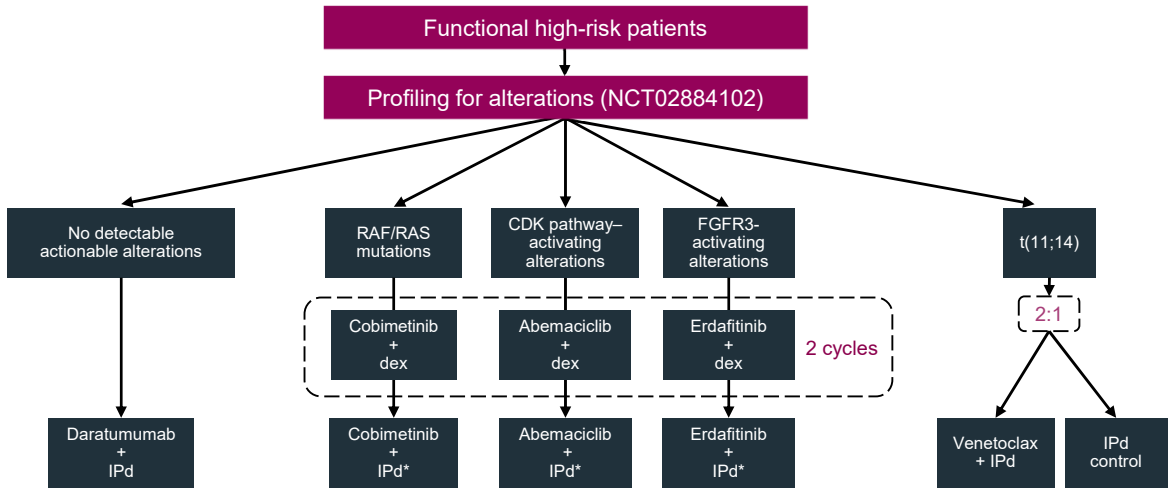
MyDRUG Trial



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

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MMRF CureCloud

Driving toward smarter treatment options

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

Join the MMRF CureCloud

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MMRF CureCloud
Recent Changes

- A new and better assay is being developed to look at patient DNA data from myeloma cells in their blood sample. While this assay is being developed, patients who join will no longer be able to receive their DNA test results, but their DNA will still be analyzed, with the results placed in 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 onsite 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

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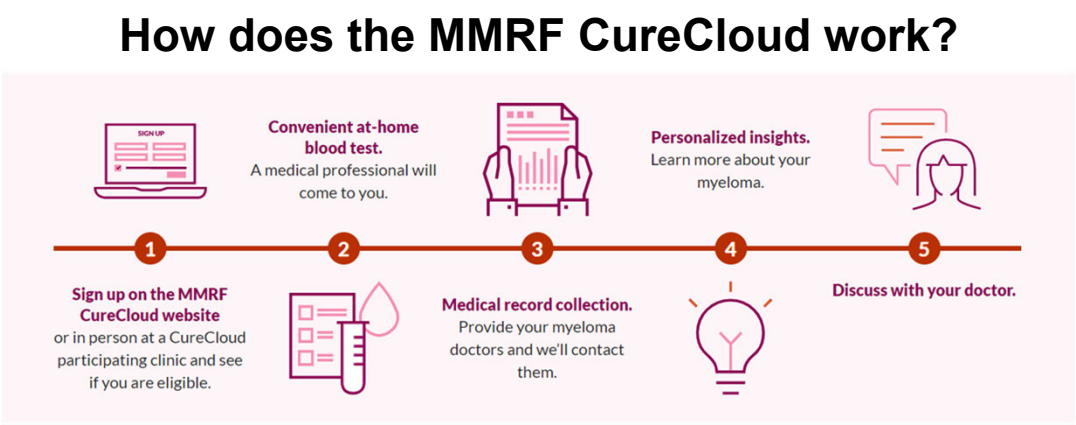
MMRF CureCloud



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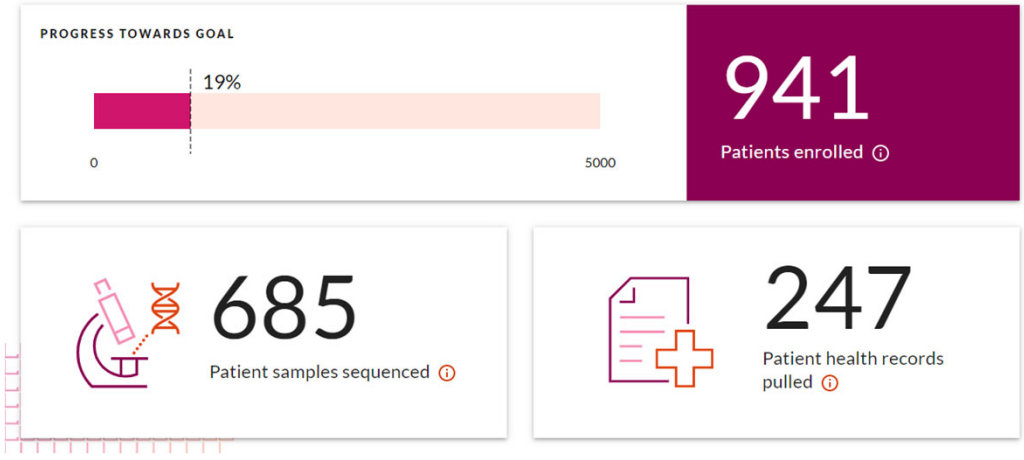
CureCloud Enrollment Tracker

This is the total number of patients who have enrolled in the CureCloud study. Monitor enrollment progress as we work toward our goal of 5,000 patient participants over 5 years. Explore anonymous CureCloud patient data below and find more information about each section in the (i) icon.



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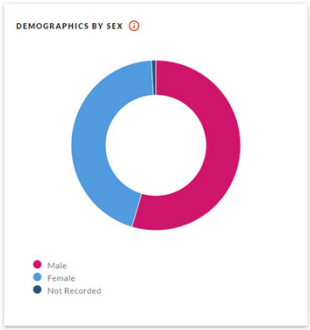
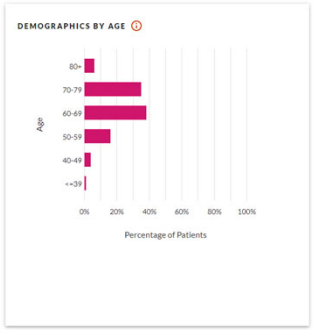
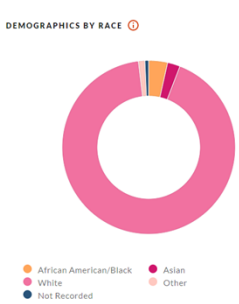
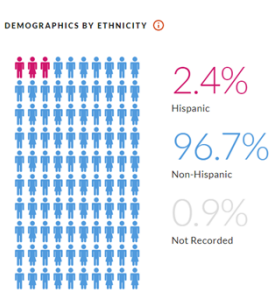
MMRF CureCloud Demographics









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Welcome!

Saad Z. Usmani, MD, MBA
Memorial Sloan Kettering Cancer Center
New York, New York

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Question

Are you a...

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

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Question

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

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.

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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

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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.

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Question

Have you and your care team ever discussed the possibility of you joining a clinical trial that you are eligible for? (If you are a caregiver, do you know if joining a clinical trial has ever been discussed?)

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

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Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy

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

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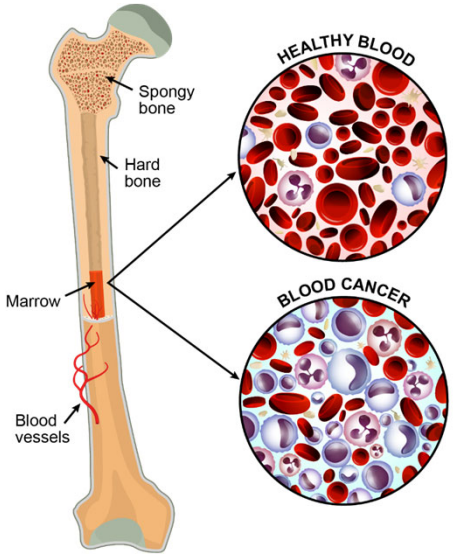
What is multiple myeloma?



- Multiple myeloma is a **blood cancer** that starts in the **bone marrow**, the place where all **blood cells** are produced
- Multiple myeloma is caused when a type of **white blood cell** called a **plasma cell** becomes cancerous and grows out of control

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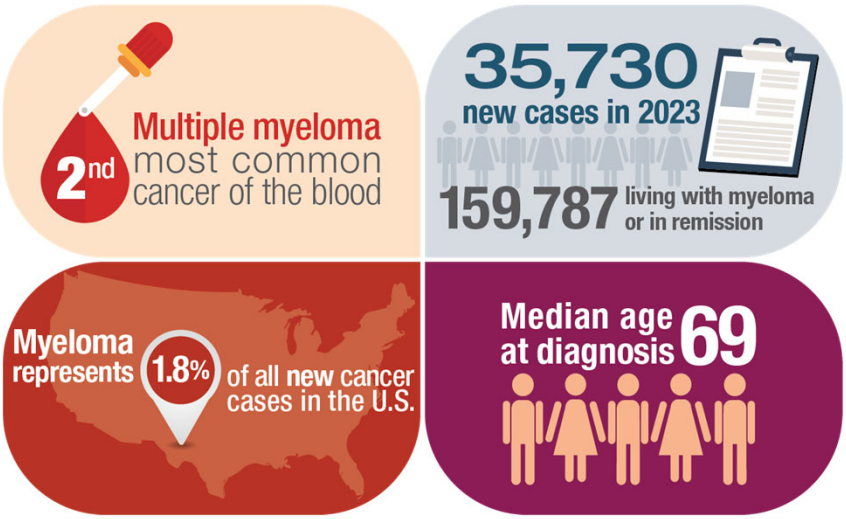
How common is multiple myeloma?



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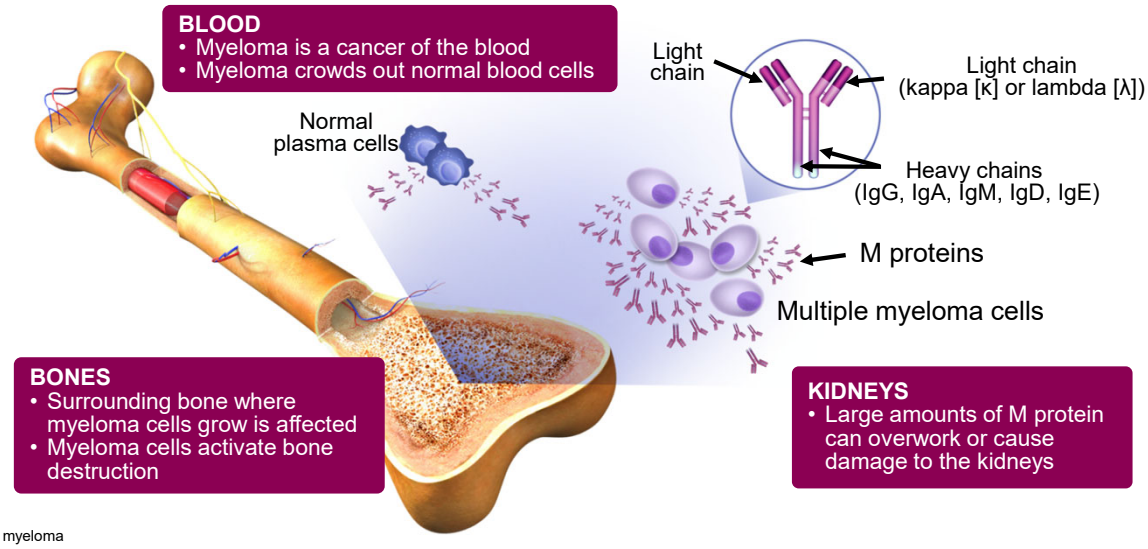
Multiple Myeloma Affects Your Bones, Blood, and Kidneys



MM, multiple myeloma

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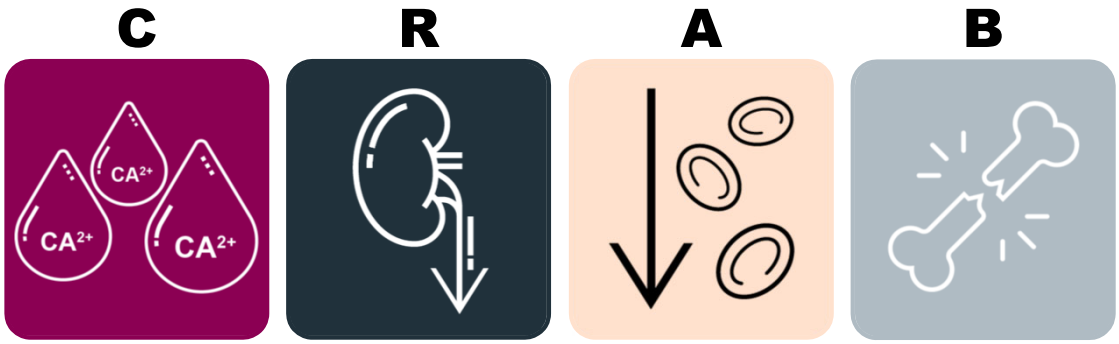
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

The clinical features that are characteristic of multiple myeloma



C	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

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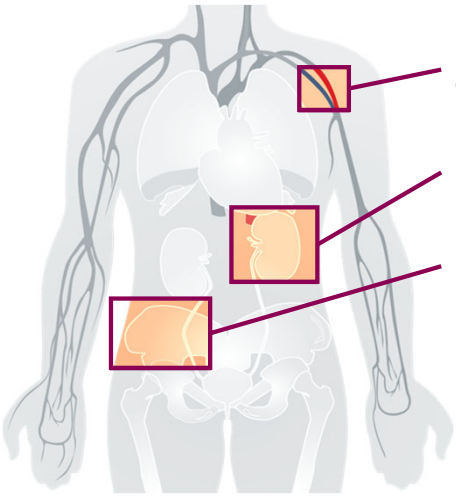
Effects of Myeloma and Common Symptoms



Low blood counts → Weakness, Fatigue, Infection

Decreased kidney function → Weakness

Bone damage → Bone pain

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

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

More common in Black patients

- Hypercalcemia
- Kidney dysfunction
  - Hemodialysis
- Anemia

Less common in Black patients

- Bone fractures

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Infections and Vaccinations in Multiple Myeloma

Risk of infection higher for myeloma patients than for general population

- Types of infections include
  - Bacterial: pneumonia (an infection of the lungs), bacteremia
  - Viral: varicella zoster (shingles), influenza, COVID

Preventive strategies (prophylaxis) are recommended

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

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Demographic Risk Factors: Multiple Myeloma

- Older age
- Male sex
- Obesity
- Race: 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.

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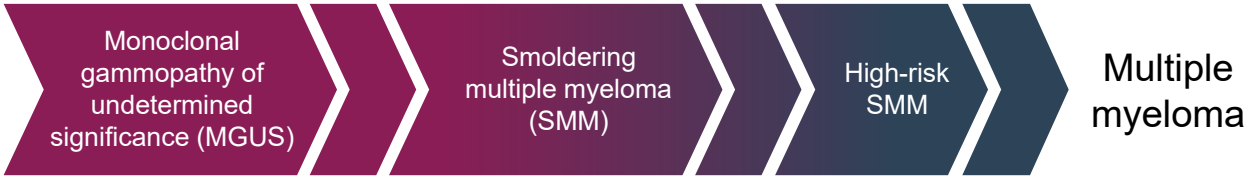
The Multiple Myeloma Disease Spectrum

Almost all patients diagnosed with multiple myeloma have had a preceding phase of disease that is characterized by changes in the bone marrow.



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Blood, Urine, Bone Marrow, and Imaging Tests Used to Identify MGUS, SMM, or Active Multiple Myeloma

	MGUS	SMM	Active multiple myeloma
M protein	<3 g/dL in blood	≥3 g/dL in blood **or** ≥500 mg/24 hrs in urine	≥3 g/dL in blood **or** ≥500 mg/24 hrs in urine
Plasma cells in bone marrow	<10%	≥10%–60%	≥60%
Clinical features	No myeloma-defining events*	No myeloma-defining events*	≥1 myeloma-defining event*, including either: • ≥1 CRAB feature ***or*** • ≥1 SLiM feature

*CRAB, calcium elevation, renal insufficiency, anemia, bone disease; SLiM, >60% plasma cells in bone marrow, free light chain involved to uninvolved ratio >100, >1 focal lesion on MRI

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

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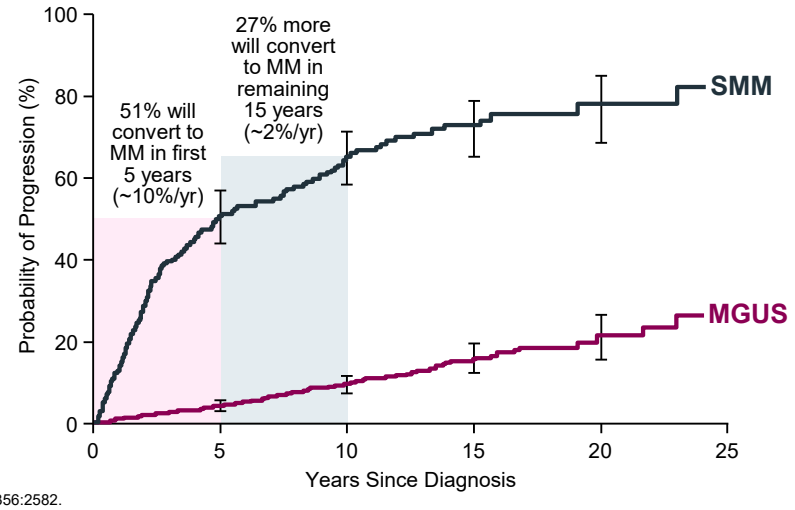
Risk of Progression to Myeloma From a Precursor Condition



Kyle RA et al. *N Engl J Med*. 2007;356:2582.
Greipp PR et al. *J Clin Oncol*. 2005;23:3412.

