Opening Remarks
Mary DeRome, MS
MMRF

Tech Support
1-719-234-7952
Resources

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

*Submit your questions throughout the program!*
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

Summit Agenda

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

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
      o Drive multiple myeloma cell growth and survival
      o Contribute to drug resistance
      o May predict which patients respond to which therapy
    • Genetic abnormalities that help refine risk assessment
  – Led to conception of the MyDRUG trial
MyDRUG Trial

Functional high-risk patients

Profiling for alterations (NCT02884102)

- No detectable actionable alterations
- RAF/RAS mutations
- CDK pathway-activating alterations
- FGFR3-activating alterations

- t(11;14)
- 2 cycles
- 2:1

- Daratumumab + IPd
- Cobimetinib + IPd*
- Abemaciclib + IPd*
- Erdafitinib + IPd*
- Venetoclax + IPd
- IPd control

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

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
Welcome!

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

Newly Diagnosed Multiple Myeloma:
Diagnosis and Induction Therapy

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

How common is multiple myeloma?

- Multiple myeloma is the 2nd most common cancer of the blood.
- There were 35,730 new cases in 2023.
- 159,787 people are living with myeloma or in remission.
- Myeloma represents 1.8% of all new cancer cases in the U.S.
- The median age at diagnosis is 69.
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

**BONES**
- Surrounding bone where myeloma cells grow is affected
- Myeloma cells activate bone destruction

**BLOOD**
- Myeloma is a cancer of the blood
- Myeloma crowds out normal blood cells

**KIDNEYS**
- Large amounts of M protein can overwork or cause damage to the kidneys

**Multiple Myeloma Affects Your Bones, Blood, and Kidneys**

The clinical features that are characteristic of multiple myeloma

<table>
<thead>
<tr>
<th>C</th>
<th>R</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>High levels of calcium in the blood</td>
<td>Decreased kidney (renal) function</td>
<td>Low amount of red blood cells (anemia)</td>
<td>Presence of bone damage</td>
</tr>
</tbody>
</table>
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

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)
Demographic Risk Factors: Multiple Myeloma

- Older age
- Male sex
- Obesity
- Race: 2x 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


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
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

The Right Tests: Common Tests Conducted in Myeloma Patients

Blood tests
- Confirms the type of myeloma or precursor condition

Urine tests

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
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
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%

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**
Know Your Bone Marrow Tests!

Types of chromosomal abnormalities

- Translocation
- Deletion
- Gain or amplification

Putting the Results Together

Staging, prognosis, and risk assessment
Multiple Myeloma Prognosis and Risk

Revised International Staging System (R-ISS)

<table>
<thead>
<tr>
<th>R-ISS stage</th>
<th>Laboratory measurements</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>• Serum β2M level &lt;3.5 mg/L</td>
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<tr>
<td></td>
<td>• Serum albumin level ≥3.5 g/dL</td>
</tr>
<tr>
<td></td>
<td>• No high-risk CA*</td>
</tr>
<tr>
<td></td>
<td>• Normal LDH level</td>
</tr>
<tr>
<td>II</td>
<td>All other possible combinations</td>
</tr>
<tr>
<td>III</td>
<td>• Serum β2M level ≥5.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>• High-risk CA* or high LDH level</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>High risk</th>
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<tbody>
<tr>
<td>• High-risk genetic abnormalities</td>
</tr>
<tr>
<td>• t(4;14)</td>
</tr>
<tr>
<td>• t(14;16)</td>
</tr>
<tr>
<td>• t(14;20)</td>
</tr>
<tr>
<td>• del 17p</td>
</tr>
<tr>
<td>• p53 mutation</td>
</tr>
<tr>
<td>• gain 1q</td>
</tr>
<tr>
<td>• R-ISS Stage 3</td>
</tr>
<tr>
<td>• High plasma cell S phase</td>
</tr>
<tr>
<td>• GEP: high-risk signature</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Standard risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All others including:</td>
</tr>
<tr>
<td>• Trisomies</td>
</tr>
<tr>
<td>• t(11;14)</td>
</tr>
<tr>
<td>• t(6;14)</td>
</tr>
</tbody>
</table>

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

β2M: beta-2 microglobulin; LDH: lactate dehydrogenase; GEP: gene-expression profiling

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

<table>
<thead>
<tr>
<th>Standard risk</th>
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<tbody>
<tr>
<td><strong>R-ISS Stage I</strong></td>
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<td>• Serum β2M level &lt;3.5 mg/L</td>
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<td>• No high-risk chromosomal abnormality*</td>
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<tr>
<td>• Normal LDH level</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R-ISS Stage III</strong></td>
</tr>
<tr>
<td>• Serum β2M level ≥5.5 mg/L</td>
</tr>
<tr>
<td>• High-risk chromosomal abnormality* or high LDH level</td>
</tr>
</tbody>
</table>

*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
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.

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.
Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

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

26.5% 27.4% 33.5% 47.2% 56.9%

Available treatments
Chemotherapy + dexamethasone + stem cell transplantation
Velcade (bortezomib)
Reblivim (lenalidomide)
Kyprolis (carfilzomib)
Pomalyst (pomalidomide)

2014 and beyond
Ninlare (ixazomib)
Empliciti (elotuzumab)
Darzalex (daratumumab)
Xpovio (selinexor)
Sarclisa (isatuximab)
Abecma (idecabtagene viclucel)
Carvykti (ciltaclambagene autoleucel)
Tecvayli (teclistamab)
Talve (talquetamab)
Elrexfio (elranatamab)

Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma

Transplant candidate
Induction therapy
± Consolidation therapy
Maintenance therapy
Non-transplant candidate
Induction therapy
Maintenance therapy
Overview of Treatment Approach for Active Multiple Myeloma

Is the patient a candidate for autologous stem cell transplantation (ASCT)?

