Multiple Myeloma Patient Management: New Agents, New Challenges

8:15 AM – 8:25 AM Community Case 1
Robert M. Rifkin, MD

8:25 AM – 8:40 AM Advances in the Diagnostic Workup: Imaging and Genomics
A. Keith Stewart, MBChB

8:40 AM – 8:55 AM Making Sense of Frontline Options
Thierry Facon, MD

8:55 AM – 9:05 AM Community Case 2
Robert M. Rifkin, MD

9:05 AM – 9:20 AM Strategies to Prolong Response
Amrita Y. Krishnan, MD

9:20 AM – 9:35 AM Panel Discussion

9:35 AM – 9:45 AM Community Case 3
Robert M. Rifkin, MD

9:45 AM – 10:00 AM New Agents, Classes in the Relapsed Setting
Faith E. Davies MD

10:00 AM – 10:15 AM The Way Forward: Immunotherapy
Paul G. Richardson, MD

10:15 AM – 10:30 AM Panel Discussion

10:30 AM – 11:00 AM Question and Answer Session
Case Study 1

- 75-year-old man referred for workup of back pain that radiated to ribs and chest.
- CT pulmonary Angiogram was negative for pulmonary embolus (creatinine 1.5).
- This showed multifocal lytic bone disease. Felt well except for pain in his back.
Case Study 1

75-year-old man referred for workup of back pain that radiated to ribs and chest.

Past medical history
• Hypertension
• T2DM
• Coronary artery disease with 2 stents

Past surgical history
• Left rotator cuff repair 7 years ago

Family history
• Brother and five sisters—all healthy
• Four children

Social history
• Married, bilingual instructor for OSHA
• Nonsmoker, rare social alcohol
• No substance use

Physical exam
• Normal
• ROS: negative except for back pain

Case Study 1: Labs

<table>
<thead>
<tr>
<th>CBC with differential</th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (×10³/mL)</td>
<td>5.4</td>
<td>(4–11)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.0</td>
<td>(13–16)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>38</td>
<td>(34–45)</td>
</tr>
<tr>
<td>Platelets (×10⁹/mL)</td>
<td>210</td>
<td>(150–400)</td>
</tr>
<tr>
<td>Neutrophils (×10³/mL)</td>
<td>4.3</td>
<td>(1.9–7.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CMP</th>
<th>Actual Value</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>34</td>
<td>(7–20)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.5</td>
<td>(0.7–1.2)</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.4</td>
<td>(8.4–10.2)</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>8.7</td>
<td>(6.3–8.2)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.7</td>
<td>(3.5–5.0)</td>
</tr>
<tr>
<td>β2M</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPEP + serum immuno-fixation</th>
<th>Actual Value</th>
<th>Normal Range</th>
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</thead>
<tbody>
<tr>
<td>IF-IgG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M protein spike (g/dL)</td>
<td>1.7</td>
<td></td>
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<table>
<thead>
<tr>
<th>Quantitative Igs</th>
<th>Actual Value</th>
<th>Normal Range</th>
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<tbody>
<tr>
<td>IgG (mg/dL)</td>
<td>2.425 (H)</td>
<td>(700–1,600)</td>
</tr>
<tr>
<td>IgA (mg/dL)</td>
<td>20 (L)</td>
<td>(70–400)</td>
</tr>
<tr>
<td>IgM (mg/dL)</td>
<td>3 (L)</td>
<td>(40–230)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLC</th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa quant Free Lite Chain (mg/L)</td>
<td>112 (H)</td>
<td>(3.30–19.40)</td>
</tr>
<tr>
<td>Lambda quant FLC (mg/L)</td>
<td>1.8 (L)</td>
<td>(5.71–26.30)</td>
</tr>
<tr>
<td>Kappa/lambda quant FLC ratio</td>
<td>62.2 (H)</td>
<td>(0.26–1.65)</td>
</tr>
</tbody>
</table>
### Case Study 1: Imaging and BM Biopsy

<table>
<thead>
<tr>
<th>Bone imaging</th>
<th>MRI</th>
<th>BM biopsy</th>
<th>Flow cytometry</th>
<th>Cytogenetics and FISH</th>
</tr>
</thead>
</table>
| **Skeletal survey**  
• 1.6 cm lytic lesion in the parietal bone; severe loss of bone mineralization—osteoporosis  
**PET scan**  
• Expansile lytic lesion in right acromion. Multiple areas of uptake in bilateral ribs, and increased uptake in T5 | **MRI**  
• Multifocal lesions in spine and ribs | **BM biopsy**  
• 70% cellular with 70%–80% plasma cells  
• Aspirate 66% plasma cells | **Flow cytometry**  
• 25.6% events positive for CD38, CD56, CD138, and kappa light chain | **Cytogenetics**  
• 46, XY  
**FISH (CD138 selected plasma cells)**  
• 74% with gain of 1q21  
• 5.4% low-level gain of 11q23  
• 91% with loss of 13q14  
• 12.0% with low-level loss of TP53  
• 92.5% positive for IgH rearrangement variant |

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**Advances in the Diagnostic Workup: Imaging and Genomics**

A. Keith Stewart, MBChB, MRCP, FRCPC, MBA  
Carlson and Nelson Endowed Director  
Center for Individualized Medicine  
Vasek and Anna Maria Polak Professor of Cancer Research  
Consultant, Division of Hematology/Oncology, Mayo Clinic  
Rochester, Minnesota and Scottsdale, Arizona
Improving Survival in MM

25% of patients live less than 3 years

Proportion Surviving

Follow Up From Diagnosis (Years)

0 2 4 6 8 10 12 14 16 18 20

2014;28:1122.

Adapted from Kumar SK et al. Leukemia.

Prognostic Systems
Combining Genetics and ISS Model

Table 2, page 3415:
Greipp PR et al.

Risk Criteria Median OS

Standard Lack of del(17p), t(4;14), t(14;16) 50.5 mo

High At least one of del(17p), t(4;14) or t(14;16) 24.5 mo (P<0.001)

Revised International Staging System (R-ISS) for MM

- R-ISS I (n=871)
  - Including ISS stage I (serum β2M level <3.5 mg/L and serum albumin level ≥3.5 g/dL)
  - No high-risk CA [del(17p) and/or t(4;14) and/or t(14;16)]
  - Normal LDH level (less than the upper limit of normal range)
- R-ISS III (n=295)
  - Including ISS stage III (serum β2M level >5.5 mg/L)
  - High-risk CA or high LDH level
- R-ISS II (n=1,894)
  - Including all the other possible combinations

<table>
<thead>
<tr>
<th></th>
<th>5-Year OS* (%)</th>
<th>5-Year PFS* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-ISS I</td>
<td>82</td>
<td>55</td>
</tr>
<tr>
<td>R-ISS II</td>
<td>62</td>
<td>36</td>
</tr>
<tr>
<td>R-ISS III</td>
<td>40</td>
<td>24</td>
</tr>
</tbody>
</table>

*At a median follow-up of 46 months


mSMART 2.0
Variable Outcomes in MM

<table>
<thead>
<tr>
<th></th>
<th>High 20%</th>
<th>Intermediate 20%</th>
<th>Standard 60%</th>
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<tbody>
<tr>
<td>FISH</td>
<td></td>
<td>FISH t(4;14)</td>
<td>Others</td>
</tr>
<tr>
<td>del 17p</td>
<td></td>
<td></td>
<td>Hyperdiploid</td>
</tr>
<tr>
<td>t(14;16)</td>
<td></td>
<td>Amplification chromosome 1q</td>
<td>t(11;14)</td>
</tr>
<tr>
<td>t(14;20)</td>
<td></td>
<td></td>
<td>t(6;14)</td>
</tr>
<tr>
<td>GEP</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High-risk signature</td>
<td></td>
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</tr>
</tbody>
</table>

3–4 years 5–6 years 8–10 years

Cytogenetics: Biologically Defined Unique Subsets

**t(4;14)**
- Translocation upregulates MMSET + FGFR3
- Found in 15% of patients
- Associated with IgA myeloma
- Immature morphology
- Often associated with del17
- Tendency for less lytic bone disease, younger age

**t(11;14)**
- Translocation upregulates cyclinD1
- Found in 20% of patients
- Associated with IgD, IgM, and nonsecretory MM
- Lymphoplasmacytoid morphology
- Often associated with B lineage–associated Ag
- Enriched for amyloid/plasma cell leukemia

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**Risk Stratification in Myeloma**

How do we customize treatment?

- **t(4;14) MM**
  - Inferior outcomes with traditional ASCT
  - Results better with integration of novel agents, particularly BTZ (consolidation or maintenance) and use of tandem transplant

- **Del17p (p53 deletion) MM**
  - Improved outcome for low-risk del17p with aggressive multi-combination and prolonged therapy
  - New treatment approaches required (eg, immune-based approaches, use of epigenetic modulators)

- **Hyperdiploid**
  - Myc dependant
  - Super responders to IMiDs

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Venetoclax in t(11;14) MM

ORR by t(11;14) Status

<table>
<thead>
<tr>
<th>Percentage of Patients</th>
<th>sCR</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
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<tbody>
<tr>
<td>All Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-t(11;14) or</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>undetermined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR 21%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3%</td>
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</tr>
<tr>
<td>9%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>13%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ORR 6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9%</td>
<td></td>
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</tbody>
</table>

Kappa FLC

Imaging in Myeloma: IMAJEM (NCT01309334)

ARM A

Randomize

ARM B

PET-CT/MRI at diagnosis

PET-CT/MRI after 3 cycles

PET-CT/MRI before maintenance

N=134

Lenalidomide 1 year

ASCT at relapse

RVD × 3

CY (3g/m²)

MOBILIZATION

Goal: 5 ×10⁶ cells/kg

RVD × 5

Lenalidomide 1 year

ASCT at relapse

RVD × 3

CY (3g/m²)

MOBILIZATION

Goal: 5 ×10⁶ cells/kg

Melphalan 200 mg/m² + ASCT

RVD × 2

Lenalidomide 1 year


A.K. Stewart, unpublished

**Imaging in Myeloma: IMAJEM (NCT01309334)**

- At diagnosis
  - MRI was positive in 127/134 (94.7%)
  - PET-CT in 122/134 (91%) patients
    (McNemar test = 0.94, \(P=0.33\))

- MRI of the spine and pelvis and whole-body PET-CT are equally effective to detect bone involvement in symptomatic patients at diagnosis


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**Imaging in Myeloma: IMAJEM (NCT01309334)**

- Univariate analysis for PFS/134 patients
- Variables tested:
  - Gender, age, Ca, creatinine, ISS, response after 3 cycles of induction, response pre-maintenance, cytogenetics, MRI after 3 cycles, PET-CT after 3 cycles, MRI pre-maintenance, PET-CT pre-maintenance

- PET-CT after 3 cycles, \(P=0.04\)
- PET-CT pre-maintenance, \(P<0.001\)
- Response after 3 cycles (≥VGPR), \(P=0.04\)

