Multiple Myeloma 2014
Brian Berryman, M.D.
March 8th, 2014
History

1844
First documented case

1845
Abnormal urine protein, later termed Bence Jones protein

1895
Description of plasma cells

1928
First large case series of myeloma

1939
Serum protein spike identified

1956
Light chain types (later termed kappa and lambda) recognized

2005
International staging system

2005
Cytogenetic classification


Urethane (N. Alwall)

Melphalan (N. Blokhin)

Corticosteroids (R. E. Maas)

1947

1958

1962

1983

Autologous transplantation (T. J. McElwain and R. L. Powles)

Thalidomide (S. Singhal and B. Barlogie)

1999

Bortezomib (R. Z. Orlowski)

2002

Lenalidomide (P. G. Richardson and K. C. Anderson)

2002

Treatment

Survival in MM

Alexanian A et al. M. D. Anderson historical MM patient survival data (unpublished)
Updates in Multiple Myeloma
CCO Independent Conference Coverage
of the 2013 Annual Meeting of the American Society of Hematology*

December 7-10, 2013
New Orleans, Louisiana

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[Logos of various companies]
Overview of Updates in Multiple Myeloma

- Newly diagnosed multiple myeloma
  - FIRST: Lenalidomide/dexamethasone vs MPT in SCT-ineligible patients
  - MPR or CPR vs lenalidomide/dexamethasone in elderly
  - Carfilzomib/thalidomide/low-dose dexamethasone
  - HOVON-65/GMMG-HD4: bortezomib induction and maintenance
  - MM-015: MP, MPR, MPR-R
  - Lenalidomide maintenance meta-analysis
  - Ixazomib/lenalidomide/dexamethasone
Overview of Updates in Multiple Myeloma

- Relapsed/refractory multiple myeloma
  - Pomalidomide
    - With low-dose dexamethasone vs high-dose dexamethasone
    - With low-dose dexamethasone in patients with del(17p) and/or t(4;14)
    - With carfilzomib/dexamethasone
  - Ixazomib in patients not refractory to bortezomib
  - HDAC-6 inhibitor ACY-1215/bortezomib
Overview of Updates in Multiple Myeloma

- Relapsed/refractory multiple myeloma
  - Kinesin spindle protein inhibitor ARRY 520 (filanesib)
  - Akt inhibitor afuresertib/bortezomib/dexamethasone
  - Daratumumab/bortezomib/dexamethasone
  - Indatuximab ravtansine/lenalidomide/low-dose dexamethasone
  - SAR650984
Newly Diagnosed
Multiple Myeloma
### Updates in Multiple Myeloma

**FIRST: Lenalidomide/Dexamethasone vs MPT in NDMM SCT-Ineligible Patients**

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Continuous Rd</th>
<th>Lenalidomide 25 mg Days 1-21/28</th>
<th>LoDex 40 mg Days 1, 8, 15, 22/28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B</td>
<td>Rd18</td>
<td>Len + LoDex 18 cycles (72 wks)</td>
<td>Lenalidomide 25 mg Days 1-21/28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LoDex 40 mg Days 1, 8, 15, 22/28</td>
<td></td>
</tr>
<tr>
<td>Arm C</td>
<td></td>
<td>Mel + Pred + Thal 12 cycles (72 wks)</td>
<td>Melphalan 0.25 mg/kg Days 1-4/42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisone 2 mg/kg Days 1-4/42</td>
<td>Thalidomide 200 mg Days 1-42/42</td>
</tr>
</tbody>
</table>

**Pts > 75 yrs:** LoDex 20 mg Days 1, 8, 15, 22/28; Thal 100 mg Days 1-42/42; Mel 0.2 mg/kg Days 1-4. Stratification: age, country, and ISS stage.

FIRST Trial: Progression-Free Survival

Median PFS
- Rd (n = 535) 25.5 mos
- Rd18 (n = 541) 20.7 mos
- MPT (n = 547) 21.2 mos

HR:
- Rd vs MPT: 0.72 (P = .00006)
- Rd vs Rd18: 0.70 (P = .00001)
- Rd18 vs MPT: 1.03 (P = .70349)

FIRST Trial: Grade 3/4 Treatment-Related Adverse Events ≥ 5%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Continuous Rd</th>
<th>Rd18</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Neutropenia*</td>
<td>27.8</td>
<td>26.5</td>
<td>44.9</td>
</tr>
<tr>
<td>▪ Anemia</td>
<td>18.2</td>
<td>15.7</td>
<td>18.9</td>
</tr>
<tr>
<td>▪ Thrombocytopenia</td>
<td>8.3</td>
<td>8.0</td>
<td>11.1</td>
</tr>
<tr>
<td><strong>Nonhematologic, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Infections</td>
<td>28.9</td>
<td>21.9</td>
<td>17.2</td>
</tr>
<tr>
<td>▪ Pneumonia</td>
<td>8.1</td>
<td>8.3</td>
<td>5.7</td>
</tr>
<tr>
<td>▪ DVT and/or PE</td>
<td>7.9</td>
<td>5.6</td>
<td>5.4</td>
</tr>
<tr>
<td>▪ PSN</td>
<td>1.1</td>
<td>0.4</td>
<td>9.4</td>
</tr>
<tr>
<td>▪ Constipation</td>
<td>2.3</td>
<td>1.9</td>
<td>5.4</td>
</tr>
<tr>
<td>▪ Cataract</td>
<td>5.8</td>
<td>2.6</td>
<td>0.6</td>
</tr>
</tbody>
</table>

*Febrile neutropenia TRAE 1.1%, 3.0%, and 2.6% for Rd, Rd18, and MPT, respectively.

