Opening Remarks

A. Keith Stewart, MBChB, MRCP, FRCPC, MBA
Vasek and Anna Maria Polak Professor of Cancer Research
Consultant, Division of Hematology/Oncology
Mayo Clinic
Scottsdale, Arizona

Building on Myeloma Therapy: Emerging Molecular Targets and Immunotherapeutic Approaches

8:15 AM – 8:20 AM  Community Case Part 1
  Saad Z. Usmani, MD

8:20 AM – 8:40 AM  Translating Molecular and Cytogenetic Profiles Into Precision Medicine
  Suzanne Trudel, MD

8:40 AM – 9:00 AM  Induction Therapy Options for Transplant Eligible and Ineligible Patients
  Maria-Victoria Mateos, MD, PhD

9:00 AM – 9:05 AM  Panel Discussion

9:05 AM – 9:10 AM  Community Case Part 2
  Saad Z. Usmani, MD

9:10 AM – 9:30 AM  Consolidation and Maintenance Therapy Options
  Sergio Giralt, MD

9:30 AM – 9:50 AM  Updates on Options for Relapsed/Refractory Disease
  Saad Z. Usmani, MD

9:50 AM – 9:55 AM  Panel Discussion

9:55 AM – 10:00 AM  Community Case Part 3
  Saad Z. Usmani, MD

10:00 AM – 10:20 AM  Immunotherapy
  Thomas G. Martin, III, MD

10:20 AM – 10:40 AM  New Agents in Development
  A. Keith Stewart, MBChB

10:40 AM – 10:50 AM  Community Case Revisited
  A. Keith Stewart, MBChB

10:50 AM – 11:00 AM  Question and Answer Session
**Which of the following best represents your professional role?**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>A.</td>
<td>Hematologist</td>
</tr>
<tr>
<td>B.</td>
<td>Hematologist-oncologist</td>
</tr>
<tr>
<td>C.</td>
<td>Oncologist</td>
</tr>
<tr>
<td>D.</td>
<td>RN/NP/PA</td>
</tr>
<tr>
<td>E.</td>
<td>Pharmacist</td>
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<tr>
<td>F.</td>
<td>Other health care provider</td>
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<tr>
<td>G.</td>
<td>Researcher</td>
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<tr>
<td>H.</td>
<td>Patient</td>
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<tr>
<td>I.</td>
<td>Other</td>
</tr>
</tbody>
</table>

**Which of the following best represents the professional setting in which you currently work?**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>A.</td>
<td>Academic</td>
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<tr>
<td>B.</td>
<td>Community</td>
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<td>C.</td>
<td>HMO</td>
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<td>D.</td>
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<td>Private</td>
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<td>F.</td>
<td>Other</td>
</tr>
<tr>
<td>G.</td>
<td>Does not apply to me</td>
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</table>
Where do you practice?

A. Asia and Australia
B. Canada
C. Central and South America
D. Europe and Israel
E. Middle East and Africa
F. United States
G. Rest of world
H. Texas

Community Case Part 1

Saad Usmani, MD, FACP
Director, Plasma Cell Disorders Program
Director, Clinical Research in Hematologic Malignancies
Department of Hematologic Oncology & Blood Disorders
Levine Cancer Institute
Charlotte, North Carolina
Disclosures

• **Consultant/Advisor:** Array BioPharma, Bristol-Myers Squibb, Celgene, Janssen, Onyx, an Amgen subsidiary, Sanofi, Takeda Oncology

• **Research Grant:** Array BioPharma, Janssen, Onyx, an Amgen subsidiary, Sanofi

• **Speakers Bureau:** Celgene, Onyx, an Amgen subsidiary, Takeda Oncology

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Case Study Part 1

54-year-old man presents with 6-month history of lower back pain, increasing fatigue, right rib pain.

- **Past medical history**
  - Hypertension for 5 years (controlled)
  - Right/left arthroscopic surgery

- **Past surgical history**

- **Family history**
  - Hypertension
  - Type 2 diabetes
  - No cancers

- **Social history**
  - Banker, marathon runner
  - Married
  - Two kids

- **Physical exam**
  - Pallor, right rib cage tenderness
Case Study Part 1

**CBC with differential**

- WBC (x10^3/mL): 5.3 (4–11)
- RBC (x10^6/mL): 2.9 (3.8–5.2)
- Hemoglobin (g/dL): 8.5 (13–16)
- Hematocrit (%): 26 (34–45)
- Platelets (x10^3/mL): 160 (150–400)
- Neutrophils (x10^3/mL): 2.5 (1.9–7.5)

**CMP**

- BUN (mg/dL): 17 (7–20)
- Creatinine (mg/dL): 1.5 (0.7–1.2)
- Calcium (mg/dL): 10.4 (9.4–10.2)
- Total protein (g/dL): 11.2 (6.3–8.2)
- Albumin (g/dL): 3.6 (3.5–5.0)
- Total protein (g/dL): 11.2 (6.3–8.2)
- Gamma (g/dL): 3.2 (0.5–1.9)
- M protein spike (g/dL): 4.2

**SPEP**

- Total protein (g/dL): 11.2 (6.3–8.2)
- Gamma (g/dL): 3.2 (0.5–1.9)
- M protein spike (g/dL): 4.2

**Quantitative Igs + serum immunofixation**

- IgG (mg/dL): 5,000 (700–1,600)
- IgA (mg/dL): 25 (70–400)
- IgM (mg/dL): 20 (40–230)

**FLC**

- Kappa quant FLC (mg/L): 112 (3.30–19.40)
- Lambda quant FLC (mg/L): 2 (0.5–1.6)
- Kappa/lambda quant FLC ratio: 53 (0.26–1.65)

**Protein random**

- Protein random: 80

**24-hr urine collection and UPEP**

- Total protein timed (mg/24 hr): 2010 (40–150)
- E/P albumin (%): 30
- α1 (%): 2.5
- α2 (%): 8
- β (%): 2
- γ (%): 20
- M protein spike (%): 20
- M protein spike (mg/24 hr): 420

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**Case Study Part 1**

- **Labs**
  - Normal LDH
  - Serum β2 microglobulin 6 mg/dL
- **Skeletal survey**
  - Numerous lytic lesions (skull, long bones, right 5th/6th/7th ribs, pelvis)
- **Bone marrow biopsy**
  - 70% cellularity, 80% kappa-restricted plasma cells
  - Cytogenetics normal in 20 metaphases
  - FISH positive for translocation (11;14) in 75% cells
Which one of the methodologies do you currently use most often?

A. Gene expression profiling
B. Conventional cytogenetics
C. FISH
D. Gene mutation panel
E. Flow cytometry
F. More than one method
G. None of the above

Is this patient considered eligible for stem cell transplantation?

A. Yes
B. No
C. Not sure
Which factors do you use to decide whether to consider aggressive therapy such as stem cell transplantation?

A. Age, comorbidity score  
B. Social support and insurance coverage  
C. Response to induction therapy  
D. Risk profile  
E. All of the above  
F. I don’t do transplants up front

What would be your recommendation for initial treatment?

A. Melphalan, prednisone, bortezomib (MPV)  
B. Bortezomib, thalidomide, dexamethasone (VTD)  
C. Lenalidomide + low-dose dexamethasone (Ld)  
D. Lenalidomide, bortezomib, dexamethasone (RVD)  
E. Cyclophosphamide, bortezomib, dexamethasone (CyBorD)  
F. Carfilzomib, lenalidomide, dexamethasone (KRD)  
G. Other
Does your practice routinely test for minimal residual disease (MRD) following therapy?

A. Yes
B. No
C. We soon will
D. Not sure
Disclosures

- Consultancy: Novartis
- Honoraria: Celgene, Amgen, BMS, Novartis
- Research funding: GSK, Oncoethix, Onyx, Trillium, Astellas

Objectives

- Describe oncogenic drivers in MM and their relationship to molecular subsets
- Describe their prognostic implication and integration of cytogenetics and molecular profiles with clinical data as new prognostic tools
- Describe the use of molecular profiling for precision therapeutic strategies in MM

This material serves as an educational resource only.
Multiple Myeloma: Molecular Pathogenesis

Intrinsic Genetic Background

Figure 3, page 3460

MM Karyotypes Identify Unique Molecular Subsets

Figure 1

Figure 4A, page 300
Cytogenetics: Biologically Defined Unique Clinical Subsets

**t(4;14)**
- Translocation between heavy Ig gene locus and MMSET + FGFR3
- Associated with IgA myeloma
- Immature morphology
- Tendency for less lytic bone disease, younger age

**t(11:14)**
- Translocation between heavy Ig gene locus and cyclinD1
- Associated with IgD, IgM and nonsecretory MM
- Lymphoplasmacytoid morphology and B lineage–Ag (CD20 and CD79a)

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Karyotypes and Prognostic Implications

**Figure 2A & 2B, page 2033**
Garand R, et al. t(11;14) and t(4;14) translocations correlated with mature lymphoplasmacytoid and immature morphology, respectively, in multiple myeloma. *Leukemia*. 2003 Oct;17(10):2032-2035.

**Figure 1, page 885**
Heterogeneity Within Cytogenetically-Defined Subsets

\( t(4;14) \) Subgroup


Combined Prognostic Models

Revised International Staging System (R-ISS)


Table 1

Figure 1A

Revised R-ISS and OS by Type of Treatment

Figure 3, page 2867

Gene Expression Profiling (GEP) for Risk Stratification

Figure 1, page 2279

**UMAS GEP70**
- Defined in patients with poor outcomes with Total Therapy 2 (TT2)
- Present in 15% of newly diagnosed patients
- High-risk signature found in all molecular subsets
- Commercially available

**Considerations:**
- No standardized high risk GEP signature (UAMS70, EMC-92 and IFM)
- Perception that they are not reproducible
- Difficult to interpret

Shaughnessy JD et al. Blood. 2007;109(27):
Technological Advances in Detecting Biomarkers in MM

Figure 1, page 811


NGS Studies Identify Recurrent Mutations in Key Cellular Pathways

Figure 1B, page 93


**Mutations accumulate in key pathways:**
- MAPK signaling
- NFκB signaling
- Cell cycle
- Chromatin-modifying
- RNA processing
NGS Studies Identify Recurrent Mutations in Key Cellular Pathways

Figure 1B, page 93


What are the clinical implications?

Impact of Mutations on Myeloma Survival

*Analysis of MRC XI Trial (IMiD-based Phase 3 in NDMM)*

Figure 3


Figure 4D & 4F

Impact on Survival of CCND1 Mutations on Whole Cohort and Among t(11;14) Patients

Figure 7B, 7D & 7F

- Significantly mutated genes occur within cytogenetic subgroups
- Mutations and cytogenetic abnormalities interact to define more homogeneous prognostic groups

Survival Analysis and Cumulative Negative Impact of NGS-Defined Molecular Abnormalities

Figure 5A, 5B, 5C & 5E
Prognostic Implications of Molecular and Cytogenetic Profiles

- MM is a heterogeneous disease even within cytogenetically defined molecular subtypes
- GEP and/or combined prognostic models demonstrate improved prognostic power and identify patients with poor outcome in the era of novel agents
- NGS identifies important prognostic molecular abnormalities
- Question remains on how do we customize treatment?

Subset Analysis of Patients With t(4;14)
Improved Results With Integration of BTZ (Induction, Consolidation or Maintenance) and Use of Tandem Transplant

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Induction/Adjuvant</th>
<th># ASCT</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tbody>
<tr>
<td>Chang 2004</td>
<td>16</td>
<td>VAD or dex</td>
<td>1</td>
<td>-</td>
<td>± Thal</td>
<td>9.9</td>
<td>18.8</td>
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<tr>
<td>Moreau 2007</td>
<td>100</td>
<td>VAD</td>
<td>2</td>
<td>-</td>
<td>± Thal</td>
<td>21 (EFS)</td>
<td>41.4</td>
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<tr>
<td>Avet-Loiseau 2010</td>
<td>106</td>
<td>BD vs VAD</td>
<td>1 or 2</td>
<td>± Len ~ 30%</td>
<td>± Len</td>
<td>28 vs 16 (EFS)</td>
<td>63% vs 32% (4 yrs), non-t(4;14) 50%</td>
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<tr>
<td>Cavo 2010</td>
<td>55</td>
<td>VTD vs TD</td>
<td>2</td>
<td>VTD vs TD</td>
<td>Dex</td>
<td>66% vs 20% (3 yr), non-t(4;14) 61%</td>
<td>NA</td>
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<tr>
<td>Sonneveld 2015</td>
<td>50</td>
<td>PAD vs VAD</td>
<td>2</td>
<td>-</td>
<td>BTZ vs Thal</td>
<td>16 vs 8% (9 yrs)</td>
<td>52% vs 33% (5 yrs), non-t(4;14) 70%</td>
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<tr>
<td>Avet-Loiseau 2010</td>
<td>65</td>
<td>BD vs VAD</td>
<td>1 or 2</td>
<td>Len</td>
<td>Len vs placebo (randomization)</td>
<td>27 vs 15</td>
<td>NA</td>
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</table>

Building on Myeloma Therapy: Emerging Molecular Targets and Immunotherapeutic Approaches
ASH 2015

Subset Analysis of Patients With del(17p)
Improved Outcome With Aggressive Multi-Combination Treatment That Includes BTZ and Prolonged Therapy

