Resources

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

Submit your questions throughout the program!
Program Faculty

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Jing Christine Ye, MD, MSc  
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Summit Agenda

<table>
<thead>
<tr>
<th>Time (CT)</th>
<th>Topic</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30 – 9:45 AM</td>
<td>Introduction to the MMRF</td>
<td>Mary DeRome, MS</td>
</tr>
<tr>
<td>9:45 – 10:00 AM</td>
<td>Welcome</td>
<td>Robert Z. Orlowski, MD, PhD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jing Christine Ye, MD, MSc</td>
</tr>
<tr>
<td>10:00 – 10:30 AM</td>
<td>Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy</td>
<td>Jonathan L. Kaufman, MD</td>
</tr>
<tr>
<td>10:30 – 11:00 AM</td>
<td>High-Dose Chemotherapy and Stem Cell Transplantation, Maintenance Therapy, and Treatment Goals</td>
<td>Jing Christine Ye, MD, MSc</td>
</tr>
<tr>
<td>11:00 – 11:30 AM</td>
<td>Relapsed/Refractory Multiple Myeloma</td>
<td>Hans C. Lee, MD</td>
</tr>
<tr>
<td>11:30 AM – 12:00 PM</td>
<td>Town Hall Q&amp;A</td>
<td>Panel</td>
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<tr>
<td>12:00 – 12:30 PM</td>
<td>Supportive Care</td>
<td>Felicia V. Diaz, MSN</td>
</tr>
<tr>
<td>12:30 – 12:45 PM</td>
<td>Patient Speaker</td>
<td>Libbyette Wright</td>
</tr>
<tr>
<td>12:45 – 1:00 PM</td>
<td>Hot Topic 1: Precursor Conditions</td>
<td>C. Ola Landgren, MD, PhD</td>
</tr>
<tr>
<td>1:00 – 1:15 PM</td>
<td>Hot Topic 2: Personalized Medicine</td>
<td>Robert Z. Orlowski, MD, PhD</td>
</tr>
<tr>
<td>1:15 – 1:30 PM</td>
<td>Hot Topic 3: Clinical Trials</td>
<td>Ajai Chari, MD</td>
</tr>
<tr>
<td>1:30 – 2:30 PM</td>
<td>Town Hall Q&amp;A</td>
<td>Panel</td>
</tr>
<tr>
<td>2:30 – 2:45 PM</td>
<td>Closing Remarks</td>
<td>Mary DeRome, MS</td>
</tr>
</tbody>
</table>
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
      • Drive multiple myeloma cell growth and survival
      • Contribute to drug resistance
      • May predict which patients respond to which therapy
    • Genetic abnormalities that help refine risk assessment
  – Led to conception of the MyDRUG trial and CureCloud Research Study
**MyDRUG Trial**

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

**Functional high-risk patients**

Profiling for alterations (NCT02884102)

- No detectable actionable alterations
  - Daratumumab + IPd

- RAF/RAS mutations
  - Cobimetinib + dex
  - Abemaciclib + Dex
  - Erdafitinib + Dex

- CDK pathway-activating alterations
  - Cobimetinib + IPd
  - Abemaciclib + IPd
  - Erdafitinib + IPd

- FGFR3-activating alterations
  - Cobimetinib + dex
  - Abemaciclib + Dex
  - Erdafitinib + Dex

- t(11;14)
  - 2:1
  - Venetoclax + IPd
  - IPd control

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**MMRF CureCloud**

**Driving toward smarter treatment options**

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

*Join the MMRF CureCloud*
MMRF CureCloud

Recent Changes

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

• Patients can sign up for CureCloud from home and will soon be able to enroll at select clinical sites with help from site research staff—sites in preparation include UTSW, WashU, Hackensack, Emory, Ochsner, Karmanos, and the VA. By the end of 2023, we anticipate that 15 sites will be approved for onsite enrollment.

• For now, patients will still provide their blood samples using an at-home blood draw.

• Patients who live in New York may now enroll in CureCloud.

• We anticipate that patients will be able to receive their DNA results from samples collected sometime in 2024.

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MMRF CureCloud

How does the MMRF CureCloud work?

1. Sign up on the MMRF CureCloud website or in person at a CureCloud participating clinic and see if you are eligible.
2. Convenient at-home blood test. A medical professional will come to you.
3. Medical record collection. Provide your myeloma doctors and we'll contact them.
4. Personalized insights. Learn more about your myeloma.
5. Discuss with your doctor.
CureCloud Enrollment Tracker

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

- Progress Towards Goal: 19%
- Patients enrolled: 941
- Patient samples sequenced: 685
- Patient health records pulled: 247

MMRF CureCloud Demographics

- By Sex:
  - Male: 55%
  - Female: 45%
  - Not Recorded: 0%

- By Age:
  - 0-10: 5%
  - 11-20: 10%
  - 21-30: 25%
  - 31-40: 15%
  - 41-50: 20%
  - 51+: 15%

- By Race:
  - White: 99.9%
  - Black: 0.1%
  - Other: 0%
  - Not Recorded: 0%

- By Ethnicity:
  - Hispanic: 96.7%
  - Non-Hispanic: 0.9%
  - Not Recorded: 2.4%
Welcome!

Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy

Jonathan L. Kaufman, MD
Winship Cancer Institute of Emory University
Atlanta, Georgia
Normal Bone Marrow

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 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

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**Light chain** (kappa [κ] or lambda [λ])

**Heavy chains** (IgG, IgA, IgM, IgD, IgE)

**M proteins**

---

MM, multiple myeloma
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

The clinical features that are characteristic of multiple myeloma

- **C**: High levels of calcium in the blood
- **R**: Decreased kidney (renal) function
- **A**: Low amount of red blood cells (anemia)
- **B**: Presence of bone damage

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

Family history

- One first-degree relative with multiple myeloma
- Relatives of multiple myeloma patients have more monoclonal gammopathy of undetermined significance (MGUS)

Demographic Risk Factors: Multiple Myeloma

- Older age
- Male sex
- Obesity
- Race

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

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

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

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

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**The Right Team**

Connect with a myeloma specialist—a doctor who diagnoses and treats a high number of myeloma patients

MMRF’s online myeloma treatment locator: themmrf.org/resources/find-a-treatment-center

Seek a second opinion at any point in your journey

Contact the MMRF Patient Navigation Center: themmrf.org/resources/patient-navigation-center

1-888-841-6673

Available resources
The Right Tests: Common Tests Conducted in Myeloma Patients

Blood tests
• Confirms the type of myeloma or precursor condition

Urine tests

Bone marrow biopsy
• 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
Learn Your Labs!

