Opening Remarks
Mary DeRome, MS
MMRF

Tech Support
1-719-234-7952
Resources

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

Submit your questions throughout the program!
Program Faculty

Ajai Chari, MD
University of California, San Francisco
San Francisco, California

Sagar Lonial, MD
Winship Cancer Institute of Emory University
Atlanta, Georgia

Nancy S. Wong, RN, MSN-FNP
University of California, San Francisco
San Francisco, California

Thomas G. Martin, III, MD
University of California, San Francisco
San Francisco, California

Jeffrey L. Wolf, MD
University of California, San Francisco
San Francisco, California

Summit Agenda

<table>
<thead>
<tr>
<th>Time (PT)</th>
<th>Topic</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 – 9:15 AM</td>
<td>MMRF Introduction</td>
<td>Mary DeRome, MS</td>
</tr>
<tr>
<td>9:15 – 9:30 AM</td>
<td>Welcome</td>
<td>Ajai Chari, MD</td>
</tr>
<tr>
<td>9:30 – 10:00 AM</td>
<td>Newly Diagnosed Multiple Myeloma: Diagnosis and Induction Therapy</td>
<td>Sagar Lonial, MD</td>
</tr>
<tr>
<td>10:00 – 10:30 AM</td>
<td>High-Dose Chemotherapy and Stem Cell Transplantation, Maintenance Therapy, and Treatment Goals</td>
<td>Ajai Chari, MD</td>
</tr>
<tr>
<td>10:30 – 11:00 AM</td>
<td>Relapsed/Refractory Multiple Myeloma</td>
<td>Thomas G. Martin, III, MD</td>
</tr>
<tr>
<td>11:00 – 11:30 AM</td>
<td>Town Hall Q&amp;A</td>
<td>All Faculty</td>
</tr>
<tr>
<td>11:30 AM – 12:00 PM</td>
<td>Supportive Care</td>
<td>Nancy S. Wong, RN, MSN-FNP</td>
</tr>
<tr>
<td>12:00 – 12:15 PM</td>
<td>Patient Speaker</td>
<td>Mike Smith</td>
</tr>
<tr>
<td>12:15 – 12:30 PM</td>
<td>Hot Topic 1: Multiple Myeloma Precursor Conditions</td>
<td>Sagar Lonial, MD</td>
</tr>
<tr>
<td>12:30 – 12:45 PM</td>
<td>Hot Topic 2: Clinical Studies</td>
<td>Ajai Chari, MD</td>
</tr>
<tr>
<td>12:45 – 1:00 PM</td>
<td>Hot Topic 3: Personalized Medicine</td>
<td>Jeffrey L. Wolf, MD</td>
</tr>
<tr>
<td>1:00 – 2:00 PM</td>
<td>Town Hall Q&amp;A</td>
<td>All Faculty</td>
</tr>
<tr>
<td>2:00 – 2:15 PM</td>
<td>Closing Remarks</td>
<td>Mary DeRome, MS</td>
</tr>
</tbody>
</table>
The MMRF does three things in relentless pursuit of its mission to accelerate a cure for each and every myeloma patient.

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

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

3. **We empower patients**
   - Putting them on The Right Track and guiding them to the right team, tests, and treatments to extend their lives
MMRF CoMMpass Study: Advancing Personalized Medicine Research

- Landmark study focusing on the genomics of myeloma
- Goals
  - Learn which patients respond best to which therapies
  - Identify new targets and new hypotheses
- Newly diagnosed patients are followed for at least 8 years

All participants undergo a type of detailed DNA testing called **genomic sequencing** at diagnosis and each relapse.

CoMMpass Is a Trial of Discovery

- CoMMpass data has
  - Provided the myeloma community with information on
    - Frequency of genetic abnormalities
    - How genetic abnormalities play a role in myeloma
      - Drive multiple myeloma cell growth and survival
      - Contribute to drug resistance
      - May predict which patients respond to which therapy
    - Genetic abnormalities that help refine risk assessment
  - Led to conception of the MyDRUG trial
MyDRUG Trial

Functional high-risk patients

Profiling for alterations (NCT02884102)

No detectable actionable alterations

Daratumumab + IPd

RAF/RAS mutations

Cobimetinib + dex

CDK pathway-activating alterations

Abemaciclib + IPd

FGFR3-activating alterations

Erdafitinib + IPd

t(11;14)

2 cycles

2:1

Venetoclax + IPd

IPd control

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

MMRF Research Initiatives

1. MMRF Myeloma Accelerator Challenge (MAC) Grants
   - Broad, multi-institutional research grants designed to advance clinical trial concepts in the areas of
     - High-risk newly diagnosed multiple myeloma (NDMM)
     - High-risk smoldering myeloma (SMM)
   - Each research network will be funded up to $10M over 3 years

2. MMRF Horizon Adaptive Platform Trials
   - Paired with MAC grants
   - Done in collaboration with 13 MMRC sites
   - Trials in relapsed/refractory myeloma, high-risk NDMM, high-risk SMM

For more information, visit themmrf.org
2023 Myeloma Accelerator Challenge Program Grant Recipients

Transforming Treatment of High-Risk Myeloma
Network includes Tisch Cancer Center at Mt Sinai, Albert Einstein Medical College, Hackensack University Medical Center, Stanford University Medical Center, UCSF, Washington University of Saint Louis

Sagar Lonial, MD

A Systems Biology Approach to High-Risk Myeloma
Network includes Erasmus Medical Center, Rotterdam; Amsterdam University Medical Centers; Julius Maximilian University of Wurzburg; University of Turin; University of Salamanca

Pieter Sonneveld, MD, PhD

Clinical and Multi-Omics Platforms to Define High-Risk Smoldering Myeloma
Network includes Emory University, Atrium Health Levine Cancer Institute, Icahn School of Medicine at Mt Sinai, Mass General Hospital, Mayo Clinic, MSKC Institute, Dana-Farber Cancer Institute

Sagar Lonial, MD

Each network will receive $7M over 3 years for a total $21M investment by the MMRF, meant to foster collaboration and advance compelling hypotheses that are ready for rapid testing in clinical trials.

Welcome!

Ajai Chari, MD
University of California, San Francisco
San Francisco, California
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, with 35,730 new cases in 2023. Myeloma represents 1.8% of all new cancer cases in the U.S.

Median age at diagnosis is 69 years. 159,787 people are living with myeloma or in remission.

Multiple Myeloma Affects Your Bones, Blood, and Kidneys

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

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

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

Light chain (kappa [κ] or lambda [λ])

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

Multiple myeloma cells

Normal plasma cells

17

18
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

The clinical features that are characteristic of multiple myeloma

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

Effects of Myeloma and Common Symptoms

- Low blood counts → Weakness
- Decreased kidney function → Fatigue, Infection
- 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

<table>
<thead>
<tr>
<th>Older age</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>• One first-degree relative with multiple myeloma</td>
</tr>
<tr>
<td>Obesity</td>
<td>• Relatives of multiple myeloma patients have more monoclonal gammopathy of undetermined significance (MGUS)</td>
</tr>
<tr>
<td>Race: 2× incidence in African Americans</td>
<td>• Current recommendation is to not screen families</td>
</tr>
</tbody>
</table>
Following the Right Track Will Help Patients Get the Best Treatment and Results for Their Specific Type of Myeloma

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

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

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

---

**The Right Team**

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

Seek a second opinion at any point in your journey

Available resources

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

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

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

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

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

Learn Your Labs!

