Opening Remarks

Mary DeRome, MS
MMRF

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Tech Support

1-719-234-7952

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Resources

- Resource tab includes
  - Speaker bios
  - Glossary
  - Copy of the slide presentation
  - Exhibit Hall

Submit your questions throughout the program!

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Program Faculty

Gurbakhash Kaur, MD
University of Texas Southwestern Medical Center
Dallas, Texas

Amrita Y. Krishnan, MD
Judy and Bernard Briskin Multiple Myeloma Center
City of Hope Medical Center
Duarte, California

Elizabeth Manthey, AGNP, DNP
Rocky Mountain Cancer Centers
Denver, Colorado

Robert M. Rifkin, MD
Sarah Cannon Research Institute
Rocky Mountain Cancer Centers
Denver, Colorado

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Summit Agenda

Time (MT)	Topic	Speakers
9:00 – 9:15 AM	Introduction to the MMRF	Mary DeRome, MS
9:15 – 9:30 AM	Welcome	Robert Rifkin, MD
9:30 – 10:00 AM	Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy	Gurbakhash Kaur, MD
10:00 – 10:30 AM	Relapsed/Refractory Multiple Myeloma	Robert Rifkin, MD
10:30 – 11:00 AM	Supportive Care	Elizabeth Manthey, AGNP, DNP
11:00 – 11:45 AM	Town Hall Q&A	Panel
11:45 AM – 12:15 PM	High-Dose Chemotherapy and Stem Cell Transplantation, Maintenance Therapy, and Treatment Goals	Amrita Krishnan, MD
12:15 – 12:30 PM	Hot Topic 1: Multiple Myeloma Precursor Conditions	Gurbakhash Kaur, MD
12:30 – 12:45 PM	Hot Topic 2: High-Risk Multiple Myeloma	Amrita Krishnan, MD
12:45 – 1:00 PM	Hot Topic 3: New Drugs on the Horizon	Robert Rifkin, MD
1:00 – 2:00 PM	Town Hall Q&A	Panel
2:00 – 2:15 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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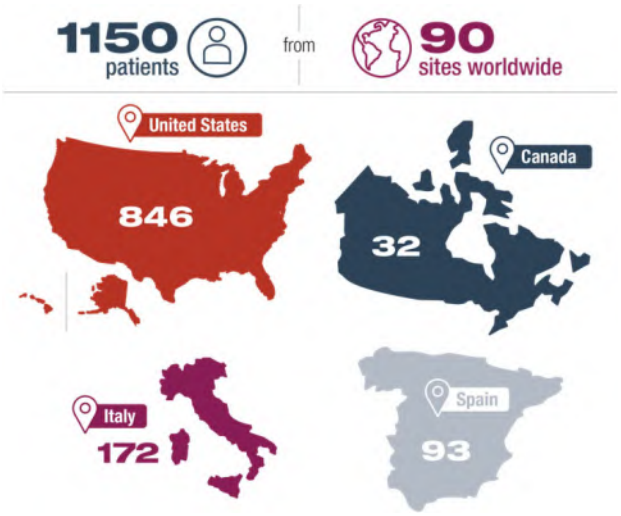
MMRF CoMMpass Study: Advancing Personalized Medicine Research

- 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

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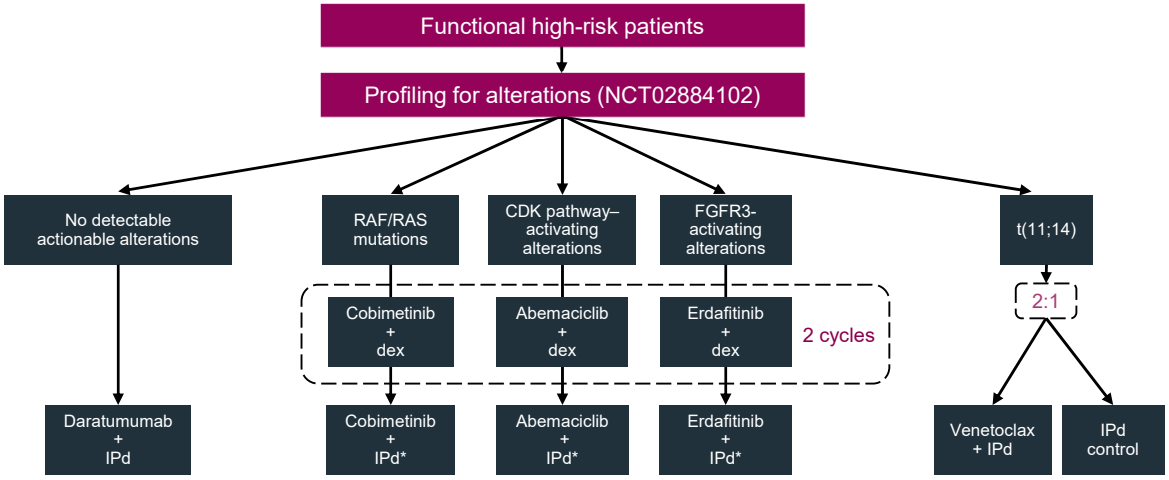
MyDRUG Trial



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

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MMRF Research Initiatives

1. MMRF Myeloma Accelerator Challenge (MAC) Grants
   - Broad, multi-institutional research grants designed to advance clinical trial concepts in the areas of
     - High-risk newly diagnosed multiple myeloma (NDMM)
     - High-risk smoldering myeloma (SMM)
   - Each research network will be funded up to $10M over 3 years
2. MMRF Horizon Adaptive Platform Trials
   - Paired with MAC grants
   - Done in collaboration with 13 MMRC sites
   - Trials in relapsed/refractory myeloma, high-risk NDMM, high-risk SMM

For more information, visit themmrf.org

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Welcome!

Robert M. Rifkin, MD
Sarah Cannon Research Institute
Rocky Mountain Cancer Centers
Denver, Colorado

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Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy

Gurbakhash Kaur, MD
University of Texas Southwestern Medical Center
Dallas, Texas

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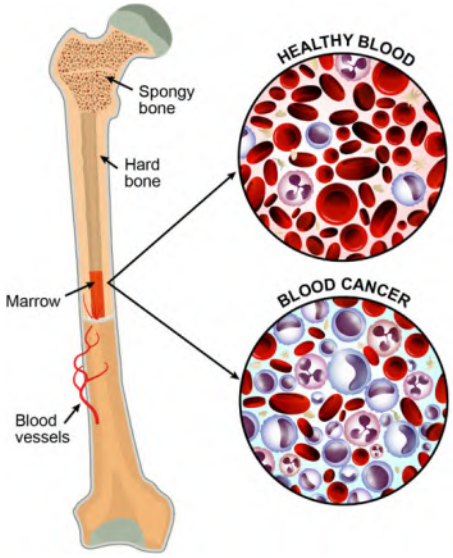
What is multiple myeloma?



- 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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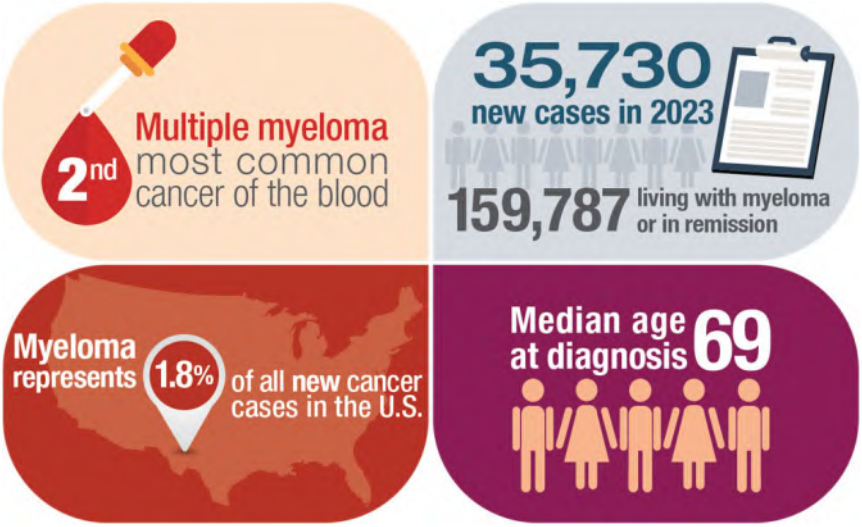
How common is multiple myeloma?



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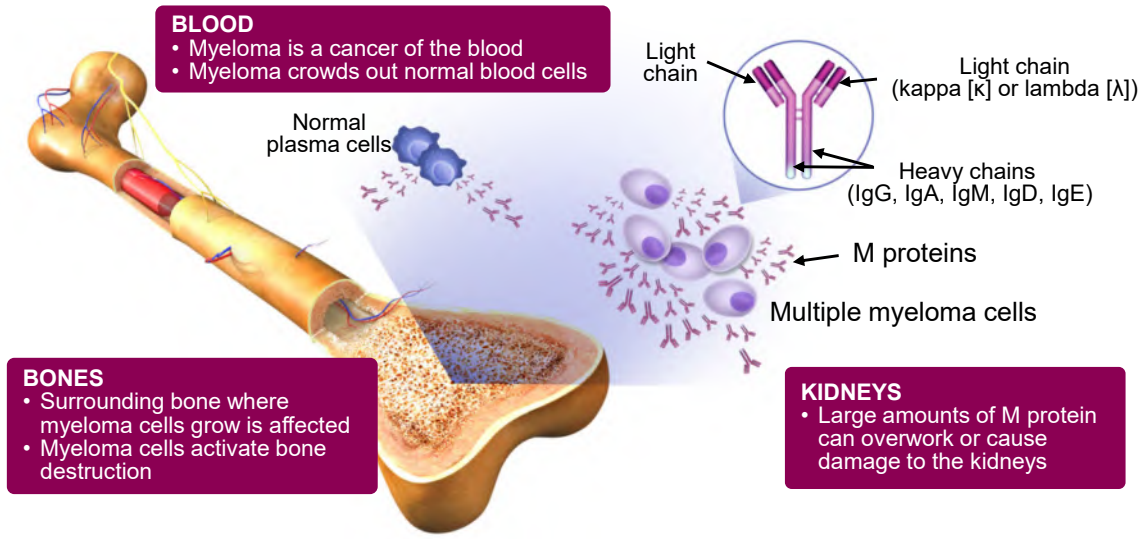
Multiple Myeloma Affects Your Bones, Blood, and Kidneys



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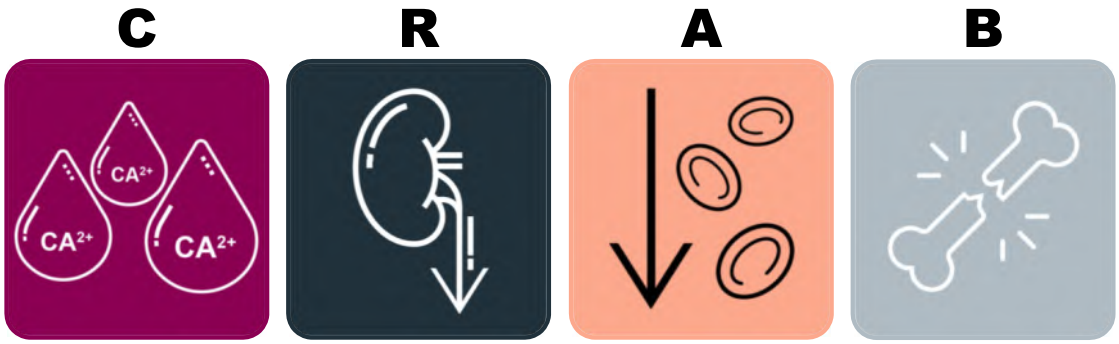
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

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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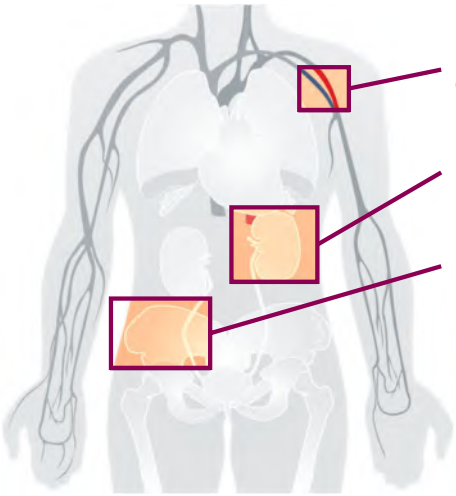
Effects of Myeloma and Common Symptoms



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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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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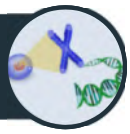
The Right Tests: Common Tests Conducted in Myeloma Patients

Blood tests Urine tests

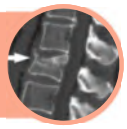
- Confirms the type of myeloma or precursor condition

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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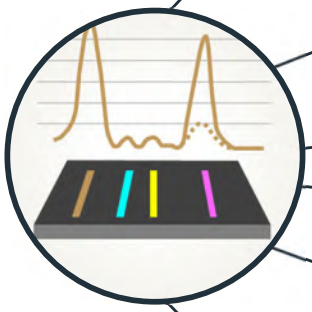
Learn Your Labs!
Blood Tests



- **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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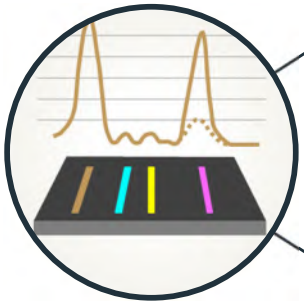
Learn Your Labs!
Urine Tests



- **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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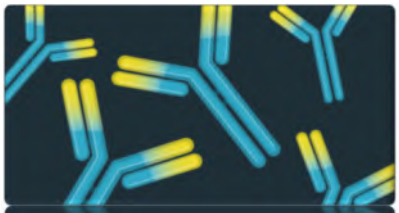
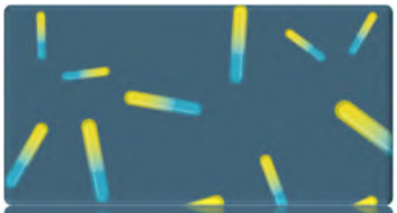
Types of Multiple Myeloma Based on Blood or Urine Tests



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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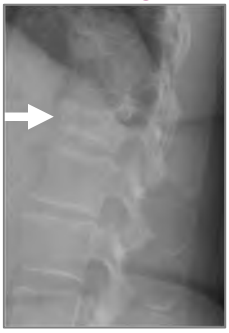
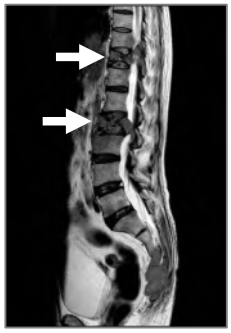
Know Your Imaging Tests!

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

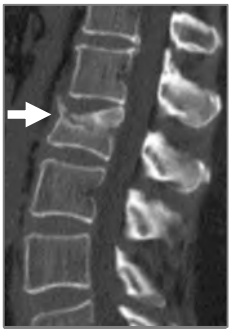
X-ray



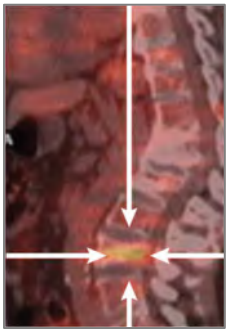
MRI



CT scan



PET scan



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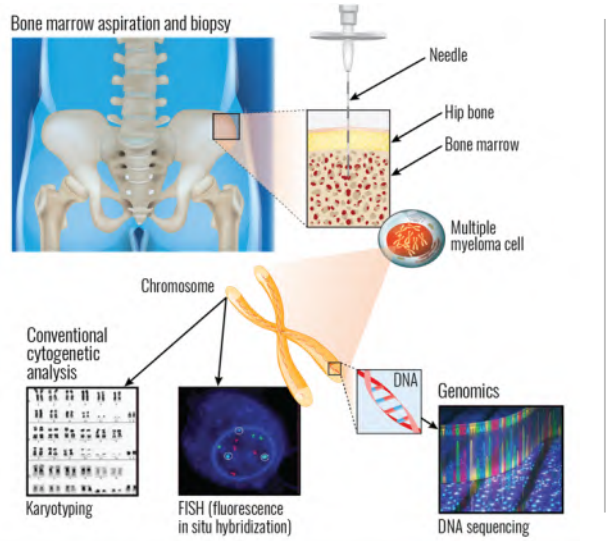
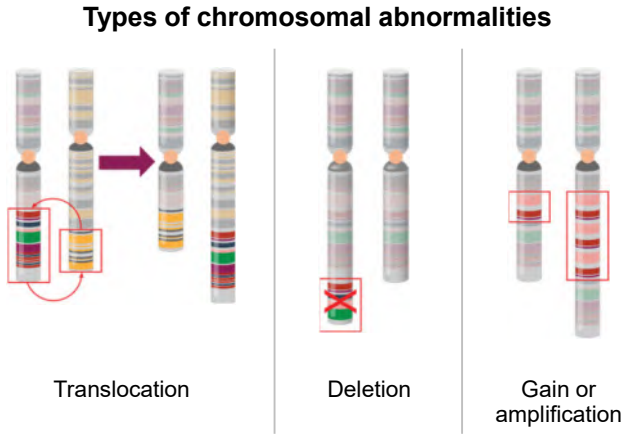
Know Your Bone Marrow Tests!