**Urine Tests**

- **UPEP**
  - Detect Bence Jones proteins (otherwise known as myeloma light chains)
  - Determine the presence and levels of M protein and Bence Jones protein

24-hr urine analysis

UPEP, urine protein electrophoresis

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### Types of Multiple Myeloma Based on Blood or Urine Tests

- **Intact M protein**
  - Named for the type of immunoglobulin and light chain pair; for example, IgG kappa (κ) or IgG lambda (λ)
  - 80%

- **Light chain only**
  - Also known as Bence Jones protein
  - Renal failure more common in light chain multiple myeloma
  - 20%

- **Non-secretory**
  - No M protein present
  - 3%
**Know Your Imaging Tests!**

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

- **X-ray**
- **MRI**
- **CT scan**
- **PET scan**

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**Know Your Bone Marrow Tests!**

Types of chromosomal abnormalities

- Translocation
- Deletion
- Gain or Amplification
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>
</thead>
<tbody>
<tr>
<td>I</td>
<td>• Serum β2M level &lt;3.5 mg/L</td>
</tr>
<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

- **High risk**
  - High-risk genetic abnormalities
    - t(4;14)
    - t(14;16)
    - t(14;20)
    - del 17p
    - p53 mutation
    - gain 1q
  - R-ISS Stage 3
  - High plasma cell S phase
  - GEP: high-risk signature
  - Double-hit myeloma: any two high-risk genetic abnormalities
  - Triple-hit myeloma: three or more high-risk genetic abnormalities

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

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

β2M: beta-2 microglobulin; LDH, lactate dehydrogenase; GEP, gene-expression profiling
Multiple Myeloma Prognosis and Risk

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

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

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

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

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

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</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>26.5%</td>
<td>27.4%</td>
<td>33.5%</td>
<td>47.2%</td>
<td>56.9%</td>
<td>56.9%</td>
</tr>
</tbody>
</table>

Available treatments:
- Ninlaro (ixazomib)
- Empliciti (elotuzumab)
- Darzalex (daratumumab)
- Xpovio (selinexor)
- Sarcisa (isatuximab)
- Blenrep (belantamab mafodotin)
- Abecma (idecabtagene vicleucel)
- Carvykti (ciltaclabtagene autoleucel)
- Tecvayli (teclistamab)
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?
- Yes
  - 3–6 cycles of induction therapy
    - 3- to 4-drug regimen generally preferred
    - Clinical trial
  - Supportive care
  - High-dose melphalan + stem cell transplant*
  - Consolidation and or continuous/maintenance therapy

- No
  - Any of the regimens used for transplant candidates*
  - Clinical trial
  - "2-drug regimen may be considered for frail patients"

*In certain circumstances, consideration for a tandem transplant
### Induction Therapy Regimens

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Recommended</th>
<th>Certain circumstances</th>
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</thead>
<tbody>
<tr>
<td>• Revlimid-Velcade-dex (RVd)*&lt;br&gt;• Kyprolis-Revlimid-dex (KRd)</td>
<td>• Darzalex-Revlimid-Velcade-dex (D-RVd)</td>
<td>• Velcade-Thalomid-dex (VTd)*&lt;br&gt;• Velcade-Cytoxan-dex (VCd)&lt;br&gt;• Velcade-Doxil-dex (VDd)&lt;br&gt;• Kyprolis-Cytoxan-dex (KCd)&lt;br&gt;• Revlimid-Cytoxan-dex (RCd)&lt;br&gt;• Darzalex-Velcade-Thalomid-dex (D-VTd)&lt;br&gt;• Darzalex-Kyprolis-Revlimid-dex (D-KRd)&lt;br&gt;• Darzalex-Cytoxan-Velcade-dex (D-VCd)&lt;br&gt;• Ninlaro-Revlimid-dex (IRd)&lt;br&gt;• Ninlaro-Revlimid-dex (ICd)&lt;br&gt;• VTD-PACE</td>
</tr>
<tr>
<td>Transplant eligible</td>
<td>Transplant ineligible</td>
<td></td>
</tr>
<tr>
<td>• Revlimid-Velcade-dex (RVd)<em>&lt;br&gt;• Darzalex-Revlimid-dex (DRud)</em></td>
<td>• Kyprolis-Revlimid-dex (KRd)&lt;br&gt;• Ninlaro-Revlimid-dex (IRd)&lt;br&gt;• Darzalex-Velcade-melphalan-prednisone (D-VMP)*&lt;br&gt;• Darzalex-Cytoxan-Velcade-dex (D-VCd)</td>
<td>• Velcade-dex (Vd)&lt;br&gt;• Revlimid-dex (Rd)*&lt;br&gt;• Velcade-Cytoxan-dex (VCd)&lt;br&gt;• Revlimid-Cytoxan-dex (RCd)&lt;br&gt;• Kyprolis-Cytoxan-dex (KCd)&lt;br&gt;• Revlimid-Velcade-dex (RVd)-lite</td>
</tr>
</tbody>
</table>

*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**
   - Neupogen, Neulasta, Leukine, Cytoxan, Mozobil
   - 3 to 6 cycles

2. **Collection of stem cells from the bloodstream**
   - Stem cell mobilization
   - -2 to -3 weeks*

3. **Freezing of stem cells**

4. **High-dose chemotherapy**
   - Melphalan
   - Day 0

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

6. **Recovery**

*The weeks leading up to the transplant; †The days after the transplant.
# Continuous or Maintenance Therapy Options

<table>
<thead>
<tr>
<th>Preferred</th>
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<th>Certain circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Revlimid*</td>
<td>- Ninlaro</td>
<td>- Velcade-Revlimid ± dex</td>
</tr>
<tr>
<td>- Ninlaro</td>
<td>- Velcade</td>
<td>- Kyprolis-Revlimid</td>
</tr>
<tr>
<td>- Velcade</td>
<td>- Darzalex</td>
<td>- Velcade-Revlimid</td>
</tr>
</tbody>
</table>

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

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## Measuring Response to Therapy

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

- **Stable disease**
- **Minor response**
- **Partial response**
- **Very good partial response**
- **Complete response (CR)**
- **Stringent CR**
- **Minimal residual disease negative**

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

*Be an informed and empowered part of your health care team!*
Overview of Treatment Approach for Active Multiple Myeloma

Is the patient a candidate for autologous stem cell transplantation?

