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.

Program Faculty

**Faith E. Davies, MBBCh, MD**
Perlmutter Cancer Center at New York University Langone Health
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MedStar Georgetown University Hospital
Georgetown University School of Medicine
John Theurer Cancer Center, Hackensack
Meridian School of Medicine
Hackensack, New Jersey
## Summit Agenda

<table>
<thead>
<tr>
<th>Time (ET)</th>
<th>Topic</th>
<th>Speakers</th>
</tr>
</thead>
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<tr>
<td>9:30 – 9:45 AM</td>
<td>Welcome</td>
<td>Saad Z. Usmani, MD, MBA</td>
</tr>
<tr>
<td>9:45 – 10:15 AM</td>
<td>Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy</td>
<td>David H. Vesole, MD, PhD</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>Faith E. Davies, MBBC, MD</td>
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<tr>
<td>10:45 – 11:00 AM</td>
<td>Break</td>
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<tr>
<td>11:00 – 11:30 AM</td>
<td>Relapsed/Refractory Multiple Myeloma</td>
<td>Sham Mailankody, MBBS</td>
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<tr>
<td>11:30 AM – 12:00 PM</td>
<td>Immunotherapy</td>
<td>Saad Z. Usmani, MD, MBA</td>
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<tr>
<td>12:00 – 12:30 PM</td>
<td>Supportive Care</td>
<td>Justina A. Kiernan, MPS, PA-C</td>
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<tr>
<td>12:30 – 1:15 PM</td>
<td>Lunch</td>
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<tr>
<td>1:15 – 1:30 PM</td>
<td>Patient Speaker</td>
<td>Gail Goode</td>
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<td>1:30 – 1:45 PM</td>
<td>Hot Topic 1: Minimal (Measurable) Residual Disease</td>
<td>Neha Kord, MD</td>
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<td>1:45 – 2:00 PM</td>
<td>Hot Topic 2: Clinical Studies</td>
<td>Gunjan L. Shah, MD</td>
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<tr>
<td>2:00 – 2:15 PM</td>
<td>Hot Topic 3: High-Risk Disease</td>
<td>Sham Mailankody, MBBS</td>
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<td>2:15 – 3:15 PM</td>
<td>Town Hall Q&amp;A</td>
<td>Panel</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

- Functional high-risk patients
  - Profiling for alterations (NCT02884102)
  - No detectable actionable alterations
  - RAF/RAS mutations
  - CDK pathway–activating alterations
  - FGFR3–activating alterations
  - t(11;14)

- 2 cycles
  - 2:1

- Daratumumab + IPd
- Cobimetinib + dex
- Anebacilib + IPd
- Erdafitinib + dex
- Venetoclax + IPd
- IPd control

*Assess single-agent activity after 2 cycles. After cycle 2, add backbone to single agent.
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.
MMRF CureCloud

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.

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.

- 19% progress towards goal
- 941 patients enrolled
- 685 patient samples sequenced
- 247 patient health records pulled
MMRF CureCloud Demographics

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

- Multiple myeloma is the 2nd most common cancer of the blood.
- In 2023, there were 35,730 new cases.
- 159,787 people were 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.

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

- More common in Black patients
  - Hypercalcemia
  - Kidney dysfunction
  - Hemodialysis
  - Anemia

- Less common in Black patients
  - Bone fractures

Infections and Vaccinations in Multiple Myeloma

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

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

- Older age
- Male sex
- Obesity
- Race: 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

The Multiple Myeloma Disease Spectrum

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

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

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

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


Risk of Progression to Myeloma From a Precursor Condition

![Graph showing the probability of progression to myeloma from MGUS and SMM over time. 51% will convert to MM in first 5 years (~10%/yr), 27% more will convert to MM in remaining 15 years (~2%/yr).]

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

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

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

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

The Right Team

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: themmrf.org/resources/find-a-treatment-center

Seek a second opinion at any point in your journey

Contact the MMRF Patient Navigation Center: themmrf.org/resources/patient-navigation-center
1-888-841-6673
The Right Tests: Common Tests Conducted in Myeloma Patients

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

**Bone marrow biopsy**
- Confirms diagnosis of myeloma
- Determines how advanced the myeloma or precursor condition is

**Imaging tests**
- Detects the presence and extent of bone disease and the presence of myeloma outside of the bone marrow

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**Learn Your Labs!**

**Blood Tests**

- **CBC**
  - Number of red blood cells, white blood cells, and platelets

- **CMP**
  - Measure levels of albumin, calcium, LDH, BUN, and creatinine. Assess function of kidney, liver, and bone status and the extent of disease

- **B2M**
  - Determine the level of a protein that indicates the presence/extent of multiple myeloma and kidney function

- **SPEP**
  - Detect the presence and level of M protein

- **IFE**
  - Identify the type of abnormal antibody proteins

- **SFLC**
  - Freelite test measures light chains (kappa or lambda)

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CBC, complete blood count; CMP, complete metabolic panel; B2M, beta-2 microglobulin; SPEP, serum protein electrophoresis; IFE, immunofixation electrophoresis; SFLC, serum free light chain assay; LDH, lactate dehydrogenase; BUN, blood urea nitrogen
Learn Your Labs!

**Urine Tests**

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

24-hr urine analysis

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

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

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

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

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

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

Know Your Bone Marrow Tests!

Types of chromosomal abnormalities:

- Translocation
- Deletion
- Gain or Amplification
Putting the Results Together

Staging, prognosis, and risk assessment

Multiple Myeloma Prognosis and Risk

Revised International Staging System (R-ISS)

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

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

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

High risk
- High-risk genetic abnormalities
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p
  - p53 mutation
  - gain 1q
- R-ISS Stage 3
- High plasma cell S phase
- GEP: high-risk signature

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

- 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.

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

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

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

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

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Chemotherapy + dexamethasone + stem cell transplantation</th>
<th>Velcade (bortezomib)</th>
<th>Revlimid (lenalidomide)</th>
<th>Kyprolis (carfilzomib)</th>
<th>Pomalyt (pomalidomide)</th>
<th>Ninlaro (ixazomib)</th>
<th>Empliciti (elotuzumab)</th>
<th>Darzalex (daratumumab)</th>
<th>Xpovio (selinexor)</th>
<th>Sarcisa (isatuximab)</th>
<th>Abecma (idecabtagene vicleucel)</th>
<th>Carvykti (ciltaclabtagene autoleucel)</th>
<th>Tecvayli (teclistamab)</th>
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<tr>
<td>1975</td>
<td>26.5%</td>
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<td>1975</td>
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<tr>
<td>1985</td>
<td>27.4%</td>
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<td>1985</td>
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<td>1995</td>
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<td>2013</td>
<td>56.9%</td>
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<td>2013</td>
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<td>2014 and beyond</td>
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Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma

**Transplant candidate**
- Induction therapy
- ± Consolidation therapy
- Maintenance therapy

**Non-transplant candidate**
- Induction therapy
- Maintenance therapy

Overview of Treatment Approach for Active Multiple Myeloma

Is the patient a candidate for autologous stem cell transplantation?