Yes

Induction
- 3–6 treatment cycles
- 3 or 4 drugs

Stem cell collection and storage

High-dose melphalan + stem cell transplant*

(± Consolidation) Maintenance

Supportive care

No

Continuous induction
- 2–4 drugs
- 6 or more treatment cycles (maybe up to 18-24 cycles)

*In certain circumstances, consideration for a tandem transplant

Induction Therapy Regimens


Preferred
- Revlimid-Velcade-dex (RVd)*
- Kyprolis-Revlimid-dex (KRd)

Recommended
- 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

Certain circumstances
- 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

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

1. **Induction therapy**
   - ~3 to 6 cycles
   - Melphalan
   - Neupogen, Neulasta, Leukine, Cytoxan, Mozobil
   - 2 to -3 weeks*

2. **Collection of stem cells from the bloodstream**
   - Stem cell mobilization
   - Neupogen, Neulasta, Leukine, Cytoxan, Mozobil
   - 2 to -3 weeks*

3. **Freezing of stem cells**
   - Melphalan
   - Alkeran, Evomela

4. **High-dose chemotherapy**
   - 3 to 6 cycles Melphalan
   - Alkeran, Evomela
   - Day 0

5. **Thawing and infusion of stem cells**
   - Days +1 to +100†

6. **Bone marrow recovery**
   - Days +1 to +100†

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Continuous or Maintenance Therapy Options

**Preferred**
- Revlimid*

**Recommended**
- Ninlara
- Velcade
- Darzalex

**Certain circumstances**
- Velcade-Revlimid ± dex
- Kyprolis-Revlimid
- Velcade-Revlimid

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

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

- **Stable disease** (no change in M protein of light chain)
- **Minor response** (>30% decrease)
- **Partial response** (>50% decrease)
- **Very good partial response** (>90% decrease)
- **Complete response** (100% decrease/<5% plasma cells in bone marrow biopsy)
- **Stringent complete response** (no plasma cells in bone marrow biopsy)

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.


**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
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!

Relapsed/Refractory Multiple Myeloma

Robert M. Rifkin, MD
Sarah Cannon Research Institute
Rocky Mountain Cancer Centers
Denver, Colorado
Multiple Myeloma Is a Marathon, Not a Sprint

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

Adapted from Borrello I. *Leuk Res.* 2012;36 Suppl 1:S3.
Biochemical Relapse or Clinical Relapse

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

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

Timing of therapy initiation/escalation dependent on many factors

Requires immediate initiation/escalation of therapy

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
Options for Relapsed/Refractory Disease Continue to Increase

<table>
<thead>
<tr>
<th>IMIDs</th>
<th>Proteasome inhibitors</th>
<th>Chemotherapy anthracyclines</th>
<th>Chemotherapy alkylators</th>
<th>Steroids</th>
<th>Other mechanisms of action</th>
<th>Monoclonal antibodies</th>
<th>Cellular therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (thalidomide)</td>
<td>Velcade (bortezomib)</td>
<td>Adriamycin (doxorubicin)</td>
<td>Cytosar (cyclophosphamide)</td>
<td>Dexamethasone</td>
<td>XPOVIO (idelalisib)</td>
<td>Empliciti (eltuzumab)</td>
<td>Abecma (idecabtagene vicellelucel)</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)</td>
<td>Kyprolis (carfilzomib)</td>
<td>Doxil (liposomal doxorubicin)</td>
<td>Bendamustine</td>
<td>Prednisone</td>
<td>Venclexta (venetoclax) *</td>
<td>Darzalex (daratumumab)</td>
<td>Carvykti (ciltaclabtagene autoleucel)</td>
</tr>
<tr>
<td>Pomalyst (pomalidomide)</td>
<td>Ninlaro (oxazolomib)</td>
<td>Melphalan</td>
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*Not yet FDA-approved for patients with multiple myeloma; † Bispecific antibody

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

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.
Treatment Approach

First relapse

Proteasome inhibitor/immunomodulatory drug/antibody-based therapy

Refractory to Velcade and Revlimid

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

Refractory to an IMiD but sensitive to a PI

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

>1 Relapse

Any options for first relapse not tried

Refractory to an IMiD but sensitive to a PI

SD, ide-cel, cita-cel, Tecvayli, Talvey, Elrexfio

Triple-class refractory

Approved therapies

Bispecific/trispecific antibodies, cellular therapies (CAR T-cells, NK cells), CELMoDs

Clinical trials

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

*Not yet approved for use in myeloma patients.

Triplet Regimens for Early Relapse
Currently Available Naked Monoclonal Antibodies for One to Three Prior Lines of Therapy

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

IV, intravenous; SC, subcutaneous

Currently Available Agents for One to Three Prior Lines of Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Approval</th>
</tr>
</thead>
</table>
| 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
### Monoclonal Antibody–Based Regimens for Early Relapse: Darzalex

<table>
<thead>
<tr>
<th>Regimens compared</th>
<th>POLLUX</th>
<th>CASTOR</th>
<th>CANDOR</th>
<th>APOLLO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimens compared</td>
<td>Darzalex-Revlimid-dex (DRd) vs Rd</td>
<td>Darzalex-Velcade-dex (DVd) vs Vd</td>
<td>Darzalex-Kyprolis-dex (DKd) vs Kd</td>
<td>Darzalex-Pomalyst-dex (DPd) vs Pd</td>
</tr>
<tr>
<td>Median PFS favored</td>
<td>DRd: 45 vs 18 months</td>
<td>DVd: 17 vs 7 months</td>
<td>DKd: 29 vs 15 months</td>
<td>DPd: 12 vs 7 months</td>
</tr>
<tr>
<td>Clinical considerations</td>
<td>Consider for relapses from non-Revlimid–based maintenance</td>
<td>Consider for patients who are Revlimid-refractory without significant neuropathy</td>
<td>Consider for younger, fit patients who are double-refractory to Revlimid and Velcade</td>
<td>Consider in patients who are double-refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro)</td>
</tr>
</tbody>
</table>

- **DRd:** 45 vs 18 months
- **DVd:** 17 vs 7 months
- **DKd:** 29 vs 15 months
- **DPd:** 12 vs 7 months

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

<table>
<thead>
<tr>
<th>Regimens compared</th>
<th>ELOQUENT-2</th>
<th>ELOQUENT-3</th>
<th>ICARIA-MM</th>
<th>IKEMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimens compared</td>
<td>Empliciti-Revlimid-dex vs Rd</td>
<td>Empliciti-Pomalyst-dex vs Pd</td>
<td>Sarclisa-Pomalyst-dex vs Pd</td>
<td>Sarclisa-Kyprolis-dex vs Kd</td>
</tr>
<tr>
<td>Median PFS favored</td>
<td>Empliciti-Rd: 19 vs 15 months</td>
<td>Empliciti-Pd: 10 vs 5 months</td>
<td>Sarclisa-Pd: 12 vs 7 months</td>
<td>Sarclisa-Kd: 42 vs 21 months</td>
</tr>
<tr>
<td>Clinical considerations</td>
<td>Consider for non-Revlimid refractory, frailer patients</td>
<td>Consider for patients refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro)</td>
<td>Consider for patients refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro)</td>
<td>Consider for patients refractory to Revlimid and Velcade</td>
</tr>
</tbody>
</table>