- **Yes**
  - **Induction**
    - 3–6 treatment cycles
    - 3 or 4 drugs
  - Stem cell collection and storage
  - High-dose melphalan + stem cell transplant*
  - (± Consolidation) Maintenance

- **No**
  - **Continuous Induction**
    - 2–4 drugs
    - 6 or more treatment cycles
  - Supportive care

*In certain circumstances, consideration for a tandem transplant
Autologous Stem Cell Transplantation

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

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

3. Freezing of stem cells

4. High-dose chemotherapy
   Melphalan
   • Alkeran, Evomela

5. Thawing and infusion of stem cells
   Day 0

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

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

What does transplant mean?
Understanding the basics of autologous stem cell transplantation

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

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

The previously collected stem cells are given back by IV infusion.
Stem cells restore blood cells with fewer myeloma cells
Other cells like hair follicles and taste buds recover.
Side Effects of High-Dose Chemotherapy

- Fatigue
  - Expected
  - May last 1–3 months
  - Symptoms much more manageable with newer anti-emetics
  - Try to prevent nausea
  - May include stomach cramping
  - Encourage small amounts of food, more often
  - Avoid milk, milk products, high-fiber foods

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

- Mucositis
  - Low White blood cells count; risk for infection
  - Hemoglobin drop.
  - Fatigue
  - Platelet count drop; bleeding risk
  - Blood transfusion
  - Platelet transfusion
  - Antibiotics
  - WBC and platelets recover in 2 weeks

- Low blood counts

- Hair loss

Early vs Late Transplant in Newly Diagnosed Myeloma

**DETERMINATION Phase 3 Study**

Newly diagnosed myeloma patients

- Early Transplant Arm
  - Revlimid + Velcade + dex (RVd)
  - Induction
  - Stem cell collection
  - ASCT
  - Transplant
  - RVd
  - Consolidation
  - R

- Late Transplant Arm
  - Revlimid + Velcade + dex (RVd)
  - Induction
  - Stem cell collection
  - ASCT
  - Transplant
  - RVd
  - Consolidation
  - R

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

Phase 3 Study of Early vs Late Autologous Stem Cell Transplantation 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 Early vs Late Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: Best Response to Treatment and Duration of Response

**Response rate, %**

- ≥PR: 97.5, 95 (P=0.55)
- ≥VGPR: 82.7, 79.6 (P=0.99)
- ≥CR: 46.8, 42 (P=0.99)

**Duration of response**

<table>
<thead>
<tr>
<th>Duration of response</th>
<th>Early transplant (RVd + ASCT)</th>
<th>Late transplant (RVd alone)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥PR, months</td>
<td>56.4</td>
<td>38.9</td>
<td>0.003</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>60.6</td>
<td>52.9</td>
<td>0.698</td>
</tr>
</tbody>
</table>

Phase 3 Study of Early vs Late Autologous Stem Cell Transplantation 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</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 Early vs Late Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: Quality of Life

Quality of Life

Phase 3 Study of Early vs Late Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: Side Effects, Second Primary Cancers

Second Cancers

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

### Hematologic second primary malignancies

<table>
<thead>
<tr>
<th>5-Year cumulative incidence, %</th>
<th>RVd-alone</th>
<th>RVd + ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.316</td>
<td>1.59</td>
<td>3.52</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Another cancer, %</th>
<th>Late transplant (N=357)</th>
<th>Early transplant (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>10.4</td>
<td>10.7</td>
</tr>
<tr>
<td>Any invasive SPM</td>
<td>5.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Any hematologic SPM</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>ALL, n</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>AML/MDS, n</td>
<td>0*</td>
<td>10*</td>
</tr>
<tr>
<td>CLL/CML, n</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Any solid tumor SPM</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>Any non-invasive solid tumor SPM</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Any non-melanoma skin cancer</td>
<td>5.9</td>
<td>4.1</td>
</tr>
</tbody>
</table>

*P=0.002


---

Phase 3 Study of Early vs Late Autologous Stem Cell Transplantation 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)</th>
<th>RVd + ASCT (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment*</td>
<td>79.6</td>
<td>69.6</td>
</tr>
<tr>
<td>Subsequent therapy</td>
<td>n=222</td>
<td>n=192</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>Dazaxilex (daratumunumab)</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, Pts, 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

**Pros**

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

**Late ASCT**
- PFS may be shorter, but OS is the same
- Less side effects without high-dose chemotherapy
- Conserve quality of life in the early part of disease journey
- Better drugs or treatments could be available later on

**Cons**

**Early ASCT**
- No proven impact on overall survival
- 20% of patients still relapse within 2 years
- More side effects including 1% risk of serious life-threatening complications
- 3 months of full clinical recovery

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

---

Early vs Late ASCT Summary

- ASCT remains the standard of care for frontline therapy of myeloma; its safety has been established and it induces long remissions.
- ASCT safety has been established and it induces long progression-free survival.
- Decision of ASCT should be individualized in every patient and deserves a thorough discussion between the patient and provider.
What is maintenance therapy?

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

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

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

Successful Maintenance Therapy Must...

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

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

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

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

Revlimid Maintenance Therapy: Improves Depth of Response

Revlimid Maintenance Duration

**STAMINA Trial (BMT-CTN0702)**

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

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

Discontinuation of Revlimid at 3 years did not impact overall second primary malignancies rates at 6 years.

Continued maintenance

Stopped maintenance

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

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.

