Opening Remarks
Mary DeRome, MS
MMRF
iPads

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

Submit your questions throughout the program!
Throughout the Summit, use the same e-mail address to log on to any iPad.

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Winston-Salem, North Carolina
# Summit Agenda

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<th>Topic</th>
<th>Speakers</th>
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<td>9:30 – 9:45 AM</td>
<td>Welcome</td>
<td>Peter M. Voorhees, MD</td>
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<td>9:45 – 10:15 AM</td>
<td>Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy</td>
<td>Craig Emmitt Cole, MD</td>
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<tr>
<td>10:15 – 10:45 AM</td>
<td>High-Dose Chemotherapy and Stem Cell Transplantation, Maintenance Therapy, and Treatment Goals</td>
<td>Cindy Varga, MD</td>
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<td>10:45 – 11:00 AM</td>
<td>Break</td>
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<td>11:00 – 11:30 AM</td>
<td>Relapsed/Refractory Multiple Myeloma</td>
<td>Monique A. Hartley-Brown, MD, MMSc</td>
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<td>11:30 AM – 12:00 PM</td>
<td>Immunotherapy</td>
<td>Peter M. Voorhees, MD</td>
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<td>12:00 – 12:30 PM</td>
<td>Supportive Care</td>
<td>Jordan D. Robinson, PA-C</td>
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<td>12:30 – 1:15 PM</td>
<td>Lunch</td>
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<td>1:15 – 1:30 PM</td>
<td>Patient Speaker</td>
<td>Tony Newberne</td>
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<tr>
<td>1:30 – 1:45 PM</td>
<td>Hot Topic 1: Multiple Myeloma Precursor Conditions</td>
<td>Cindy Varga, MD</td>
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<td>1:45 – 2:00 PM</td>
<td>Hot Topic 2: High-Risk Multiple Myeloma</td>
<td>Craig Emmitt Cole, MD</td>
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<tr>
<td>2:00 – 2:15 PM</td>
<td>Hot Topic 3: New Drugs on the Horizon</td>
<td>Monique A. Hartley-Brown, MD, MMSc</td>
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<tr>
<td>2:15 – 3:15 PM</td>
<td>Town Hall Q&amp;A</td>
<td>All Faculty</td>
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<tr>
<td>3:15 – 3:30 PM</td>
<td>Closing Remarks</td>
<td>Mary DeRome, MS</td>
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**MMRF Introduction**

**Mary DeRome, MS**

MMRF
The Work of the MMRF

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

1. We accelerate new treatments
   Bringing next-generation therapies to patients faster

2. We drive precision medicine
   Using data to deliver better answers and more precise treatments for patients

3. We empower patients
   Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives

MMRF CoMMpass Study: Advancing Personalized Medicine Research

- Landmark study focusing on the genomics of myeloma

- Goals
  - Learn which patients respond best to which therapies
  - Identify new targets and new hypotheses

- Newly diagnosed patients are followed for at least 8 years

All participants undergo a type of detailed DNA testing called genomic sequencing at diagnosis and each relapse.
CoMMpass Is a Trial of Discovery

- CoMMpass data has
  - Provided the myeloma community with information on
    - Frequency of genetic abnormalities
    - How genetic abnormalities play a role in myeloma
      - 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
How does the MMRF CureCloud work?

1. **Convenient at-home blood test.** A medical professional will come to you.
2. **Sign up on the MMRF CureCloud website or in person at a CureCloud participating clinic and see if you are eligible.**
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.**

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.
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.

CureCloud Enrollment Tracker

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

- 941 Patients enrolled
- 685 Patient samples sequenced
- 247 Patient health records pulled

Progress towards goal: 19%
MMRF CureCloud Demographics

Welcome!
Peter M. Voorhees, MD
Atrium Health Levine Cancer Institute
Charlotte, North Carolina
Wake Forest University School of Medicine
Winston-Salem, North Carolina
Question

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

Question

At what stage is your myeloma? (If you are a caregiver, what is the stage of the patient's myeloma?)
1. Newly diagnosed
2. Relapsed/refractory
3. Remission: still on therapy
4. Remission: not on therapy
5. MGUS or smoldering myeloma not currently requiring treatment
6. Other
7. I don’t know.
Question

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

Question

Do you know if you had any molecular characterization performed on your tumor, such as FISH, cytogenetics, or sequencing?
1. No
2. Yes, I had FISH.
3. Yes, I had cytogenetics.
4. Yes, I had sequencing.
5. Yes, I had more than one of these tests performed.
6. I don’t know.
Question

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

1. Yes
2. No
3. I don’t know.
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?

- **35,730** new cases in 2023
- **159,787** living with myeloma or in remission
- Myeloma represents **1.8%** of all new cancer cases in the U.S.
- **Median age at diagnosis**: 69
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

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

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

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

### Diseases 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

## Spectrum of Plasma Cell Disorders and Myeloma

### MGUS
- Monoclonal gammopathy of undetermined significance
  - M protein under 3 g/dL
  - AND
  - Plasma cells in bone marrow <10%
  - AND
  - No CRAB or SLiM high-risk features

  - 1% risk of progression/year to multiple myeloma or related conditions

  - Observation
  - Clinical trials

### Smoldering myeloma
- M protein over 3 g/dL (serum) or over 500 mg/24 hrs (urine)
  - AND
  - Plasma cells in Bone Marrow 10%–60%
  - AND
  - No CRAB or “SLiM” high risk features

  - 10% risk of progression/year to active myeloma

  - Observation
  - Clinical trials

### High-risk smoldering
- M protein over 2 g/dL
  - AND
  - Plasma cells in bone marrow 20%–60%
  - AND
  - Free light chain ratio >20
  - “Evolving type” SMM increase >10% protein within 6 mo
  - AND
  - No CRAB or SLiM high-risk features

  - >45% risk of progression in 2 yr to active myeloma

  - Close observation
  - Clinical trials
  - ??Treatment??

### Multiple myeloma
- Malignant plasma cells seen on any biopsy (usually bone marrow)
  - AND ≥1 “CRAB” feature

  - C: Calcium elevation (>11 mg/dL)
  - R: Renal: low kidney function; (serum creatinine >2 mg/dL)
  - A: Anemia: low red blood count (Hb <10 g/dL)
  - B: Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

  - OR have ≥1 SLiM high-risk features:
    - S: >60% plasma cells on bone marrow biopsy
    - Li: Serum light chain ratio >100
    - M: >1 lytic lesions on MRI (or PET/CT scan)

  - Frontline treatment
  - Clinical trials
Infections and Vaccinations in Multiple Myeloma

- Risk of infection higher for myeloma patients than for general population
- Types of infections include:
  - Bacterial: pneumonia (an infection of the lungs), bacteremia
  - Viral: varicella zoster (shingles), influenza, COVID

Preventive strategies (prophylaxis) are recommended:
- Hand-washing, avoiding sick contacts
- Vaccines/pre-exposure antibodies
- Other precautions (antibiotics, growth factors)

Demographic Risk Factors: Multiple Myeloma

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

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

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**

**Available resources**

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

MMRF’s online myeloma treatment locator: [themrfr.org/resources/find-a-treatment-center](http://themrfr.org/resources/find-a-treatment-center)

Seek a second opinion at any point in your journey

Contact the MMRF Patient Navigation Center: [themrfr.org/resources/patient-navigation-center](http://themrfr.org/resources/patient-navigation-center)

1-888-841-6673
The Right Tests: Common Tests Conducted in Myeloma Patients

**Blood tests**
- Confirms the type of myeloma or precursor condition

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

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

**Imaging tests**

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**, urine protein electrophoresis
  - 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**

**Serum Protein Electrophoresis**

- Normal
- Antibodies
- Albumin
- α Zone proteins
- β Zone proteins
- γ Zone proteins
- Lightest
- Heaviest
- Plasma cells
- IgG
- IgA
- IgM
Types of Multiple Myeloma Based on Blood or Urine Tests

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

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

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

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

X-ray  MRI  CT scan  PET scan

Know Your Bone Marrow Tests!