- **Empliciti-Rd:** 19 vs 15 months
- **Empliciti-Pd:** 10 vs 5 months
- **Sarclisa-Pd:** 12 vs 7 months
- **Sarclisa-Kd:** 42 vs 21 months

- **Sarclisa-Pd** associated with severe low white blood cell counts, more dose reductions, upper respiratory infections, and diarrhea
- **Sarclisa-Kd** associated with higher MRD negativity rates
- **Sarclisa-Kd** associated with severe respiratory infections
Update From the 2022 American Society of Hematology (ASH) Meeting

Sarclisa After Early or Late Relapse

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

<table>
<thead>
<tr>
<th></th>
<th>Early relapse</th>
<th>Late relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa-Kd</td>
<td>24.7</td>
<td>42.7</td>
</tr>
<tr>
<td>Kd</td>
<td>17.2</td>
<td>21.9</td>
</tr>
<tr>
<td>Sarclisa-Kd</td>
<td>82</td>
<td>90.4</td>
</tr>
<tr>
<td>Kd</td>
<td>82.6</td>
<td>86.1</td>
</tr>
<tr>
<td>≥VGPR rate (%)</td>
<td>67.2</td>
<td>76</td>
</tr>
<tr>
<td>MRD negativity rate (%)</td>
<td>24.6</td>
<td>37.5</td>
</tr>
<tr>
<td>MRD-negative CR rate (%)</td>
<td>18</td>
<td>13.9</td>
</tr>
</tbody>
</table>

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

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

*<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].

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

**OPTIMISMM**
- Velcade-Pomalyst-dex (VPd) vs Vd
- Kyprolis-Revlimid-dex (KRd) vs Rd

**ASPIRE**
- Ninlaro-Rd (IRd) vs Rd

**TOURMALINE-MM1**
- XPOVIO-Velcade-dex (XPO-Vd) vs Vd

**BOSTON**
- XPO-Vd: 14 vs 9 months

**Regimens compared**

**Median PFS favored**
- VPd: 11 vs 7 months
- KRd: 26 vs 17 months
- IRd: 21 vs 15 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
Treatment Approach

First relapse

Proteasome inhibitor/ immunomodulatory drug/ antibody-based therapy

Refractory to Velcade and Revlimid

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

Refractory to an IMiD but sensitive to a PI

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

>1 Relapse

Any options for first relapse not tried

Approved therapies

Sd, ide-cel, cila-cel, Tecvayli, Talve, Elrexfio

Clinical trials

Bispecific/ trispecific antibodies, CAR T cells, CELMoDs

Triple-class refractory

Refactory to Velcade and Revlimid

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 vicelucel (Abecma); cila-cel, cilacabtagene autoleucel (Carvykti)

*Not yet approved for use in myeloma patients.

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

• Velcade (bortezomib)
• Kyprolis (carfilzomib)
• Ninlaro (ixazomib)

Immunomodulatory drugs

• Revlimid (lenalidomide)
• Pomalyst (pomalidomide)

Anti-CD38 monoclonal antibodies

• Darzalex (daratumumab)
• Sarclisa (isatuximab)
Currently Available Drugs for Triple-Class Refractory Myeloma

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Formulation</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nuclear export inhibitor</td>
<td>XPOVIO (selinexor)</td>
<td>Twice-weekly pill</td>
<td>• 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</td>
</tr>
</tbody>
</table>

### XPOVIO + dexamethasone in relapsed/refractory myeloma

<table>
<thead>
<tr>
<th>No. patients with ≥PR (%)</th>
<th>1XPOVIO + dexamethasone in relapsed/refractory myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>32 (26)</td>
</tr>
<tr>
<td>Previous therapies to which the disease was refractory, n (%)</td>
<td></td>
</tr>
<tr>
<td>Velcade, Kyprolis, Revlimid, Pomalyst, and Darzalex</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Kyprolis, Revlimid, Pomalyst, and Darzalex</td>
<td>26 (26)</td>
</tr>
<tr>
<td>Velcade, Kyprolis, Pomalyst, and Darzalex</td>
<td>25 (27)</td>
</tr>
<tr>
<td>Kyprolis, Pomalyst, and Darzalex</td>
<td>31 (26)</td>
</tr>
</tbody>
</table>

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

---

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.
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.

Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma

Abecma

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>ORR 73%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ide-cel (n=128)</td>
<td>26</td>
</tr>
<tr>
<td>PR</td>
<td>100</td>
</tr>
<tr>
<td>VGPR</td>
<td>90</td>
</tr>
<tr>
<td>CR or sCR and MRD NE</td>
<td>80</td>
</tr>
<tr>
<td>CR or sCR and MRD-</td>
<td>70</td>
</tr>
</tbody>
</table>

Average PFS 9 months

Carvykti

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>ORR 97.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cilta-cel (n=97)</td>
<td>82.5</td>
</tr>
<tr>
<td>PR</td>
<td>100</td>
</tr>
<tr>
<td>VGPR</td>
<td>90</td>
</tr>
<tr>
<td>sCR</td>
<td>80</td>
</tr>
</tbody>
</table>

27-month PFS 55%

CAR, chimeric antigen receptor; BCMA, B-cell maturation antigen

Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma

ORR, overall response rate; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; MRD, minimal residual disease; PFS, progression-free survival
**Abecma or Standard Regimens in Relapsed and Refractory Multiple Myeloma**

### Progression-free survival

- **Standard regimen (n=132)**
  - Median PFS: 4.4 months
- **Abecma (n=254)**
  - Median PFS: 13.3 months

**Treatment response**

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

*P<0.001

---

**Carvykti in Relapsed and Refractory Multiple Myeloma**

- **ORR**: 97.9%
- **27-month PFS**: 55%
- **Patients (%)**
  - PR: 82.5%
  - VGPR: 12.4%
  - sCR: 3%

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


---

### Carvykti in Earlier Use of Relapsed and Refractory Multiple Myeloma

**CARTITUDE-4 Phase 3 Study**

211 patients with relapsed/refractory myeloma patients with 1–3 prior lines of therapy and refractory to Revlimid were randomized to the Carvykti arm or the standard of care arm. Patients were treated with Pomalyst + Velcade or Darzalex + Pd or Bridging PVd or DPd.