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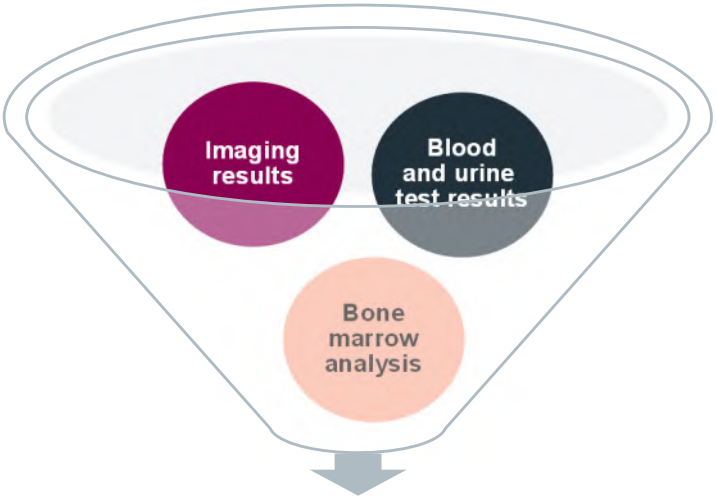
Putting the Results Together



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.

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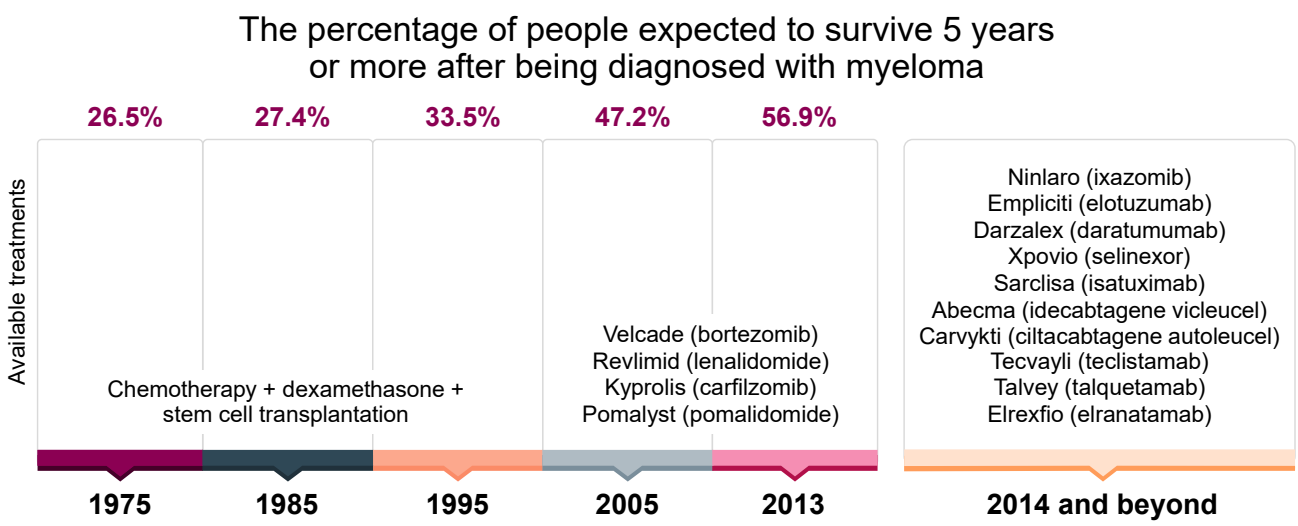
Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs



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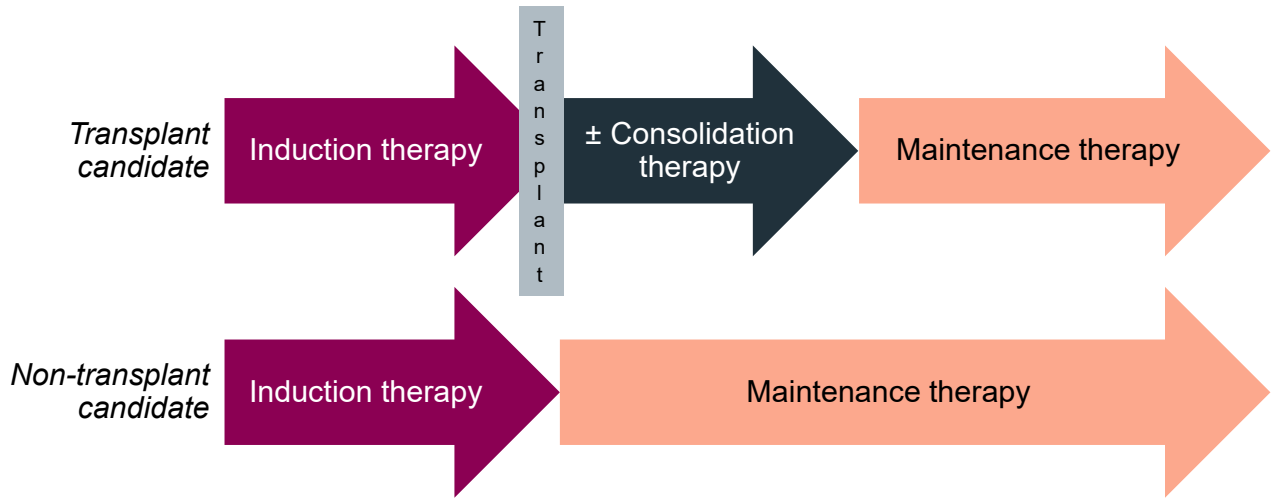
Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma



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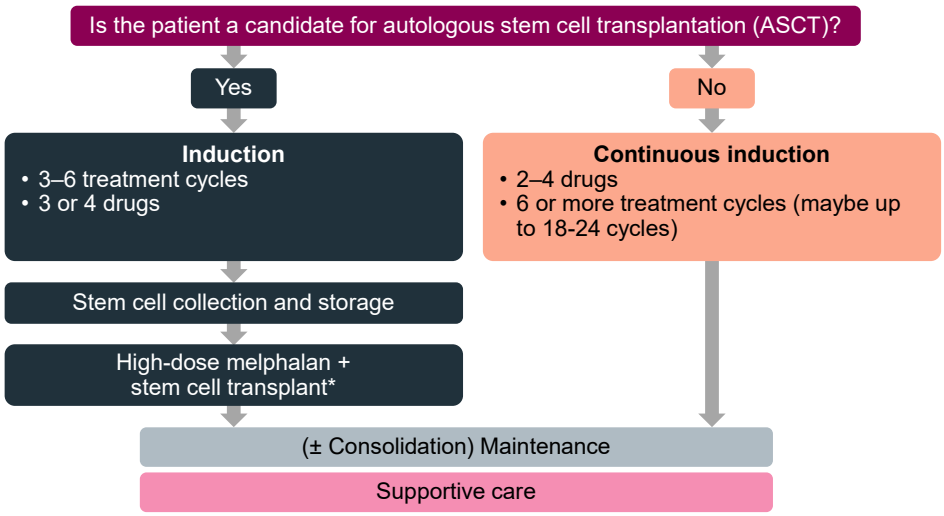
Overview of Treatment Approach for Active Multiple Myeloma



*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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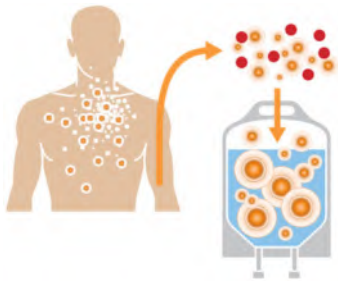
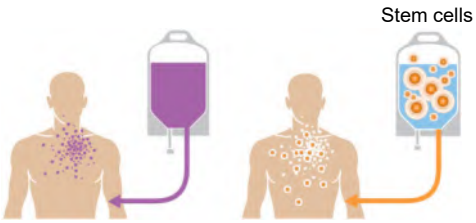
Autologous Stem Cell Transplantation





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

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

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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.

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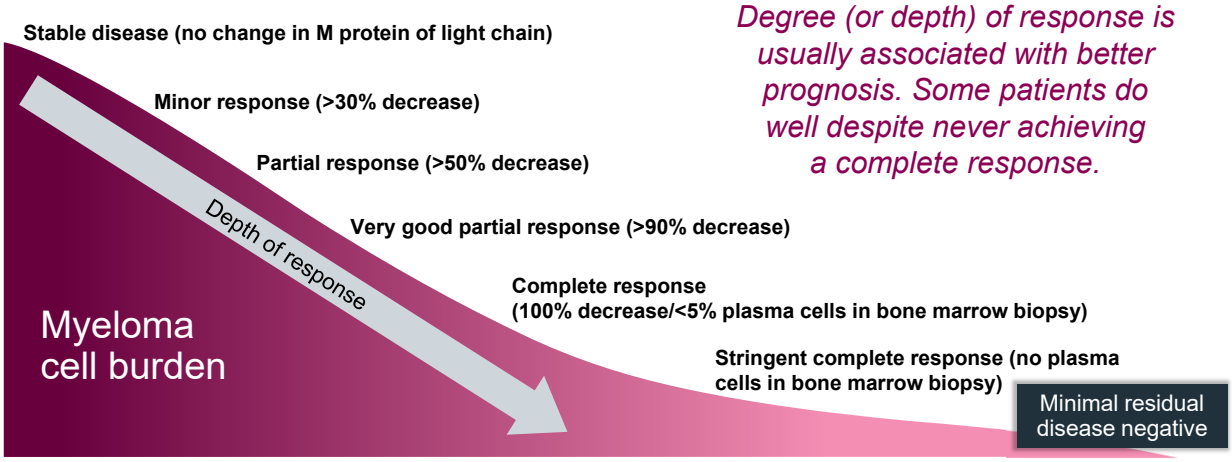
Measuring Response to Therapy



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

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

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

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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 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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MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Relapsed/Refractory Multiple Myeloma

Robert M. Rifkin, MD
Sarah Cannon Research Institute
Rocky Mountain Cancer Centers
Denver, Colorado

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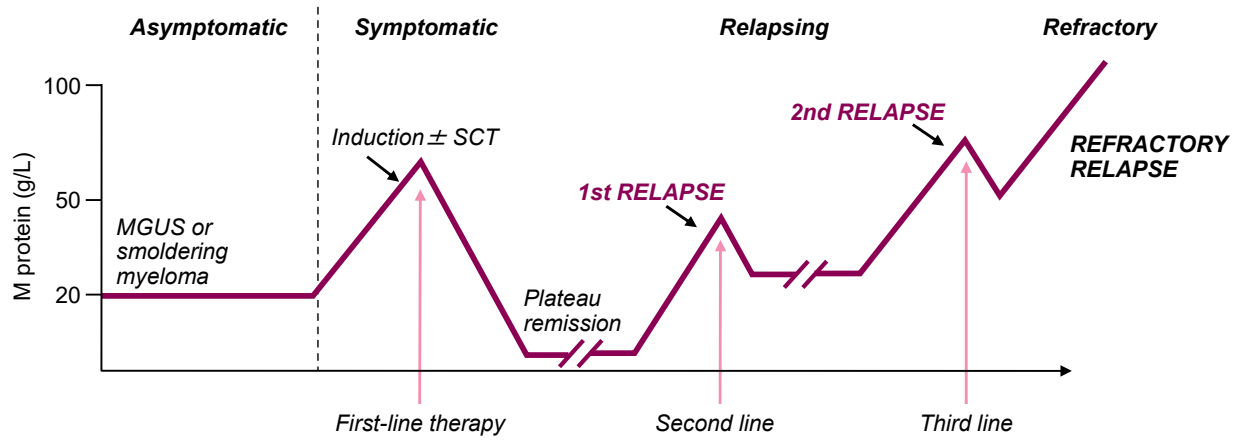
Multiple Myeloma Is a Marathon, Not a Sprint



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

45

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			Sarclisa (isatuximab)	
						Tecvayli (teclistamab)†	
						Talvey (talquetamab)†	
						Elrexfio (elranatamab)†	

*Not yet FDA-approved for patients with multiple myeloma; †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 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

OS, overall survival; PFS, progression-free survival

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

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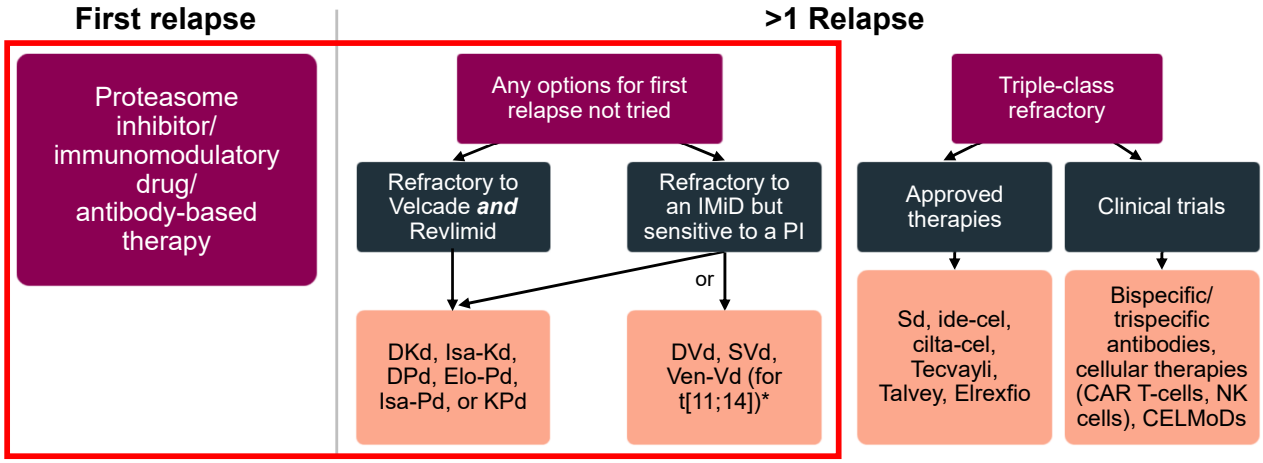
Treatment Approach



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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MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

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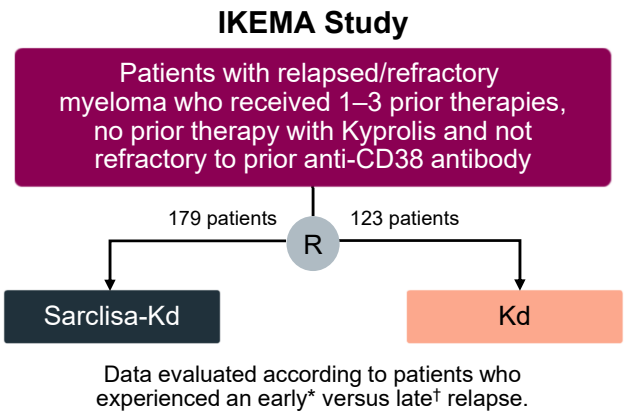
Update From the 2022 American Society of Hematology (ASH) Meeting
Sarclisa After Early or Late Relapse



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. *Haematologica*. 2023;Aug 17 [Epub ahead of print].