**Blood Tests**

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

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

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

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

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

- **SFLC**
  - Freelite test measures light chains (kappa or lambda)
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
- Double-hit myeloma: any two high-risk genetic abnormalities
- Triple-hit myeloma: three or more high-risk genetic abnormalities

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

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

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

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

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

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

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

R-ISS, Revised International Staging System; β2M, β2 microglobulin; LDH, lactate dehydrogenase; FISH, fluorescence in situ hybridization

---

The Right Treatment

- **Know the treatment options available to you based on your myeloma subtype at each stage of your disease.**

- **Be aware of the pros and cons of each option.**

- **Clearly communicate your treatment goals and concerns to the care team.**

- **Find clinical trials that are right for you.**
Getting the Right Treatment: Goals of Multiple Myeloma Therapy

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

Myeloma Survival Has Improved Over Time, Mainly Due to Novel Agents and Immune Therapies (including mAbs)

The percentage of people expected to survive 5 years or more after being diagnosed with myeloma has dramatically improved in the last 20 years:

- 1975: 26.5%
- 1985: 27.4%
- 1995: 33.5%
- 2005: 47.2%
- 2013: 56.9%
- ~ 65% (2014 and beyond)

Available treatments:

- Ninlaro (ixazomib)
- Empliciti (elotuzumab)
- Darzalex (daratumumab)
- Xpovio (selinexor)
- Sardisa (isatuximab)
- Abecma (idecabtagene videocel)
- Carvykti (ciltaclabtagene autoleucel)
- Tecvayli (teclistamab)
- Talvye (talquetamab)
- Eltrombopag (etranatamab)

Treatments from 1975 to 2013:
Overview of Treatment Approach for Active Multiple Myeloma

Is the patient a candidate for autologous stem cell transplantation?

Yes

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

- **Stem cell collection and storage**

- **High-dose melphalan + stem cell transplant**

No

- **Continuous induction**
  - 2–4 drugs
  - 6 or more treatment cycles

- **(± Consolidation) Maintenance**

Supportive care

*In certain circumstances, consideration for a tandem transplant

Induction Therapy Regimens

**Preferred**

- Revlimid-Velcade-dex (RVd)*
- Kyprolis-Revlimid-idex (KD)

**Recommended**

- Darzalex-Revlimid-ID-Idex (D-RVd)

**Certain circumstances**

- Vonca-dex (VCd)
- Velcade-Doxil-dex (VDd)
- Kyprolis-Cytoxan-dex (KCd)
- Darzalex-Velcade-Thalomid-dex (D-VTd)
- Darzalex-Kyprolis-Revlimid-dex (D-KRd)
- Darzalex-Cytoxan-Velcade-dex (D-VCd)
- Sarclisa-Revlimid-ID-Ve bade-dex
- VTD-PACE

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

**National Comprehensive Cancer Network Guidelines Version 2.2024. Multiple Myeloma.**
RVd Induction Therapy (N=1,000 Patients)

PFS and OS Based on Response
Phase 3 Study of Darzalex-Velcade-Revlimid-Dex vs Velcade-Revlimid-Dex in NDMM


PFS

OS

Median PFS, D-RVd vs RVd: NR vs 67.5 months; p<0.001
Median OS, D-RVd vs RVd: NR vs 128.95 months; p<0.034
1-year PFS, D-RVd vs RVd: 98% vs 93%
2-year PFS, D-RVd vs RVd: 93% vs 82%
1-year OS, D-RVd vs RVd: 99% vs 97%
2-year OS, D-RVd vs RVd: 94% vs 91%

D-RVd vs RVd

Joseph et al. IMS 2023.
### Measuring Response to Therapy

**Stable disease** (no change in M protein of light chain)

**Minor response** (>30% decrease)

**Partial response** (>50% decrease)

**Very good partial response** (>90% decrease)

**Complete response** (100% decrease/<5% plasma cells in bone marrow biopsy)

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

- **Minimal residual disease negative**

---

### 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-directed/response-adapted therapy**
- **Minimize long-term toxicities since myeloma patients living (much) longer and the evolving role of autologous stem cell transplant**
- **New drug classes and impact of immunotherapies**
Summary

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

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

Survival rates are improving because of new drugs and new combinations of drugs, including immune therapies and especially monoclonal antibodies.

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!
High-Dose Chemotherapy and Stem Cell Transplantation

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

What does transplant mean?

Understanding the basics of autologous stem cell transplantation

- Blood-forming stem cells are collected from the patient's own blood. Stem cells are frozen and stored.
- Patient gets high-dose chemotherapy: melphalan. Most myeloma cells are destroyed; some normal cells (hair follicles, taste buds, and blood cells) are also temporarily destroyed.
- The previously collected stem cells are given back by IV infusion. Stem cells restore blood cells with fewer myeloma cells. Other cells (hair follicles and taste buds) recover.
Current Treatment Paradigm for Newly Diagnosed Multiple Myeloma

- Induction therapy
- ± Consolidation therapy
- Maintenance therapy

**Transplant candidate**

1. **Induction therapy**
2. **± Consolidation therapy**
3. **Maintenance therapy**

**Non-transplant candidate**

1. **Induction therapy**
2. **Maintenance therapy**

---

**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**

5. **Thawing and infusion of stem cells**

6. **Bone marrow recovery**

   Day 0

   Days +1 to +100†

**Stem cells**

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

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

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

Hair loss

Is transplant still required in newly diagnosed myeloma?

Q: Should I get a transplant up front or not?

[Diagram showing the stages of treatment for newly diagnosed myeloma patients, including induction, consolidation, and maintenance phases, with options for RVd + ASCT ARM and RVd ALONE ARM.]

Phase 3 Study of ASCT for NDMM: Survival Analysis

**Progression-free survival (PFS)**

- **RVd + ASCT** (median PFS, 67.5 mos)
- **RVd alone** (median PFS, 46.2 mos)

**Overall survival (OS)**

- **RVd + ASCT**
- **RVd alone**

**Primary end point**
- PFS for RVd + ASCT: approximately 5.5 years
- PFS for RVd alone: approximately 4 years

Transplant extended time to progression by 20 months

**Length of overall survival: no difference (with a median follow up time of 76 months).**

Phase 3 Study of ASCT for NDMM: Best Response to Treatment and Duration of Response

**Response rate (%)**

- **≥PR**: RVd-alone 97.5, RVd+ASCT 95, p=0.55
- **≥VGPR**: RVd-alone 82.7, RVd+ASCT 79.6, p=0.99
- **≥CR**: RVd-alone 46.8, RVd+ASCT 42, p=0.99

**Duration of response**

<table>
<thead>
<tr>
<th>Duration of response</th>
<th>RVd + ASCT</th>
<th>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>88.3</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>19.8</td>
<td>39.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>18.2</td>
<td>29.0</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>6.2</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>8.0</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 NDMM: Quality of Life

![Graphs showing quality of life metrics](image)
Phase 3 Study of ASCT for NDMM: Subsequent Therapy and Rate of ASCT in RVD-Alone Arm (Late ASCT)

<table>
<thead>
<tr>
<th>Subsequent therapy in patients off-protocol therapy (%)</th>
<th>RVd alone (N=279)</th>
<th>RVd + ASCT (N=276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment*</td>
<td>19.6</td>
<td>69.6</td>
</tr>
<tr>
<td>Subsequent therapy</td>
<td>n=212</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>6.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Marizom b</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Any monoclonal antibody</td>
<td>16.2</td>
<td>27.6</td>
</tr>
<tr>
<td>Darzalex (daratumumab)</td>
<td>11.3</td>
<td>21.4</td>
</tr>
<tr>
<td>Empliciti (elotuzumab)</td>
<td>4.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Sarclisa (isatuximab)</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

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

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

Early vs Late Transplant Pros and Cons

**Pros**

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

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

**Cons**

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

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

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

Emerging data suggests patients with an extremely good response (that is, CR and ideally minimal residual disease negative) to induction therapy may have a long PFS. Studies are ongoing to determine whether these patients require ASCT.