PET-CT Normalization Before Maintenance Impact on PFS (62% Normalized)


PET-CT -ve correlates with OS

- Univariate analysis for OS/134 patients
- Variables tested:
  Gender, age, Ca, creatinine, ISS, response after 3 cycles of induction, response pre-maintenance, cytogenetics, MRI after 3 cycles, PET-CT after 3 cycles, MRI pre-maintenance, PET-CT pre-maintenance

- PET-CT pre-maintenance, $P=0.003$

Conclusions

- PET-CT and MRI are equally effective to detect bone involvement in symptomatic patients at diagnosis
- MRI is not a good imaging method during follow-up
- PET-CT after 3 cycles of RVD and pre-maintenance is a powerful prognostic marker for PFS
- PET-CT pre-maintenance is a powerful prognostic marker for OS
Genomic Landscape in MM

- >1000 whole-exome/genome sequences
- A limited set of genes is recurrently mutated in MM: KRAS, NRAS, TP53, DIS3, FAM46C, BRAF, TRAF3
- Results are predominantly obtained from newly-diagnosed MM

Figure 1, page 93

Myeloma Mutation Panel (M³P)

- Recurrently mutated putative MM genes: FAM46C, TP53, DIS3
- Actionable genes: RAS, BRAF, IDH1
- Pathways: MAPK, Cereblon, MYC
- Drug resistance: IMiDs, proteasome inhibitors, glucocorticoid
- Copy-number changes and common translocations
- Biallelic deletions of tumor suppressors
- Sample purity measurement: J regions IGH, IGL-K and IGL-L
  → 88 genes, 1,327 amplicons, 373 Kb

51% of genes shared with Foundation Heme panel, 35% with Foundation ONE

Most Mutations Are Subclonal

Figure 1

Myeloma-Specific Gene Mutation Panel Tracks Clonal Changes Over Time

<table>
<thead>
<tr>
<th>Gene</th>
<th>Patient One</th>
<th>Patient Two</th>
<th>Patient Three</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26.1 26.2</td>
<td>44.1 44.2</td>
<td>77.1 77.2</td>
</tr>
<tr>
<td>FAM46C</td>
<td></td>
<td>24%</td>
<td>92% 88%</td>
</tr>
<tr>
<td>FAT1</td>
<td></td>
<td>24%</td>
<td>77%</td>
</tr>
<tr>
<td>KRAS</td>
<td>48%</td>
<td>28%</td>
<td>60% 53%</td>
</tr>
<tr>
<td>SP140</td>
<td>37%</td>
<td></td>
<td>85% 23%</td>
</tr>
<tr>
<td>SPEN</td>
<td></td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>24%</td>
<td>82% 94%</td>
<td>78% 88%</td>
</tr>
</tbody>
</table>

Impact of Mutation on Myeloma Survival

Figure 3, page 3913

Figure 4, page 3916

Mutations in the Cereblon Pathway in at Least 26% of Relapsed/Refractory Patients

- In a patient refractory to Len/Dex therapy we identified mutations in both CRBN and IRF4
- One patient had 4 different CRBN mutations
- Probably higher as we did not look for structural change on chromosome 3
- 4 out of 5 IRF4-mutated patients shared a K123R variant

**gene found mutated in cohort**

CoMMpass Enrollment

- 1,000+ patients enrolled from >90 sites worldwide, with over 850 samples molecularly profiled at baseline and >100 sequentially

CoMMpass: Triplets versus Doublets

Early data suggests that patients on a triplet regimen (for ex. Bor-Len-Dex) appear to be doing better than those on a doublet (ex. Bor-Dex or Len-Dex)
CoMMpass: High Risk Disease

Integrative analyses using CoMMpass data will help identify patients at greater risk of progression upfront and optimize their treatment.

<table>
<thead>
<tr>
<th>Feature</th>
<th>CoMMpass MMRF2172</th>
<th>CoMMpass MMRF2250</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Caucasian</td>
</tr>
<tr>
<td>ISS stage</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>Baseline treatment</td>
<td>VRD</td>
<td>VRD</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>t(4;14), del13, del17p</td>
<td>t(4;14), del13, del17p</td>
</tr>
<tr>
<td>Time to progression (mos)</td>
<td>1</td>
<td>&gt;18</td>
</tr>
<tr>
<td>p53 status</td>
<td>mutated</td>
<td>WT</td>
</tr>
<tr>
<td>MM cells in blood (%)</td>
<td>1.7</td>
<td>0</td>
</tr>
<tr>
<td>Circulating MM cells</td>
<td>36,648</td>
<td>614</td>
</tr>
</tbody>
</table>

Finding New Treatment Options

By looking closely at the molecular changes happening at progression, one can identify potential new therapeutic options (for ex. a BRAF inhibitor here).
Summary

• Revised ISS can assist therapeutic decision making
• PET-CT normalization is also predictive
• Clinical mutation panels now available
  – Clonal depth of mutation
  – Actionable mutation
  – Prognosis
  – Drug resistance
• CoMMpass study largest genomics cohort in cancer, leading to precision therapy trials
  – Additional CoMMpass data to be presented Saturday, 12/3 at 2:00PM

Making Sense of Frontline Options for Transplant Ineligible Patients

Thierry Facon, MD
Professor of Haematology
Department of Haematology
Lille University Hospital
Lille, France
Patient Case

- 75-year-old patient
- Significant previous medical history
- No significant previous surgical history
- Physical examination: normal
- Lytic bone disease
- Impaired renal function
- Revised ISS stage II

The patient is an ELDERLY patient with comorbidities, but good performance status. He needs treatment.

The Transplant Eligibility Discussion (1)

- Patient is considered transplant candidate and so needs induction-ASCT with or without consolidation and maintenance
- Patient is (most likely) not a transplant candidate and needs conventional treatment
The Transplant Eligibility Discussion (2)

- ASCT remains a standard of care for patients ≤65 years of age in most countries
  - IFM 2009 and EMN studies¹,²

- No large phase 3 randomized study has established the role of ASCT in elderly patients in the era of novel agents

- ASCT (single or even double) is routinely performed in some countries/centers for elderly patients between 65 and 75 years of age


IFM 99-06 Study Protocol
Newly Diagnosed MM Patients 65–75 Years

<table>
<thead>
<tr>
<th>Arm MP</th>
<th>Arm MP-T</th>
<th>Arm MEL100</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP 1</td>
<td>MP 1</td>
<td>MP 3</td>
</tr>
<tr>
<td>MP 2</td>
<td>Thalidomide ≤ 400 mg/d</td>
<td>VAD 1</td>
</tr>
<tr>
<td>MP 3</td>
<td></td>
<td>Cyclophosphamide 3g/m² + lenograstim + PBSC harvest</td>
</tr>
<tr>
<td>MP 12</td>
<td></td>
<td>MEL 100 mg/m² + PBSC + lenograstim</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEL 100 mg/m² + PBSC + lenograstim</td>
</tr>
</tbody>
</table>

Overall Survival According to Treatment

**IFM 2017 Study**

A Phase III Trial Evaluating Conventional Dose Combination Immunochemotherapy With Ixazomib-Lenalidomide-Dexamethasone and Daratumumab (IRD2) to High-Dose Treatment With ASCT in the Initial Management of Fit MM Patients Aged 65–75.

**Arm A**
- Ixazomib
- Lenalidomide
- Dexamethasone
- Collection
- DR maintenance

**Arm B**
- Ixazomib
- Lenalidomide
- Dexamethasone
- Collection
- ASCT
- DR maintenance

---

**MPT and VMP Become Standards of Care (2008)**

FIRST (IFM2007-01/MM-020): Study Design

Screening

Active Treatment + PFS Follow-Up Phase

Randomization 1:1:1

Arm A

Rd Continuous

LEN + LoDEX Continuously
LENALIDOMIDE 25 mg D1-21/28
LoDEX 40 mg D1, 8, 15 & 22/28

Arm B

Rd18

LEN + LoDEX 18 Cycles (72 wks)
LENALIDOMIDE 25 mg D1-21/28
LoDEX 40 mg D1, 8, 15 & 22/28

Arm C

MPT

MEL + PRED + THAL 12 Cycles (72 wks)
MELPHALAN 0.25 mg/kg D1-4/42
PREDNISONE 2 mg/kg D1-4/42
THALIDOMIDE 200 mg D1-42/42

All pts received thromboprophylaxis.

• Stratification: age, country, and ISS stage

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

LT Follow-Up

PD, OS, and Subsequent AMT

PD or Unacceptable Toxicity

IN: LENALIDOMIDE Continuously

LENALIDOMIDE 25 mg D1-21/28
LoDEX 40 mg D1, 8, 15 & 22/28

Arm A

Rd Continuous

LT Follow-Up

PD or Unacceptable Toxicity

PD, OS, and Subsequent AMT

IFM 2007-01 FIRST Trial: PFS and OS

PFS as per investigator assessment

Data cut-off: 3 March 2014
Median follow-up: 45.5 mos

Median PFS

Rd (n = 535) 26.0 mos
Rd18 (n = 541) 21.0 mos
MPT (n = 547) 21.9 mos

Hazard ratio

Rd vs MPT: 0.69; P<0.001
Rd vs Rd18: 0.71; P<0.001
Rd18 vs MPT: 0.90; P=0.866

33%

14%

13%

OS

Data cut-off: 3 March 2014
Median follow-up: 45.5 mos
697 deaths (43% of ITT)

Median OS 4-year OS

Rd (n = 535) 58.9 mos 60%
Rd18 (n = 541) 56.7 mos 57%
MPT (n = 547) 48.5 mos 51%

Hazard ratio

Rd vs MPT: 0.75; P<0.001
Rd vs Rd18: 0.91; P=0.33


IFM 2007-01, FIRST Trial: Age Analysis, OS

Median follow-up of 45.5 months as of 3 March 2014

<table>
<thead>
<tr>
<th>Age ≤75 Years</th>
<th>Median, months</th>
<th>4-yr, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>60.9</td>
<td>64</td>
</tr>
<tr>
<td>Rd18</td>
<td>69.4</td>
<td>67</td>
</tr>
<tr>
<td>MPT</td>
<td>55.3</td>
<td>57</td>
</tr>
</tbody>
</table>

Median follow-up of 45.5 months as of 3 March 2014

<table>
<thead>
<tr>
<th>Age &gt;75 Years</th>
<th>Median, months</th>
<th>4-yr, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>62.3</td>
<td>62</td>
</tr>
<tr>
<td>Rd18</td>
<td>45.7</td>
<td>48</td>
</tr>
<tr>
<td>MPT</td>
<td>37.8</td>
<td>39</td>
</tr>
</tbody>
</table>


SWOG S0777: Study Design

Randomization
N = 525
Stratification:
- ISS (I, II, III)
- Intent to transplant at progression (yes/no)