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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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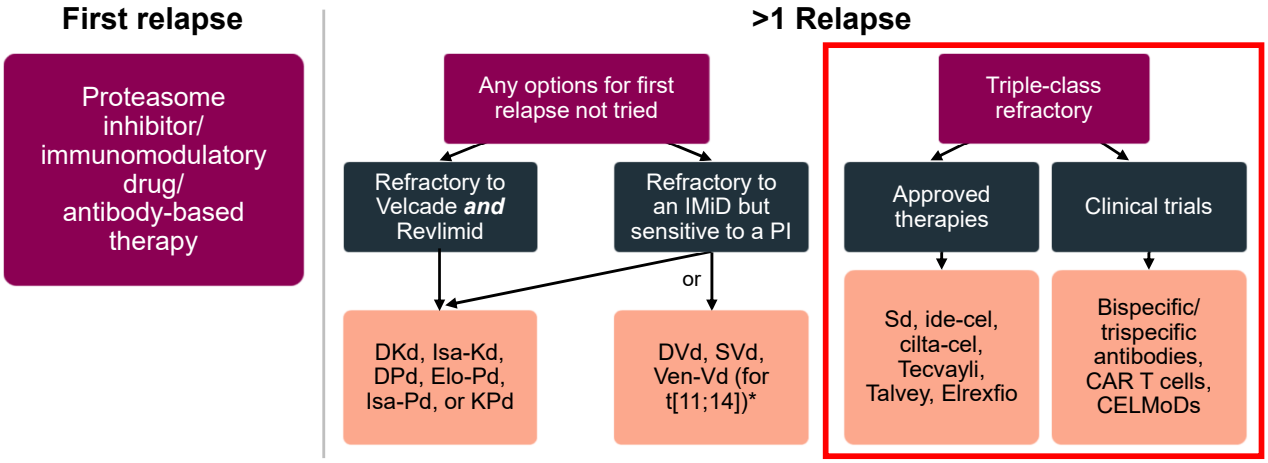
Treatment Approach



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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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	
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
CAR T cell	Carvykti (ciltacabtagene autoleucel)†		0.5 to 1.0 × 10^6 genetically modified autologous CAR T cells/kg of body weight
Bispecific antibody	Tecvayli (teclistamab)‡		Step-up dosing§ the first week then once weekly thereafter by subcutaneous injection
Bispecific antibody	Talvey (talquetamab)‡		Step-up dosing§ the first week then once weekly thereafter by subcutaneous injection
Bispecific antibody	Elrexfio (elranatamab)‡		Step-up dosing¶ the first week then once weekly thereafter by subcutaneous injection

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.
¶Patients are hospitalized for 48 hours after administration first step-up dose and for 24 hours after second step-up dose.

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

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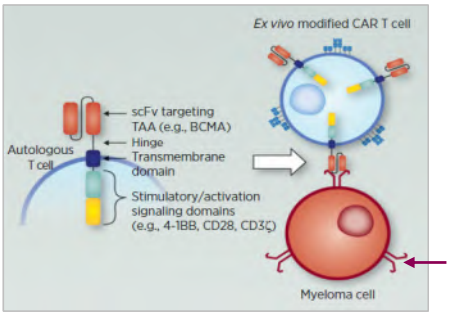
CAR T-Cell Therapy

- Genetically modified T cells are 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 in the body.
- CAR T cells are created from a patient's own blood cells, but the technology is evolving to develop "off-the-shelf" varieties.



B-cell maturation antigen (BCMA)

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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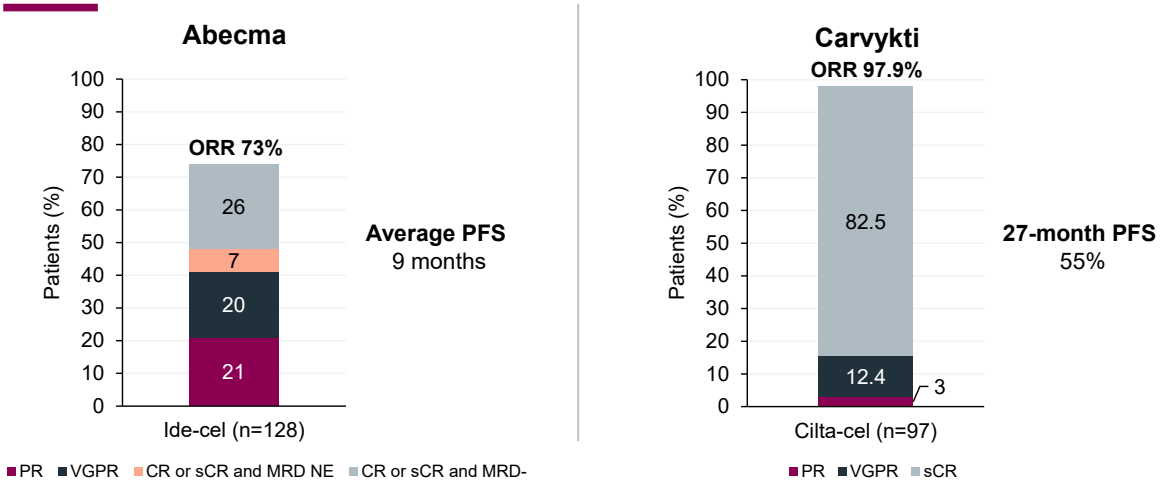
Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma



Average PFS
9 months

27-month PFS
55%

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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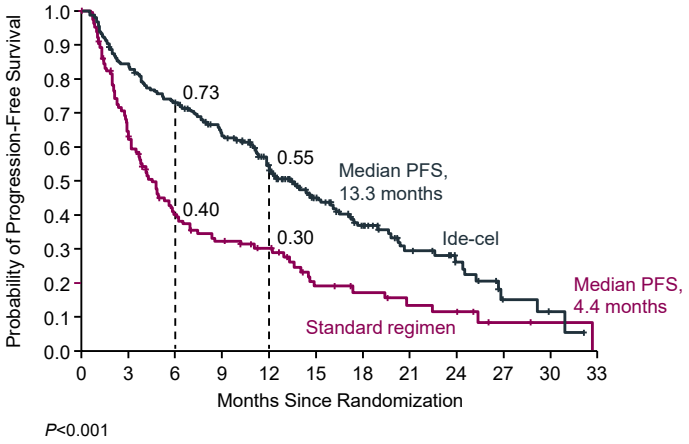
Abecma or Standard Regimens in Relapsed and Refractory Multiple Myeloma

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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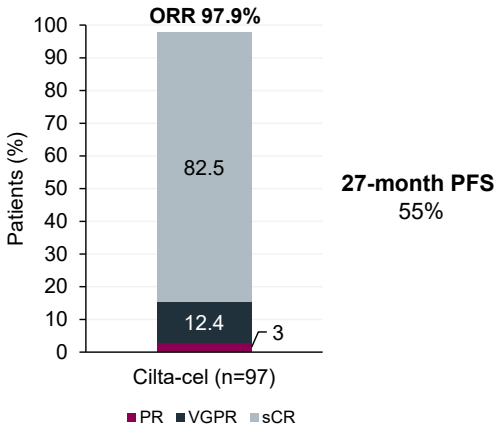
Carvykti in Relapsed and Refractory Multiple Myeloma



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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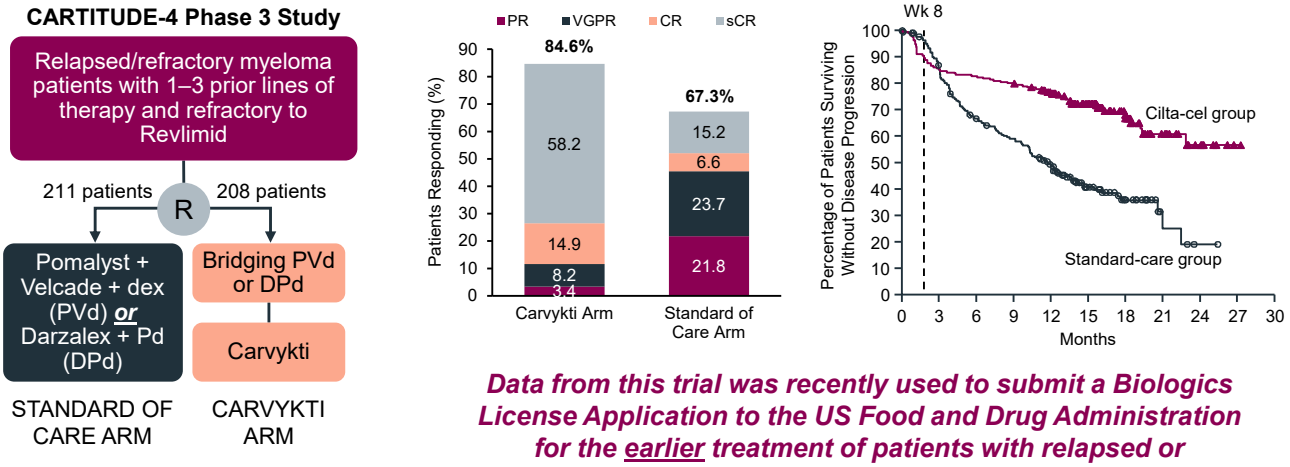
Carvykti in Earlier Use of Relapsed and Refractory Multiple Myeloma



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

San-Miguel J et al. *N Engl J Med.* June 5, 2023 [Epub ahead of print].

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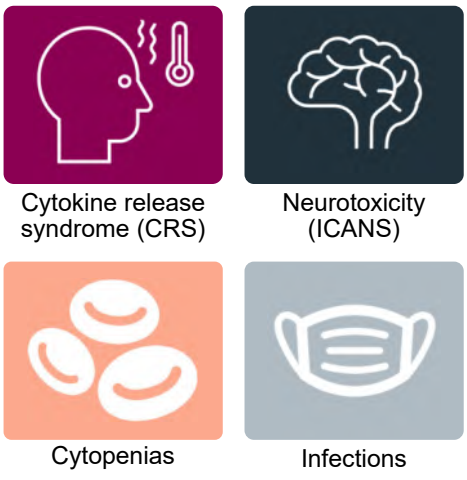
CAR T: Expected Toxicities



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

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

ICANS, immune effector cell-associated neurotoxicity syndrome

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

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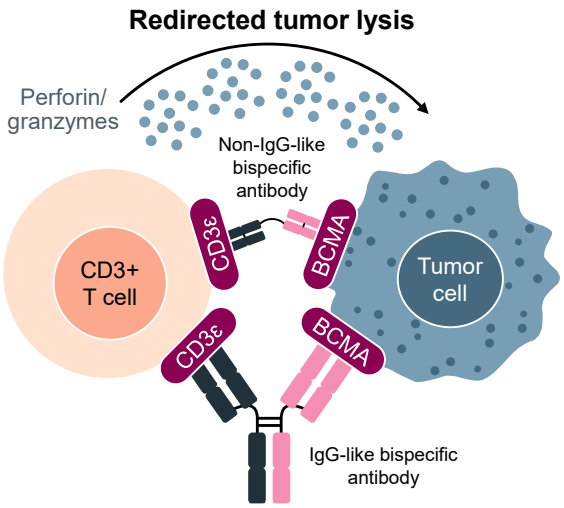
Bispecific Antibodies

- 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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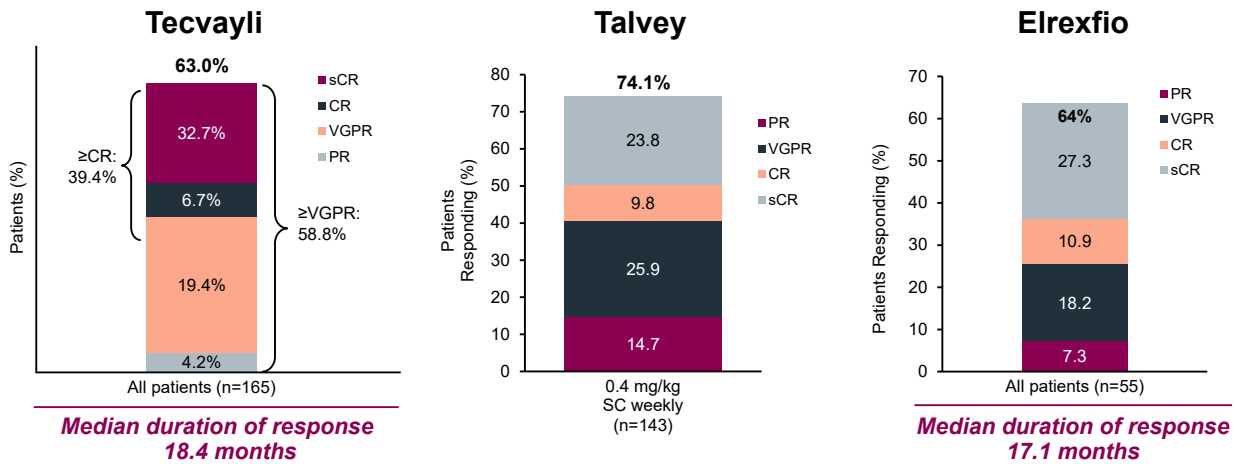
Now Approved: Three Bispecific Antibodies!



Median duration of response 18.4 months

Median duration of response 17.1 months

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

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Bispecific Antibodies: Expected Toxicities

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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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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Supportive Care

Elizabeth Manthey, AGNP, DNP
Rocky Mountain Cancer Centers
Denver, Colorado

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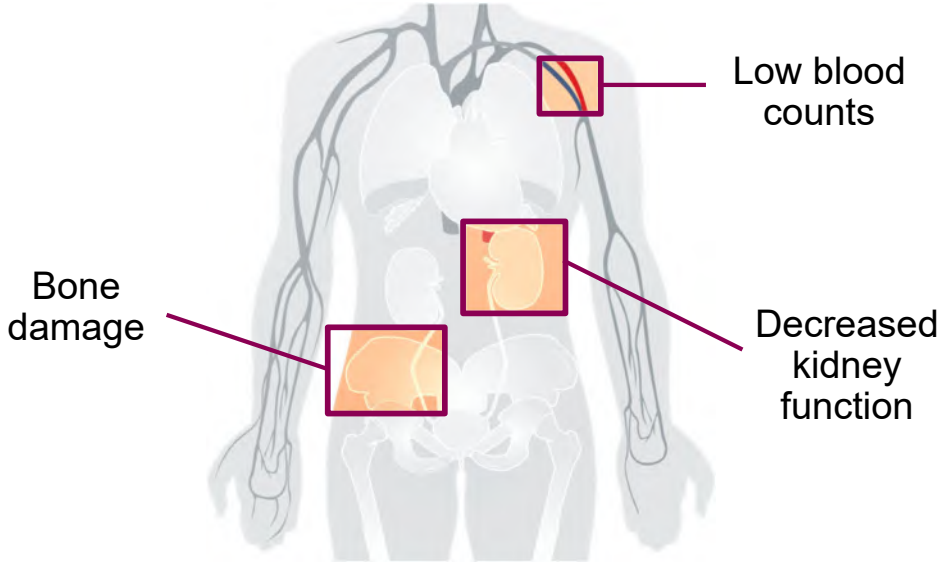
Effects of Myeloma



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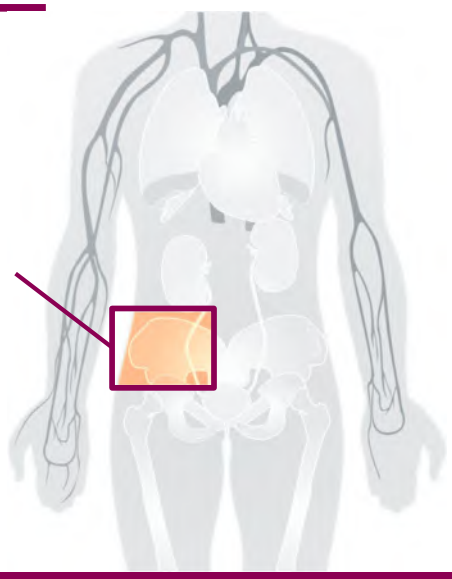
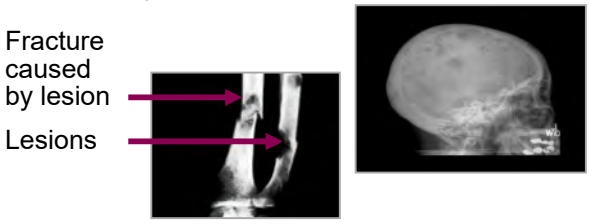
Effects of Myeloma: Bone Disease



- 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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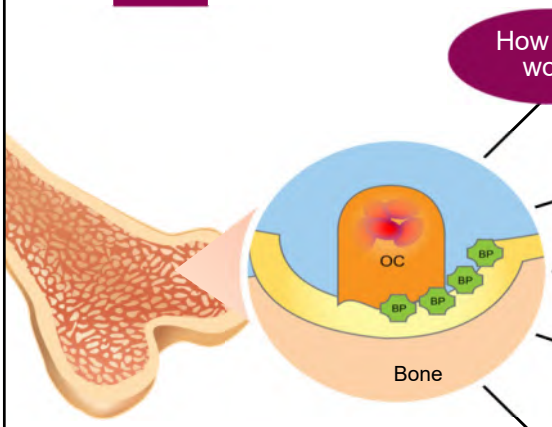
Bone Strengthening Agents for Myeloma Bone Disease