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>N</th>
<th>Induction</th>
<th># ASCT</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>PFS (months)</th>
<th>OS (months)</th>
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<tr>
<td>Chang 2004†</td>
<td>10</td>
<td>VAD or Dex</td>
<td>1</td>
<td>—</td>
<td>± Thal</td>
<td>7.9</td>
<td>14.7</td>
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<tr>
<td>Shaughnessy 2009‡ Low-risk group GEP</td>
<td>35</td>
<td>VAD ± Thal</td>
<td>2</td>
<td>DPACE × 4 ± Thal</td>
<td>± Thal</td>
<td>31% (4 yr EFS)</td>
<td>55% (4 yrs)</td>
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<tr>
<td>Shaughnessy 2009‡ Low-risk group GEP</td>
<td>42</td>
<td>VTDPACE × 2 Thal-Dex × 2</td>
<td>2</td>
<td>VTDPACE × 2 Thal-Dex × 2</td>
<td>VTD × 1 yr Thal-Dex × 2 yrs</td>
<td>81% (4 yr EFS)</td>
<td>81% (4 yrs)</td>
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<tr>
<td>Avet-Loiseau 2010§</td>
<td>35</td>
<td>BD vs VAD</td>
<td>1 or 2</td>
<td>± Len ≥ 30%</td>
<td>± Len</td>
<td>14 mo P=0.32 (EFS)</td>
<td>50% (4 yrs) P=0.49, non-del(17p) 79%</td>
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<tr>
<td>Sonneveld 2015</td>
<td>37</td>
<td>PAD vs VAD</td>
<td>2</td>
<td>—</td>
<td>Bz vs Thal</td>
<td>32 vs 5% (5 yrs), morph. responses, 26% vs 22%, P=0.02</td>
<td>65 vs 5% (5 yrs), morph. responses, 26% vs 22%, P=0.02</td>
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<tr>
<td>Avet-Loiseau 2015</td>
<td>32</td>
<td>BD or VAD</td>
<td>1 or 2</td>
<td>Len</td>
<td>Len vs placebo (randomization)</td>
<td>29 vs 14</td>
<td>NA</td>
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</table>

Risk Stratification in Myeloma
How do we customize treatment?

- **t(4;14) and del(17p) MM**
  - Need to better define the high-risk t(4;14) and 17p
  - New treatment approaches required (eg, immune-based approaches, use of epigenetic modulators, targeted therapies)

- **Targeted therapies being designed**
  - TKIs, monoclonal antibody, EZH2 inhibitors for t(4;14)
  - Nutlins, PRIMA-1, and PARP inhibitors for del 17p
**Molecular Profiling for Precision Therapeutic Strategies in MM**

**BRAFi have now been validated clinically in MM**

**MM Genomics Initiative (MMGI) FINDING:**
BRAF V600E (4%); confirmed in CoMMpass
Preclinical validation of BRAFi

**CLINICAL VALIDATION:**
Treatment with vemurafenib,
Morgan G, ASH 2012;
Andrulis M et al. Cancer Discov 2013

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**The MMRF CoMMpass Study**
*Accelerating the Path to Precision Medicine*

- Unreached multiple myeloma n=1,000
- BM + PB collected
- IMID-based regimen
- Proteasome-based regimen
- IMID + proteasome-based regimen
- Relapse 1, 2, 3, …
- n=800
- BM + PB collected

- Clinical parameters collected every 3 months for a minimum of 8 years
- Assays
  - Flow cytometry
  - Molecular profiling (whole genome, exome, transcriptome)
  - NGS MRD
“Actionable” Alterations in MM

MMRF CoMMpass and other efforts have identified “actionable” molecular alterations in about 60% of relapsed myeloma patients.

- KRAS and NRAS (40%)
- CDKN2C and CCND1 (18%)
- PI3K-AKT (5%)
- FGFR3 (5%)
- IGF1R and ALK (5%)
- PI3K-AKT (5%)
- MyD88 (3%)
- Others (11%)

Auclair D, unpublished data.

Selected Academic Molecular Screening Programs

<table>
<thead>
<tr>
<th>Program</th>
<th>Number of Genes</th>
<th>Tumor Types</th>
<th>Tissue</th>
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</thead>
<tbody>
<tr>
<td>MSKCC (IMPACT)</td>
<td>347</td>
<td>All</td>
<td>Archival</td>
</tr>
<tr>
<td>Dana Farber (PROFILE)</td>
<td>305 (OncoPanel)</td>
<td>All</td>
<td>Archival</td>
</tr>
<tr>
<td>EORTC (SPECTA)</td>
<td>~360</td>
<td>Disease specific</td>
<td>Archival</td>
</tr>
<tr>
<td>UCSF (Genomic Medicine)</td>
<td>500 (UCSF 500)</td>
<td>All</td>
<td>Archival</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>50–200</td>
<td>All</td>
<td>Archival</td>
</tr>
<tr>
<td>Princess Margaret (IMPACT/COMPACT)</td>
<td>~550</td>
<td>All</td>
<td>Archival or fresh</td>
</tr>
<tr>
<td>Mayo (MM panel) MP3</td>
<td>~88 (including chromosomal abnormalities)</td>
<td>Myeloma</td>
<td>Fresh</td>
</tr>
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</table>

Cell-Free DNA Provides Access to the Tumor Genome
An alternative to bone marrow aspirates?


Ultra-Deep, Full-Length Sequencing of cfDNA is Feasible and a Powerful Tool for Molecular Profiling of MM Patients

Trudel S, unpublished data.
Conclusions

- Risk stratification should include combination of ISS (β2M and albumin), LDH, and chromosomal abnormalities: del(17p), t(4;14), t(14;16), and 1q21 by FISH or GEP
- Prognostic implications are now impacting treatment decisions (use of BTZ, tandem transplant, prolonged treatment)
- NGS studies have uncovered novel prognostic biomarkers and actionable mutations and has the potential to replace iFISH
- With the right small-molecule therapeutic tools we should be able to therapeutically manipulate the key deregulated pathways (eg, clinical data now supports the strategy of targeting MAPK signaling)

Induction Therapy Options for Transplant-Eligible and -Ineligible Patients

María-Victoria Mateos, MD, PhD
Consultant Physician
Haematology Department
University Hospital of Salamanca
Salamanca, Spain
Disclosures

- María-Victoria Mateos, MD, PhD, has disclosed the following relevant financial relationships:
  - Janssen, Celgene, Takeda, Amgen, BMS, Novartis

- Dr. Mateos will discuss the unlabeled or investigational use of a commercial product.

Main Objectives for NDMM Patients

A. Cure
B. Prolong overall survival (OS)
C. Prolong progression-free survival (PFS)
D. Maintain quality of life
E. Prolong PFS, OS, and ensure good quality of life
Maximal Eradication of Tumor Clone Through Achievement of Best Possible Response

Figure 2, page 532

Main Objectives for NDMM Patients

A. Cure
B. Prolong OS
C. Prolong PFS
D. Maintain quality of life
E. Prolong PFS, OS, and ensure good quality of life
Main Objectives for NDMM Patients

A. Cure
B. Prolong OS
C. Prolong PFS
D. Maintain quality of life
E. Prolong PFS, OS, and ensure good quality of life

Does quality of the response predict final outcome?

Impact of MRD Detected by Flow Cytometry on Clinical Outcomes

Figure 4A & 4B, page 2544

**Flow-MRD Monitoring in Large Clinical Trials**

*The GEM/PETHEMA Experience*

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**Figure 1C & 1D, page 688**


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**Flow-MRD negativity in favorable biology MM to predict “operational cure”**

- **MGUS-like + MRD negative**
  - Median: 3y
  - P<0.001
- **MM-like + MRD negative**
  - Median: 6y
  - P<0.001
- **MM-like + MRD positive**
  - Median: 10y
- **MM-like + MRD negative**
  - Median: NR (79%, 10y)
- **MM-like + MRD positive**
  - Median: 9y
  - Median: 5.5y
  - P<0.001

8 cycles of CRd → lenalidomide (2-year)

Figure 3B & 3C, page 752


- MRD testing was clinically feasible in 55 of 56 (98%) patient samples by MFC (1 patient sample was not processed due to equipment breakdown)
- NGS assay at MRD was technically successful in 45 of 56 (80%) patient samples (8 with undetectable clonotypes; 3 without available sample)

**Important Aim of Treatment**

- CR should be an important objective in this patient
- Achievement of high-quality, sustained CR balanced with acceptable toxicity can translate into an “operational cure”

*Does imaging assessment matter in this young patient with bone disease?*
Impact of Post-ASCT PET-CT Negativity on Clinical Outcomes

Figure 3, page 5994


Important Aim of Treatment

- CR should be an important objective in this patient
- Achievement of high-quality, sustained CR balanced with acceptable toxicity can translate into an “operational cure”*

*What is the best option of therapy for this patient?*
54-Year-Old Man With Newly Diagnosed MM IgGκ: Anemia, Hypercalcemia, and Bone Lesions

What is the option of therapy proposed?

A. **Induction** + ASCT + consolidation + maintenance
B. **Induction** + consolidation and maintenance
C. **Induction** + ASCT
D. **Induction** + ASCT + maintenance

Is there something better than VAD or thalidomide/dexamethasone?

Modified from Figure 2, page 5438

Bortezomib-Based vs Nonbortezomib-Based Induction: A Meta-Analysis of Phase 3 Randomized, Controlled Trials (2,086 pts)

Bz-based induction results in significant improvements in PFS/OS compared with nonbortezomib-based induction.

Bortezomib/Thalidomide-Based Induction Regimens

<table>
<thead>
<tr>
<th>Induction Regimen</th>
<th>Number of Cycles</th>
<th>Phase</th>
<th>Study Details</th>
<th>Response Postinduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTD vs TD¹</td>
<td>3</td>
<td>3</td>
<td>VTD vs TD as induction and consolidation</td>
<td>CR = 5, VGPR = 28</td>
</tr>
<tr>
<td>VTD vs TD²</td>
<td>6</td>
<td>3</td>
<td>VBMCP/VBAD vs V vs TD vs VTD induction + α-FN, thalidomide, or thalidomide/bortezomib maintenance</td>
<td>CR = 14, VGPR = 29</td>
</tr>
<tr>
<td>VTD vs VD³</td>
<td>4</td>
<td>3</td>
<td>Comparison of induction regimens</td>
<td>CR = 13, VGPR = 49*</td>
</tr>
</tbody>
</table>

*P value statistically significant

VTD, bortezomib-thalidomide-dexamethasone; TD, thalidomide- dexamethasone; VBMCP, vincristine-BCNU-melphalan-cyclophosphamide-prednisone; VBAD, vincristine-BCNU-adriamycin- dexamethasone.

### Bortezomib/Lenalidomide-Based Induction Regimens

<table>
<thead>
<tr>
<th>Induction Regimen</th>
<th>Cycles</th>
<th>Study Details</th>
<th>CR</th>
<th>≥VGPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD(^1)</td>
<td>Up to 8</td>
<td>Phase 1/2: up to 8 cycles VRD</td>
<td>29</td>
<td>67</td>
</tr>
<tr>
<td>RVD(^2)</td>
<td>3</td>
<td>Phase 2: VRD induction and consolidation, len maintenance</td>
<td>23</td>
<td>58</td>
</tr>
</tbody>
</table>


What is the value of the alkylator as part of the induction in young NDMM patients?
## Retrospective, Case-Matched Analysis: VTD vs VCD Induction

Patients enrolled in GIMEMA MMY-3006 study and EMN-02 study

<table>
<thead>
<tr>
<th></th>
<th>VTD (n=236)</th>
<th>VCD (n=236)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response to induction therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>19%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>64%</td>
<td>37%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>93%</td>
<td>81%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade 3–4 hematological AE</td>
<td>2%</td>
<td>8%</td>
<td>0.003</td>
</tr>
<tr>
<td>Any grade 3–4 PN</td>
<td>7%</td>
<td>2%</td>
<td>0.009</td>
</tr>
</tbody>
</table>

No difference between regimens in terms of efficiency to mobilize PBSC.

AE, adverse event; PN, peripheral neuropathy; PBSC, peripheral blood stem cell.  Cavo M et al. Leukemia. 2015;Oct 7 [Epub ahead of print].

---

What has been the value of addition a fourth drug for induction in young NDMM patients so far?
Building on Myeloma Therapy: Emerging Molecular Targets and Immunotherapeutic Approaches
ASH 2015

### Is the Alkylator Necessary as Part of the Induction?

*Phase 2 Randomized European Trial*

<table>
<thead>
<tr>
<th>Response, %</th>
<th>VTD (N=49)</th>
<th>VTDCy (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR (%)</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>Post ASCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/nCR (%)</td>
<td>85</td>
<td>77</td>
</tr>
<tr>
<td>MRD negative (%)</td>
<td>35</td>
<td>27</td>
</tr>
<tr>
<td>3-y OS (%)</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>G3–4 AEs/SAEs (%)</td>
<td>47/22</td>
<td>57/41</td>
</tr>
</tbody>
</table>

The addition of the alkylator as fourth drug does not add any significant benefit

SAE, serious adverse events.