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Following the Right Track Will Help Patients Get the Best Treatment and Results for Their Specific Type of Myeloma

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

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

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

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The Right Team

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**

1-888-841-6673

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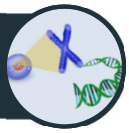
The Right Tests: Common Tests Conducted in Myeloma Patients

Blood tests
Urine tests

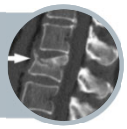
- Confirms the type of myeloma or precursor condition

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

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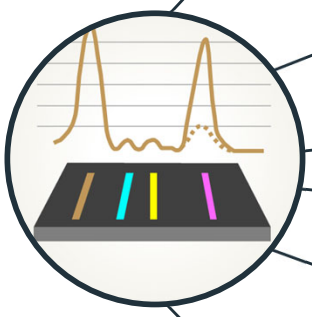
Learn Your Labs!
Blood Tests



- **CBC** – Number of red blood cells, white blood cells, and platelets
- **CMP** – Measure levels of albumin, calcium, LDH, 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 multiple myeloma 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; LDH, lactate dehydrogenase; BUN, blood urea nitrogen

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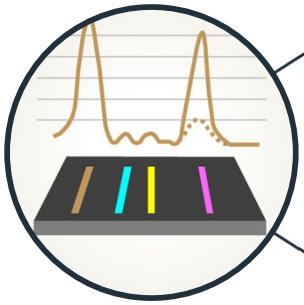
Learn Your Labs!
Urine Tests



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

24-hr urine analysis
- Determine the presence and levels of M protein and Bence Jones protein

UPEP, urine protein electrophoresis

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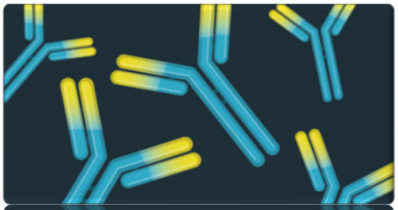
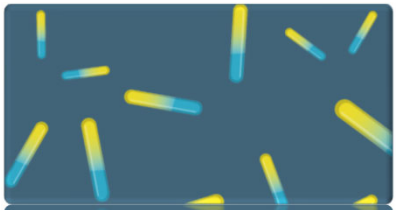
Types of Multiple Myeloma Based on Blood or Urine Tests



Intact M protein
- Named for the type of immunoglobulin and light chain pair; for example, IgG kappa (κ) or IgG lambda (λ)

80%



Light chain only
- Also known as Bence Jones protein
- Renal failure more common in light chain multiple myeloma

20%

Non-secretory
- No M protein present

3%

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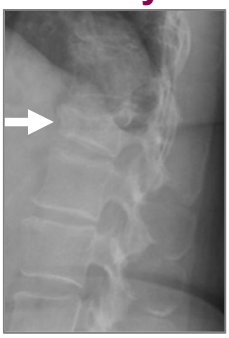
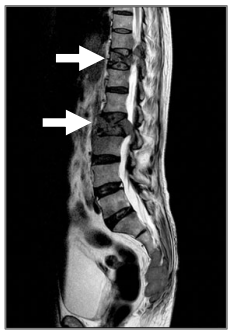
Know Your Imaging Tests!

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

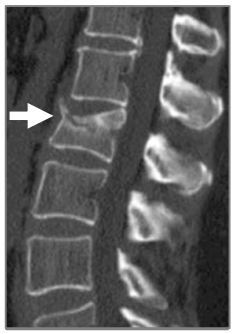
X-ray



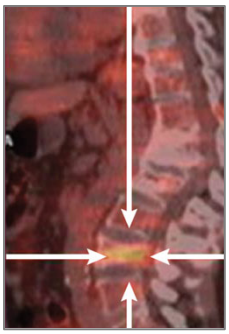
MRI



CT scan



PET scan



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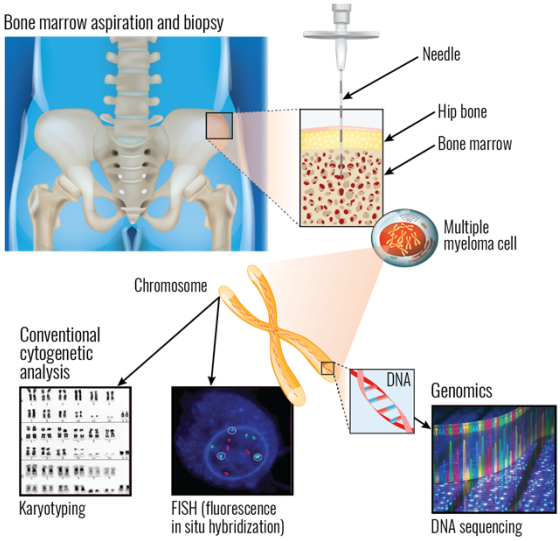
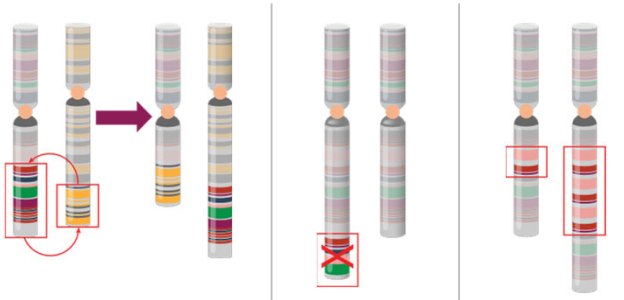
Know Your Bone Marrow Tests!



Types of chromosomal abnormalities



Translocation | Deletion | Gain or Amplification

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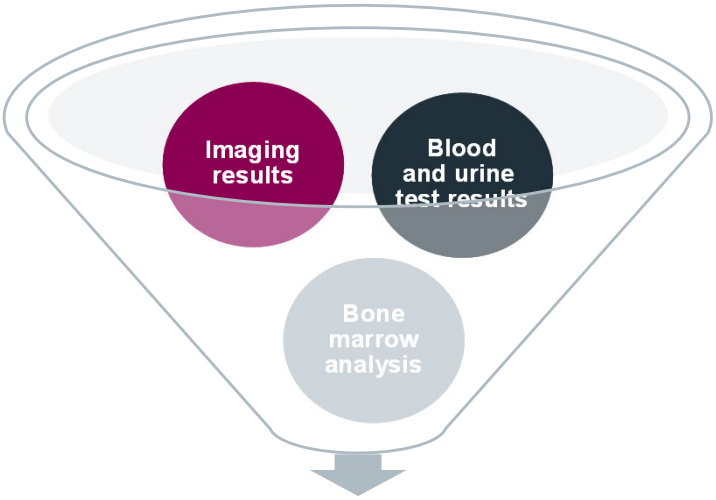
Putting the Results Together



Staging, prognosis, and risk assessment

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Multiple Myeloma Prognosis and Risk

Revised International Staging System (R-ISS)

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

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

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

High risk
- High-risk genetic abnormalities
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p
  - p53 mutation
  - gain 1q
- 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)

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.

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Multiple Myeloma Prognosis and Risk

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

Standard risk

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

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

High risk

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

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

R-ISS, Revised International Staging System; β2M; beta-2 microglobulin; LDH, lactate dehydrogenase; FISH, fluorescence in situ hybridization

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The Right Treatment

- Know the treatment options available to you based on your myeloma subtype at each stage of your disease.
- Be aware of the pros and cons of each option.
- Clearly communicate your treatment goals and concerns to the care team.
- Find clinical trials that are right for you.

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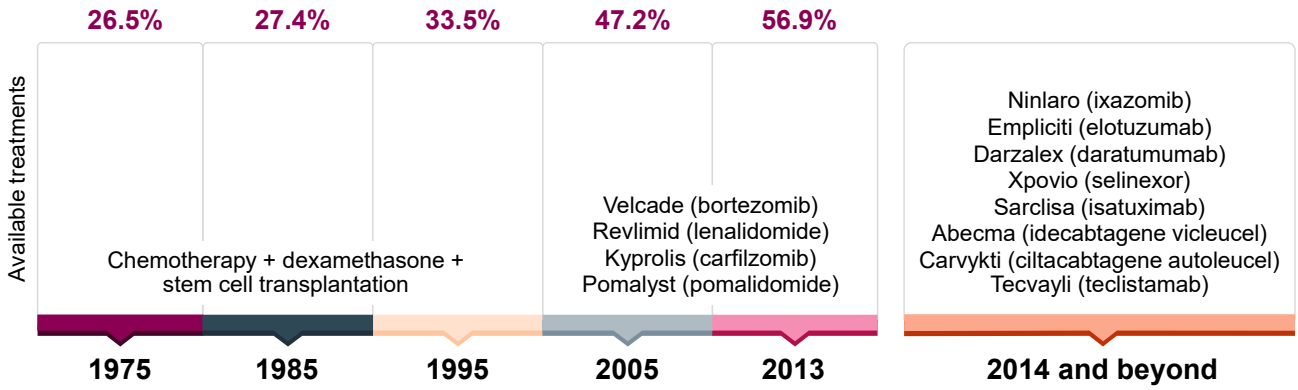
Getting the Right Treatment: Goals of Multiple Myeloma Therapy

- Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible.
- Eliminate myeloma cells from the bone marrow (as measured via minimal residual disease [MRD] testing).
- Improve quality of life with as few treatment side effects as possible.
- Provide the longest possible period of response before first relapse.
- Prolong overall survival.

45

Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

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



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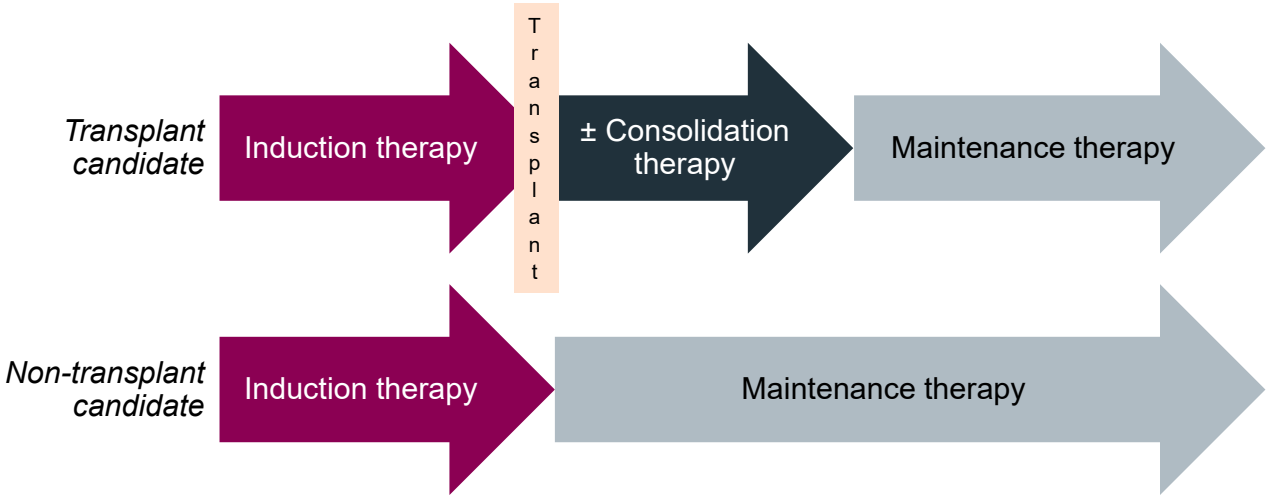
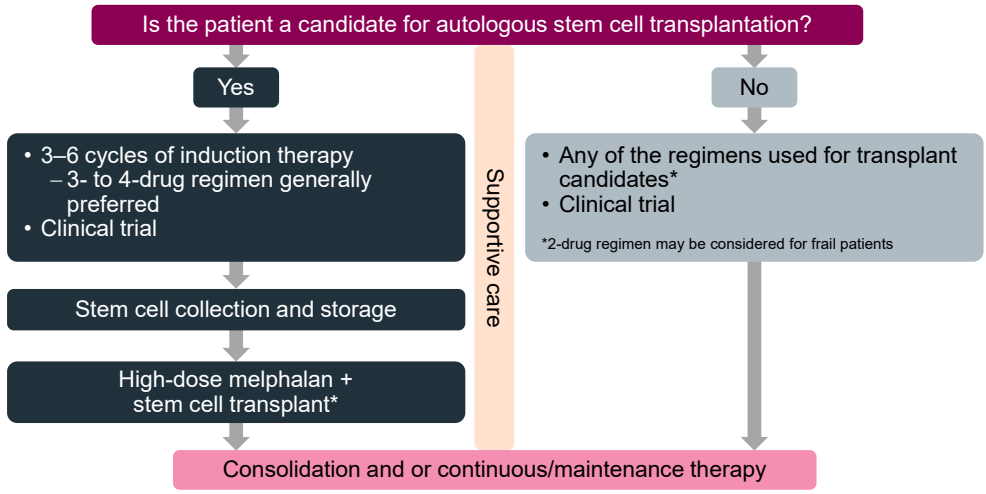
Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma



47

Overview of Treatment Approach for Active Multiple Myeloma



*In certain circumstances, consideration for a tandem transplant

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Induction Therapy Regimens

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

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

National Comprehensive Cancer Network Guidelines Version 3.2023. Multiple Myeloma.

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Continuous or Maintenance Therapy Options

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

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

National Comprehensive Cancer Network Guidelines Version 3.2023. Multiple Myeloma.

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Measuring Response to Therapy

Response type	Response criteria
Sustained **minimal (measurable) residual disease** (MRD)-negative	• MRD negativity in the bone marrow and by imaging—confirmed minimum of 1 year apart
MRD negative	• Absence of clonal plasma cells in bone marrow samples by one of two methodologies: ○ **Next-generation flow (NGF)** (for example, flow MRD negative), or ○ **Next-generation sequencing (NGS)** (for example, sequencing MRD negative) • MRD negativity as defined by NGF or NGS plus disappearance of every area of lesions found at baseline found by **positron emission tomography (PET)/computed tomography (CT)** imaging (for example, imaging plus MRD negative)
Stringent complete response (sCR)	• A CR plus normal Freelite and absence of clonal cells in bone marrow by immunohistochemistry
Complete response (CR)	• Negative immunofixation on serum and urine • Disappearance of any soft tissue plasmacytomas • <5% plasma cells in bone marrow
Very good partial response (VGPR)	• Serum and urine M protein detectable by immunofixation (but not on electrophoresis), or • ≥90% reduction in serum M protein plus urine M protein level to <100 mg per 24 h
Partial response (PR)	• ≥50% reduction in serum M protein plus urine M protein level to <200 mg per 24 h (or reduction in 24-hour urinary M protein by ≥90%)
Minimal response (MR)	• ≥25% but ≤49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89%
Stable disease (SD)	• Does not meet criteria for response or progressive disease
Progressive disease (PD)	• An increase of 25% in M protein • An increase of 10% in bone marrow plasma cells

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

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Where is the myeloma field going?

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

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Summary

- Multiple myeloma is a rare blood cancer that can negatively affect the bones, kidneys, and the bone marrow, leading to lowered blood counts.
- The prognosis of multiple myeloma depends on the genetic makeup of myeloma cell chromosomes; R-ISS is used for staging in multiple myeloma.
- Survival rates are improving because of new drugs and new combinations of drugs.
- The treatment paradigm will continue to change with the approval of additional novel agents.
- Knowledge is power: right team, right test, right treatment.

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

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

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

Faith E. Davies, MBBCh, MD
Perlmutter Cancer Center at New York University Langone Health
NYU Grossman School of Medicine
New York, New York

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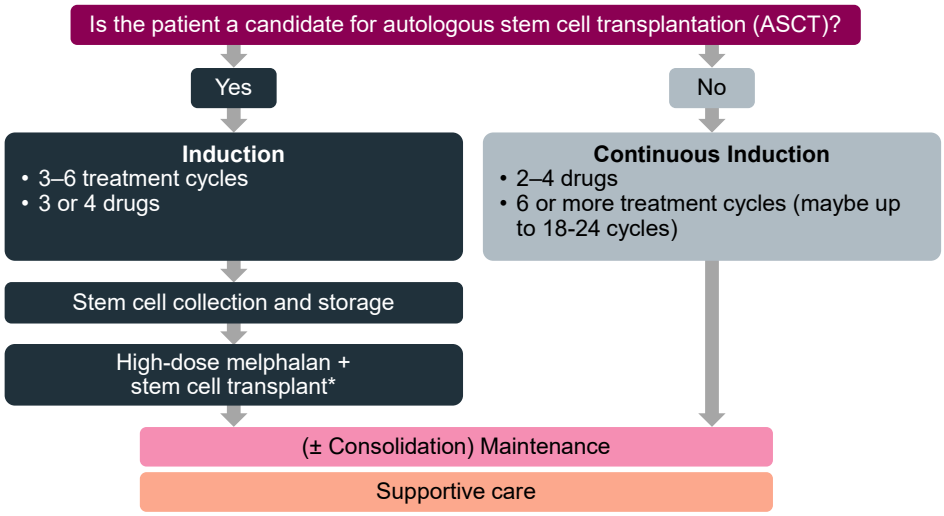
Overview of Treatment Approach for Active Multiple Myeloma



*In certain circumstances, consideration for a tandem transplant

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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.

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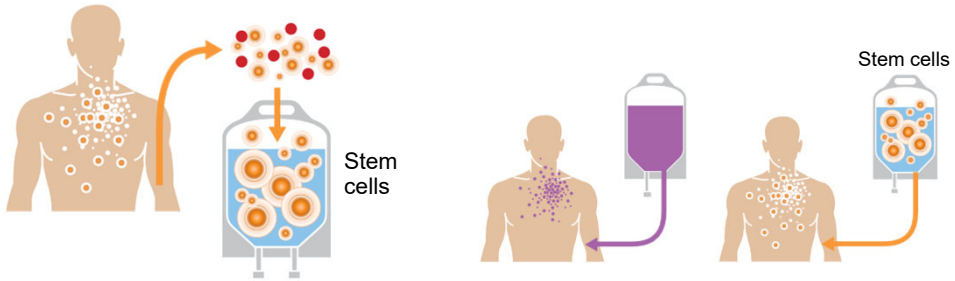
Autologous Stem Cell Transplantation



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

-2 to -3 weeks*

~3 to 6 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.