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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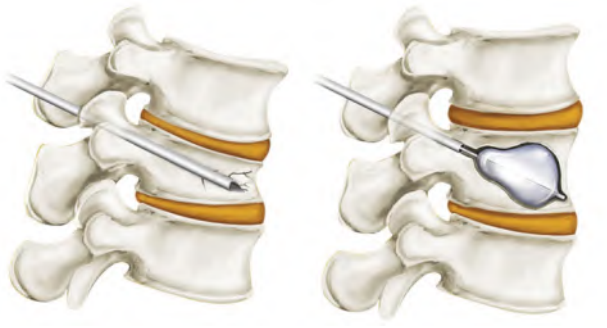
Orthopedic Procedures to Stabilize the Spine

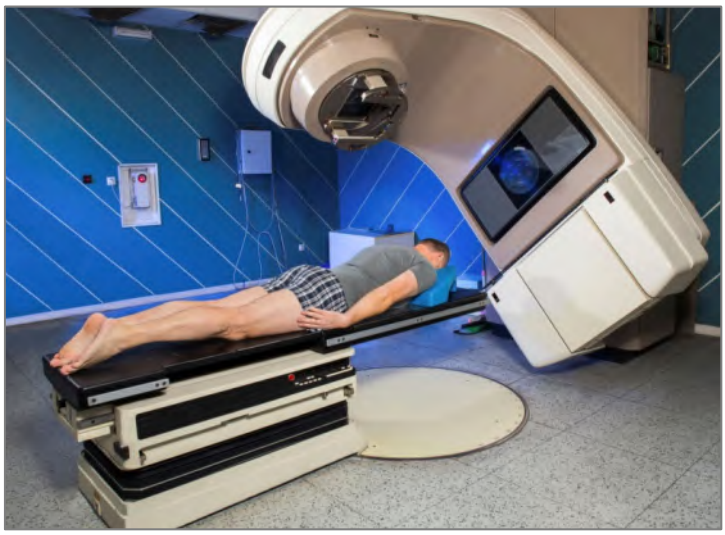
- Minimally invasive procedures
- Can be performed without hospitalization
- Small incision
- Cement filler stabilizes bone
- Potential for relatively rapid symptom relief (approximately 1 month with kyphoplasty)

Vertebroplasty **Kyphoplasty**



78

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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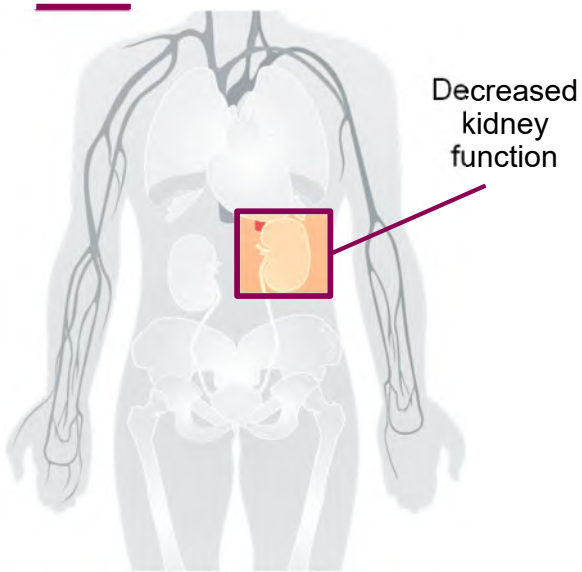
Effects of Myeloma: Decreased Kidney Function



- 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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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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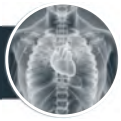
Class: Proteasome Inhibitors Side Effects and Management

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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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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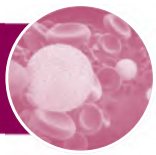
Class: Monoclonal Antibodies Side Effects and Management

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.

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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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Side Effects of Steroids (Dexamethasone)

Insomnia

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

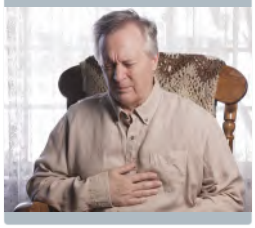
Fluid retention

- 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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Bispecific Antibody 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 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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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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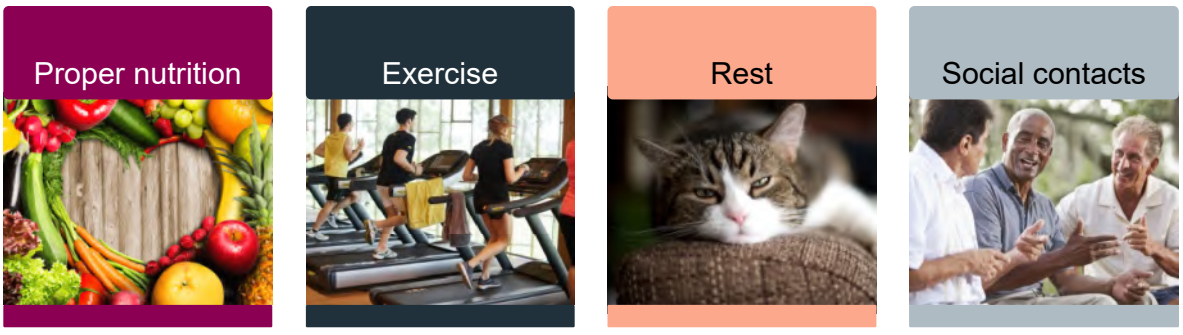
Daily Living



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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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Patient Experience

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Questions & Answers

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

Amrita Y. Krishnan, MD
City of Hope Medical Center
Duarte, California

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High-Dose Chemotherapy and Stem Cell Transplantation

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

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What does transplant mean?

Understanding the basics of autologous stem cell transplantation

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

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

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

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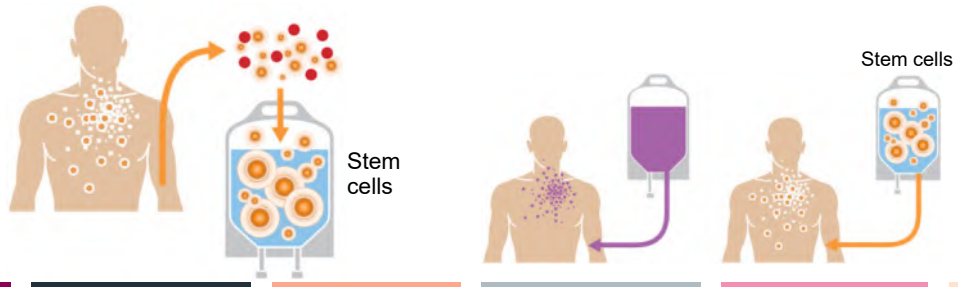
Autologous Stem Cell Transplantation



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*

Day 0

Days +1 to +100†

~3 to 6 cycles

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

Melphalan
- Alkeran, Evomela

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

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Side Effects of High-Dose Chemotherapy

Fatigue
- Expected
- May last 1–3 months

Nausea, vomiting, and diarrhea
- 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

Mucositis
- Pain, sores in mouth; sore throat
- Pain meds, mouth swishes
- Avoid tart, acidic, salty, spicy foods
- Soft food better tolerated

Low blood counts
- 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

Hair loss

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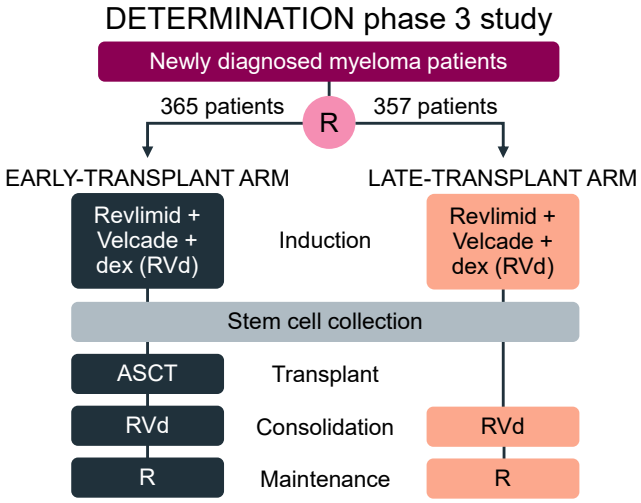
Is transplant still required in newly diagnosed myeloma?



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

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

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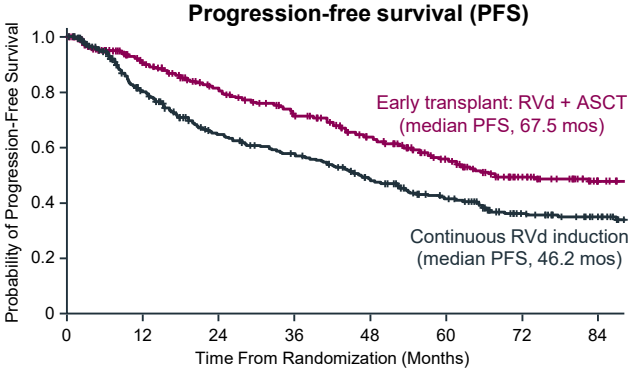
Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Survival Analysis

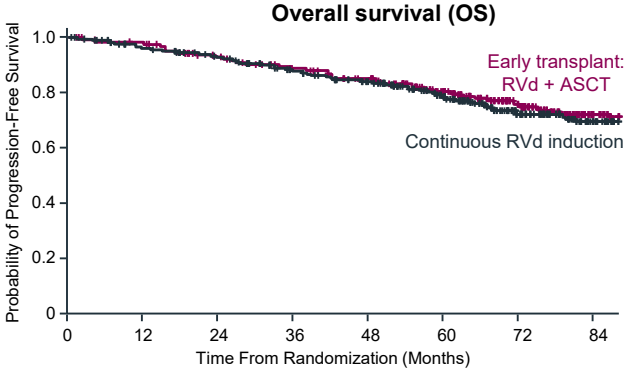
Progression-free survival (PFS)



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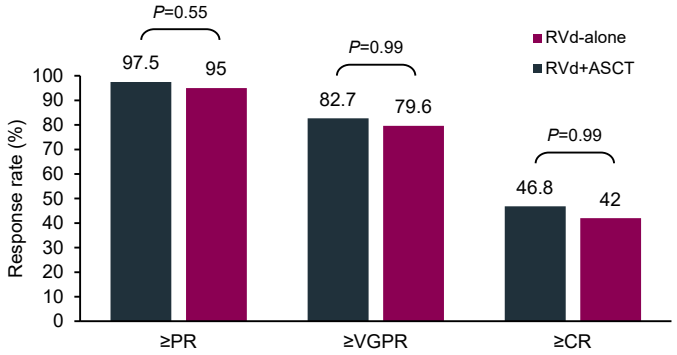
Phase 3 Study of ASCT for Newly Diagnosed Myeloma: Best Response to Treatment and Duration of Response



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.

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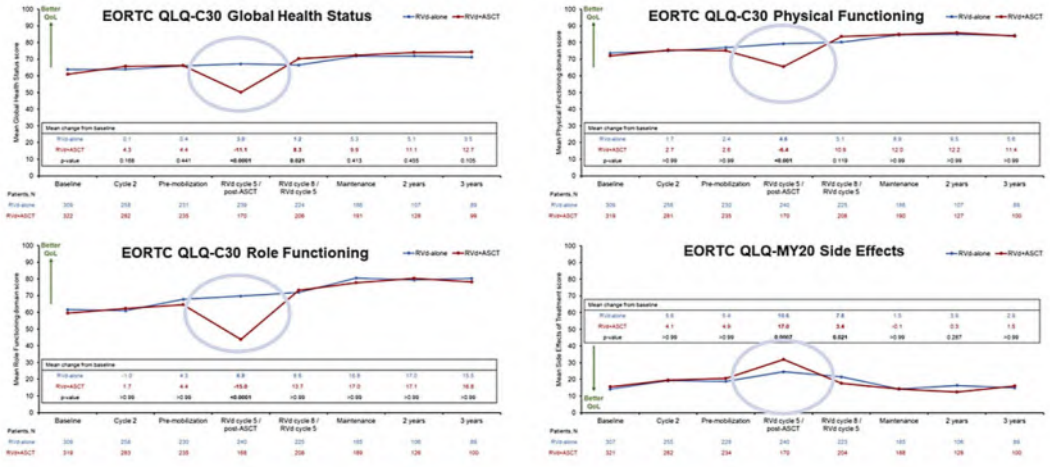
Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Quality of Life



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: 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

Late ASCT
- 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

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

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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 (that is, CR and ideally MRD negative) 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, reducing the risk of relapse, and prolonging 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

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Maintenance Therapy

The preferred, FDA-approved 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.

*Results from interim analyses of TOURMALINE MM3 and MM4 trials of ixazomib in the maintenance setting suggest a potential decrease in overall survival.

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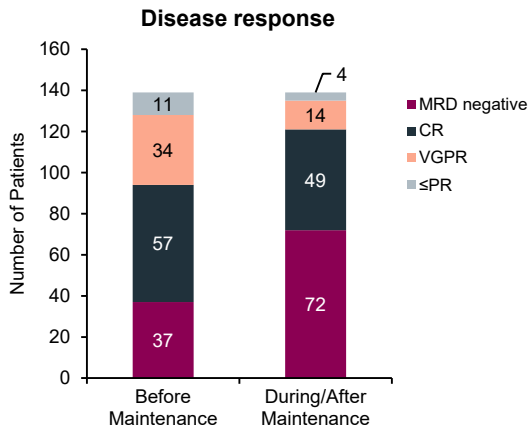
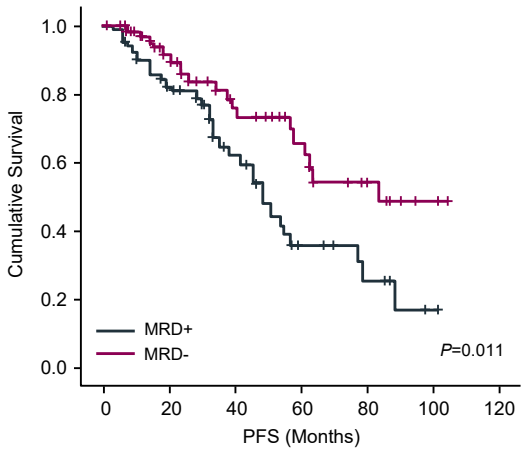
Revlimid Maintenance Therapy: Improves Depth of Response





At maximal response during or after maintenance treatment with Revlimid

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

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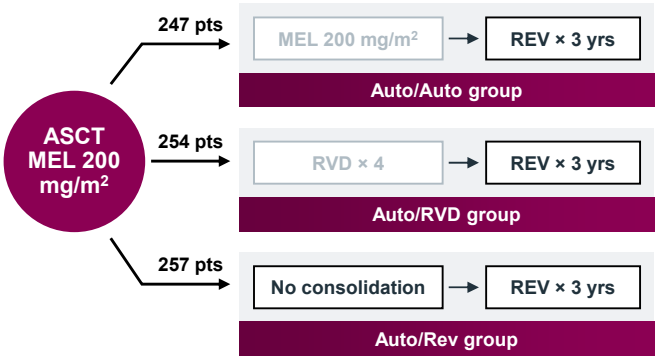
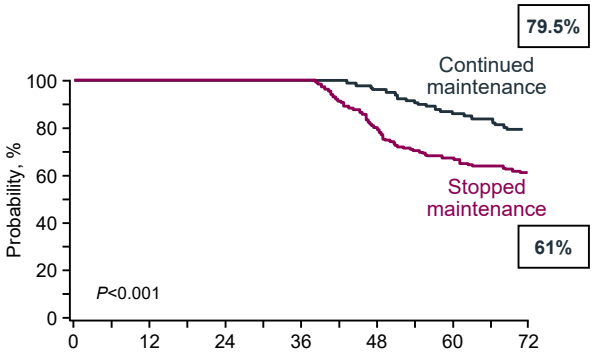
Revlimid Maintenance Duration

STAMINA Trial (BMT-CTN0702)



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



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

MEL, melphalan; RVD, Revlimid-Velcade-dex; REV, Revlimid

STAMINA Trial. Stadtmauer EA et al. *J Clin Oncol*. 2019;37:589; Hari P et al. *J Clin Oncol*. 2020;38. Abstract 8506.