### EVOLUTION Trial: Three- and Four-Drug Combinations for NDMM Patients

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>VDCR (n=40)</th>
<th>VDR (n=41)</th>
<th>VDC (n=32)</th>
<th>VDC-mod (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>2 (5)</td>
<td>3 (7)</td>
<td>1 (3)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>sCR</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td>0</td>
<td>2 (12)</td>
</tr>
<tr>
<td>VGPR</td>
<td>11 (26)</td>
<td>10 (24)</td>
<td>3 (9)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>13 (33)</td>
<td>13 (32)</td>
<td>4 (13)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>≥ nCR</td>
<td>4 (10)</td>
<td>3 (7)</td>
<td>1 (3)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>32 (80)</td>
<td>30 (73)</td>
<td>20 (63)</td>
<td>14 (82)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients categorized as VGPR include those who have no measurable M-protein but have not yet had bone marrow assessments to confirm CR/nCR status.

No substantial advantage was observed in four- vs three-drug combinations.

What about the second-generation proteasome inhibitors?

Carfilzomib + Thal + Dex (KTd): Responses

<table>
<thead>
<tr>
<th>Dosing Level of Carfilzomib</th>
<th>20/27 mg/m²</th>
<th>20/36 mg/m²</th>
<th>20/45 mg/m²</th>
<th>All pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts, n</td>
<td>50</td>
<td>20</td>
<td>21</td>
<td>91</td>
</tr>
<tr>
<td>Response induction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>20</td>
<td>30</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>56</td>
<td>85</td>
<td>81</td>
<td>68</td>
</tr>
<tr>
<td>HDM (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>28</td>
<td>40</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>64</td>
<td>90</td>
<td>90</td>
<td>76</td>
</tr>
<tr>
<td>Response consolidation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>58</td>
<td>70</td>
<td>67</td>
<td>63</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>86</td>
<td>90</td>
<td>95</td>
<td>89</td>
</tr>
</tbody>
</table>

3-year PFS was 72%

HDM, high-dose melphalan.

Phase 2: KRd (Carfilzomib, Lenalidomide, Dexamethasone) in NDMM Patients

N: 53 patients

<table>
<thead>
<tr>
<th></th>
<th>Post-Induction</th>
<th>Post-Transplant</th>
<th>Post-Consolidation</th>
<th>Post-KRd</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ PR (%)</td>
<td>98</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>≥ VGPR (%)</td>
<td>78</td>
<td>97</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>≥ nCR (%)</td>
<td>14</td>
<td>44</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>sCR (%)</td>
<td>10</td>
<td>25</td>
<td>70</td>
<td>86</td>
</tr>
</tbody>
</table>

• At the end of 8 cycles, 15/17 evaluable pts (88%) MRD-negative
• Median follow-up 9.7 months: all pts alive; 52 of 53 progression free

Weekly Oral Ixazomib + Lenalidomide and Dexamethasone in Previously Untreated MM: Response

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Phase 1 (n=15)</th>
<th>Phase 2 (n=49)</th>
<th>Total (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥PR)</td>
<td>15 (100)</td>
<td>44 (90)</td>
<td>59 (92)</td>
</tr>
<tr>
<td>CR</td>
<td>5 (33)</td>
<td>12 (24)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>sCR</td>
<td>2 (13)</td>
<td>5 (10)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>VGPR</td>
<td>3 (20)</td>
<td>17 (35)</td>
<td>20 (31)</td>
</tr>
<tr>
<td>nCR</td>
<td>1 (7)</td>
<td>4 (8)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>8 (53)</td>
<td>29 (59)</td>
<td>37 (58)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (47)</td>
<td>15 (31)</td>
<td>22 (34)</td>
</tr>
</tbody>
</table>

• 14 patients were evaluated for MRD
  - 7 patients achieved CR at the time of assessment
  - All 7 were MRD negative
  - 9 patients achieved VGPR or better at the time of assessment
  - 8/9 were MRD negative


What about the addition of “a different fourth drug” in the near future?

Daratumumab + Bortezomib-Thalidomide-Dex
Elotuzumab + Bortezomib-Lenalidomide-Dex

- Dara-bortezomib (sc)-thalidomide-dexamethasone (VTD)$^1$
  - 100% ORR
  - Daratumumab does not appear to have a negative effect on stem cell mobilization

- Phase 3 study is ongoing
  - VTD + daratumumab (induction, MMY3006/IFM-HOVON-CASSIOPEIA)

- Elo-bortezomib (sc)-lenalidomide-dexamethasone (VRD)$^2$
  - The addition of Elo is feasible with no major additive adverse events


*In high-risk patients
GEM2005MAS65: VMP/VTP→VT/VP
Impact of Response in the Whole Series of Patients (n=260)

Figure 3A & 3B, page 1891

GEM2005MAS65: VMP/VTP→VT/VP
Impact of Flow-CR in the Whole Series After Induction (n=153)

Modified from Figure 3C & 3D, page 1891
New Standards of Care for Elderly MM Patients

**Alkylator-based regimens**
- MP
- VMP

Six randomized trials: benefit in PFS & OS...6 m

**Alkylator-free regimens**
- IMiDs
- Len-dex

One randomized trial: benefit in PFS & OS

One randomized trial: benefit in PFS & OS vs MPT

MP + Bortezomib (VMP) vs MP: VISTA

*Bortezomib Twice a Week × 4 Cycles + Weekly × 5 Cycles*

---

**Figure 1**

**Figure 2, page 451**
### Modified-VISTA Schemes: Weekly Bortezomib

<table>
<thead>
<tr>
<th>Study Details</th>
<th>Grade 3/4 GI Toxicity (%)</th>
<th>Grade 3/4 Peripheral Neuropathy (%)</th>
<th>ORR (%)</th>
<th>CR (%)</th>
<th>PFS (mos)</th>
<th>OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VISTA²: VMP</td>
<td>20</td>
<td>14</td>
<td>71</td>
<td>30</td>
<td>21</td>
<td>56</td>
</tr>
<tr>
<td>Bortezomib twice weekly (5+4 cycles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETHEMA/GEM²: VMP</td>
<td>7</td>
<td>7</td>
<td>80</td>
<td>20</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bortezomib once weekly except 1st cycle (6 cycles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIMEMA⁴: VMP</td>
<td>—</td>
<td>5</td>
<td>81</td>
<td>24</td>
<td>25</td>
<td>54</td>
</tr>
<tr>
<td>Bortezomib once weekly (8 cycles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Further optimization was done through *subcutaneous* administration.²

---

### FIRST Trial: Study Design

<table>
<thead>
<tr>
<th>Arm A Rd Continuous</th>
<th>LEN + LoDEX Continuously¹</th>
<th>LENALIDOMIDE 25 mg D1-21/28</th>
<th>LoDEX 40 mg D1,8,15 &amp; 22/28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B Rd18</td>
<td>LEN + LoDEX 18 Cycles¹ (72 wks)</td>
<td>LENALIDOMIDE 25 mg D1-21/28</td>
<td>LoDEX 40 mg D1,8,15 &amp; 22/28</td>
</tr>
<tr>
<td>Arm C MPT</td>
<td>MEL + PRED + THAL 12 Cycles²³ (72 wks)</td>
<td>MELPHALAN 0.25 mg/kg D1-4/2</td>
<td>PREDNISONE 2 mg/kg D1-4/24</td>
</tr>
</tbody>
</table>

**Patients >75 yrs:** LoDEX 20 mg D1, 8, 15, 22/28; THAL 100 mg D1–42/42; MEL 0.2 mg/kg D1–4.

**All patients received thromboprophylaxis.**

**Stratification: age, country, and ISS stage**

**AMT, antimonyeloma therapy; ISS, International Staging System; LEN, lenalidomide; LoDEX, low-dose dexamethasone; LT, long-term; MEL, melphalan; PD, progressive disease; PRED, prednisone; THAL, thalidomide.**

FIRST Trial: Progression-Free Survival & Overall Survival

Figure 1A & 1B, page 912

Elderly MM Patients Are a Heterogeneous Group

Moderately fit: Not regularly active but routinely walking

Very fit: Active, exercise regularly

Severely frail: Dependent on other people

Mildly frail: Need help for household tasks

Moderately frail: Need partial help for personal care

Vulnerable: Can perform limited activities; don’t need help

Optimization of the Treatment

Elderly patients with myeloma are a very heterogeneous population.

Activity of Daily Living, Instrumental Activity of Daily Living, Charlson Comorbidity Score, Freiburg Comorb Index, GAH scale...

- We need a simple and time-efficient tool to evaluate the status of patients
  - Age
  - Comorbidities
  - Cognitive condition
  - Physical condition


Options for Elderly Patients

Fit
Unfit
Frail

Alkylator-based comb
Alkylator-free comb

VMP
CyBorD
VTP
RVD
Rd until DP

Bz biweekly the 1st cycle and weekly thereafter; Bz SQ
Thal doses up to 200 mg
Len full doses
Cy at 500 mg/m² days 1, 8, 15
Melph full doses
Dex low doses: 40 mg weekly

This material serves as an educational resource only.
VMP/Rd: GEM/Pethema GEM2010 Trial

231 symptomatic newly diagnosed MM patients >65 years

**Sequential scheme**

- **VMP × 9 cycles**
- **Lendex × 9 cycles**

**Alternating scheme***

Both schemes were equivalent in terms of efficacy and safety:
- ORR of 77% and 80%, respectively
- CR rate of 42% and 40%, respectively

---

VMP/RD According to the Age (65–80 vs ≥80 yrs)

**Median f/u: 37 m (3 yrs)**

- **PFS**
  - <80 yrs: 33 m
  - ≥80 yrs: 24 m
  - \( P < 0.01 \)

- **OS**
  - <80 yrs: 80% at 3 yrs
  - ≥80 yrs: 30 m
  - \( P < 0.0001 \)

---

**Options for Elderly Patients**

**Fit**
- Alkylator-based comb
  - VMP
  - CyBorD

**Unfit**
- Alkylator-free comb
  - VTP/Vd
  - RVD x9c
  - Ld until DP

**Frail**
- Bz weekly since the beginning; Bz SQ
- Thal doses not superior to 100 mg
- Len 25 mg daily in Ld, but 15 mg in RVD
- Cy 300 mg/m² days 1, 8, 15
- Melph reduced doses: 6–7 mg/m²
- Dex reduced doses: 20 mg weekly

**Options for Elderly Patients**

**Fit**
- Alkylator-based comb
  - CyTP
  - CyBorP
  - VMP lite

**Unfit**
- Alkylator-free comb
  - VP
  - Ld until DP

**Frail**
- Bz weekly since the first cycle; Bz SQ
- Thal doses not superior 50 mg
- Len dose of 10–15 mg
- Cy dose of 50 mg daily
- Melph reduced doses
- Prednisone instead of dex
What about the second-generation proteasome inhibitors?

Second-Generation Proteasome Inhibitors in Elderly Newly Diagnosed MM Patients: Carfilzomib & Ixazomib

<table>
<thead>
<tr>
<th></th>
<th>Carf-MP¹ Phase 1/2</th>
<th>Carf-Cydex² Phase 2</th>
<th>Carf-Rd³ Phase 1/2</th>
<th>I-Rd⁴ Phase 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>50</td>
<td>58</td>
<td>23 ≥65 years</td>
<td>65 (34 ≥65 years)</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>90</td>
<td>95</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>58 (12% CR)</td>
<td>71 (49% nCR, 20% sCR)</td>
<td>91 (≥ nCR 87%, sCR 85%)</td>
<td>60 (sCR/CR 24%)</td>
</tr>
<tr>
<td>Safety profile</td>
<td>G3: PN: 1%</td>
<td>No PN</td>
<td>G3–4: PN 13%</td>
<td>G3–4: PN 6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(all grades 1/2)</td>
<td>Skin rash 17%</td>
</tr>
<tr>
<td>Phase 3</td>
<td>KMP vs VMP</td>
<td>–</td>
<td>Carf-Rd vs Rd</td>
<td>IRd vs Rd</td>
</tr>
</tbody>
</table>

Carf-Cydex has been also evaluated with carfilzomib weekly.

What will be the addition of “a different fourth drug” in the near future?

- Bortezomib (sc)-melphalan and prednisone (VMP) + dara
  - 100% ORR
- Phase 3 studies are ongoing
  - VMP +/- Daratumumab (Alcyone trial)
  - Rd +/- Daratumumab (Maia trial)
  - Rd +/- Elotuzumab (Eloquent-1 trial): completed recruitment

Conclusions

- **Highest quality of the response (inside/outside BM) should be the goal for all MM patients**
- **PI-based combinations plus IMiDs will be the standard of care as induction for NDMM patients, plus the addition of mAbs**
- **Number of cycles undecided:**
  - 4–6 for trx-eligible
  - Fixed vs continuous for non-trx eligible
- **Dose adjustments** should be considered based on age and comorbidities to enable optimal delivery of effective therapy
- **Numerous planned/ongoing studies addressing questions of optimal regimen, schedule, treatment duration...to optimize and individualize induction therapy**

Panel Discussion
Community Case Part 2

Case Study Part 2

- Induction chemotherapy: RVd × 4 cycles
  - Aspirin and acyclovir prophylaxis
- Bone health: bisphosphonates every month
- Best response: VGPR by IMWG criteria
- Relevant events during induction
  - Grade II peripheral neuropathy after cycle #2
    - Started on gabapentin, symptoms controlled
  - Increasing lower back pain during cycle #3
    - L3 compression fracture, undergoes kyphoplasty with near complete resolution of back pain
Based on the patient’s response to induction therapy, you collect stem cells. What would you consider next?