Eight 21-day cycles of VRd
- Bortezomib 1.3/mg² IV Days 1, 4, 8, and 11
- Lenalidomide 25 mg/day PO Days 1–14
- Dexamethasone 20 mg/day PO Days 1, 2, 4, 5, 8, 9, 11, 12

Six 28-day cycles of Rd
- Lenalidomide 25 mg/day PO Days 1-21
- Dexamethasone 40 mg/day PO Days 1, 8, 15, 22

After induction

Rd maintenance until PD, toxicity, or withdrawal

Lenalidomide 25 mg PO days 1–21
Dexamethasone 40 mg PO days 1, 8, 15, 22

- All patients received aspirin 325 mg/day
- VRd patients received HSV prophylaxis

SWOG S0777: PFS and OS by Assigned Treatment Arm

**PFS by assigned treatment arm**

- Events/N: VRd 137/242, Rd 166/229
- Median in months: VRd 43 (39, 52), Rd 30 (25, 38)

**OS by assigned treatment arm**

- Events/N: VRd 76/242, Rd 100/229
- Median in months: VRd 75 (66, -), Rd 64 (56, -)

* Stratified


---

Combination Study of Carfilzomib, Lenalidomide, and Dexamethasone in Patients With NDMM: Study Design

**Key inclusion criteria**

- Age ≥18 years
- NDMM with measurable disease
- Creatinine clearance ≥60 mL/min
- ECOG PS 0–2
- ANC ≥1.0 × 10^9/L, hemoglobin ≥8.0 g/dL, platelet count ≥75 × 10^9/L
- Adequate hepatic function

**Eight 28-day cycles**

Key inclusion criteria for transplant-eligible patients

- Cycle 1, days 1, 2, 8, 9, 15, 16: Carfilzomib 20/36 mg/m² IV, daily
- Cycle 1, days 1, 2: Lenalidomide 25 mg/day PO
- Cycle 1, days 1, 2, 8, 9, 15, 16: Dexamethasone 20/10 mg IV or PO

**KRD**

- Carfilzomib
- Lenalidomide 25 mg/day PO, days 1–21
- Dexamethasone 20/10 mg IV or PO, days 1, 2, 8, 9, 15, 16, 22, 23

**Eight 28-day cycles**

- Stem cell harvest after 4 cycles of KRD
- Extended dosing 24 cycles

**Primary end point**

- Rate of PN grade ≥3

**Secondary end point**

- MRD* assessment
- Response rates
- Progression-free survival
- Duration of response
- Safety

*Assessed at the following time points: baseline, achievement of a CR and/or at the completion of cycles 8, 20, and 32, and at termination of protocol therapy.

Combination Study of Carfilzomib, Lenalidomide, and Dexamethasone in Patients With NDMM: Efficacy

Table 3, page 50

What about the evaluation of frailty?
Do we need specific studies for frail patients?
FIRST (MM-020): Frailty Analysis-Frailty Algorithm

- Patients were categorized into three severity groups (fit, intermediate, frail) as described by a proxy algorithm based on the IMWG frailty scale

<table>
<thead>
<tr>
<th>IMWG Frailty Scale</th>
<th>Proxy for MM-020 Analysis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≤75 yrs</td>
<td>≤75 years</td>
<td>0</td>
</tr>
<tr>
<td>76-80 yrs</td>
<td>76-80 yrs</td>
<td>1</td>
</tr>
<tr>
<td>&gt;80 yrs</td>
<td>&gt;80 yrs</td>
<td>2</td>
</tr>
<tr>
<td>Activity of Daily Living score</td>
<td>EQ-5D: Self Care score</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>1 (no problem)</td>
<td>0</td>
</tr>
<tr>
<td>≤4</td>
<td>2-3 (moderate or severe problem)</td>
<td>1</td>
</tr>
<tr>
<td>Instrumental Activity of Daily Living score</td>
<td>EQ-5D: Usual Activities score</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 (no problem)</td>
<td>0</td>
</tr>
<tr>
<td>≤5</td>
<td>2-3 (moderate or severe problem)</td>
<td>1</td>
</tr>
<tr>
<td>Charlson Comorbidity Index score</td>
<td>Charlson Comorbidity Index score</td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>≤1</td>
<td>0</td>
</tr>
<tr>
<td>≥2</td>
<td>≥2</td>
<td>1</td>
</tr>
</tbody>
</table>

Total
0: Fit
1: Intermediate
≥2: Frail


FIRST (MM-020): Frailty Analysis
PFS and OS by Severity Group With ISS Stage

- No treatment effects seen in these groups, likely due to small patient numbers

<table>
<thead>
<tr>
<th>Severity</th>
<th>n</th>
<th>Median PFS, mos (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit + ISS I</td>
<td>84</td>
<td>24.1 (95.2-43.7)</td>
<td>0.71 (0.50-0.99)</td>
</tr>
<tr>
<td>Fit + ISS III</td>
<td>171</td>
<td>23.3 (21.2-30.2)</td>
<td>0.63 (0.49-0.80)</td>
</tr>
<tr>
<td>Int + ISS II</td>
<td>238</td>
<td>23.7 (22.6-25.4)</td>
<td>0.63 (0.49-0.80)</td>
</tr>
<tr>
<td>Int + ISS III</td>
<td>150</td>
<td>23.9 (22.9-25.8)</td>
<td>0.69 (0.58-0.82)</td>
</tr>
<tr>
<td>Frail + ISS III</td>
<td>437</td>
<td>23.0 (22.5-23.6)</td>
<td>0.69 (0.58-0.82)</td>
</tr>
<tr>
<td>Frail + ISS III</td>
<td>377</td>
<td>17.1 (14.1-19.5)</td>
<td>0.69 (0.58-0.82)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity</th>
<th>n</th>
<th>Median OS, mos (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit + ISS I</td>
<td>84</td>
<td>NR</td>
<td>0.57 (0.33-1.00)</td>
</tr>
<tr>
<td>Fit + ISS III</td>
<td>171</td>
<td>NR</td>
<td>0.43 (0.32-0.59)</td>
</tr>
<tr>
<td>Int + ISS II</td>
<td>238</td>
<td>63.1 (58.2-69.0)</td>
<td>0.57 (0.47-0.69)</td>
</tr>
<tr>
<td>Int + ISS III</td>
<td>150</td>
<td>63.5 (59.5-67.1)</td>
<td>0.57 (0.47-0.69)</td>
</tr>
<tr>
<td>Frail + ISS III</td>
<td>437</td>
<td>63.5 (60.5-66.5)</td>
<td>0.57 (0.47-0.69)</td>
</tr>
<tr>
<td>Frail + ISS III</td>
<td>377</td>
<td>35.6 (32.5-40.6)</td>
<td>0.57 (0.47-0.69)</td>
</tr>
</tbody>
</table>

UKMRA Myeloma XIV: FITNESS
Frailty-Adjusted Therapy in Transplant Non-Eligible Patients With Symptomatic Myeloma

First-line therapy in the nonintensive setting for myeloma

CI: Prof Graham Jackson & Prof Gordon Cook

**Trial design**

Transplant-ineligible NDMM

Frailty indexing (FI) performed in all patients at baseline

**REACTIVE**

Non-adjusted

CRDa

IRDa

**INDUCTION**

1:2

FIT

UNFIT

FRAIL

**ADAPTIVE**

Frailty index–adjusted therapy

CRDa

IRDa

↓CRDa

↓IRDa

↓↓CRDa

↓↓IRDa

FIT: C – 500 mg D1 & D8, R – 25 mg D1–21, D – 20 mg, I – 4 mg weekly

UNFIT: C – 350 mg D1 & D8, R – 15 mg D1–21, D – 10 mg/wk, I – 3 mg/wk

FRAIL: C – 250 mg D1 & D8, R – 10 mg D1–21, D – 10 mg/wk, I – 3 mg/wk

TREAT TO MAXIMUM RESPONSE (6–8 cycles)

Lenalidomide

Ixazomib/Lenalidomide
Treatment of MM in Elderly Patients: Landscape and Perspectives

1. DaraVMP vs. VMP. Available at: https://clinicaltrials.gov/ct2/show/NCT02195479
4. IRD vs RD (Tourmaline 2). Available at: https://clinicaltrials.gov/ct2/show/NCT01850524.
6. DaraRD vs. RD. Available at: https://clinicaltrials.gov/ct2/show/NCT02252172.
7. KMP vs. VMP (Clarion). Available at: https://clinicaltrials.gov/ct2/show/NCT01818752.

Phase 3 Rd-Based Continuous Studies for Elderly Patients

2. IRD vs RD (Tourmaline 2). Available at: https://clinicaltrials.gov/ct2/show/NCT01850524.
3. DaraRD vs. RD. Available at: https://clinicaltrials.gov/ct2/show/NCT02252172.

Primary end point for all studies is PFS
Case Study 2

- 52-year-old woman referred for workup of anemia that proved to be iron deficiency. This was only partly corrected with oral iron supplementation. Due to her incomplete response to iron replacement, further workup was undertaken.
Case Study 2

52-year-old woman referred for workup of anemia.

### Past medical history
- None

### Past surgical history
- Appendectomy and varicose vein stripping

### Family history
- Sister-in-law has myeloma and failed two SCTs

### Social history
- Married, works at a uniform supply firm
- Nonsmoker, rare social alcohol
- No substance use

### Physical exam
- Normal
- ROS: negative except for mild fatigue

### Case Study 2: Labs

<table>
<thead>
<tr>
<th></th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBC with differential</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC (×10³/mL)</td>
<td>3.7</td>
<td>(4–11)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.8</td>
<td>(13–16)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>30.1</td>
<td>(34–45)</td>
</tr>
<tr>
<td>Platelets (×10³/mL)*</td>
<td>278</td>
<td>(150–400)</td>
</tr>
<tr>
<td>Neutrophils (×10³/mL)</td>
<td>5.8</td>
<td>(1.9–7.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>16</td>
<td>(7–20)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8</td>
<td>(0.7–1.2)</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.6</td>
<td>(8.4–10.2)</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>8.0</td>
<td>(6.3–8.2)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.4</td>
<td>(3.5–5.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG (mg/dL)</td>
<td>3,431 (H)</td>
<td>(700–1,600)</td>
</tr>
<tr>
<td>IgA (mg/dL)</td>
<td>158 (H)</td>
<td>(70–400)</td>
</tr>
<tr>
<td>IgM (mg/dL)</td>
<td>40 (H)</td>
<td>(40–230)</td>
</tr>
<tr>
<td>Kappa quant FLC (mg/L)</td>
<td>437.6 (H)</td>
<td>(3.30–19.40)</td>
</tr>
<tr>
<td>Lambda quant FLC (mg/L)</td>
<td>13.67 (H)</td>
<td>(5.71–26.30)</td>
</tr>
<tr>
<td>Kappa/lambda quant FLC ratio</td>
<td>31.9 (H)</td>
<td>(0.26–1.65)</td>
</tr>
</tbody>
</table>