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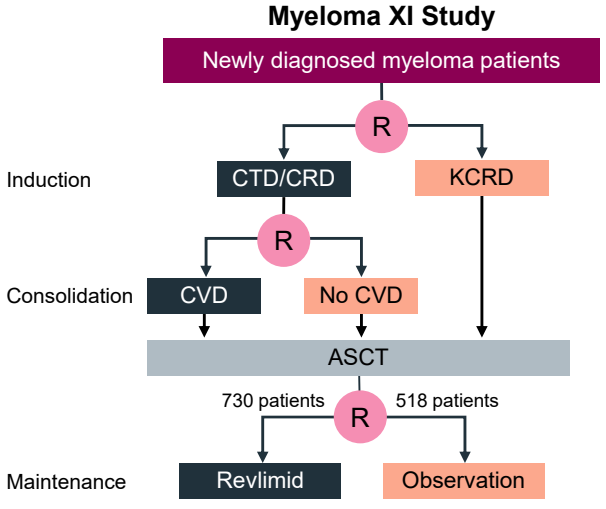
Maintenance Duration



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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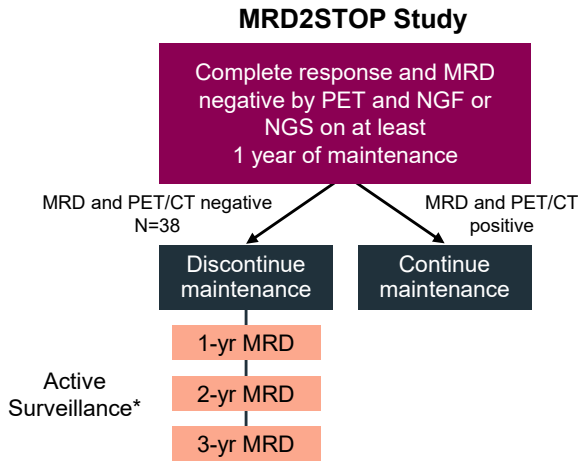
Using MRD Negativity to Guide Discontinuation of Maintenance Therapy



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

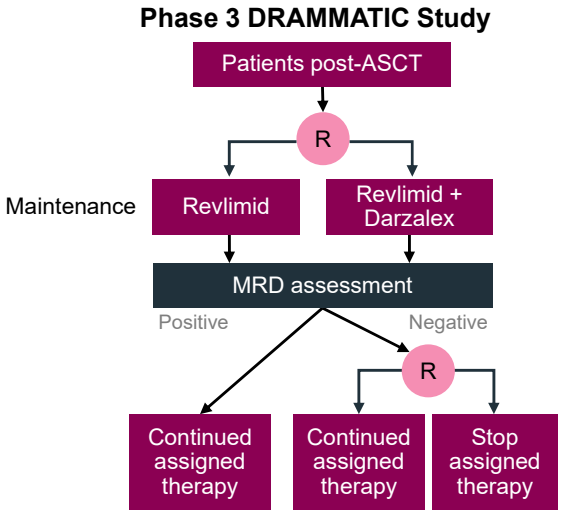
Derman BA et al. *Blood*. 2022;140. Abstract 870.

- After median follow-up of 14 months, 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.

119

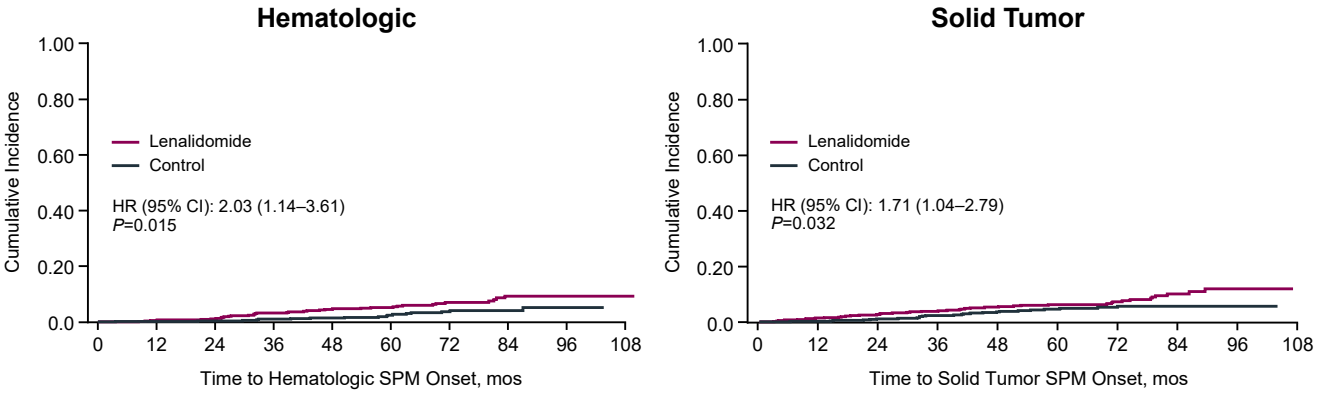
Ongoing Study Using MRD Results to Direct Therapy



clinicaltrials.gov/ct2/show/NCT04071457.

120

Revlimid Maintenance: Cumulative Incidence of Second Primary Malignancies



Cumulative incidence rates of progression or death as a result of myeloma were all higher with placebo

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

121

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).

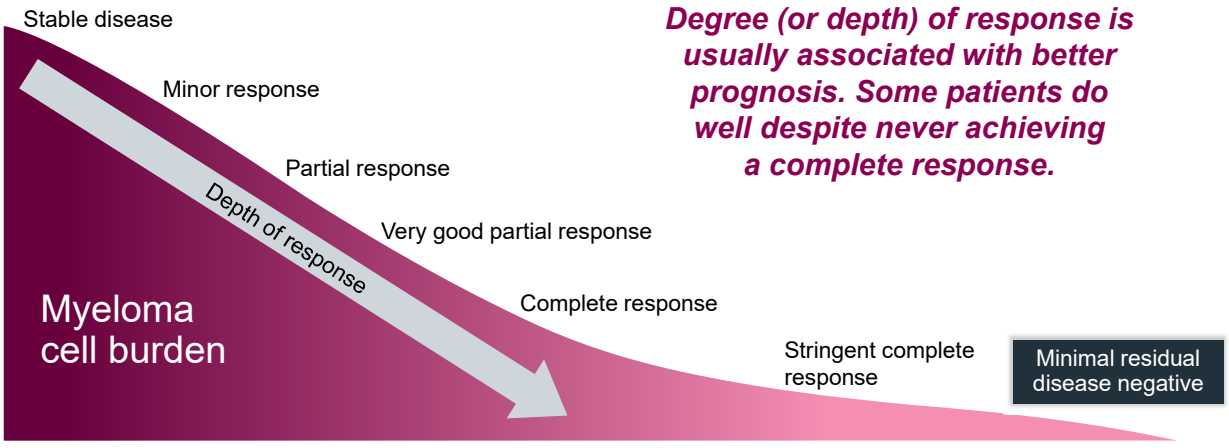
122

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.

123

Measuring Response to Therapy



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

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

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

124

What is MRD?

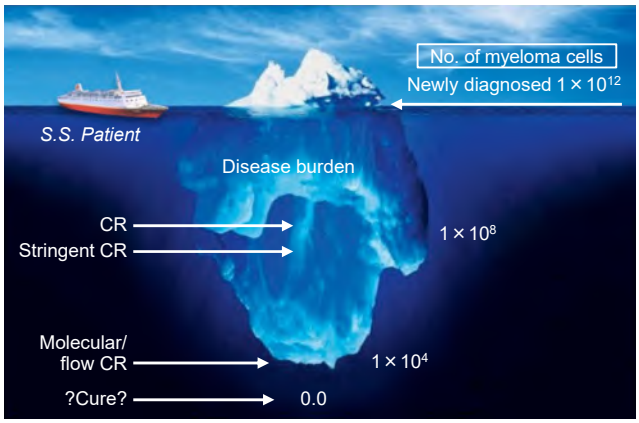
The presence of small amounts of myeloma cells in the body after treatment

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

125

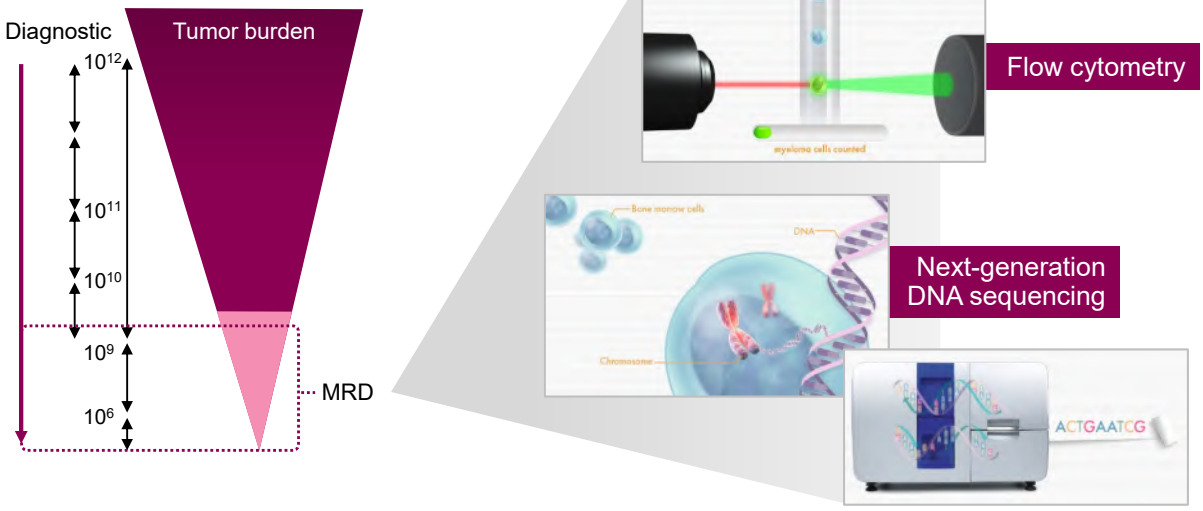
Why do we need to measure MRD?

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



126

How is MRD measured?



127

Comprehensive Response Assessment

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

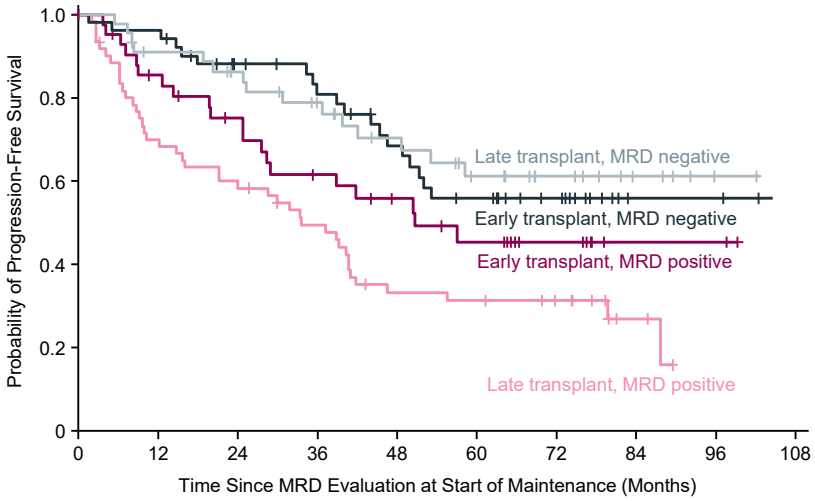
What about other areas of the body?

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

128

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.

129

MRD Summary

- MRD is the deepest response after myeloma treatment, including bone marrow MRD and imaging MRD. NGF and NGS are the two most commonly used marrow MRD tests. Blood-based MRD is in exploration.
- MRD has been associated with longer progression-free and overall survival to predict lower risk of progression. Modern combination therapies show increasingly higher MRD negativity rates.
- 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.

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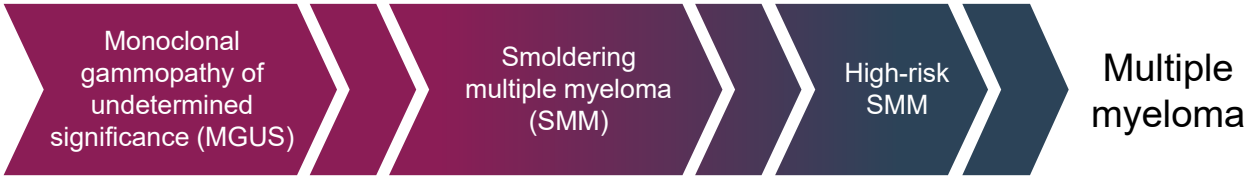
Multiple Myeloma Precursor Conditions

Gurbakhash Kaur, MD
University of Texas Southwestern Medical Center
Dallas, Texas

131

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

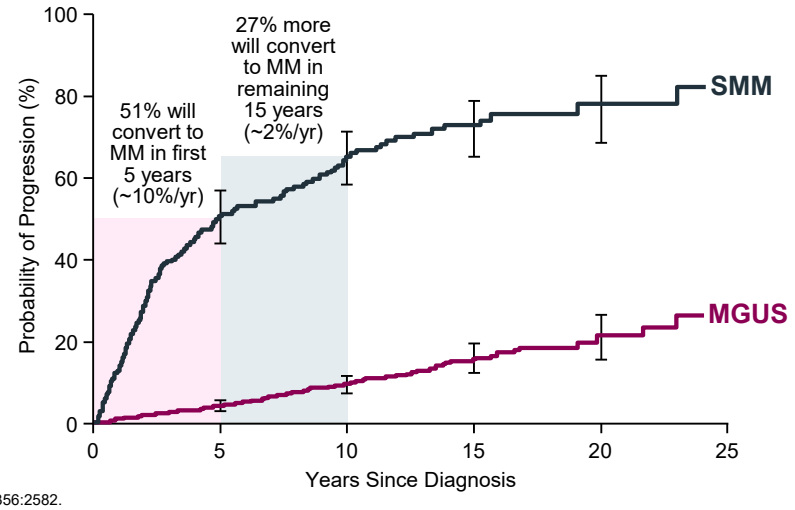
	MGUS	SMM	Active MM
M protein	<3 g/dL in blood	≥3 g/dL in blood ***or*** ≥500 mg/24 hrs in urine	≥3 g/dL in blood ***or*** ≥500 mg/24 hrs in urine
Plasma cells in bone marrow	<10%	≥10%–60%	≥60%
Clinical features	No myeloma-defining events*	No myeloma-defining events*	≥1 myeloma-defining event*, including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

133

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.

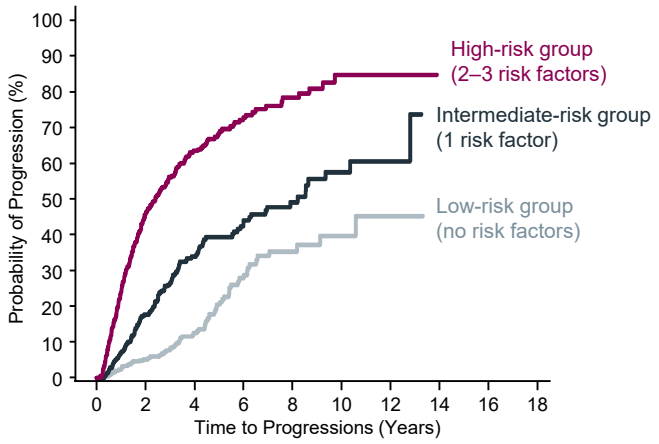
134

Risk Assessment in Smoldering Myeloma: 2/20/20 Model to Identify High-Risk SMM Patients

2/20/20 Risk assessment for SMM

- **2** >2 g/dL M protein
- **20** >20 free light chain ratio
- **20** >20% bone marrow plasma cells

Patients with two or more risk factors are considered high risk. This model does not include any biological or immune factors that may account for interpatient heterogeneity.



Risk of progression at 2 Years
44.2%
17.9%
6.2%

Mateos MV et al. *Blood Cancer J.* 2020;10:102.

135

Personalized Progression Prediction in Patients With MGUS or SMM (PANGEA)

- A new model to assess risk of progression using accessible, time-varying biomarkers
- Biomarkers tested include monoclonal protein concentration, free light chain ratio, age, creatinine concentration, and bone marrow plasma cell percentage + hemoglobin trajectories
- Improves prediction of progression from SMM to multiple myeloma compared with the 20/2/20 model

Cowan A et al. *Lancet Haematol.* 2023;10:e203.

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Can we identify everyone who has a precursor condition?

137

Studies Focusing on Myeloma Precursor Conditions

Large ongoing precursor studies

Iceland

iStopMM
Iceland Screens, Treats or Prevents Multiple Myeloma

Focus: role of population screening

United States and Canada

THE PROMISE STUDY

Focus: racial disparities and familial aggregation

United States

TRANSFORMM study

Focus: genomic markers of progression

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Prevalence of MGUS and SMM

iStopMM Study

148,704 individuals 40 years of age or older in Iceland enrolled

↓

75,422 screened for M protein and abnormal free light chain

↓

3,358 individuals with MGUS

Key Observations

SMM[1]

- SMM prevalence is 0.53% in individuals 40 years or older
- One third of SMM patients have an intermediate or high risk* of progression to myeloma

MGUS[2-4]

- 3.9% of individuals screened have MGUS (5% in individuals over 50 years of age)
- **MGUS subtypes:** 57% IgG; 21% IgM; 12% IgA. IgA prevalence rises slowly with age and plateaus after age 70.
- **Risk categories*:** 43% low; 40.4% low-intermediate; 16.3% high-intermediate; and 0.3% high.
- **No evidence of MGUS progression following SARS-CoV-2 vaccination**
- A prediction model created to identify patients with MGUS that have ≥10% bone marrow plasma cells to help clinicians determine which of their MGUS patients may defer a bone marrow biopsy.