- **Yes**
  - 3–6 cycles of induction therapy
    - 3- to 4-drug regimen generally preferred
    - Clinical trial
  - Stem cell collection and storage
  - High-dose melphalan + stem cell transplant*
  - Consolidation and or continuous/maintenance therapy

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

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

<table>
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<tr>
<th>Preferred</th>
<th>Recommended</th>
<th>Certain circumstances</th>
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<tbody>
<tr>
<td>• Revlimid-Velcade-dex (RVd)*</td>
<td>• Darzalex-Revlimid-Velcade-dex (D-RVd)</td>
<td>• Velcade-Thalomid-dex (VTd)*</td>
</tr>
<tr>
<td>• Kyprolis-Revlimid-dex (KRd)</td>
<td>• Kyprolis-Revlimid-dex (KRd)</td>
<td>• Velcade-Cytoxan-dex (VCd)</td>
</tr>
<tr>
<td>• Darzalex-Revlimid-dex (DRd)*</td>
<td>• Ninlaro-Revlimid-dex (IRd)</td>
<td>• Velcade-Cytoxan-dex (VCd)</td>
</tr>
<tr>
<td></td>
<td>• Darzalex-Velcade-melphalan-prednisone (D-VMP)*</td>
<td>• Velcade-Cytoxan-dex (VCd)</td>
</tr>
<tr>
<td></td>
<td>• Darzalex-Cytoxan-Velcade-dex (D-VCd)</td>
<td>• Kyprolis-Cytoxan-dex (KCd)</td>
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</table>

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

### Continuous or Maintenance Therapy Options

<table>
<thead>
<tr>
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<th>Recommended</th>
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<tbody>
<tr>
<td>• Revlimid*</td>
<td>• Ninlaro</td>
<td>• Velcade-Revlimid ± dex</td>
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<tr>
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<td>• Velcade</td>
<td>• Kyprolis-Revlimid</td>
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<tr>
<td></td>
<td>• Darzalex</td>
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<tr>
<td>Transplant eligible</td>
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<tr>
<td>Transplant ineligible</td>
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<td>• Velcade-Revlimid</td>
</tr>
<tr>
<td></td>
<td>• Velcade</td>
<td></td>
</tr>
</tbody>
</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.

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained minimal (measurable) residual disease (MRD-negative)</td>
<td>* MRD negativity in the bone marrow and by imaging—confirmed minimum of 1 year apart</td>
</tr>
</tbody>
</table>
| MRD-negative | * Abnormal clone of plasma cells in bone marrow samples by one of two methodologies:  
  - Next-generation flow (NGF) (for example, flow MRD negative), or  
  - Next-generation sequencing (NGS) (for example, sequencing MRD negative)  
  - MRD negativity as defined by NGS or NGS plus disappearance of every area of lesions found at baseline found by positron emission tomography (PET) or computed tomography (CT) imaging (for example, imaging plus MRD negative) |
| Partial response (PR) | * ≥25% but ≤49% reduction in serum M protein and reduction in 24-hour urine M protein by ≥50% to ≤95% |
| Minimal response (MR) | * ≥50% reduction in serum M protein plus ≥90% reduction in 24-hour urine M protein |
| Stable disease (SD) | * Does not meet criteria for response or progressive disease |
| Progressive disease (PD) | * An increase of ≥25% in M protein  
  * An increase of ≥10% in bone marrow plasma cells |

Where is the myeloma field going?

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

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

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

Please take a moment to answer two questions about this presentation.
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
What does transplant mean?

Understanding the basics of autologous stem cell transplantation

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

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

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

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
   • Akeran, 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**

---

How do we decide who is appropriate for a transplant?

- **Transplant candidate**
  - Induction therapy

- **Non-transplant candidate**
  - Induction therapy

**General health**
- Reasonable heart and lung function

**Myeloma status**
- Responded to induction therapy

**Patient preference**
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
- 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**

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

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

- PFS for early transplant: approximately 5.5 years
- PFS for continuous induction: approximately 4 years
- Transplant extended time to progression by 20 months
- Length of overall survival: no difference.
Phase 3 Study of ASCT for Newly Diagnosed Multiple Myeloma: Best Response to Treatment and Duration of Response

![Graph showing response rates and duration of response](image)

<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

**Quality of life**

![Graphs showing quality of life measures](Image)

**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>Pomalyst (pomalidomide)</td>
<td>30.2</td>
<td>29.2</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)</td>
<td>25.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Any proteasome inhibitor</td>
<td>55.9</td>
<td>50.0</td>
</tr>
<tr>
<td>Velcade (bortezomib)</td>
<td>27.5</td>
<td>25.5</td>
</tr>
<tr>
<td>Kyprolis (carfilzomib)</td>
<td>21.2</td>
<td>16.7</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>8.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Marizomib</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Any monoclonal antibody</td>
<td>16.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Darzalex (daratumumab)</td>
<td>11.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Empliciti (elotuzumab)</td>
<td>4.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Sarcilib (isatuximab)</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Only 28.0% of RVd-alone (late transplant) patients had received ASCT at any time following end of study treatment.
Early vs Late Transplant
Pros and Cons

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

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, reduce the risk of relapse, and prolong survival

Successful Maintenance Therapy Must...

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

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

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

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

Revlimid Maintenance Therapy: Improves Depth of Response

Revlimid Maintenance Duration

**STAMINA Trial (BMT-CTN0702)**

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

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

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

Discontinuation of Revlimid @ 3 years did not impact overall second primary malignancies (SPM) rates @ 6 years.

Probability, %

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>40</td>
<td>60</td>
<td>80</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continued maintenance

Stopped maintenance

P<0.001

Discontinuation of Revlimid @ 3 years did not impact overall second primary malignancies (SPM) rates @ 6 years.