A. Continue current regimen  
B. Wait to transplant after relapse  
C. Proceed to transplant  
D. Provide consolidation therapy

Case Study Part 2

- Transplant eligible  
- Collects 13.5 million CD34 cells/kg BW in six bags  
- Mel-200 ASCT with 4.2 million CD34 cells/kg BW in two bags  
- Transplant course: grade 3 diarrhea, resolved by Day +28  
- Restaging post-ASCT  
  - M spike 0  
  - Normal k/l ratio  
  - BM biopsy shows no clonal PCs and normal hematopoiesis  
  - sCR by IMWG criteria  
- Patient comes to discuss maintenance
Is now an appropriate time for MRD testing?

A. Yes
B. No
C. Not sure

Do you recommend maintenance?

A. Yes
B. No
C. Not sure
Would the MRD result affect your decision to use maintenance therapy?

A. Yes
B. No
C. Not sure

Which maintenance treatment do you recommend?

A. Lenalidomide
B. Bortezomib
C. Lenalidomide, bortezomib
D. Thalidomide
E. Prednisone
F. Clinical trial
G. I don’t use maintenance
Would your maintenance choice change if the patient had low-risk cytogenetics?

A. Yes
B. No
C. Not sure

High-Dose Therapy and Hematopoietic Cell Transplantation: Current Status in Myeloma

Sergio A. Giralt, MD
Melvin Berlin Family Chair in Myeloma Research
Professor of Medicine
Weill Cornell Medical College
Chief, Adult Bone Marrow Transplant Service
Division of Hematologic Oncology
Department of Medicine
Memorial Sloan Kettering Cancer Center
New York, New York
Disclosures

• **Consultant/Advisor:** Celgene, Jazz Pharmaceuticals, Onyx Pharmaceuticals, an Amgen subsidiary, Sanofi, Takeda Oncology

• **Research Grant:** Celgene, Sanofi, Takeda Oncology

Rationale for High-Dose Therapy

![Graph showing the rationale for high-dose therapy.](image)

- 100% Cures
- Dose
- Lethal bone marrow toxicity
- Lethal toxicity to other organs
Transplant Eligible vs Transplant Ineligible

**Transplant ineligible**
- Poor performance status
  - Elderly and frail
  - Unable to perform activities of daily living
  - Decompensated comorbidity
    - Congestive heart failure (CHF)
    - Uncontrolled diabetes
    - Unstable angina
- Socioeconomic factors
  - Lack of caregiver
  - Distance from transplant center
  - Inability to comply with peritransplant follow-up care
- Patient choice
- Very low–risk disease
  - Asymptomatic myeloma
  - Solitary plasmacytoma
- AGE PER SE SHOULD NOT BE CONSIDERED AN ABSOLUTE CONTRAINDIcation FOR STEM CELL COLLECTION AND TRANSPLANTATION

**Transplant eligible**
- Good performance status
- Adequate organ function
  - Compensated comorbidities
    - No active CHF
    - Patients with renal failure stable on dialysis are appropriate candidates
    - No active uncontrolled infections
    - No acute bleeding or recent thromboembolic events
- Socioeconomic factors
  - Adequate caregivers
  - Adequate support for transport to and from transplant center
  - Ability to comply with peritransplant follow-up care
- Willing to proceed
Case Studies

Case 1
- 55-year-old woman presents with asymptomatic anemia of 10 gm/dL and total serum protein 10 gm/L
- Workup reveals
  - 30% plasma cells
  - Cytogenetic diploid
  - IgA kappa peak of 3.2
  - β2M of 3.0
- Receives 4 cycles of Bz/Thal/Dex
- Achieves stringent CR

Case 2
- 55-year-old woman presents with asymptomatic anemia of 10 gm/dL and total serum protein 10 gm/L
- Workup reveals
  - 30% plasma cells
  - Cytogenetic t(4;14)
  - IgA kappa peak of 3.2
  - β2M of 3.0
- Receives 4 cycles of Bz/Thal/Dex
- Paraprotein peak stays at 2.8 gm/dl

Timing of HCT
- What are the issues?
  - Early vs late
  - After fixed number of cycles
    - 4–6, 8–10?
  - After a defined response
    - VGPR?
    - Plateau?
    - What about the nonresponder?
- NO RANDOMIZED TRIALS BEING PERFORMED
Effect of Pre-transplant Salvage Therapy Prior to Autologous Transplant (AHCT) in Patients Not Responding to Initial Induction for Multiple Myeloma (MM)

CIBMTR Study MM06-04

Methods

Salvage chemotherapy

Autologous transplant

No salvage cohort

Autologous transplant

< PR to induction

Diagnosis and initial induction

12 months from diagnosis to AHCT

AHCT

Outcomes With/Without Pre-AHCT Salvage


Study Design
Age ≤65

- 2 phase 3 trials comparing Mel 200-ASCT vs CC+R

GIMEMA MM-RV-209
Rd induction (N=402)

EMN-441
Rd induction (N=389)

Mel200-ASCT
N=268
Rd-Mel200
Rd-Mel200-R
Rd-Mel200-RP

CC+R
N=261
Rd-MPR-R
Rd-MPR
Rd-CRD-R
Rd-CRD-RP

Mel200-ASCT vs CC+R: PFS1
Median Follow-Up From Randomization: 4 Years

PFS1: from random to first progression
- First line
- Second line
- Subsequent lines
- Death

Median PFS1
- Mel200-ASCT: 41 months
- CC+R: 26 months

HR 0.55 (95% CI 0.45–0.69) P < 0.0001

Mel200-ASCT
CC+R

Mel200-ASCT vs CC+R: Second-Line Therapy

- Only 57% of patients relapsing from CC+R actually received ASCT
- Most of the patients who received ASCT at first relapse were re-induced with bortezomib (66% in Mel200-ASCT and 84% in CC+R)

Mel200-ASCT vs CC+R: OS
Median Follow-Up From Randomization: 4 Years

OS: from random to death

<table>
<thead>
<tr>
<th>First line</th>
<th>Second line</th>
<th>Subsequent lines</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-year OS</td>
<td>Mel200-ASCT</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC+R</td>
<td>71%</td>
<td></td>
</tr>
</tbody>
</table>

- OS: 4-year survival
- Mel200-ASCT: 84%
- CC+R: 71%

HR 0.59 (95% CI 0.40–0.87) P=0.008

**Mel200-ASCT vs CC+R OS Subgroup Analysis**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60</td>
<td>0.67 (0.41–1.11)</td>
<td>0.117</td>
</tr>
<tr>
<td>Age ≥60</td>
<td>0.44 (0.23–0.86)</td>
<td>0.015</td>
</tr>
<tr>
<td>KPS 60%–70%</td>
<td>0.76 (0.33–1.72)</td>
<td>0.506</td>
</tr>
<tr>
<td>KPS 80%–100%</td>
<td>0.54 (0.34–0.85)</td>
<td>0.008</td>
</tr>
<tr>
<td>ISS I/II</td>
<td>0.55 (0.34–0.89)</td>
<td>0.016</td>
</tr>
<tr>
<td>ISS III</td>
<td>0.75 (0.38–1.45)</td>
<td>0.376</td>
</tr>
<tr>
<td>No del17, t(4;14), t(14;16)</td>
<td>0.57 (0.34–0.94)</td>
<td>0.029</td>
</tr>
<tr>
<td>Del17, t(4;14), t(14;16)</td>
<td>0.60 (0.31–1.14)</td>
<td>0.118</td>
</tr>
<tr>
<td>LDH &lt; ULN</td>
<td>0.62 (0.41–0.95)</td>
<td>0.027</td>
</tr>
<tr>
<td>LDH ≥ ULN</td>
<td>0.23 (0.03–1.92)</td>
<td>0.177</td>
</tr>
</tbody>
</table>

Design of European Phase 3 Studies

**IFM 2005-1**
VD ± DCEP → ASCT1 ± ASCT2 → Len maintenance
VAD ± DCEP → ASCT1 ± ASCT2 → Len maintenance

**HOVON-65/GMMG-HD4**
PAD → ASCT1 ± ASCT2 → Bort maintenance
VAD → ASCT1 ± ASCT2 → Thal maintenance

**GIMEMA MM-BO2005**
VTD → ASCT1 + ASCT2 → + VTD cons. → Dex maintenance
TD → ASCT1 + ASCT2 → + TD cons. → Dex maintenance

**PETHEMA GEM05MNOS65**
VTD → ASCT1 → VT
TD → ASCT1 → Thal
CHT + Bort → ASCT1 → IFN


**Multivariate Analysis of Prognostic Factors for PFS**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFS</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt; CR at induction</td>
<td>1.80</td>
<td>1.29–2.51</td>
</tr>
<tr>
<td>Del(17p) and/or t(4;14)</td>
<td>1.56</td>
<td>1.18–2.05</td>
</tr>
<tr>
<td>ISS &gt;2</td>
<td>1.57</td>
<td>1.14–2.17</td>
</tr>
<tr>
<td>Plts &lt;150 (10^9/L)</td>
<td>1.48</td>
<td>1.05–2.08</td>
</tr>
<tr>
<td>Hb &lt;10.5 (g/dL)</td>
<td>1.32</td>
<td>1.03–1.70</td>
</tr>
<tr>
<td>Del(13q)</td>
<td>1.20</td>
<td>0.94–1.54</td>
</tr>
<tr>
<td>IgA isotype</td>
<td>1.13</td>
<td>0.85–1.50</td>
</tr>
<tr>
<td>Creat &gt;1.2 (mg/dL)</td>
<td>0.87</td>
<td>0.64–1.19</td>
</tr>
</tbody>
</table>

## Score System Definition

**(Assessable Pts = 606)**

<table>
<thead>
<tr>
<th>Score Group</th>
<th>ISS</th>
<th>Cytogenetic Abnormalities</th>
<th>Response at Induction</th>
<th># of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1–2</td>
<td>Del(17p) – t(4;14)-</td>
<td>CR</td>
<td>77 (12.71%)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Presence of a single adverse variable</td>
<td></td>
<td>369 (60.88%)</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>Del(17p) – t(4;14)-</td>
<td>&lt; CR</td>
<td>330 (54.45%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Del(17p) – t(4;14)-</td>
<td>CR</td>
<td>22 (3.63%)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Presence of 2 out of 3 adverse variables</td>
<td></td>
<td>141 (23.27%)</td>
</tr>
<tr>
<td></td>
<td>1–2</td>
<td>Del(17p) ± t(4;14)</td>
<td>&lt; CR</td>
<td>70 (11.55%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Del(17p) – t(4;14)-</td>
<td>&lt; CR</td>
<td>65 (10.73%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Del(17p) ± t(4;14)</td>
<td>CR</td>
<td>6 (0.99%)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Del(17p) ± t(4;14)</td>
<td>&lt; CR</td>
<td>19 (3.14%)</td>
</tr>
</tbody>
</table>


## PFS According to Score Groups

Kaplan-Meier survival estimates

Log-rank test: score 0 vs 1 \( P=0.0546 \)

\( P<0.0001 \) score 1 vs 2 \( P=0.0001 \)

trend \( P=0.0001 \) score 2 vs 3 \( P=0.0103 \)

What is the role of consolidation?

PFS According to Preplanned Number of ASCT(s)

Kaplan-Meier survival estimates

Log-rank test: $P<0.0005$

HR 0.72 (0.60–0.87) $P<0.001$

### PFS According to Preplanned ASCT(s) for Pts With del(17p) and/or t(4;14) and Who Failed CR After B-based Induction Regimens

<table>
<thead>
<tr>
<th>Score</th>
<th>ISS</th>
<th>Cytogenetic Abnormalities</th>
<th>Response at Induction</th>
<th># of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1-2</td>
<td>Del(17p) ± t(4;14)</td>
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<td>141 (23.27%)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Del(17p) ± t(4;14)</td>
<td>&lt; CR</td>
<td>70 (11.55%)</td>
</tr>
</tbody>
</table>


### OS According to Preplanned ASCT(s) for Pts With del(17p) and/or t(4;14) and Who Failed CR After B-based Induction Regimens

<table>
<thead>
<tr>
<th>Score</th>
<th>ISS</th>
<th>Cytogenetic Abnormalities</th>
<th>Response at Induction</th>
<th># of Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1-2</td>
<td>Del(17p) ± t(4;14)</td>
<td>&lt; CR</td>
<td>141 (23.27%)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Del(17p) ± t(4;14)</td>
<td>&lt; CR</td>
<td>70 (11.55%)</td>
</tr>
</tbody>
</table>

Building on Myeloma Therapy: Emerging Molecular Targets and Immunotherapeutic Approaches
ASH 2015

BMT CTN 0702: SCHEMA

Register and randomize
MEL 200 mg/m²
VRD × 4
MEL 200 mg/m²
Lenalidomide maintenance†
Lenalidomide maintenance

*Bortezomib 1.3 mg/m² days 1, 4, 8, 11
Lenalidomide 15 mg days 1–15
Dexamethasone 40 mg days 1, 8, 15
†Lenalidomide 15 mg daily × 3 years


IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT Candidates)

Randomize, stratification ISS & FISH

Induction
CY (3g/m²) MOBILIZATION
Goal: 5 x 10⁶ cells/kg
Melphalan 200 mg/m² + ASCT
VRD × 2
Lenalidomide 12 mos

Collection

Consolidation

Maintenance

SCT at relapse
MEL 200 mg/m² if <65 yrs,
≥65 yrs 140 mg/m²

What is the role of maintenance?