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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 cells 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	

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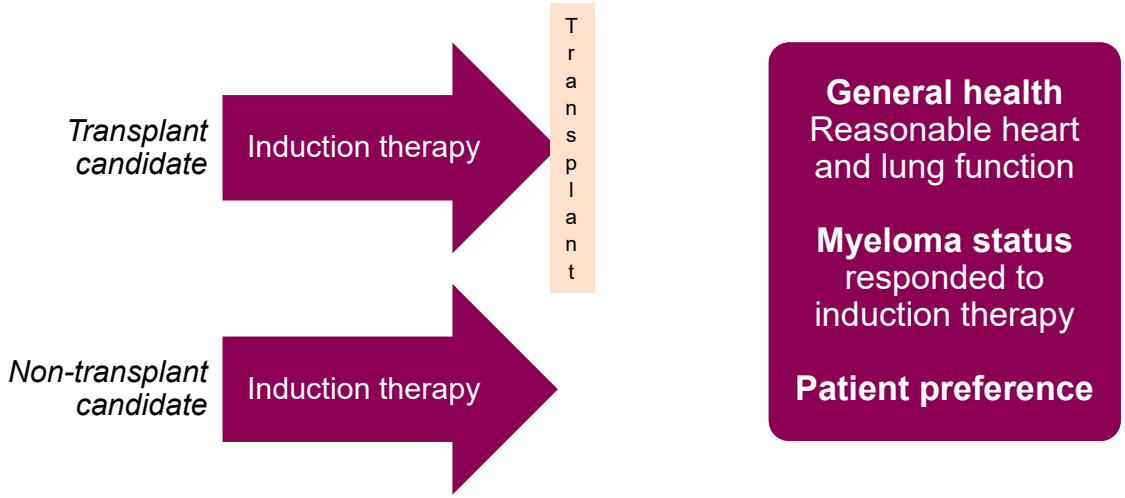
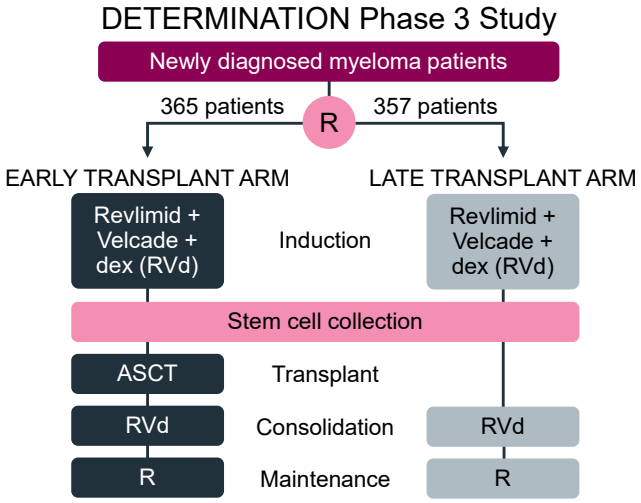
How do we decide who is appropriate for a transplant?



60

Is transplant still required in newly diagnosed myeloma



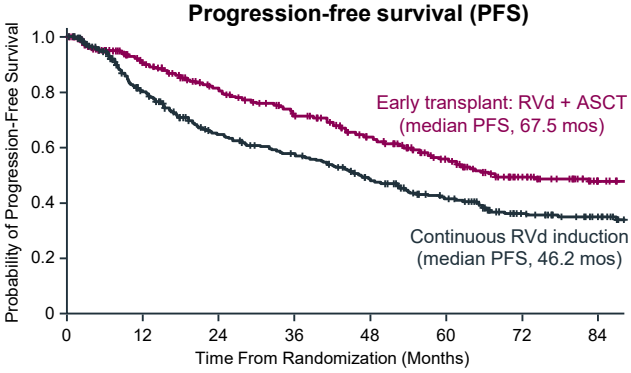
Q: Should I get a transplant after induction OR wait until relapse?

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

61

Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Survival Analysis

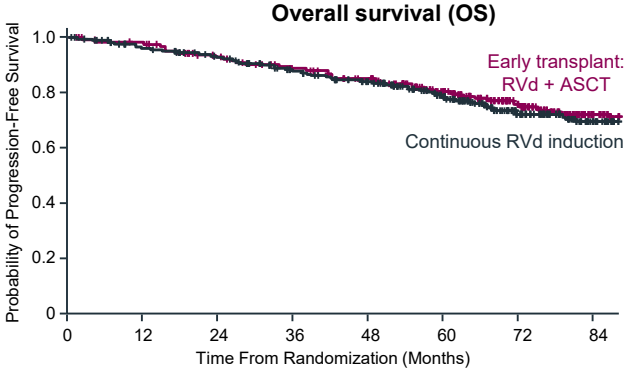
Progression-free survival (PFS)



PFS for early transplant: approximately 5.5 years
PFS for continuous induction: approximately 4 years

Transplant extended time to progression by 20 months

Overall survival (OS)



Length of overall survival: no difference.

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

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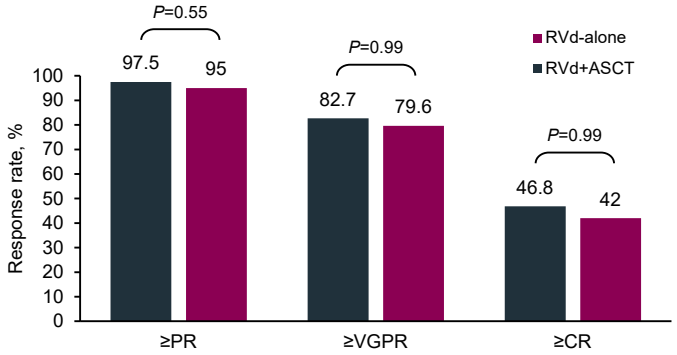
Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Best Response to Treatment and Duration of Response



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

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

63

Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Side Effects

Side effect, %	RVd alone (N=357)	RVd + ASCT (N=365)
Any	78.2	94.2
Fatal side effects	0.3	1.6*
Low blood counts	60.5	89.9
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
Fever	2.0	5.2
Pneumonia	5.0	9.0
Diarrhea	3.9	4.9
Nausea	0.6	6.6
Mouth sores	0	5.2
Fatigue	2.8	6.0
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*. 2022;387:132.

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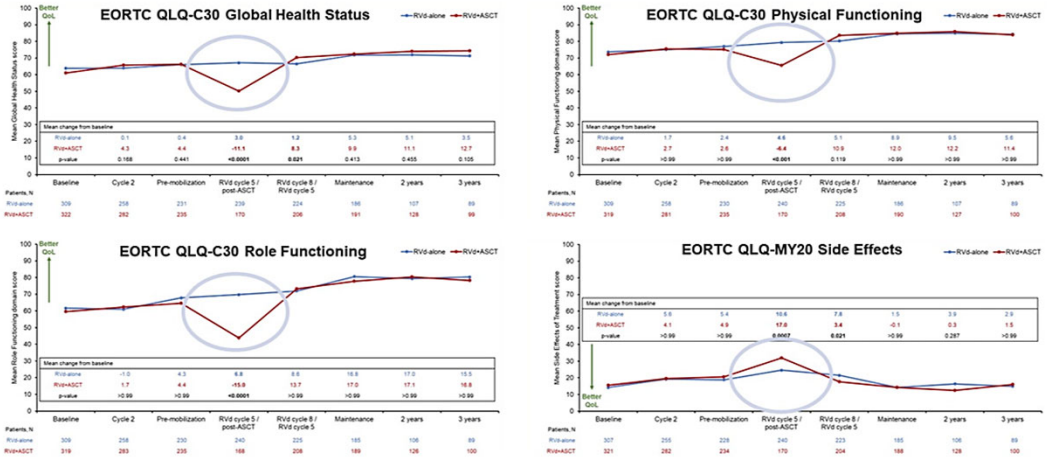
Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Quality of Life

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.

65

Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: 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.* 2022;387:132.

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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

No ASCT up front
- PFS may be shorter, but currently appears OS is the same
- Less 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

No ASCT up front
- Need more cycles of induction
- May need next treatment sooner, including (late) transplant
- Not all patients relapsing are able to undergo salvage ASCT

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Early vs Late ASCT Summary

- ASCT remains the standard of care for frontline therapy of myeloma.
- ASCT safety has been established and it induces long PFS.
- 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 to induction therapy may have a long PFS. Studies are ongoing to determine whether these patients require ASCT.

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What is maintenance therapy?

- A prolonged, and often low-dose, less intensive 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

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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

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Maintenance Therapy

The preferred maintenance therapy following transplant is Revlimid (lenalidomide).

Other maintenance options are Velcade (bortezomib) or Darzalex (daratumumab) (or Ninlaro [ixazomib]).

In certain high-risk cases, maintenance therapy may include Revlimid plus Velcade or Kyprolis (carfilzomib), with or without dexamethasone.

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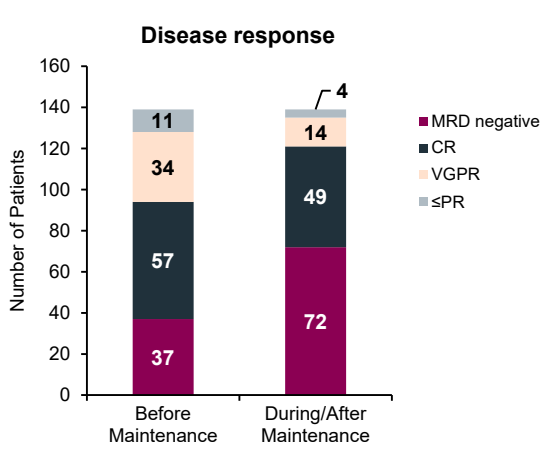
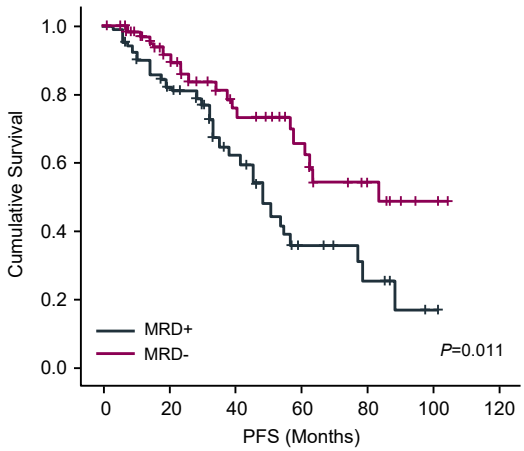
Revlimid Maintenance Therapy: Improves Depth of Response





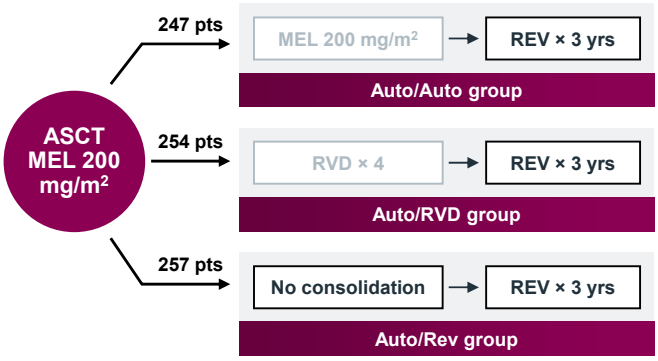
At maximal response during or after maintenance treatment with Revlimid

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

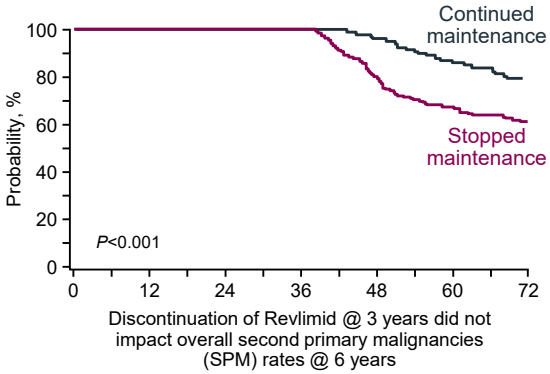
72

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.

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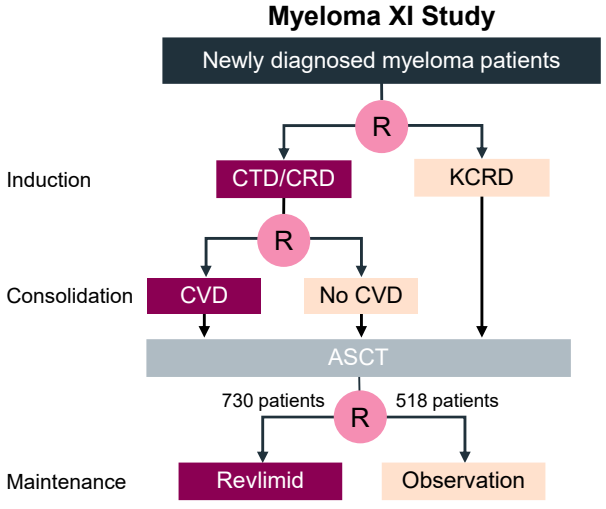
Maintenance Duration



Median PFS (mos)	At time of randomization to maintenance therapy (median follow up 44.7 mos)
	All patients*
Revlimid	64
Observation	32
Hazard ratio	0.52
P Value	<0.001

*PFS benefit across all patient subgroups on Revlimid maintenance therapy: standard risk; molecular high risk which included the presence of del(17p), gain(1q), t(4;14), t(14;16), or t(14;20); MRD positive; and MRD negative.

More evidence for the benefit of longer duration of Revlimid maintenance in patients who are MRD positive than MRD negative. And evidence of ongoing benefit beyond 2–3 years for patients with both standard- and high-risk disease.

Pawlyn C et al. *Blood*. 2022;140. Abstract 570.

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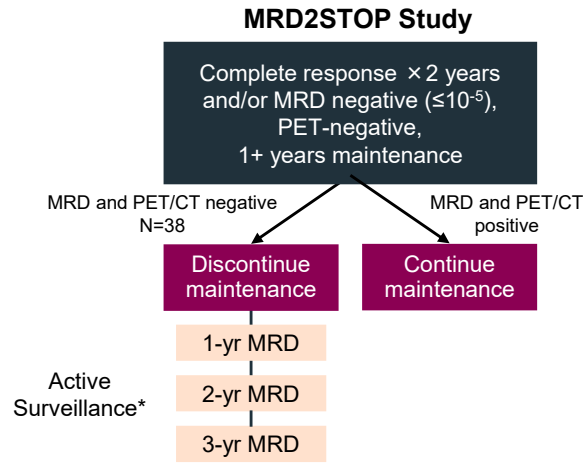
Using MRD Negativity to Guide Discontinuation of Maintenance Therapy



*MRD assessment performed with PET, flow cytometry (10^{-5}), next-generation sequencing (10^{-6}), and CD138-selected next-generation sequencing (10^{-7})

Derman BA et al. *Blood*. 2022;140. Abstract 870.

- 89% remain on study (5% with PD, 6% withdrew).
- MRD resurgence occurred in 13% of patients (2 patients had resurgence of M protein and disease progression).
- MRD negativity (at 10^{-6} and 10^{-7}) is sustained even after discontinuation of maintenance therapy.

MRD-guided discontinuation of maintenance may carry significant cost savings.

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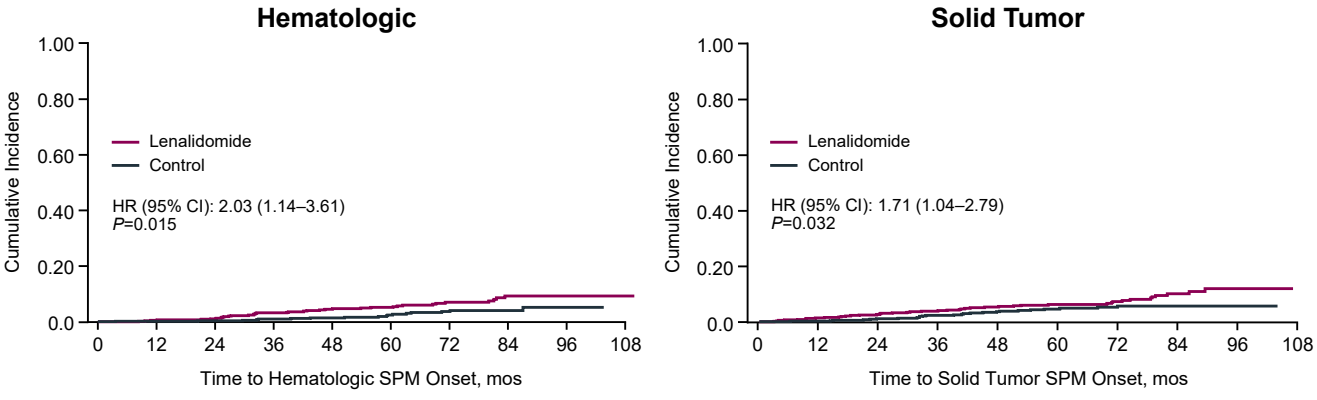
Revlimid Maintenance: Cumulative Incidence of Second Primary Malignancies



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

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Maintenance Therapy Summary

- The body of evidence from phase 3 trials indicates that maintenance therapy improves PFS and likely OS.
- 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 are not yet FDA-approved for use as maintenance. Several clinical trials are under way.
- When you are in remission and receiving maintenance (or being observed off treatment), it is important to continue your regular health checks (colonoscopy, breast screening, PSA, mole checks, etc).

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Goals of Multiple Myeloma Therapy

- Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible.
- Eliminate myeloma cells from the bone marrow (as measured via minimal residual disease [MRD] testing).
- Improve quality of life with as few treatment side effects as possible.
- Provide the longest possible period of response before first relapse.
- Prolong overall survival.

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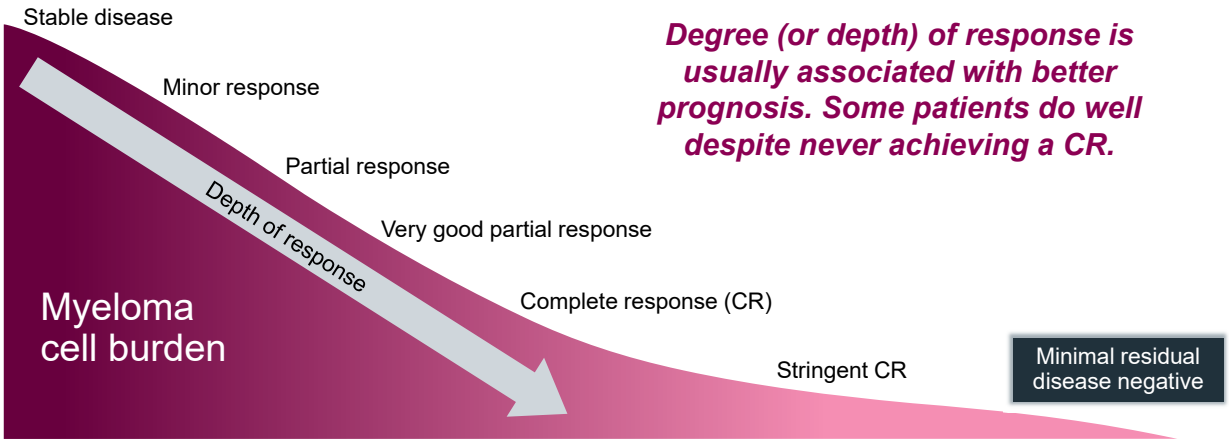
Measuring Response to Therapy



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 multiple myeloma patients.