**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.**


### CAR T: Expected Toxicities

<table>
<thead>
<tr>
<th>CRS</th>
<th>ICANS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>1–9 days after CAR T-cell infusion</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>5–11 days</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>- Fever</td>
</tr>
<tr>
<td></td>
<td>- Difficulty breathing</td>
</tr>
<tr>
<td></td>
<td>- Dizziness</td>
</tr>
<tr>
<td></td>
<td>- Nausea</td>
</tr>
<tr>
<td></td>
<td>- Headache</td>
</tr>
<tr>
<td></td>
<td>- Rapid heartbeat</td>
</tr>
<tr>
<td></td>
<td>- Low blood pressure</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>- Actemra (tocilizumab)</td>
</tr>
<tr>
<td></td>
<td>- Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>- Supportive care</td>
</tr>
</tbody>
</table>

*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

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.

---

Now Approved: Three Bispecific Antibodies!

### Tecvayli

- **sCR:** 63.0%
- **CR:** 32.7%
- ≥**VGPR:** 6.7%
- ≥**PR:** 19.4%
- **All patients (n=165):** 4.2%

**Median duration of response**

**18.4 months**

### Talveey

- **sCR:** 74.1%
- **PR:** 23.8%
- **VGPR:** 9.8%
- **CR:** 25.9%
- **All patients (n=143):** 14.7%

**Median duration of response**

**17.1 months**

### Elrexfio

- **sCR:** 64%
- **VGPR:** 27.3%
- **CR:** 10.9%
- **All patients (n=55):** 18.2%

**Median duration of response**

**17.1 months**

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

**Singh A et al. Br J Cancer. 2021;124:1037.**


**Chari A et al. N Engl J Med. 2022;387:2232.**

**Schinke CD et al. J Clin Oncol. 2023;41. Abstract 8036.**
Bispecific Antibodies: Expected Toxicities

ICANS, immune effector cell-associated neurotoxicity syndrome

Summary

1. We now have many different options for relapsed myeloma depending on patient and myeloma factors at relapse.

2. Therapy choices will depend on teamwork between physician, patient, and caregivers and are based on many decision points.

3. Combinations of proteasome inhibitors with either immunomodulatory drugs or selinexor improve PFS.

4. We have three different monoclonal antibodies that improve PFS when added to other standard therapies without significantly increasing side effects.

5. CAR T and bispecific antibodies are very active even in heavily pre-treated patients with unprecedented response rates and durations of response.
Supportive Care

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

Effects of Myeloma

Low blood counts
Bone damage
Decreased kidney function
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

Bone damage

Bone damage

Fracture caused by lesion
Lesions

Bone Strengthening Agents for Myeloma Bone Disease

• Prevent bone disease from getting worse
• Decrease pain and reduce skeletal-related fractures

Benefits

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

Medication types

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
**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

**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)
Radiation Therapy for Pain Management

Pain Management Medications

- **Acetaminophen (Tylenol)**
  - Will not hurt your kidneys; high dosage can hurt your liver

- **NSAIDs (nonsteroidal anti-inflammatory drugs)**
  - Prefer to avoid with multiple myeloma due to increased risk of kidney injury

- **Opioids**
  - Will not hurt kidneys, liver, stomach; potential for constipation, sedation, confusion, dependence, addiction

- **Corticosteroids (dexamethasone, prednisone)**
  - Will not hurt kidneys; can raise blood sugar; short- and long-term effects

- **Anti-seizure medications (gabapentin and Lyrica)**
  - Potential for drowsiness and dizziness
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

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)
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.

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

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

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
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
### 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
- Monitor for heart, lung, and kidney side effects
  - Use with caution in older patients with cardiovascular risk factors
- High blood pressure
- No dose adjustment for kidney issues; adjust for liver issues

#### Kryprolis
- 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 cardiovascular 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

### Class: Monoclonal Antibodies

#### Side Effects and Management

<table>
<thead>
<tr>
<th>Empliciti</th>
<th>Darzalex*/Sarclisa</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low blood counts</td>
<td>• Infusion reactions</td>
<td>• Premedication in anticipation of infusion reactions</td>
</tr>
<tr>
<td>• Infusion reactions</td>
<td>• Fatigue</td>
<td>• Post-infusion medications (Darzalex)</td>
</tr>
<tr>
<td></td>
<td>• Upper respiratory tract infection</td>
<td></td>
</tr>
</tbody>
</table>

*Now approved as subcutaneous injection with fewer side effects.
### 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

---

### 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, anxious, 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

---

SC, subcutaneous; IVIG, intravenous immunoglobulin
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

Infection Prevention

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

IVIG, intravenous immunoglobulin; PJP, Pneumocystis jiroveci pneumonia; CMV, cytomegalovirus
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)

---

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
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)

Daily Living

- Proper nutrition
- Exercise
- Rest
- Social contacts
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.

Patient Experience
Questions & Answers

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

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

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.
Autologous Stem Cell Transplantation

1. Induction therapy
   - Stem cell mobilization
     • Neupogen, Neulasta, Leukine, Cytoxan, Mozobil
   - ~3 to 6 cycles

2. Collection of stem cells from the bloodstream
   - -2 to -3 weeks

3. Freezing of stem cells

4. High-dose chemotherapy
   - Melphalan
     • Alkeran, Evomela
   - Day 0

5. Thawing and infusion of stem cells
   - Days +1 to +100†

6. Bone marrow recovery
   - †The days after the transplant.

Image description:
- Stem cells are mobilized and collected from the bloodstream.
- They are then frozen and thawed before being infused.
- Recovery occurs over several weeks.

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
  • Antibiotics
  • White blood cells and platelets recover in 2 weeks

- Hair loss

*The weeks leading up to the transplant; †The days after the transplant.
Is transplant still required in newly diagnosed myeloma?