*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow.

1. Thorsteinsdottir S et al. *Blood*. 2021;138. Abstract 151. **2.** Love TJ et al. *Blood*. 2022;140. Abstract 103. **3.** Palmason R et al. *Blood*. 2022;140. Abstract 105. **4.** Eythorsson E et al. *Blood*. 2022;140. Abstract 107.

139

High Prevalence of Monoclonal Gammopathy in a Population at Risk

The PROMISE Study

7,622 individuals screened*

6,305 patients → High-risk features for myeloma

- Blacks (n=2,439)
- Non-Blacks with family history of HM (n=3,866)

1,317 patients → No high-risk features for myeloma

- Negative family history of HM (n=631)
- Unknown family history of HM (n=686)

*The PROMISE study and Mass General Brigham Biobank—detected by mass spectrometry.

HM, hematologic malignancy

El-Khoury H et al. *Blood*. 2021;138. Abstract 152.

MGUS estimated in 13% to 17% of a high-risk screened population (rates increase with age).

Higher detection rates of free light chains by mass spectrometry than conventional methods.

Older adults who are Black or have a first-degree relative with a HM have an increased prevalence for MGUS.

Older individuals who are Black or have a first-degree relative with a HM may benefit from screening to allow for early detection and possible clinical intervention.

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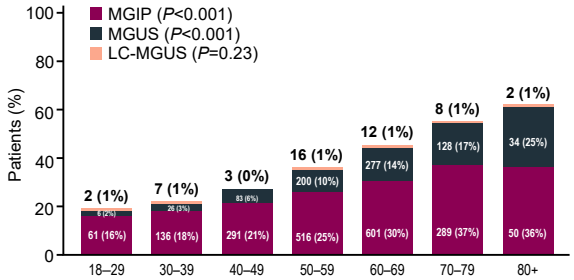
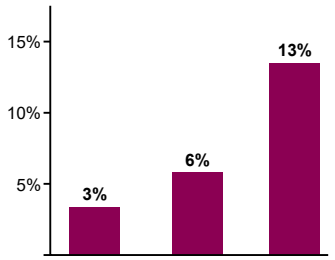
High Prevalence of Monoclonal Gammopathy in a Population at Risk

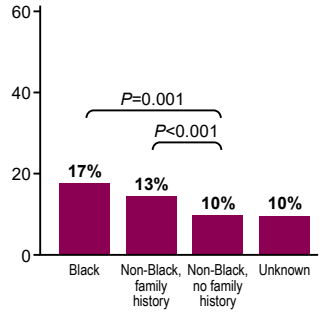
Rates of all monoclonal gammopathies* increase with age



MGUS more prevalent in individuals older than 50 years at risk



Higher rates of MGUS* in Blacks or individuals with a family history of HM and older than 50 years at risk



*Free light chains detected by mass spectrometry.

HM, hematologic malignancy; MGUS, monoclonal gammopathy of undetermined significance; MGIP, monoclonal gammopathies of indeterminate potential; LC, light chain; SPEP, serum protein electrophoresis; IFX, immunofixation; MS, mass spectrometry; MGBB, Mass General Brigham Biobank

El-Khoury H et al. *Blood*. 2021;138. Abstract 152.

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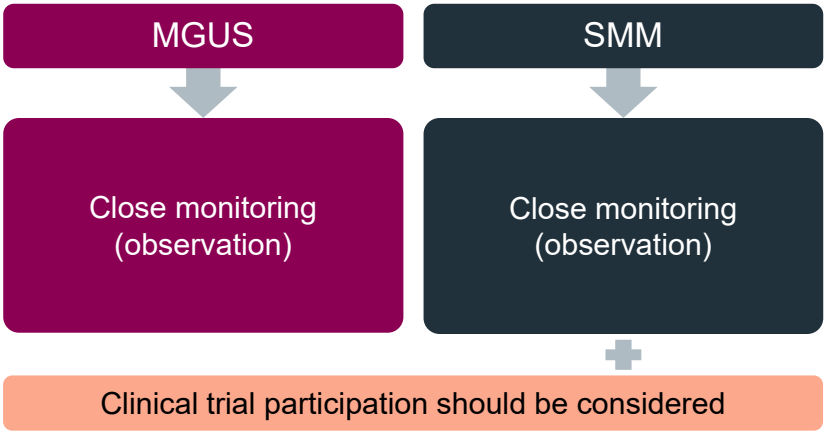
Overview of Current Treatment Approach



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Approaches to SMM Treatment: *Only in the Context of a Clinical Study*

Immunologic therapy
(control approach)

Intensive therapy
(curative intent)

Len, Len/Dex, Dara

IRD, KRD, ERD

CESAR, ASCENT

Pros
- Fewer side effects
- More likely to induce long-term effects

Cons
- Low OR
- Does not eliminate the clone

Pros
- High ORR
- Deep responses

Cons
- Toxicity similar to myeloma treatment
- May result in resistant clones

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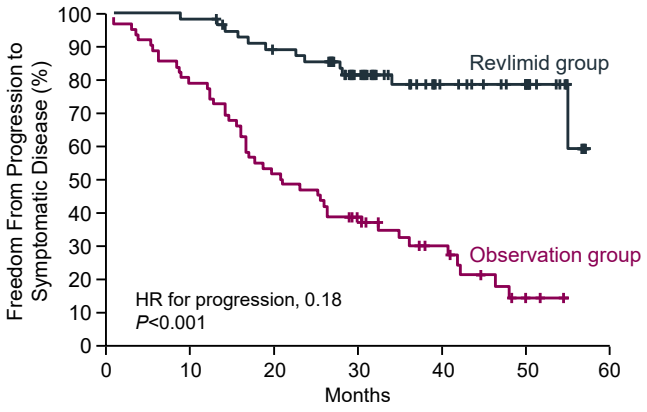
Early Therapeutic Intervention

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Eduardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

Progression-free survival for early treatment



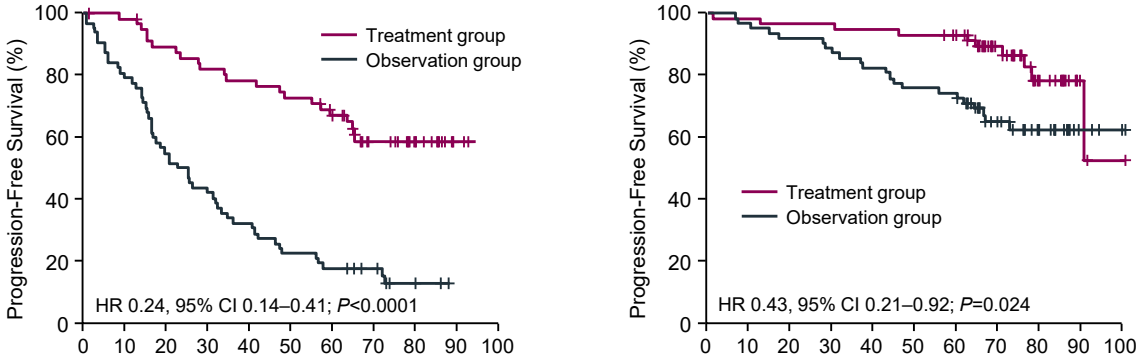
HR, hazard ratio

Mateos MV et al. *N Engl J Med.* 2013;369:438.

144

QuiRedex Phase 3 Trial
Len-dex vs No Treatment in High-Risk SMM

Median follow-up (n=119): 75 mos

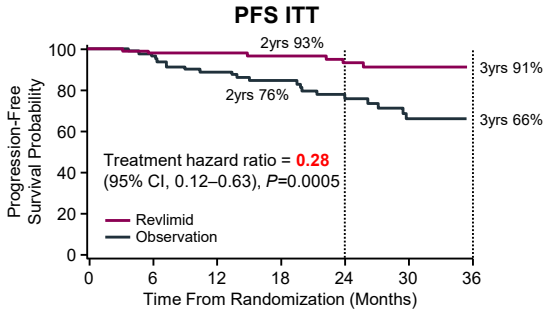


Early treatment with Rd significantly delayed the TTP to myeloma with a benefit in OS

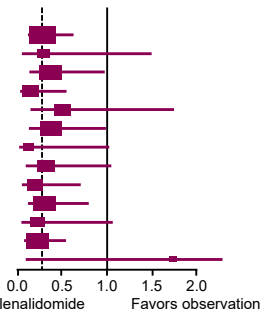
Mateos MV et al. *N Engl J Med*. 2013.
Mateos MV et al. *Lancet Oncol*. 2016.

145

Revlimid vs Observation Alone in Patients With SMM



Group	n	HR	95% ci
All patients	182	0.28	(0.12, 0.62)
Mayo 2008 risk high	29	0.29	(0.06, 1.49)
Mayo 2008 risk intermediate	104	0.37	(0.14, 0.97)
Mayo 2018 risk high	56	0.09	(0.02, 0.44)
Mayo 2018 risk intermediate	68	0.52	(0.15, 1.85)
Age <70	135	0.37	(0.14, 0.98)
Age ≥70	47	0.13	(0.02, 1.01)
Male	88	0.32	(0.10, 1.03)
Female	94	0.20	(0.06, 0.70)
ECOG PS 0	134	0.30	(0.12, 0.79)
ECOG PS 1–2	48	0.22	(0.05, 1.05)
White	140	0.22	(0.09, 0.54)
Black	31	1.73	(0.10, 30.76)



Criteria: PCBM ≥10% and sFLC ratio >8 or <0.125

Mayo2008: PCBM ≥10% + MC ≥3 g/dL
Mayo 2018: 2/20/20

- N=182, intermediate/high-risk SMM (BMPC% ≥10% and aberrant (FLC) ratio (<0.26 or >1.65)
- 1:1 randomization lenalidomide 25 mg day 1 to 21 in 28-day cycle vs observation
- Median FU 35 mnd, median time on len 23 cycles, len discontinued in 51% of patients

Early treatment with R significantly prevented the progression to MM, especially in the high-risk subgroup.

E3A06 Study. Lonial S et al. *J Clin Oncol*. 2019;38:1126.

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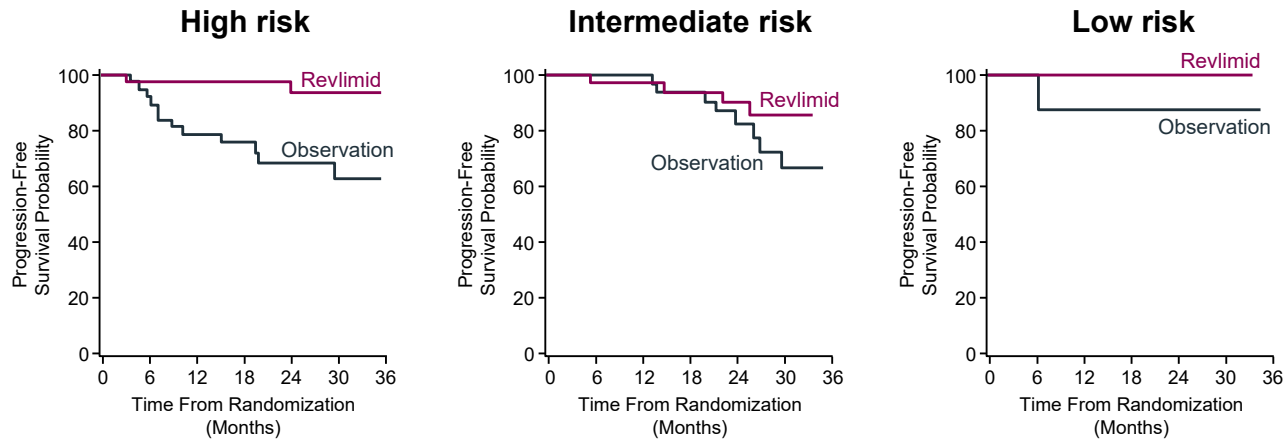
Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria



Lonial S et al. *J Clin Oncol*. 2020;38:1126.

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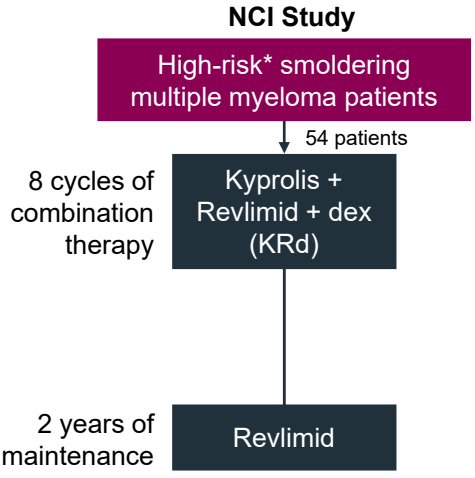
Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex for High-Risk SMM Patients



- At a median potential follow-up time of 31.9 months (range, 6.7–102.9 months), the MRD-negative CR rate was 70.4%
- The median sustained MRD duration was 5.5 years
- The 8-year probability of being free from progression to multiple myeloma was 91.2%, and no deaths occurred

Very encouraging results for a curative approach to high-risk SMM.

*According to the Mayo and/or Spanish models.

Kazandjian D et al. *JAMA Oncol*. 2021 Nov 1;7(11):1678-1685

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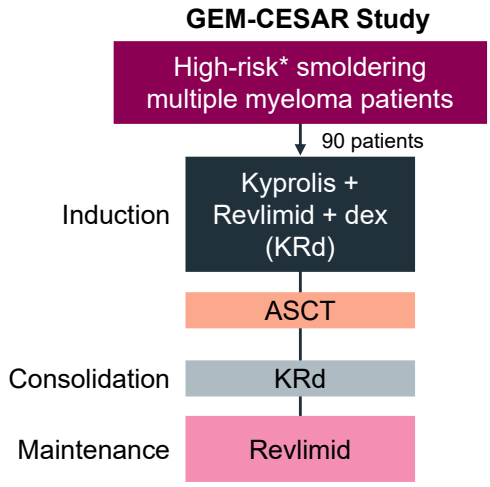
Multicenter, Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex for High-Risk SMM Patients



- At 70 months, 94% of patients have not progressed to multiple myeloma; 48% have biochemically progressed (rescue therapy with DPd resulted in 80% overall response rate)
- The presence of SLiM criteria and MRD at the end of maintenance predicted progression.
- The achievement of MRD negativity after maintenance and 4 years after ASCT predicted sustained MRD negativity.

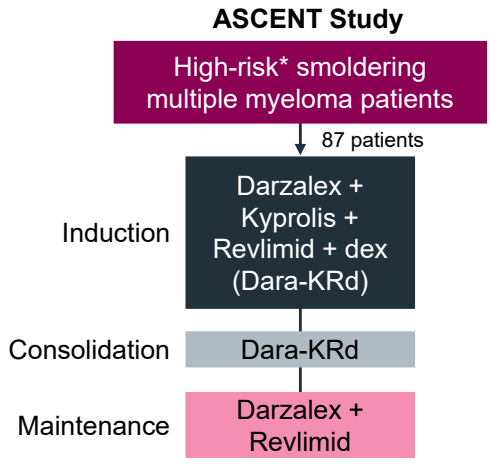
Encouraging results for a curative approach to high-risk SMM.

*According to the Mayo and/or Spanish models.

Mateos MV et al. *Blood*. 2022;140. Abstract 118.

149

Four-Drug Combination Strategy for High-Risk SMM Patients



- Best overall response rate was 97% (92% ≥VGPR); 84% of patients achieved MRD negativity.
- Grade ≥3 hematologic toxicity in 18% of patients; non-hematologic toxicity in 51% of patients.
- 89.9% of patients are progression-free at 3 years.

High response rates and outcomes data similar to NCI study. Longer follow up is needed.

*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow; or a total score of ≥9 on IMWG scoring system.

Kumar SK et al. *Blood*. 2022;140. Abstract 757.

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Summary

- Precursor plasma cell disorders are characterized by the presence of abnormal clonal plasma cells without any end organ damage.
- MGUS is a common condition; prevalence increases with age.
- There is variable risk of progression from MGUS and SMM to overt myeloma; clinical risk models associated with risk of progression. We are still lacking molecular markers.
- Screening efforts are under way.
- Single arm study data show benefit with early intervention.
- Patients with high-risk SMM should be offered treatment on clinical trials.
- Participation in observational/interventional studies is key to finding out which patients can benefit the most from early treatment and what is the best treatment to offer early. To identify molecular markers of progression vs stable disease.