Types of chromosomal abnormalities

Translocation  Deletion  Gain or Amplification
Putting the Results Together

Staging, prognosis, and risk assessment

Multiple Myeloma Prognosis and Risk

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

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

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

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

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

**Double-hit myeloma**: any two high-risk genetic abnormalities

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

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

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

Multiple Myeloma Prognosis and Risk

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

**Standard risk**

- R-ISS Stage I

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

**High risk**

- R-ISS Stage III

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

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

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

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

The Right Treatment

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

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

Myeloma Survival Has Improved Over Time Mainly Due to Current Drugs

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

|------|------|------|------|------|------|-----------------|
| Survival Rate | 26.5% | 27.4% | 33.5% | 47.2% | 56.9% | Ninlaro (ixazomib)  
Empliciti (elotuzumab)  
Darzalex (daratumumab)  
Xpovio (selinexor)  
Sarcisla (isatuximab)  
Abecma (idecabtagene vicaleucel)  
Carvykti (ciltaclabtagene autoleucel)  
Tecvayli (teclistamab) |

Available treatments

- Chemotherapy + dexamethasone + stem cell transplantation
- Velcade (bortezomib)
- Revlimid (lenalidomide)
- Kyprolis (carfilzomib)
- Pomalyt (pomalidomide)
Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma

**Overview of Treatment Approach for Active Multiple Myeloma**

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

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

**Recommended**
- Darzalex-Revlimid-Velcade-dex (D-RVd)

**Certain circumstances**
- Velcade-Thalomid-dex (VTd)*
- Velcade-Cytoxan-dex (VCd)
- Velcade-Doxil-dex (VDd)
- Kyprolis-Cytoxan-dex (KCd)
- Revlimid-Cytoxan-dex (RCd)
- Darzalex-Velcade-Thalomid-dex (D-VTd)
- Darzalex-Kyprolis-Revlimid-dex (D-KRd)
- Darzalex-Cytoxan-Velcade-dex (D-VCd)
- Ninlaro-Revlimid-dex (IRd)
- Ninlaro-Cytoxan-dex (ICd)
- VTD-PACE

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

---

**Which is the right therapy for YOU?**

- Clinical Trial
- Lifestyle goals of therapy
- Access
- Risk Profile
- Geography
- Myeloma symptoms
- Co morbid conditions
- Patient preference
- age
Continuous or Maintenance Therapy Options

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

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

Measuring Response to Therapy

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

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

Where is the myeloma field going?

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

Summary

- Multiple myeloma is a rare blood cancer that can negatively affect the bones, kidneys, and bone marrow, leading to lowered blood counts.

- The prognosis of multiple myeloma depends on the genetic makeup of myeloma cell chromosomes; R-ISS is used for staging in multiple myeloma.

- Survival rates are improving because of new drugs and new combinations of drugs.

- The treatment paradigm will continue to change with the approval of additional novel agents.

- Knowledge is power: right team, right test, right treatment.

*Be an informed and empowered part of your health care team!*
Please take a moment to answer two questions about this presentation.

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

Cindy Varga, MD
Atrium Health Levine Cancer Institute
Charlotte, North Carolina
Wake Forest University School of Medicine
Winston-Salem, North Carolina
Overview of Treatment Approach for Active Multiple Myeloma

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

Yes

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

Stem cell collection and storage

High-dose melphalan + stem cell transplant*

(± Consolidation) Maintenance

Supportive care

No

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

*In certain circumstances, consideration for a tandem transplant

High-Dose Chemotherapy and Stem Cell Transplantation

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

Understanding the basics of autologous stem cell transplantation

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

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

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

Autologous Stem Cell Transplantation

1. Induction therapy
   -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.
Side Effects of High-Dose Chemotherapy

- **Fatigue**
  - Expected
  - May last 1–3 months

- **Nausea, vomiting, and diarrhea**
  - Symptoms much more manageable with newer anti-emetics
  - Try to prevent nausea
  - May include stomach cramping
  - Encourage small amounts of food, more often
  - Avoid milk, milk products, high-fiber foods

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

- **Low blood counts**
  - Low white blood cells count (risk for infection)
  - Hemoglobin drop (fatigue)
  - Platelet count drop (bleeding risk)
  - Blood transfusion
  - Platelet transfusion
  - Antibiotics
  - White blood cells and platelets recover in 2 weeks

- **Hair loss**

---

Is transplant still required in newly diagnosed myeloma?

**DETERMINATION phase 3 study**

- Newly diagnosed myeloma patients
  - 365 patients
  - 357 patients

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

**LATE-TRANSPLANT ARM**
- Revlimid + Velcade + dex (RVD)
- Induction
- Stem cell collection
- Transplant
- Consolidation
- RVd
- R

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

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

![Graph showing progression-free survival (PFS) and overall survival (OS).]

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

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

Transplant extended time to progression by 20 months.

Length of overall survival: no difference.


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

![Graph showing response rates for different groups.]

- Response rate (%)
  - ≥PR: RVd-alone 97.5, RVd+ASCT 95, P=0.55
  - ≥VGPR: RVd-alone 82.7, RVd+ASCT 79.6, P=0.99
  - ≥CR: RVd-alone 46.8, RVd+ASCT 42, P=0.99

<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>Median duration of ≥PR, months</td>
<td>56.4</td>
<td>38.9</td>
<td>0.003</td>
</tr>
<tr>
<td>5-year duration of ≥CR, %</td>
<td>60.6</td>
<td>52.9</td>
<td>0.698</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Side effect (%)</th>
<th>RVd alone (N=357)</th>
<th>RVd + ASCT (N=365)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>78.2</td>
<td>94.2</td>
</tr>
<tr>
<td>Fatal side effects</td>
<td>0.3</td>
<td>1.6*</td>
</tr>
<tr>
<td>Low blood counts</td>
<td>60.5</td>
<td>89.9</td>
</tr>
<tr>
<td>Very low white cell count</td>
<td>42.6</td>
<td>86.3</td>
</tr>
<tr>
<td>Low platelet count</td>
<td>19.9</td>
<td>82.7</td>
</tr>
<tr>
<td>Low white cell count</td>
<td>19.6</td>
<td>39.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>18.2</td>
<td>29.6</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Infections with low WBC</td>
<td>4.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Fever</td>
<td>2.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.6</td>
<td>6.6</td>
</tr>
<tr>
<td>Mouth sores</td>
<td>0</td>
<td>5.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Numbness, tingling nerve</td>
<td>5.6</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Severe side effects were more common with transplant.

*Includes one death related to ASCT


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

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

<table>
<thead>
<tr>
<th>Subsequent therapy in patients off protocol therapy (%)</th>
<th>RVD alone (N=279) late transplant</th>
<th>RVD + ASCT (N=276) early transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment*</td>
<td>79.6</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>Pomalyx (pomalidomide)</td>
<td>30.2</td>
<td>29.2</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)</td>
<td>25.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Any proteasome inhibitor</td>
<td>55.9</td>
<td>50.0</td>
</tr>
<tr>
<td>Velcade (bortezomib)</td>
<td>27.5</td>
<td>25.5</td>
</tr>
<tr>
<td>Kyprolis (carfilzomib)</td>
<td>21.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>8.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Marizomib</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Any monoclonal antibody</td>
<td>16.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Darzalex (daratumumab)</td>
<td>11.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Empliciti (elotuzumab)</td>
<td>4.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Sarclisa (isatuximumab)</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

*Including IMiDs, PIs, mAbs, HDACi (panobinostat), ASCT, chemotherapy, RT, steroids, other

Only 28.0% of RVD-alone (late transplant) patients had received ASCT at any time following end of study treatment.

Early vs Late Transplant Pros and Cons

**Pros**

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

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

**Cons**

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

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

- ASCT remains the standard of care for frontline therapy of myeloma.
- ASCT safety has been established and it induces long PFS.
- Decision of ASCT should be individualized in every patient and deserves a thorough discussion between the patient and provider.
- Emerging data suggests patients with an extremely good response to induction therapy may have a long PFS. Studies are ongoing to determine whether these patients require ASCT.