**Maintenance Duration**

**Myeloma XI Study**

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

**Median PFS (mos)**

<table>
<thead>
<tr>
<th>Maintenance to maintenance therapy (median follow up 44.7 mos)</th>
<th>At time of randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>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.</em>**</td>
<td></td>
</tr>
<tr>
<td>Revlimid</td>
<td>64</td>
</tr>
<tr>
<td>Observation</td>
<td>32</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.52</td>
</tr>
<tr>
<td>*P Value</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 × 2 years and/or MRD negative (≤10⁻⁴), PET-negative, 1+ years maintenance
- MRD and PET/CT negative
- MRD and PET/CT positive
- N=38

- Discontinue maintenance
- Continue maintenance

**Active Surveillance***

- 1-yr MRD
- 2-yr MRD
- 3-yr MRD

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

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


---

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

Second Primary Malignancies With Revlimid

Myeloma XI Study

Transplant eligible:
- 5.5% developed an SPM overall
- SPM incidence was 12.2% at 7 years in lenalidomide maintenance arm compared to 5.8% in the observation arm

Transplant ineligible:
- 9.9% developed an SPM overall
- SPM incidence was 17.1% at 5 years in lenalidomide maintenance arm compared to 10% in the observation arm

Double-exposure to lenalidomide (induction and maintenance) is associated with higher incidence of SPM and is more marked in transplant-ineligible patients.

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.
Minimal Residual Disease Negativity as a Multiple Myeloma Treatment Goal

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 CR.

What is MRD?

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

MRD tests can detect at least 1 cell in 100,000.
Why do we need to MRD?

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

How is MRD measured?

Diagnostic Tumor burden

MRD

Flow cytometry

Next-generation DNA sequencing
Comprehensive Response Assessment

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

What about other areas of the body?

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

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.

Probability of Progression-Free Survival

Time Since MRD Evaluation at Start of Maintenance (Months)

MRD by next-generation sequencing (sensitivity $1 \times 10^{-5}$)

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

**Key points from 14 studies analyzed***

- Being MRD negative is correlated with longer progression-free and overall survival.

- MRD negativity may not (?) carry the same weight in patients with standard-risk vs high-risk disease.

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


---

**MRD Is Important for Clinical Care and New Drug Registration**

- Currently assessed by BM-based technologies
  - Flow cytometry
  - Next-generation sequencing

- Progress being made with blood-based technologies
  - MS
  - Cell-free DNA

- A surrogate for patient outcome in clinical trials

- Many clinical trials are using MRD-driven strategies

- Accelerate innovative trials leading to regulatory approval

BM, bone marrow; MS, mass spectrometry

Minimal Residual Disease 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 PFS and OS to predict lower risk of progression. Modern combination therapies show increasingly higher MRD negativity rate.

MRD response-directed therapy has been applied in more and more clinical trials to explore how to guide treatment decisions in myeloma.

MRD is also useful as an end point in clinical trials helping to expedite new drug approval in myeloma.

Relapsed/Refractory Multiple Myeloma

Hans C. Lee, MD
The University of Texas MD Anderson Cancer Center
Houston, Texas
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 (cytoxan)</td>
<td>Cyclophosphamide</td>
<td>Dexamethasone</td>
<td>XPOVIO (selinexor)</td>
<td>Empliciti (elotuzumab)</td>
<td>Abecma (idecabtagene vicleucel)</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 (ixazomib)</td>
<td>Melphalan</td>
<td></td>
<td></td>
<td></td>
<td>Farydak (Panobinostat)*</td>
<td>Sarclisa (isatuximab)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pepaxto (melflufen)*</td>
<td>Blenrep (belantamab mafodotin)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tacvayli (teclistamab)*</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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 after at least two prior lines of therapy showed that progression-free survival with Blenrep was not improved versus Pomalyst-dex

• The DREAMM clinical study program is continuing as a path forward for approval with two ongoing phase 3 studies (DREAMM-7 and DREAMM-8) testing Blenrep in combinations in an earlier treatment setting for patients who have tried at least one prior line of therapy

• Results are anticipated in the first half of 2023

Withdrawn 2022*

Blenrep (belantamab mafodotin)

• Results from the confirmatory phase 3 DREAMM-3 study that compared Blenrep with Pomalyst-dex in patients with relapsed/refractory myeloma after at least two prior lines of therapy showed that progression-free survival with Blenrep was not improved versus Pomalyst-dex

• The DREAMM clinical study program is continuing as a path forward for approval with two ongoing phase 3 studies (DREAMM-7 and DREAMM-8) testing Blenrep in combinations in an earlier treatment setting for patients who have tried at least one prior line of therapy

• Results are anticipated in the first half of 2023

*Marketing of Blenrep continues in other countries where it has been approved.
**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
  - Any options for first relapse not tried
  - Refractory to an IMiD but sensitive to a PI
    - DVd, SVd, Ven-Vd (for t[11;14])

**>1 Relapse**
- Triple-class refractory
  - Approved therapies
    - Sd, ide-cel, ciltacabtagene viegecel (Abecma); idelalisib, ciltacabtagene autoleucel (Carvykti)
  - Clinical trials
    - Bispecific/trispecific antibodies, cellular therapies (CAR T-cells, NK cells), CELMoDs

---

**Triplet Regimens for Early Relapse**

- 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, idelalisib, ciltacabtagene viegecel (Abecma); ciltacabtagene autoleucel (Carvykti)

*Not yet approved for use in myeloma patients.*
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>
</tr>
</thead>
<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 relapsed/refractory 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 relapsed/refractory 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 relapsed/refractory 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>
<tbody>
<tr>
<td>Velcade (bortezomib)</td>
<td>• IV infusion • SC injection</td>
<td>• For relapsed/refractory myeloma</td>
</tr>
<tr>
<td>Kyprolis (carfilzomib)</td>
<td>• IV infusion • Weekly dosing</td>
<td>• For relapsed/refractory myeloma as a single agent, as a doublet with dexamethasone, and as a triplet with Revlimid or Darzalex plus dexamethasone</td>
</tr>
<tr>
<td>Ninlaro (ixazomib)</td>
<td>Once-weekly pill</td>
<td>• For relapsed/refractory myeloma as a triplet with Revlimid and dexamethasone</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)*</td>
<td>Once-daily pill</td>
<td>• For relapsed/refractory myeloma in combination with dexamethasone</td>
</tr>
<tr>
<td>Pomalyst (pomalidomide)*</td>
<td>Once-daily pill</td>
<td>• For relapsed/refractory myeloma in combination with dexamethasone</td>
</tr>
<tr>
<td>XPOVIO (selinexor)</td>
<td>Once-weekly pill</td>
<td>• For relapsed/refractory myeloma as a triplet with Velcade and dexamethasone</td>
</tr>
</tbody>
</table>