What is maintenance therapy?

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

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

Maintenance Therapy

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

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

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

*Results from interim analyses of TOURMALINE MM3 and MM4 trials of ixazomib in the maintenance setting suggest a potential decrease in overall survival.
**Revlimid Maintenance Therapy: Improves Depth of Response**

**Disease response**

<table>
<thead>
<tr>
<th></th>
<th>Before Maintenance</th>
<th>During/After Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD negative</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>CR</td>
<td>34</td>
<td>57</td>
</tr>
<tr>
<td>VGPR</td>
<td>57</td>
<td>40</td>
</tr>
<tr>
<td>≤PR</td>
<td>72</td>
<td>2</td>
</tr>
</tbody>
</table>

At maximal response during or after maintenance treatment with Revlimid

**Cumulative Survival**

**Revlimid Maintenance Duration**

**STAMINA Trial (BMT-CTN0702)**

- 247 pts
  - ASCT MEL 200 mg/m²
  - Auto/Rev group

- 254 pts
  - Auto/Auto group
  - MEL 200 mg/m² → REV × 3 yrs

- 257 pts
  - Auto/RVD group
  - RVD × 4 → 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

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

### Maintenance Duration

**Myeloma XI Study**

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

<table>
<thead>
<tr>
<th>Median PFS (mos)</th>
<th>At time of randomization to maintenance therapy (median follow up 44.7 mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revlimid</td>
<td>64</td>
</tr>
<tr>
<td>Observation</td>
<td>32</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.52</td>
</tr>
<tr>
<td>P Value</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*PFS benefit across all patient subgroups on Revlimid maintenance therapy: standard risk; molecular high risk, which included the presence of del(17p), gain (1q), t(4;14), t(14;16), or t(14;20); MRD positive; and MRD negative.

More evidence for the benefit of longer duration of Revlimid maintenance in patients who are MRD positive than MRD negative. And evidence of ongoing benefit beyond 2–3 years for patients with both standard- and high-risk disease.

### Using MRD Negativity to Guide Discontinuation of Maintenance Therapy

**MRD2STOP Study**

- **Complete response and MRD negative by PET and NGF or NGS on at least 1 year of maintenance**
  - MRD and PET/CT negative
    - Discontinue maintenance
  - MRD and PET/CT positive
    - Continue maintenance

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

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

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

MRD negativity (at 10⁻⁸ and 10⁻⁷) is sustained even after discontinuation of maintenance therapy.

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

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

Ongoing Study Using MRD Results to Direct Therapy

Phase 3 DRAMMATIC Study

Patients post-ASCT → R → Maintenance

MRD assessment

Positive → Continued assigned therapy
Negative → Stop assigned therapy

Revlimid + Darzalex

Revlimid

Clinicaltrials.gov/ct2/show/NCT04071457.

Revlimid Maintenance: Cumulative Incidence of Second Primary Malignancies

Hematologic

Solid Tumor

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

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. High-risk patients may benefit from two-drug maintenance regimen. 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 MRD testing).
- Improve quality of life with as few treatment side effects as possible.
- Provide the longest possible period of response before first relapse.
- Prolong overall survival.
Measuring Response to Therapy

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

Myeloma cell burden

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

What is MRD?

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

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

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

How is MRD measured?

- Diagnostic
- Tumor burden
- Flow cytometry
- Next-generation DNA sequencing
Right now, measurement of MRD depends on counting cells or DNA sequences in bone marrow samples.

What about other areas of the body?

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

Comprehensive Response Assessment

Why is it important to achieve MRD negativity?

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

Probability of Progression-Free Survival

Time Since MRD Evaluation at Start of Maintenance (Months)

MRD by next-generation sequencing (sensitivity 1 x 10^-5)

MRD Negativity in the Bone Marrow is Just One Tool!

- Not as important if disease persists in blood, urine, or imaging
- MRD negativity must be sustained over time so repeated testing essential
- Prognostic value depends on
  - Treatment used: chemotherapy vs bispecifics vs transplant vs CART
  - Patient (e.g., history of MGUS/SMM, high-risk, extramedullary disease)

Need blood-based MRD testing!

MRD Is Important for Clinical Care and New Drug Registration

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

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

A surrogate for patient outcome in clinical trials

Many clinical trials are using MRD-driven strategies

Accelerate innovative trials leading to regulatory approval
MRD Summary

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

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

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

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

Relapsed/Refractory Multiple Myeloma

Tom Martin, MD
University of California, San Francisco
San Francisco, California
Multiple Myeloma Is a Marathon, Not a Sprint

![Graph showing the stages of multiple myeloma progression](image)

Definitions: What is relapsed/refractory disease and a line of therapy?

- **Relapsed**: recurrence (reappearance of disease) after a response to therapy
- **Refractory**: progression despite ongoing therapy
- **Progression**: increase in M protein/light chain values
- **Line of therapy**: change in treatment due to either progression of disease or unmanageable side effects
  - **Note**: initial (or induction) therapy + stem cell transplant + consolidation/maintenance therapy = 1 line of therapy
Biochemical Relapse or Clinical Relapse

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

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

Timing of therapy initiation/escalation dependent on many factors

Requires immediate initiation/escalation of therapy

---

Choosing Therapy for First or Second Relapse

**Choices are broadest and guided by**
- Disease biology
- Nature of relapse
- Patient preference

**Factors to consider**
- Prior autologous stem cell transplant
- Prior therapies
- Aggressiveness of relapse
- Comorbidities
- Psychosocial issues
- Access to care
Options for Relapsed/Refractory Disease Continue to Increase

<table>
<thead>
<tr>
<th>MIds</th>
<th>Proteasome inhibitors</th>
<th>Chemotherapy anthracyclines</th>
<th>Chemotherapy alkylators</th>
<th>Steroids</th>
<th>Other mechanisms of action</th>
<th>Monoclonal and bispecific antibodies</th>
<th>Cellular therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (thalidomide)</td>
<td>Velcade (bortezomib)</td>
<td>Adriamycin (cytotoxic)</td>
<td>Cytoxan (cyclophosphamide)</td>
<td>Dexamethasone</td>
<td>XPO40 (selinexor)</td>
<td>Empliciti (elotuzumab)</td>
<td>Abecma (idecabtagene vicleucel)</td>
</tr>
<tr>
<td>Revlimid (lenalidomide)</td>
<td>Kyprolis (carfilzomib)</td>
<td>Doxil (liposomal doxorubicin)</td>
<td>Bendamustine</td>
<td>Prednisone</td>
<td>Venolexa (venetoclax)*</td>
<td>Darzalex (daratumumab)</td>
<td>Carvykti (ciltacabtagene autoleucel)</td>
</tr>
<tr>
<td>Pomalyst (pomalidomide)</td>
<td>Ninlaro (ixazomib)</td>
<td>Melphalan</td>
<td></td>
<td></td>
<td></td>
<td>Sarcolisa (sataliximab)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Treatment Approach