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

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

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Relapsed/Refractory Multiple Myeloma

Sham Mailankody, MBBS
Memorial Sloan Kettering Cancer Center
New York, New York

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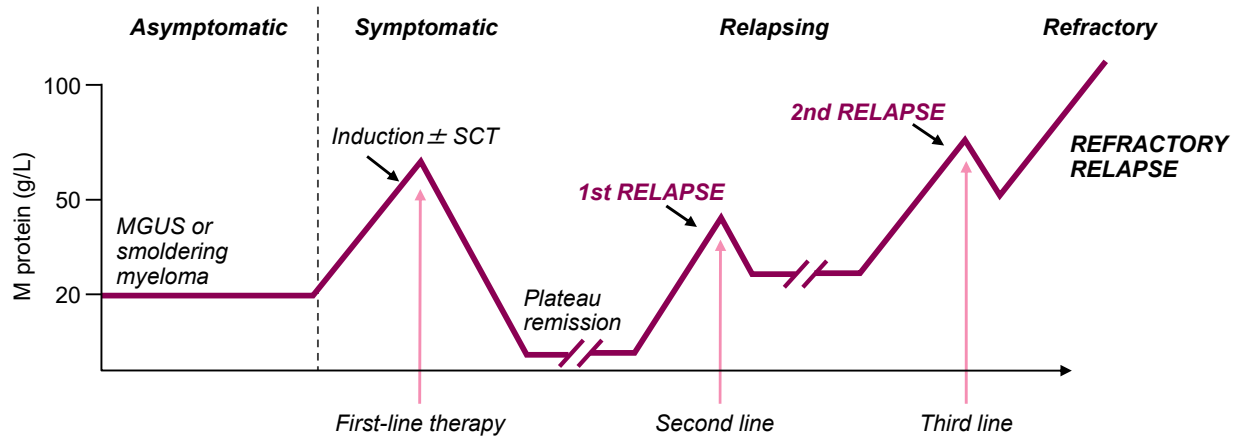
Multiple Myeloma Is a Marathon, Not a Sprint



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

82

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

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Biochemical Relapse or Clinical Relapse

Biochemical

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

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

Clinical

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

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

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Choosing Therapy for First or Second Relapse

Choices are broadest and guided by

- Disease biology
- Nature of relapse
- Patient preference

Factors to consider

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

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Options for Relapsed/Refractory Disease Continue to Increase

IMiDs	Proteasome inhibitors	Chemotherapy anthracyclines	Chemotherapy alkylators	Steroids	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!

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Three Drugs Withdrawn From US Market
What happened?

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

Withdrawn 2021

Farydak (panobinostat)

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

Pepaxto (melflufen)

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

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

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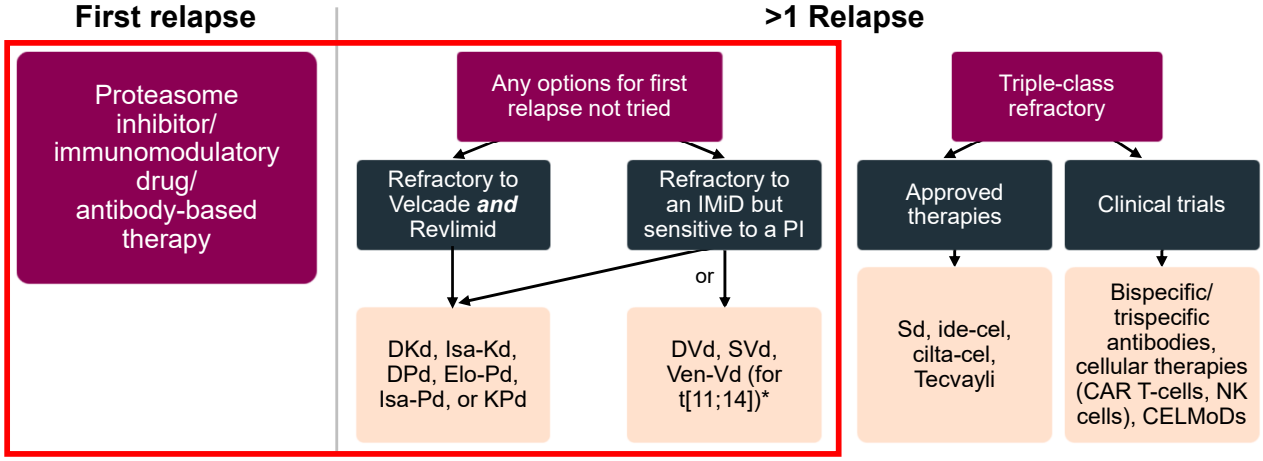
Treatment Approach



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

*Not yet approved for use in myeloma patients.

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Triplet Regimens for Early Relapse

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

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

IV, intravenous; SC, subcutaneous

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Currently Available Agents for One to Three Prior Lines of Therapy

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

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

IV, intravenous; SC, subcutaneous

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Monoclonal Antibody–Based Regimens for Early Relapse: Darzalex

	POLLUX	CASTOR	CANDOR	APOLLO
Regimens compared	• Darzalex-Revlimid-dex (DRd) vs Rd	• Darzalex-Velcade-dex (DVd) vs Vd	• Darzalex-Kyprolis-dex (DKd) vs Kd	• Darzalex-Pomalyst-dex (DPd) vs Pd
Median PFS favored	• DRd: 45 vs 18 months	• DVd: 17 vs 7 months	• DKd: 29 vs 15 months	• DPd: 12 vs 7 months
Clinical considerations	• Consider for relapses from non-Revlimid–based 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	• Consider in patients who are double-refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro) • Severe low white blood cell counts

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

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

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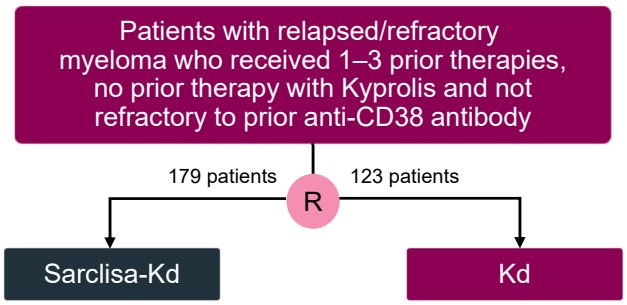
Update From the 2022 American Society of Hematology (ASH) Meeting
Sarclisa After Early or Late Relapse

IKEMA Study



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

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

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

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

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

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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 PFS 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 nausea, vomiting, weight loss, low platelet counts and fatigue with triplet, but less neuropathy than the Vd

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Important Considerations for Use of Monoclonal Antibodies

Darzalex

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

Empliciti

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

Sarclisa

- **Infusion reactions**
- Risk of **shingles**
  - Use appropriate vaccination
- Increased risk of **hypogammaglobulinemia** and upper respiratory infections

SC, subcutaneous; IVIG, intravenous immunoglobulin

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Important Considerations for Use of Proteasome Inhibitors

Velcade

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

Kyprolis

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

Ninlaro

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

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Important Considerations for Use of Immunomodulatory Drugs

Revlimid*

- **Rash**
  - Consider antihistamines and L-lysine
- **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**
- Dose adjustment for patients on hemodialysis

*Black box warning

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Important Considerations for Use of XPOVIO

Gastrointestinal

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

Low sodium (hyponatremia)

Maintain fluid intake.
Salt tabs

Fatigue

Stay hydrated and active.

Low blood counts (cytopenias)

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

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

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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

Refractory to an IMiD but sensitive to a PI

or

DKd, Isa-Kd, DPd, Elo-Pd, Isa-Pd, or KPd

DVd, SVd, Ven-Vd (for t[11;14])*

Triple-class refractory

Approved therapies

Clinical trials

Sd, ide-cel, cilta-cel, Tecvayli

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

*Not yet approved for use in myeloma patients.

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Triple-Class Refractory

- 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)

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Currently Available Drugs for Triple-Class Refractory Myeloma

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

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.

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Currently Available Drugs for Triple-Class Refractory Myeloma

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

IMiD, immunomodulatory agent; PI, proteasome inhibitor; mAb, monoclonal antibody
*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
†Black box warning: cytokine release syndrome; neurologic toxicities; Parkinsonism and Guillain-Barré syndrome; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
‡Black box warning: cytokine release syndrome; neurologic toxicities
§Patients are hospitalized for 48 hours after administration of all step-up doses.
Abecma, Carvykti, and Tecvayli are available only through a restricted distribution program.

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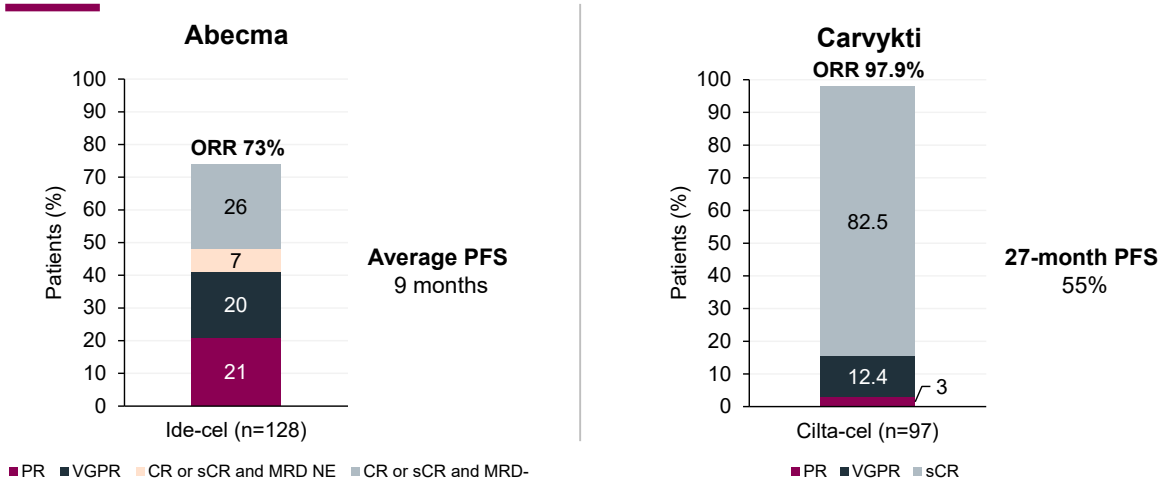
Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma



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

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

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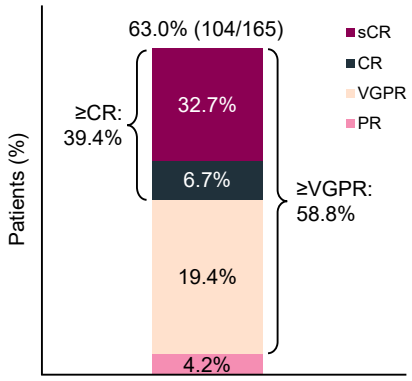
Now Approved: Tecvayli, the First Bispecific Antibody

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

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



Median duration of response 18.4 months

MajesTEC-1 Study. Moreau P et al. *N Engl J Med*. 2022;387:495.

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Emerging Treatment Options

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

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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.

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

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Immunotherapy

Saad Z. Usmani, MD, MBA
Memorial Sloan Kettering Cancer Center
New York, New York

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Why do multiple myeloma cells still grow and survive if the immune system is ready to attack?

- Myeloma cells arise from normal plasma cells and therefore they may not look like invaders.
- Myeloma cells can fool the immune system by disguising themselves in a way that lets them go unnoticed by immune cells.
- They can actively resist the immune system; myeloma cells are able to produce substances that inactivate existing immune cells.

Immunotherapy is a therapeutic strategy that is specifically designed to overcome these defensive tactics used by myeloma cells!

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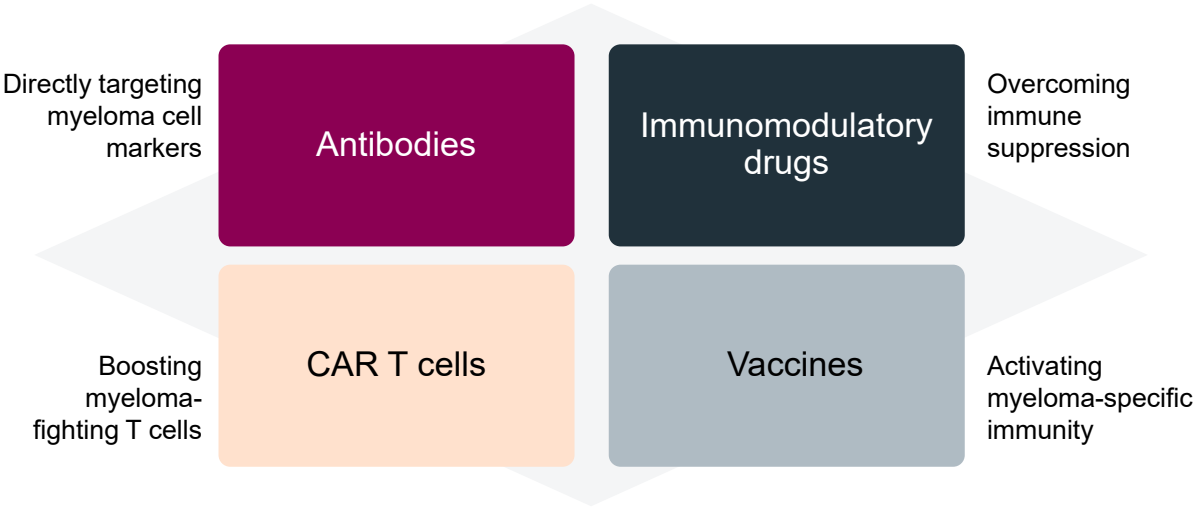
Types of Immunotherapy



Rodriguez-Otero P et al. *Haematologica*. 2017;102:423.

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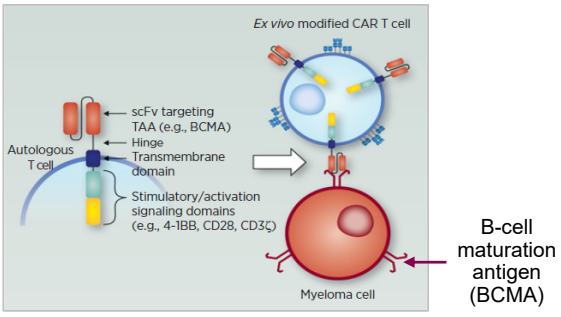
CAR T-Cell Therapy

- Genetically modified T cells designed to recognize specific proteins on myeloma cells
- CAR T cells are activated once in contact with the myeloma cell and can destroy it
- 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



Two CAR T-cell therapies approved!
- Abecma (ide-cel)
- Carvykti (cilta-cel)

CAR, chimeric antigen receptor; BCMA, B-cell maturation antigen
Cohen A et al. *Clin Cancer Res*. 2020;26:1541.

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CAR T-Cell Therapy Patient Journey

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

*Patient must be recovered from any toxicity incurred from bridging therapy before starting lymphodepletion

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CAR T-Cell Therapy Insights

Prognostic value of depth of response following CAR T-cell therapy[1]

- Achieving sustained, undetectable MRD after Abecma is associated with prolonged PFS
- Only MRD status—not complete response (CR) status—predicted early relapse 1 month after Abecma
- Both MRD and CR status at 12 months were required to identify patients with longer PFS

Real-world outcome with Abecma after BCMA-targeted therapy[2]

- 11 US academic centers conducted a retrospective analysis on the real-world outcome for patients treated with Abecma after previously receiving BCMA-targeted therapy
- Prior BCMA-targeted treatment is associated with inferior PFS and a trend toward inferior outcomes for patients receiving Abecma within 6 months of having received prior BCMA-targeted therapy
- Warrants further investigation into the optimal timing of Abecma infusion

Outcomes and options following relapse from CAR T[3]

- A retrospective analysis of 78 patients with RRMM who received BCMA-targeted CAR T-cell therapy
- Patients who had previously been refractory to a specific drug class re-responded after CAR-T relapse
- Median OS after progressing on CAR T was 14.8 months and 18 months for patients who received subsequent BCMA CAR T or BCMA bispecific antibodies within 6 months of progressing on CAR T

Assessment of cytopenias from CAR T[4]

- Retrospective review of data from 90 patients 4 months after CAR T-cell infusion
- Patients with poor hematologic recovery (28%) compared with adequate recovery (72%) were older, more heavily pretreated, and more likely to have received ≥1 ASCT

Abecma in earlier lines of treatment[5]

- KarMMa-2 phase 2 multicenter study of Abecma in 37 patients with RRMM with high-risk disease*
- Results show a benefit to Abecma in earlier line of treatment

*Early relapse after frontline therapy or inadequate response after frontline ASCT

1. Paiva B et al. *Blood*. 2022;140. Abstract 868. **2.** Ferreri CJ et al. *Blood*. 2022;140. Abstract 766. **3.** Reyes KR et al. *Blood*. 2022;140. Abstract 250.
4. Thibaud S et al. *Blood*. 2022;140. Abstract 249. **5.** Usmani S et al. *Blood*. 2022;140. Abstract 361.

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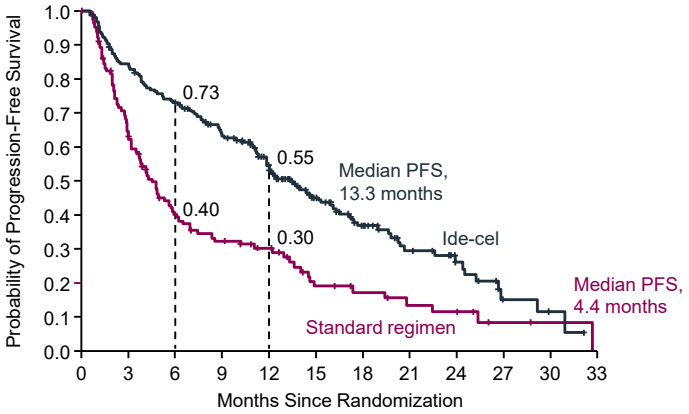
Abecma or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Progression-free survival



P<0.001

Treatment response

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

**P*<0.001

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

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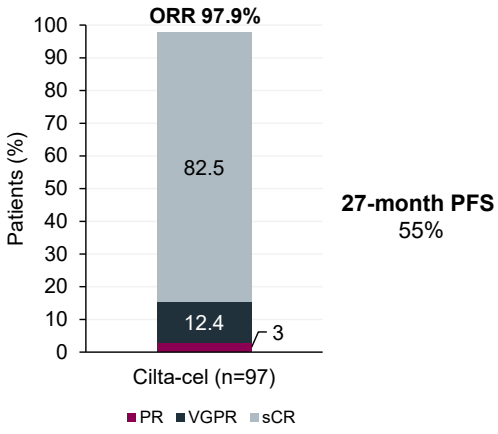
Carvykti in Relapsed and Refractory Multiple Myeloma



27-month PFS
55%

ORR, overall response rate; PR, partial response; VGPR, very good partial response; sCR, stringent complete response; PFS, progression-free survival

CARTITUDE-1 Trial. Berdeja JG et al. *Lancet.* 2021;398:314; Martin T et al. *J Clin Oncol.* June 4, 2022 [Epub ahead of print].