*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>Pollux</th>
<th>Castor</th>
<th>Candor</th>
<th>Apollo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimens compared</strong></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>
</tr>
<tr>
<td><strong>Median progression-free survival favored</strong></td>
<td>DRd: 45 vs 18 months</td>
<td>DVd: 17 vs 7 months</td>
<td>DKd: 29 vs 15 months</td>
</tr>
<tr>
<td><strong>Clinical considerations</strong></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 patients who are double-refractory to Revlimid and Velcade</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Eloquent-2</th>
<th>Eloquent-3</th>
<th>ICaria-MM</th>
<th>Ikema</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimens compared</strong></td>
<td>Empliciti-Revlimid-dex vs Rd</td>
<td>Empliciti-Pomalyst-dex vs Pd</td>
<td>Sarclisa-Pomalyst-dex vs Pd</td>
</tr>
<tr>
<td><strong>Median progression-free survival favored</strong></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>
</tr>
<tr>
<td><strong>Clinical considerations</strong></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>
</tr>
<tr>
<td></td>
<td>Empliciti-Rd associated with more infections</td>
<td>Sarclisa-Pd associated with severe low white blood cell counts, more dose reductions, upper respiratory infections, and diarrhea</td>
<td>Sarclisa-Kd associated with higher MRD negativity rates</td>
</tr>
</tbody>
</table>
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>Early Relapse</th>
<th>Late Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa-Kd</td>
<td>Kd</td>
</tr>
<tr>
<td>Sarclisa-Kd</td>
<td>Kd</td>
</tr>
<tr>
<td>Median progression-free survival (months)</td>
<td>24.7</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>82</td>
</tr>
<tr>
<td>≥VGPR rate (%)</td>
<td>67.2</td>
</tr>
<tr>
<td>MRD negativity rate (%)</td>
<td>24.6</td>
</tr>
<tr>
<td>MRD-negative CR rate (%)</td>
<td>18</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.

*<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)


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

**OPTIMISMM**

- Velcade-Pomalyst-dex (VPd) vs Vd

**ASPIRE**

- Kyprolis-Revlimid-dex (KRd) vs Rd

**TOURMALINE-MM1**

- Ninlaro-Rd (IRd) vs Rd

**BOSTON**

- XPOVIO-Velcade-dex (XPO-Vd) vs Vd

<table>
<thead>
<tr>
<th>Regimens compared</th>
<th>Median progression-free survival favored</th>
<th>Clinical considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPd: 11 vs 7 months</td>
<td>K Rd: 26 vs 17 months</td>
<td>Consider for relapse on Revlimid</td>
</tr>
<tr>
<td>K Rd associated with more upper respiratory infections and high blood pressure than Rd</td>
<td>IRd: 21 vs 15 months</td>
<td>VPd associated with more low blood counts, infections, and neuropathy than Pd</td>
</tr>
<tr>
<td>IRd an oral regimen</td>
<td>XPO-Vd: 14 vs 9 months</td>
<td>XPO-Vd associated with nausea, vomiting, weight loss, low platelet counts and fatigue with triplet, but less neuropathy than the Vd</td>
</tr>
<tr>
<td>Gastrointestinal toxicities and rashes</td>
<td>Lower incidence of peripheral neuropathy</td>
<td></td>
</tr>
</tbody>
</table>
Important Considerations for Use of Monoclonal Antibodies

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

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

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

SC, subcutaneous; IVIG, intravenous immunoglobulin

---

Important Considerations for Use of Proteasome Inhibitors

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

**Kyprolis**
- Less PN than Velcade
- Increased risk of shingles
  - Use appropriate prophylaxis
- Monitor for heart, lung, and kidney side effects
  - Use with caution in older patients with 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
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

Important Considerations for Use of XPOVIO

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

- **Low sodium (hyponatremia)**
  - Maintain fluid intake.
  - Salt tabs

- **Fatigue**
  - Stay hydrated and active.

- **Low blood counts (cytopenias)**
  - Report signs of bleeding right away.
  - Report signs of fatigue or shortness of breath.

Treatment Approach

First relapse

Proteasome inhibitor/immunomodulatory drug/antibody-based therapy

Any options for first relapse not tried

Refractory to Velcade and Revlimid

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

Refractory to an IMiD but sensitive to a PI or

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

Refactory to an IMiD but sensitive to a PI

Approved therapies

Sd, ide-cel, cilta-cel, Tecvayli

Clinical trials

Bispecific/trispecific antibodies, CAR T cells, CELMoDs

>1 Relapse

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 vicereucel (Abecma); cilta-cel, ciltacabtagene 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>
<tr>
<td>Chimeric antigen receptor (CAR) T cell</td>
<td>Abecma (idecamabtagene vicleucel)*</td>
<td>300 to 460 × 10⁶ genetically modified autologous CAR T cells in one or more infusion bags</td>
<td>• For relapsed/refractory myeloma (after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb</td>
</tr>
<tr>
<td>CAR T cell</td>
<td>Carvykti (ciltacabtagene autoleucel)†</td>
<td>0.5 to 1.0 × 10⁵ genetically modified autologous CAR T cells/kg of body weight</td>
<td>• For relapsed/refractory myeloma (after 4 or more prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb</td>
</tr>
<tr>
<td>Bispecific antibody</td>
<td>Tecvayli (teclistamab)‡</td>
<td>Step-up dosing† the first week then once weekly thereafter by subcutaneous injection</td>
<td>• For relapsed/refractory myeloma (after 4 or more prior lines of therapy, including an IMiD, a PI, and an anti-CD38 mAb</td>
</tr>
</tbody>
</table>

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

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

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

XPOVIO + Dexamethasone in Relapsed/Refractory Myeloma

<table>
<thead>
<tr>
<th></th>
<th>No. patients with ≥PR (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>32 (26)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous therapies to which the disease was refractory, n (%)</th>
<th>No. patients with ≥PR (%)†</th>
</tr>
</thead>
<tbody>
<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

CAR T-Cell Therapy

Genetically modified T cells designed to recognize specific proteins on MM cells

CAR T cells are activated once in contact with the MM cell and can destroy the MM cell

CAR T cells can persist for long periods of time in the body

CAR T cells are created from a patient’s own blood cells, but the technology is evolving to develop “off-the-shelf” varieties

Currently approved:
• Abecma (ide-cel)
• Carvykti (cilta-cel)

CAR, chimeric antigen receptor; MM, multiple myeloma


Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma

Abecma

PR 73%

ORR 73%

Average PFS 9 months

Carvykti

PR 97.9%

27-month PFS 55%

Patients (%)

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

CAR T: Expected Toxicities

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

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

BCMA, GPRC5D, or FcRH5

Currently approved:
- Tecvayli (teclistamab)

Now Approved: Tecvayli, the First Bispecific Antibody!