Maintenace Duration

**Myeloma XI Study**

- **Newly diagnosed myeloma patients**
  - **Induction**
    - CTD/CRD → KCRD
    - R
  - **Consolidation**
    - CVD → No CVD
    - R
  - **ASCT**
    - 730 patients
    - 518 patients

**Maintenance**

- **Revlidim**
- **Observation**

**Median PFS (mos)**

<table>
<thead>
<tr>
<th>At time of randomization to maintenance therapy (median follow up 44.7 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients*</td>
</tr>
<tr>
<td><strong>Revlidim</strong></td>
</tr>
<tr>
<td><strong>Observation</strong></td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
</tr>
<tr>
<td><strong>P Value</strong></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**

<table>
<thead>
<tr>
<th>MRD and PET/CT negative (N=38)</th>
<th>Complete response × 2 years and/or MRD negative (≤10⁻⁴), PET-negative, 1+ years maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue maintenance</td>
<td>Continue maintenance</td>
</tr>
<tr>
<td>1-yr MRD</td>
<td>2-yr MRD</td>
</tr>
<tr>
<td>3-yr MRD</td>
<td>Active Surveillance*</td>
</tr>
</tbody>
</table>

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
- Control

HR (95% CI): 2.03 (1.14–3.61)

P=0.015

**Solid Tumor**

- Lenalidomide
- Control

HR (95% CI): 1.71 (1.04–2.79)

P=0.032

---

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

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


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

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

Myeloma cell burden

Depth of response

Please take a moment to answer two questions about this presentation.
Relapsed/Refractory Multiple Myeloma

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

Multiple Myeloma Is a Marathon, Not a Sprint

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

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

Factors to consider

**Nature of relapse**

- Disease biology
- Nature of relapse
- Patient preference

**Patient preference**

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 (cytosine)</td>
<td>Cytoxan (cyclophosphamide)</td>
<td>Dexamethasone</td>
<td>XPOVIO (selinexor)</td>
<td>Empliciti (elotuzumab)</td>
<td>Abecma (decabtagene vilucel)</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 (cilatamab autoleucel)</td>
</tr>
<tr>
<td>Pomalyst (pomalidomide)</td>
<td>Ninlaro (ixazomib)</td>
<td>Melphalan</td>
<td></td>
<td></td>
<td>Farydak (Panobinostat)</td>
<td>Sardisa (sultumab)</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
  – OS with Pepaxto-dex was not improved vs Pomalyst-dex, which didn’t pass the regulatory hurdles to confirm the accelerated approval in the U.S.

Withdrawn 2022*

Blenrep (belantamab mafodotin)

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

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

Treatment Approach

<table>
<thead>
<tr>
<th>First relapse</th>
<th>&gt;1 Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteasome inhibitor/immunomodulatory drug/antibody-based therapy</td>
<td>Any options for first relapse not tried</td>
</tr>
<tr>
<td>Refractory to Velcade and Revlimid</td>
<td>Refractory to an IMiD but sensitive to a PI</td>
</tr>
<tr>
<td>DKd, Isa-Kd, DPd, Elo-Pd, Isa-Pd, or KPd</td>
<td>DVd, SVd, Ven-Vd (for t[11;14])*</td>
</tr>
<tr>
<td>Approved therapies</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Sd, ide-cel, cilt-a-cel, Tecvayli</td>
<td>Bispecific/trispecific antibodies, cellular therapies (CAR T-cells, NK cells), CELMoDs</td>
</tr>
</tbody>
</table>

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

*Not yet approved for use in myeloma patients.
## Triplet Regimens for Early Relapse

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Approval</th>
</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 Pomalyt 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 Pomalyt 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 Pomalyt or Kyprolis and dexamethasone</td>
</tr>
</tbody>
</table>

IV, intravenous; SC, subcutaneous
Currently Available Agents for One to Three Prior Lines of Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velcade (bortezomib)</td>
<td>• IV infusion</td>
<td>• For relapsed/refractory myeloma</td>
</tr>
<tr>
<td></td>
<td>• SC injection</td>
<td></td>
</tr>
<tr>
<td>Kyprolis (carfilzomib)</td>
<td>• IV infusion</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></td>
<td>• Weekly dosing</td>
<td></td>
</tr>
<tr>
<td>Ninlaro (ixazomib)</td>
<td>Once-weekly pill</td>
<td>• For relapsed/refractory myeloma as a triplet with Revlimid and dexamethasone</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)*</td>
<td>Once-daily pill</td>
<td>• For relapsed/refractory myeloma in combination with dexamethasone</td>
</tr>
<tr>
<td>Pomalyst (pomalidomide)*</td>
<td>Once-daily pill</td>
<td>• For relapsed/refractory myeloma in combination with dexamethasone</td>
</tr>
<tr>
<td>XPOVIO (selinexor)</td>
<td>Once-weekly pill</td>
<td>• For relapsed/refractory myeloma as a triplet with Velcade and dexamethasone</td>
</tr>
</tbody>
</table>

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

IV, intravenous; SC, subcutaneous

Monoclonal Antibody–Based Regimens for Early Relapse: Darzalex

<table>
<thead>
<tr>
<th>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>
</tbody>
</table>

Clinical considerations

• Consider for relapses from non-Revlimid–based maintenance
• DRd associated with more upper respiratory infections, low blood white blood cell counts, and diarrhea
• Consider for patients who are Revlimid-refractory without significant neuropathy
• DVd associated with more low blood cell counts
• Consider for younger, fit patients who are double-refractory to Revlimid and Velcade
• DKd associated with more respiratory infections
• Consider in patients who are double-refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro)
• Severe low white blood cell counts
Monoclonal Antibody–Based Regimens for Early Relapse: Sarclisa and Empliciti

### ELOQUENT-2
- **Regimens compared**: Empliciti-Revlimid-dex vs Rd
- **Median PFS favored**: Empliciti-Rd: 19 vs 15 months
- **Clinical considerations**: Consider for non-Revlimid refractory, frailer patients
- **Empliciti-Rd associated with**
  - More infections

### ELOQUENT-3
- **Regimens compared**: Empliciti-Pomalyst-dex vs Pd
- **Median PFS favored**: Empliciti-Pd: 10 vs 5 months
- **Clinical considerations**: Consider for patients refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro)
- **Empliciti-Pd associated with**
  - Severe low white blood cell counts, more dose reductions, upper respiratory infections, and diarrhea

### ICARIA-MM
- **Regimens compared**: Sarclisa-Pomalyst-dex vs Pd
- **Median PFS favored**: Sarclisa-Pd: 12 vs 7 months
- **Clinical considerations**: Consider for patients refractory to Revlimid and Velcade
- **Sarclisa-Pd associated with**
  - Higher MRD negativity rates
  - Severe respiratory infections