*With normal iron studies
Case Study 2: Imaging and BM Biopsy

Bone imaging
- Skeletal survey
  - Indeterminate lesions in right intertrochanteric area
- DEXA scan
  - Osteopenia

BM biopsy
- 40% cellular with 30% plasma cells
- Aspirate 24% plasma cells

Flow cytometry
- 2% events positive for CD38, CD56, CD138, and cytoplasmic kappa light chains

Cytogenetics
- 46, XX

FISH*
- Negative for gain of 1q21
- Negative for loss of chromosome 13q
- Negative for loss of TP53 and ATM
- Negative for IgH (14q32) and IGH/CCND1 [t(11;14)] rearrangement

*CD138 selected plasma cells

Strategies to Prolong Response

Amrita Y. Krishnan, MD
Professor, Department of Hematology & Hematopoietic Cell Transplantation
Director, Judy and Bernard Briskin Center for Multiple Myeloma Research
City of Hope Medical Center
Duarte, California
Options to Prolong Remission

- Increase depth of response
  - High dose chemotherapy (single versus tandem)
    - EMN02,[1] BMT-CTN0702[2]
- Prolong therapy
  - Consolidation
    - RVD: EMN02/HO95,[3] BMTCTN0702 Stamina²
    - Zimmerman (KRd)⁴ Roussel (KRd)⁵
  - Maintenance
    - Myeloma XI[⁶]


IFM/DFCI 2009 Study Schema

Registration, newly diagnosed MM pts ≤ 65 years (ASCT candidates)

1. Randomize, stratification ISS & FISH

   ARM A: Late transplant arm

   1 cycle RVD

   Induction

   PBSC collection

   Consolidation

   Maintenance

   US len maintenance till progression

   RVD, cycles 2, 3

   CY (3g/m²) + G-CSF MOBILIZATION

   Goal: 5 x 10⁸ cells/kg

   RVD × 5

   Lenalidomide (10–15 mg/d)

   12 mos

   SCT at relapse

   MEL 200 mg/m² if <65 yrs,

   ≥ 65 yrs 140 mg/m²

   ARM B: Early transplant arm

   1 cycle RVD

   Induction

   PBSC collection

   Consolidation

   Maintenance

   US len maintenance till progression

   RVD, cycles 2, 3

   CY (3g/m²) + G-CSF MOBILIZATION

   Goal: 5 x 10⁸ cells/kg

   RVD × 2

   Lenalidomide (10–15 mg/d)

   12 mos

   MEL 200 mg/m²

IFM 2009: Best Response

<table>
<thead>
<tr>
<th></th>
<th>RVD Arm N=350</th>
<th>Transplant Arm N=350</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (%)</td>
<td>49</td>
<td>59</td>
<td>0.02</td>
</tr>
<tr>
<td>VGPR (%)</td>
<td>29</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>PR (%)</td>
<td>20</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>&lt;PR (%)</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>At least VGPR (%)</td>
<td>78</td>
<td>88</td>
<td>0.001</td>
</tr>
<tr>
<td>Neg MRD by FCM, n (%)</td>
<td>228 (65%)</td>
<td>280 (80%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

IFM 2009: PFS (9/2015)

![Graph showing PFS (Progression-Free Survival) comparison between HDT and no HDT groups. The graph illustrates the percentage of patients at risk over time.](image)

At least VGPR (%) 78 88 0.001
Neg MRD by FCM, n (%) 228 (65%) 280 (80%) 0.001

**IFM 2009: OS (9/2015)**

![Graph showing patients' survival rates with and without high-dose therapy (HDT) over months of follow-up. The graph includes data from Attal M et al. Blood. 2015;126: Abstract 391.](image)

**N at risk**
- HDT: 350, 328, 309, 226, 55
- no HDT: 350, 338, 320, 244, 56

**IFM 2009: Cause of Death (9/2015)**

<table>
<thead>
<tr>
<th></th>
<th>RVD Arm N=48</th>
<th>Transplant N=54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma, n (%)</td>
<td>40/48 (83)</td>
<td>35/54 (65)</td>
</tr>
<tr>
<td>Toxicity, n (%)</td>
<td>4/48 (8)</td>
<td>9*/54 (16)</td>
</tr>
<tr>
<td>SPM, n (%)</td>
<td>1/48 (2)</td>
<td>6/54 (11)</td>
</tr>
<tr>
<td>Others, n (%)</td>
<td>3/48 (6)</td>
<td>4/54 (7)</td>
</tr>
</tbody>
</table>

*Including 5 transplant related deaths.

Intensification Therapy with Bortezomib-Melphalan-Prednisone Versus Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: An Intergroup, Multicenter, Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial)

Upfront HDM and ASCT significantly improved PFS and increased the rate of high quality responses.

High Dose Therapy: Single vs Tandem


Increase Depth of Response: MRD

RVD Arm

Transplant Arm

N at risk
MRD pos 89 75 54 22 2
MRD neg 140 135 113 72 14

N at risk
MRD pos 65 57 43 30 4
MRD neg 172 166 151 86 17

Flow cytometry
- Feasible in 100% of patients
- Does not require diagnostic sample
- Widely available/low cost

NGS (adaptive)
- Sensitivity <10^{-6}
- Frozen samples
- Fully standardized

MRD: Still ??

Advantages

Disadvantages

Flow cytometry
- Fresh sample (<24–48 h)
- Sensitivity 10^{-4}–10^{-5}
- Lack of standardization (operator)

NGS (adaptive)
- Requires diagnostic sample (clone ID)
- Feasibility
Sensitivity Matters

MRD at post-maintenance

N at risk (events)

\[10^{-4}; 10^{-3}\] 86 (0) 86 (0) 86 (0) 86 (0) 86 (0) 86 (5) 77 (3) 61 (5) 36 (0) 10

\[10^{-5}; 10^{-4}\] 29 (0) 29 (0) 29 (0) 29 (0) 28 (5) 22 (3) 16 (4) 4 (1) 4 (1) 1

\[10^{-6}; 10^{-5}\] 23 (0) 23 (0) 23 (0) 23 (1) 22 (3) 19 (2) 14 (5) 3 (0) 2

\[10^{-7}; 10^{-6}\] 40 (0) 40 (0) 40 (0) 40 (0) 33 (9) 23 (6) 15 (4) 4 (1) 2

Patients Without Progression (%)

P value (trend): P<0.0001

Association of MRD With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-Analysis

- 14 studies
- MRD negativity correlated with PFS/OS
- 5 trials included ASCT
- PCR > MFC (sensitivity)
- Only 1 study showed predictive value in unfavorable cytogenetics
- 10 studies maintenance (2 post maintenance)


**IMWG Criteria for Response and MRD Assessment in MM**

**Sustained MRD-negative**
- MRD negativity in the marrow (NGF, NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)

**Flow MRD-negative**
- Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher

**Sequencing MRD-negative**
- Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher

**Imaging plus MRD-negative**
- MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue

**Kumar S et al. Lancet Oncol. 2016;17:e328.**

---

**Prolong Response: Consolidation**

**BMT CTN 0702**

- Register and Randomize
- MEL 200mg/m²
- VRD x 4
- MEL 200mg/m²
- Lenalidomide Maintenance AM
- Lenalidomide Maintenance ACM
- Lenalidomide Maintenance TAM

<table>
<thead>
<tr>
<th></th>
<th>ASCT with Len Maintenance (AM)</th>
<th>Consolidation with Len Maintenance (ACM)</th>
<th>Tandem ASCT with Len Maintenance (TAM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>257</td>
<td>254</td>
<td>247</td>
</tr>
<tr>
<td>38-mo PFS (%)</td>
<td>52</td>
<td>57</td>
<td>56</td>
</tr>
</tbody>
</table>

**Stadtmayer EA et al. Blood. 2016;128: Abstract LBA-1.**
**Prolong Response: Consolidation**

EMN02/HO95

- **R1**
  - Induction: 3-4, 21-day cycles (CyBorD)
  - Consolidation: VMP (4, 42-day cycles)
  - Maintenance: HDM + Double ASCT

- **R2**
  - Induction: 3-4, 21-day cycles (CyBorD)
  - Consolidation: HDM + Single ASCT
  - Maintenance: Lenalidomide

### Induction

<table>
<thead>
<tr>
<th>Consolidation</th>
<th>No Consolidation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year PFS (%)</td>
<td>65</td>
<td>60</td>
</tr>
</tbody>
</table>

Not retained in high risk cytogenetics (0.91)


**Prolong Response: Consolidation**

### Phase 2 US Study

- **Induction** (Cycles 1–4): KRd
- **Consolidation** (Cycles 5–8): ASCT
- **Maintenance** (Cycles 9–18): KRd

### Phase 2 IFM Study

- **Induction** (Cycles 1–4): KRd
- **Consolidation** (Cycles 5–8): ASCT
- **Maintenance**: Lenalidomide, 1 Year

<table>
<thead>
<tr>
<th>KRd is now being compared with VRd in a randomized clinical trial.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Phase 2 US Study</th>
<th>Post SCT</th>
<th>Post KRd Consol</th>
<th>Post KRd Maint</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD (%) MFC/NGS</td>
<td>--</td>
<td>82/66</td>
<td>90/71</td>
</tr>
<tr>
<td>sCR (%)</td>
<td>20</td>
<td>69</td>
<td>82</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2 IFM Study</th>
<th>Post Induction (n=46)</th>
<th>Post ASCT (n=42)</th>
<th>Post Consol (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD (%) by flow</td>
<td>63</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>CR + sCR (%)</td>
<td>26</td>
<td>45</td>
<td>69</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>98</td>
<td>98</td>
<td>98</td>
</tr>
</tbody>
</table>

Prolonging Response: Maintenance

- What is the optimal drug?
- What is the optimal duration of maintenance?
- What is the benefit of maintenance?
- Ultimate goal; prolonged survival

Maintenance Therapy Post SCT: What Is Known

- Bortezomib maintenance; HOVON\(^1\)
- Lenalidomide maintenance after ASCT reduces the risk of progression or death by approximately 50\%\(^2-5\)
- All phase 3 studies had progression-free survival as the primary end point

**HOVON Study Schema**

- **MM Stage II or III, Age 18–65**
- **3 x VAD**
  - CAD + GCSF
  - MEL 200 + PBSCT
  - Thalidomide maintenance 50 mg/day for 2 years
- **3 x PAD**
  - CAD + GCSF
  - MEL 200 + PBSCT
  - Allogeneic transplant
- **Bortezomib 1.3 mg/m² i.v., 2x/w**
  - Maintenance 1.3 mg/m²/2 weeks for 2 years
- **Doxorubicin 9 mg/m²**
- **Dexameth 40 mg**