What is maintenance therapy?

- A prolonged, and often low-dose, less-intensive treatment given to myeloma patients after achieving a desired response to initial therapy
- To prevent disease progression for as long as possible while maintaining favorable quality of life
- To deepen responses by reducing minimal residual disease (MRD) or maintaining the response achieved, reducing the risk of relapse, and prolonging survival
Successful Maintenance Therapy Must...

1. Be convenient
2. Be safe and well tolerated long term
3. Not interfere with the use of other future treatments
   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)

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

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

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

MEL, melphalan; RVD, Revlimid-Velcade-dex; REV, Revlimid
**Maintenance Duration**

**Myeloma XI Study**

- Newly diagnosed myeloma patients
  - Induction: CTD/CRD
    - R
  - Consolidation: CVD, No CVD
    - R
  - Maintenance: Revlimid, Observation

<table>
<thead>
<tr>
<th>Median PFS (mos)</th>
<th>All patients*</th>
</tr>
</thead>
<tbody>
<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 and MRD negative by PET and NGF or NGS on at least 1 year of maintenance

<table>
<thead>
<tr>
<th>MRD and PET/CT negative N=38</th>
<th>Discontinue maintenance</th>
<th>Continue maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD and PET/CT positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Active Surveillance*
  - 1-yr MRD
  - 2-yr MRD
  - 3-yr MRD

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

After median follow-up of 14 months, 89% remain on study (5% with PD, 6% withdrew).

MRD resurgence occurred in 13% of patients (2 patients had resurgence of M protein and disease progression).

MRD negativity (at $10^{-6}$ and $10^{-7}$) is sustained even after discontinuation of maintenance therapy.

MRD-guided discontinuation of maintenance may carry significant cost savings.
Revlimid Maintenance: Cumulative Incidence of Second Primary Malignancies

Hematologic

- Lenalidomide vs Control
  - HR (95% CI): 2.03 (1.14–3.61)
  - P = 0.015

Solid Tumor

- Lenalidomide vs Control
  - HR (95% CI): 1.71 (1.04–2.79)
  - P = 0.032

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

Maintenance Therapy Summary

- The body of evidence from phase 3 trials indicates that maintenance therapy improves PFS and likely OS.

- Most patients should receive maintenance who are thought to be Revlimid responsive and able to tolerate the side effects.

  - For patients who are unable to tolerate Revlimid, there are other agents such as Ninlaro, Kyprolis, and Darzalex that are effective but are not yet FDA approved for use as maintenance. Several clinical trials are under way.

  - When you are in remission and receiving maintenance (or being observed off treatment), it is important to continue your regular health checks (colonoscopy, breast screening, PSA, mole checks, etc).
Goals of Multiple Myeloma Therapy

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

Measuring Response to Therapy

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

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

What is MRD?

- The presence of small amounts of myeloma cells in the body after treatment
- MRD tests can detect at least 1 cell in 1,000,000.

Why do we need to measure MRD?

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

Right now, measurement of MRD depends on counting cells or DNA sequences in bone marrow samples. Imaging (with PET/CT scan) is also required to detect residual disease outside of the bone marrow.

What about other areas of the body?
Why is it important to achieve MRD negativity?

Patients who achieve MRD negativity following treatment experience longer remission than those who are still MRD positive after treatment.


MRD Summary

MRD is the deepest response after myeloma treatment, including bone marrow MRD and imaging MRD. NGF and NGS are the two most commonly used marrow MRD tests. Blood-based MRD is in exploration.

MRD has been associated with longer progression-free and overall survival to predict lower risk of progression. Modern combination therapies show increasingly higher MRD negativity rates.

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

MRD is also useful as an end point in clinical trials helping to expedite new drug approval in myeloma.
Please take a moment to answer two questions about this presentation.

Relapsed/Refractory Multiple Myeloma

Monique A. Hartley-Brown, MD, MMSc
Harvard Medical School, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute
Boston, Massachusetts
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
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 viclucel)</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>Farydak (Panobinostat)*</td>
<td>Sarcida (isatuximab)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pepaxto (melflufen)*</td>
<td>Blenrep (belantamab mafodotin)§</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tecvayli (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 PFS with Pepaxto was not improved vs Pomalyst-dex, which didn’t pass the regulatory hurdles to confirm the accelerated approval in the U.S.

Withdrawn 2022*

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

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

First relapse

Proteasome inhibitor/ immunomodulatory drug/ antibody-based therapy

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

Refractory to Velcade and Revlimid

Dvd, Svd, Ven-Vd (for t[11;14])

Refractory to an IMiD but sensitive to a PI

Approved therapies

Sd, ide-cel, cilt-a-cel, Tecvayli

Clinical trials

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

>1 Relapse

Any options for first relapse not tried

Refractory to an IMiD but sensitive to a PI

Approved therapies

Venetoclax (Ven)-Vd (for t[11;14])

Clinical trials

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

*Not yet approved for use in myeloma patients.

D: daratumumab (Darzalex); K: carfilzomib (Kyprolis); d: dexamethasone; Isa, isatuximab (Sarcisia); P: pomalidomide (Pomalyst); Elo, elotuzumab (Empliciti); V: bortezomib (Velcade); S, selinexor (Xpovio); Ven, venetoclax (Venclexta); ide-cel, idecabtagene vicleucel (Abecma); cilt-a-cel, cilta-cel, L19-cel, ciltacabtagene autoleucel (Carvykti)

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Approval</th>
</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>

**Notes:** 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

**Notes:** IV, intravenous; SC, subcutaneous
### Monoclonal Antibody–Based Regimens for Early Relapse: Darzalex

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

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

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

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

<table>
<thead>
<tr>
<th>Early relapse</th>
<th>Late relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa-Kd</td>
<td>Sarclisa-Kd</td>
</tr>
<tr>
<td>Kd</td>
<td>Kd</td>
</tr>
<tr>
<td>Median PFS (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

Regimens compared

- Velcade-Pomalyst-dex (VPd) vs Vd
- Kyprolis-Revlimid-dex (KRd) vs Rd
- Ninlaro-Rd (IrD) vs Rd
- XPOVIO-Velcade-dex (XPO-Vd) vs Vd

Median PFS favored

- VPd: 11 vs 7 months
- KRd: 26 vs 17 months
- IRd: 21 vs 15 months
- XPO-Vd: 14 vs 9 months

Clinical considerations

- Consider for relapse on Revlimid
- VPd associated with more low blood counts, infections, and neuropathy than Pd
- KRd associated with more upper respiratory infections and high blood pressure than Rd
- IRd an oral regimen
- Gastrointestinal toxicities and rash
- Lower incidence of peripheral neuropathy
- XPO-Vd associated with nausea, vomiting, weight loss, low platelet counts and fatigue with triplet, but less neuropathy than the Vd
## Important Considerations for Use of Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Monoclonal Antibody</th>
<th>Infusion Reactions</th>
<th>Risk of Shingles</th>
<th>Increased Risk of Hypogammaglobulinemia and Upper Respiratory Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darzalex</td>
<td>Less with SC use</td>
<td>Use appropriate vaccination</td>
<td>IVIG support</td>
</tr>
<tr>
<td>Empliciti</td>
<td>Less PN than Velcade</td>
<td>Use appropriate prophylaxis</td>
<td>Use with caution in older patients with cardiovascular risk factors; high blood pressure; no dose adjustment for kidney issues; adjust for liver issues</td>
</tr>
<tr>
<td>Sarclisa</td>
<td>Less PN than Velcade</td>
<td>Use appropriate prophylaxis</td>
<td>Use with caution in older patients with cardiovascular risk factors; high blood pressure; no dose adjustment for kidney issues; adjust for liver issues</td>
</tr>
</tbody>
</table>

SC, subcutaneous; IVIG, intravenous immunoglobulin

---

## Important Considerations for Use of Proteasome Inhibitors

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Velcade</td>
<td>Numbness, tingling, burning sensations and/or pain due to nerve damage</td>
<td>Use appropriate prophylaxis</td>
<td>Use with caution in older patients with cardiovascular risk factors</td>
<td>GI effects occur early</td>
<td>Needs to be taken at least 1 hour before or 2 hours after a meal</td>
<td></td>
</tr>
<tr>
<td>Kyprolis</td>
<td>Less PN than Velcade</td>
<td>Use appropriate prophylaxis</td>
<td>Monitor for heart, lung, and kidney side effects</td>
<td>GI effects occur early</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ninlaro</td>
<td>Less PN than Velcade</td>
<td>Use appropriate prophylaxis</td>
<td>GI effects occur early</td>
<td>GI effects occur early</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

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

RKd, Isa-Rk, DPd, Elo-Pd, Isa-Pd, or Kpd

>1 Relapse

Triple-class refractory

Approved therapies

Sd, ide-cel, cilt-cel, Tecvayli

Clinical trials

Bispecific/trispecific antibodies, CAR T cells, CELMoDs

Approved therapies

Clinical trials

*Not yet approved for use in myeloma patients.