Median duration of response 18.4 months


Tecvayli Side Effects

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

Side Effect Management

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

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

Emerging Treatment Options

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

- We now have many different options for relapsed myeloma depending on patient and myeloma factors at relapse.
- Therapy choices will depend on teamwork between physician, patient, and caregivers and are based on many decision points.
- Combinations of proteasome inhibitors with either immunomodulatory drugs or selinexor improve progression-free survival.
- We have three different monoclonal antibodies that improve progression-free survival when added to other standard therapies without significantly increasing side effects.
- CAR T and bispecific antibodies are very active even in heavily pre-treated patients with unprecedented response rates and durations of response.

Town Hall Questions & Answers
Supportive Care
Felicia V. Diaz, MSN
The University of Texas MD Anderson Cancer Center
Houston, Texas

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

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

**How they work**

**Benefits**

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

**Medication types**

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

**Dosing**

- 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

ONJ, osteonecrosis of the jaw

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; depression/mood changes; difficulty breathing; rapid heartbeat; dizziness
  - Other causes:
    - Low levels of iron, folate, and vitamin B12
  - Treatments:
    - 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
  - Treatment:
    - Medications to stimulate production of white blood cells; antibiotics; antifungal medications; infection prevention

- **Low platelets (thrombocytopenia)**
  - Symptoms:
    - Easy or excessive bruising; superficial bleeding into the skin; prolonged bleeding from cuts; bleeding from the gums or nose; blood in urine or stool
  - Other causes:
    - Viral infection (hep B or C); immune thrombocytopenia; medications
  - Treatment:
    - Identify and treat causes other than myeloma; platelet transfusion; hold anticoagulation

---

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)
  - 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

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

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

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

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

**Ninlaro**
- 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

Class: Monoclonal Antibodies
Side Effects and Management

**Empliciti**
- Low blood counts
- Infusion reactions

**Darzalex**/
**Sarclisa**
- Infusion reactions
- Fatigue
- Upper respiratory tract infection

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

*Now approved as subcutaneous injection with fewer side effects.
XPOVIO: Selective Inhibitor of Nuclear Export Side Effects and Management

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

Low sodium (hyponatremia)
- Maintain fluid intake

Fatigue
- Stay hydrated and active

Low blood counts (cytopenias)
- Report signs of bleeding right away
- Report signs of fatigue or shortness of breath

Bispecific Antibodies

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

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

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

ALP, alkaline phosphatase; CPK, creatine phosphokinase; CRP, C-reactive protein; CRS, cytokine release syndrome; LDH, lactate dehydrogenase; O2, oxygen; TLS, tumor lysis syndrome.


Immune dysfunction

7–10-fold increased risk of bacterial and viral infections for people with myeloma
Report fever of more than 100.4°F, shaking chills even without fever, dizziness, shortness of breath, low blood pressure to HCP as directed.

Multiple myeloma

Multiple myeloma

Immune dysfunction

Multiple myeloma

General infection-prevention tips

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

As recommended by your health care team

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

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

Infection Prevention

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

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

**Fluid retention**
- Monitor for swelling of extremities and "puffy" face
- Monitor weight changes/gain
- Reduce dose

**Mood changes**
- Irritable, anxiety, difficulty concentrating
- Severe cases → depression, euphoria

**Dyspepsia-heartburn**
- Dietary modifications (spicy, acidic foods)
- Avoid NSAIDs
- Acid-blocking medications
- Take steroid with food; use enteric-coated aspirin with food

**Elevation in glucose**
- Monitor glucose and refer/treat as needed

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)
Marijuana

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

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
Libbyette Wright
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:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥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

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

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

- **Risk of progression at 2 Years**
  - 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

Genomic Prediction of Progression in Patients With MGUS or SMM

Low-input DNA whole genome sequencing

17 samples from 15 MGUS

Introducing Myeloma-Defining Genomic Events

<table>
<thead>
<tr>
<th>Myeloma-defining genomic events</th>
<th>Monoclonal gammopathy (stable MGUS/SMM)</th>
<th>Early detection of multiple myeloma (progressive MGUS/SMM)</th>
<th>Multiple myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex SV events</td>
<td>✓✓</td>
<td>✓✓</td>
<td>✓✓</td>
</tr>
<tr>
<td>Mutations in driver genes</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Copy number changes (i.e. deletions)</td>
<td>✓✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Canonical APOBEC</td>
<td>✓✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>MYC translocations</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Canonical events (IGH translocations)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>


Detection of Multiple Myeloma Earlier Using Myeloma-Defining Genomic Events

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

TRANSFORMM 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

- 10.8% of individuals screened have SMM; SMM prevalence is 0.53%
- One third of SMM patients have an intermediate or high risk* of progression to myeloma

MGUS

- 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.

Key Observations

*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.