**First relapse**
- Proteasome inhibitor/immunomodulatory drug/antibody-based therapy
- Any options for first relapse not tried
  - Refractory to Velcade and Revlimid
    - DKd, Isa-Kd, DPd, Elo-Pd, Isa-Pd, or KPd
  - Refractory to an IMiD but sensitive to a PI
    - DVd, SVd, Ven-Vd (for t[11;14])*

**>1 Relapse**
- Triple-class refractory
  - Approved therapies
  - Clinical trials
  - Bispecific/trispecific antibodies, cellular therapies (CAR T-cells, NK cells), CELMoDs

*D, daratumumab (Darzalex); K, carfilzomib (Kyprolis); d, dexamethasone; Isa, Isatuximab (Sarclisa); P, pomalidomide (Pomalyst); Elo, elotuzumab (Empliciti); V, bortezomib (Velcade); G, selinexor (Ixazomib); Ven, venetoclax (Venclexta); ide-cel, idecabtagene vicleucel (Abecma); cilta-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 <em>relapsed/refractory</em> myeloma as a single agent and as a triplet with Revlimid or Velcade or Kyprolis or Pomalystr plus dexamethasone</td>
</tr>
<tr>
<td>Empliciti (elotuzumab)</td>
<td>IV once a week for first 8 weeks, then every 2 weeks (or every 4 weeks with pom)</td>
<td>For <em>relapsed/refractory</em> myeloma as a triplet with Revlimid or Pomalystr and dexamethasone</td>
</tr>
<tr>
<td>Sarcdisa (isatuximab)</td>
<td>IV once a week for first 4 weeks, then every 2 weeks</td>
<td>For <em>relapsed/refractory</em> myeloma as a triplet with Pomalystr 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</td>
</tr>
<tr>
<td></td>
<td>• Weekly dosing</td>
<td>dexamethasone, and as a triplet with Revlimid or Darzalex plus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dexamethasone</td>
</tr>
<tr>
<td>Ninlaro (ixazomib)</td>
<td>Once-weekly pill</td>
<td>• For relapsed/refractory myeloma as a triplet with Revlimid and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dexamethasone</td>
</tr>
</tbody>
</table>

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

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>DRd vs Rd</td>
<td>Darzalex-Revlimid-dex</td>
<td>Darzalex-Velcade-dex</td>
<td>Darzalex-Kyprolis-dex</td>
<td>Darzalex-Pomalyst-dex</td>
</tr>
<tr>
<td>DVd vs Vd</td>
<td>Darzalex-Velcade-dex</td>
<td>Darzalex-Kyprolis-dex</td>
<td>Darzalex-Pomalyst-dex</td>
<td>Darzalex-Pomalyst-dex</td>
</tr>
<tr>
<td>DKd vs Kd</td>
<td>Darzalex-Kyprolis-dex</td>
<td>Darzalex-Pomalyst-dex</td>
<td>Darzalex-Pomalyst-dex</td>
<td>Darzalex-Pomalyst-dex</td>
</tr>
<tr>
<td>DPd vs Pd</td>
<td>Darzalex-Pomalyst-dex</td>
<td>Darzalex-Pomalyst-dex</td>
<td>Darzalex-Pomalyst-dex</td>
<td>Darzalex-Pomalyst-dex</td>
</tr>
</tbody>
</table>

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

**Clinical considerations**
- Consider for relapses from non-Revlimid–based maintenance
- DRd associated with more upper respiratory infections, low blood white cell counts, and diarrhea
- Consider for patients who are Revlimid-refractory without significant neuropathy
- DVd associated with more low blood cell counts
- Consider for 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**
- Empliciti-Revlid-dex vs Rd
- Median PFS: 10 vs 5 months
- Consider for non-Revlid refractory, frailer patients
- Empliciti-Rd associated with more infections

**ELOQUENT-3**
- Empliciti-Pomalyst-dex vs Pd
- Median PFS: 12 vs 7 months
- Consider for patients refractory to Revlimid and a proteasome inhibitor (Velcade, Kyprolis, Ninlaro)
- Sarclisa-Pd associated with severe low white blood cell counts, more dose reductions, upper respiratory infections, and diarrhea

**ICARIA-MM**
- Sarclisa-Pomalyst-dex vs Pd
- Median PFS: 10 vs 5 months
- Sarclisa-Kyprolis-dex vs Kd
- Consider for patients refractory to Revlimid and Velcade
- Sarclisa-Kd associated with higher MRD negativity rates
- Sarclisa-Kd associated with severe respiratory infections

**IKEMA**
- Sarclisa-Kd: 42 vs 21 months
- Consider for patients refractory to Revlimid and Velcade
- Sarclisa-Kd associated with severe respiratory infections

**Clinical Considerations**
- Sarclisa-Pd: 12 vs 7 months
- Sarclisa-Pomalyst-dex vs Pd
- Sarclisa-Kd: 42 vs 21 months

**Median PFS favored**
- Empliciti-Rd: 19 vs 15 months
- Empliciti-Revlimid-dex vs Rd
- Empliciti-Pomalyst-dex vs Pd
- Empliciti-Revlimid-dex vs Rd

**Sarclisa After Early or Late Relapse**

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

- 179 patients
- 123 patients

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

<table>
<thead>
<tr>
<th>IKEMA Study</th>
<th>Early relapse</th>
<th>Late relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarclisa-Kd</td>
<td>24.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Kd</td>
<td>42.7</td>
<td>21.9</td>
</tr>
<tr>
<td>Sarclisa-Kd</td>
<td>82.0</td>
<td>90.4</td>
</tr>
<tr>
<td>Kd</td>
<td>88.1</td>
<td>58.3</td>
</tr>
<tr>
<td>2VGPR rate (%)</td>
<td>67.2</td>
<td>76</td>
</tr>
<tr>
<td>MRD negativity rate (%)</td>
<td>24.6</td>
<td>37.5</td>
</tr>
<tr>
<td>MRD-negative CR rate (%)</td>
<td>18</td>
<td>13.9</td>
</tr>
</tbody>
</table>

*Data evaluated according to patients who experienced an early* vs *versus late* relapse.
Proteasome Inhibitor– and Immunomodulatory Drug–Based Regimens for Early Relapse

<table>
<thead>
<tr>
<th>OPTIMISMM</th>
<th>ASPIRE</th>
<th>TOURMALINE-MM</th>
<th>BOSTON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimens compared</td>
<td>Velcade-Pomalyst-dex (VPd) vs Vd</td>
<td>Kyprolis-Revlimid-dex (KRd) vs Rd</td>
<td>Ninlaro-Rd (IRd) vs Rd</td>
</tr>
<tr>
<td>Median PFS favored</td>
<td>VPd: 11 vs 7 months</td>
<td>KRd: 26 vs 17 months</td>
<td>IRd: 21 vs 15 months</td>
</tr>
<tr>
<td>Clinical considerations</td>
<td>Considered for relapse on Revlimid</td>
<td>KRd associated with more upper respiratory infections and high blood pressure than Rd</td>
<td>IRd an oral regimen</td>
</tr>
</tbody>
</table>

**Treatment Approach**

**First relapse**
- Proteasome inhibitor/immunomodulatory drug/antibody-based therapy
- Refractory to Velcade and Revlimid
  - DKd, Isa-Kd, DPd, Elo-Pd, Isa-Pd, or KPd
- Refractory to an IMiD but sensitive to a PI
  - Dvd, SVd, Ven-Vd (for t[11;14])