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CAR T: Expected Toxicities

Cytokine release syndrome (CRS)

Neurotoxicity (ICANS)

Cytopenias

Infections

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

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

ICANS, immune effector cell-associated neurotoxicity syndrome

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

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Transplant vs CAR T Cells

Cellular therapies	CAR T-cell therapy	Autologous stem cell transplantation
Patient's cells collected	Yes	Yes
Types of cells collected	T cells*	Stem cells†
Collected cells are genetically engineered in a lab	Yes	No
Patient given chemotherapy before cells are infused back into patient	Yes, lymphodepleting therapy	Yes, melphalan
When in the course of myeloma is this *usually* done?	After multiple relapses	As part of initial treatment
Side effects of treatment	Cytokine release syndrome; confusion	Fatigue, nausea, diarrhea

*An immune cell that is the "business end" of the system, in charge of maintaining order and removing cells.
†Precursor cells that give rise to many types of blood cells. We actually collect CD34+ve cells.

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What's next for CAR T-cell therapy?

	BMS-986354[1]	FasT CAR-T GC012F[2]	BMS-986393[3]	ALLO-715[4]
Features	• Targets BCMA with a shortened manufacturing time through the NEXT-T process	• Targets BCMA *and* CD19 • Manufacturing process that takes as little as 24 hours	• Targets GPRC5D	• An allogeneic anti-BCMA CAR T-cell product
Trial details	• Phase 1 trial of 55 patients with RRMM with a median of 5 prior lines of therapy	• Phase 1 trial of 13 newly diagnosed high-risk myeloma patients ineligible for stem cell transplant	• Phase 1 trial of 17 heavily pretreated patients with RRMM, including those who relapsed from BCMA CAR-T therapy	• Phase 1 trial of 53 patients with RRMM with a median of 5 prior lines of therapy
Clinical results	• CRS occurred in 80% of patients with only 1 patient experiencing ≥G3. • Neurotoxicity occurred in 10.9% of patients (one grade 4) • Overall response rate was 98.1% with 57.4% achieving ≥VGPR (29.6% ≥CR)	• 100% of patients achieved ≥VGPR (69% sCR) • All patients achieved MRD negativity (by EuroFlow) • CRS observed in 23% of patients (all low grade)	• Neutropenia and thrombocytopenia most frequent grade 3/4 adverse events • Additional adverse events include skin- and nail-related; dysgeusia and/or dysphagia; CRS; ICANS • 86% evaluable patients responded including 7 of 11 patients treated with prior BMCA-targeted treatment	• CRS occurred in 52% of patients; neurotoxicity in 11% • Infections occurred in 56% of patients (29% ≥G3) • Overall response rate was between 64% and 80% in the most active cell doses studied

1. Costa LJM et al. *Blood*. 2022;140. Abstract 566. **2.** Du J et al. *Blood*. 2022;140. Abstract 366. **3.** Bal S et al. *Blood*. 2022;140. Abstract 364. Mailankody S et al. *N Engl J Med*. 2022.387:1196. **4.** Mailankody S et al. Presented at ASH 2022. Abstract 651. Mailankody S et al. *Nat Med*. 2023;29:422.

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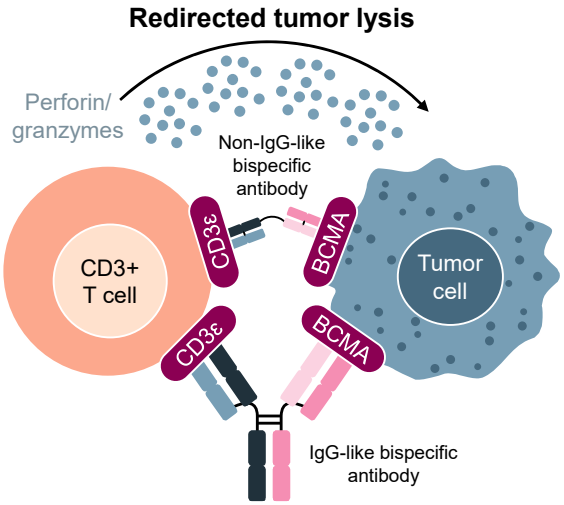
Bispecific Antibodies

- Bispecific antibodies are also referred to as *dual-specific antibodies, bifunctional antibodies,* or *T-cell engaging antibodies*
- Bispecific antibodies can target two cell surface molecules at the same time (one on the myeloma cell and one on a T cell)
- Many different bispecific antibodies are in clinical development; one approved for use in myeloma!
- Availability is off-the-shelf, allowing for immediate treatment



Cohen A et al. *Clin Cancer Res*. 2020;26:1541.
Singh A et al. *Br J Cancer*. 2021;124:1037.

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Bispecific Antibodies Under Investigation

Bispecific antibody	Target (on MM cell × T cell)	Status
Tecvayli (teclistamab)	BCMA × CD3	Approved for use in myeloma patients
Elranatamab	BCMA × CD3	Clinical studies; granted priority review by the FDA
Linvoseltamab	BCMA × CD3	Clinical studies
Alnuctamab	BCMA × CD3	Clinical studies
ABBV-383	BCMA × CD3	Clinical studies
Talquetamab	GPRC5D × CD3	
Forimtamig (RG6234)	GPRC5D × CD3	
Cevostamab	FcRH5 × CD3	

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

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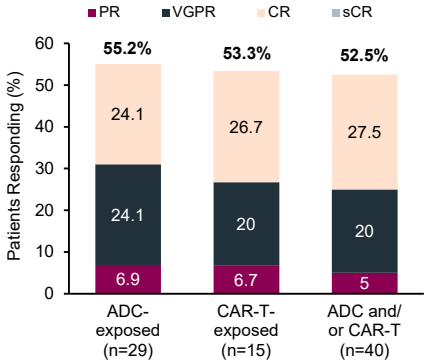
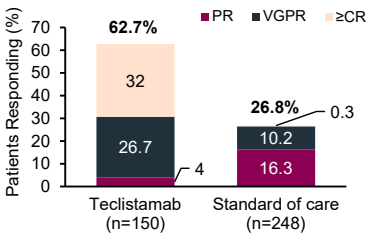
Additional Studies of Tecvayli in Patients With Relapsed/Refractory Myeloma

Teclistamab in patients *with prior* BCMA-targeted treatment (MajesTEC-1 Study)[1]



Teclistamab experience vs real-world clinical practice (LocoMMotion Study)[2]



	Teclistamab	Standard of care
PFS (mos)	10.1	4.3
OS (mos)	18.3	13.0

1. Touzeau C et al. *J Clin Oncol*. 2022;40. Abstract 8013. **2.** van de Donk NWCJ et al. *J Clin Oncol*. 2022;40. Abstract 8016.

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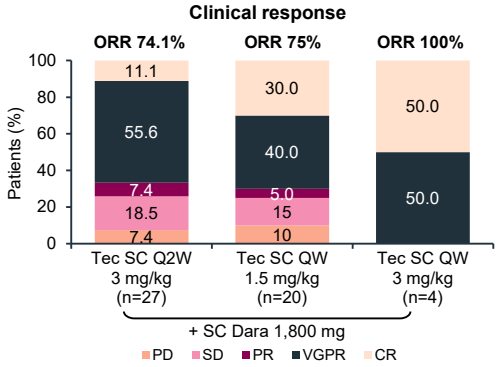
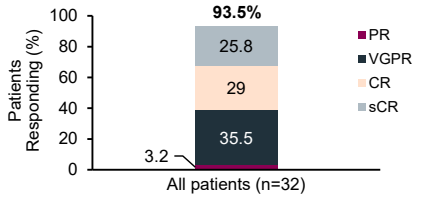
Tecvayli Combinations

Teclistamab + Darzalex in patients with 3 or more prior lines of therapy (TRIMM-2 Study)[1]



Teclistamab + Darzalex + Revlimid in patients with 1–3 prior lines of therapy (MajesTEC-2 Study)[2]



Most frequent non-hematologic adverse events, %	Any grade	Grade 3/4
CRS	81.3	0
Fatigue	46.9	6.3
Infections (≥1)	90.6	37.5

1. Rodriguez-Otero P et al. *HemaSphere*. 2022;6. Abstract S188. **2.** Searl E et al. *Blood*. 2022;140. Abstract 160.

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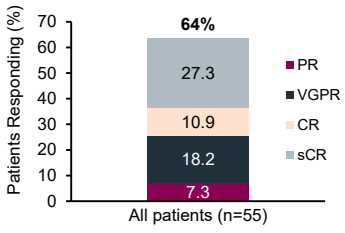
Elranatamab in Patients With Relapsed/Refractory Myeloma

Updated efficacy and safety results with elranatamab (MagnetisMM-1 Study)[1]

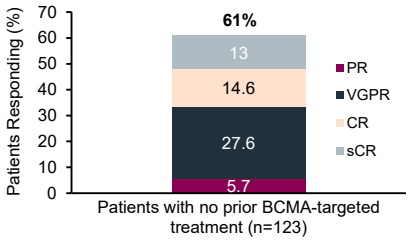
Phase 1 study in RRMM (91% triple-class refractory)



Median duration of response 17.1 months.

Elranatamab in patients with no prior BCMA-directed treatment (MagnetisMM-3 Study)[2]

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



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

The FDA has granted priority review for elranatamab for the treatment of patients with relapsed or refractory multiple myeloma.

IMiD, immunomodulatory drug; PI, proteasome inhibitor

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

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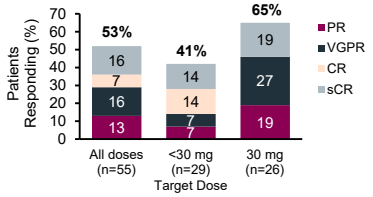
Additional BCMA-Targeted Bispecific Antibodies

Alnuctamab[1]

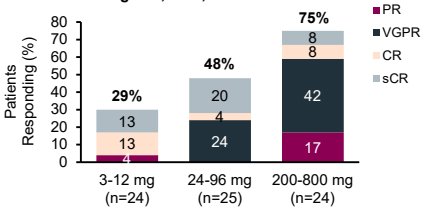
Subcutaneous formulation results



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

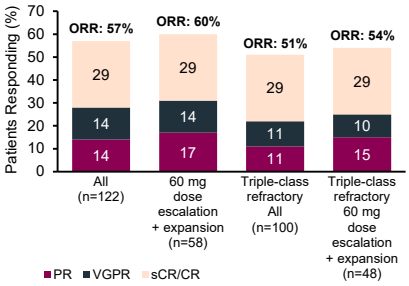
Linvoseltamab[2]

Patients who were refractory or intolerant to 2 or more prior lines of systemic therapy, including a PI, IMiD, and anti-CD38 mAb



Most frequent adverse events, %	Any grade	Grade 3/4
Hematologic		
Anemia	32	23
Neutropenia	23	22
Thrombocytopenia	21	13
Non-hematologic		
CRS	38	0
Pneumonia	23	11

ABBV-383[3]



Cytokine release syndrome, %	60 mg dose escalation + expansion (n=60)	All patients (n=124)
All grades	72	57
Grade ≥3	2	2
Serious	27	18

1. Wong SW et al. *Blood*. 2022;140. Abstract 162. **2.** Zonder J et al. IMS 2022. Abstract OAB-056. **3.** Voorhees P et al. IMS 2022. Abstract OAB-55.

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MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Non-BCMA–Targeted Bispecific Antibodies

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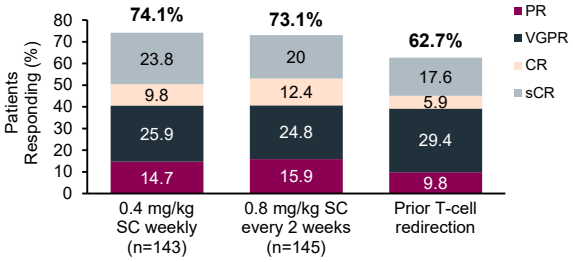
Talquetamab in Patients With Relapsed/Refractory Multiple Myeloma

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

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

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



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

IMiD, immunomodulatory drug; PI, proteasome inhibitor

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

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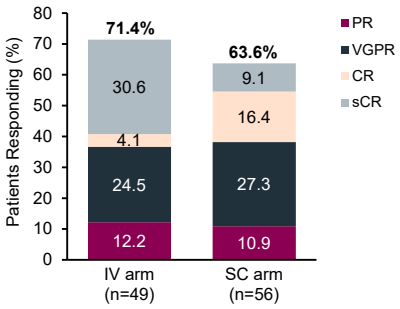
Forimtamig and Cevostamab in Patients With Relapsed/Refractory Multiple Myeloma

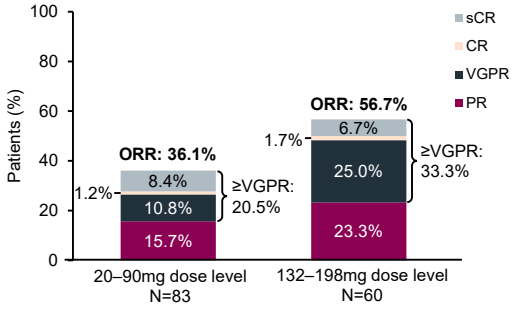
Forimtamig (RG6234)—targets GPRC5D[1]

Phase 1 study of 105 patients



Cevostamab—targets FcRH5[2]

Best response rates in efficacy-evaluable patients by dose level



1. Carlo-Stella C A et al. *Blood*. 2022;140. Abstract 161.
2. Trudel S et al. *Blood*; 138. Abstract 158.

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

Cytokine release syndrome (CRS)

Infections

Cytopenias

Neurotoxicity (ICANS)

Off target effects (with GPRC5D targeted agents)

Cytokeratin changes/rash
Dysgeusia

ICANS, immune effector cell-associated neurotoxicity syndrome

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Bispecific Antibodies Are Associated With an Increased Risk of Infections

A pooled analysis of 1,185 RRMM patients in 11 different clinical trials treated with single agent bispecific antibodies (with no prior use of different bispecifics)

Majority of patients (72%) treated with BCMA-targeted bispecific antibodies

	Patients (%)	
Adverse event	**All grades**	**Grade 3/4**
Neutropenia	38.6	34.8
Infections	50	24.5
CRS	59.6	NR
Pneumonia	NR	10
COVID-19	NR	11.4

Hypogammaglobulinemia occurred in 75.3% of patients with intravenous immunoglobulin used in 48%.

Death was reported in 110 patients of which 28 (25.5%) were reported to be secondary to infections.

Certain precautions should be used when using bispecific antibodies to mitigate the risk and/or identify and treat infections promptly.

NR, not reported

Lancman G et al. *Blood Adv*. March 1, 2023 [Online ahead of print].

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Infection Prevention

Avoid crowds	Ensure handwashing, hygiene	Growth factors	IVIG for hypo-gammaglobulinemia
Immunizations (no live vaccines)	COVID-19 prevention	Zoster and PJP prophylaxis	Consider CMV monitoring

IVIG, intravenous immunoglobulin; PJP, *Pneumocystis jirovecii* pneumonia; CMV, cytomegalovirus

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

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

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Cereblon E3 Ligase Modulators (CELMoDs)

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

- Iberdomide
- Mezigdomide

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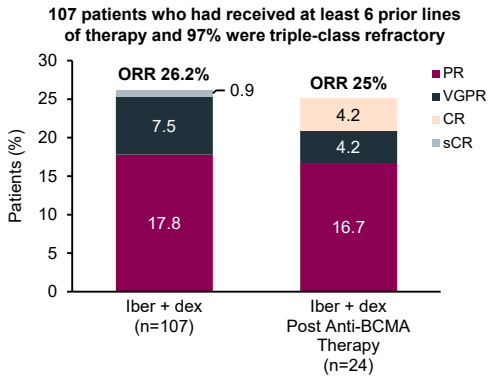
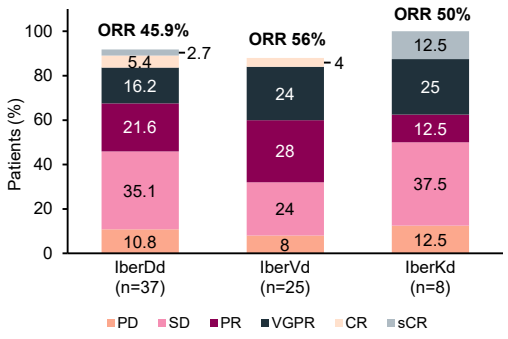
Iberdomide: A Cereblon E3 Ligase Modulator (CELMoD)

Iberdomide in combination with dexamethasone in patients with RRMM[1]



Iberdomide in combination with dex and daratumumab, bortezomib, or carfilzomib in patients with RRMM[2]



1. Lonial S et al. *Blood*. 2021;138. Abstract 162. **2.** Lonial S et al. Presented at the 2021 IMW. Abstract OAB-013.

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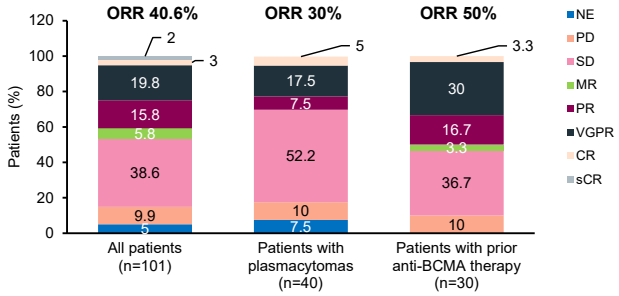
Mezigdomide: A Cereblon E3 Ligase Modulator (CELMoD)

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

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

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



Most frequent hematologic adverse events, %	Grade 3	Grade 4
Neutropenia	21.8	53.5
Anemia	34.7	1.0
Thrombocytopenia	13.9	13.9
Febrile neutropenia	12.9	2.0

Most frequent non-hematologic adverse events, %	Grade 3	Grade 4
Infections	28.7	5.9
Pneumonia	12.9	3.0
COVID-19	6.9	0

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

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Key Points

- CAR T and bispecific antibodies are very active even in heavily pre-treated patients.
- Side effects of CAR T cells and bispecific antibodies include cytokine release syndrome, confusion, and low blood counts, all of which are treatable.
- Abecma and Carvykti are only the first-generation CAR T cells and target the same protein; different CAR Ts and different targets are on the way.
- Bispecific antibodies represent an “off-the-shelf” immunotherapy; Tecvayli was approved in October 2022.
- Several additional bispecific antibodies are under clinical evaluation.
- CELMoDs are emerging as active oral agents, even in patients who have received BCMA directed therapies including CAR-Ts.