Phase 3 IFM 2005-02: Lenalidomide as Consolidation/Maintenance Post-ASCT

Consolidation

- Lenalidomide: 25 mg/d Days 1–21/month 2 months
- Lenalidomide: 10–15 mg/d until relapse
- Placebo until relapse

First-line ASCT <65 years

- ≤6 months
- No PD

N=614

Primary end point: PFS

Phase 3 IFM 2005-02: PFS According to Response Preconsolidation

- PR or SD: 
P \leq 10^{-5}

- VGPR or CR: 
P = 0.001

HR 0.37 (CI 95% 0.25–0.58)

HR 0.54 (CI 95% 0.37–0.78)


CALGB 100104 Schema

Registration

Stage 1–3, <70 years
Therapy at least 2 cycles
Stable disease or better
≤1 year from Rx initiation
2 \times 10^6 \text{CD34 cells/kg}

Mel 200
ASCT

CR
PR
SD

Restaging Days 90–100

Placebo

Lenalidomide 10 mg/d with ↑↓ (5–15 mg)

Stratification based on diagnostic β2M and IMiD use during Induction

Figure S2e, supplement to:

Figure 2A & 2B, page 1776
**Impact of Response on Outcome: OS After 1 or 2 Transplants**

IFM 99 trials courtesy of JL Harousseau.

**Making Transplant Easier**
Symptoms, Toxicities, and Cytokines

Global Mean Symptom Severity

Global Mean (log) Cytokine

Mean MDASI Severity

IL-6

Symptoms

Does high-dose therapy and transplant cure myeloma?

Long-term disease control is possible, and some patients may never have to deal with their disease again... Are they cured?
**Natural History of CR on Myeloma Outcomes**

**Role for HDT in CR Patients**

- Primary → CR (24)
- Median 14 yrs
- CR → CR (31)
- Median 16 yrs
- PR → CR (79)

**Percent Living vs Years of Treatment**

- >4 years (44)
- 2–4 years (42)
- <2 years (56)

**AHCT as Initial Therapy**

- Cohort 1
- Cohort 1
- Cohort 1
- Cohort 1

CR Definition Does Matter With Regards to Depth of Remission

![Figure 1](figure1.png)


In My Humble Opinion

- High-dose melphalan is one of the most active agents in myeloma today
  - 30%–40% CR
  - 24 months median remission duration without maintenance
  - Name another agent with similar single-agent activity
  - It is also cost-effective
- With stem cell support it can be given safely to older patients with comorbidities
- Thus, not planning for its use up front is similar to telling a patient, “I am never going to use bortezomib or lenalidomide during your disease course because I don’t like it or I don’t believe in it”
- Early or late or once, twice, or more times, it remains an active agent that can be extremely effective in all stages of the patient’s disease journey
- Continued exploration in clinical trials is essential
Updates on Options for Relapsed/Refractory Disease

Saad Usmani, MD, FACP
Director, Plasma Cell Disorders Program
Director, Clinical Research in Hematologic Malignancies
Department of Hematologic Oncology & Blood Disorders
Levine Cancer Institute
Charlotte, North Carolina

Outline

• Practical considerations in choosing therapy for relapsed and/or refractory MM
• New options for relapsed MM (1–3 prior therapies)
• Role of transplant in relapsed and/or refractory MM
When to Consider Retreatment in Relapsed/Refractory MM

- Nature of relapse/progression
  - Slow/biochemical vs rapid/high burden
  - Renal failure, sPCL, EMD, bone fractures, cytogenetic abnormalities
- Host factors
  - Age, comorbidities, performance status, organ failure
- Prior therapies/treatment-related factors
  - Tolerability, dose reductions, adverse events (AEs)/serious adverse events (SAEs)
  - Duration of therapy and durability of previous response
- Socioeconomic aspects
  - Insurance issues, access to care, adequate social support
- Availability of clinical trials

Treatment Approaches in Relapsed/Refractory MM

Figure 1, page S72

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**ASPIRE Study Design**

- **Randomization**
  - N=792
- **Stratification:**
  - β2 microglobulin
  - Prior bortezomib
  - Prior lenalidomide

**KRd**
- Carfilzomib 27 mg/m² IV (10 min)
- Days 1, 2, 8, 9, 15, 16 (20 mg/m² Days 1, 2, cycle 1 only)
- Lenalidomide 25 mg Days 1–21
- Dexamethasone 40 mg Days 1, 8, 15, 22

**After cycle 12, carfilzomib given on Days 1, 2, 15, 16**
**After cycle 18, carfilzomib discontinued**

**Rd**
- Lenalidomide 25 mg Days 1–21
- Dexamethasone 40 mg Days 1, 8, 15, 22

**LEN NÀÏVE OR LEN SENSITIVE**

**ASPIRE Results**

<table>
<thead>
<tr>
<th></th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>26.3</td>
<td>17.6</td>
<td>0.69</td>
<td>0.0001</td>
</tr>
<tr>
<td>24-mo OS, %</td>
<td>73.3</td>
<td>65</td>
<td>0.79</td>
<td>0.04</td>
</tr>
<tr>
<td>≥CR, %</td>
<td>31.8</td>
<td>9.3</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>15.3</td>
<td>17.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AEs, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 cardiac failure</td>
<td>3.8</td>
<td>1.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥G3 ischemic heart disease</td>
<td>3.3</td>
<td>2.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥G3 hypertension</td>
<td>4.3</td>
<td>1.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥G3 acute renal failure</td>
<td>3.3</td>
<td>3.1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

No benefit observed in patients who were previously non-responsive to bortezomib and refractory to immunomodulatory agent.

ELOQUENT-2 Study Design

**Key inclusion criteria**
- RRMM
- 1–3 prior lines of therapy
- Prior Len exposure permitted in 10% of study population (patients not refractory to Len)

**Elo + Len/Dex (E-Rd) schedule (n=321)**
- **Elo (10 mg/kg IV):** Cycle 1 and 2: weekly; Cycles 3+: every other week
- **Len (25 mg PO):** days 1–21
- **Dex:** weekly equivalent, 40 mg

**Len/Dex (Rd) schedule (n=325)**
- **Len (25 mg PO):** days 1–21;
- **Dex:** 40 mg PO days 1, 8, 15, 22

**Assessment**
- Tumor response: every 4 weeks until progressive disease
- Survival: every 12 weeks after disease progression

**End points:**
- Co-primary: PFS and overall response rate (ORR)
- Other: OS (data not yet mature); duration of response, quality of life, safety
- All patients received premedication to mitigate infusion reactions prior to Elo administration

Repeat every 28 days

**ELOQUENT-2 Results**

<table>
<thead>
<tr>
<th></th>
<th>E-Rd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>19.4</td>
<td>14.9</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ORR, %</td>
<td>79</td>
<td>66</td>
<td>—</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥VGPR, %</td>
<td>33</td>
<td>28</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AEs, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 cardiac failure</td>
<td>4</td>
<td>6</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>≥G3 acute renal failure</td>
<td>4</td>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

No benefit observed in patients who were previously exposed to immunomodulatory agent.

Patients with del17p, 1q21 amplifications, and t(4;14) fared as well as standard risk.
TOURMALINE-MM1 Study Design

28-day cycles

Randomization
N=722
Stratification:
  • Number of prior therapies
  • PI exposure
  • ISS stage

IRd
Ixazomib 4 mg Days 1, 8, 15
Lenalidomide 25 mg Days 1–21
Dexamethasone 40 mg Days 1, 8, 15, 22

Rd
Lenalidomide 25 mg Days 1–21
Dexamethasone 40 mg Days 1, 8, 15, 22

LEN NAÏVE OR LEN SENSITIVE


TOURMALINE-MM1 Results

<table>
<thead>
<tr>
<th></th>
<th>I-Rd (n=360)</th>
<th>Rd (n=362)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>20.6</td>
<td>14.7</td>
<td>0.742</td>
<td>0.012</td>
</tr>
<tr>
<td>ORR, %</td>
<td>78.3</td>
<td>71.5</td>
<td>–</td>
<td>0.035</td>
</tr>
<tr>
<td>≥VGPR, %</td>
<td>48.1</td>
<td>39.0</td>
<td>–</td>
<td>0.014</td>
</tr>
<tr>
<td>AEg, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 Diarrhea</td>
<td>6</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥G3 PN</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Benefit with IRd was also noted in pts with high-risk cytogenetics.

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ENDEAVOR Study Design

**Kd**
- **Carfilzomib 56 mg/m² IV**
- **Days 1, 2, 8, 9, 15, 16 (20 mg/m² Days 1, 2, cycle 1 only)**
- **Infusion duration: 30 minutes for all doses**
- **Dexamethasone 20 mg**
- **Days 1, 2, 8, 9, 15, 16, 22, 23**
- **28-day cycles until disease progression or unacceptable toxicity**

**Vd**
- **Bortezomib 1.3 mg/m² (3–5 second IV bolus or subcutaneous injection)**
- **Days 1, 4, 8, 11**
- **Dexamethasone 20 mg**
- **Days 1, 2, 4, 5, 8, 9, 11, 12**
- **21-day cycles until disease progression or unacceptable toxicity**

**BOR NAÏVE OR BOR SENSITIVE**

Randomization 1:1
- **N=929**

Stratification:
- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of administration

ENDEAVOR Results

<table>
<thead>
<tr>
<th></th>
<th>Kd (n=464)</th>
<th>Vd (n=465)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, mos</strong></td>
<td>18.7</td>
<td>9.4</td>
<td>0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>≥CR, %</strong></td>
<td>12.5</td>
<td>6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>≥VGPR, %</strong></td>
<td>54.3</td>
<td>28.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Discontinuation</strong></td>
<td>14.0</td>
<td>15.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AEs, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 Hypertension</td>
<td>8.9</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 Dyspnea</td>
<td>5.6</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 Cardiac failure</td>
<td>4.8</td>
<td>1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 Acute renal failure</td>
<td>4.1</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G2 PN</td>
<td>6.3</td>
<td>32.0</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

No benefit observed in patients refractory to lenalidomide
### PANORAMA1 Study Design

**Randomization**
- N=768

**Stratification:**
- Number of previous treatment lines
- Prior bortezomib

**Pano-Vd**
- Panobinostat 20 mg Days 1, 3, 5, 8, 10, 12
- Bortezomib 1.3 mg/m² Days 1, 4, 8, 11
- Dexamethasone 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12

**Vd**
- Bortezomib 1.3 mg/m² Days 1, 4, 8, 11
- Dexamethasone 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12

21-day cycles


### PANORAMA1 Results

<table>
<thead>
<tr>
<th></th>
<th>Pano-Vd (n=387)</th>
<th>Vd (n=381)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, mos</strong></td>
<td>12</td>
<td>8.1</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>60.7</td>
<td>54.6</td>
<td>-</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>≥nCR, %</strong></td>
<td>27.6</td>
<td>15.7</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>IMiD + bortezomib, mos</strong></td>
<td>10.6</td>
<td>5.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>IMiD + bortezomib + ≥2 prior lines, mos</strong></td>
<td>12.5</td>
<td>4.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>AEs, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥G3 Diarrhea</td>
<td>25</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥G3 Atenia</td>
<td>24</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥G3 PN</td>
<td>17</td>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Benefit less pronounced in women and patients > 65 years BUT more evident in patients who with previous exposure to bortezomib and immunomodulatory agent.**

## Summary of PI Combination Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>ORR Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib + lenalidomide + LoDex¹</td>
<td>2</td>
<td>84</td>
<td>69</td>
<td>4.8</td>
<td>35.7</td>
<td>28.6</td>
<td>ORR similar in bor- or len-refractory pts</td>
</tr>
<tr>
<td>Bortezomib + pomalidomide + LoDex²</td>
<td>1</td>
<td>28</td>
<td>70</td>
<td>7</td>
<td>37</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Carfilzomib + pomalidomide + dexamethasone³</td>
<td>2</td>
<td>79</td>
<td>70</td>
<td>–</td>
<td>27</td>
<td>43</td>
<td>PFS: 9.7 mos</td>
</tr>
<tr>
<td>Carfilzomib + cyclophosphamide + thalidomide + dexamethasone⁴</td>
<td>1b/2</td>
<td>64*</td>
<td>91</td>
<td>5</td>
<td>51</td>
<td>22</td>
<td>PFS 76% (24 mos)</td>
</tr>
</tbody>
</table>

¹In newly diagnosed MM

CR, complete response; MTD, maximum tolerated dose; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.