### IKEMA
- **Regimens compared**: Sarclisa-Kyprolis-dex vs Kd
- **Median PFS favored**: Sarclisa-Kd: 42 vs 21 months
- **Clinical considerations**: Consider for patients refractory to Revlimid and Velcade
- **Sarclisa-Kd associated with**
  - Higher MRD negativity rates
  - Severe respiratory infections

---

Update From the 2022 American Society of Hematology (ASH) Meeting

**Sarclisa After Early or Late Relapse**

<table>
<thead>
<tr>
<th>IKEMA Study</th>
<th>Early relapse</th>
<th>Late relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa-Kd</td>
<td>Sarclisa-Kd</td>
<td>Kd</td>
</tr>
<tr>
<td>Kd</td>
<td>Kd</td>
<td></td>
</tr>
<tr>
<td>Patients with relapsed/refractory myeloma who received 1–3 prior therapies, no prior therapy with Kyprolis and not refractory to prior anti-CD38 antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>179 patients</td>
<td>123 patients</td>
<td></td>
</tr>
</tbody>
</table>

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

### IKEMA Study
- **Regimes compared**: Sarclisa-Kd vs Kd
- **Outcome Measures**:
  - Median PFS (months)
  - Overall response rate (%)
  - \( \geq VGPR \) rate (%)
  - MRD negativity rate (%)
  - MRD-negative CR rate (%)

<table>
<thead>
<tr>
<th></th>
<th>Early relapse</th>
<th>Late relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa-Kd</td>
<td>Sarclisa-Kd</td>
<td>Kd</td>
</tr>
<tr>
<td>Kd</td>
<td>Kd</td>
<td></td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>24.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>82</td>
<td>82.6</td>
</tr>
<tr>
<td>( \geq VGPR ) rate (%)</td>
<td>67.2</td>
<td>52.2</td>
</tr>
<tr>
<td>MRD negativity rate (%)</td>
<td>24.6</td>
<td>15.2</td>
</tr>
<tr>
<td>MRD-negative CR rate (%)</td>
<td>18</td>
<td>10.9</td>
</tr>
</tbody>
</table>

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

---

*<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

### Clinical considerations

**VPd**: 11 vs 7 months
- Consider for relapse on Revlimid
- VPd associated with more low blood counts, infections, and neuropathy than Rd

**KRd**: 26 vs 17 months
- KRd associated with more upper respiratory infections and high blood pressure than Rd
- IRd associated with more upper respiratory infections and high blood pressure than Rd
- Lower incidence of peripheral neuropathy

**IRd**: 21 vs 15 months
- Ninlaro-Rd (IRd) vs Rd

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

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

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

**Sarclisa**
- Infusion reactions
- Risk of shingles
  - Use appropriate vaccination
- Increased risk of hypogammaglobulinemia and upper respiratory infections
### Important Considerations for Use of Proteasome Inhibitors

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

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

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

### Important Considerations for Use of Immunomodulatory Drugs

**Revlimid***
- **Rash**
  - Consider antihistamines and L-lysine
- **Diarrhea**
  - Consider bile acid sequestrants
- Risk of **blood clots**
- Risk of second primary **malignancies**
- Dose adjustment based on kidney function

**Pomalyst***
- Low blood counts
- Less rash than Revlimid
- Risk of second primary **malignancies**
- Risk of **blood clots**
- Dose adjustment for patients on hemodialysis

*Black box warning
Important Considerations for Use of XPOVIO

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

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

**Fatigue**
- Stay hydrated and active.

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


---

Treatment Approach

**First relapse**
- Proteasome inhibitor/immunomodulatory drug/antibody-based therapy

**>1 Relapse**
- Any options for first relapse not tried
- Refractory to Velcade and Revlimid
- FKd, 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))

**Triple-class refractory**
- Approved therapies
- Bispecific/trispecific antibodies, CAR T cells, CELMoDs
- Sd, ide-cel, citta-cel, Tecvayli

---

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

*Not yet approved for use in myeloma patients.*
### Triple-Class Refractory

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

#### Proteasome inhibitors
- Velcade (bortezomib)
- Kyprolis (carfilzomib)
- Ninlaro (ixazomib)

#### Immunomodulatory drugs
- Revlimid (lenalidomide)
- Pomalyst (pomalidomide)

#### Anti-CD38 monoclonal antibodies
- Darzalex (daratumumab)
- Sarclisa (isatuximab)

### Currently Available Drugs for Triple-Class Refractory Myeloma

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

**XPOVIO + dexamethasone in relapsed/refractory myeloma**

<table>
<thead>
<tr>
<th>No. patients with ≥PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Previous therapies to which the disease was refractory, n (%)</td>
</tr>
<tr>
<td>Velcade, Kyprolis, Revlimid, Pomalyst, and Darzalex</td>
</tr>
<tr>
<td>Kyprolis, Revlimid, Pomalyst, and Darzalex</td>
</tr>
<tr>
<td>Velcade, Kyprolis, Pomalyst, and Darzalex</td>
</tr>
<tr>
<td>Kyprolis, Pomalyst, and Darzalex</td>
</tr>
</tbody>
</table>

*Additional analyses showed clinical benefit with XPOVIO regardless of patient age and kidney function.*

---

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

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

*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia

†Black box warning: cytokine release syndrome; neurologic toxicities; Parkinsonism and Guillain-Barré syndrome; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia

‡Black box warning: cytokine release syndrome; neurologic toxicities

§Patients are hospitalized for 48 hours after administration of all step-up doses.

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

---

## Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma

### Abecma

- **ORR 73%**
- **Average PFS 9 months**

### Carvykti

- **ORR 97.9%**
- **27-month PFS 55%**

**Abecma**

<table>
<thead>
<tr>
<th>PR</th>
<th>VGPR</th>
<th>CR or sCR and MRD NE</th>
<th>CR or sCR and MRD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>21</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

**Carvykti**

<table>
<thead>
<tr>
<th>PR</th>
<th>VGPR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>82.5</td>
<td>12.4</td>
</tr>
</tbody>
</table>

**Patients (%)**

- **PR**
- **VGPR**
- **CR or sCR and MRD NE**
- **CR or sCR and MRD-**

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

Now Approved: Tecvayli, the First Bispecific Antibody

<table>
<thead>
<tr>
<th>All patients (n=165)</th>
<th>MRD negative ($10^{-5}$), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All treated: 26.7</td>
</tr>
<tr>
<td></td>
<td>MRD evaluable: 81.5</td>
</tr>
<tr>
<td></td>
<td>MRD negativity with ≥CR (%)</td>
</tr>
<tr>
<td></td>
<td>46.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All patients (n=165)</th>
<th>Median time to first response (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Median time to best response (mos)</td>
</tr>
<tr>
<td></td>
<td>3.8</td>
</tr>
</tbody>
</table>