**>1 Relapse**
- Any options for first relapse not tried
- Refractory to an IMiD but sensitive to a PI or
- Approved therapies
  - Sd, ide-cel, cit-a-cel, Tecvayli, Talve, Elrexfio
- Clinical trials
  - Bispecific/trispecific antibodies, CAR T cells, CELMoDs

---

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

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

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

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

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

Currently Available Drugs for Triple-Class Refractory Myeloma

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

<table>
<thead>
<tr>
<th>XPOVIO + dexamethasone in relapsed/refractory myeloma</th>
<th>No. patients with ≥PR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>32 (28)</td>
</tr>
<tr>
<td>Previous therapies to which the disease was refractory, n (%)</td>
<td></td>
</tr>
<tr>
<td>Velcade, Kyprolis, Revlimid, Pomalyst, and Darzalex</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Kyprolis, Revlimid, Pomalyst, and Darzalex</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Velcade, Kyprolis, Pomalyst, and Darzalex</td>
<td>25 (27)</td>
</tr>
<tr>
<td>Kyprolis, Pomalyst, and Darzalex</td>
<td>31 (28)</td>
</tr>
</tbody>
</table>

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

Currently Available Drugs for Triple-Class Refractory Myeloma

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chimeric antigen receptor (CAR) T cell</td>
<td>Abecma (idecabtagene vilucel)*</td>
<td>300 to 460 × 10⁶ genetically modified autologous CAR T cells in one or more infusion bags</td>
</tr>
<tr>
<td>CAR T cell</td>
<td>Carvykti (ciltacabtagene autoleucel)†</td>
<td>0.5 to 1.0 × 10⁶ genetically modified autologous CAR T cells/kg of body weight</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>
</tr>
<tr>
<td>Bispecific antibody</td>
<td>Talvey (talquetamab)‡</td>
<td>Step-up dosing the first week then once weekly thereafter by subcutaneous injection</td>
</tr>
<tr>
<td>Bispecific antibody</td>
<td>Elrexfio (elranatamab)‡</td>
<td>Step-up dosing the first week then once weekly thereafter by subcutaneous injection</td>
</tr>
</tbody>
</table>

*Black box warning: cytokine release syndrome; neurologic toxicities; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
†Black box warning: cytokine release syndrome; neurologic toxicities; Parkinsonism and Guillain-Barré syndrome; hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS); prolonged cytopenia
‡Black box warning: cytokine release syndrome; neurologic toxicities
§Patients are hospitalized for 48 hours after administration of all step-up doses.
¶Patients are hospitalized for 48 hours after administration of first step-up dose and for 24 hours after second step-up dose.

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

CAR T-Cell Therapy

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

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

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

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

Two CAR T-cell therapies approved:
- Abecma (ide-cel)
- Carvykti (cilta-cel)
Abecma and Carvykti in Relapsed and Refractory Multiple Myeloma

**Abecma**

- ORR 73%
- 9 months average PFS

- Ide-cel (n=128)
  - PR: 7 patients
  - VGPR: 1 patient
  - CR or sCR and MRD NE: 20 patients
  - CR or sCR and MRD: 26 patients

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

- Cilt-a-cell (n=97)
  - PR: 3 patients
  - VGPR: 12.4 patients
  - sCR: 3 patients

**CAR T-Cell Journey**

**Initial consult**
- Evaluation
- Apheresis 4-6 hr
- +/- bridging chemotherapy

**Lymphodepletion**
- -5
- -4
- -3
- -2
- -1
- 0

**CAR infusion**
- 14
- 30

**Hospitalization (+/-; duration varies)**
- Patient stays close to treating facility until ~day 30

**Frequent follow-up**

**Toxicity timeline**
- CRS
- ICANS
- Infection: Bacterial, fungal, viruses
- Cytopenias: Ne, e, throm b, a, lb, ha

*Perica K et al. Biol Blood Marrow Transplant, 2018;24:1135.*
Abecma or Standard Regimens in Relapsed and Refractory Multiple Myeloma

**Progression-free survival**

- Standard regimen (Median PFS, 4.4 months)
- Abecma (Ide-cel) (Median PFS, 13.3 months)

**Treatment response**

<table>
<thead>
<tr>
<th></th>
<th>Abecma (n=254)</th>
<th>Standard regimen (n=132)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (%)*</td>
<td>71</td>
<td>42</td>
</tr>
<tr>
<td>Complete response (%)</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Best overall response (%)</td>
<td></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>30</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 Earlier Use of Relapsed/Refractory Multiple Myeloma

**CARTITUDE-4 Phase 3 Study**

- Relapsed/refractory myeloma patients with 1–3 prior lines of therapy and refractory to Revlimid
- 211 patients
- 208 patients
- Pomalyct + Velcade + dex (P/Vd) or Darzalex + Pd (D/Pd)
- Standard Arm
- Carvykti Arm

**Patients Responding (%)**

- Carvykti Arm: 68.2% (PR), 14.9% (VGPR), 8.2% (CR), 21.8% (sCR)
- Standard Arm: 67.1% (PR), 15.2% (VGPR), 6.6% (CR), 23.7% (sCR)

**Percentage of Patients Without Disease Progression (Wk 8)**

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

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

Onset 3–17 days
Duration 5–11 days
Symptoms
• Cytokine release syndrome (CRS)
• Neurotoxicity (ICANS)
• Cytopenias
• Infections

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

Evolution of CAR T-Cell Therapy

1st Generation
- Single target
- Allogeneic

2nd Generation
- Single target
- Autogeneic

3rd Generation
- Dual targets
- Healthy donor

4th Generation (Armored CARs)
- Dual targets
- Allogeneic

Improving efficacy
Improving safety
Improving access

1st Generation: GC012F (BCMA/CD19)
- Allo-CART

2nd Generation: Abecma
- Carvykti

3rd Generation: CT03A
- CT103A
- C-CAR 008
- P-BCMA-101

4th Generation: ARI-002h
- ALLO-715

100,000
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; three 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>Brexifo (elranatamab)</td>
<td>BCMA × CD3</td>
<td>Approved for use in myeloma patients</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>Talvezy (talquetamab)</td>
<td>GPRC5D × CD3</td>
<td>Approved for use in myeloma patients</td>
</tr>
<tr>
<td>Forintamig (RO8234)</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
Now Approved: Three Bispecific Antibodies!


Median duration of response 18.4 months

Tecvayli

Medietal

Median duration of response 18.4 months

Talvey

Elrexfio

Median duration of response 17.1 months

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
GPRC5D-Associated Side Effects

<table>
<thead>
<tr>
<th>Affected area</th>
<th>Symptoms and effects</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Rash, skin peeling</td>
<td>Relatively benign, not painful, self-limiting, and manageable with emollients</td>
</tr>
<tr>
<td>Nails</td>
<td>Nail thinning and loss</td>
<td>Mostly aesthetic but take time to resolve</td>
</tr>
<tr>
<td>Oral</td>
<td>Difficulty swallowing, dry mouth, taste changes</td>
<td>Can lead to weight loss; have longer duration and can affect quality of life. Most successfully managed with dose modification. Supportive measures may be used (eg, NaCl mouth rinse, artificial saliva spray, diet modification)</td>
</tr>
</tbody>
</table>

Myeloma patients respond well to treatment, and GPRC5D-associated side effects improve over time, becoming more tolerable; notable reduction in side effects is seen with dose modification.

Evolution of Bispecific Antibodies

Current Bispecific antibodies: dual targets

Future Trispecific antibodies: triple targets

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.