**DETERMINATION phase 3 study**

- Newly diagnosed myeloma patients
- 365 patients
- 357 patients

**EARLY-TRANSPLANT ARM**
- Induction
- Revlimid + Velcade + dex (RVd)
- Stem cell collection
- ASCT
- RVd
- R

**LATE-TRANSPLANT ARM**
- Induction
- Revlimid + Velcade + dex (RVd)
- Transplant
- Consolidation
- RVd
- Maintenance
- R

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

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

- **Progression-free survival (PFS)**
  - Early transplant: RVd + ASCT (median PFS, 67.5 mos)
  - Continuous RVd induction (median PFS, 46.2 mos)

- **Overall survival (OS)**
  - Early transplant: RVd + ASCT
  - Continuous RVd induction

- **PFS** for early transplant: approximately 5.5 years
- **PFS** for continuous induction: approximately 4 years
- **Transplant extended time to progression by 20 months**

- **Length of overall survival**: no difference.
Phase 3 Study of ASCT for Newly Diagnosed Myeloma: Best Response to Treatment and Duration of Response

P value

Late transplant (RVd alone)

Early transplant (RVd + ASCT)

Duration of response

<table>
<thead>
<tr>
<th></th>
<th>Early transplant</th>
<th>Late transplant</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of ≥PR, months</td>
<td>56.4</td>
<td>38.9</td>
<td>0.003</td>
</tr>
<tr>
<td>5-year duration of ≥CR, %</td>
<td>60.6</td>
<td>52.9</td>
<td>0.698</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Side effect (%)</th>
<th>RVd alone (N=357)</th>
<th>RVd + ASCT (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>78.2</td>
<td>94.2</td>
</tr>
<tr>
<td>Fatal side effects</td>
<td>0.3</td>
<td>1.6*</td>
</tr>
<tr>
<td>Low blood counts</td>
<td>60.5</td>
<td>89.9</td>
</tr>
<tr>
<td>Very low white cell count</td>
<td>42.6</td>
<td>86.3</td>
</tr>
<tr>
<td>Low platelet count</td>
<td>19.9</td>
<td>82.7</td>
</tr>
<tr>
<td>Low white cell count</td>
<td>19.6</td>
<td>39.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>18.2</td>
<td>29.6</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Infections with low WBC</td>
<td>4.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Fever</td>
<td>2.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.6</td>
<td>6.6</td>
</tr>
<tr>
<td>Mouth sores</td>
<td>0.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Numbness, tingling nerve</td>
<td>5.6</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Severe side effects were more common with transplant.

*Includes one death related to ASCT

### Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Subsequent Therapy and Rate of ASCT in RVD-Alone Arm (Late ASCT)

<table>
<thead>
<tr>
<th>Subsequent therapy in patients off protocol therapy (%)</th>
<th>RVd alone (N=279) late transplant</th>
<th>RVd + ASCT (N=276) early transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment*</td>
<td>79.8</td>
<td>69.6</td>
</tr>
<tr>
<td>Subsequent therapy</td>
<td>55.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Any immunomodulatory drug</td>
<td>55.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Pomalyst (pomalidomide)</td>
<td>30.2</td>
<td>29.2</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)</td>
<td>25.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Any proteasome inhibitor</td>
<td>55.9</td>
<td>50.0</td>
</tr>
<tr>
<td>Velcade (bortezomib)</td>
<td>27.5</td>
<td>25.5</td>
</tr>
<tr>
<td>Kyprolis (carfilzomib)</td>
<td>21.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>8.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Marizomib</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Any monoclonal antibody</td>
<td>16.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Darzalex (daratumumab)</td>
<td>11.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Empliciti (elotuzumab)</td>
<td>4.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Sarclisa (isatuximab)</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

*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.
## Early vs Late Transplant Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early ASCT</strong></td>
<td><strong>Early ASCT</strong></td>
</tr>
<tr>
<td>• Deeper and more durable response</td>
<td>• No proven impact on overall survival</td>
</tr>
<tr>
<td>• Youngest/healthiest you are going to be</td>
<td>• 20% of patients still relapse within 2 years</td>
</tr>
<tr>
<td>• Allows for fewer cycles of induction treatment</td>
<td>• More side effects including a small risk of serious life-threatening complications</td>
</tr>
<tr>
<td></td>
<td>• 3 months to full clinical recovery</td>
</tr>
<tr>
<td><strong>Late ASCT</strong></td>
<td><strong>Late ASCT</strong></td>
</tr>
<tr>
<td>• PFS may be shorter, but currently appears OS is the same</td>
<td>• Need more cycles of induction</td>
</tr>
<tr>
<td>• Less side effects without high-dose chemotherapy</td>
<td>• May need next treatment sooner, including (late) transplant</td>
</tr>
<tr>
<td>• Conserve quality of life in the early part of disease journey</td>
<td>• Not all patients relapsing are able to undergo salvage ASCT</td>
</tr>
</tbody>
</table>

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.
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.

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.
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.

Revlimid Maintenance Therapy: Improves Depth of Response

### Revlimid Maintenance Duration

#### STAMINA Trial (BMT-CTN0702)

- **ASCT MEL 200 mg/m²**
  - **Auto/Auto group**
    - 247 pts
    - MEL 200 mg/m² → REV × 3 yrs
  - **Auto/RVD group**
    - 254 pts
    - RVD × 4 → REV × 3 yrs
  - **Auto/Rev group**
    - 257 pts
    - No consolidation → REV × 3 yrs

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.

#### Maintenance Duration

##### Myeloma XI Study

- Newly diagnosed myeloma patients
  - **Induction**
    - CTD/CRD
    - KCRD
  - **Consolidation**
    - CVD
    - No CVD
  - **Maintenance**
    - Revlimid
    - Observation

730 patients
718 patients

**Median PFS (mos)**
- **At time of randomization to maintenance therapy (median follow up 44.7 mos)**

|          | All patients*
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Revlimid</strong></td>
<td>64</td>
</tr>
<tr>
<td><strong>Observation</strong></td>
<td>32</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>0.52</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*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.
Using MRD Negativity to Guide Discontinuation of Maintenance Therapy

**MRD2STOP Study**

- Complete response and MRD negative by PET and NGF or NGS on at least 1 year of maintenance
- MRD and PET/CT negative
  - N=38
  - Discontinue maintenance
  - 1-yr MRD
  - 2-yr MRD
  - 3-yr MRD
- MRD and PET/CT positive
  - Continue maintenance

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


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.

---

Ongoing Study Using MRD Results to Direct Therapy

**Phase 3 DRAMMATIC Study**

- Patients post-ASCT
  - R
  - Maintenance
    - Revlimid
    - Revlimid + Darzalex
  - MRD assessment
    - Positive
    - Negative
    - R
    - Continued assigned therapy
    - Continued assigned therapy
    - Stop assigned therapy

clinicaltrials.gov/ct2/show/NCT04071457.
Revlimid Maintenance: Cumulative Incidence of Second Primary Malignancies

**Hematologic**

- **Lenalidomide**
- **Control**

HR (95% CI): 2.03 (1.14–3.61)

\( P = 0.015 \)

**Solid Tumor**

- **Lenalidomide**
- **Control**

HR (95% CI): 1.71 (1.04–2.79)

\( P = 0.032 \)

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


---

**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).
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.

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.