FIRST Trial: Conclusions

- PFS significantly superior with continuous Rd therapy vs MPT (HR: 0.72; \( P = .00006 \)) and Rd18 (HR: 0.70; \( P = .00001 \))
- PFS superiority of Rd consistent across most subgroups
- Planned interim 4-yr OS of Rd vs MPT: 59.4% to 51.4% (HR: 0.78; \( P = .0168 \))
- Safety profile of hematologic and nonhematologic AEs similar across all arms
- Neutropenia higher in MPT than Rd; infection higher in Rd vs MPT

### MPR or CPR vs Lenalidomide/LoDex in Elderly Patients With NDMM

#### 1st randomization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Courses</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| **Rd** (n = 220) | 9 28-day courses | **R**: 25 mg Days 1-21  
**d**: 40 mg Days 1,8,15,22 |
| **MPR** (n = 217) | 9 28-day courses | **M**: 0.18 mg/kg Days 1-4  
**P**: 1.5 mg/kg Days 1-4  
**R**: 10 mg Days 1-21 |
| **CPR** (n = 222) | 9 28-day courses | **C**: 50 mg Days 1-21  
**P**: 25 mg 3 x wk  
**R**: 25 mg Days 1-21 |

#### 2nd randomization

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| **R maintenance** | 28-day cycle until relapse  
**R**: 10 mg/day Days 1-21 |
| **PR maintenance** | 28-day cycle until relapse  
**P**: 25 mg 3 x wk  
**R**: 10 mg/day Days 1-21 |

Dose adjustments for patients > 75 yrs of age: dexamethasone 20 mg/wk; melphalan 0.13 mg/kg; cyclophosphamide 50 mg QOD on days 1-21.

CPR vs MPR vs Rd Survival Outcome: PFS and OS

**PFS**
- Median PFS:
  - CPR: 24 mos
  - MPR: 27 mos
  - Rd: 22 mos

**OS**
- 2-Yr OS:
  - CPR: 84%
  - MPR: 81%
  - Rd: 80%

CPR vs MPR vs Rd: Grade 3/4 AEs

- Neutropenia
- Thrombocytopenia
- Anemia
- Infective
- Dermatologic
- Cardiologic
- Vascular
- PN
- SPM
- Discontinuation
- Len Dose Reduction
- Alkylant Dose Reduction

CPR vs MPR vs Rd: Conclusions

- In 660 elderly patients with newly diagnosed multiple myeloma, similar efficacy seen with frontline CPR, MPR, and Rd
  - 2-yr PFS rate: 50% vs 54% vs 48%, respectively
  - 2-yr OS rate: 84% vs 81% vs 80%, respectively
- MPR had worse safety profile: significantly higher rates of grade 3/4 anemia, thrombocytopenia, and neutropenia vs CPR and Rd

Carfilzomib With Thalidomide and Dexamethasone

**Induction**
(Four 28-day cycles)
- **Carfilzomib 20/27 mg/m²**
  Days 1, 2, 8, 9, 15, 16
- **Thalidomide 200 mg**
  Days 1-28
- **Dexamethasone 40 mg**
  Days 1, 8, 15, 21

**Intensification***
(1 cycle)
- **Carfilzomib 27 mg/m²**
  Days 1, 2, 8, 9, 15, 16
- **Thalidomide 50 mg**
  Days 1-28
- **Dexamethasone 40 mg**
  Days 1, 8, 15, 21

**Consolidation**
(Four 28-day cycles)
- **Carfilzomib 27 mg/m²**
  Days 1, 2, 8, 9, 15, 16
- **Thalidomide 50 mg**
  Days 1-28
- **Dexamethasone 40 mg**
  Days 1, 8, 15, 21

*High-dose melphalan 200 mg/m² plus ASCT.
Carfilzomib 27 mg/m² dose escalation: cohort 1 treatment as above; cohort 2 to 36 mg/m²; cohort 3 to 45 mg/m²; cohort 4 to 56 mg/m²

## Carfilzomib/Thalidomide/Dexamethasone: Response and AEs

<table>
<thead>
<tr>
<th>Patient Response, %</th>
<th>High-Risk* Patients (n = 30)</th>
<th>Standard-Risk Patients (n = 25)</th>
<th>All Patients (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/sCR</td>
<td>57</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>90</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>PR</td>
<td>90</td>
<td>90</td>
<td>96</td>
</tr>
</tbody>
</table>