Questions & Answers
Supportive Care

Nancy S. Wong, RN, MSN-FNP
University of California, San Francisco
San Francisco, California

Effects of Myeloma

- Low blood counts
- Bone damage
- Decreased kidney function
Effects of Myeloma: 

**Bone Disease**

- Occurs in 85% of patients
- Weakened bone due to lesions or "holes"
- Increased levels of calcium in the blood (hypercalcemia)
- Leads to
  - Pathologic fractures
  - Spinal cord compression/collapse
  - Bone pain

Bone damage

Bone damage caused by lesion

Lesions

Bone Strengthening Agents for Myeloma Bone Disease

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

**How they work**

**Benefits**

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

**Medication types**

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

**Dosing**

**Side effects**

- Fracture of the femur
- Osteonecrosis of the jaw (ONJ)

**Recommendation:**
- Vit D and calcium supplementation
- Monitor renal function

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

*Dose adjusted for renal function
Recommendations for Reducing the Risk of ONJ and Infection

- Complete major dental work before beginning treatment for bone disease
- Practice good oral hygiene
- Schedule regular dental visits/antibiotic prophylaxis
- 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

Purpose
- Destroy myeloma cells and stop further bone destruction
- Pain control

Limitations
- Targeted and localized therapy

Risks
- Can affect bone marrow function

Pain Management Medications

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

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

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

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

- **GABA analogues (gabapentin and Lyrica)**
  - Potential for drowsiness and dizziness
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)

---

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
Main Body Systems Affected by Myeloma Treatment

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

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

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

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

Class: Immunomodulatory Drugs

**Side Effects and Management**

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

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

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

**Velcade**
- Low blood counts
- Infusion reactions

**Kyprolis**
- Infusion reactions
- Fatigue
- Upper respiratory tract infection

**Ninlaro**
- PN occurs less often when subcutaneous or once weekly dosing is used for Velcade
- Other interventions
  - 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

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

**Darzalex**
- 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.
Side Effects of Steroids (Dexamethasone)

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

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

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

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

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

Chimeric Antigen Receptor T Cell (CAR T)

- Cytokine release syndrome (CRS)
- Neurotoxicity/ICANS
- Low blood counts
- Infection risk

How CAR T-cell therapy is used to treat cancer:

1. Healthcare providers collect blood to obtain T-cells.
2. T-cells are separated and removed.
3. T-cells are genetically altered to have special receptors called chimeric antigen receptors (CAR).
4. New CAR T-cells are introduced into bloodstream.
5. Chemotherapy is given before CAR T-cell therapy.
6. Millions of CAR T-cells are given.
Bispecific Antibodies:
New Drug Class in Multiple Myeloma

- Cytokine release syndrome (CRS)
- Neurotoxicity/ICANS
- Infection risk
- GPRC5D target: oral, skin, nail toxicities

Interventions
- Step-up dosing
- Premedications and prophylactic medications
- Acetaminophen, tocilizumab, dexamethasone
- Supportive care (oral, skin, and nail care)
- Patient wallet card

Bispecific Antibody Therapies:
Risk of Infections

- Both viral and bacterial
  - Up to ⅓ of patients in clinical trials have serious infections (requiring IV antibodies or hospitalization)
  - Oral prophylactic antimicrobials; IVIG

- Increased risk of serious COVID complications despite history of vaccination
  - Immediate treatment with nirmatrelvir with ritonavir (Paxlovid) or alternative for patients with severe renal impairment
    - Start as soon as possible; must begin within 5 days of when symptoms start
Infection Prevention

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

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

Symptom Management:
Constipation vs. Diarrhea

**Constipation**
- Stimulants:
  - Senna/sennoside (Senokot)
    - 1–2 pills twice a day
  - Bisacodyl (Dulcolax)
- Osmotics: gentle, pulls water into the intestine
  - Lactulose
  - Miralax
- Bulking agents
  - Soluble fiber: psyllium (Metamucil)
- Dried prunes, prune juice

**Diarrhea**
- Loperamide (Imodium)
- Diphenoxylate/atropine (Lomotil)
- Cholestyramine (Questran, Prevalite)
- Tincture of opium
- BRAT diet
Symptom Management: 
**Acid Reflux/Heartburn**

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

**A few ways to treat**

1. Decrease the amount of acid the stomach is making
   a) Famotidine (Pepcid)
   b) Prilosec, Prevacid, Protonix, Nexium
2. Absorb excess acid: Tums, Maalox, Mylanta
3. Coat stomach: Carafate
4. Lifestyle and dietary changes

---

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, breathing exercises
  - Counseling support
- Medications: useful but with potential side effects
  - Lorazepam (Ativan)
  - Zolpidem (Ambien)
  - Trazodone
  - Diphenhydramine (Benadryl)
Daily Living

**Proper nutrition**

**Exercise**

**Rest**

**Social contacts**

---

**Taking Care of Yourself**

- Talk to your provider about side effects... there is usually a way to make treatment tolerable.
- Pay attention to your own needs and don't be afraid to ask for help.
- Learn more about multiple myeloma.
- Look for the positive.
Patient Experience

Multiple Myeloma
Precursor Conditions

Sagar Lonial, MD
Winship Cancer Institute of Emory University
Atlanta, Georgia
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.

Blood, Urine, Bone Marrow, and Imaging Tests Used to Identify MGUS, SMM, or Active Multiple Myeloma

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

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

Risk of Progression to Myeloma From a Precursor Condition

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

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

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

Patients with two or more risk factors are considered high risk. This model does not include any biological or immune factors that may account for interpatient heterogeneity.
Personalized Progression Prediction in Patients With MGUS or SMM (PANGEA)

A new model to assess risk of progression using accessible, time-varying biomarkers

Biomarkers tested include monoclonal protein concentration, free light chain ratio, age, creatinine concentration, and bone marrow plasma cell percentage + hemoglobin trajectories.

Improves prediction of progression from SMM to multiple myeloma compared with the 20/2/20 model

Can we identify everyone who has a precursor condition?
Studies Focusing on Myeloma Precursor Conditions

Large ongoing precursor studies

Iceland

iStopMM
Iceland Screen, Treats or Prevents Multiple Myeloma

Focus: role of population screening

United States and Canada

TRANSFORMM
study

Focus: racial disparities and familial aggregation

United States

Focus: genomic markers of progression

Prevalence of MGUS and SMM

iStopMM Study

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

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

3,358 individuals with MGUS

SMM\(^1\)

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

MGUS\(^2-4\)

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

*Based on the 2020/20 risk stratification model where three risk factors are associated with progression to active myeloma: (1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow.

High Prevalence of Monoclonal Gammopathy in a Population at Risk

The PROMISE Study

7,622 individuals screened*

6,305 patients

1,317 patients

High-risk features for myeloma

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

Blacks (n=2,439)

NEGATIVE family history of HM (n=631)

NEGATIVE family history of HM (n=686)

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

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

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

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

*Free light chains detected by mass spectrometry.

Rates of all monoclonal gammopathies' increase with age

MGUS more prevalent in individuals older than 50 years at risk

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

*Free light chains detected by mass spectrometry.

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

Preventing Evolution of Gammopathies to Prevent Myeloma

Antigen-mediated regulation in monoclonal gammopathy

Microbial/environmental triggers?

SMM, to treat or not?

Delaying symptomatic progression
Maintain/increase quality of life by treating early
Possibility of cure?