63.0% (104/165) 32.7% 6.7% 19.4% 4.2%

Median duration of response 18.4 months


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.
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
  - Activating myeloma-specific immunity

- **Vaccines**
  - Activating myeloma-specific immunity

---

**CAR T-Cell Therapy**

- Genetically modified T cells designed to recognize specific proteins on myeloma cells
- CAR T cells are activated once in contact with the myeloma cell and can destroy it
- CAR T cells can persist for long periods of time in the body
- CAR T cells are created from a patient’s own blood cells, but the technology is evolving to develop “off-the-shelf” varieties

---

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

CAR T-Cell Therapy Patient Journey

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

2. (Manufacturing)  
   Patients return home
   4–6 weeks

3. Lymphodepletion (chemotherapy)  
   Standard-of-care therapy is permitted until CAR T cells are ready for infusion
   3 days*

4. Infusion
   Fludara and Cytoxan are used to create “immunologic space” to CAR T cells to expand
   2 weeks

5. Follow up
   Within 2 weeks

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

CAR T-Cell Therapy Insights

- 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

- 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

- 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

- 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
- Warrants further investigation into the optimal timing of Abecma infusion

- 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

Abecma or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Progression-free survival

<table>
<thead>
<tr>
<th>Treatment response</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


Carvykti in Relapsed and Refractory Multiple Myeloma

ORR 97.9%

27-month PFS 55%

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

CAR T: Expected Toxicities

Cytokine release syndrome (CRS)  Neurotoxicity (ICANS)

ICANS, immune effector cell-associated neurotoxicity syndrome


Transplant vs CAR T Cells

<table>
<thead>
<tr>
<th>Cellular therapies</th>
<th>CAR T-cell therapy</th>
<th>Autologous stem cell transplantation</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></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Targets BCMA with a shortened manufacturing time through the NEXT-T process</td>
<td>• Targets BCMA and CD19</td>
<td>• Manufacturing process that takes as little as 24 hours</td>
<td>• Targets GPRC5D</td>
<td>• An allogeneic anti-BCMA CAR T-cell product</td>
</tr>
<tr>
<td>Trial details</td>
<td>• Phase 1 trial of 55 patients with RRMM with a median of 5 prior lines of therapy</td>
<td>• Phase 1 trial of 13 newly diagnosed high-risk myeloma patients ineligible for stem cell transplant</td>
<td>• Phase 1 trial of 17 heavily pretreated patients with RRMM, including those who relapsed from BCMA CAR-T therapy</td>
<td>• Phase 1 trial of 53 patients with RRMM with a median of 5 prior lines of therapy</td>
</tr>
<tr>
<td>Clinical results</td>
<td>• CRS occurred in 80% of patients with only 1 patient experiencing ≥G3.</td>
<td>• Neurotoxicity occurred in 10.9% of patients (1 grade 4)</td>
<td>• Overall response rate was 98.1% with 57.4% achieving ≥VGPR (29.6% ≥CR)</td>
<td>• CRS occurred in 52% of patients; neurotoxicity in 11%</td>
</tr>
<tr>
<td></td>
<td>• Neurotoxicity occurred in 10.9% of patients (one grade 4)</td>
<td></td>
<td>• 100% of patients achieved ≥VGPR (69% ≥sCR)</td>
<td>• Infections occurred in 56% of patients (29% ≥G3)</td>
</tr>
<tr>
<td></td>
<td>• Overall response rate was 98.1% with 57.4% achieving ≥VGPR (29.6% ≥CR)</td>
<td></td>
<td>• All patients achieved MRD negativity (by EuroFlow)</td>
<td>• Overall response rate was between 64% and 80% in the most active cell doses studied</td>
</tr>
</tbody>
</table>


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

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>Forintamig (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

GPRC5D, G protein-coupled receptor family C group 5 member D

Additional Studies of Tecvayli in Patients With Relapsed/Refractory Myeloma

Teclistamab in patients *with prior* BCMA-targeted treatment (MajesTEC-1 Study)\(^1\)

![Graph showing patients responding with different treatments](image)

<table>
<thead>
<tr>
<th>Patients Responding (%)</th>
<th>PR</th>
<th>VGPR</th>
<th>CR</th>
<th>sCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC-exposed (n=29)</td>
<td>6.9</td>
<td>24.1</td>
<td>26.7</td>
<td>20</td>
</tr>
<tr>
<td>CAR-T-exposed (n=15)</td>
<td>6.7</td>
<td>20</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>ADC and/or CAR-T (n=40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Teclistamab experience vs real-world clinical practice (LocoMMotion Study)\(^2\)

![Graph showing patients responding with different treatments](image)

<table>
<thead>
<tr>
<th>Patients Responding (%)</th>
<th>PR</th>
<th>VGPR</th>
<th>≥CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teclistamab (n=150)</td>
<td>32</td>
<td>26.7</td>
<td>10.2</td>
</tr>
<tr>
<td>Standard of care (n=248)</td>
<td>4</td>
<td>16.3</td>
<td>16.3</td>
</tr>
</tbody>
</table>

**Tecvayli Combinations**

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR 100%</th>
<th>ORR 75%</th>
<th>ORR 41.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tec SC Q2W 3 mg/kg (n=27)</td>
<td>7.4</td>
<td>7.4</td>
<td>65.6</td>
</tr>
<tr>
<td>+ SC Dar 1,800 mg</td>
<td></td>
<td>PD</td>
<td></td>
</tr>
</tbody>
</table>

Clinical response

Patients (%)

- PD
- SD
- PR
- VGPR
- VGPR
- CR

Teclistamab + Darzalex in patients with 1–3 prior lines of therapy (MajesTEC-2 Study)\(^2\)

Patients Responding (%)

- PR
- VGPR
- CR
- sCR

Most frequent non-hematologic adverse events, %

<table>
<thead>
<tr>
<th>Adverse Event</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>90.6</td>
<td>37.5</td>
</tr>
</tbody>
</table>

Teclistamab + Darzalex + Revlimid in patients with 3 or more prior lines of therapy


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

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

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

Patients Responding (%)

- PR
- VGPR
- CR
- sCR

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 (%)

- PR
- VGPR
- CR
- sCR

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

### Alnuctamab

**Subcutaneous formulation results**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Patients Responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses (n=55)</td>
<td>53% 65%</td>
</tr>
<tr>
<td>&lt;30 mg (n=25)</td>
<td>16 19</td>
</tr>
<tr>
<td>30 mg (n=26)</td>
<td>16 14</td>
</tr>
</tbody>
</table>