**OS by Treatment Arm**

- **A: VAD**
  - Randomization Arm
  - Overall Survival
  - Cox LR Stratified $P=0.22$
  - OS at 96 m: 48% vs 45%
  - HR: 0.87, 95% CI 0.71–1.04; $P=0.22$
  - RMST8y: 4.8 months (95% CI 0.2–9.5; $P=0.04$)


Studies Included in Meta-Analysis

**CALGB 100104**

- **INDUCTION ASCT**
  - 1:1 RANDOMIZATION
  - "NO EVIDENCE OF PD"

- **LEN MNTCa** (n=231)
- **PLACEBO** (n=229)

**IFM 2005-02**

- **INDUCTION ASCT**
  - 1:1 RANDOMIZATION
  - "NO EVIDENCE OF PD"

- **LEN MNTCb** (n=67)
- **NO TREATMENT** (n=68)

**GIMEMA (RV-MM-PI-209)**

- **2 × 2 DESIGN LEN + DEX × 4 INDUCTION**

**Primary Analysis**

- **LEN MNTCa** (n=307)
- **PLACEBO** (n=307)

**TARGET POPULATION OF PATIENTS WITH NDMM WHO RECEIVED LEN MAINTENANCE OR PLACEBO/NO MAINTENANCE AFTER ASCT**

- **INTERIM ANALYSIS AND UNBLINDING**
  - Dec 2009
  - Jan 2010

- **CROSSOVER BEFORE PD ALLOWED**
  - CONTINUED TREATMENT

- **ALL TREATMENT DISCONTINUED**
  - Jan 2011

- **INTERIM ANALYSIS AND UNBLINDING**
  - Dec 2009
  - Jan 2010

- **CROSSOVER BEFORE PD ALLOWED**
  - CONTINUED TREATMENT

**Overall Survival: Median Follow-Up of 80 Months**

There is a 26% reduction in risk of death, representing an estimated 2.5-year increase in median survival.a

<table>
<thead>
<tr>
<th>Overall Survival, mos</th>
<th>Survival Probability</th>
<th>Patients at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 0.0 10 20 30 40 50 60 70 80 90 100 110 120</td>
<td>0.0 0.2 0.4 0.6 0.8 1.0</td>
<td>605 604 578 555 509 474 431 385 282 200 95 20 1 0</td>
</tr>
</tbody>
</table>

- **Median for lenalidomide treatment arm was extrapolated to be 116 months based on median of the control arm and HR (median, 86 months; HR = 0.74).**

**Overall Survival of 7 Years**

- **Median OS (95% CI), mos**
  - LEN: 86.0 (79.8–96.0)
  - CONTROL: NE (NE–NE)

- **HR (95% CI)**
  - 0.74 (0.62–0.89)
  - **P value**
    - 0.001

**Cumulative Incidence of Second Primary Malignancies**

**Hematologic**

- **Lenalidomide**
  - HR (95% CI): 2.03\(^a\) (1.14–3.61)
  - \(P=0.015\)^\(^b\)

- **Control**

**Solid Tumor**

- **Lenalidomide**
  - HR (95% CI): 1.71\(^a\) (1.04–2.79)
  - \(P=0.032\)^\(^b\)

\(^a\) HR based on Cox proportional hazards model.
\(^b\) \(P\) value is based on log-rank test.

---

**Lenalidomide is Highly Effective Maintenance Therapy in MM: Phase 3 Myeloma XI study**

- Lenalidomide continued to disease progression versus no therapy in both newly diagnosed transplant eligible (TE) and transplant non-eligible (TNE) populations

<table>
<thead>
<tr>
<th></th>
<th>TE (n=828)</th>
<th>TNE (n=722)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maint</td>
<td>No Maint</td>
<td>Maint</td>
</tr>
<tr>
<td>Median PFS (mos)</td>
<td>60</td>
<td>28</td>
<td>26</td>
</tr>
</tbody>
</table>

- Hematologic second primary malignancy 0.9% with maintenance vs 0.3% with no maintenance
Ultimate Goal: Prolong Survival

- High dose therapy (IFM/DFCI, EMN02, BMTCTN)
- Consolidation (EMN02, BMTCTN)
- Maintenance
  - Lenalidomide: Estimated 2.5-year improvement in median overall survival
  - Bortezomib: Estimated 5-month improvement in overall survival

Future: MRD-directed therapy

Panel Discussion
Patient Case 3

Robert M. Rifkin, MD
Associate Chair – US Oncology Research
Disease Lead – Multiple Myeloma
Attending Physician
Rocky Mountain Cancer Centers
Denver, Colorado

Case Study 3

• 73-year-old man with a 7-year history of IgG kappa MGUS

• Experiences evolution of disease to symptomatic myeloma:
  – IgG has increased to 7,233 mg/dL
  – Hgb has fallen to 8.5 gm/dL
  – Bone marrow is 60% cellular with 50% plasma cells that are CD138(+)
  – Marrow cytogenetics shows 46,XY
  – Myeloma FISH panel is negative

• The patient is placed on lenalidomide and dexamethasone
  – Achieves VGPR after 2½ years of therapy
  – Stops this due to diarrhea and asthenia
Case Study 3

- Patient becomes anemic again after being off of therapy for 9 months
- He then moves to Colorado, where he reports dyspnea that he feels is due to the altitude
  - IgG is 8592 mg/dL
  - Hgb is 8.0 gm/dL
  - Bone marrow biopsy shows 75% cellularity with 80% plasma cells, some in sheets
  - Conventional cytogenetics are normal
  - FISH panel shows new del17p

Case Study 3

- The patient elects to begin therapy with carfilzomib and dexamethasone; refuses further lenalidomide
- After two cycles, the patient presents with dyspnea; a cardiac echo shows a LVEF of 40%
- Patient also notes left tibial pain; a plain x-ray shows a destructive lesion
- Patient undergoes surgery to place an IM rod in his left femur following treatment of his presumed carfilzomib cardiomyopathy
- Patient now returns to clinic to discuss his next therapy after completion of five fractions of radiation to his tibia
## Case Study 3: Labs

<table>
<thead>
<tr>
<th>CBC with differential</th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC ($\times 10^3$/mL)</td>
<td>3,400</td>
<td>(4–11)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.9</td>
<td>(13–16)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>31.6</td>
<td>(34–45)</td>
</tr>
<tr>
<td>Platelets ($\times 10^3$/mL)</td>
<td>164</td>
<td>(150–400)</td>
</tr>
<tr>
<td>Neutrophils ($\times 10^3$/mL)</td>
<td>2.1</td>
<td>(1.9–7.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CMP</th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>24</td>
<td>(7–20)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.85</td>
<td>(0.7–1.2)</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>7.6</td>
<td>(8.4–10.2)</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>10.6</td>
<td>(6.3–8.2)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>1.7</td>
<td>(3.5–5.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SPEP</th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF-IgGk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M protein spike (g/dL)</td>
<td>4.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quantitative IgG + serum immunofixation</th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (mg/dL) (H)</td>
<td>8,431</td>
<td>(700–1,800)</td>
</tr>
<tr>
<td>IgA (mg/dL) (L)</td>
<td>&lt;30</td>
<td>(70–400)</td>
</tr>
<tr>
<td>IgM (mg/dL) (L)</td>
<td>&lt;5</td>
<td>(40–230)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FLC</th>
<th>Actual Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kappa quant FLC (mg/L)</td>
<td>760.4 (H)</td>
<td>(3.30–19.40)</td>
</tr>
<tr>
<td>Lambda quant FLC (mg/L)</td>
<td>13.67 (H)</td>
<td>(5.71–26.30)</td>
</tr>
<tr>
<td>Kappa/lambda quant FLC ratio</td>
<td>55.62 (H)</td>
<td>(0.26–1.65)</td>
</tr>
</tbody>
</table>

## New Agents, Classes in the Relapsed Setting

**Faith E. Davies, MBBCh, MRCP, MD, FRCPPath**

Professor of Medicine
Medical Director, Myeloma Institute
University of Arkansas for Medical Sciences
Little Rock, Arkansas
Factors Affecting Treatment Decisions in RRMM

**First-line therapy**
- Class of prior therapy*: degree of response to prior therapy; PFS: tolerability of prior therapy (treatment-related AEs)

**Salvage therapies**
- Patient-related factors: age, PS, counts, PN, VTE, RI, cytogenetic profile, extramedullary involvement, etc
- Aggressiveness of disease and prognostic features
- Number and degree of relapses and refractory disease

Disease progression

*IMiD-based, proteasome-based, alkylators, dexamethasone.

Current Therapies for RRMM 1–3 Lines Can Be Classified by the Drug’s Mechanism of Action

- **Proteasome inhibitors**
  - Bortezomib
  - Carfilzomib
  - Ixazomib

- **Immunomodulators**
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
  - Daratumumab

- **Alkylators**
  - High-dose melphalan
  - Bendamustine
  - Cyclophosphamide

- **Steroids**
  - Dexamethasone
  - Prednisolone
  - Methyl prednisolone

Critical to understand treatment patterns specific to your own country/region as drug approval variability exists.
Two Important Questions

• Which drugs do I use in the combination?
  – Individualize the drug choice toward the specific patient
  – Take advantage of different mechanisms of action

• How many drugs should I use?
  – Aim for a triplet
  – Monitor closely and manage the side effects
  – Staying on treatment is the key
### Plethora of New Randomized Studies to Help Guide Treatment Decisions

<table>
<thead>
<tr>
<th>Control Arm</th>
<th>Comparator Arm</th>
<th>Trial Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide and dexamethasone</td>
<td>Carfilzomib, lenalidomide, and dexamethasone</td>
<td>ASPIRE</td>
</tr>
<tr>
<td></td>
<td>Elotuzumab, lenalidomide, and dexamethasone</td>
<td>ELOQUENT 2</td>
</tr>
<tr>
<td></td>
<td>Ixazomib, lenalidomide, and dexamethasone</td>
<td>TOURMALINE 1</td>
</tr>
<tr>
<td>Bortezomib and dexamethasone</td>
<td>Carfilzomib and dexamethasone</td>
<td>ENDEAVOR</td>
</tr>
<tr>
<td></td>
<td>Panobinostat, bortezomib, and dexamethasone</td>
<td>PANORAMA 1</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Pomalidomide and dexamethasone</td>
<td>MM03 NIMBUS</td>
</tr>
<tr>
<td>No transplant</td>
<td>High-dose melphalan</td>
<td>Myeloma X</td>
</tr>
</tbody>
</table>

### Differences Between Studies in Baseline Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRE¹</td>
<td>792</td>
<td>Carfilzomib-lenalidomide-dexamethasone (KRd) vs lenalidomide-dexamethasone (Rd)</td>
</tr>
<tr>
<td>ELOQUENT-2²</td>
<td>646</td>
<td>Elotuzumab-lenalidomide-dexamethasone (Erd) vs lenalidomide-dexamethasone (Rd)</td>
</tr>
<tr>
<td>TOURMALINE-MM1³</td>
<td>722</td>
<td>Ixazomib-lenalidomide-dexamethasone (Ird) vs placebo-lenalidomide-dexamethasone (Rd)</td>
</tr>
<tr>
<td>ENDEAVOR⁴</td>
<td>929</td>
<td>Carfilzomib-dexamethasone (Kd) vs bortezomib-dexamethasone (Vd)</td>
</tr>
</tbody>
</table>