## Summary of Other Notable Combination Therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Phase (N)</th>
<th>ORR</th>
<th>CBR Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panobinostat + carfilzomib + dexamethasone¹</td>
<td>1 (36)</td>
<td>77%</td>
<td>(1 pt CR, 10 pts VGPR, 16 pts PR, 4 pts MR, 4 pts SD)</td>
</tr>
<tr>
<td>Daratumumab + lenalidomide + dexamethasone²</td>
<td>1/2 (32)</td>
<td>68%</td>
<td>–</td>
</tr>
<tr>
<td>Daratumumab + pomalidomide + dexamethasone³</td>
<td>1b (77)</td>
<td>58.5%</td>
<td>–</td>
</tr>
<tr>
<td>Ricolinostat ± bortezomib + dexamethasone⁴</td>
<td>1 (20)</td>
<td>25%  (heavily pretreated)</td>
<td>60% (2 pts VGPR, 3 pts PR, 2 pts MR, 5 pts SD)</td>
</tr>
<tr>
<td>Ricolinostat + lenalidomide + dexamethasone⁵</td>
<td>1 (22)</td>
<td>64%</td>
<td>100% (1 pt CR, 5 pts VGPR, 8 pts PR, 3 pts MR, 5 pts SD)</td>
</tr>
</tbody>
</table>

Summary of Combination Therapy

<table>
<thead>
<tr>
<th>Median Lines of Tx:</th>
<th>ORR (%)</th>
<th>Survival (MOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>60</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
<td>70</td>
</tr>
</tbody>
</table>

*Data from phase 3 trials, all others from phase 1 or 2 trials


Salvage Autologous Stem Cell Transplant

- **Option for:**
  - Patients who deferred autologous stem cell transplant for first relapse
  - ≥18 month PFS benefit from first autologous stem cell transplant
  - Special considerations: improve cytopenias and bridge to clinical trial or allogeneic stem cell transplant

Salvage Allogeneic Stem Cell Transplant

- Nonrandomized experience showing long-term disease control in some patients
- Randomized tandem auto-SCT vs auto-SCT/allo-SCT: nonrelapse mortality higher, survival similar
- Option for young, fit MM patients, BMT-CTN 1302 phase 2 trial accruing for high-risk patients

Monoclonal Antibody–Based Therapeutic Targeting of MM

- Apoptosis/growth arrest via targeting signaling pathways
- Complement-dependent cytotoxicity (CDC)
  - Lucatumumab or Dacetuzumab (CD40)
  - Elotuzumab (CS1)
  - Daratumumab (CD38)
  - XmAb®5592 (HM1.24)
- Antibody-dependent cellular cytotoxicity (ADCC)
  - Daratumumab (CD38)
  - huN901-DM1 (CD56)
  - nBT62-maytansinoid (CD138)
  - 1339 (IL-6)
  - BHQ880 (DKK1)
  - RAP-011 (activin A)
  - Daratumumab (CD38)

Tai YT, Anderson KC. Bone Marrow Res. 2011;2011:924058.
Thank you for your attention!

Panel Discussion
Community Case Part 3

Case Study Part 3

- Patient deferred Len maintenance and prefers close observation
- Traveling for new job, starts to train for half-marathon 6 months post ASCT
- Monthly CBC, CMP, SPEP, FLC; doctor visits every 2–3 months
- Successfully runs half marathon for MMRF and raises $26K 1 year after ASCT
- Returns 2 years post-ASCT with increasing shoulder pain while working out in the gym, increasing fatigue, and urinary frequency with frothiness
### Case Study Part 3

**CBC with differential**
- WBC (x10^3/mL): 4.5 (4–11)
- RBC (x10^6/mL): 3.3 (3.8–5.2)
- Hemoglobin (g/dL): 10 (13–16)
- Hematocrit (%): 31 (24–45)
- Platelets (x10^3/mL): 175 (150–400)
- Neutrophils (x10^3/mL): 3 (1.9–7.5)

**CMP**
- BUN (mg/dL): 1.8 (0.7–1.2)
- Creatinine (mg/dL): 2.4 (1.2–2.0)
- Calcium (mg/dL): 9.4 (8.4–10.2)
- Phosphate (mg/dL): 4.8 (2.7–4.5)
- Total protein (g/dL): 9.8 (6.3–8.2)
- Albumin (g/dL): 3.7 (3.5–4.5)

**SPEP**
- Gamma (g/dL): 2.8 (0.5–1.6)
- M protein spike (g/dL): 2.1

**Quantitative Igs + serum immunofixation**
- IgG (mg/dL): 2,400 (700–1,600)
- IgA (mg/dL): 75 (70–400)
- IgM (mg/dL): 45 (40–230)

**FLC**
- Kappa quant FLC (mg/L): 300 (3.30–19.40)
- Lambda quant FLC (mg/L): 0.9 (0.71–2.50)
- Kappa/lambd ratio: 600 (0.26–1.65)

**24–hr urine collection and UPEP**
- Protein random: 120
- Total protein timed (mg/24 hr): 3,200 (40–150)
- E/P albumin (%): 30
- M protein spike (%): 58
- M protein spike (mg/24 hr): 1,856

### Case Study Part 3

- **BM biopsy:**
  - 60% cellularity, 50% kappa-restricted plasma cells
  - FISH positive for translocation (11;14) in 50% cells, del17p in 20%
- He is here to discuss treatment options
What would you use for treatment of MM in first relapse?

A. Bortezomib + dexamethasone ± cyclophosphamide
B. Lenalidomide + dexamethasone
C. Pomalidomide + dexamethasone
D. Bortezomib, lenalidomide, and dexamethasone
E. Carfilzomib + dexamethasone
F. Carfilzomib + lenalidomide + dexamethasone
G. Elotuzumab + lenalidomide + dexamethasone
H. Daratumumab
What Is Immunotherapy in Myeloma?

- Passive immunity
  - Monoclonal antibodies (mAbs)/aptamers
  - Targeting a receptor
    - MM cell
    - Immune cell

- Adjuvant therapy
  - Vaccines
  - Whole-cell vaccine

- Active therapy
  - Allogeneic transplantation
  - CAR T cells
  - NK cell infusions

Disclosures

- Speakers Bureau: Millennium
mAb-Based Therapeutic Targeting of Tumor

- Elotuzumab (SLAMF7)
- Daratumumab/isatuximab (CD38)
- Lucatumumab or dacezuumab (CD40)
- Daratumumab/isatuximab (CD38)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)

Tai YT, Anderson KC. Bone Marrow Res. 2011;2011:924058.

Excitement of Monoclonal Antibodies

**Advantages**
- Novel mechanism of action
  - Additive or synergistic effects with current anti-MM drugs
- Generally well tolerated
  - Toxicity profile nonoverlapping with approved anti-MM drugs
- Can be combined with other immune therapies
- May be ideally suited to eliminate MRD
- May be beneficial in all patient groups (SMM, ND, RR, MRD)
- Many targets possible
  - MM cell
  - Microenvironment
  - Immune signals

**Disadvantages**
- Infusion reactions can limit therapy in some
- No biomarkers for response to predict who may most benefit
- Few long-term survivors
- Cost: very expensive to produce
Building on Myeloma Therapy: Emerging Molecular Targets and Immunotherapeutic Approaches
ASH 2015

Targets for mAbs in MM

- **FDA Approved**
  - Elotuzumab
  - Daratumumab

- **In clinical development**
  - Milatuzumab
  - Pembrolizumab
  - Nivolumab
  - Atezolizumab

- **Preclinical activity**
  - Siltuximab

Elotuzumab in Relapsed/Refractory Multiple Myeloma: Potential Synergy With Lenalidomide

- **Elotuzumab**
  - Humanized IgG1 mAb, binds SLAMF7
  - Induces myeloma cell killing through NK cell–mediated ADCC
  - Directly activates NK cells through binding to SLAMF7 on NK cells

- **Lenalidomide**
  - Enhances immune system through production of IL-2 to increase NK cell activity
  - Direct anti-MM effects

Elotuzumab in Relapsed/Refractory Multiple Myeloma: Clinical Synergy With Lenalidomide

- Elotuzumab in combination with lenalidomide and dexamethasone (E-Ld) demonstrated a high response rate and progression-free survival (PFS) benefits in an open-label phase 1b/2 study in patients with MM.
- Elotuzumab has FDA breakthrough therapy designation in MM.

Maximum Percent Reduction in Serum M Protein in Multiple Myeloma – Study 1703

- 10 mg/kg elotuzumab (n=36)
- 20 mg/kg elotuzumab (n=29)*

*Eight patients without measurable disease (baseline and all on-study M-protein levels <0.5 g/dL) were not included.

ELOQUENT-2 Study Design

- Open-label, international, randomized, multicenter, phase 3 trial (168 global sites)

Key inclusion criteria:
- RRMM
- 1–3 prior lines of therapy
- Prior Len exposure permitted in 10% of study population (patients not refractory to Len)

Elo + Len/Dex (E-Ld) schedule (n=321):
- Elo (10 mg/kg IV): cycle 1 and 2: weekly; cycles 3+: every other week
- Len (25 mg PO): days 1–21
- Dex: weekly equivalent, 40 mg

Len/Dex (Ld) schedule (n=325):
- Len (25 mg PO): days 1–21
- Dex: 40 mg PO days 1, 8, 15, 22

End points:
- Co-primary: PFS and overall response rate (ORR)
- Other: overall survival (data not yet mature); duration of response, quality of life, safety

All patients received premedication to mitigate infusion reactions prior to Elo administration

Assessment:
- Tumor response: every 4 weeks until progressive disease
- Survival: every 12 weeks after disease progression

Of note: ELOQUENT-1 Study: similar design in newly diagnosed MM; ongoing

ELOQUENT-2 Study
Baseline Demographics and Disease Characteristics

Table 1, page 625

ELOQUENT-2 Study Results
Co-Primary End Point: Overall Response Rate

<table>
<thead>
<tr>
<th>Response Rate (%)</th>
<th>E-Ld</th>
<th>Ld</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR*</td>
<td>79</td>
<td>66</td>
</tr>
<tr>
<td>Combined Response (sCR + CR + VGPR)</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Complete Response (sCR + CR)†</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Very Good Partial Response</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Partial Response</td>
<td>46</td>
<td>38</td>
</tr>
</tbody>
</table>

\[ p = 0.0002 \]

*Defined as partial response or better.
†Complete response rates in the E-Ld group may be underestimated due to interference from therapeutic antibody in immunofixation and serum protein electrophoresis assay.

ELOQUENT-2 Study Results

E-Ld-treated patients had a 30% reduction in the risk of disease progression or death; treatment difference at 1 and 2 years was 11% and 14%, respectively.

Figure 1A, page 626

Progression-Free Survival by Tumor Response

Patients achieving ≥PR showed improved PFS with E-Ld vs Ld alone.

ELOQUENT-2 Study Results

Progression-Free Survival According to Age

<65 years

≥65 years

Hazard ratio: 0.75
(95% CI, 0.55–1.02)

Hazard ratio: 0.65
(95% CI, 0.50–0.85)

E-Ld

Ld

40%

30%

42%

25%

Progression-Free Patients (%)

Time (months)

Progression-Free Patients (%)

Time (months)

ELOQUENT-2 Study Results

Progression-Free Survival of Patients With del(17p) and t(4;14) Translocation

del(17p)+

Hazard ratio: 0.65
(95% CI, 0.45–0.94)

E-Ld

Ld

t(4;14)+

Hazard ratio: 0.53
(95% CI, 0.29–0.95)

E-Ld

Ld

Maximal Reduction of Serum M-Component

RRMM:
Dose 4–24 mg/kg QW
ORR ~42%


Daratumumab: A Novel Anti-CD38 Monoclonal Antibody

Study design
- Open-label, international, multicenter study of Simon-2-stage design
- Initially, patients randomized 1:1 to receive DARA
  - 8 mg/kg every 4 weeks (Q4W) or
  - 16 mg/kg every week (QW) for 8 weeks, every 2 weeks (Q2W) for 16 weeks, then Q4W thereafter
- 16 mg/kg DARA was established as the recommended dose for further study
- Results are reported for all patients who were treated with 16 mg/kg DARA (n=106)


Daratumumab Phase 2 Study
Single Agent in RRMM
### Daratumumab Phase 2 Study

**Single Agent in RRMM**

#### Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic (n=106)</th>
<th>Median (range) age, y</th>
<th>63.5 (31–84)</th>
<th>Age ≥75 y, n (%)</th>
<th>12 (11)</th>
<th>Renal function (CrCl), n (%)</th>
<th>≥60 mL/min</th>
<th>60 (57)</th>
<th>&lt;60 mL/min</th>
<th>46 (43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISS staging, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECOG score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>26 (25)</td>
<td>0</td>
<td>29 (27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>40 (38)</td>
<td>1</td>
<td>69 (65)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>40 (38)</td>
<td>2</td>
<td>8 (9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range) time since diagnosis, y</td>
<td>4.8 (1–24)</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk cytogenetics, n (%)</td>
<td>20 (19)</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior therapies (n=106)</th>
<th>Median (range) number of prior therapies</th>
<th>5 (2–14)</th>
<th>&gt;3 lines of prior therapy, n (%)</th>
<th>87 (82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior chemotherapy, n (%)</td>
<td>106 (100)</td>
<td>106 (100)</td>
<td>Prior IMiD, n (%)</td>
<td>106 (100)</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>106 (100)</td>
<td>106 (100)</td>
<td>LEN</td>
<td>106 (100)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>95 (92)</td>
<td>95 (92)</td>
<td>POM</td>
<td>67 (63)</td>
</tr>
<tr>
<td>Prior ASCT, n (%)</td>
<td>85 (80)</td>
<td>85 (80)</td>
<td>THAL</td>
<td>47 (44)</td>
</tr>
<tr>
<td>Prior PI, n (%)</td>
<td>106 (100)</td>
<td>106 (100)</td>
<td>CARF</td>
<td>53 (50)</td>
</tr>
<tr>
<td>ROST</td>
<td>106 (93)</td>
<td>106 (93)</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

CrCl, creatinine clearance; ISS, International Staging System; LEN, lenalidomide; POM, pomalidomide; THAL, thalidomide; ASCT, autologous stem cell transplantation; BORT, bortezomib; CARF, carfilzomib.