High Prevalence of Monoclonal Gammopathy in a Population at Risk

**The PROMISE Study**

- **7,622 individuals screened***
  - 6,305 patients
  - 1,317 patients

**High-risk features for myeloma**
- Blacks (n=2,439)
- Non-Blacks with family history of HM (n=3,866)

**No high-risk features for myeloma**
- Negative family history of HM (n=631)
- Unknown family history of HM (n=686)

**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.**

---

**Rates of all monoclonal gammopathies* increase with age**

- MGIP (P<0.001)
- MGUS (P<0.001)
- LC-MGUS (P=0.23)

<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>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>30-39</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>40-49</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>50-59</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>60-69</td>
<td>0.5%</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
<tr>
<td>70-79</td>
<td>0.6%</td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>80+</td>
<td>0.7%</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

**MGUS more prevalent in individuals older than 50 years at risk**

- MGUS by SPEP/IFX in general population >50 years old
- MGUS by SPEP/IFX in high risk >50 years old from PROMISE
- MS-MGUS in high risk >10 years old from PROMISE and MGBB

<table>
<thead>
<tr>
<th>Group</th>
<th>MGUS (%)</th>
<th>Higher rates of MGUS* in Blacks or individuals with a family history of HM and older than 50 years at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td>Non-Blacks, no family history</td>
<td>6%</td>
<td>13% by PROMISE</td>
</tr>
<tr>
<td>Non-Blacks, family history</td>
<td>13%</td>
<td>10% by MGBB</td>
</tr>
<tr>
<td>Unknown</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

---

*Free light chains detected by mass spectrometry.

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

Overview of Current Treatment Approach

MGUS

Close monitoring (observation)

SMM

Close monitoring (observation)

Clinical trial participation should be considered

Approaches to SMM Treatment*

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

Pros
• High ORR
• Deep responses

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

*Only in the context of a clinical trial.
Early Therapeutic Intervention

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma


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

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

*According to the Mayo and/or Spanish models.
Kazandjian D et al. JAMA Oncol. 2021 Nov 1;7(11):1678-1685

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

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

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.

*According to the Mayo and/or Spanish models.
Four-Drug Combination Strategy for High-Risk SMM Patients

**ASCENT Study**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)</td>
<td>Best overall response rate was 97% (92% ≥VGPR); 84% of patients achieved MRD negativity.</td>
</tr>
<tr>
<td>Consolidation</td>
<td>Dara-KRd</td>
<td>Grade ≥3 hematologic toxicity in 18% of patients; non-hematologic toxicity in 51% of patients.</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Darzalex + Revlimid</td>
<td>89.9% of patients are progression-free at 3 years.</td>
</tr>
</tbody>
</table>

*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.
Multiple Myeloma Is Not Just One Disease!

Multiple myeloma is a heterogeneous disease even within cytogenetically defined molecular subtypes.

In the future, the goal is to go beyond a one-size-fits-all approach.

*How do we customize treatment?*
*Personalized medicine*
Treatment of Multiple Myeloma

Where are we now?

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

What We Need

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

IMiDs, immunomodulatory drugs; ASCT, autologous stem cell transplantation

An Example of the Importance of Personalized Medicine

<table>
<thead>
<tr>
<th></th>
<th>CoMMpassMMRF2172</th>
<th>CoMMpassMMRF2250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>ISS stage</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Baseline treatment</td>
<td>VRD</td>
<td>VRD</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>t(4;14), del13</td>
<td>t(4;14), del13</td>
</tr>
<tr>
<td>Time of progression</td>
<td>11 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>1.6 years</td>
<td>6.3 years</td>
</tr>
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An Example of the Importance of Personalized Medicine

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<td>36 months</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>1.6 years</td>
<td>6.3 years</td>
</tr>
<tr>
<td>Other Genetic Events</td>
<td>1q21, del17p + TP53 mut</td>
<td>No 1q21, No 17p or TP53 mut</td>
</tr>
</tbody>
</table>

Actionable Alterations in MM

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

- **KRAS and NRAS** (40%)
- **BRAF** (8%)
- **IDH1/2** (5%)
- **MYD88** (3%)
- **Others** (11%)
- **CDKN2C and CCND1** (18%)
- **PI3K-AKT** (5%)
- **FGFR3** (5%)
- **IGF1R and ALK** (5%)
- **Others** (11%)

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

BRAF mutations are driver mutations (eg, in melanoma) and can be important in multiple myeloma.
### Personalized Medicine Agents Under Clinical Investigation

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

*Being studied in the MyDRUG trial

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### BRAF and MEK

**Before**

**A**

**B**

**After**

Significant improvement in bone lesions.

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

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

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


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\text{high} MM

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

**Umbrella/platform studies**
- Myeloma patients:
  - No specific lesion
  - Molecular lesion A
  - Molecular lesion B
  - Molecular lesion C

**Basket/bucket studies**
- All patients with molecular lesion A:
  - Patient with myeloma
  - Patient with cancer X
  - Patient with cancer Y
  - Patient with cancer Z

**MyDRUG Study**

**Functional high-risk patients**

- Profiling for alterations (NCT02884102)
  - No detectable Actionable alterations
  - RAF/FRAS mutations
  - CDK pathway-activating alterations
  - FGFR3-activating alterations
  - t(11;14)

**2 cycles**

- Daratumumab + IPd
- Cobimetinib + dex
- Abemaciclib + Dex
- Erdafitinib + Dex

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

Precision Medicine in Myeloma: MyDRUG (NCT03732703)

Case study: Man, age 59

Treatments

1st Line
- VRd/KRd induction, ASCT, Rev maintenance
- Best response: CR
- Progressed in 30 months (22 months post-ASCT/maint.)

2nd Line
- EPd
- Best response: MR
- Progressed in 4 months

3rd Line
- MyDRUG

The Road Ahead

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

- Efforts are under way to better understand the nature of the disease and to provide patients with a more personalized approach to treatment.
- Genomic sequencing and data from myeloma patients are key to identifying subtype: our goal is to help individualize treatment for better outcomes.
- Participation in clinical studies to provide bone marrow and peripheral blood is paramount.
- Personalized medicine provides the right treatment at the right time for each myeloma patient.

Clinical Trials

Ajai Chari, MD
Icahn School of Medicine at Mount Sinai
New York, New York
Goal of Clinical Trials: Making Progress Against Myeloma

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

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

- Increase the understanding of the disease
  - Identify rational selection of existing drugs

Impact of Clinical Trials in Myeloma: Dramatic Improvements in Survival

- Survival rates have nearly doubled; further improvements expected in near future.
- Many new drugs approved since 2003.
- Many new drugs being studied in clinical trials.
- Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine.
Evolution of Multiple Myeloma Treatment:
Several New Drugs Approved in Last Two Decades

Conventional therapy
- High-dose chemotherapy with autologous bone marrow transplant
- VAD
- High-dose melphalan
- Prednisone

Novel therapy
- High-dose chemotherapy with autologous stem cell support
- Revlimid
- Thalomid
- Velcade
- Doxil
- Kyprolis
- Ninlaro
- Empliciti
- Darzalex
- XPOVIO
- Carvykti
- Tecvayli
- Abecma

VAD, vincristine, doxorubicin, dexamethasone; IMiD, immunomodulatory drug.