Triple-Class Refractory

- Patients with relapsed or refractory multiple myeloma who have received treatment with—and did not respond satisfactorily to, or progressed while on treatment with—the three main classes of drugs currently used to treat myeloma

Proteasome inhibitors

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

Immunomodulatory drugs

- Revlimid (lenalidomide)
- Pomalyst (pomalidomide)

Anti-CD38 monoclonal antibodies

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

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

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

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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.
Abecma and Carvykti in Relapsed
and Refractory Multiple Myeloma

Abecma

ORR 73%

Average PFS
9 months

Carvykti

ORR 97.9%

Now Approved: Tecvayli, the First
Bispecific Antibody

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 PFS.
- We have three different monoclonal antibodies that improve PFS when added to other standard therapies without significantly increasing side effects.
- CAR T and bispecific antibodies are very active even in heavily pre-treated patients with unprecedented response rates and durations of response.
Please take a moment to answer two questions about this presentation.

Immunotherapy

Peter M. Voorhees, MD
Atrium Health Levine Cancer Institute
Charlotte, North Carolina
Wake Forest University School of Medicine
Winston-Salem, North Carolina
Why do multiple myeloma cells still grow and survive if the immune system is ready to attack?

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

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

---

**Types of Immunotherapy**

- **Antibodies**: Directly targeting myeloma cell markers
- **Immunomodulatory drugs**: Overcoming immune suppression
- **CAR T cells**: Boosting myeloma-fighting T cells
- **Vaccines**: Activating myeloma-specific immunity

CAR T-Cell Therapy

Genetically modified T cells are designed to recognize specific proteins on myeloma cells.

CAR T cells are activated once in contact with the myeloma cell and can destroy it.

CAR T cells can persist for long periods in the body.

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

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

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

---

CAR T-Cell Therapy Patient Journey

1. Apheresis
   - 1 day
   - Immune cells from the patient are collected

2. (Manufacturing)
   - 4–6 weeks
   - Patient returns home
   - Standard-of-care therapy is permitted until CAR T cells are ready for infusion

3. Lymphodepletion (chemotherapy)
   - 3 days*
   - Fludara and Cytoxan are used to create "immunologic space" to CAR T cells to expand

4. Infusion
   - 2 weeks

5. Follow up
   - Within 2 weeks

*Patient must be recovered from any toxicity incurred from bridging therapy before starting lymphodepletion
**Abecma or Standard Regimens in Relapsed and Refractory Multiple Myeloma**

### Progression-free survival

- **Standard regimen**
  - Median PFS, 13.3 months

- **Ide-cel**
  - Median PFS, 4.4 months

### Treatment response

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

*P<0.001

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**CAR T-Cell Therapy Insights**

**Prognostic value of depth of response following CAR T-cell therapy**
- Achieving sustained, undetectable MRD after Abecma is associated with prolonged PFS
- Only MRD status—not complete response (CR) status—predicted early relapse 1 month after Abecma
- Both MRD and CR status at 12 months were required to identify patients with longer PFS

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

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

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

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

*Early relapse after frontline therapy or inadequate response after frontline ASCT
Carvykti in Relapsed and Refractory Multiple Myeloma


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

**Fig. 1.**
- **Bar graph:** Cilta-cel (n=97)
  - **PR:** 82.5%
  - **VGPR:** 12.4%
  - **sCR:** 3%
  - **ORR:** 97.9%
  - **27-month PFS:** 55%

- **Patients (%):**
  - 0
  - 10
  - 20
  - 30
  - 40
  - 50
  - 60
  - 70
  - 80
  - 90
  - 100

- **Legend:**
  - **PR**
  - **VGPR**
  - **sCR**

**Table 1.**
- **Patients Responding (%):**
  - **PR**
  - **VGPR**
  - **CR**
  - **sCR**
  - **Cilta-cel group**
  - **Standard of Care Arm**
  - **Wk 8**
  - **Carvykti Arm**
  - **Standard of Care Arm**
  - **58.2**
  - **14.9**
  - **8.2**
  - **21.8**

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


**Fig. 2.**
- **Patient Survival:**
  - **Cilta-cel group**
  - **Standard-care group**

- **Percentage of Patients Surviving Without Disease Progression:**
  - **Wk 8**
  - **Months:** 0 3 6 9 12 15 18 21 24 27 30

**Table 2.**
- **Patients Responding (%):**
  - **PR**
  - **VGPR**
  - **CR**
  - **sCR**
  - **Cilta-cel group**
  - **Standard of Care Arm**
  - **Relapsed/refractory myeloma patients with 1–3 prior lines of therapy and refractory to Revlimid**
  - **211 patients**
  - **208 patients**
  - **Pomalyst + Velcade + dex (PVd) or Darzalex + Pd (DPd)**

**Table 3.**
- **Patients Responding (%):**
  - **PR**
  - **VGPR**
  - **CR**
  - **sCR**
  - **Cilta-cel group**
  - **Standard of Care Arm**
  - **STANDARD OF CARE ARM**
  - **CARVYKTI ARM**
  - **Relapsed/refractory myeloma patients with 1–3 prior lines of therapy and refractory to Revlimid**
  - **211 patients**
  - **208 patients**
  - **Pomalyst + Velcade + dex (PVd) or Darzalex + Pd (DPd)**

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

## CAR T: Expected Toxicities

<table>
<thead>
<tr>
<th>CRS</th>
<th>ICANS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>1–9 days after CAR T-cell infusion</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>5–11 days</td>
</tr>
</tbody>
</table>
| **Symptoms** | - Fever  
- Difficulty breathing  
- Dizziness  
- Nausea  
- Headache  
- Rapid heartbeat  
- Low blood pressure | - Headache  
- Confusion  
- Language disturbance  
- Seizures  
- Delirium  
- Cerebral edema |
| **Management** | - Antiseizure medications  
- Corticosteroids  
- Supportive care | - Antiseizure medications  
- Corticosteroids |

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

---

## Transplant vs CAR T Cells

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

*An immune cell that is the “business end” of the system, in charge of maintaining order and removing cells.  
†Precursor cells that give rise to many types of blood cells. We actually collect CD34+ve cells.
What’s next for CAR T-cell therapy?