97% refractory to last therapy, 95% double refractory, 63% Pom refractory. Lonial S et al. J Clin Oncol. 2015;33. Abstract LBA8512.

### Daratumumab Phase 2 Study

**Single Agent in RRMM**

#### Overall response rate

- **ORR was 29% (95% CI, 21–39)** in patients receiving 16 mg/kg DARA
- Stringent complete response (sCR) in 3% of patients (95% CI, 0.6–8.0)
- VGPR or better achieved in 12% (95% CI, 7–20) of patients
- Clinical benefit rate (ORR + MR) was 34% (95% CI, 25–44)

![Overall Response Rate](image)
Daratumumab Phase 2 Study
Single Agent in RRMM

Change in Paraprotein From Baseline

- The majority of patients had reductions in paraprotein from baseline
  - 40 patients (38%) had reductions >50%
  - 17 patients (16%) had reductions >90%

Daratumumab Phase 2 Study
Single Agent in RRMM

ORR by Subgroup

- ORR, %
- Group

Refactory to

Daratumumab Phase 2 Study
Single Agent in RRMM

Progression-Free and Overall Survival

- Median PFS = 3.7 months (95% CI, 2.8–4.6)
- Median OS = NE (95% CI, 13.7–NE)

- 29 of 31 responders are still alive
- The 1-year survival rate was 65% (95% CI, 51.2–75.5)


Phase 1 Isatuximab Monotherapy Study: Results High-Risk Cohort

Key eligibility criteria
- 17 p del, t(4;14), t(14;16), t(14;20), or >3 copies of 1q21
- Relapsed <6 months of autologous transplantation
- A high-risk GEP signature

Patient characteristics
- Median prior lines of treatment: 4.5 (range 2–8)
- All patients received IMiD and proteasome inhibitor
- Majority (72.2%) received pomalidomide or carfilzomib

High-risk criteria

<table>
<thead>
<tr>
<th>High-risk criteria</th>
<th>N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>17p del</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>t(14;14)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>&gt;3 copies of 1q21</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>t(19;14)</td>
<td>1 (5.6%)</td>
</tr>
</tbody>
</table>

Overall response rate

- ORR = 22% (4/18)

Presented by Tom Martin at IMW Rome, Italy 2015
Antibody Treatment in Combination With Lenalidomide/Dex

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Target</th>
<th>No.</th>
<th>ORR (≥PR), %</th>
<th>PFS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT062(^{(1)})</td>
<td>CD138</td>
<td>41</td>
<td>78</td>
<td>Too early</td>
</tr>
<tr>
<td>SAR650984 (^{(2)})</td>
<td>CD38</td>
<td>31</td>
<td>58</td>
<td>6.2</td>
</tr>
<tr>
<td>Daratumumab(^{(3)})</td>
<td>CD38</td>
<td>32</td>
<td>88</td>
<td>Too early</td>
</tr>
<tr>
<td>Elotuzumab(^{(4,5)})</td>
<td>SLAMF7</td>
<td>73</td>
<td>84</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>321</td>
<td>79</td>
<td>19.4</td>
</tr>
</tbody>
</table>


Factors Impacting mAb Activity

- **CDC**
  - CDC inhibitors
- **ADCC**
  - FcγRIIIa variant
  - PDL-1/PD-1 interaction
  - TGFβ
  - C3b deposition
  - HLA-KIR match
- **ADCP**
  - FcγRII variants
  - CD47
Hypothesis: KIR-HLA Interactions Impact Response to ISA/LEN/DEX

KIR-HLA interactions that affect NK cell activation
1. Licensing: iKIR binds to ligand
2. Missing ligand: KIR-ligand not present on target cell
3. Activating KIRs: present on NK cells

UCSF Biomarker Study: NK Cell Results
Isatuximab, Lenalidomide, and Dexamethasone in RRMM

Inhibitory KIR, KIR3DL1
Ligand: HLA-B Bw4-I80

Gene dosage effects: HLA-B Bw4-I80 and KIR3DL1

Conclusions:
1. ISA provides NK activation signal through Fc
2. Lenalidomide activates NK cells through IL-2
3. The licensed NK cell then kills the target
4. Provocative: needs confirmation in a larger trial

When and How Should We Incorporate These Antibodies Into Practice?

- Are all patients candidates for mAb therapy?
- Which mAb therapy do we use first?
- Can we combine these with any/all direct anti-MM based approaches (rituximab approach)?
- For a patient progressing on maintenance lenalidomide → which mAb should we choose?
- If a patient does not respond to 1 mAb → will they be resistant to all mAbs?
- What do we need to know to better answer these questions?
  - DATA, DATA, DATA!
- For now → follow the label
  - Early relapse → elotuzumab + lenalidomide + dexamethsone
  - Late relapse/double refractory → daratumumab
- Future trials will interrogate sequence, biomarkers, and combos

The Practical Part: Infusion Info

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Pre-Meds</th>
<th>IARs</th>
<th>Infusion Rate/Time</th>
<th>Rapid Infusion (&lt;90 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELO¹</td>
<td>10 mg/kg Q wk × 8, then Q 2 wks</td>
<td>Dex 8 mg IV (28 mg PO), Acetaminophen 650–1,000 mg, Diphenhydramine 25–50 mg, Ranitidine 50 mg IV</td>
<td>~ 10% • G1–2 • 1st inf • 1% DC</td>
<td>Start 8.5 ml/min, increase to 2 ml/min (~2–3 hours)</td>
<td>Yes</td>
</tr>
<tr>
<td>DARA²</td>
<td>16mg/kg Q wk × 8, Q 2wk × 16, Q 4wk</td>
<td>Methylprednisolone 100 mg, Acetaminophen 1,000 mg, Cetirizine 10 mg or equiv, Dex 4 mg give on Day 2 + 3</td>
<td>~ 49–71% • G1–2 • 1st-2nd inf (8%) • &lt;1% DC</td>
<td>1,000 mls • @50–200/hr 1st: 7h 2nd: 3.25–4 h</td>
<td>TBD</td>
</tr>
<tr>
<td>ISA³</td>
<td>TBD</td>
<td>Dex 20–40 mg, Acetaminophen 650–1,000 mg, Diphenhydramine 25–50 mg, Famotidine 20 mg</td>
<td>~ 50% • G1–2 • 1st inf • 2% DC</td>
<td>10 mg/kg • 1st: 3.5 h • 2nd: 2.5 h 20 mg/kg • 1st: 5.5 h • 2nd: 4 h</td>
<td>TBD</td>
</tr>
</tbody>
</table>

The Practical Part: Infusion Reactions

A. Common symptoms

**Anti-CD38 mAb**
1. Sinus/nasal congestion
2. Throat irritation
3. Cough, dyspnea, wheezing
4. Rare: anaphylaxis, severe HTN, CP, arrhythmias

**Elotuzumab**
1. Fever, chills
2. Hypertension
3. Less: bradycardia, hypoTN

B. Treatment
1. Recognize early and stop infusion (37% Dara, 5% Elo)
2. Give additional premedications
3. Restart at ½ the rate (discontinue if Gr 4 or recurs)

Be prepared:
- Start infusions early
- Pre-med everyone → additional meds likely to be needed

---

The Practical Part: Response and Blood Typing

A. Assessing response
- mAb may be detectable on SPEP/IFE
- Can obscure CR assessment

B. Infection: VZV prophylaxis

C. Blood banking
- Anti-CD38 may interfere with blood bank tests
  - CD38 on reagent RBCs
  - Positive DAT
  - Positive antibody screen
- Approaches to resolve anti-CD38 interference
  *Send type and screen BEFORE first dose-DARA*
  - Genotype/phenotype recipient’s RBCs
  - DTT-treating reagent RBCs (+/− available, give Kell cells)
  - Neutralize anti-CD38 in plasma (anti-idiotype, sCD38)

---

**References:**
FUTURE:
Where do we go from here?

- **Novel antibodies**
  - More specific targets
  - Checkpoint inhibitors (PD-1, PDL-1)
  - Stromal compartment/ cell-cell interactions

- **Antibody-drug conjugates**
  - BT-062 (anti-CD138)
  - GSK2857916 (anti-BCMA)

- **Can we combine mAbs with?**
  - Novel drugs
  - ELO + anti-KIR, ELO + CD137
  - Vaccines + antibodies

Conclusions

- **Antibody therapy has “come of age”**
  - ELO with Len/Dex for early relapse in Len sensitive
  - DARA for double refractory

- **Combinations actively be tested**
  - Frontline, early relapse, and refractory
  - Proteasome inhibitors, pomalidomide, other mAbs

- **Future efforts need to focus on:**
  - Identifying biomarkers for response/relapse
  - Optimizing the combinations and dosing strategies
  - Potentially using genomic data to help select patients

- **All patients are appropriate for clinical trials**
Novel Therapeutics in Myeloma: Update

A. Keith Stewart, MBChB, MRCP, FRCPC, MBA
Vasek and Anna Maria Polak Professor of Cancer Research
Consultant, Division of Hematology/Oncology
Mayo Clinic
Scottsdale, Arizona

Disclosures

- Consultant/Advisor: Bristol-Myers Squibb, Celgene, Janssen, MedImmune, Novartis, Takeda Oncology
Progression-Free Survival in Late-Stage Disease

**Figure 2A, page 1059**

What’s New in MM Therapeutics?

- **Oral proteasome inhibitors**
  - Ixazomib
  - Oprozomib

- **Monoclonal antibodies**
  - Elotuzumab
  - Daratumumab
  - Isatiximab

- **Kinase inhibitors**
  - Afuresertib
  - Dinaciclib
  - PIM (LGH447)
  - Trametinib

- **HDACs**
  - Panobinostat
  - Ricolinostat

- **Novel mechanisms**
  - ABT-199
  - Selinexor

- **Immunotherapies**
  - CAR-T
  - BITE
  - PDL-1/PD-1

HDAC, histone deacetylase.
Profile of Single-Agent Oprozomib in Patients With Multiple Myeloma: Updated Results From a Multicenter, Open-Label, Dose-Escalation Phase 1b/2 Study


1Washington University, St. Louis, MO; 2Vanderbilt University, Nashville, TN; 3John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ; 4Winship Cancer Institute, Emory University, Atlanta, GA; 5University of Maryland, Baltimore, MD; 6Dana-Farber Cancer Institute, Boston, MA; 7Rush University, Chicago, IL; 8Mt. Sinai Hospital, New York, NY; 9University of Chicago Medical Center, Chicago, IL; 10Mayo Clinic, Scottsdale, AZ; 11Mayo Clinic, Rochester, MN; 12Onyx Pharmaceuticals, Inc., an Amgen subsidiary, South San Francisco, CA; 13Sarah Cannon Research Institute, Nashville, TN

Phase 1b/2 Study of Single-Agent Oprozomib in MM: Efficacy

<table>
<thead>
<tr>
<th>Phase 1b</th>
<th>Phase 1b + 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>150–330 mg/d (n=16)</td>
<td>150–270 mg/d (n=43)</td>
</tr>
<tr>
<td>CBR 50%</td>
<td>CBR 32.6%</td>
</tr>
<tr>
<td>ORR 31.3%</td>
<td>ORR 23.3%</td>
</tr>
<tr>
<td>PD</td>
<td>PD</td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>MR</td>
<td>MR</td>
</tr>
<tr>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>VGPR</td>
<td>VGPR</td>
</tr>
<tr>
<td>CR</td>
<td>CR</td>
</tr>
</tbody>
</table>

1 2/7 schedule: 1 patient (6%) was not evaluable.
2 5/14 schedule: 5 patients (12%) were not evaluable and 2 patients (5%) were off study before response assessment.
3 ORR in 11 CFZ-refractory patients (phase 2): 18.2%.

Phase 1b/2 Study of Single-Agent Oprozomib in MM

Authors’ Conclusions

- The most common grade ≥3 nonhematologic AEs were diarrhea, nausea, and vomiting; rates of treatment-emergent PN and rash were low.
- Recommended phase 2 dose and schedule: 240/300 mg/day in the 2/7 step-up schedule and 150/180 mg/day in the 5/14 step-up schedule.
- Preliminary data suggest that step-up dosing is associated with improved tolerability.
- Enrollment of patients with MM continues both schedules in the phase 2 study with a target of 94 patients; all patients are now receiving a new (extended-release) formulation of oprozomib.
- Single-agent oprozomib has promising antitumor activity, with responses observed in patients who had carfilzomib-refractory MM.


Phase 1b Study of Ricolinostat (ACY-1215) + LEN-DEX in Patients With RRMM: Efficacy and Authors’ Conclusions

- ORR was 64% and CBR was 80%; response rate was 85% in LEN-sensitive and -naive patients, and 50% in LEN-refractory patients.
- Continuous bid treatment for 21 days is ongoing.
- ORR: 64% for all evaluable patients.
- ORR: 50% for LEN-refractory patients.