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High-Risk Multiple Myeloma

Amrita Y. Krishnan, MD
City of Hope Medical Center
Duarte, California

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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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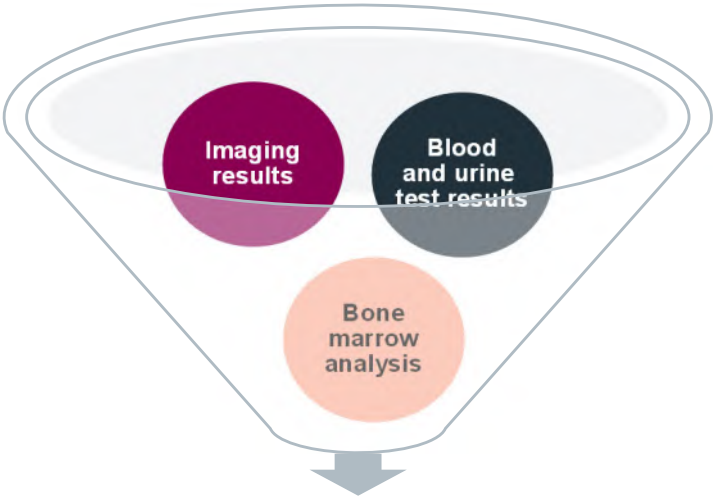
Assessing Risk



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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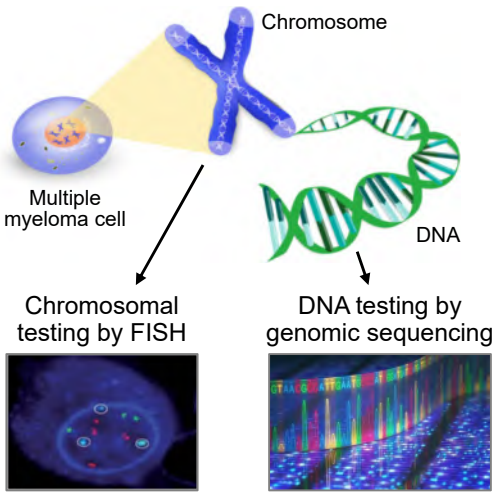
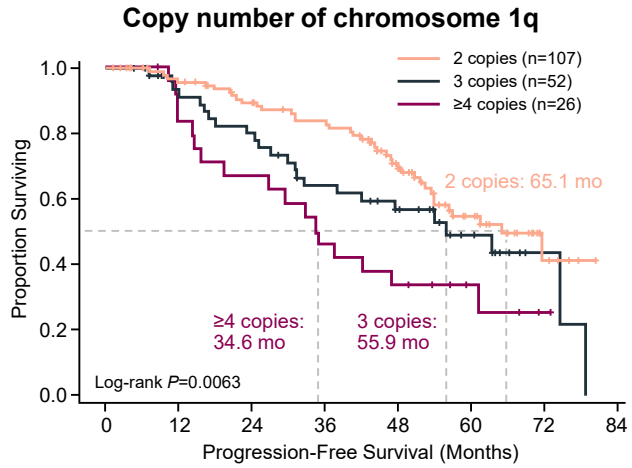
Why is genomic sequencing important in myeloma risk assessment?

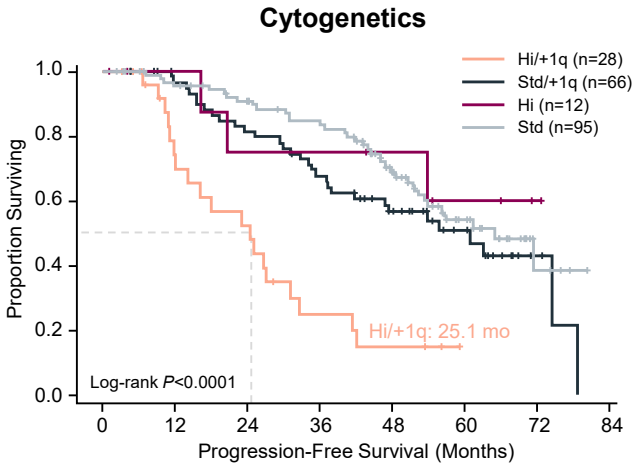
- Genetic changes in myeloma cells may affect prognosis and treatment selection
- Using samples from the bone marrow—specific tests look at these genetic changes
- Some tests are used routinely and look at the ***chromosomal*** changes (FISH)
- Newer tests assess changes in the ***DNA*** (gene expression 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!



156

MMRF CoMMpass Findings: Chromosome 1 Copy Number and Other Cytogenetics



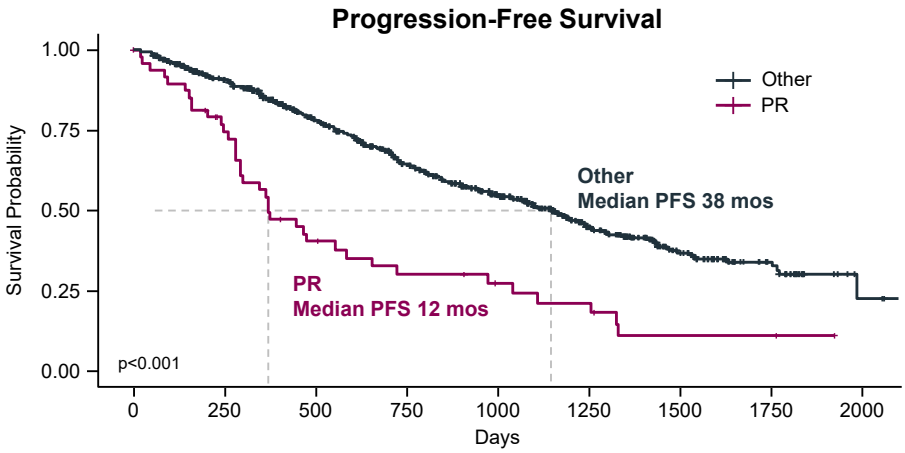


Hi, high-risk cytogenetics: t(4;14), t(14;16) and/or del(17p); Std, standard-risk cytogenetics

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

157

MMRF CoMMpass Findings: 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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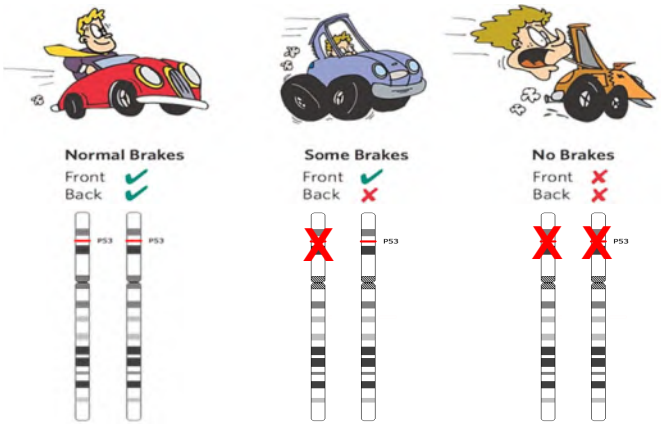
MMRF CoMMpass Findings: Identifying Double-Hit Multiple Myeloma

- 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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MULTIPLE MYELOMA Research Foundation 25th ANNIVERSARY

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.

162

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.

163

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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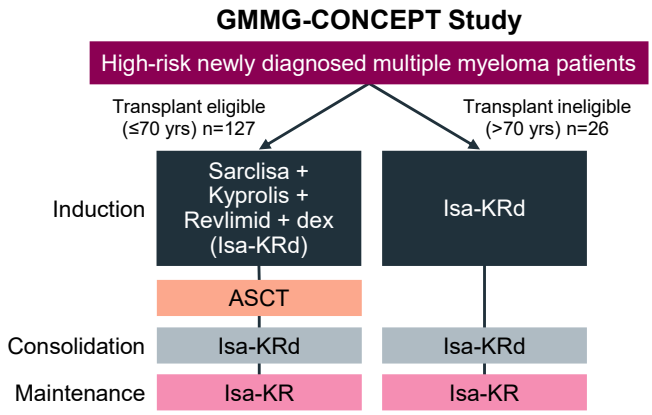
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease



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
Progression-free survival (months)	Not reached	Not reached

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

Leypoldt LB et al. *J Clin Oncol*. 2023;Sept 27 [Online ahead of print].

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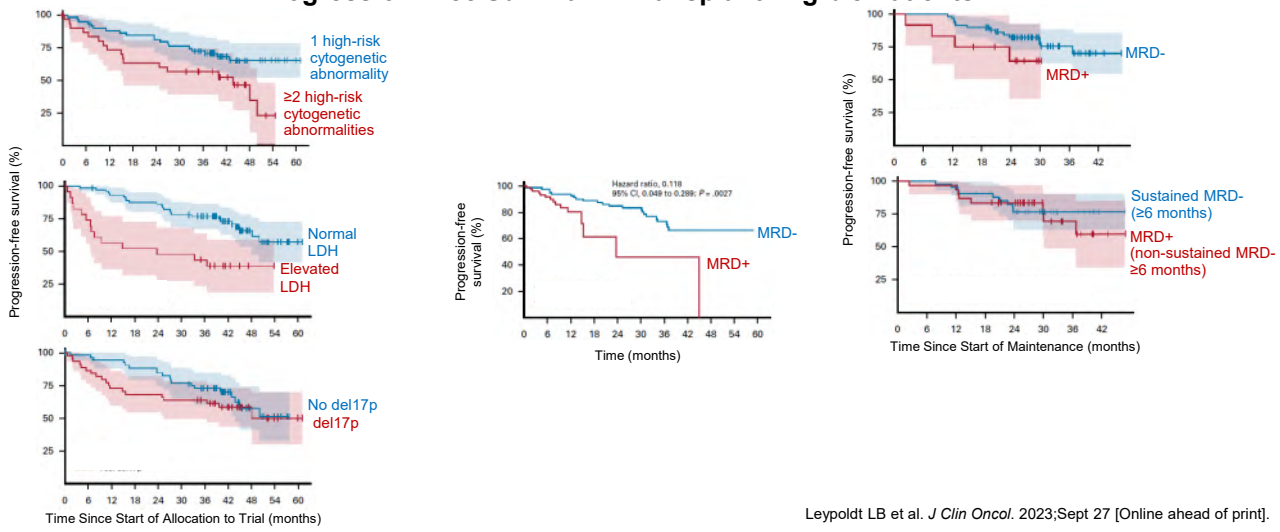
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

Progression-Free Survival in Transplant Eligible Patients



Leypoldt LB et al. *J Clin Oncol*. 2023;Sept 27 [Online ahead of print].

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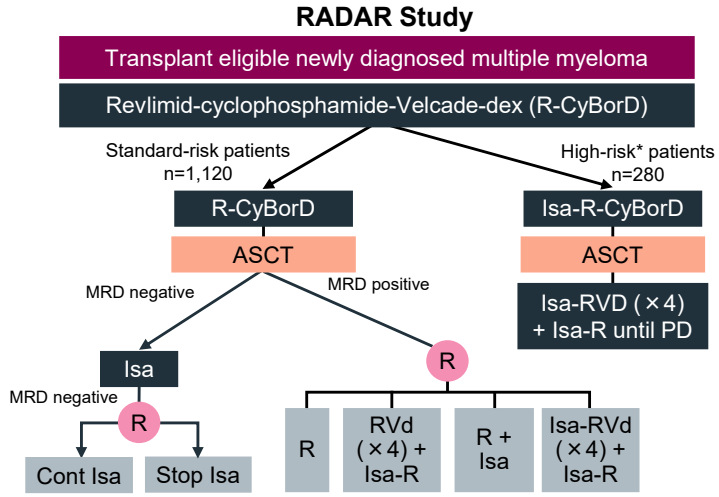
Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease



*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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New Drugs on the Horizon

Robert M. Rifkin, MD
Sarah Cannon Research Institute
Rocky Mountain Cancer Centers
Denver, Colorado

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Emerging Treatment Options

- Cereblon E3 ligase modulators (CELMoDs)
- Immunocytokines
- Checkpoint inhibitors
- Small-molecule inhibitors
- Next-generation cellular therapies and trispecific antibodies

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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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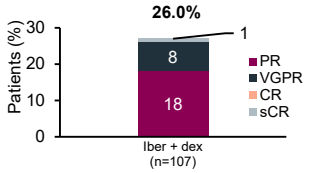
Iberdomide: A CELMoD

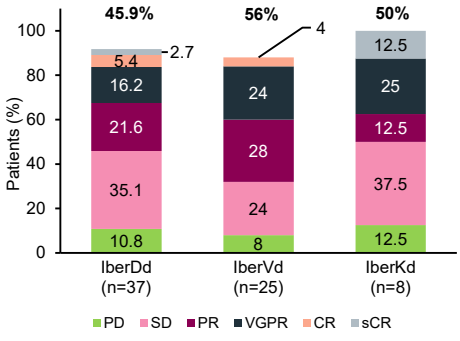
Iberdomide in combination with dexamethasone in patients with RRMM[1]

107 patients who had received at least 6 prior lines of therapy and 97% were triple-class refractory



Adverse events (%)	Grades 1–2	Grade 3	Grade 4
All infections	31	24	3
Fatigue	21	2	1
Insomnia	13	1	0
Diarrhea	22	1	0
Muscle spasms	7	0	0

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

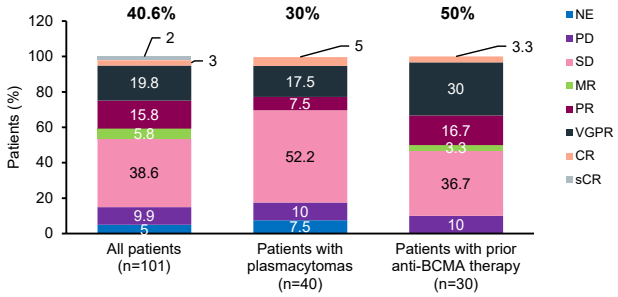


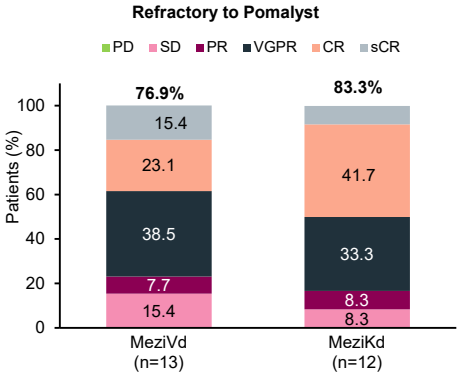
A phase 3 study is under way comparing IberDd with DVd in patients with RRMM

1. Lonial S et al. *Lancet Haematol*. 2022;9: e822. **2.** Lonial S et al. Presented at the 2021 IMW. Abstract OAB-013.

172

Mezigdomide: A CELMoD





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

Two phase 3 studies are under way comparing (1) mezigdomide + Kyprolis-dex with Kyprolis-dex and (2) mezigdomide + Velcade-dex with Pomalyst-Velcade-dex in patients with RRMM.

Richardson PG et al. *Blood*. 2022;140. Abstract 568.
Oriol A et al. *Clin Lymphoma Myeloma Leuk*. 2023;23. Abstract OA-49.