<table>
<thead>
<tr>
<th>CAR T Features</th>
<th>FaST CAR-T GC012F(2)</th>
<th>BMS-986393(3)</th>
<th>ALLO-715(4)</th>
<th>PHE885(5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Targets BCMA</td>
<td>• Targets BCMA and CD19</td>
<td>Targets GPRC5D</td>
<td>• Targets BCMA</td>
</tr>
<tr>
<td></td>
<td>• Shortened</td>
<td>• Manufacturing process that takes as little as 24 hours</td>
<td>An allogeneic anti-BCMA CAR T-cell product</td>
<td>• Less than 2 days manufacturing time</td>
</tr>
<tr>
<td></td>
<td>manufacturing time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Details</td>
<td>• Phase 1 trial</td>
<td>• Phase 1 trial</td>
<td>• Phase 1 trial</td>
<td>• Phase 1 trial</td>
</tr>
<tr>
<td></td>
<td>• 55 patients with RRMM</td>
<td>• 13 newly diagnosed high-risk myeloma patients ineligible for stem cell transplant</td>
<td>• 53 patients with RRMM</td>
<td>• 46 patients with RRMM</td>
</tr>
<tr>
<td></td>
<td>• Median of 5 prior lines of therapy</td>
<td></td>
<td>• Median of 5 prior lines of therapy</td>
<td>• Median of 4 prior lines of therapy</td>
</tr>
<tr>
<td>Study Results</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responses</td>
<td>Overall response rate was 98.1% with 96.7% achieving ≥VGPR (28.8% ≥CR)</td>
<td>100% of patients achieved ≥VGPR (69% ≥CR)</td>
<td>All patients achieved MRD negativity (by EuroFlow)</td>
<td>86% evaluable patients responded, including 7 of 11 patients treated with prior BMCA-targeted treatment</td>
</tr>
<tr>
<td>Side effects</td>
<td>• CRS occurred in 86% of patients with only 1 patient experiencing ≥G3.</td>
<td>Neutropenia and thrombocytopenia most frequent grade 3/4 adverse events</td>
<td>Neutropenia and thrombocytopenia; CRS; ICANS</td>
<td>CRS observed in 23 of 24 patients (all low grade)</td>
</tr>
<tr>
<td></td>
<td>• Neurotoxicity occurred in 10.9% of patients (one grade 4)</td>
<td>• Additional adverse events include skin- and nail-related; dysgeusia and/or dysphagia; CRS; ICANS</td>
<td></td>
<td>CRS observed in 23% of patients (all low grade)</td>
</tr>
</tbody>
</table>

BCMA, B-cell maturation antigen; RRMM, relapsed/refractory multiple myeloma; CR, complete response; CRS, cytokine release syndrome; G, grade; VGPR, very good partial response; 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.


1. BCMA, B-cell maturation antigen; RRMM, relapsed/refractory multiple myeloma; CR, complete response; CRS, cytokine release syndrome; G, grade; VGPR, very good partial response; ICANS, immune effector cell-associated neurotoxicity syndrome


3. Bispecific antibodies are also referred to as dual-specific antibodies, bifunctional antibodies, or T-cell engaging antibodies.

4. Bispecific antibodies can target two cell surface molecules at the same time (one on the myeloma cell and one on a T cell).

5. Many different bispecific antibodies are in clinical development; one approved for use in myeloma!

6. Availability is off-the-shelf, allowing for immediate treatment.
Bispecific Antibodies Under Investigation

<table>
<thead>
<tr>
<th>Bispecific antibody</th>
<th>Target (on MM cell × T cell)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecvayli (teclistamab)</td>
<td>BCMA × CD3</td>
<td>Approved for use in myeloma patients</td>
</tr>
<tr>
<td>Elranatamab</td>
<td>BCMA × CD3</td>
<td>Clinical studies; granted priority review by the FDA</td>
</tr>
<tr>
<td>Linvoseltamab</td>
<td>BCMA × CD3</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Alnuctamab</td>
<td>BCMA × CD3</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>ABBV-383</td>
<td>BCMA × CD3</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Talquetamab</td>
<td>GPRC5D × CD3</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Formintamig (RG6234)</td>
<td>GPRC5D × CD3</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Cevostamab</td>
<td>FcRH5 × CD3</td>
<td>Clinical studies</td>
</tr>
</tbody>
</table>

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

**GPRC5D**
- Highly expressed on myeloma cells in the bone marrow
- Lowly expressed on hair follicles but not on other healthy cells
- Expression on myeloma cells is independent of BCMA

**FcRH5**
- Selectively expressed on B cells and plasma cells

**CD3**: a T-cell receptor

Additional Studies of Tecvayli in Patients With Relapsed/Refractory Myeloma

**Tecvayli Combinations**

**Clinical response**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>ORR 74.1%</th>
<th>ORR 75%</th>
<th>ORR 100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tec SC Q2W 3 mg/kg (n=27)</td>
<td>11.1</td>
<td>55.6</td>
<td>7.4</td>
</tr>
<tr>
<td>Tec SC QW 1.5 mg/kg (n=20)</td>
<td>18.5</td>
<td>40.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Tec SC QW 3 mg/kg (n=4)</td>
<td>7.4</td>
<td>50.0</td>
<td>10.0</td>
</tr>
</tbody>
</table>

- PD: Progressed disease
- SD: Stable disease
- PR: Partial response
- VGPR: Very good partial response
- CR: Complete response
- sCR: Strict complete response

**Most frequent non-hematologic adverse events, %**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>81.3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Infections (≥1)</td>
<td>90.5</td>
<td>37.5</td>
</tr>
</tbody>
</table>


---

**Elranatamab in Patients With Relapsed/Refractory Myeloma**

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

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

- Patients Responding (%): 64%
- PR: 27.3
- VGPR: 10.9
- CR: 18.2
- sCR: 7.3

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

- Patients Responding (%): 61%
- PR: 13
- VGPR: 14.6
- CR: 27.6
- sCR: 5.7

**Patients with no prior BMCA-targeted treatment (n=123)**

- ORR 74%
- ORR 75%
- ORR 100%

**Patients with no prior BMCA-directed treatment**

- ORR 74%
- ORR 75%
- ORR 100%

**Patients with no prior BCMA-directed treatment (n=123)**

- ORR 74%
- ORR 75%
- ORR 100%

**Patients with prior BCMA-directed therapies (Pooled analysis of MagnetisMM studies)**

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

IMiD, immunomodulatory drug; PI, proteasome inhibitor

Additional BCMA-Targeted Bispecific Antibodies


![Subcutaneous formulation results](image)

### Alnuctamab

**Patients who progressed on or after 3 or more lines of therapy, including a PI, IMiD, and anti-CD38 mAb**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>PR (%)</th>
<th>VGPR (%)</th>
<th>CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses (n=55)</td>
<td>53</td>
<td>41</td>
<td>19</td>
</tr>
<tr>
<td>&lt;30 mg (n=29)</td>
<td>16</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>30 mg (n=26)</td>
<td>27</td>
<td>14</td>
<td>19</td>
</tr>
</tbody>
</table>

### Linvoseltamab

**Patients Responding (%)**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>50 mg (n=1024)</th>
<th>200 mg (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer PR</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>VGPR</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>CR/SCR</td>
<td>27</td>
<td>12</td>
</tr>
</tbody>
</table>

### ABBV-383

**Patients Responding (%)**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>60 mg dose escalation + expansion (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer PR</td>
<td>29</td>
</tr>
<tr>
<td>VGPR</td>
<td>29</td>
</tr>
<tr>
<td>CR/SCR</td>
<td>29</td>
</tr>
</tbody>
</table>


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Non-BCMA–Targeted Bispecific Antibodies

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Talquetamab in Patients With Relapsed/Refractory Multiple Myeloma

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

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

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

IMiD, immunomodulatory drug; PI, proteasome inhibitor


Most frequent adverse events, %

<table>
<thead>
<tr>
<th>Event</th>
<th>0.4 mg/kg SC weekly (n=143)</th>
<th>0.8 mg/kg SC every 2 weeks (n=145)</th>
<th>Prior T-cell redirection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>44.8</td>
<td>31.5</td>
<td>39.3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>34.3</td>
<td>30.8</td>
<td>28.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>28</td>
<td>25.9</td>
<td>26.2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27.3</td>
<td>20.3</td>
<td>26.9</td>
</tr>
<tr>
<td>Infections</td>
<td>57.3</td>
<td>16.8</td>
<td>50.3</td>
</tr>
</tbody>
</table>

Non-hematologic

<table>
<thead>
<tr>
<th>Event</th>
<th>0.4 mg/kg SC weekly (n=143)</th>
<th>0.8 mg/kg SC every 2 weeks (n=145)</th>
<th>Prior T-cell redirection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS</td>
<td>76.3</td>
<td>3.2</td>
<td>73.5</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>61.2</td>
<td>47.1</td>
<td>61.2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>55.9</td>
<td>38.3</td>
<td>55.9</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>53.8</td>
<td>52.9</td>
<td>53.8</td>
</tr>
<tr>
<td>Nail disorder</td>
<td>46.2</td>
<td>41.2</td>
<td>46.2</td>
</tr>
</tbody>
</table>