Stable disease
Minor response
Partial response
Very good partial response
Complete response
Stringent complete response
Minimal residual disease negative

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

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
How is MRD measured?

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.
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 $1 \times 10^{-5}$)


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.
Multiple Myeloma Precursor Conditions

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

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.

- Monoclonal gammopathy of undetermined significance (MGUS)
- Smoldering multiple myeloma (SMM)
- High-risk SMM
- Multiple myeloma
Blood, Urine, Bone Marrow, and Imaging Tests Used to Identify MGUS, SMM, or Active Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>SMM</th>
<th>Active MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>M protein</td>
<td>&lt;3 g/dL in blood</td>
<td>≥3 g/dL in blood or ≥500 mg/24 hrs in urine</td>
<td>≥3 g/dL in blood or ≥500 mg/24 hrs in urine</td>
</tr>
<tr>
<td>Plasma cells in bone marrow</td>
<td>&lt;10%</td>
<td>≥10%–60%</td>
<td>≥60%</td>
</tr>
<tr>
<td>Clinical features</td>
<td>No myeloma-defining events*</td>
<td>No myeloma-defining events*</td>
<td>≥1 myeloma-defining event*, including either: • ≥1 CRAB feature or • ≥1 SLiM feature</td>
</tr>
</tbody>
</table>

*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

Risk of Progression to Myeloma From a Precursor Condition

- 51% will convert to MM in first 5 years (~10%/yr)
- 27% more will convert to MM in remaining 15 years (~2%/yr)

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

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

- High-risk group (2–3 risk factors): 44.2%
- Intermediate-risk group (1 risk factor): 17.9%
- Low-risk group (no risk factors): 6.2%

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
Can we identify everyone who has a precursor condition?

Studies Focusing on Myeloma Precursor Conditions

Large ongoing precursor studies

- **Iceland**
  - Focus: role of population screening

- **United States and Canada**
  - Focus: racial disparities and familial aggregation

- **United States**
  - **TRANSFORMMM study**
  - Focus: genomic markers of progression
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

**SMM**
- 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

**Key Observations**
- 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.

---

High Prevalence of Monoclonal Gammopathy in a Population at Risk

**The PROMISE Study**
- 7,622 individuals screened*
- 6,305 patients with high-risk features for myeloma
- 1,317 patients with no high-risk features for myeloma

**MGUS**
- 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.**

---

*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.


---

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

HM, hematologic malignancy
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.

Rates of MGUS and MGIP

<table>
<thead>
<tr>
<th>Age Group</th>
<th>MGIP (%)</th>
<th>MGUS (%)</th>
<th>LC-MGUS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>12 (16%)</td>
<td>27 (16%)</td>
<td>81 (10%)</td>
</tr>
<tr>
<td>30–39</td>
<td>15 (19%)</td>
<td>31 (21%)</td>
<td>75 (10%)</td>
</tr>
<tr>
<td>40–49</td>
<td>16 (21%)</td>
<td>39 (27%)</td>
<td>77 (10%)</td>
</tr>
<tr>
<td>50–59</td>
<td>16 (21%)</td>
<td>38 (27%)</td>
<td>74 (10%)</td>
</tr>
<tr>
<td>60–69</td>
<td>12 (17%)</td>
<td>26 (19%)</td>
<td>65 (10%)</td>
</tr>
<tr>
<td>70–79</td>
<td>8 (11%)</td>
<td>17 (13%)</td>
<td>36 (6%)</td>
</tr>
<tr>
<td>80+</td>
<td>2 (1%)</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

Rates of MGUS by SPEP/IFX in black vs non-black

<table>
<thead>
<tr>
<th>MGUS by SPEP/IFX in general population &gt;50 years old</th>
<th>MGUS by SPEP/IFX in high risk &gt;50 years old from PROMISE</th>
<th>MGUS-MGUS in high risk &gt;50 years old from PROMISE and MGBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>6%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Rates of MGUS by SPEP/IFX in population of individuals with a family history of HM

<table>
<thead>
<tr>
<th>MGUS by SPEP/IFX in high risk &gt;50 years old from PROMISE and MGBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>17%</td>
</tr>
</tbody>
</table>

Rates of MGUS by SPEP/IFX in individuals with a family history of HM

<table>
<thead>
<tr>
<th>MGUS by SPEP/IFX in high risk &gt;50 years old from PROMISE and MGBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>13%</td>
</tr>
</tbody>
</table>

Rates of MGUS by SPEP/IFX in individuals with a family history of HM and older than 50 years at risk

<table>
<thead>
<tr>
<th>MGUS by SPEP/IFX in high risk &gt;50 years old from PROMISE and MGBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
</tr>
</tbody>
</table>

Rates of MGUS by SPEP/IFX in individuals with a family history of HM and older than 50 years at risk

<table>
<thead>
<tr>
<th>MGUS by SPEP/IFX in high risk &gt;50 years old from PROMISE and MGBB</th>
</tr>
</thead>
<tbody>
<tr>
<td>10%</td>
</tr>
</tbody>
</table>

Overview of Current Treatment Approach

MGUS

Close monitoring (observation)

SMM

Close monitoring (observation)

Clinical trial participation should be considered
Approaches to SMM Treatment: *Only in the Context of a Clinical Study*

**Immunologic therapy**  
(control approach)

- Len, Len/Dex, Dara

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

**Cons**
- Low OR
- Does not eliminate the clone

**Intensive therapy**  
(curative intent)

- IRD, KRD, ERD
- CESAR, ASCENT

**Pros**
- High ORR
- Deep responses

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

---

**Early Therapeutic Intervention**

*Lenalidamide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma*


**Progression-free survival for early treatment**

- Revlimid group
- Observation group

**Freedom From Progression to Symptomatic Disease (%)**

- HR for progression, 0.18
  - P<0.001

---

HR, hazard ratio

QuiRedex Phase 3 Trial

**Len-dex vs No Treatment in High-Risk SMM**

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

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

Revlid vs Observation Alone in Patients With SMM

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

- 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.
Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria

High risk Intermediate risk Low risk

Progression-Free Survival Probability

0 20 40 60 80 100

Time From Randomization (Months)

Revlimid Observation

Revlimid Observation

Revlimid Observation

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

NCI Study

High-risk* smoldering multiple myeloma patients

8 cycles of combination therapy

Kyprolis + Revlimid + dex (KRd)

2 years of maintenance

Revlimid

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

**GEM-CESAR Study**

- High-risk* smoldering multiple myeloma patients

  **Induction**
  - Kyprolis + Revlimid + dex (KRd)
  - ASCT

  **Consolidation**
  - KRd

  **Maintenance**
  - Revlimid

90 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.