Proportion of patients with refractory disease, disease stage ISS III, low creatinine clearance, high risk cytogenetics

ASPIRE: Carfilzomib-Lenalidomide-Dexamethasone (KRd) vs Lenalidomide-Dexamethasone (Rd)

• Phase 3, open-label, randomized, multicenter study

N=792 RRMM patients

KRd
CFZ: 20/27 mg/m², d 1–2*, 8–9, 15–16
LEN: 25 mg, d 1–21
DEX: 40 mg, d 1, 8, 15, 22
Twelve 28-day cycles

KRd
CFZ: 27 mg/m², d 1, 2, 15, 16
LEN: 25 mg, d 1–21
DEX: 40 mg, d 1, 8, 15, 22
Six 28-day cycles

Rd
LEN: 25 mg, d 1–21
DEX: 40 mg, d 1, 8, 15, 22
28-day cycles until progression

• Stratified for previous Bortezomib therapy
• Patients received antiviral and antithrombotic prophylaxis
• Primary end point: PFS
• Secondary end points: OS, ORR, DoR, HRQoL, safety

*Carfilzomib is administered at 20 mg/m² on Days 1 and 2


ASPIRE: KRd vs Rd

Efficacy

<table>
<thead>
<tr>
<th></th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
<th>HR; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>26.3</td>
<td>17.6</td>
<td>HR = 0.69; (P=0.0001^*)</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>NR</td>
<td>73.3</td>
<td>HR = 0.79; (P=0.04^†)</td>
</tr>
<tr>
<td>2-year OS, %</td>
<td>NR</td>
<td>65.0</td>
<td>—</td>
</tr>
<tr>
<td>Time to response, months</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>28.6</td>
<td>21.2</td>
<td>NR</td>
</tr>
</tbody>
</table>

• Median follow-up was 32.3 months for KRd and 31.5 months for Rd
• PFS benefit for KRd was observed across all predefined subgroups‡

*Prespecified stopping boundary was met
†Interim analysis, prespecified stopping boundary was not met
‡Predefined subgroups included sex, age, geographic region, β2M level, cytogenetics, peripheral neuropathy at baseline, prior BORT, prior LEN, any prior IMiD, nonresponsive to BORT in prior regimen, refractory to prior IMiD

ASPIRE: KRd vs Rd
Progression-Free Survival

Figure 1, page 148

Rd (n = 325)
LEN: 25 mg, d1–21
DEX: 40 mg, d1, 8, 15, 22
28-day cycles until progression

ERd (n = 321)
ELO: 10 mg/kg, d1, 8, 15, 22 IV (cycles 1–2); d1, 15 (cycles ≥ 3);
LEN: 25 mg, d1–21
DEX: weekly equivalent, 40 mg
28-day cycles until progression

ELOQUENT 2: Elotuzumab-Rd (ERd) vs Rd

N=646 RRMM
1–3 prior lines
Not LEN-refractory

ERd (n = 321)
ELO: 10 mg/kg, d1, 8, 15, 22 IV (cycles 1–2); d1, 15 (cycles ≥ 3);
LEN: 25 mg, d1–21
DEX: weekly equivalent, 40 mg
28-day cycles until progression

Rd (n = 325)
LEN: 25 mg, d1–21
DEX: 40 mg, d1, 8, 15, 22
28-day cycles until progression

• Primary end points: PFS, ORR
• Secondary end points: OS, DoR, QoL, safety

**ELOQUENT-2: ERd vs Rd**

**Efficacy**

<table>
<thead>
<tr>
<th>Responses</th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR 79%a</td>
<td>4</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>ORR 66%*</td>
<td>7</td>
<td>21</td>
<td></td>
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</tbody>
</table>

**Median PFS, months**

<table>
<thead>
<tr>
<th></th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19.4</td>
<td>14.9</td>
<td>0.73; 0.0014</td>
</tr>
</tbody>
</table>

**Median TTNT, months**

<table>
<thead>
<tr>
<th></th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33</td>
<td>21</td>
<td>0.62 (95% CI 0.50–0.77)</td>
</tr>
</tbody>
</table>

**Median OS, months**

<table>
<thead>
<tr>
<th></th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.7</td>
<td>39.6</td>
<td>0.77; 0.0257</td>
</tr>
</tbody>
</table>

**Median DoR, months**

<table>
<thead>
<tr>
<th></th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20.7</td>
<td>16.7</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Values may not sum due to rounding.


---

**ELOQUENT-2: ERd vs Rd**

**Progression-Free Survival**

**Figure 1, page 627**


---

**Figure 1, page 627**


**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
<th>HR; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19.4 (16.6–22.2)</td>
<td>14.9 (12.1–17.2)</td>
<td>0.73; 0.0014</td>
</tr>
</tbody>
</table>

**3-yr PFS, %**

<table>
<thead>
<tr>
<th></th>
<th>ERd (n=321)</th>
<th>Rd (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26</td>
<td>18</td>
</tr>
</tbody>
</table>

TOURMALINE-MM1: Ixazomib-Lenalidomide-Dexamethasone vs Lenalidomide-Dexamethasone

**FOLLOW-UP**
Every 4 weeks until PD, then every 12 weeks for OS

**N=722**
Pts with RRMM
1–3 prior therapies
Not LEN- or PI-refractory

Stratification:
- Prior treatment
- ISS stage
- PI exposure

• Primary end point: PFS by independent review committee using IMWG criteria
• Key secondary end points: OS, OS in high-risk patients† with del(17)

**IRd**
LEN: 25 mg* PO d1–21
DEX: 40 mg PO d1, 8, 15, 22
IXA: 4 mg PO d1, 8, 15
28-day cycles

**Rd + Placebo**
LEN: 25 mg* PO d1–21
DEX: 40 mg PO d1, 8, 15, 22
Placebo: PO d1, 8, 15
28-day cycles

*10 mg for pts with CrCl ≤ 60 or ≤ 50 mL/min, depending on local practice/label.
†High-risk was defined as del(17p), t(4;14), or t(l4;16), including 10% del(17p).


---

**TOURMALINE-MM1: IRd vs Rd**

**Efficacy Summary**

Table 2, page 1626


*Values may not sum due to rounding.

TOURMALINE-MM1: IRd vs Rd
PFS Analysis

Figure 1, page 1627

- Consistent PFS benefit across pre-specified patient subgroups

ENDEAVOR Study Design

Randomization 1:1
N=929
Stratification:
- Prior proteasome inhibitor therapy
- Prior lines of treatment
- ISS stage
- Route of administration

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 NÀÏVE OR BOR SENSITIVE

ENDEAVOR: Kd vs Vd in RRMM

Progression-Free Survival

- Median follow-up: 11.9 mos for Kd; 11.1 mos for Vd

<table>
<thead>
<tr>
<th></th>
<th>Kd (n=464)</th>
<th>Vd (n=465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>18.7</td>
<td>9.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(15.6–NE)</td>
<td>(9.4–0.4)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P value</td>
<td>(0.44–0.65)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Predefined subgroups included sex, age, geographic region, ECOG performance status, baseline creatinine clearance, previous peripheral neuropathy, disease stage, cytogenetics, number of prior regimens, prior transplant, prior BORT, prior IMiD, prior LEN, prior THAL, refractory to prior BORT, refractory to prior LEN.

PANORAMA 1: Panobinostat + Bortezomib and Dexamethasone vs Bortezomib and Dexamethasone

- Multicenter, randomized, double-blind, placebo-controlled, phase 3 study

Study population

- N = 768
- 1–3 lines prior therapy
- Measurable M protein component in serum or urine at study screening
- ECOG ≤2

Treatment phase 1 (TP1)

- PanVD (21-day cycle)
  - Panobinostat
  - 20 mg PO on d1, 3, 5, 8, 10, 12
  - Bortezomib
  - 1.3 mg/m² IV on d1, 4, 8, 11
  - Dexamethasone
  - 20 mg PO on d1, 2, 4, 5, 8, 9, 11, 12

Treatment phase 2 (TP2)

- Placebo + VD (21-day cycle)
  - Placebo
  - Bortezomib
  - As above
  - Dexamethasone
  - As above

PanoVD for RRMM Patients Who Received Prior Bortezomib and IMiDs

- Subgroup analysis of patients who received ≥2 previous treatments, including bortezomib and an IMiD indication based on subgroup analysis

Figure 1, page 716

MM-003 NIMBUS: Pomalidomide Dexamethasone vs Dexamethasone

28-day cycles

RANDOMIZATION 2:1 (N=455)

POM*: 4 mg/day Day 1–21 +
LoDEX: 40 mg (≤75 years)
20 mg (>75 years)
Day 1, 8, 15, 22

(n=302)

HiDEX: 40 mg (≤75 years)
20 mg (>75 years)
Day 1–4, 9–12, 17–20

(n=153)

Follow-up for OS and SPM until 5 years post-enrollment

PD

Companion trial MM-003C
POM 21/28 days

Companion trial MM-003C
POM 21/28 days

Stratification
- Age (≤75 vs >75 yrs)
- Number of prior treatments (2 vs >2)
- Disease population (primary refractory vs relapsed/refractory vs intolerance/failure)

Primary end point: PFS

*Thromboprophylaxis was indicated for those receiving POM or with deep vein thrombosis history.