Talquetamab Combinations

Talquetamab + Darzalex in patients with 3 or more prior lines of therapy (TRIMM-2 Study)


PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response; CRS, cytokine release syndrome; EMD, extramedullary disease

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Forimtamig and Cevostamab in Patients With Relapsed/Refractory Multiple Myeloma

Forimtamig (RG6234)—targets GPRC5D


Phase 1 study of 105 patients

Best response rates in efficacy-evaluable patients by dose level

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

Cytokine release syndrome (CRS)

Infections

Cytopenias

Neurotoxicity (ICANS)

Off target effects (with GPRC5D targeted agents)

Cytokeratin changes/rash

Dysgeusia

ICANS, immune effector cell-associated neurotoxicity syndrome
Bispecific Antibodies Are Associated With an Increased Risk of Infections

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

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

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>All grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>38.6</td>
<td>34.8</td>
</tr>
<tr>
<td>Infections</td>
<td>50</td>
<td>24.5</td>
</tr>
<tr>
<td>CRS</td>
<td>59.6</td>
<td>NR</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NR</td>
<td>10</td>
</tr>
<tr>
<td>COVID-19</td>
<td>NR</td>
<td>11.4</td>
</tr>
</tbody>
</table>

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

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

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

Infection Prevention

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

IVIG, intravenous immunoglobulin; PJP, Pneumocystis jiroveci pneumonia; CMV, cytomegalovirus
### Similarities and Differences Between CAR T-Cell Therapy and Bispecific Antibodies

<table>
<thead>
<tr>
<th>Approved product</th>
<th>CAR T-cell therapy</th>
<th>Bispecific antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abecma, Carvykti</td>
<td>Tecvayli</td>
</tr>
<tr>
<td>Efficacy</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>How given</td>
<td>One-and-done</td>
<td>IV or SC, weekly to every 3 weeks until progression</td>
</tr>
<tr>
<td>Where given</td>
<td>Academic medical centers</td>
<td>Academic medical centers</td>
</tr>
<tr>
<td>Notable adverse events</td>
<td>CRS and neurotoxicity</td>
<td>CRS and neurotoxicity</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Availability</td>
<td>Wait time for manufacturing</td>
<td>Off-the-shelf, close monitoring for CRS and neurotoxicity</td>
</tr>
<tr>
<td>Advantages</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 (“one and done”)</td>
<td>• No lymphodepletion</td>
</tr>
<tr>
<td></td>
<td>• Potentially persistent</td>
<td>• Minimal steroids</td>
</tr>
<tr>
<td>Disadvantages</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>

### Key Points

- CAR T and bispecific antibodies are very active even in heavily pre-treated patients.

- Side effects of CAR T cells and bispecific antibodies include cytokine release syndrome, confusion, and low blood counts, all of which are treatable.

- Abecma and Carvykti are only the first-generation CAR T cells and target the same protein; different CAR Ts and different targets are on the way.

- Bispecific antibodies represent an “off-the-shelf” immunotherapy; Tecvayli was approved in October 2022.

- Several additional bispecific antibodies are under clinical evaluation.
Please take a moment to answer two questions about this presentation.

Supportive Care

Jordan D. Robinson, PA-C
Atrium Health Levine Cancer Institute
Charlotte, North Carolina
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

**How they work**
- Prevent bone disease from getting worse

**Benefits**
- Decrease pain and reduce skeletal-related fractures

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

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

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

---

**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)

Vertebroplasty  Kyphoplasty

Radiation Therapy for Pain Management
Pain Management Medications

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

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

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

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

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

---

Effects of Myeloma: Low Blood Counts

- **Low red blood cells (anemia)**
  - Symptoms
    - Fatigue; weakness; difficulty breathing; rapid heartbeat; dizziness
  - Other causes
    - Low levels of iron, folate, and vitamin B12
  - Treatment: Identify and treat causes other than myeloma; supplements; medications to increase number of red blood cells; blood transfusions

- **Low white blood cells (leukopenia)**
  - Symptoms
    - Fatigue; frequent infections
  - Other causes
    - Radiotherapy
    - Infection
  - Treatment: Medications to stimulate production of white blood cells; antibiotics; antifungal medications; infection prevention

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

- Detection
  - Decreased amount of urine
  - Increase in creatinine and other proteins
- Other causes beside myeloma
  - Hypertension
  - Diabetes
  - Some medications
- Treatment
  - Fluids
  - Avoid nonsteroidal anti-inflammatory drugs such as Aleve, Advil/Motrin
  - Plasmapheresis
  - Treat other causes
  - Dialysis (severe)

Main Body Systems Affected by Myeloma Treatment

- Blood
  - Myeloma patients are at increased risk of developing blood clots
  - Several myeloma drugs are associated with an increased risk of deep vein thrombosis (DVT)

- Central nervous system
  - Peripheral neuropathy is a condition that affects the nerves, resulting in pain, tingling, burning sensations, and numbness in the hands and feet
  - Peripheral neuropathy may be caused by myeloma or its treatments

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

- Gastrointestinal
  - Commonly used myeloma drugs may cause a variety of gastrointestinal problems, such as constipation, diarrhea, and nausea/vomiting
Class: Immunomodulatory Drugs
Side Effects and Management

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

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

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

---

*Black box warning.
G.I. 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

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

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

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

---

*Do not take any supplements without consulting with your doctor.
P.N., peripheral neuropathy; G.I. gastrointestinal
Class: Monoclonal Antibodies Side Effects and Management

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

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

*Now approved as subcutaneous injection with fewer side effects.

**Management**

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

---

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

---

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 \(\rightarrow\) 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

---

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
Infection Can Be Serious for Patients With Myeloma

7–10-fold increased risk of bacterial and viral infections for people with myeloma

Report fever of more than 100.4°F, shaking chills even without fever, dizziness, shortness of breath, low blood pressure to HCP as directed.

General infection-prevention tips

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

As recommended by your health care team

Multiple myeloma

Immune dysfunction

Treatment


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

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

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Infection Prevention

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

Symptom Management

**Constipation**

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

**Acid Reflux/Heartburn**

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

**A few ways to treat**

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

Symptom Management

**Insomnia**

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

- Proper nutrition
- Exercise
- Rest
- Social contacts

Taking Care of Yourself

- Talk to your provider about side effects... there is usually a way to make treatment tolerable.
- Pay attention to your own needs and don’t be afraid to ask for help.
- Learn more about multiple myeloma.
- Look for the positive.
Please take a moment to answer two questions about this presentation.

Patient Experience

Tony Newberne
Multiple Myeloma Precursor Conditions

Cindy Varga, MD
Atrium Health Levine Cancer Institute
Charlotte, North Carolina
Wake Forest University School of Medicine
Winston-Salem, North Carolina

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>Test</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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• ≥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

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.

2/20/20
Time to Progressions (Years)
Probability of Progression (%)
90
80
70
60
50
40
30
20
10
0
0 2 4 6 8 10 12 14 16 18
Low-risk group
(no risk factors)
Intermediate-risk group
(1 risk factor)
High-risk group
(2–3 risk factors)
Risk of progression at 2 Years
44.2%
17.9%
6.2%

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

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

Can we identify everyone who has a precursor condition?