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

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Supportive Care

Justina A. Kiernan, MPS, PA-C
Memorial Sloan Kettering Cancer Center
New York, New York

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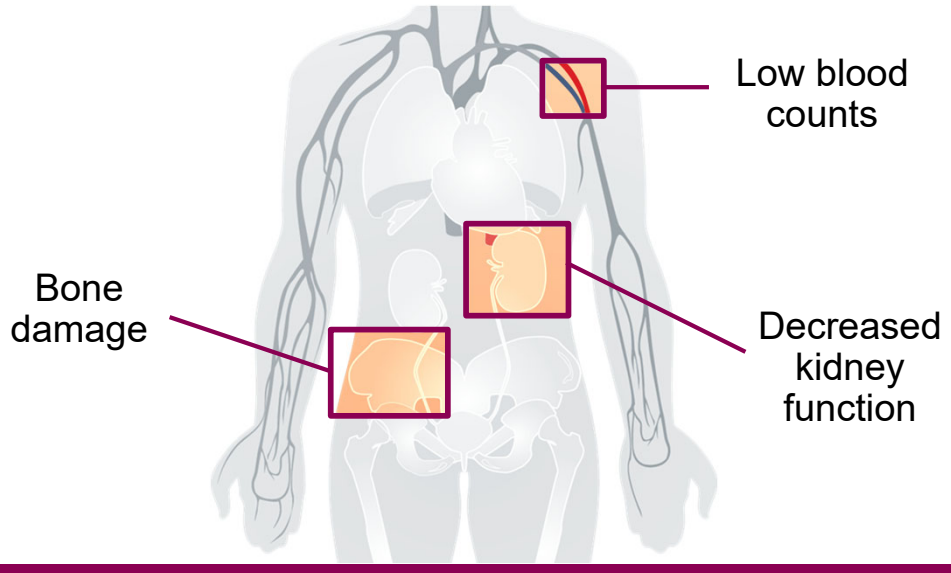
Effects of Myeloma



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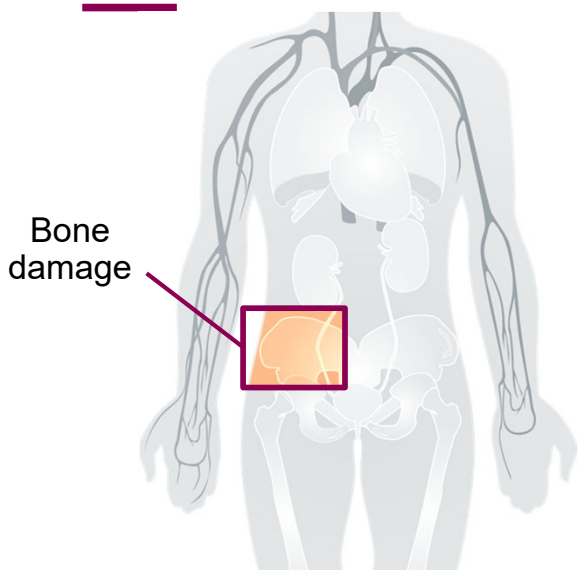
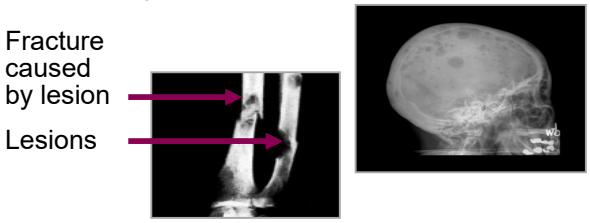
Effects of Myeloma: Bone Disease



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



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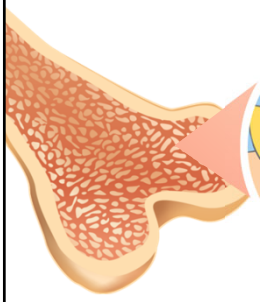
Bone Strengthening Agents for Myeloma Bone Disease



How they work
- Prevent bone disease from getting worse

Benefits
- Decrease pain and reduce skeletal-related fractures

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

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

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

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

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Recommendations for Reducing the Risk of ONJ

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

ONJ, osteonecrosis of the jaw

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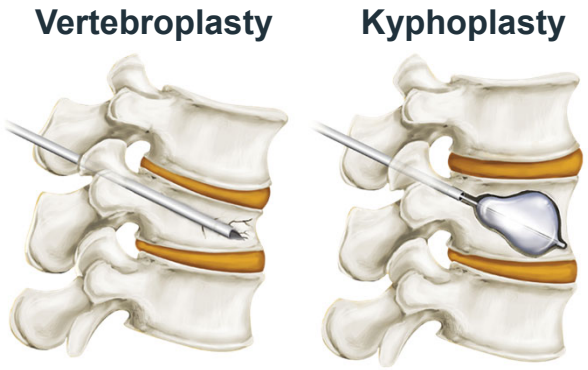
Orthopedic Procedures to Stabilize the Spine

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



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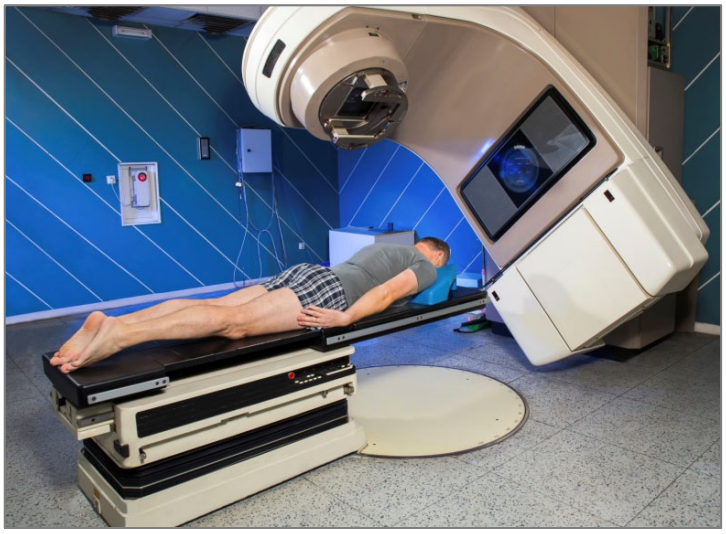
Radiation Therapy for Pain Management



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Pain Management Medications

Acetaminophen (Tylenol)	NSAIDs (nonsteroidal anti-inflammatory drugs)	Opioids	Corticosteroids (dexamethasone, prednisone)	Anti-seizure medications (gabapentin and Lyrica)
Will not hurt your kidneys; high dosage can hurt your liver	Prefer to avoid with multiple myeloma 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	Potential for drowsiness and dizziness

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Effects of Myeloma: Low Blood Counts

Low red blood cells (anemia)

- Symptoms
  - Fatigue; weakness; 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; immune thrombocytopenia; medications

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

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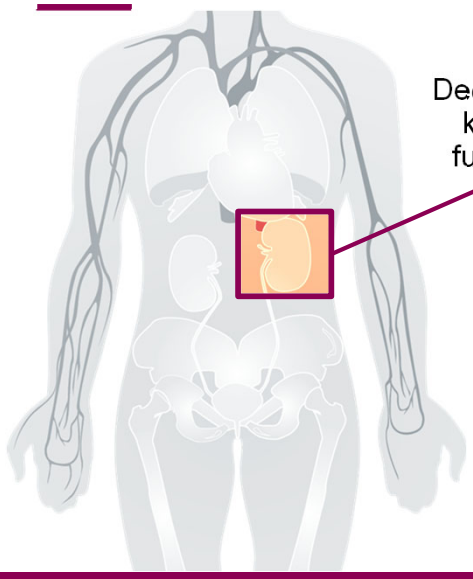
Effects of Myeloma: Decreased Kidney Function



- 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)

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

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Class: Immunomodulatory Drugs Side Effects and Management

Revlimid*

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

Pomalyst*

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

Management

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

*Black box warning.
GI, gastrointestinal

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Class: Proteasome Inhibitors Side Effects and Management

Velcade

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

Kyprolis

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

Ninlaro

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

Management

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

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

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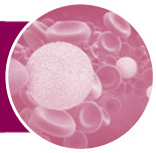
Class: Monoclonal Antibodies Side Effects and Management

Empliciti



- Low blood counts
- Infusion reactions

Darzalex*/ Sarclisa

- Infusion reactions
- Fatigue
- Upper respiratory tract infection

Management

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

*Now approved as subcutaneous injection with fewer side effects.

151

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.

152

Bispecific Antibodies

Tecvayli

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

Management

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

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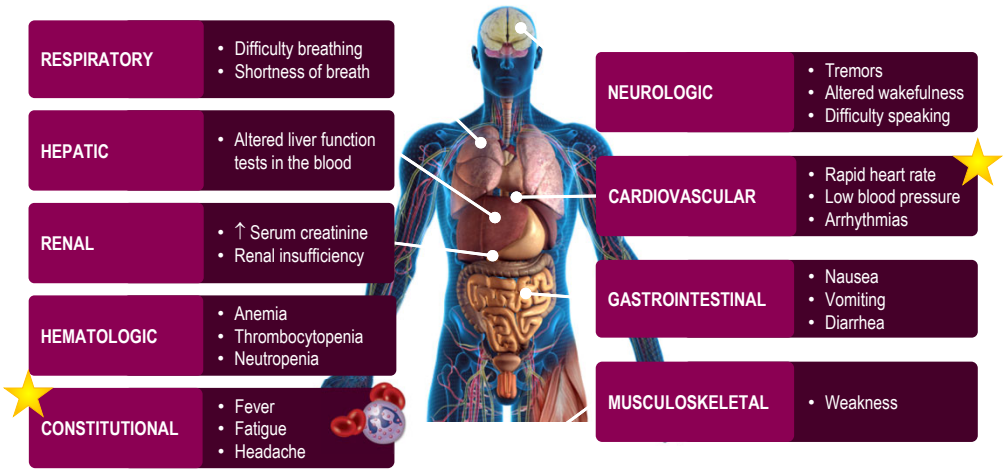
CRS With Bispecifics Severity Is Typically Mild: Early Recognition and Treatment Is Key



Mitigation and monitoring for 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; O2, 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 A et al. *J Immunother Cancer*. 2018;6:56. Lee DW et al. *Biol Blood Marrow Transplant*. 2019;25:625.

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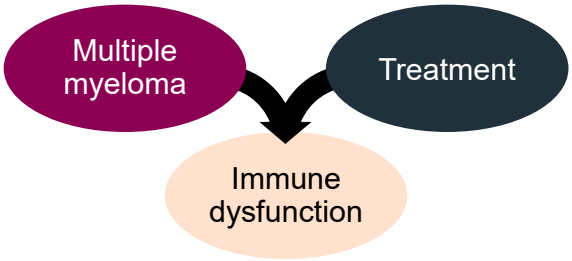
Infection Can Be Serious for Patients With Myeloma



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

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

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

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Infection Prevention

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

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Side Effects of Steroids (Dexamethasone)

Insomnia

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

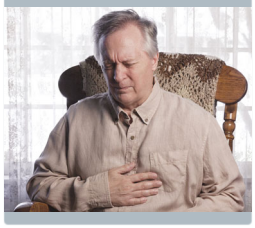
Fluid retention

- 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

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Symptom Management
Constipation

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

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Symptom Management
Acid Reflux/Heartburn

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

A few ways to treat

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

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Symptom Management
Insomnia

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

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Marijuana

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

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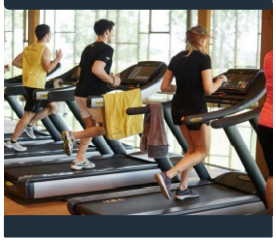
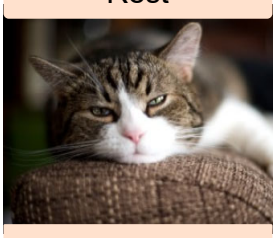
Daily Living

Proper nutrition

Exercise



Rest



Social contacts

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Taking Care of Yourself

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

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

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Patient Experience

Gail Goode

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Minimal Residual Disease

Neha Korde, MD
Memorial Sloan Kettering Cancer Center
New York, New York

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Goals of Multiple Myeloma Therapy

- Reduce the amount of M protein (as measured by serum protein electrophoresis) or light chains (as measured via the free light chain test) to the lowest level possible.
- **Eliminate myeloma cells from the bone marrow (as measured via minimal residual disease [MRD] testing).**
- Improve quality of life with as few treatment side effects as possible.
- Provide the longest possible period of response before first relapse.
- Prolong overall survival.

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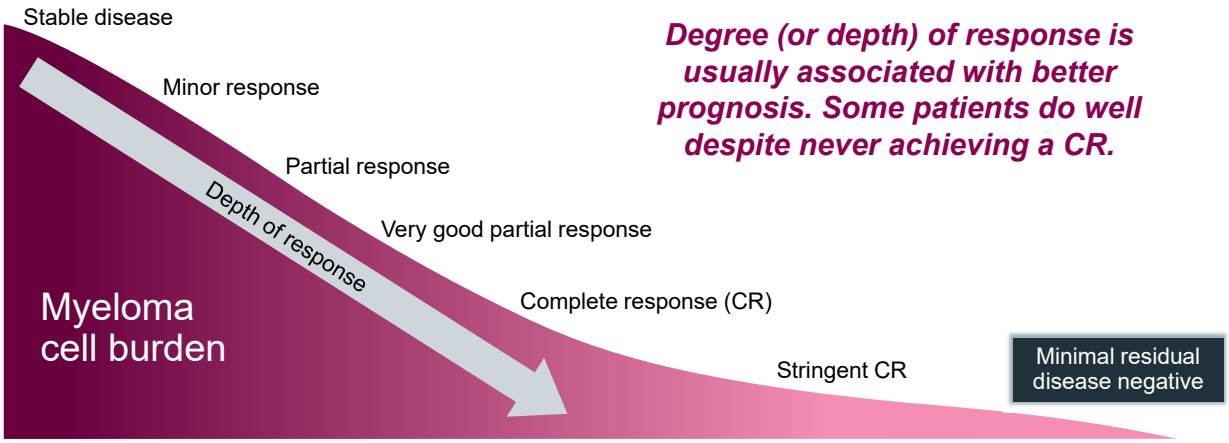
Measuring Response to Therapy



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 multiple myeloma patients.

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

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What is MRD?

- The presence of small amounts of myeloma cells left in the bone marrow following the achievement of a CR after treatment
- MRD tests can detect at least 1 cell in 100,000 or better. Ideally, we want to use more sensitive assays that can find 1 cell in a million

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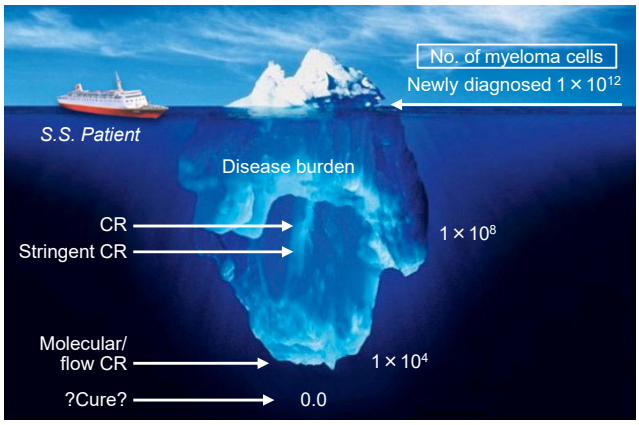
Why do we need to measure MRD?

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



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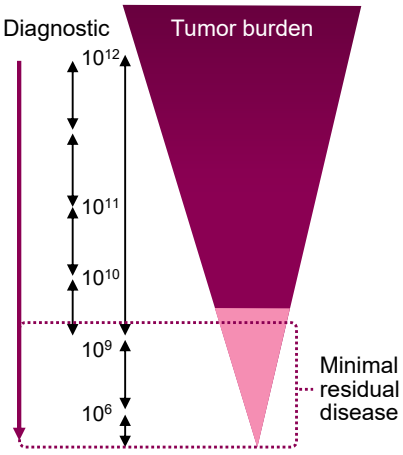
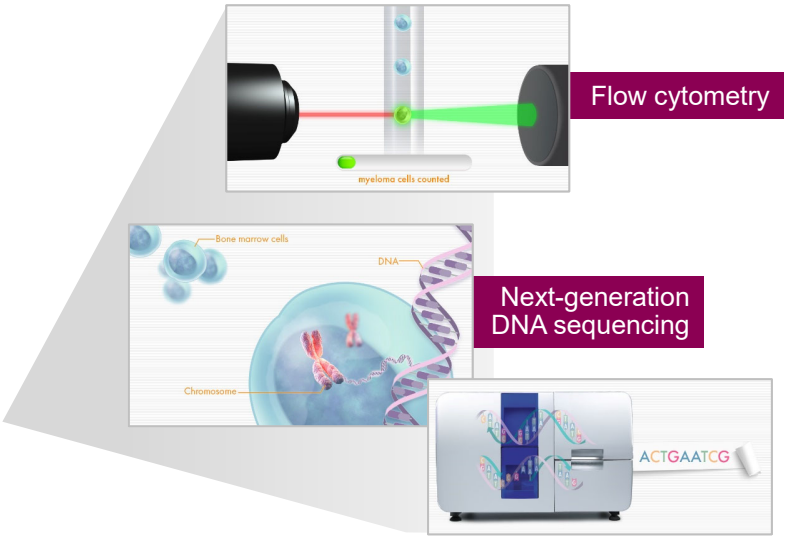
How is MRD measured?