MM-003 NIMBUS: POM + LoDEX vs HiDEX PFS

Median Follow-Up 15.4 months

Adapted from Figure 2, page 1059


Myeloma X: Autologous Transplantation vs Ongoing Chemotherapy

N=297

Bortezomib, doxorubicin, dexamethasone (PAD)

Response ≥SD

PBSC mobilization

PD or CD34+ cells <2 x 10^6/kg

Off study

Melphalan 200mg/m² IV ASCT

Cyclophosphamide 400 mg/m² PO/week × 12

Follow-up

N=89

N=89

ASPIRE: Carfilzomib (KRd vs Rd)

**Safety Profile**

- 15% of patients in the KRd group and 18% in the Rd group discontinued treatment due to AEs
- 8% of patients in the KRd group and 9% in the Rd group died while on treatment or within 30 days of last dose
## ENDEAVOR: Carfilzomib (Kd vs Vd)
### Cardiac Substudy

<table>
<thead>
<tr>
<th>All grades</th>
<th>Cardiac Substudy</th>
<th>Overall Safety Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kd (N=74)</td>
<td>Vd (N=74)</td>
</tr>
<tr>
<td>Cardiac arrhythmias (SMQN)</td>
<td>3 (4.1)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Cardiac failure (SMQN)</td>
<td>8 (10.8)</td>
<td>3 (4.1)</td>
</tr>
<tr>
<td>Decreased ejection fraction</td>
<td>4 (5.4)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>3 (4.1)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Cardiac failure acute</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac failure chronic</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Right ventricular failure</td>
<td>0</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Ischemic heart disease (SMQN)</td>
<td>0</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>31 (41.9)</td>
<td>25 (33.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (20.3)</td>
<td>6 (8.1)</td>
</tr>
</tbody>
</table>

---

## ELOQUENT-2: Elotuzumab (ERd vs Rd)
### Safety Profile

Table 3, page 630


---


TOURMALINE-MM1: IRd vs Rd
Safety Profile

Table 4, page 1630

MM03 NIMBUS Pom Dex vs Dex
Safety Profile

Table 4, page 1630
Conclusions

• Many choices
  – Good response, improved PFS, good safety profiles
• Individualize the choice toward the specific patient
  – Type of relapse
  – Previous therapy received
  – Previous side effects
  – Oral vs IV
• Aim for a triplet
• Monitor closely and manage side effects
  – Staying on treatment is the key

The Way Forward: Immunotherapy

Paul G. Richardson, MD
R.J. Corman Professor of Medicine
Harvard Medical School
Clinical Program Leader and Director of Clinical Research
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Boston, Massachusetts
Key Targets in MM

- Excess protein production
  >> Target protein degradation
- Genomic abnormalities and acquired resistance
  >> Target and overcome mutations
- Immune suppression
  >> Restore anti-MM immunity

WGS at Diagnosis

Courtesy of Nikhil Munshi MD, DFCI
Restoring Immune Function

- Immunomodulatory drugs, other small molecules (eg, HDACi’s)
- Monoclonal antibodies
- Checkpoint inhibitors
- Vaccines
- Cellular therapies
Lenalidomide and Pomalidomide in MM


Immunomodulatory Agents
IMiDs: Mechanism of Action

Adapted from Figure, page 347
Model of Lenalidomide and Pomalidomide Costimulation of T Cells via Degradation of Aiolos and Ikaros

Figure 9, page 819


Efficacy Results of POMALIDOMIDE + LoDEX in Advanced RRMM (Phase 2/3: MM002 & MM003)

ORR = 33%
ORR = 32%

<table>
<thead>
<tr>
<th>Percentage Response</th>
<th>MM-002</th>
<th>MM-003</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-002 (n=113)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM-003 (n=302)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up, months</td>
<td>14.2</td>
<td>15.4</td>
</tr>
<tr>
<td>Median DoR, months</td>
<td>8.3</td>
<td>7.5</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>4.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>16.5</td>
<td>13.1</td>
</tr>
</tbody>
</table>

Monoclonal Antibodies Kill MM Through Multiple Mechanisms

**DIRECT EFFECTS**
- Interferes with survival or delivers myeloma-killing substances

**INDIRECT EFFECTS**
- Labels myeloma cells for killing by complement
- Labels myeloma cells for killing by NK cells
- Activates T cells by taking the brakes off

Elotuzumab: Immunostimulatory Mechanism of Action

- Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7, a protein highly expressed by myeloma and natural killer cells
- Elotuzumab causes myeloma cell death via a dual mechanism of action

A Directly activating natural killer cells
B Tagging for recognition (ADCC)

Adapted from Richardson PG, ASH 2012

ELOQUENT-2 demonstrated clinical benefits of E-Ld compared with lenalidomide and dexamethasone (Ld) alone.


From Table 2, page 629


Elotuzumab in High-Risk Patients

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)

- **t(4;14)+**
  - Hazard ratio: 0.53
  - (95% CI, 0.29–0.95)

Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity\(^1\)-\(^5\)
- Depletes CD38+ immunosuppressive regulatory cells\(^5\)
- Promotes T-cell expansion and activation\(^5\)


Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma

Daratumumab Monotherapy: Efficacy in Combined Analysis

Figure 4, page 42

Daratumumab Phase 2 Study
Single Agent in RRMM

Daratumumab Phase 2 Study
Single Agent in RRMM

**Progression-Free and Overall Survival**

- **Median PFS = 3.7 months** (95% CI, 2.8–4.6)
- 29 of 31 responders are still alive
- 1-year survival rate 65% (95% CI, 51.2–75.5)

Figure 4, page 1558

Synergistic With Other Standard MM Therapies, Including Bortezomib and Lenalidomide

Modified from Figure 1, page e42
Phase 3 Randomized Controlled Study of DVd vs Vd in Pts With Relapsed or Refractory MM: CASTOR

CASTOR Study Design
Multicenter, randomized, open-label, active-controlled phase 3 study

Key eligibility criteria
- RRMM
- ≥1 prior line of therapy
- Prior bortezomib exposure, but not refractory

Randomize 1:1

DVd (n=251)
- Daratumumab (16 mg/kg IV)
  - Every week: cycles 1–3
  - Every 3 weeks: cycles 4–8
  - Every 4 weeks: cycles 9+
- Vel: 1.3 mg/m² SC, days 1, 4, 8, 11: cycles 1–8
- Dex: 20 mg PO-IV, days 1, 2, 4, 5, 8, 9, 11, 12: cycles 1–8

Vd (n=247)
- Vel: 1.3 mg/m² SC, days 1, 4, 8, 11: cycles 1–8
- Dex: 20 mg PO-IV, days 1, 2, 4, 5, 8, 9, 11, 12: cycles 1–8

Primary end point
- PFS

Secondary end point
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

Statistical analyses
- 295 PFS events: 85% power for 4.3 month PFS
- Interim analysis: ~177 PFS events

Daratumumab IV administered in 1,000 mL to 500 mL; gradual escalation from 50 mL to 200 mL/hour permitted.
Phase 3 Randomized Controlled Study of DVd vs Vd in Pts With Relapsed or Refractory MM: CASTOR

### CASTOR Efficacy

<table>
<thead>
<tr>
<th></th>
<th>DVd</th>
<th>Vd</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>251</td>
<td>247</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>NR</td>
<td>7.2</td>
<td>0.39</td>
<td>0.28–0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-year PFS (%)</td>
<td>60.7</td>
<td>26.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median TTP (mos)</td>
<td>NR</td>
<td>7.3</td>
<td>0.30</td>
<td>0.21–0.43</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>83</td>
<td>63</td>
<td>–</td>
<td>–</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥VGPR (%)</td>
<td>59</td>
<td>29</td>
<td>–</td>
<td>–</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥CR (%)</td>
<td>19</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>0.0012</td>
</tr>
<tr>
<td>MRD-negative (10^-4) (%)</td>
<td>14</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median duration of response (mos)</td>
<td>NR</td>
<td>7.9</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>


---

Phase 3 Randomized Controlled Study of DVd vs Vd in Pts With Relapsed or Refractory MM: CASTOR

**CASTOR PFS**

- Median: not reached
- Median: 7.2 months
- 1-year PFS:
  - DVd: 60.7%
  - Vd: 26.9%
- HR: 0.39 (95% CI, 0.28–0.53); P<0.0001
- 61% reduction in the risk of disease progression or death for DVd vs Vd

Daratumumab + Lenalidomide + Dexamethasone: Overall Response Rate

- ORR = 81%
- Clinical benefit rate (ORR + minimal response) = 88%

From Table 4, page 1825


Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma


Phase 3 Randomized Controlled Study of DRd vs Rd in Pts With Relapsed or Refractory MM: POLLUX

**POLLUX Study Design**

**Key eligibility criteria**
- RRMM
- ≥1 prior line of therapy
- Prior lenalidomide exposure, but not refractory
- Patients with creatinine clearance ≥30 mL/min

**Stratification factors**
- No prior lines of therapy
- ISS stage at study entry
- Prior lenalidomide

**Randomize**

1:1

**Cycles: 28 days**

Pre-medication for the DRd treatment group consisted of dexamethasone 20 mg i.v., paracetamol, and an antihistamine.

**RDr (n=286)**
- Daratumumab 16 mg/kg V Qw in Cycles 1–2, q2w in Cycles 3–6, then q4w until PD
- R 25 mg PO
- Days 1–21 of each cycle until PD
- d 40 mg PO
- 40 mg weekly until PD

**Rd (n=283)**
- R 25 mg PO
- Days 1–21 of each cycle until PD
- d 40 mg PO
- 40 mg weekly until PD

**Primary end point**
- PFS

**Secondary end point**
- TTP
- OS
- ORR, VGPR, CR
- MRD
- Time to response
- Duration of response

**Statistical analyses**
- 295 PFS events: 85% power for 7.7 month PFS improvement
- Interim analysis: ~177 PFS events


---

**POLLUX PFS**

12-month PFS* 83%
18-month PFS* 78%

HR: 0.37 (95% CI, 0.27–0.52); P<0.0001

Median PFS: 18.4 months

63% reduction in the risk of disease progression or death for DRd vs Rd

### Phase 3 Randomized Controlled Study of DRd vs Rd in Pts With Relapsed or Refractory MM: POLLUX

#### POLLUX Efficacy

<table>
<thead>
<tr>
<th></th>
<th>DRd</th>
<th>Rd</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>286</td>
<td>283</td>
<td>—</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>93</td>
<td>76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>76</td>
<td>44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥CR</td>
<td>43</td>
<td>19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median duration of response (mos)</td>
<td>NR</td>
<td>17.4</td>
<td>—</td>
</tr>
</tbody>
</table>


#### POLLUX MRD-Negativity Rate

- **MRD-neg (10^-4)**
  - DRd: 30%
  - Rd: 8%
  - P < 0.0001

- **MRD-neg (10^-5)**
  - DRd: 23%
  - Rd: 5%
  - P < 0.0001

- **MRD-neg (10^-6)**
  - DRd: 10%
  - Rd: 2%
  - P < 0.0001

Daratumumab in High-Risk Patients


Updated Data From a Dose Finding Phase II Trial of Single Agent Isatuximab (Anti-CD38 mAb) in Relapsed/Refractory Multiple Myeloma [ASCO 2016]

Joshua Richter,1 Thomas Martin,2 Ravi Vij,3 Craig Cole,4 Djordje Atanackovic,5 Jeffrey Zonder,6 Jonathan Kaufman,7 Joseph Mikhail,8 William Bensinger,9 Meletios Dimopoulos,10 Todd Zimmerman,11 Nikoletta Lendvai,12 Parameswaran Hari,13 Enrique Ocio,14 Cristina Gasparetto,15 Shaji Kumar,16 Corina Oprea,17 Eric Charpentier,17 Stephen Strickland,18 Jesús San Miguel19