Studies Focusing on Myeloma Precursor Conditions

Large ongoing precursor studies

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

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

- **United States**
  - Focus: genomic markers of progression
Prevalence of MGUS and SMM

**iStopMM Study**

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

- 75,422 screened for M protein and abnormal free light chain
- 3,358 individuals with MGUS

**SMM**

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

**Key Observations**

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

---

**High Prevalence of Monoclonal Gammopathy in a Population at Risk**

**The PROMISE Study**

7,622 individuals screened*

- 6,305 patients with high-risk features for myeloma
- 1,317 patients with no high-risk features for myeloma

- 3,866 Blacks
- 2,439 with family history of HM
- 3,866 Non-Blacks
- 631 with family history of HM
- 686 Unknown family history of HM

**MGUS**

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

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

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

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

---

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


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

HM, hematologic malignancy

**High Prevalence of Monoclonal Gammopathy in a Population at Risk**

*Free light chains detected by mass spectrometry.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>MGIP (P&lt;0.001)</th>
<th>MGUS (P=0.001)</th>
<th>LC-MGUS (P=0.23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–29</td>
<td>2 (1%)</td>
<td>7 (1%)</td>
<td>8 (1%)</td>
</tr>
<tr>
<td>30–39</td>
<td>16 (10%)</td>
<td>31 (10%)</td>
<td>31 (10%)</td>
</tr>
<tr>
<td>40–49</td>
<td>33 (21%)</td>
<td>61 (20%)</td>
<td>61 (20%)</td>
</tr>
<tr>
<td>50–59</td>
<td>22 (14%)</td>
<td>41 (13%)</td>
<td>41 (13%)</td>
</tr>
<tr>
<td>60–69</td>
<td>12 (1%)</td>
<td>27 (1%)</td>
<td>27 (1%)</td>
</tr>
<tr>
<td>70–79</td>
<td>12 (1%)</td>
<td>10 (1%)</td>
<td>10 (1%)</td>
</tr>
<tr>
<td>80+</td>
<td>2 (1%)</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
</tr>
</tbody>
</table>

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

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

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

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

*P<0.001

**Overview of Current Treatment Approach**

- **MGUS**
  - Close monitoring (observation)
  - Clinical trial participation should be considered

- **SMM**
  - Close monitoring (observation)
Approaches to SMM Treatment*

**Immunologic therapy**  
(control approach)

- Len, Len/Dex, Dara

**Intensive therapy**  
(curative intent)

- IRD, KRD, ERD

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

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

**Pros**
- High ORR
- Deep responses

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

*Only in the context of a clinical trial.

---

Early Therapeutic Intervention

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

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

HR, hazard ratio

**QuiRedex Phase 3 Trial**

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


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

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

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

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

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

Revlimid vs Observation Alone in Patients With SMM

**PFS ITT**

Treatment hazard ratio = 0.28 (95% CI, 0.12–0.63), *P*=0.0005

- 2yrs 93%
- 2yrs 76%
- 3yrs 91%
- 3yrs 66%

**Mayo2008: PCBM ≥10% + MC ≥3 g/dL**

Mayo 2018: 2/20/20

- Criteria: PCBM ≥10% and sFLC ratio >8 or <0.125
- N=182, intermediate/high-risk SMM (BMPC% ≥10% and aberrant (FLC) ratio (<0.26 or >1.65)
- 1:1 randomization lenalidomide 25 mg day 1 to 21 in 28-day cycle vs observation
- Median FU 35 mnd, median time on len 23 cycles, len discontinued in 51% of patients

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

Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria

High risk

Intermediate risk

Low risk

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

2 years of maintenance

At a median potential follow-up time of 31.9 months (range, 6.7–102.9 months), the MRD-negative CR rate was 70.4%

The median sustained MRD duration was 5.5 years

The 8-year probability of being free from progression to multiple myeloma was 91.2%, and no deaths occurred

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

*According to the Mayo and/or Spanish models.

Kazandjian D et al. JAMA Oncol. 2021 Nov 1;7(11):1678-1685
**Multicenter, Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex for High-Risk SMM Patients**

**GEM-CESAR Study**
- High-risk* smoldering multiple myeloma patients
- Induction: Kyprolis + Revlimid + dex (KRd)
- Consolidation: KRd
- Maintenance: Revlimid
- 90 patients

At 70 months, 94% of patients have not progressed to multiple myeloma; 48% have biochemically progressed (rescue therapy with DPd resulted in 80% overall response rate)

- The presence of SLiM criteria and MRD at the end of maintenance predicted progression.
- The achievement of MRD negativity after maintenance and 4 years after ASCT predicted sustained MRD negativity.

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

---

**Four-Drug Combination Strategy for High-Risk SMM Patients**

**ASCENT Study**
- High-risk* smoldering multiple myeloma patients
- Induction: Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)
- Consolidation: Dara-KRd
- Maintenance: Darzalex + Revlimid
- 87 patients

Best overall response rate was 97% (92% ≥VGPR); 84% of patients achieved MRD negativity.

Grade ≥3 hematologic toxicity in 18% of patients; non-hematologic toxicity in 51% of patients.

89.9% of patients are progression-free at 3 years.

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

---


*Based on the 2/20/20 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow; or a total score of ≥9 on IMWG scoring system. Kumar SK et al. Blood. 2022;140. Abstract 757.
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.

Please take a moment to answer two questions about this presentation.
What is high-risk multiple myeloma and why is it important to find out if you have it?

Patients may not respond well to standard treatment.

Patients can have poorer outcomes.

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

Helps your doctor

• Determine your prognosis
• Select the treatment that is right for you
Assessing Risk

Staging, prognosis, and risk assessment

High-Risk Disease Definitions

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

<table>
<thead>
<tr>
<th>R-ISS Stage I</th>
<th>R-ISS Stage II</th>
<th>R-ISS Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ISS&lt;sup&gt;2&lt;/sup&gt; stage I&lt;br&gt;  ‒ Serum β2M level &lt;3.5 mg/L&lt;br&gt;  ‒ Serum albumin level ≥3.5 g/dL&lt;br&gt;  ‒ No high-risk CA*&lt;br&gt;  ‒ Normal LDH level</td>
<td>• All other possible combinations</td>
<td>• ISS&lt;sup&gt;2&lt;/sup&gt; stage III&lt;br&gt;  ‒ Serum β2M level ≥5.5 mg/L&lt;br&gt;  ‒ High-risk CA* or high LDH level</td>
</tr>
</tbody>
</table>

**High risk**

- Genetic abnormalities<br>  ‒ t(4;14)<br>  ‒ t(14;16)<br>  ‒ t(14;20)<br>  ‒ R-ISS Stage 3<br>  ‒ High plasma cell S-phase<br>  ‒ GEP: high-risk signature<br>  ‒ Double-hit myeloma: any two high-risk genetic abnormalities<br>  ‒ Triple-hit myeloma: three or more high-risk genetic abnormalities

**Standard risk**

- All others including:<br>  ‒ Trisomies<br>  ‒ t(11;14)<br>  ‒ t(6;14)<br>  ‒ By FISH or equivalent

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

**Additional high-risk features**

- Disease features<br>  ‒ Other cytogenetic and genetic abnormalities<br>  ‒ Plasma cell leukemia<br>  ‒ Extramedullary disease<br>  ‒ Renal failure

- Patient features<br>  ‒ Comorbidities<br>  ‒ Frailty

- Response features<br>  ‒ Lack of response to therapy<br>  ‒ Short first PFS

---

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

Why is genomic sequencing important in myeloma risk assessment?

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

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

<table>
<thead>
<tr>
<th>Copy number of chromosome 1q</th>
<th>Cytogenetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image.png" alt="Graph" /></td>
<td><img src="image.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

| Hi, high-risk cytogenetics: t(4;14), t(14;16) and/or del(17p); Std, standard-risk cytogenetics |
| Hi+1q (n=28) | Std+1q (n=66) | Std (n=95) |
| 2 copies (n=107) | 3 copies (n=52) | ≥4 copies (n=26) |
| Hi+1q: 25.1 mo | Std+1q: 34.6 mo | Std: 55.9 mo |

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

**Progression-Free Survival**

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

<table>
<thead>
<tr>
<th>Survival Probability</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>0</td>
</tr>
<tr>
<td>0.75</td>
<td>250</td>
</tr>
<tr>
<td>0.50</td>
<td>500</td>
</tr>
<tr>
<td>0.25</td>
<td>750</td>
</tr>
<tr>
<td>0.00</td>
<td>1000</td>
</tr>
</tbody>
</table>

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

MMRF CoMMpass Findings: Identifying Double-Hit Multiple Myeloma

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

**Key CoMMpass finding:**

*FISH testing alone cannot identify whether patients have double-hit myeloma.*
Despite recent improvements in treatment, high-risk patients have not experienced the same benefit as patients with standard risk. Therefore, the treatment of high-risk patients is a very important focus of research.