### Linvoseltamab

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

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Patients Responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All doses (n=122)</td>
<td>29% 80%</td>
</tr>
<tr>
<td>60 mg dose escalation + expansion (n=58)</td>
<td>29% 80%</td>
</tr>
<tr>
<td>Triple-class refractory All (n=100)</td>
<td>57% 72%</td>
</tr>
<tr>
<td>Triple-class refractory 60 mg dose escalation + expansion (n=48)</td>
<td>29% 72%</td>
</tr>
</tbody>
</table>

### ABBV-383

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

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Patients Responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grades</td>
<td>72 57</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td>2 2</td>
</tr>
<tr>
<td>Serious</td>
<td>27 18</td>
</tr>
</tbody>
</table>

---


---

## Non-BCMA–Targeted Bispecific Antibodies
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

Forimtamig and Cevostamab in Patients With Relapsed/Refractory Multiple Myeloma

Forimtamig (RG6234)—targets GPRC5D

Forimtamig (RG6234)—targets GPRC5D

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**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38.6</td>
</tr>
<tr>
<td>Infections</td>
<td>50.0</td>
</tr>
<tr>
<td>CRS</td>
<td>59.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NR</td>
</tr>
<tr>
<td>COVID-19</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

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

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

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

NR, not reported

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>CAR T-cell therapy</th>
<th>Bispecific antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved product</td>
<td>Abecma, Carvykti</td>
</tr>
<tr>
<td>Efficacy</td>
<td>+++</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Tecvayl</td>
</tr>
<tr>
<td>How given</td>
<td>One-and-done</td>
</tr>
<tr>
<td>Where given</td>
<td>Academic medical centers</td>
</tr>
<tr>
<td>Notable adverse events</td>
<td>CRS and neurotoxicity</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>+++</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>++</td>
</tr>
<tr>
<td>Availability</td>
<td>Wait time for manufacturing</td>
</tr>
<tr>
<td>Availability</td>
<td>Off-the-shelf, close monitoring for CRS and neurotoxicity</td>
</tr>
<tr>
<td>Advantages</td>
<td>Personalized</td>
</tr>
<tr>
<td></td>
<td>Targeted immunocytotoxicity</td>
</tr>
<tr>
<td></td>
<td>Single infusion (&quot;one and done&quot;)</td>
</tr>
<tr>
<td></td>
<td>Potentially persistent</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>FACT-accredited center required (hospitalization likely required)</td>
</tr>
<tr>
<td></td>
<td>CRS and neurotoxicity; requires ICU and neurology services</td>
</tr>
<tr>
<td></td>
<td>Dependent on T-cell health (manufacturing failures)</td>
</tr>
<tr>
<td></td>
<td>Requires significant social support; caregiver required</td>
</tr>
<tr>
<td></td>
<td>Initial hospitalization required</td>
</tr>
<tr>
<td></td>
<td>CRS and neurotoxicity possible</td>
</tr>
<tr>
<td></td>
<td>Dependent on T-cell health (T-cell exhaustion)</td>
</tr>
<tr>
<td></td>
<td>Requires continuous administration</td>
</tr>
<tr>
<td></td>
<td>$$$</td>
</tr>
</tbody>
</table>
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 Cereblon E3 Ligase Modulator (CELMoD)

Iberdomide in combination with dexamethasone in patients with RRMM

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

**Key Points**

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

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

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

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

- Several additional bispecific antibodies are under clinical evaluation.

- CELMoDs are emerging as active oral agents, even in patients who have received BCMA directed therapies including CAR-Ts.
Please take a moment to answer two questions about this presentation.

Supportive Care

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

- Low blood counts
- Decreased kidney function
- Bone damage

**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)

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

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

ONJ, osteonecrosis of the jaw
Orthopedic Procedures to Stabilize the Spine

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

Radiation Therapy for Pain Management
Pain Management Medications

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (Tylenol)</td>
<td>Will not hurt your kidneys; high dosage can hurt your liver</td>
</tr>
<tr>
<td>NSAIDs (nonsteroidal anti-inflammatory drugs)</td>
<td>Prefer to avoid with multiple myeloma due to increased risk of kidney injury</td>
</tr>
<tr>
<td>Opioids</td>
<td>Will not hurt kidneys, liver, stomach; potential for constipation, sedation, confusion, dependence, addiction</td>
</tr>
<tr>
<td>Corticosteroids (dexamethasone, prednisone)</td>
<td>Will not hurt kidneys; can raise blood sugar; short- and long-term effects</td>
</tr>
<tr>
<td>Anti-seizure medications (gabapentin and Lyrica)</td>
<td>Potential for drowsiness and dizziness</td>
</tr>
</tbody>
</table>

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

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

#### Side Effects and Management

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

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

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

*Black box warning.

---

### Class: Proteasome Inhibitors

#### Side Effects and Management

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

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

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

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

*Do not take any supplements without consulting with your doctor.

*PN, peripheral neuropathy; GI, gastrointestinal*
Class: Monoclonal Antibodies Side Effects and Management

Empliciti
- Low blood counts
- Infusion reactions

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

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

*Now approved as subcutaneous injection with fewer side effects.

XPOVIO: Selective Inhibitor of Nuclear Export Side Effects and Management

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

Low sodium (hyponatremia)
- Maintain fluid intake

Fatigue
- Stay hydrated and active

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

Bispecific Antibodies

Tecvayli

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

Management

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

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

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

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

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.

Multiple myeloma ➔ Treatment

Immune dysfunction

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

As recommended by your health care team

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

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


155

156
Infection Prevention

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

Side Effects of Steroids (Dexamethasone)

- Insomnia
  - Healthy sleep habits
  - Timing
  - Medication to assist with sleeping as needed
- Fluid retention
  - Monitor for swelling of extremities and “puffy” face
  - Monitor weight changes/gain
  - Reduce dose
- Mood changes
  - Irritable, anxious, difficulty concentrating
  - Severe cases → depression, euphoria
- Dyspepsia-heartburn
  - Dietary modifications (spicy, acidic foods)
  - Avoid NSAIDs
  - Acid-blocking medications
  - Take steroid with food; use enteric-coated aspirin with food
- Elevation in glucose
  - Monitor glucose and refer/treat as needed
Symptom Management

### Constipation

- **Stimulant laxatives**
  - Mild: senna/sennoside (Senokot)
    - 1–2 pills twice a day
  - More potent: bisacodyl (Dulcolax)

- **Osmotic laxatives**
  - Gentle, pulls water into the intestine
    - Lactulose
    - Miralax

- **Bulking agents**
  - Soluble fiber: psyllium (Metamucil)

### Acid Reflux/Heartburn

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

**A few ways to treat**

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

**Insomnia**

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

Marijuana

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

- Proper nutrition
- Exercise
- Rest
- Social contacts

Taking Care of Yourself

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

Patient Experience
Gail Goode
Minimal Residual Disease
Neha Korde, MD
Memorial Sloan Kettering Cancer Center
New York, New York

Goals of Multiple Myeloma Therapy

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

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

What is MRD?