Selection of resistant clone?
Toxicity
Costs of treatment
Overtreatment
Overview of Current Treatment Approach

**MGUS**
- Close monitoring (observation)

**SMM**
- Close monitoring (observation)

Clinical trial participation should be considered

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

**Immunologic therapy**
(control approach)
- Len, Len/Dex, Dara

**Intensive therapy**
(curative intent)
- IRD, KRD, ERD

- CESAR, ASCENT, PRISM

**Pros**
- Fewer side effects
- More likely to induce long-term effects
- High ORR
- Deep responses

**Cons**
- Low OR
- Does not eliminate the clone
- Toxicity similar to myeloma treatment
- May result in resistant clones
Early Therapeutic Intervention

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


**QuiRedex Phase 3 Trial**

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


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

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


Revlimid vs Observation Alone in Patients With SMM

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

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

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

**Mayo 2008: PCBM ≥10% + MC ≥3 g/dL**
**Mayo 2018: 2/20/20**

**Phase 3 PFS by Mayo 2018 Risk Criteria**

**High risk**

**Intermediate risk**

**Low risk**
Phase 2 Trial of Darzalex for Intermediate- and High-Risk SMM Patients

**CENTAURUS Study**

<table>
<thead>
<tr>
<th></th>
<th>Short</th>
<th>Intermediate</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS including extension (months)</td>
<td>74.1</td>
<td>84.4</td>
<td>Not reached</td>
</tr>
<tr>
<td>84-month OS rate (%)</td>
<td>88.1</td>
<td>89.5</td>
<td>81.3</td>
</tr>
<tr>
<td>Overall response rate (%)</td>
<td>37.5</td>
<td>53.7</td>
<td>58.5</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>20.0</td>
<td>24.4</td>
<td>29.3</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>72.7</td>
<td>83.4</td>
<td>Not reached</td>
</tr>
<tr>
<td>Grade 3/4 adverse events (%)</td>
<td>15.0</td>
<td>41.5</td>
<td>65.0</td>
</tr>
<tr>
<td>≥1 reasonably related to D</td>
<td>5.0</td>
<td>2.4</td>
<td>12.2</td>
</tr>
<tr>
<td>Discontinued treatment due to adverse events (%)</td>
<td>5.0</td>
<td>2.4</td>
<td>7.3</td>
</tr>
<tr>
<td>≥1 reasonably related to D</td>
<td>2.5</td>
<td>0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

41 patients

- Short
  - Dose once a week for 1 cycle
  - Median follow-up ~7 years

- Intermediate
  - Dose once a week for 1 cycle then every other week for 2 cycles then every month for 4 cycles then every other month for 13 cycles + optional extension
  - Median follow-up ~7 years

- Intense
  - Dose once a week for 1 cycle then every other month for 19 cycles + optional extension
  - Median follow-up ~7 years

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

**NCI Study**

High-risk* SMM patients

- 8 cycles of combination therapy
- Kyprolis + Revlimid + dex (KRd)
- 2 years of maintenance

54 patients

*According to the Mayo and/or Spanish models.

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

The median sustained MRD duration was 5.5 years.

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

Very encouraging results for a curative approach to high-risk SMM.
### Multicenter, Open-Label, Phase 2 Trial of Kyprolis-Revlimid-dex for High-Risk SMM Patients

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

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

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

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


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

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

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

- Grade ≥3 hematologic toxicity in 18% of patients; non-hematologic toxicity in 51% of patients.
- 89.9% of patients are progression-free at 3 years.

*Based on the 2020/20 risk stratification model where three risk factors are associated with progression to active myeloma:
(1) M protein levels, (2) free light chain ratio, and (3) the number of plasma cells in the bone marrow; or a total score of ≥9 on IMWG scoring system.
Immuno-PRISM (PRecision Intervention Smoldering Myeloma): A Randomized Phase 2 Platform Study of Select Immunotherapies for High-Risk Smoldering Myeloma (DFCI 22-154)

Inclusion criteria
High-risk SMM defined as having one of the following two criteria:
1. High risk per "20-2-20" Criteria defined as presence of any two of the following:
   - Serum M spike ≥ 2 g/dL
   - Involved to uninvolved free light chain (FLC) ratio ≥ 20
   - Bone marrow PC% ≥ 20%
   OR total score of 9 using the following scoring system:
     - FLC ratio: > 10–25 = 2, > 25–40 = 3, > 40 = 5
     - Serum M protein (g/dL): > 1.5–3 = 3, > 3 = 4
     - BMPC%: > 15–20 = 2, > 20–30 = 3, > 30–40 = 5, > 40 = 6
     - FISH abnormality t(4;14), t(14;16), 1q gain, or del13q = 2
2. Presence of ≥ 10% BMPC and at least one of the following:
   - Evolving pattern
   - Abnormal PC immunophenotype (≥ 95% of BMPCs are clonal) and reduction of ≥ 1 uninvolved immunoglobulin isotype. (Only IgG; IgA and IgM will be considered)
   - High-risk cytogenetics defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain

Primary end point
- CR rate
Secondary end point
- Safety
- MRD status at 10^-6
- ORR
- TTP and PFS
- Clonal evolution

High-risk SMM

Revlimid and dexamethasone
Max 24 cycles

Tecvayli
Max 24 cycles

TBD

Primary end point
- CR rate
Secondary end point
- Safety
- MRD status at 10^-6
- ORR
- TTP and PFS
- Clonal evolution

Tecvayli dosing
Cycle 1
- Step-up dose: days 1 and 3
- Treatment dose: days 8, 15, 22
Cycle 2
- Tecvayli (subcutaneous): Days 1, 8, 15 and 22
Cycle 3-24
- Tecvayli (subcutaneous): Days 1 and 15

Is the malignant evolution in myeloma more like solid tumors and real estate? Location, location, location!

Spatial regulation of immune infiltration and tumor growth in malignant transformation

Ports of entry
- Spatial regulation of immune infiltration and tumor growth in malignant transformation

Robinson, Villa, Zhodapkar. Under review
Summary

- Precursor plasma cell disorders are characterized by the presence of abnormal clonal plasma cells without any end organ damage.
- MGUS is a common condition; prevalence increases with age.
- There is variable risk of progression from MGUS and SMM to overt myeloma; clinical risk models associated with risk of progression. We are still lacking molecular markers.
- Screening efforts are under way.
- Single arm study data show benefit with early intervention.
- Patients with high-risk SMM should be offered treatment on clinical trials.

Participation in observational/interventional studies is key to finding out which patients can benefit the most from early treatment and what is the best treatment to offer early. To identify molecular markers of progression vs stable disease.