Approach to Treatment: Risk-Adapted Therapy

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

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

Patients with high-risk myeloma are given a stronger treatment designed to be effective against their specific form of myeloma.
# Summary of High-Risk Subsets in Contemporary Newly Diagnosed Multiple Myeloma Trials

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

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


---

# Darzalex Meta-Analysis in High-Risk Multiple Myeloma

Six phase 3 trials comparing standard treatment regimens with or without Darzalex in newly diagnosed¹-³ or relapsed/refractory⁴-⁶ myeloma patients with high-risk cytogenetics

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

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

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

Results were similar regardless of backbone regimens.


Treatment Regimens for High-Risk Disease Features

**Kyprolis-Revlimid-dex (KRd) vs Revlimid-Velcade-dex (RVd) retrospective chart review\(^1\)**

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

**OPTIMUM Study\(^2\)**

- Study to evaluate the efficacy of Darzalex-cyclophosphamide-Velcade-Revlimid-dex (Dara-CyVRd) induction followed by ASCT and 2 rounds of consolidation with Dara-VR (with or without dex) in 107 ultra high-risk\(^1\) patients with multiple myeloma and plasma cell leukemia (PCL)
- By end of second consolidation, 46.7% of patients were MRD negative (10\(^{-5}\)); 84% of patients who were MRD negative after ASCT sustained their MRD negativity at the end of second consolidation
- 86% of patients were alive and 77% were progression free at 30 months

---

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


Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

**GMMG-CONCEPT Study**

- High-risk newly diagnosed multiple myeloma patients
  - Induction:
    - Transplant eligible (≤70 yrs) n=127
    - Transplant ineligible (>70 yrs) n=26
  - Consolidation:
    - Isa-KRd
    - Isa-KR
  - Maintenance:
    - Isa-KR

**Best response (through consolidation) (%)**

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

**Adverse events (≥ grade 3)**

<table>
<thead>
<tr>
<th></th>
<th>Transplant eligible (n=97)</th>
<th>Transplant ineligible (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>39.2</td>
<td>28</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24.7</td>
<td>4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26.8</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>14.4</td>
<td>12</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>27.8</td>
<td>28</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2.1</td>
<td>20</td>
</tr>
</tbody>
</table>

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

Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

**RADAR Study**

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

**Standard-risk patients**: n=1,120

**High-risk* patients**: n=280

- MRD negative
- MRD positive

- **R-CyBorD**
- **ASCT**
- **Isa**
- **Cont Isa**
- **Stop Isa**
- **R**
- **Rvd (× 4)**
- **R + Isa**
- **Isa-RvD (× 4) + Isa-R until PD**

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

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

Additional Studies for High-Risk Myeloma

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Phase</th>
<th>Patient populations/study design</th>
<th>High risk definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>KarMMa-4</td>
<td>Abecma</td>
<td>1</td>
<td>High-risk, newly diagnosed MM</td>
<td>R-ISS III</td>
</tr>
<tr>
<td>BMT-CTN 1901</td>
<td>Abecma</td>
<td>2</td>
<td>High-risk, newly diagnosed MM</td>
<td>R-ISS III; no prior progression</td>
</tr>
</tbody>
</table>
Please take a moment to answer two questions about this presentation.

New Drugs on the Horizon

Monique A. Hartley-Brown, MD, MMSc
Harvard Medical School, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute
Boston, Massachusetts
Emerging Treatment Options

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

Cereblon E3 Ligase Modulators (CELMoDs)

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

Iberdomide
Mezigdomide
Iberdomide: A CELMoD

Iberdomide in combination with dexamethasone in patients with RRMM


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

Adverse events (%)  IberDd (n=37) IberVd (n=25) IberKd (n=8)
All infections 31 24 3
Fatigue 21 2 1
Insomnia 13 1 0
Diarrhea 22 1 0
Muscle spasms 7 0 0

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

Mezigdomide: A CELMoD

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

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

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

**Actionable Alterations in MM**

Personalized medicine efforts have identified molecular alterations for which there are drugs in the clinic. These alterations may be the Achilles’ heel of myeloma cells.

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>
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</thead>
<tbody>
<tr>
<td></td>
<td>Personalized medicine</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Venetoclax*</td>
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<tr>
<td></td>
<td>Abemaciclib*</td>
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<tr>
<td></td>
<td>Cobimetinib*</td>
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<td>Dabrafenib</td>
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<td>Enasidenib</td>
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<td>Erdafitinib*</td>
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<td>Idasanutilin</td>
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<td>Trametinib</td>
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<td>Vemurafenib</td>
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</table>

*Being studied in the MyDRUG trial*
**BRAF and MEK**

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

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

**Venetoclax and t(11;14)**

Venetoclax is a Bcl-2 inhibitor

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

Venetoclax and t(11;14)

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

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

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

MyDRUG Study

Functional high-risk patients

Profiling for alterations (NCT02884102)

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

2 cycles

- Cobimetinib +
  - dexamethasone (Dex)
- Abemaciclib +
  - Dex
- Erdafitinib +
  - Dex

2:1

- Daratumumab +
  - IPd
- Cobimetinib +
  - IPd\textsuperscript{a}
- Abemaciclib +
  - IPd\textsuperscript{a}
- Erdafitinib +
  - IPd\textsuperscript{a}

*Assess single-agent activity after 2 cycles: after cycle 2, add backbone to single agent
100 patients who had a median of 7 prior lines of therapy were treated with different doses of modakafusp (19% had prior CAR T-cell therapy and 14% prior T-cell engagers).

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

Immunocytokines

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

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

Evolution of CAR T-Cell Therapy

Single target

Abecma

Carvykti

CT003

CT03A

C-CAR088

P-BCMA-101

ARI-002h

Dual targets

GC012F(BCMA/CD19)

Allogeneic

Improving efficacy

Improving safety

Improving access

Evolution of Bispecific Antibodies

Bispecific antibodies: dual targets

- Redirected tumor lysis

- CD3+ T cell
- Tumor cell
- Non-IgG-like bispecific antibody
- IgG-like bispecific antibody
- Perforin/granzymes

Trispecific antibodies: triple targets

- Two T-cell targets
- One myeloma cell target
- One T-cell or NK-cell target
- Two myeloma-cell targets

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

- Checkpoint inhibitors: activate T cells by “taking the brakes off”

- The cell surface immune checkpoint proteins PD-1/PD-L1 play a crucial role in regulating an immune response
  - Plasma cells in patients with MM have increased PD-L1 expression and when it binds to PD-1 on T cells, T cell activation is blocked

- Additional checkpoint proteins include
  - LAG3
  - TIM-3
  - TIGIT

- Many checkpoint inhibitors (which are monoclonal antibodies) are FDA approved for other cancers
  - Pembrolizumab (anti-PD-1)
  - Nivolumab (anti-PD-1)
  - Cemiplimab (anti-PD-1)
  - Atezolizumab (anti-PD-L1)
  - Durvalumab (anti-PD-L1)
  - Opdualag (anti-LAG3)
Summary

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

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

Thank you!
Don’t Forget!

Complete your evaluation
Leave the iPad at your seat
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>American Society of Clinical Oncology 2023 FAQs Livestream</td>
<td>Wednesday, June 28 2:30 PM to 3:30 PM</td>
<td>Nisha Joseph, MD Roseann Pruitt, PA-C Danielle Roberts, PA-C</td>
</tr>
<tr>
<td>Webinar: Minimal Residual Disease</td>
<td>Friday, July 14 1:00 PM to 2:00 PM</td>
<td>Benjamin Derman, MD Rafael Fonseca, MD</td>
</tr>
</tbody>
</table>

For more information or to register, visit themmrf.org/resources/education-program
Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

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

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

To Learn More & Find Your Event today!
www.theMMRF.org/Events
Need help with travel to a clinical study?

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