Four-Drug Combination Strategy for High-Risk SMM Patients

**ASCENT Study**

- High-risk* smoldering multiple myeloma patients

  **Induction**
  - Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)

  **Consolidation**
  - Dara-KRd

  **Maintenance**
  - Dara-KRd

87 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.

*According to the Mayo and/or Spanish models.

*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.
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.

High-Risk Multiple Myeloma

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

Assessing Risk

Staging, prognosis, and risk assessment
High-Risk Disease Definitions

**Revised International Staging System (R-ISS)**

**R-ISS Stage I**
- ISS² 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**
- ISS³ stage III
  - Serum β2M level ≥5.5 mg/L
  - High-risk CA* or high LDH level

**High risk**
- Genetic abnormalities*
  - t(4;14)
  - t(14;16)
  - t(14;20)
- 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)

**Mayo Clinic Stratification for Myeloma & Risk-Adapted Therapy (mSMART)**

**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

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

*By FISH or equivalent

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Why is genomic sequencing important in myeloma risk assessment?

- Genetic changes in myeloma cells may affect prognosis and treatment selection

- Using samples from the bone marrow—specific tests look at these genetic changes

- Some tests are used routinely and look at the chromosomal changes (FISH)

- Newer tests assess changes in the DNA (gene expression profiling and next-generation sequencing)
  - Ask your doctor if these tests are available

- All patients in the MMRF CoMMpass study had genomic sequencing from diagnosis to relapse. The resulting data provides detailed genetic profiles for every myeloma patient at every stage of their disease!

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155

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156
MMRF CoMMpass Findings: Chromosome 1 Copy Number and Other Cytogenetics

Copy number of chromosome 1q

- 2 copies (n=107)
- 3 copies (n=52)
- ≥4 copies (n=26)

Log-rank P=0.0063

Progression-Free Survival (Months)

Proportion Surviving

2 copies: 65.1 mo
≥4 copies: 34.6 mo
3 copies: 55.9 mo

Cytogenetics

- Hi/+1q (n=28)
- Std/+1q (n=66)
- Hi (n=12)
- Std (n=95)

Log-rank P<0.0001

Progression-Free Survival (Months)

Proportion Surviving

Hi/+1q: 25.1 mo

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


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.
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

**Key CoMMpAss finding:**
FISH testing alone cannot identify whether patients have double-hit myeloma.

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

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.
### 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>Total number of patients</th>
<th>High risk definition</th>
<th>Number of high-risk myeloma patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG-1211¹</td>
<td>RVd vs RVd-Empliciti</td>
<td>100</td>
<td>GEP&lt;sup&gt;+&lt;/sup&gt;, del17p, t(14;16), t(14;20), Amp1q21, elevated LDH, pPCL</td>
<td>RVd = 52</td>
</tr>
<tr>
<td>SWOG-0777²</td>
<td>RVd vs Rd</td>
<td>525</td>
<td>del17p, t(14;16), or t(4;14)</td>
<td>Combined n=44</td>
</tr>
<tr>
<td>MAIA³</td>
<td>DRd vs Rd</td>
<td>737</td>
<td>del17p, t(14;16), or t(4;14)</td>
<td>DRd = 48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rd = 44</td>
</tr>
<tr>
<td>ALCYONE⁴</td>
<td>D-VMP vs VMP</td>
<td>706</td>
<td>del17p, t(14;16), or t(4;14)</td>
<td>D-VMP = 53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VMP = 45</td>
</tr>
<tr>
<td>CASSIOPEIA⁵</td>
<td>Darzalex-VTd vs VTd</td>
<td>1,085</td>
<td>del17p or t(4;14)</td>
<td>Dara-VTd = 82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VTd = 86</td>
</tr>
<tr>
<td>STAMINA⁶</td>
<td>Tandem transplant vs ASCT/RVD vs ASCT</td>
<td>758</td>
<td>ISS 3, del13, del 17p, t(4;14), t(14;16), t(14;20)</td>
<td>Tandem = 72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ASCT/RVD = 76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ASCT = 75</td>
</tr>
</tbody>
</table>

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

Darzalex Meta-Analysis in High-Risk Multiple Myeloma

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


Results were similar regardless of backbone regimens.

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.

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

Treatment Regimens for High-Risk Disease Features

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

• 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

• 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.

Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

**GMMG-CONCEPT Study**

<table>
<thead>
<tr>
<th>High-risk newly diagnosed multiple myeloma patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant eligible (&lt;70 yrs) n=127</td>
<td>Transplant ineligible (&gt;70 yrs) n=26</td>
</tr>
</tbody>
</table>

**Induction**
- Sarclisa + Kyprolis + Revlimid + dex (Isa-KRd)
- Isa-KRd

**Consolidation**
- ASCT
- Isa-KRd
- Isa-KRd

**Maintenance**
- Isa-KR

**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) (%)**

<table>
<thead>
<tr>
<th>Overall response rate</th>
<th>Transplant eligible (n=99)</th>
<th>Transplant ineligible (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR/CR</td>
<td>94.9</td>
<td>88.5</td>
</tr>
<tr>
<td>VGPR</td>
<td>72.7</td>
<td>57.7</td>
</tr>
<tr>
<td>PR</td>
<td>18.2</td>
<td>30.8</td>
</tr>
<tr>
<td>SD</td>
<td>4.0</td>
<td>0</td>
</tr>
<tr>
<td>MRD negative (1 × 10⁻⁵) in evaluable patients</td>
<td>67.7</td>
<td>54.2</td>
</tr>
</tbody>
</table>

**Progression-free survival (months)**

- Not reached

**Adverse events (% grade ≥3)**

<table>
<thead>
<tr>
<th>Hematologic</th>
<th>Transplant eligible (n=97)</th>
<th>Transplant ineligible (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>39.2</td>
<td>28</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24.7</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26.8</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>14.4</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-hematologic</th>
<th>Transplant eligible (n=97)</th>
<th>Transplant ineligible (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>27.8</td>
<td>28</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2.1</td>
<td>20</td>
</tr>
</tbody>
</table>