The presence of small amounts of myeloma cells left in the bone marrow following the achievement of a CR after treatment

MRD tests can detect at least 1 cell in 100,000 or better. Ideally, we want to use more sensitive assays that can find 1 cell in a million.
Why do we need to measure MRD?

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

How is MRD measured?

Diagnostic

Tumor burden

Minimal residual disease

10^{12}

10^{11}

10^{10}

10^9

10^6

Flow cytometry

Next-generation DNA sequencing
Key Terms for MRD

MRD positive or MRD positivity (MRD+)
- Myeloma cells are still detectable

MRD negative or MRD negativity (MRD-)
- Myeloma cells are not detected

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

Comprehensive Response Assessment

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

What about other areas of the body?

Imaging (with PET/CT scan) is also required to detect residual disease outside of the bone marrow
Why is it important to achieve MRD negativity?

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

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

Key points from 14 studies analyzed*

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

*5 trials included stem cell transplantation/10 studies included maintenance
MRD Negativity Achieved by Various Regimens

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>ASCT</th>
<th>MRD-negativity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triplet regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRd 8 cycles</td>
<td>Yes</td>
<td>58%</td>
</tr>
<tr>
<td>KRd 12 cycles</td>
<td>No</td>
<td>54%</td>
</tr>
<tr>
<td>VRd ×6 cycles</td>
<td>Yes</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Quadruplet regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VRd-daratumumab ×6 cycles</td>
<td>Yes</td>
<td>51%</td>
</tr>
<tr>
<td>KRd-daratumumab ×8 cycles</td>
<td>No</td>
<td>71%</td>
</tr>
</tbody>
</table>


MRD Response-Adapted Consolidation and Treatment Cessation

**MASTER Trial**

<table>
<thead>
<tr>
<th>Newly diagnosed myeloma patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction</strong></td>
</tr>
<tr>
<td>Darzalex + Kyprolis + Revlimid + dex (Dara-KRd)</td>
</tr>
<tr>
<td>*MRD ↓ ASCT</td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
</tr>
<tr>
<td>Dara-KRd</td>
</tr>
<tr>
<td>2nd MRD- (&lt;10^-5)</td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
</tr>
<tr>
<td>Dara-KRd</td>
</tr>
<tr>
<td>2nd MRD- (&lt;10^-5)</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
</tr>
<tr>
<td>Revlimid</td>
</tr>
<tr>
<td>Treatment-free observation and MRD surveillance*</td>
</tr>
</tbody>
</table>

80% of patients achieved MRD negativity (at <1 x 10^-5) and 66% achieved MRD negativity at <1 x 10^-6.

86% of patients achieved a CR or better.

Responses deepened with each phase of treatment—and were similar in patients with zero, one, or two or more high-risk genetic abnormalities.

ASCT increased the rates of MRD negativity following induction therapy, benefitting patients with highest-risk disease features.

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

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

Ongoing Studies Using MRD Results to Direct Therapy

**Phase 3 DRAMMATIC Study**

- Patients post-ASCT
  - MRD assessment
    - Positive
      - Revlimid
      - Revlimid + Darzalex
      - Continue assigned therapy
    - Negative
      - MRD assessment
        - Positive
          - Revlimid
          - Stop assigned therapy
        - Negative
          - Revlimid + Darzalex
          - Continue assigned therapy

**Phase 3 OPTIMUM Study**

- Patients post-ASCT
  - MRD assessment
    - Positive
      - Revlimid + Ninlaro
      - Continue treatment until progression or unacceptable toxicity
    - Negative
      - Revlimid
      - Off study


MRD Is Important for Clinical Care and New Drug Registration

- Currently assessed by BM-based technologies
  - Flow cytometry
  - Next-generation sequencing
- A potential surrogate for patient outcome in clinical trials
- Progress being made with blood-based technologies
  - MS
  - Cell-free DNA
- Many clinical trials are using MRD-driven strategies
- Accelerate innovative trials leading to regulatory approval

BM, bone marrow; MS, mass spectrometry
Potential Blood-Based MRD Testing: Mass Spectrometry

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

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

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

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

Key Points

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

MRD has been associated with longer PFS and OS to predict lower risk of progression. Modern combination therapies show increasingly higher MRD negativity rate.

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

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

MRD, minimal residual disease; NGF, next-generation flow cytometry; NGS, next-generation sequencing.
Please take a moment to answer two questions about this presentation.

Clinical Trials
Gunjan L. Shah, MD
Memorial Sloan Kettering Cancer Center
New York, New York
Goal of Clinical Trials: Making Progress Against Myeloma

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

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

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

Impact of Clinical Trials in Myeloma

- Survival rates have nearly doubled; further improvements expected in near future.
- Many new drugs approved since 2003.
- Many new drugs being studied in clinical trials.
- Understanding of the biology of myeloma improving, with the eventual goal of personalized medicine.
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

- 1975: 26.5%
- 1985: 27.4%
- 1995: 33.5%
- 2005: 47.2%
- 2013: 56.9%
- 2014 and beyond: 56.9%

Available treatments:
- Chemotherapy + dexamethasone + stem cell transplantation
- Velcade (bortezomib)
- Revlimid (lenalidomide)
- Kyprolis (carfilzomib)
- Pomalyst (pomalidomide)
- Ninlaro (ixazomib)
- Empliciti (elotuzumab)
- Darzalex (daratumumab)
- Xpovio (selinexor)
- Sarclisa (isatuximab)
- Abecma (idecabtagene vicleucel)
- Carvykti (ciltaclabtagene autoleucel)
- Tecvayli (teclistamab)

New Drug Development

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

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

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

The whole process costs millions of dollars and years of effort!
Designing Clinical Studies

When a treatment is ready to be tested, researchers design a research plan called a protocol that includes such details as:
- How many patients will be enrolled
- How the treatment will be administered
- When and how participants will be monitored
- The goals of the trial: determine safety, identify the right dose, measure the efficacy