Clinical Studies

Ajai Chari, MD
University of California, San Francisco
San Francisco, California
Goal of Clinical Studies: Making Progress Against Myeloma

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

- Develop treatments and strategies to potentially lengthen lives
  - Improve the way we use currently available drugs and regimens
  - Develop new medications
- Increase the understanding of the disease
  - Identify rational selection of existing drugs

Impact of Clinical Trials in Myeloma: Dramatic Improvements in Survival

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

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


Chemotherapy

Steroid

Proteasome inhibitor

Monoclonal antibody

Transplant

Bone support

Cellular therapy

Conventional Trial Design
New Drug Development

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

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

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

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

---

Traditional Clinical Study Types

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatment dose</th>
<th>Number of patients</th>
<th>Questions answered*</th>
</tr>
</thead>
</table>
| Phase 1 | 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? |
| Phase 3 | Two different treatments | Large              | Is the treatment safe?  
Does this treatment work better than other treatments?  
Does this treatment cause fewer side effects than other treatments? |

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

<table>
<thead>
<tr>
<th>Steroids</th>
<th>Conventional Chemotherapy</th>
<th>Immunomodulatory Drugs</th>
<th>Proteasome Inhibitors</th>
<th>HDAC Inhibitor</th>
<th>Immunologic Approaches</th>
<th>XPO Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>Melphalan</td>
<td>Thalomid (thalidomide)</td>
<td>Velcade (bortezomib)</td>
<td>Farydak (panobinostat)</td>
<td>Darzalex (daratumumab; anti-CD38)</td>
<td>Xpovio (selinexor)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Pepaxto (melflufen)</td>
<td>Revlimid (lenalidomide)</td>
<td>Kyprolis (carfilzomib; low/high dose)</td>
<td>Sarcolisa (isatuximab; anti-CD38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Pomalyst (pomalidomide)</td>
<td>Ninlaro (ixazomib)</td>
<td>Blenrep (belantamab mafodotin; anti-BCMA + MMAE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxil (liposomal doxorubicin)</td>
<td></td>
<td></td>
<td>Tecvayli (teclistamab; anti-BCMA × CD3 bispecific)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOEP/D-PACE</td>
<td></td>
<td></td>
<td>Carmustine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td></td>
<td></td>
<td>Carvykti (ciltaclabtagene autoleucel; anti-BCMA CART)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Three Drugs Withdrawn From US Market

**What happened?**

All drugs were granted accelerated approval by the FDA, which requires further clinical studies to verify a drug’s clinical benefit.

**Withdrawn 2021**

- **Farydak (panobinostat)**
  - The required clinical studies were not completed within the FDA-specified time frame

- **Pepaxto (melflufen)**
  - The phase 3 OCEAN study compared Pepaxto-dex with Pomalyst-dex in patients with relapsed/refractory myeloma – OS with Pepaxto-dex was not improved vs Pomalyst-dex, which didn’t pass the regulatory hurdles to confirm the accelerated approval in the U.S.

**Withdrawn 2022**

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

OS, overall survival; PFS, progression-free survival

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

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

Umbrella/platform trials

Basket/bucket trials

Participation in a Clinical Study

Will I be treated like a guinea pig?

The Nuremberg Code
The Declaration of Helsinki
The Belmont Report

Ethics Committees and Research Boards

Three influential documents
Benefits of Clinical Trials

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

Considering Entering Clinical Trials

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

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

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

- No one is expected to be a guinea pig; research and clinical trials are under very tight supervision and standards.
- Open, clear communication between the physician and the patient is essential.

Personalized Medicine

Jeffrey L. Wolf, MD
University of California, San Francisco
San Francisco, California
Multiple Myeloma Is Not Just One Disease!

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

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

*How do we customize treatment?*

Personalized medicine

Treatment of Multiple Myeloma

**Where are we now?**

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

**What We Need**

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

IMiDs, immunomodulatory drugs; ASCT, autologous stem cell transplantation
An Example of the Importance of Personalized Medicine

<table>
<thead>
<tr>
<th></th>
<th>CoMMpass MMRF2172</th>
<th>CoMMpass MMRF2250</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td><strong>ISS stage</strong></td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td><strong>Baseline treatment</strong></td>
<td>VRD</td>
<td>VRD</td>
</tr>
<tr>
<td><strong>Cytogenetics</strong></td>
<td>t(4;14), del13</td>
<td>t(4;14), del13</td>
</tr>
<tr>
<td><strong>Time of progression</strong></td>
<td>11 months</td>
<td>36 months</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td>1.6 years</td>
<td>6.3 years</td>
</tr>
</tbody>
</table>

Other Genetic Events:
- CoMMpass MMRF2172: 1q21, del17p + TP53 mut
- CoMMpass MMRF2250: No 1q21, No 17p or TP53 mut
Actionable Alterations in MM

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

Personalized Medicine Agents Under Clinical Investigation

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

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

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

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

---

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

*Venetoclax is a Bcl-2 inhibitor*

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

---

**References**

- Venetoclax and t(11;14) paper.
Venetoclax and t(11;14)

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

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

Venetoclax especially active in t(11;14) or BCL2high MM


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

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

133 patients 130 patients

Venetoclax- dex Pomalyst- dex

P=0.001

ORR 62%
(V95% Cl: 53-70)

VenDex (n=133)

P=0.002

MRD <10^4

8% (95% Cl: 0-12)

P=0.006

MRD <10^4

0% (95% Cl: 0-3)

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

**Umbrella/platform studies**

- Myeloma patients: No specific lesion
- Molecular lesion A
- Molecular lesion B
- Molecular lesion C

**Basket/bucket studies**

- All patients with molecular lesion A:
  - Patient with myeloma
  - Patient with cancer X
  - Patient with cancer Y
  - Patient with cancer Z

---

**MyDRUG Study**

Functional high-risk patients

Profiling for alterations (NCT02884102)

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

- t(11;14)

- Cobimetinib + dex
- Abemaciclib + Dex
- Entinostat + Dex

- Daratumumab + IPd
- Cobimetinib + IPd
- Abemaciclib + IPd
- Entinostat + IPd

- *Assess single-agent activity after 2 cycles. After cycle 2, add backbone to single agent*
Precision Medicine in Myeloma: MyDRUG (NCT03732703)

Case study: Man, age 59

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

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

3rd Line
- MyDRUG

Response on MyDRUG

Genomics
- Hyperdiploid, del13q, del1p, Myc ampl.
- NRAS Q61H, 56% allelic fraction

The Road Ahead

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

- Efforts are under way to better understand the nature of the disease and to provide patients with a more personalized approach to treatment.

- Genomic sequencing and data from myeloma patients are key to identifying subtype: our goal is to help individualize treatment for better outcomes.

- Participation in clinical studies to provide bone marrow and peripheral blood is paramount.

- Personalized medicine provides the right treatment at the right time for each myeloma patient.

Questions & Answers
Thank you!
## Resources

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

## Upcoming Patient Education Events

**Save the Date**

<table>
<thead>
<tr>
<th>Program</th>
<th>Date and Time (ET)</th>
<th>Speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Equities in Multiple Myeloma</td>
<td>Wednesday, January 24, 2024 3:00 PM – 4:00 PM</td>
<td>Craig Emmitt Cole, MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amy E. Pierre, RN, MSN, ANP-BC</td>
</tr>
<tr>
<td>Bispecific Antibodies in Multiple Myeloma</td>
<td>Wednesday, February 14, 2024 2:00 PM – 3:00 PM</td>
<td>Noa Biran, MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gurbakhash Kaur, MD</td>
</tr>
</tbody>
</table>

For more information or to register, visit [https://themmrf.org/educational-resources](https://themmrf.org/educational-resources)
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.
Join the MMRF Community!

National Walk/Run Program
- Atlanta | 10.26.24
- Boston | 10.12.24
- Chicago | 9.8.24
- Dallas | 11.16.24
- Houston | 11.23.24
- Los Angeles | 8.17.24
- National Virtual | 12.14.24
- New York City | 10.5.24
- Philadelphia | 10.19.24
- San Francisco | 8.24.24
- Scottsdale | 12.7.24
- Southeast Michigan | TBD
- Tampa | TBD
- Washington D.C. | 9.28.24

Other MMRF Event Programs
- Moving Mountains for Multiple Myeloma
- Half and Full Marathons
- Bike/Road to Victories
- Create Your Own Fundraiser

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.