Conventional Trial Design
New Drug Development

**STEP 1**
Identify a target for therapy in the laboratory

**STEP 2**
Confirm the anti-cancer activity in laboratory and animal studies

**STEP 3**
Clinical trials (human studies) to determine safety, dosing, and effectiveness

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

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Traditional Clinical Study Types

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment dose</td>
<td>Number of patients</td>
<td>Questions answered*</td>
</tr>
<tr>
<td>Different doses</td>
<td>Small</td>
<td>What is the best dose? Is the drug safe? What are the side effects?</td>
</tr>
<tr>
<td>Same dose</td>
<td>Moderate</td>
<td>Does the drug work? What are the side effects?</td>
</tr>
<tr>
<td>Two different treatments</td>
<td>Large</td>
<td>Is the treatment safe? Does this treatment work better than other treatments? Does this treatment cause fewer side effects than other treatments?</td>
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</tbody>
</table>

*The FDA approves treatments that are safe, effective, and shown to be better than the standard treatments available. †When no standard treatment is available, the FDA may approve drugs based on study results of phase 2 studies. ‡Conducted to receive FDA approval of new drugs, in most cases.*
# Recent Agents Receiving Initial Accelerated vs Full Approval in Myeloma

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Conventional Chemotherapy</th>
<th>Immunomodulatory Drugs</th>
<th>Proteasome Inhibitors</th>
<th>HDAC Inhibitor</th>
<th>Immunologic Approaches</th>
<th>XPO Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Melphalan (thalidomide)</td>
<td>XPO Inhibitor (selinexor)</td>
<td>Xpovio (daratumumab; anti-CD38)</td>
<td>Xpovio (daratumumab; anti-CD38)</td>
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<tr>
<td>Dexamethasone</td>
<td>Pepaxto (melphufen)</td>
<td>Farydak (panobinostat)</td>
<td>Velcade (bortezomib)</td>
<td>XPO Inhibitor (sarinomab; anti-CD38)</td>
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<tr>
<td></td>
<td>Revlimid (lenalidomide)</td>
<td>Sarclisa (isatuximab; anti-CD38)</td>
<td>Kyprolis (carfilzomib; low/high dose)</td>
<td>Sarclisa (isatuximab; anti-CD38)</td>
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<tr>
<td></td>
<td>Pomalyst (pomalidomide)</td>
<td>Ninlaro (ixazomib)</td>
<td>Ninlaro (ixazomib)</td>
<td>Ninlaro (ixazomib)</td>
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<td></td>
<td>Doxil (liposomal doxorubicin)</td>
<td>Ninlaro (ixazomib)</td>
<td>Ninlaro (ixazomib)</td>
<td>Ninlaro (ixazomib)</td>
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<td>DCEP/D-PACE</td>
<td>Ninlaro (ixazomib)</td>
<td>Ninlaro (ixazomib)</td>
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<td></td>
<td>Carmustine</td>
<td>Ninlaro (ixazomib)</td>
<td>Ninlaro (ixazomib)</td>
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<tr>
<td></td>
<td>Bendamustine</td>
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<td>Ninlaro (ixazomib)</td>
<td>Ninlaro (ixazomib)</td>
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</tbody>
</table>

- In the U.S., after Investigational New Drug Application (IND) filed, accelerated approval for life-threatening conditions for which no other drug treatment exists (ie, refractory or intolerant to all available agents)
  - Can be based on surrogate endpoints eg, ORR but requires subsequent confirmatory, randomized controlled trial (RCT)
- In contrast, full approval requires RCTs with PFS as end point

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**Innovative Study Design**
Innovative Trial Designs: Guiding the Future of Cancer Research Toward Precision Medicine

Umbrella/platform trials

Basket/bucket trials


Participation in a Clinical Study

Mendelssohn Cancer Research Center

Multiple Myeloma Research Foundation
Will I be treated like a guinea pig?

Three influential documents

The Nuremberg Code

The Declaration of Helsinki

The Belmont Report

Ethics Committees and Research Boards

Benefits of Clinical Trials

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

• Find a clinical trial
  – Contact the MMRF Patient Navigator Center at 1-888-841-6673
  – Visit themmrf.org/resources/clinical-trial-finder/
  – Ask your treating hematologist/oncologist about any available trials
  – Check with any academic medical centers close to your home

• Talk to your doctor about your eligibility
• Meet with the research nurse to learn more
• Carefully review the informed consent paperwork

Key Points

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

Thank you!
Resources

• Resource tab includes
  – Speaker bios
  – Copy of the slide presentation
  – Exhibit Hall
Upcoming Patient Education Events

Save the Date

<table>
<thead>
<tr>
<th>Topic</th>
<th>Date and Time (ET)</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Webinar: Clinical Studies</td>
<td>Friday, May 5 1:00 to 2:00 PM</td>
<td>Elizabeth O’Donnell, MD Andrew J. Yee, MD</td>
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<tr>
<td>Facebook Live FAQs</td>
<td>Wednesday, May 17 11:00 AM to 12:00 PM</td>
<td>Noopur Raje, MD</td>
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<tr>
<td>Patient Summit</td>
<td>Saturday, May 20 9:00 AM to 3:45 PM</td>
<td>Saad Usmani, MD Faith Davies, MBCh Justina Kieman, PA Neha Korde, MD Sham Mailankody, MBBS Gunjan Shah, MD</td>
</tr>
</tbody>
</table>

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

MMRF Patient 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.

**MMRF Events**

Our events are returning live and in-person, and there are so many ways to get involved. Most have a virtual option, too.

Join us today!

**Endurance Events**

**5K Walk/Run Events**

**Independent Events**

FIND AN EVENT AND JOIN US: https://themmrf.org/get-involved/mmrfevents/
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.