1Hackensack University Medical Center, Hackensack, NJ, USA; 2University of California at San Francisco, San Francisco, CA, USA; 3Washington University, St. Louis, MO, USA; 4University of Michigan Comprehensive Cancer Center, Ann Arbor, MI, USA; 5 Huntsman Cancer Institute, Salt Lake City, UT, USA; 6Karmanos Cancer Center, Detroit, MI, USA; 7Winship Cancer Institute of Emory University, Atlanta, GA, USA; 8Mayo Clinic, Scottsdale, AZ, USA; 9Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 10National and Kapodistrian University of Athens, Athens, Greece; 11University of Chicago, Chicago, IL, USA; 12Memorial Sloan-Kettering Cancer Center, New York, NY, USA; 13Medical College of Wisconsin, Milwaukee, WI, USA; 14University Hospital of Katmandu, Katmandu, Nepal; 15Duke University Medical Center, Durham, NC, USA; 16Mayo Clinic, Rochester, MN, USA; 17Sanofi-Genzyme Oncology, Cambridge, MA, USA; 18Vanderbilt-Ingram Cancer Center, Nashville, TN; 19University of Navarra, Pamplona, Spain
**ASCO 2016: Summary**

- Isatuximab was generally well tolerated at ≥10 mg/kg
  - Most infusion reactions were grade 1/2, and occurred during the first infusion
  - Median infusion duration is shorter following the first infusion
- Isatuximab demonstrated single-agent activity in heavily pretreated patients with RRMM
  - Median 5 (2–14) prior lines of therapy
- The ORR was 20%–29% at isatuximab ≥10 mg/kg
  - ORR was similar across subgroups, including high-risk cytogenetics
  - Median duration of response was 8.75–12.9 (3.7–14.8) months
- At isatuximab ≥10 mg/kg, PFS was 3.65 months and OS was 18.63 months
  - 11 patients remained on treatment at data cutoff
  - Median OS has not been reached in the 20 mg/kg QW/Q2W and 10 mg/kg Q2W/Q4W cohorts

---

**Immune Suppressive Microenvironment in MM**

- Tumor promotion and induction of PD-L1 expression
- Stroma

---


Immune Checkpoint Inhibitors in MM

**Target PD-1, PDL-1**

**Allow T cells to function**

**Current agents under investigation in MM:**
- nivolumab and pembrolizumab

**Activity only in combination with other MM agents**

---

**Immune Checkpoint Inhibitors for Relapsed/Refractory Multiple Myeloma**

<table>
<thead>
<tr>
<th></th>
<th>Keynote-023: Pembrolizumab + Lenalidomide and Dexamethasone¹</th>
<th>Phase 2 of Pembrolizumab + Pomalidomide and Dexamethasone²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>RRMM for whom ≥2 prior therapies, including a proteasome inhibitor and an IMiD, have failed</td>
<td>RRMM for whom ≥2 prior therapies, including a proteasome inhibitor and an IMiD, have failed</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>200 mg fixed dose*</td>
<td>200 mg IV every 2 weeks</td>
</tr>
<tr>
<td>IMiD</td>
<td>Lenalidomide: 25 mg</td>
<td>Pomalidomide: 4 mg daily × 21 days</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg (low-dose)</td>
<td>40 mg weekly</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>17 patients; 76% response rate</td>
<td>11 of 22 evaluable patients (50% response rate)</td>
</tr>
</tbody>
</table>

¹Used in the phase 2 portion of study based on MTD/MAD

Harnessing the Immune System to Fight Myeloma

Types of Immunotherapy, Immuno-Oncology

Passive

Monoclonal antibodies

Direct effects
Monoclonal antibody

Antigen

CDC

C1q

MAC

Cell death

Lysis

ADCC

Myeloma cell

Chimeric antigen receptor (CAR) T cells

1. Extract WBCs from patient

2. Modify and expand cells in lab

3. Infuse MM-targeted cells back to patient

Vaccines (therapeutic not preventive)

2. Modify and expand cells in lab

3. Infuse MM-targeted cells back to patient

Durvalumab

Figure 1, page 475
Phase 1 Trial of Vaccination With DC/MM Fusions in RRMM

- Well tolerated, no autoimmunity
- Induced tumor reactive lymphocytes in a majority of patients
- Induced humoral responses to novel antigens (SEREX analysis)
- Disease stabilization in 70% of patients
- DC/MM fusions induce anti-MM immunity in vitro and inhibit MM cell growth in vivo in xenograft models

Vaccines Targeting MM-Specific Peptides in Smoldering MM

- Goal is to prevent evolution of smoldering to active myeloma
- Cocktails of immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses
- Clinical trials:
  - Immune responses to vaccine in all patients
  - Lenalidomide with vaccine to augment immune response
  - Lenalidomide and PDL-1 with vaccine to induce memory
  - Immune response against myeloma
### Therapeutic Vaccines in Development

<table>
<thead>
<tr>
<th>MM Vaccine</th>
<th>Patient Types</th>
<th>Study Phase</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dendritic cell fusion vaccine + CT-011 (monoclonal antibody) Post-transplant*</td>
<td>2</td>
<td>Beth Israel Deaconess Medical Center/ Dana-Farber</td>
<td></td>
</tr>
<tr>
<td>Hiltonol (MAGE-A3 vaccine Poly-ICLC) Post-transplant*</td>
<td>2</td>
<td>University of Pennsylvania</td>
<td></td>
</tr>
<tr>
<td>Oncolytic measles virus (MV-NIS) RR 1</td>
<td>Mayo Clinic (Rochester, MN)</td>
<td>2 University of Arkansas</td>
<td></td>
</tr>
<tr>
<td>Oncolytic measles virus (MV-NIS) RR 2</td>
<td></td>
<td>Emory/Illinois Cancer Specialists/ Beth Israel Deaconess Medical Center/Massachusetts General Hospital/ DFCI/ MD Anderson Cancer Center</td>
<td></td>
</tr>
<tr>
<td>PVX-410 SMM 1/2</td>
<td></td>
<td>Emory University</td>
<td></td>
</tr>
</tbody>
</table>

*Goal of eliminating any remaining cancer cells

### Immune Cell Therapy in Development

<table>
<thead>
<tr>
<th>Type</th>
<th>Trial</th>
<th>Patient Types</th>
<th>Study Phase</th>
<th>Site(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR T</td>
<td>CART-19 for multiple myeloma</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td></td>
<td>Safety study of CAR-modified T cells targeting NKG2D-ligands</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>Dana-Farber Cancer Institute</td>
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<tr>
<td></td>
<td>Study of T cells targeting B-cell maturation antigen (BCMA) for previously treated multiple myeloma</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>National Cancer Institute University of Pennsylvania</td>
</tr>
<tr>
<td>MILs</td>
<td>Tadalafil and lenalidomide maintenance with or without activated marrow infiltrating lymphocytes (MILs) in high-risk myeloma</td>
<td>Newly diagnosed; relapsed (without prior ASCT)</td>
<td>2</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td></td>
<td>Adoptive immunotherapy with activated marrow- infiltrating lymphocytes and cyclophosphamide graft-versus-host disease prophylaxis in patients with relapse of hematologic malignancies after allogeneic hematopoietic cell transplantation</td>
<td>Relapsed/ refractory</td>
<td>1</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
</tr>
<tr>
<td>Affinity-enhanced T cells</td>
<td>Engineered autologous T cells expressing an affinity-enhanced TCR specific for NY-ESO-1 and LAGE-1</td>
<td>Relapsed/ refractory</td>
<td>1/2</td>
<td>City of Hope University of Maryland</td>
</tr>
<tr>
<td>DLI</td>
<td>CD3/CD28 activated Id-KLH primed autologous lymphocytes</td>
<td>Post-transplant</td>
<td>2</td>
<td>University of Pennsylvania</td>
</tr>
</tbody>
</table>
Myeloma CAR Therapy

- Multiple promising targets:
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1 (SLAMF7), BCMA
- Functional CAR T cells can be generated from MM patients
- CAR T and NK cells have in vitro and in vivo activity against MM
- Clinical trials under way
  - Anecdotal prolonged responses but no robust efficacy data available yet
- Many questions remain about CAR design:
  - Optimal costimulatory domains
  - Optimal vector
  - Optimal dose and schedule
  - Need for chemotherapy
  - Perhaps “cocktails” of multiple CARs or CARs + chemotherapy will be required for best outcomes

MM Pt #1:
Response to CD19 CAR Therapy

Figures 1 and 2, page 1042
**CAR-BCMA T Cells in MM: Study Design**

First-in-human phase 1 trial

- Pts with advanced RRMM; ≥3 prior lines of therapy; normal organ function; clear, uniform BCMA expression on MM cells (N=12)

- CAR-BCMA expression determined by flow cytometry

- Cyclophosphamide 300 mg/m² Fludarabine 30 mg/m² QD for 3 days

- CAR-BCMA T cells* Single Infusion

  *Dose escalation of CAR+ T cells/kg
  0.3 × 10⁶
  1.0 × 10⁶
  3.0 × 10⁶
  9.0 × 10⁶


**CAR-BCMA T Cells in MM: Response**

- Table 1, page 1690

Bi-Specific Antibody (bsAb) Constructs

- Bivalent Antibody conjugates
- Tetravalent Small molecules (eg, BiTEs)


Integration and Impact of Novel Agents, including Immune Therapies

- Innovations (PIs, IMiDs) to date have produced significant improvements in PFS and OS: recent approvals (eg, carfilzomib, ixazomib) will augment this
- Next wave of therapies…crucially, agnostic to mutational thrust?
- Baseline immune function appears to also be a key barrier to success but may be targetable (eg, use of PD1/PDL1 blockade)
- MoAbs (Elo, DARA, ISA) have activity in high-risk disease and represent true new novel mechanisms, as well as other immuno-therapeutics (eg, checkpoint inhibitors, vaccines)
- New insights to mechanisms of drug action (eg, AC 241) are further expanding therapeutic opportunities with combinations
- Numerous other small molecule inhibitors show promise (eg, HDACis, CXCR4, BCL, AKT, CDK, HSP 90, Nuclear Transport, KSP, BET bromodomain proteins/Myc, DUBs, MEK)
- Further refinement of prognostics and MRD will guide therapy
Continuing Evolution of MM Treatment: Selected New Classes and Targets 2016

1st-Generation Novel Agents

- Lenalidomide
- Thalidomide
- Bortezomib
- Bortezomib + Dexamethasone
- Carfilzomib
- Pomalidomide

2nd-Generation Novel Therapies/Immunotherapy

- Monoclonal antibody
- Proteasome inhibitor

- Chemotherapy
- Adoptive T cell therapy
- Checkpoint inhibitors


IMiD HDAC inhibitor Monoclonal antibody Vaccines
Proteasome inhibitor Chemotherapy Adoptive T cell therapy Checkpoint inhibitors

*Not yet FDA-approved for MM; available in clinical trials

Ongoing MM Collaborative Model for Rapid Translation From Bench to Bedside

Pharmaceuticals

Academia

Advocacy

MMRF/C; IMF

IMWG; IMS

NIH NCI

FDA EMEA

19 new FDA-approved drugs/combos/indications in last 13 yrs
Multiple Myeloma Patient Management

NEW AGENTS, NEW CHALLENGES

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