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Key Terms for MRD

MRD positive or MRD positivity (MRD+)

- Myeloma cells are still detectable

MRD negative or MRD negativity (MRD-)

- Myeloma cells are not detected

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

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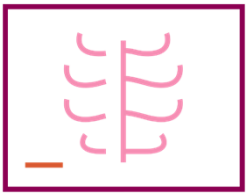
Comprehensive Response Assessment

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



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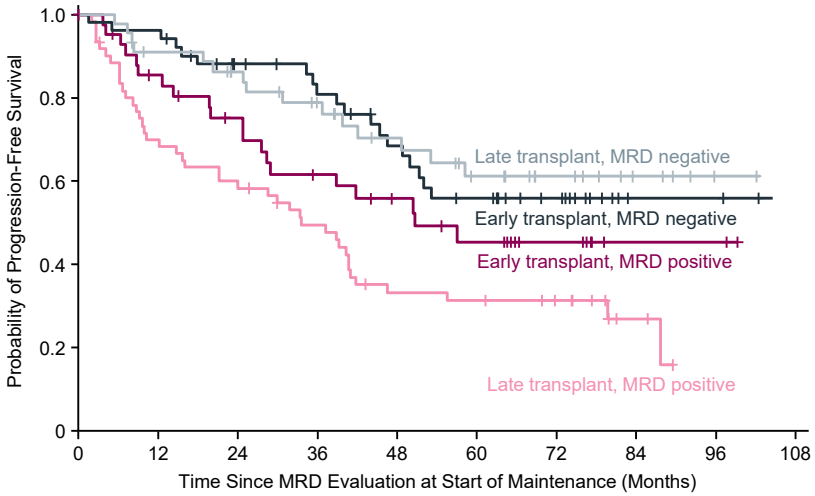
Why is it important to achieve MRD negativity?

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.

175

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

Key points from 14 studies analyzed*

Patients who are MRD negative live longer, and their response lasts longer before they relapse.

*5 trials included stem cell transplantation/10 studies included maintenance
Munshi NC et al. *JAMA Oncol*. 2017;3:28.

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MRD Negativity Achieved by Various Regimens

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

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

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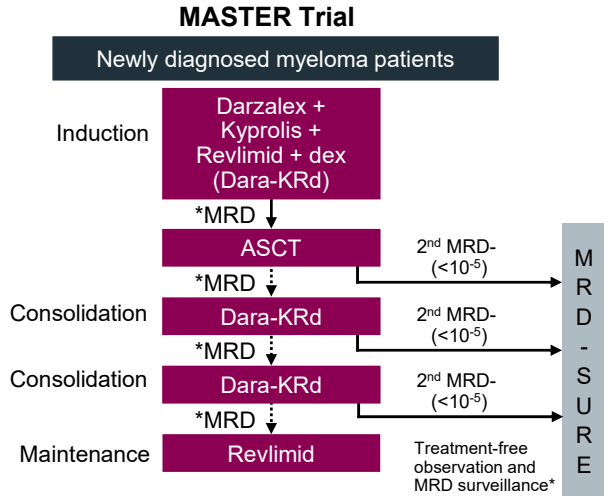
MRD Response-Adapted Consolidation and Treatment Cessation



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

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

*24 and 72 weeks after completion of therapy (by next-generation sequencing)

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

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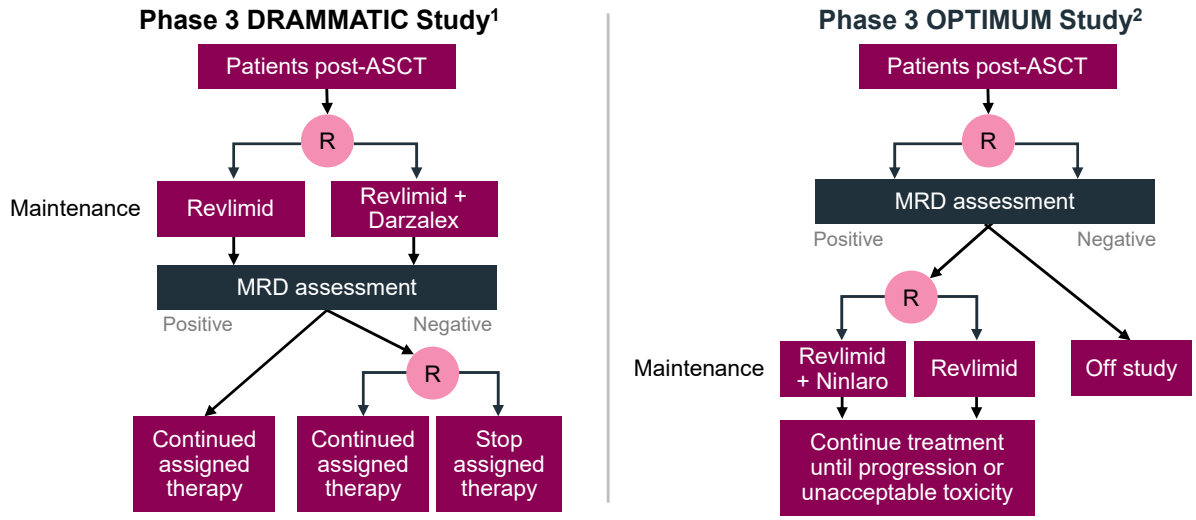
Ongoing Studies Using MRD Results to Direct Therapy



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

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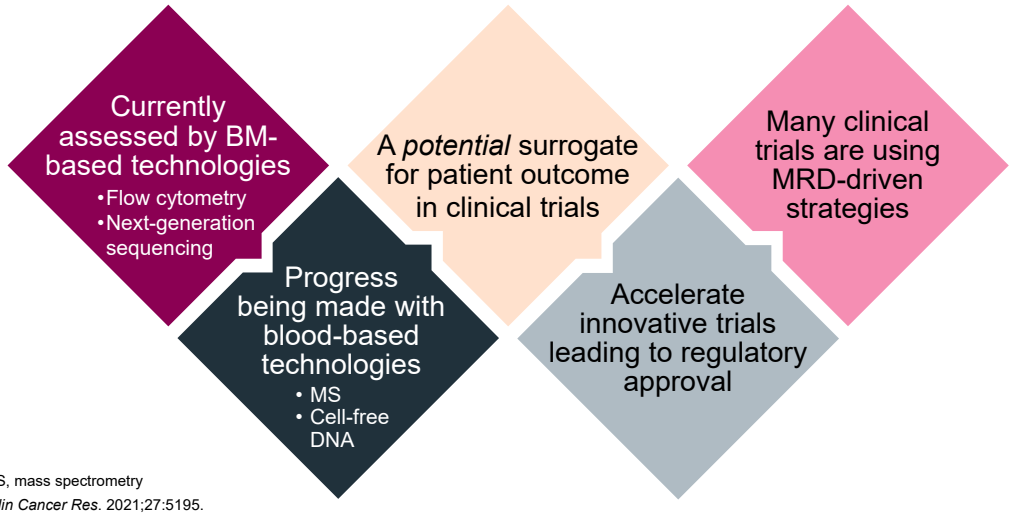
MRD Is Important for Clinical Care and New Drug Registration



BM, bone marrow; MS, mass spectrometry

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

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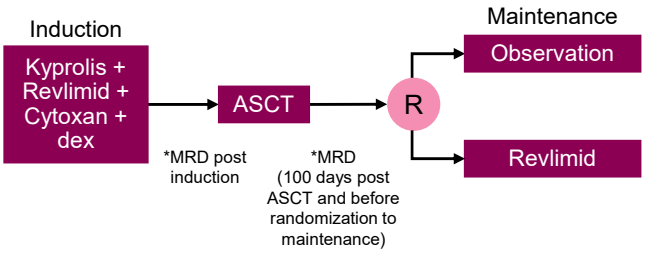
Potential Blood-Based MRD Testing: Mass Spectrometry



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

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

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

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

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

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

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

Giles HV et al. *Blood*. 2021;138. Abstract 820.

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Key Points

- 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 PFS and OS 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.

MRD, minimal residual disease; NGF, next-generation flow cytometry; NGS, next-generation sequencing

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

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Clinical Trials

Gunjan L. Shah, MD
Memorial Sloan Kettering Cancer Center
New York, New York

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Goal of Clinical Trials: Making Progress Against Myeloma

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

Increase the understanding of the disease and how the treatment works
- Identify rational selection of existing drugs

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

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Impact of Clinical Trials in Myeloma

Survival rates have nearly doubled; further improvements expected in near future.

Many new drugs approved since 2003.

Many new drugs being studied in clinical trials.

Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine.

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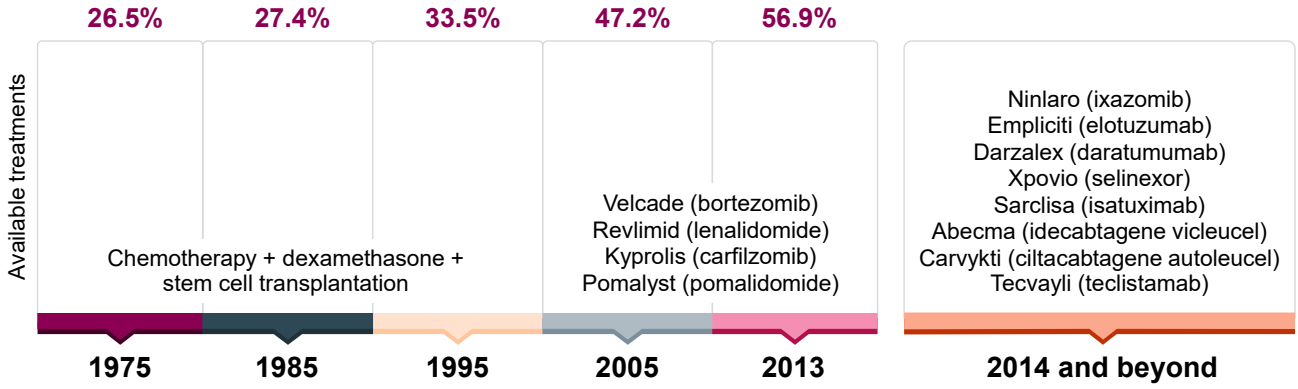
Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

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



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New Drug Development

STEP 1

Identify a target for therapy in the laboratory

STEP 2

Confirm the anti-cancer activity in laboratory and animal studies

STEP 3

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

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

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Designing Clinical Studies

When a treatment is ready to be tested, researchers design a research plan called a protocol that includes such details as:

- How many patients will be enrolled
- How the treatment will be administered
- When and how participants will be monitored
- The goals of the trial: determine safety, identify the right dose, measure the efficacy

Clinical studies pass high standards of scientific design and an ethics review to ensure that they protect the rights and welfare of all participants.

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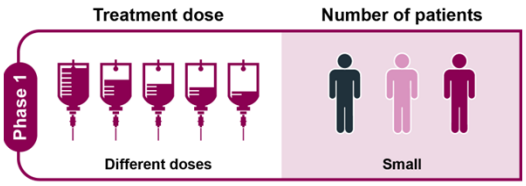
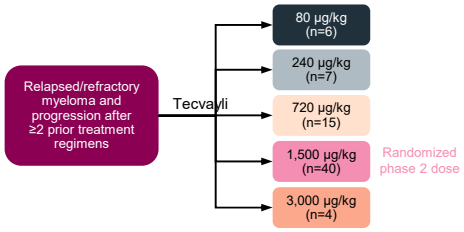
Traditional Clinical Study Types



Questions answered*

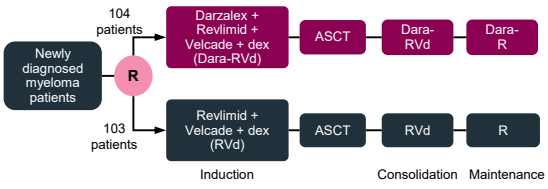
- What is the best dose?
- Is the drug safe?
- What are the side effects?

Example: Phase 1 MajesTEC-1 Study



- Does the drug work?
- What are the side effects?

Example: Phase 2 GRIFFIN Study



*The FDA approves treatments that are safe, effective, and shown to be better than the standard treatments available.
†When no standard treatment is available, the FDA may approve drugs based on study results of phase 2 studies.

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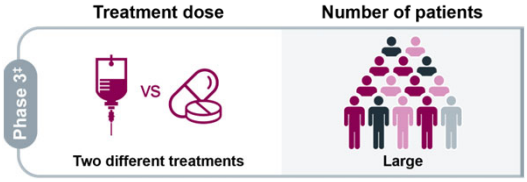
Traditional Clinical Study Types

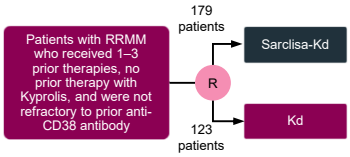


Questions answered*

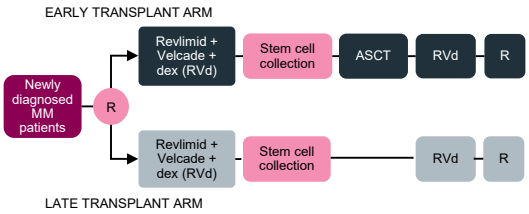
- Is the treatment safe?
- Does this treatment work better than other treatments?
- Does this treatment cause fewer side effects than other treatments?

*The FDA approves treatments that are safe, effective, and shown to be better than the standard treatments available.
‡Conducted to receive FDA approval of new drugs, in most cases.

Example: Phase 3 IKEMA Study



Example: Phase 3 DETERMINATION Study



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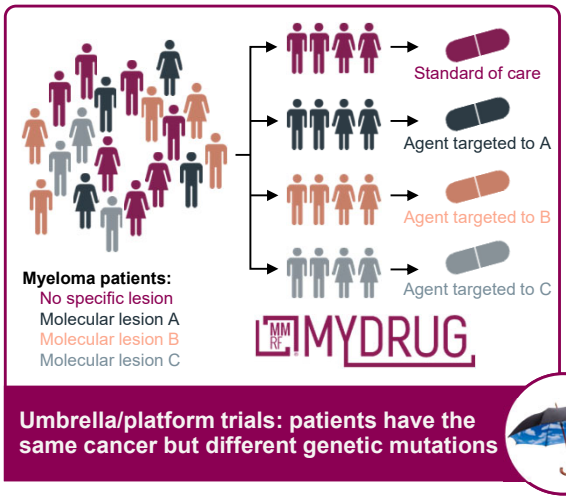
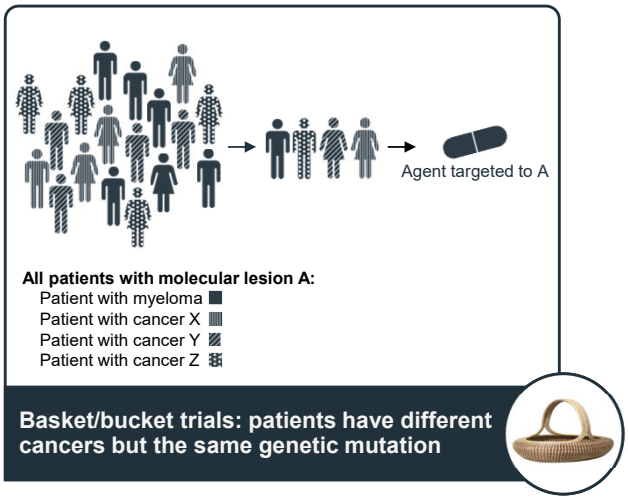
Innovative Trial Designs: Guiding the Future of Cancer Research Toward Personalized Medicine





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

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Other Types of Clinical Studies

Longitudinal Studies

- Long-term studies with a large number of patients

CoMMpass Study℠

Registry Studies

- Patients are treated using available therapies
- Efficacy and safety are analyzed following treatment
- Typically involve a large number of patients

MMRF CureCloud®

Expanded-Access Programs

- Allow early access to experimental therapies when no alternatives are available

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Participation in a Clinical Study

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Aren't clinical studies for people who are running out of options?

- Today, clinical studies are used at all stages of disease
  - Clinical studies are available for induction (first) therapy, maintenance therapy, all stages of relapsed disease, and myeloma precursor conditions
- If you have become resistant to standard therapies, clinical studies may offer you another type of treatment—but that is not the only situation in which they are useful

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Will I be treated like a guinea pig? *No!*

The Nuremberg Code

The Declaration of Helsinki

The Belmont Report

Ethics Committees and Research Boards

Three influential documents

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Benefits of Clinical Trials

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

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Considering Entering Clinical Trials

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

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Key Points

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

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

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High-Risk Myeloma

Sham Mailankody, MBBS
Memorial Sloan Kettering Cancer Center
New York, New York

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What is high-risk multiple myeloma and why is it important to find out if you have it?

Patients may not respond well to standard treatment.

Patients can have poorer outcomes.

Risk is related to changes (mutations) in the DNA of the myeloma cells.

Helps your doctor

- Determine your prognosis
- Select the treatment that is right for you

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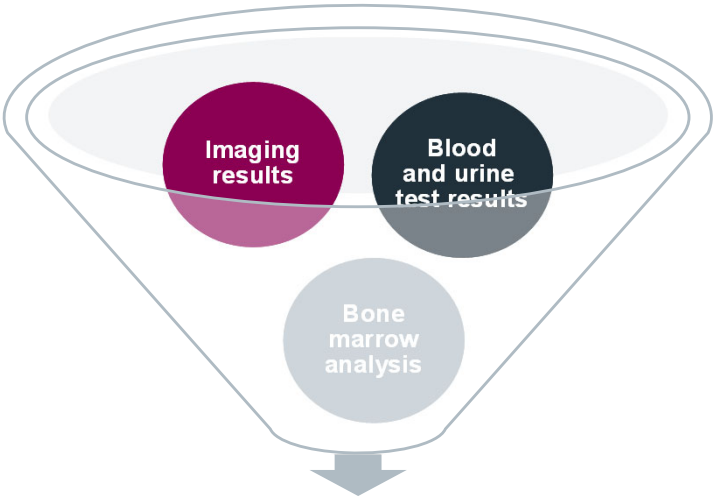
Assessing Risk



Staging, prognosis, and risk assessment

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High-Risk Disease Definitions

Revised International Staging System (R-ISS)[1]

R-ISS Stage I
- ISS[2] stage I
  - **Serum β2M level** <3.5 mg/L
  - **Serum albumin level** ≥3.5 g/dL
- No **high-risk CA***
- Normal **LDH level**

R-ISS Stage II
- All other possible combinations

R-ISS Stage III
- ISS[2] stage III
  - Serum β2M level ≥5.5 mg/L
- High-risk CA* or high LDH level

*Deletion 17p and/or t(4;14) and/or t(14;16)

Mayo Clinic Stratification for Myeloma & Risk-Adapted Therapy (mSMART)[3]

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)

*By FISH or equivalent

Additional high-risk features
- **Disease features**
  - Other cytogenetic and genetic abnormalities
  - Plasma cell leukemia
  - Extramedullary disease
  - Renal failure
- **Patient features**
  - Comorbidities
  - Frailty
- **Response features**
  - Lack of response to therapy
  - Short first PFS

1. Palumbo A et al. *J Clin Oncol*. 2015;33:2863. **2.** Griepp PR et al. *J Clin Oncol*. 2005;23:3412. **3.** Mikhael J et al. *Mayo Clin Proc*. 2013;88:360.