---

Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

**Progression-Free Survival in Transplant Eligible Patients**

- 1 high-risk cytogenetic abnormality
- ≥2 high-risk cytogenetic abnormalities

- Normal LDH
- Elevated LDH

- No del17p
del17p

- MRD-
- MRD+

- Sustained MRD-
- (≥6 months)
- MRD+
- (non-sustained MRD-
- (≥6 months))

Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

**RADAR Study**
- Transplant eligible newly diagnosed multiple myeloma
- Revlimid-cyclophosphamide-Velcade-dex (R-CyBorD)

**High-risk** patients
- n=280
- Isa-R-CyBorD + Isa-R until PD

**Standard-risk patients**
- n=1,120
- R-CyBorD + Isa
- ASCT
- MRD negative
- Cont Isa
- Stop Isa
- MRD positive
- R
- RvD (×4) + Isa-R
- R + Isa

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

*At least 2 of t(4;14), t(14;16), del(17p), 1q+, 1p-
Yong K et al. Blood 2022;140. Abstract 762.

---

Additional Studies for High-Risk Myeloma

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Phase</th>
<th>Patient populations/ study design</th>
<th>High risk definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>KarMMa-4</td>
<td>Abecma</td>
<td>1</td>
<td>High-risk, newly diagnosed MM</td>
<td>R-ISS III</td>
</tr>
<tr>
<td>BMT-CTN 1901</td>
<td>Abecma</td>
<td>2</td>
<td>High-risk, newly diagnosed MM</td>
<td>R-ISS III; no prior progression</td>
</tr>
</tbody>
</table>
New Drugs on the Horizon

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

Emerging Treatment Options

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

---

### Iberdomide: A CELMoD

**Iberdomide in combination with dexamethasone in patients with RRMM**

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

<table>
<thead>
<tr>
<th>Adverse events (%)</th>
<th>Grades 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infections</td>
<td>31</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Mezigdomide: A CELMoD

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.

Most frequent hematologic adverse events (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>21.8</td>
<td>53.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>34.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13.9</td>
<td>13.9</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Most frequent non-hematologic adverse events (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>28.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12.9</td>
<td>3.0</td>
</tr>
<tr>
<td>COVID-19</td>
<td>6.9</td>
<td>0</td>
</tr>
</tbody>
</table>

Refactory to Pomalyst

Patients (%)

- MeziVd (n=13)
  - PD: 15.4%
  - SD: 76.9%
  - PR: 38.5%
  - VGPR: 33.3%
  - CR: 8.3%
  - sCR: 8.3%

- MeziKd (n=12)
  - PD: 10%
  - SD: 83.3%
  - PR: 10%
  - VGPR: 10%
  - CR: 38.6%
  - sCR: 52.2%

Actionable Alterations in MM

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

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

- KRAS and NRAS (40%)
- BRAF (8%)
- MYD88 (11%)
- IGF1R and ALK (5%)
- FGFR3 (5%)
- PI3K-AKT (5%)
- IDH1/2 (5%)
- CDKN2C and CCND1 (18%)
- Others (11%)
Personalized Medicine Agents Under Clinical Investigation

### Novel agents

<table>
<thead>
<tr>
<th>Clinical phase</th>
<th>Personalized medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>Venetoclax*</td>
</tr>
<tr>
<td>Phase 1, 2</td>
<td>Abemaciclib*</td>
</tr>
<tr>
<td></td>
<td>Cobimetinib*</td>
</tr>
<tr>
<td></td>
<td>Dabrafenib</td>
</tr>
<tr>
<td></td>
<td>Enasidenib</td>
</tr>
<tr>
<td></td>
<td>Erdafitinib*</td>
</tr>
<tr>
<td></td>
<td>Idasanutlin</td>
</tr>
<tr>
<td></td>
<td>Trametinib</td>
</tr>
<tr>
<td></td>
<td>Vemurafenib</td>
</tr>
</tbody>
</table>

*Being studied in the MyDRUG trial

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**BRAF and MEK**

- 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


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


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\textsuperscript{high} MM

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

Relapsed/refractory myeloma patients with t(11;14)

Venetoclax-dex  Pomalyt-dex

133 patients  130 patients


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

PFS IRC-Assessed

PFS – Post-hoc Sensitivity Analysis

**MyDRUG Study**

Functional high-risk patients

Profiling for alterations (NCT02884102)

- No detectable actionable alterations
- RAF/RAS mutations
- CDK pathway-activating alterations
- FGFR3-activating alterations
- t(11;14)

2 cycles

- Cobimetinib + dex
- Abemaciclib + IPd
- Erdfitinib + dex

1:2

- Daratumumab + IPd
- Cobimetinib + IPd
- Abemaciclib + IPd
- Erdfitinib + IPd

2:1

- Venetoclax + IPd
- IPd control

*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.

Evolution of CAR T-Cell Therapy

**Single target**
- 1st Generation
- 2nd Generation
- 3rd Generation

**Dual targets**
- 1st Generation
- 2nd Generation
- 3rd Generation

**4th generation ("Armed" CARs)**
- GC012F (BCMA/CD19)
- Abecma
- Carvykti
- CT03A
- CT103A
- C-CAR088
- P-BCMA-101
- ARI-002h
- ALLO-715

**Improving efficacy**
- Improving safety
- Improving access

Evolution of Bispecific Antibodies

**Bispecific antibodies: dual targets**
- Redirected tumor lysis
- CD3+ T cell

**Trispecific antibodies: triple targets**
- One myeloma cell target
- Two myeloma cell targets
- One T-cell or NK-cell target

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

- 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)

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.
Questions & Answers

Thank you!
Resources
• Resource tab includes
  – Speaker bios
  – Glossary
  – Copy of the slide presentation
  – Exhibit Hall
# Upcoming Patient Education Events

**Save the Date**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Date and Time</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-BCMA Bispecific Antibodies 2023 FAQs Livestream</td>
<td>Monday, October 30 2:00 PM to 3:00 PM (ET)</td>
<td>Hearn Jay Cho, MD, PhD  Chlo Ray, MSN, AGPCNP-BC, OCN</td>
</tr>
</tbody>
</table>
| 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)  
Saturday, January 13, 2024 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](http://themmrf.org/educational-resources)
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.

To Learn More & Find Your Event today! themmrf.org/get-involved/mmrf-events
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.