Phase 1b Study of Ricolinostat (ACY-1215) and BTZ-DEX in Patients With RRMM

Authors’ Conclusions

- Ricolinostat is tolerable with clinical benefit in combination with bortezomib/dexamethasone.
- No differences in PK were observed for the strength formulations.
- Toxicities were generally manageable.
- Responses were observed in this heavily pretreated population.
- An expansion cohort at 160 mg QD is ongoing to better define a recommended phase 2 dose.


A Phase 1/2 Trial of Dinaciclib, a Small Molecule Inhibitor of Cyclin-Dependent Kinase 5 (CDK5)

- 29 patients were accrued (19 phase 1, 9 phase 2)
- Median time from diagnosis to registration was 3.5 years
- Median follow-up for patients still alive is 3.2 months (range: 0.7–20.8)
- Toxicity profile was hematological, fatigue, nausea, and mucositis
- Preclinical work indicates high synergy with bortezomib phase 1b trials now under way

Dinaciclib: CDK Inhibitor


Afuresertib (AKT Inhibitor)

- ATP-competitive, reversible inhibitor of all 3 AKT kinases
- Orally bioavailable
- Single-agent activity in heavily pretreated MM patients in FTIH

Afuresertib, Bortezomib, Dex

Maximum % Change in M Protein or FLC From Baseline

- Change From Baseline (%)
- Subject

<table>
<thead>
<tr>
<th>FLC (κ or λ)</th>
<th>M protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
<td>-100</td>
</tr>
<tr>
<td>-90</td>
<td>-90</td>
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<tr>
<td>-80</td>
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<td>-70</td>
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<td>80</td>
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<tr>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Afuresertib, Bortezomib, Dex: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All (%)</th>
<th>&gt;Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonhematologic (≥20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>51.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>37.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>33.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>32.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>28.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27.0</td>
<td>2.0</td>
</tr>
<tr>
<td>PN</td>
<td>22.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>20.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rash</td>
<td>20.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>38.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>22.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Serious adverse events recorded in 31 patients:
- Infections
- Acute renal injury
- Skin disorders
- Gastrointestinal
- Bone-related events
- Vascular events

- 1 death: septic shock (F, age 61 years)
- 23% discontinuation rate for AEs
PIM Inhibition Most Effective in Hematologic Malignancies

Modified from Figure 4A, page 1841


Phase 1 Study Of LGH447 in Patients With Relapsed/ Refractory Multiple Myeloma

- ORR: 10.5%; CBR: 21.1%; DCR: 71.9%
- Median duration of response was 23.0 weeks

Selinexor, Novel Anticancer Agent: Restores Tumor Suppressors

Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276

J Schmidt1, E Braggio1, KM Kortuem1, JB Egan1, YX Zhu1, CS Xin1, RE Tiedemann2, SE Palmer1, VM Garbitt1, D McCauley3, M Kauffman3, S Shacham3, M Chesi1, PL Bergsagel1, and AK Stewart1

1Division of Hematology-Oncology, Mayo Clinic, Scottsdale, AZ, USA
2Princess Margaret Hospital, Ontario Cancer Institute, University of Toronto, Toronto, Ontario, Canada
3Karyopharm Therapeutics, Natick, MA, USA


Selinexor, Novel Anticancer Agent: Restores Tumor Suppressors

Selinexor: First-in-Class, Oral Selective Inhibitor of Nuclear Export (XPO1)

- Novel, small molecule selective inhibitor of XPO1
- Oral drug given 2–3 times per week
- No known drug-drug interactions through CYP450s
- Potent antileukemic effects in vitro and in vivo in AML models
- Antitumor activity in ongoing Phase 1 and 2 studies in advanced hematologic and solid tumors

Selinexor


Best Responses in Evaluable Patients: Single-Agent Selinexor vs Selinexor + Low Dex

Best Responses in Evaluable* (n=29) MM Patients Oral Selinexor Single-Agent (as of 1-December-2014)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>CBR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor low dose: ≤30 mg/m²</td>
<td>15</td>
<td>4 (27%)</td>
<td>—</td>
<td>4 (27%)</td>
<td>8 (53%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Selinexor high dose: ≥35 mg/m²</td>
<td>14</td>
<td>3 (21%)</td>
<td>1 (7%)</td>
<td>2 (14%)</td>
<td>8 (57%)</td>
<td>3 (21%)</td>
</tr>
</tbody>
</table>

Best Responses in Evaluable (N=9) Group A MM Patients Oral Selinexor (45 mg/m²) + Dexamethasone (as of 1-Dec-2014)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>CBR</th>
<th>ORR</th>
<th>sCR</th>
<th>PR</th>
<th>MR</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor (45 mg/m²) + Low Dose Dex (20 mg)</td>
<td>9</td>
<td>8 (89%)</td>
<td>6 (67%)</td>
<td>1 (11%)</td>
<td>5 (55%)</td>
<td>2 (22%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

Selinexor + Dexamethasone: Common Related AEs in >2 Patients

- Sel(45)-Dex shows reduction in nausea grades and very little weight loss compared with selinexor alone
- The MTD/RP2D of Sel-Dex is 45 mg/m² + 20 mg Dex, twice weekly


Durable Responses After Multiple Prior Therapies in Relapsed/Refractory MM Patients

Patients With RR MM (7 Median Prior Tx) Treated With Twice-Weekly Oral Combination Selinexor + Dexamethasone (Selinexor 45 mg/m² + Dexamethasone 20 mg)

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Maximal Δ</th>
<th>Best Response</th>
<th># Prior Tx</th>
<th>Study Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>076</td>
<td>-71%</td>
<td>PR</td>
<td>7</td>
<td>301+</td>
</tr>
<tr>
<td>079</td>
<td>-53%</td>
<td>PR</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>081</td>
<td>-99%</td>
<td>sCR</td>
<td>5</td>
<td>280</td>
</tr>
<tr>
<td>084</td>
<td>-84%</td>
<td>PR</td>
<td>9</td>
<td>170</td>
</tr>
<tr>
<td>090</td>
<td>41%</td>
<td>PD</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>092</td>
<td>-55%</td>
<td>PR</td>
<td>10</td>
<td>121</td>
</tr>
<tr>
<td>093</td>
<td>-41%</td>
<td>MR</td>
<td>9</td>
<td>114</td>
</tr>
<tr>
<td>098</td>
<td>-48%</td>
<td>MR</td>
<td>16</td>
<td>79</td>
</tr>
<tr>
<td>099</td>
<td>-82%</td>
<td>PR</td>
<td>6</td>
<td>201+</td>
</tr>
</tbody>
</table>

Overall: DCR: 88% ORR: 67% Median: 7 DOR: ~7 months

Inhibition of Bcl-2 Critical for Apoptosis

Death
- BH3-only Death triggers: Bim, Bid, Puma, Bad, Bik, Hrk, Noxa, Bim
- Multidomain Executioners: Bax, Bak
- Mitochondria: Activated BAX/BAK
- Caspase activation
- Cell death (apoptosis)

Survival
- Bcl-2: GDC-0199
- Bcl-xL, A1, Mcl-1

Targets Bcl-2

Venetoclax in t(11;14) MM

Therapy started

Kappa FLC

Stewart AK, unpublished
Chimeric Antigen Receptor (CAR) T Cells Against CD19 for Multiple Myeloma

Figure 1A-C, page 1042

B-Cell Maturation Antigen (BCMA) CAR-T

Remissions of Multiple Myeloma during a First-in-Humans Clinical Trial of T Cells Expressing an Anti-BCMA Chimeric Antigen Receptor

• BCMA targeted CAR-T cells infused after 3 days of cyclophosphamide and fludarabine
• Highest dose level in 2 patients—severe cytokine release syndrome
• 90-100% clearance of bone marrow plasma cells

Pembrolizumab in Combination with Lenalidomide and Low-Dose Dexamethasone for Relapsed/Refractory Multiple Myeloma (RRMM)

- Pembrolizumab, a highly selective, humanized IgG4 anti–PD-1 monoclonal antibody designed to block interaction of PD-1 with PD-L1 and PD-L2
- RRMM who have failed ≥2 prior therapies including a proteasome inhibitor and an IMiD
- MTD/MAD was defined as pembrolizumab 200 mg fixed dose in combination with lenalidomide 25 mg and low-dose dexamethasone 40 mg.
- 17 patients; 76% response rate


A Phase 2 Study of Anti PD-1 Antibody Pembrolizumab, Pomalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (RRMM)

- Pembrolizumab, a highly selective, humanized IgG4 anti–PD-1 monoclonal antibody designed to block interaction of PD-1 with PD-L1 and PD-L2
- RRMM who have failed ≥2 prior therapies including a proteasome inhibitor and an IMiD
- Pembrolizumab 200 mg IV every 2 weeks plus pomalidomide (4 mg daily x 21 days) and dexamethasone 40 mg weekly
- 11 of 22 evaluable patients (50% response rate)

Summary

- Oral proteasome inhibitors seem active; likely approval(s)
- Monoclonal antibodies: likely to be approved
  elotuzumab, daratumumab, isatuximab
- Kinase inhibitors dinaciclib (CDK5), afuresertib
  (AKT), PIM kinase have some single-agent activity
  and now in combination
- HDACs: ricolinostat too soon to say
- Selinexor, ABT-199 t(11;14) also promising
- Checkpoint inhibitors and CAR-T: too soon to say but
  potential paradigm shift

Community Case Revisited
Case Study Part 1

- 54-year-old man presents with 6-month history of lower back pain, increasing fatigue, right rib pain.
- Labs
  - Normal LDH
  - Serum β2 microglobulin 6 mg/dL
- Skeletal survey
  - Numerous lytic lesions (skull, long bones, right 5th/6th/7th ribs, pelvis)
- Bone marrow biopsy:
  - 70% cellularity, 80% kappa-restricted plasma cells
  - Cytogenetics normal in 20 metaphases
  - FISH positive for translocation (11;14) in 75% cells

Having completed this program, which one of the methodologies do you plan to use most often?

A. Gene expression profiling
B. Conventional cytogenetics
C. FISH
D. Gene mutation panel
E. More than one method
F. None of the above
Is this patient considered eligible for stem cell transplantation?

A. Yes  
B. No  
C. Not sure

Having completed this program, which factors do you plan to use to decide whether to consider aggressive therapy such as stem cell transplantation?

A. Age, comorbidity score  
B. Social support and insurance coverage  
C. Response to induction therapy  
D. Risk profile  
E. All of the above  
F. I don’t do transplants up front
What would be your recommendation for initial treatment?

A. Melphalan, prednisone, bortezomib (MPV)
B. Bortezomib, thalidomide, dexamethasone (VTD)
C. Lenalidomide + low-dose dexamethasone (Ld)
D. Lenalidomide, bortezomib, dexamethasone (RVD)
E. Cyclophosphamide, bortezomib, dexamethasone (CyBorD)
F. Carfilzomib, lenalidomide, dexamethasone (KRD)
G. Other

Having completed this program, will your practice plan to routinely test for minimal residual disease (MRD) following therapy?

A. Yes
B. No
C. Not sure
Case Study Part 2

- Induction chemotherapy: RVd × 4 cycles
- Bone health: bisphosphonates every month
- Best response: VGPR by IMWG criteria
- Relevant events during induction
  - Grade II peripheral neuropathy after cycle #2
  - Increasing lower back pain during cycle #3

Based on the patient’s response to induction therapy, you collect stem cells. What would you consider next?

A. Continue current regimen
B. Wait to transplant after relapse
C. Proceed to transplant
D. Provide consolidation therapy
Case Study Part 2

- Transplant eligible
- Restaging post-ASCT: sCR by IMWG criteria
- Patient comes to discuss maintenance

Is now an appropriate time for MRD testing?

A. Yes
B. No
C. Not sure
Do you recommend maintenance?
A. Yes
B. No
C. Not sure

Would the MRD result affect your decision to use maintenance therapy?
A. Yes
B. No
C. Not sure
Which maintenance treatment do you recommend?

A. Lenalidomide  
B. Bortezomib  
C. Lenalidomide, bortezomib  
D. Thalidomide  
E. Prednisone  
F. Clinical trial  
G. I don’t use maintenance

Would your maintenance choice change if the patient had low-risk cytogenetics?

A. Yes  
B. No  
C. Not sure
Case Study Part 3

- Patient deferred Len maintenance and prefers close observation
- Returns 2 years post-ASCT with increasing shoulder pain while working out in the gym, increasing fatigue, and urinary frequency with frothiness
- BM biopsy:
  - 60% cellularity, 50% kappa-restricted plasma cells
  - FISH positive for translocation (11;14) in 50% cells, del17p in 20%
- He is here to discuss treatment options

What would you use for treatment of MM in first relapse?

A. Bortezomib + dexamethasone ± cyclophosphamide
B. Lenalidomide + dexamethasone
C. Pomalidomide + dexamethasone
D. Bortezomib, lenalidomide, and dexamethasone
E. Carfilzomib + dexamethasone
F. Carfilzomib + lenalidomide + dexamethasone
G. Elotuzumab + lenalidomide + dexamethasone
H. Daratumumab
Questions and Answers

Active now: YouKnowIt!—Round 2 and Evaluation