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

Traditional Clinical Study Types

<table>
<thead>
<tr>
<th>Treatment dose</th>
<th>Number of patients</th>
<th>Questions answered*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Different doses| Small             | • What is the best dose?  
|                |                   | • Is the drug safe?      
|                |                   | • What are the side effects? |
| Phase 2        |                   |                     |
| Same dose      | Moderate          | • Does the drug work?   
|                |                   | • What are the side effects? |

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

Example: Phase 1 MajesTEC-1 Study
- Relapsed/refractory myeloma and progression after ≥2 prior treatment regimens
- 80 μg/kg (n=6)
- 240 μg/kg (n=7)
- 720 μg/kg (n=16)
- 1,500 μg/kg (n=40)
- 3,000 μg/kg (n=4)

Randomized phase 2 dose

Example: Phase 2 GRIFFIN Study
- Newly diagnosed myeloma patients
- 104 patients
- Dasazol + Revlimid + Velcade + dex (Dara-RVd)
- Induction
- ASCT
- Darzalex
- Darzalex
- RVd
- R
- Maintenance
- Consolidation
- 103 patients
- ASCT
- RVd
- R
Traditional Clinical Study Types

Treatment dose vs Number of patients

- Phase 1: Small, exploratory trials (10-20 patients)
- Phase 2: Intermediate, confirmatory trials (50-100 patients)
- Phase 3: Large, confirmatory trials (1000-5000 patients)

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

Example: Phase 3 IKEMA Study
- Patients with RRMM who received 1–3 prior therapies, no prior therapy with Kyprolis, and were not refractory to prior anti-CD38 antibody
- 179 patients
- Sarciza-Kd
- 123 patients

Example: Phase 3 DETERMINATION Study
- EARLY TRANSPLANT ARM
  - Newly diagnosed MM patients
  - Revlimid + Velcade + dex (RVd)
  - Stem cell collection
  - ASCT
  - Rvd

- LATE TRANSPLANT ARM
  - Revlimid + Velcade + dex (RVd)
  - Stem cell collection
  - Rvd

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

Umbrella/platform trials: patients have the same cancer but different genetic mutations

Basket/bucket trials: patients have different cancers but the same genetic mutation

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

- **Longitudinal Studies**
  - Long-term studies with a large number of patients

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

- **Expanded-Access Programs**
  - Allow early access to experimental therapies when no alternatives are available

---

Participation in a Clinical Study
Aren’t clinical studies for people who are running out of options?

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

Will I be treated like a guinea pig?

No!

Three influential documents:
- The Nuremberg Code
- The Declaration of Helsinki
- The Belmont Report

Ethics Committees and Research Boards
Benefits of Clinical Trials

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

Considering Entering Clinical Trials

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

- Myeloma survival rates have nearly doubled; further improvements are expected.
- Many new drugs approved since 2003.
- The drive of research and clinical trials has brought us to where we are.

Clinical trials are available for patients at all stages of myeloma, including those who have precursor conditions, those who are newly diagnosed, and those who have received previous treatments and whose myeloma has relapsed.

- No one is expected to be a guinea pig; research and clinical trials are under very tight supervision and standards.

- Open, clear communication between the physician and the patient is essential.

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)*

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

R-ISS Stage II
- All other possible combinations

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

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

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

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

- Disease features
  - Other cytogenetic and genetic abnormalities
  - Plasma cell leukemia
  - Extramedullary disease
  - Renal failure

- Patient features
  - Comorbidities
  - Frailty

- Response features
  - Lack of response to therapy
  - Short first PFS

Additional high-risk features

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

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!

CoMMpass Findings: Chromosome 1 Copy Number and Other Cytogenetics

- **Copy number of chromosome 1q**
  - 2 copies (n=107)
  - 3 copies (n=52)
  - ≥4 copies (n=26)
  - ≥4 copies: 34.6 mo
  - 3 copies: 55.9 mo

- **Cytogenetics**
  - Hi/1q (n=28)
  - Std/1q (n=66)
  - Hi (n=12)
  - Std (n=95)
  - Hi/1q: 25.1 mo

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

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

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

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.

CoMMpass: Identifying Double-Hit Multiple Myeloma

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

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

Having no brakes is a bad thing but having half the brakes is okay.
Despite recent improvements in treatment, high-risk patients have not experienced the same benefit as patients with standard risk. Therefore, the treatment of high-risk patients is a very important focus of research.

Approach to Treatment: Risk-Adapted Therapy

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>Total number of patients</th>
<th>High risk definition</th>
<th>Number of high-risk myeloma patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG-1211</td>
<td>RVd vs RVd-Empliciti</td>
<td>100</td>
<td>GEP&lt;sup&gt;++&lt;/sup&gt;, del17p, t(14;16), t(14;20), Amp1q21, elevated LDH, pPCL</td>
<td>RVd = 52</td>
</tr>
<tr>
<td>SWOG-0777</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>MAIA&lt;sup&gt;2&lt;/sup&gt;</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>ALCYONE&lt;sup&gt;4&lt;/sup&gt;</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>CASSIOPEIA&lt;sup&gt;5&lt;/sup&gt;</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>STAMINA&lt;sup&gt;6&lt;/sup&gt;</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 ASCT/RVD = 76</td>
</tr>
</tbody>
</table>

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


---

## Darzalex Meta-Analysis in High-Risk Multiple Myeloma

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

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

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

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

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

Results were similar regardless of backbone regimens.


Treatment Regimens for High-Risk Disease Features

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

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

**OPTIMUM Study**

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

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

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


Sarclisa Combinations in Newly Diagnosed Patients With High-Risk Disease

**GMMG-CONCEPT Study**

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidation</th>
<th>Maintenance</th>
</tr>
</thead>
</table>

Transplant eligible (≤70 yrs) n=127
Transplant ineligible (>70 yrs) n=26

Best response (through consolidation), %

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

Adverse events, % grade ≥3

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

Non-hematologic

| Infection | 27.8 | 28 |
| Cardiac   | 2.1  | 20 |

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
- R-CyBorD
- Isa
- Stop Isa
- Cont Isa
- R

**High-risk* patients**

- n=280
- Revlimid-cyclophosphamide-Velcade-dex-dex (R-CyBorD)
- Isa-R-CyBorD
- 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.

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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.

Town Hall 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>
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</thead>
<tbody>
<tr>
<td>Patient Summit</td>
<td>Saturday, June 24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9:00 AM to 3:45 PM</td>
<td>Peter Voorhees, MD</td>
</tr>
</tbody>
</table>

Charlotte, North Carolina

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

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

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

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