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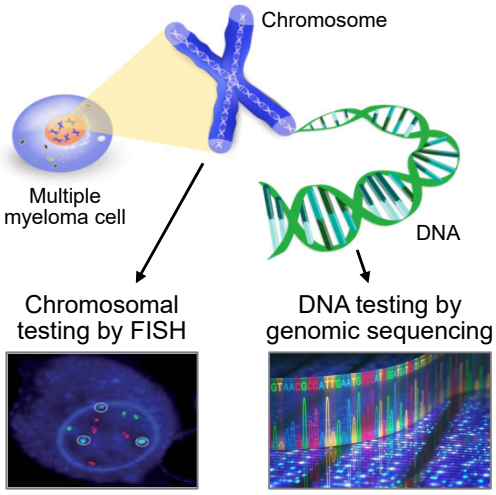
Why is genomic sequencing important in myeloma risk assessment?

- Genetic changes in myeloma cells may affect prognosis and treatment selection
- Using samples from the bone marrow—specific tests look at these genetic changes
- Some tests are used routinely and look at the ***chromosomal*** changes (FISH)
- Newer tests assess changes in the ***DNA*** (gene expression profiling and next-generation sequencing)
  - Ask your doctor if these tests are available
- All patients in the MMRF CoMMpass study had **genomic sequencing** from diagnosis to relapse. The resulting data provides detailed genetic profiles for every myeloma patient at every stage of their disease!



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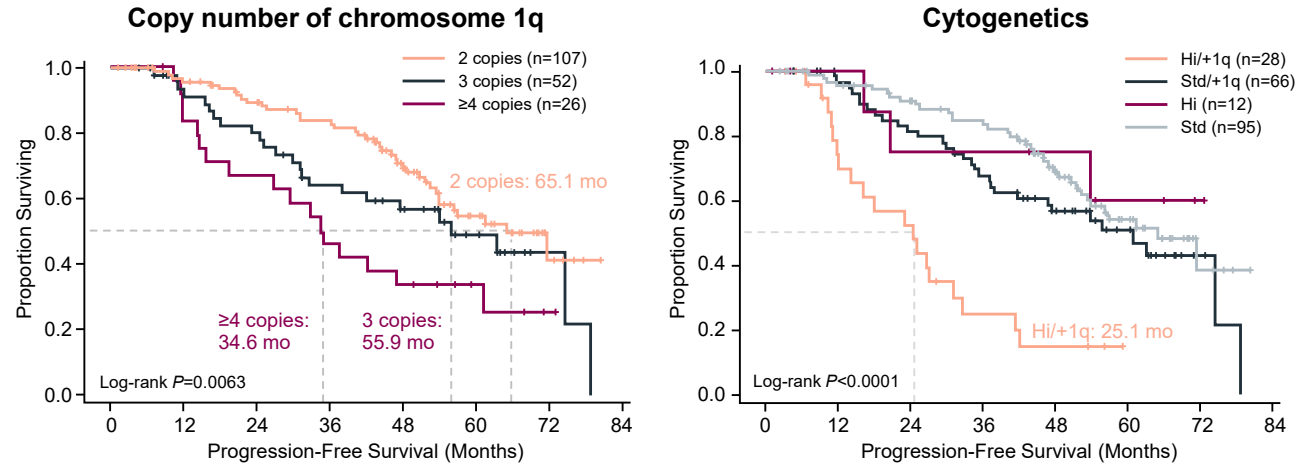
CoMMpass Findings: Chromosome 1 Copy Number and Other Cytogenetics



Hi, high-risk cytogenetics: t(4;14), t(14;16) and/or del(17p); Std, standard-risk cytogenetics

Schmidt TM et al. *Blood Cancer J.* 2019;9:94.

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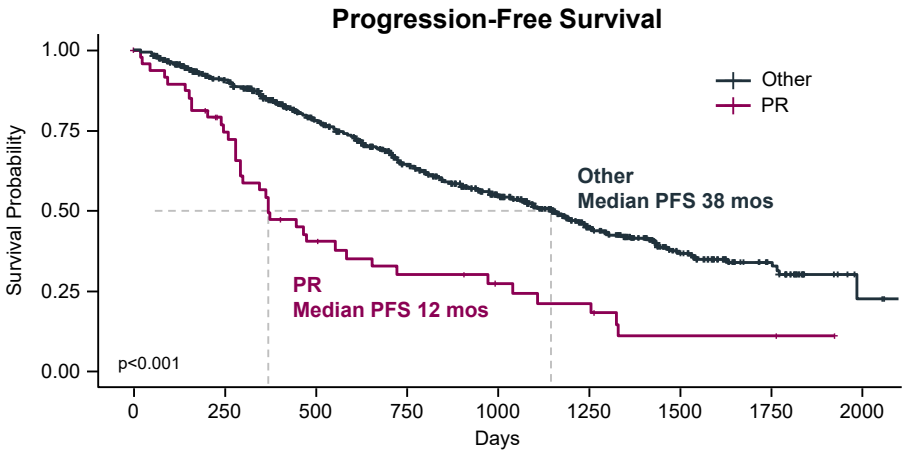
CoMMpass: Uncovering a High-Risk Proliferation Group (PR)



Approximately 25% of multiple myeloma patients transition to the PR group at relapse, which is mostly characterized by RAS/RAF and CDK pathway-activating alterations.

PR patients progress almost three times as fast as all other groups combined.

PFS, progression-free survival

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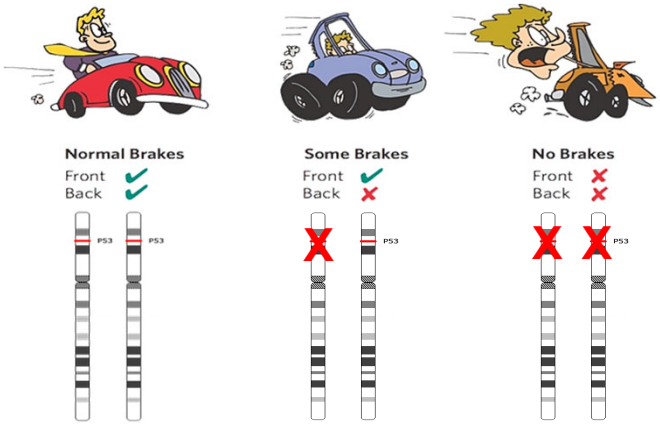
CoMMpass: Identifying Double-Hit Multiple Myeloma

- Identification of high-risk disease is evolving from FISH testing to genetic mutation analysis
- CoMMpass has identified the ***highest-risk group***, known as double-hit multiple myeloma

<u>Key CoMMpass finding</u>: FISH testing alone cannot identify whether patients have double-hit myeloma.

The concept of double-hit myeloma



Having no brakes is a bad thing but having half the brakes is okay.

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Despite recent improvements in treatment, high-risk patients have not experienced the same benefit as patients with standard risk.

Therefore, the treatment of high-risk patients is a very important focus of research.

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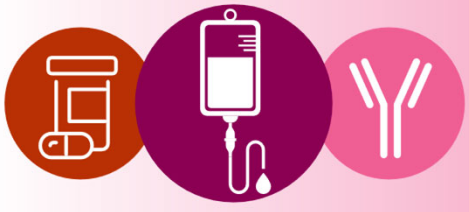
Approach to Treatment: Risk-Adapted Therapy

Risk-adapted therapy
Aims to treat patients with the therapy that will work best for them while decreasing the side effects from treatment

Patients with **standard-risk** myeloma are given a less-intense but effective treatment that should control their myeloma



Patients with **high-risk** myeloma are given a stronger treatment designed to be effective against their specific form of myeloma

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Summary of High-Risk Subsets in Contemporary Newly Diagnosed Multiple Myeloma Trials

Study	Treatment arms	Total number of patients	*High risk* definition	Number of high-risk myeloma patients
SWOG-1211[1]	RVd vs RVd-Empliciti	100	GEP^{hi}, del17p, t(14;16), t(14;20), Amp1q21, elevated LDH, pPCL	RVd = 52 RVd-Elo = 48
SWOG-0777[2]	RVd vs Rd	525	del17p, t(14;16), or t(4;14)	Combined n=44
MAIA[3]	DRd vs Rd	737	del17p, t(14;16), or t(4;14)	DRd = 48 Rd = 44
ALCYONE[4]	D-VMP vs VMP	706	del17p, t(14;16), or t(4;14)	D-VMP = 53 VMP = 45
CASSIOPEIA[5]	Darzalex-VTd vs VTd	1,085	del17p or t(4;14)	Dara-VTd = 82 VTd = 86
STAMINA[6]	Tandem transplant vs ASCT/RVD vs ASCT	758	ISS 3, del13, del 17p, t(4;14), t(14;16), t(14;20)	Tandem = 72 ASCT/RVD = 76 ASCT = 75

The high-risk myeloma definition is not uniform across the contemporary randomized phase 3 trials and accounts for a small subset of study populations.

1. Usmani SZ et al. *Lancet Haematol*. 2021. **2.** Durie B et al. *Lancet*. 2017. **3.** Facon T et al. *N Engl J Med*. 2018. **4.** Mateos MV et al. *N Engl J Med*. 2018. **5.** Moreau P et al. *Lancet*. 2019. **6.** Staudtmaeur E et al. *J Clin Oncol*. 2018.

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Darzalex Meta-Analysis in High-Risk Multiple Myeloma

Six phase 3 trials comparing standard treatment regimens with or without Darzalex in newly diagnosed[1-3] or relapsed/refractory[4-6] myeloma patients with high-risk cytogenetics

High risk defined as the presence of t(4;14), t(14;16), or del(17p)

Addition of Darzalex to backbone regimens improved PFS of patients with high-risk cytogenetic features in both frontline and relapsed settings.

PFS benefit for high-risk patients was greater in relapsed setting compared to frontline.

PFS benefit for standard-risk patients was similar in both relapsed and frontline settings.

Results were similar regardless of backbone regimens.

Giri S et al. *JAMA Oncol*. 2020;6:1.
1. MAIA Trial. Facon T et al. *N Engl J Med*. 2019;380:2104. **2.** CASSIOPEIA Trial. Moreau P et al. *Lancet*. 2019;394:29. **3.** ALCYONE Trial. Mateos MV et al. *Lancet*. 2020;395:132. **4.** POLLUX Trial. Dimopoulos MA et al. *N Engl J Med*. 2016;375:1319. **5.** CASTOR Trial. Palumbo A et al. *N Engl J Med*. 2016;375:754. **6.** CANDOR Trial. Usmani SZ et al. *Blood*. 2019;134. Abstract LBA-6.

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Treatment Regimens for High-Risk Disease Features

Kyprolis-Revlimid-dex (KRd) vs Revlimid-Velcade-dex (RVd) retrospective chart review[1]

- 154 consecutive high-risk* newly diagnosed myeloma patients treated with KRd (n=87) and RVd (n=67) at Memorial Sloan Kettering Cancer Center from 2015 to 2019
- Patients receiving KRd vs RVd had:
  - Greater depth of response
  - Significant improvement in PFS (especially those who received early ASCT)
- R-ISS stage II and III (compared to stage I) were significant predictors for progression or death
- More than 6 cycles of treatment was associated with longer PFS and OS

*High risk cytogenetic abnormalities defined as 1q+ (gain or amp), t(4;14), t(14;16), t(14;20), and/or del(17p) or monosomy 17.

OPTIMUM Study[2]

- Study to evaluate the efficacy of Darzalex-cyclophosphamide-Velcade-Revlimid-dex (Dara-CyVRd) induction followed by ASCT and 2 rounds of consolidation with Dara-VR (with or without dex) in 107 ultra high-risk† patients with multiple myeloma and plasma cell leukemia (PCL)
- By end of second consolidation, 46.7% of patients were MRD negative (10^{-5}); 84% of patients who were MRD negative after ASCT sustained their MRD negativity at the end of second consolidation
- 86% of patients were alive and 77% were progression free at 30 months

†≥2 high risk lesions: t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p), or SKY92 risk signature.

1. Tan C et al. *Blood*. 2022;140. Abstract 752. **2.** Kaiser MF et al. *Blood*. 2022;140. Abstract 758.

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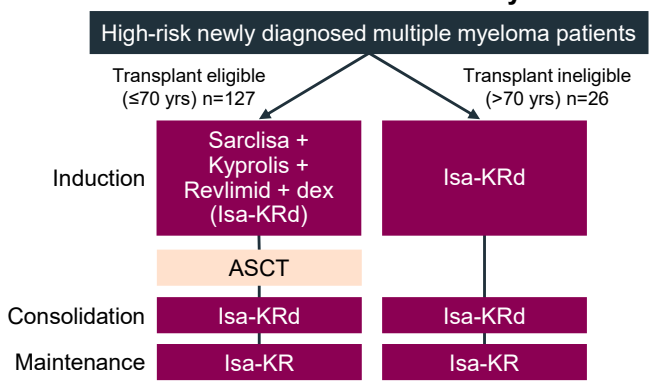
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

GMMG-CONCEPT Study



Total population cytogenetic abnormalities: 44% del(17p); 38.4% t(4;14); 15.2% t(14;16); 36% >3 copies of 1q21; 30.4% ≥2 high-risk cytogenetic abnormalities

Best response (through consolidation), %	Transplant eligible (n=99)	Transplant ineligible (n=26)
Overall response rate	**94.9**	**88.5**
sCR/CR	72.7	57.7
VGPR	18.2	30.8
PR	4.0	0
SD	0	0
MRD negative (1×10^{-5}) in evaluable patients	67.7	54.2

Adverse events, % grade ≥3	Transplant eligible (n=97)	Transplant ineligible (n=25)
Hematologic		
Neutropenia	39.2	28
Leukopenia	24.7	4
Thrombocytopenia	26.8	16
Anemia	14.4	12
Non-hematologic		
Infection	27.8	28
Cardiac	2.1	20

Weisel KC et al. *Blood*. 2022;140. Abstract 759.

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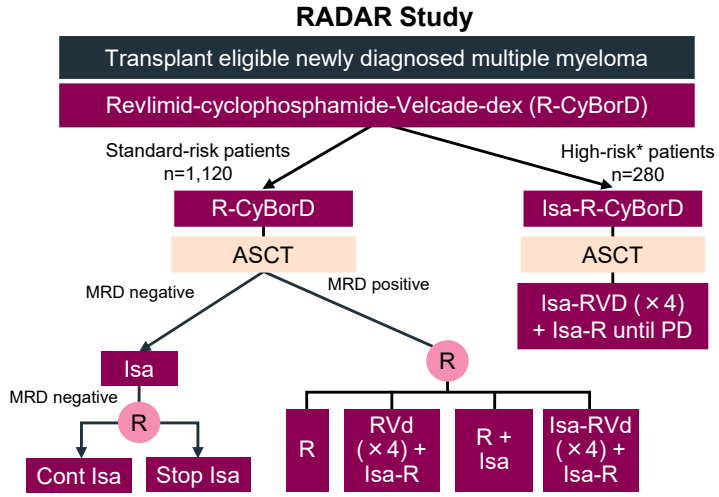
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease



*At least 2 of t(4;14), t(14;16), del(17p), 1q+, 1p-

Yong K et al. *Blood*. 2022;140. Abstract 762.

Innovative study design to tailor treatment:
- De-escalate for MRD neg patients
- Deepen response for MRD positive patients
- Manage ultra-HR disease

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Additional Studies for High-Risk Myeloma

Moving the use of CAR T-cell therapy in earlier stage of disease

Study	Agent	Phase	Patient populations/ study design	*High risk* definition
KarMMa-4	Abecma	1	High-risk, newly diagnosed MM	R-ISS III
BMT-CTN 1901	Abecma	2	High-risk, newly diagnosed MM	R-ISS III; no prior progression

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

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Town Hall Questions & Answers

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Thank you!

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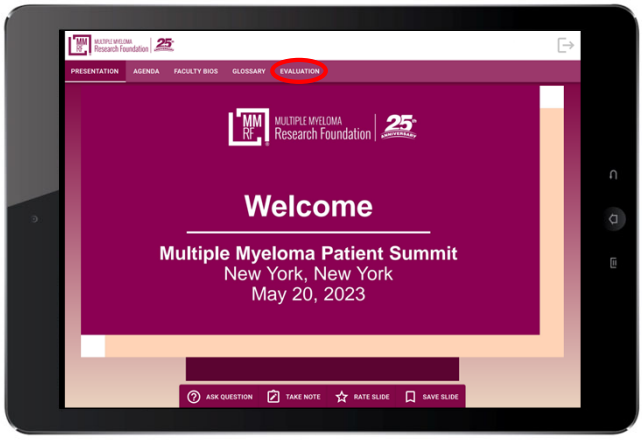
Don’t Forget!

Complete your evaluation
Leave the iPad at your seat



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Upcoming Patient Education Events
Save the Date

Topic	Date and Time (ET)	Speakers
Patient Summit Charlotte, North Carolina	Saturday, June 24 9:00 AM to 3:45 PM	Peter Voorhees, MD

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

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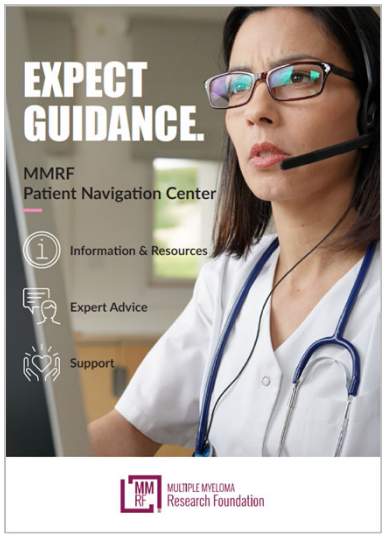
MMRF Patient Resources



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Myeloma Mentors®

Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

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

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To **Learn More** & **Find Your Event today**!
www.theMMRF.org/Events

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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
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CANCER FOUNDATION

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