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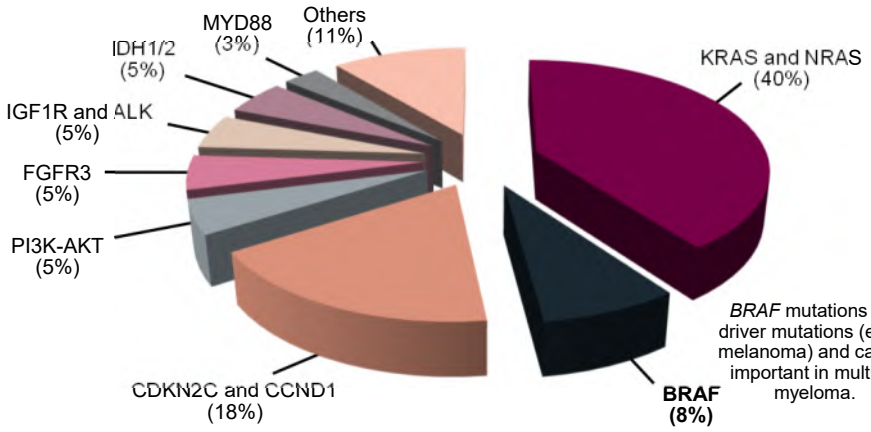
Actionable Alterations in MM

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

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



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

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Personalized Medicine Agents Under Clinical Investigation

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

*Being studied in the MyDRUG trial

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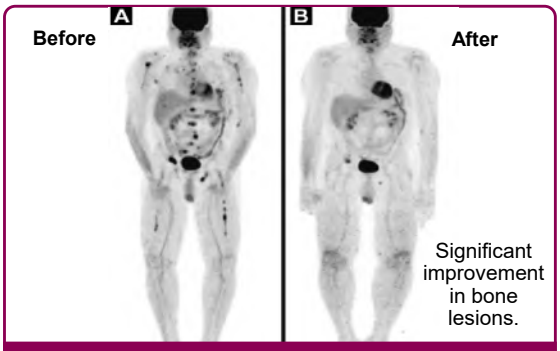
BRAF and MEK



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

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

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

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

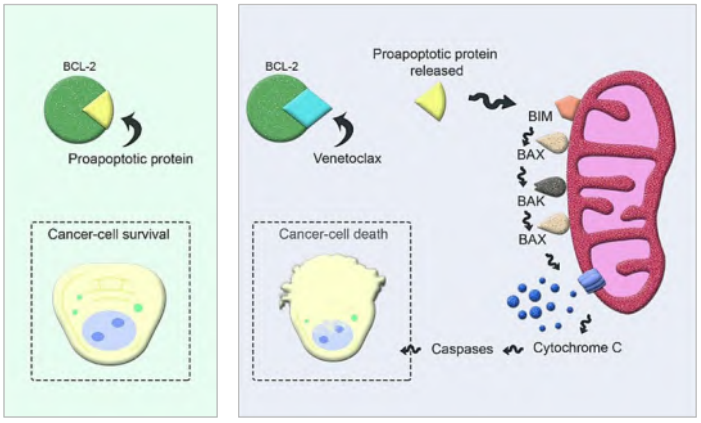
GMMG-Birma Trial. Giesen N et al. *Blood*. 2023;141:1685.

176

Venetoclax and t(11;14)

Venetoclax is a Bcl-2 inhibitor

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



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

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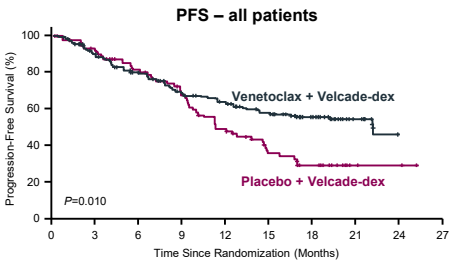
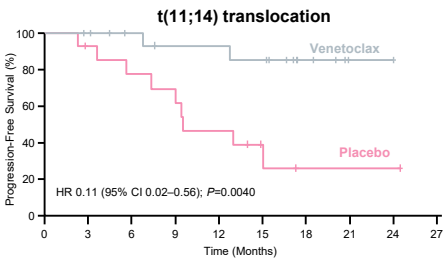
Venetoclax and t(11;14)

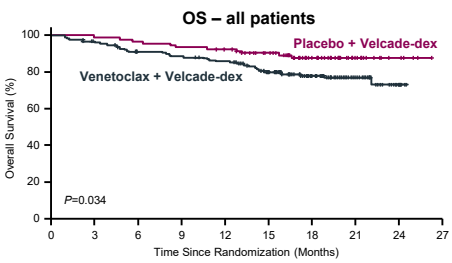
Venetoclax bortezomib dex vs placebo bortezomib dex; 1–3 prior lines

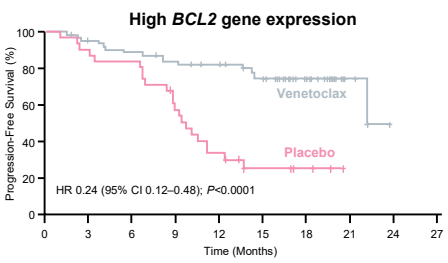
Median follow-up 18.7 m
mPFS
22.4 m venetoclax
11.5 m placebo

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









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

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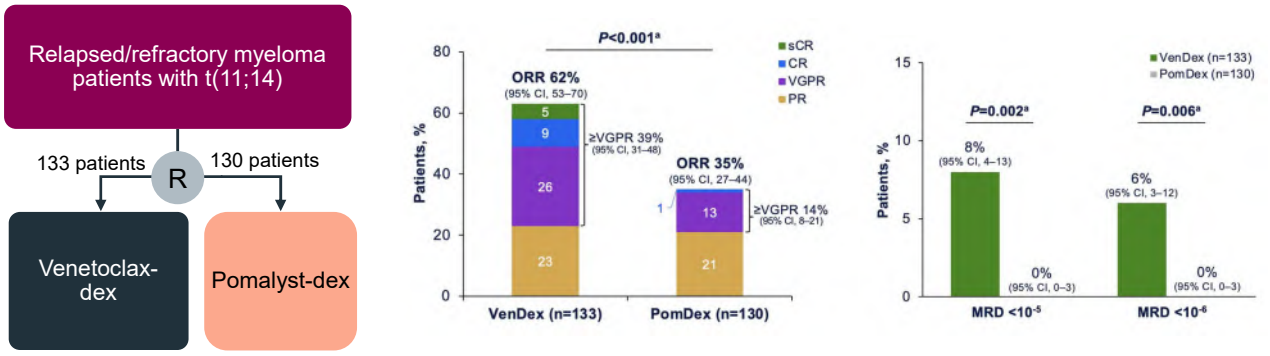
Phase 3 Study of Venetoclax in t(11;14)-Positive RRMM Patients



CANOVA Study. Mateos MV et al. *Clin Lymphoma Myeloma Leuk*. 2023;23. Abstract.

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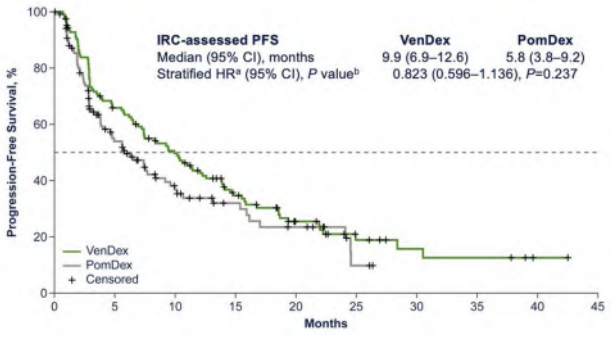
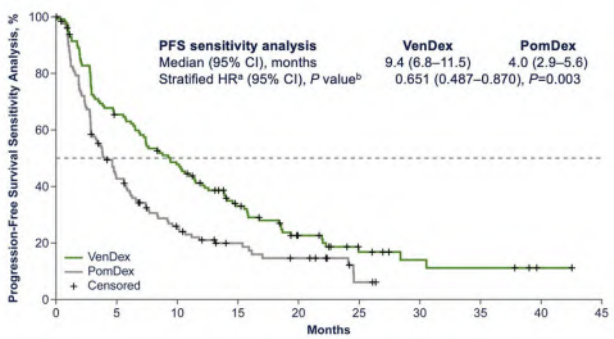
Phase 3 Study of Venetoclax in t(11;14)-Positive RRMM Patients

PFS IRC-Assessed



PFS – Post-hoc Sensitivity Analysis



CANOVA Study. Mateos MV et al. *Clin Lymphoma Myeloma Leuk*. 2023;23. Abstract.

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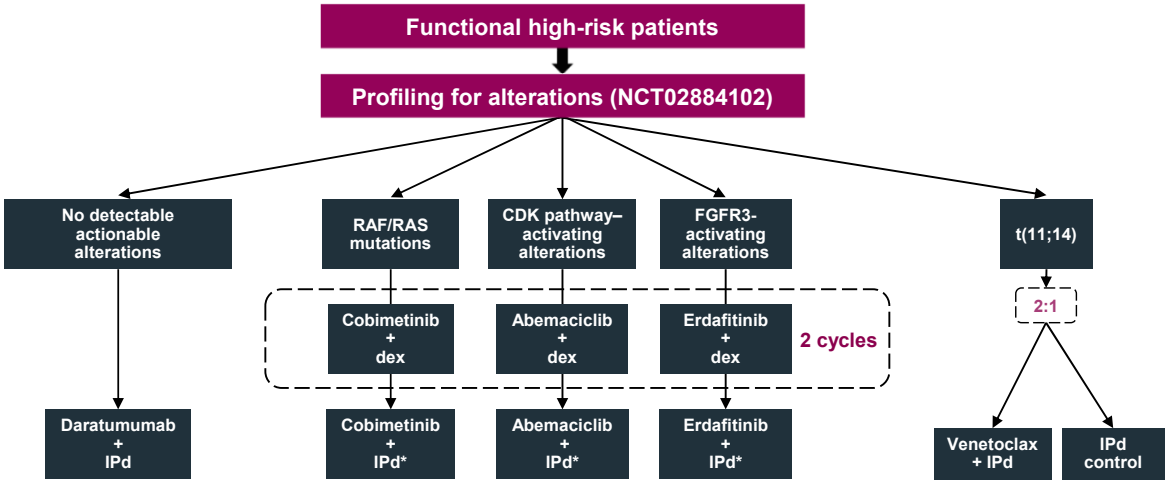
MyDRUG Study



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

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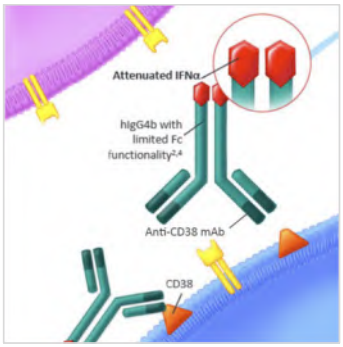
Immunocytokines

Modakafusp alfa is an antibody fused to the cytokine interferon-alpha that can bind to CD38 on myeloma cells



100 patients who had a median of 7 prior lines of therapy were treated with different doses of modakafusp (19% had prior CAR T-cell therapy and 14% prior T-cell engagers).

Overall response rate was 43% in patients receiving 1.5 mg/kg dose every 4 weeks (n=30); 27% of anti-BCMA exposed patients responded.

Immunocytokines are engineered to deliver cytokines (a protein produced by immune cells) that can prevent myeloma cells from dividing and to help boost myeloma-fighting immune cells.

Vogl DT et al. *Blood*. 2022;140. Abstract 565.

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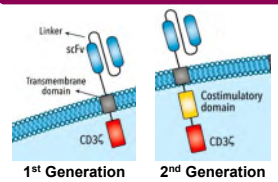
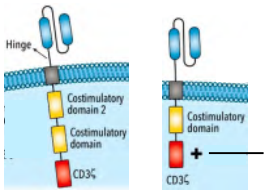
Evolution of CAR T-Cell Therapy

Single target



1st Generation | 2nd Generation

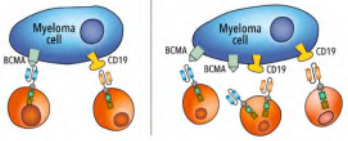
Abecma
Carvykti
CT053
CT103A
C-CAR088
P-BCMA-101
ARI-002h



3rd generation | 4th generation ("Armored" CARs)

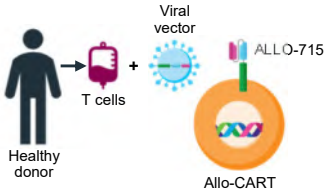
Cytokines, enzymes, costimulatory ligands

Dual targets



GC012F(BCMA/CD19)

Allogeneic



Improving efficacy

Improving safety

Improving access

Rodriguez-Lobato LG et al. *Hematol*. 2021;2:1.

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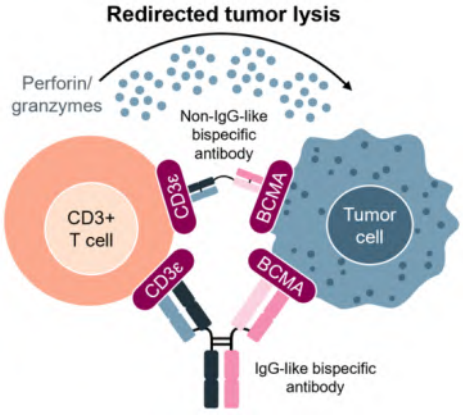
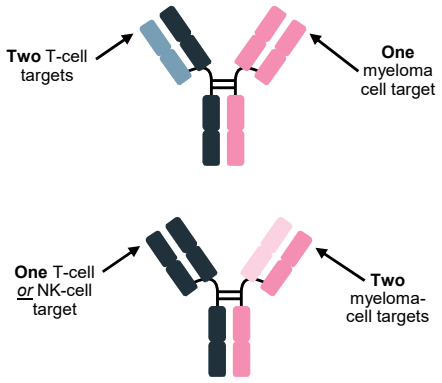
Evolution of Bispecific Antibodies

Bispecific antibodies: dual targets



Trispecific antibodies: triple targets



Lancman G et al. *Hematology Am Soc Hematol Educ Program*. 2020;2020:264.

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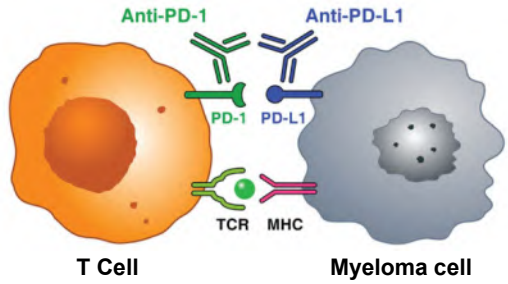
Strategies to Improve Immune Regulation of T Cells in MM: Checkpoint Inhibitors

Checkpoint inhibitors: activate T cells by "taking the brakes off"



- The cell surface immune checkpoint proteins PD-1/PD-L1 play a crucial role in regulating an immune response
  - Plasma cells in myeloma patients have increased PD-L1 expression; when it binds to PD-1 on T cells, T cell activation is blocked
- Additional checkpoint proteins include
  - LAG3
  - TIM-3
  - TIGIT
- Many checkpoint inhibitors (which are monoclonal antibodies) are FDA approved for other cancers
  - Pembrolizumab (anti-PD-1)
  - Nivolumab (anti-PD-1)
  - Cemiplimab (anti-PD-1)
  - Atezolizumab (anti-PD-L1)
  - Durvalumab (anti-PD-L1)
  - Opdualag (anti-LAG3)

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Summary

- CELMoDs are emerging as active oral agents, even in patients who have received BCMA directed therapies including CAR Ts.
- Efforts are under way to better understand the nature of the disease and to provide patients with a more personalized approach to treatment.
- New immunotherapies are emerging, including immunocytokines, next-generation CAR Ts, bispecific/trispecific antibodies, and checkpoint inhibitors.

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MULTIPLE MYELOMA Research Foundation 25th ANNIVERSARY

Questions & Answers

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MULTIPLE MYELOMA Research Foundation 25th ANNIVERSARY

Thank you!

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Resources

- Resource tab includes
  - Speaker bios
  - Glossary
  - Copy of the slide presentation
  - Exhibit Hall

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Upcoming Patient Education Events
Save the Date

Topic	Date and Time	Speakers
Non-BCMA Bispecific Antibodies 2023 FAQs Livestream	Monday, October 30 2:00 PM to 3:00 PM (ET)	Hearn Jay Cho, MD, PhD Chloe Ray, MSN, AGPCNP-BC, OCN
Patient Summit *Boston, MA*	Saturday, November 11 9:00 AM – 3:15 PM (ET)	Shonali Midha, MD Clifton C. Mo, MD Omar Nadeem, MD Paul G. Richardson, MD Sarah Patches Baker, FNP-BC, MSN
Patient Summit *Virtual*	Saturday, January 13, 2024 12:00 PM – 5:15 PM (ET) 9:00 AM – 2:15 PM (PT)	Ajai Chari, MD Tom Martin, MD Sagar Lonial, MD Nancy S. Wong, MSN

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

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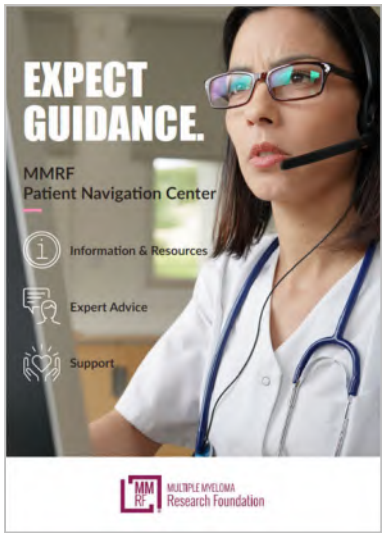
MMRF Patient Resources



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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**!
themmrf.org/get-involved/mmrf-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

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