*<sup>t(4;14) and/or del(17p) and/or 1q and/or ISS3.</sup>*

- **Grade 3/4 AEs ≥ 5% by carfilzomib dose:**
  - 20/27 mg/m<sup>2</sup>: GI toxicity, 16%; skin, 12%; metabolism, 10%; myelotoxicity, 8%; fatigue, 8%; cardiovascular, 6%
  - 20/36 mg/m<sup>2</sup>: metabolism, 10%; myelotoxicity, 8%; GI toxicity, 5%
  - Neuropathy < 5% in both cohorts

Carfilzomib/Thalidomide/Dexamethasone: Conclusions

- CTd for induction and consolidation showed activity in patients with NDMM
- 96% ORR, with 84% of patients achieving at least VGPR after consolidation
- High-risk patients achieved substantial benefit with CTd
- CTd well tolerated, with gastrointestinal, metabolic, and dermatologic toxicities the most common adverse events
- Few patients experienced peripheral neuropathy
- Longer follow-up time needed to assess PFS and OS

HOVON-65/GMMG-HD4: Bortezomib Treatment in NDMM—Extended Follow-up

Newly diagnosed patients with MM
18-65 yrs of age

VAD* x three 28-day cycles (n = 414)

Stem cell collection

High-Dose Melphalan
Number of cycles depends on group:
- HOVON uses a single cycle
- GMMG uses 2 cycles

Thalidomide maintenance
50 mg/day for 2 yrs

Stem cell collection

Allogeneic transplant

3 × PAD† x three 28-day cycles (n = 413)

High-Dose Melphalan
Number of cycles depends on group:
- HOVON uses a single cycle
- GMMG uses 2 cycles

Thalidomide maintenance
1.3 mg/m² Q2W for 2 yrs

*Vincristine 0.4 mg IV Days 1-4; doxorubicin 9 mg/m² IV Days 1-4; dexamethasone 40 mg PO Days 1-4, 9-12, 17-20.

†Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11; doxorubicin 9 mg/m² IV Days 1-4; dexamethasone 40 mg PO Days 1-4, 9-12, 17-20.

Progression-Free Survival and Overall Survival, PAD vs VAD


HR: 0.76 (95% CI: 0.64-0.91; \( P = .001 \))

HR: 0.78 (95% CI: 0.64-0.91; \( P = .01 \))
Survival of Patients With Renal Failure, PAD vs VAD

PAD vs VAD: Conclusions

- Long-term follow-up of HOVON-65/GMMG-HD4 trial
- PAD significantly improved PFS and OS in transplant-eligible NDMM patients vs VAD
- PAD improved long-term outcomes in patients with renal failure
- PAD improved outcome in patients with intermediate- and poor-risk cytogenetics
- No increased risk of developing second primary malignancies observed with PAD
- Fewer patients receiving bortezomib maintenance therapy discontinued due to adverse events vs thalidomide maintenance therapy

MM-015 PFS2: Second PFS With MP, MPR, and MPR-R

- Original study randomized, double-blind 459 patients: 3 arms: MP + PBO maintenance, MPR + PBO, MPR + R
  - Median PFS: MPR + R, 31 mos; MPR, 14 mos; MP, 13 mos
  - HR: MPR + R vs MPR = 0.49, $P < .001$; vs MP = 0.40, $P < .001$

- OS similar between arms, raising concern continuous lenalidomide therapy may impact efficacy at relapse

- In PFS2, all patients with DP treated with open-label 2nd-line therapy
  - PFS: MPR + R, 39.7 mos; MPR, 27.8 mos; MP, 28.8 mos
  - HR: MPR + R vs MPR = 0.77, $P = .065$; vs MP = 0.70, $P = .009$

Lenalidomide Maintenance Therapy: Meta-analysis of Randomized Trials

- In a study of 4 RCTs (N = 1935), lenalidomide maintenance vs no maintenance or placebo associated with:
  - Improved PFS (overall HR: 0.49; \(P < .001\))
  - Trend toward improved OS (overall HR: 0.77; \(P = .071\))
  - Significantly higher risk of grade 3/4 neutropenia, VTE, thrombocytopenia, fatigue
  - Significantly higher risk of secondary malignancies (Overall OR: 1.62; \(P = .006\))

- Patient subset most benefitting from lenalidomide maintenance therapy remains undefined

**Ixazomib in Combination With Lenalidomide and Dexamethasone**

**Induction: up to 16× 21-day treatment cycles**

- **Ixazomib**: Days 1, 4, 8, 11
- **Lenalidomide 25 mg, Days 1-14**

- **Ixazomib**: Days 1, 4, 8, 11
- **Dex**: Days 1, 4, 8, 11

- **Ixazomib**: Days 1, 4, 8, 11
- **Dex**: Days 1, 4, 8, 11

**Maintenance**

- **Ixazomib**: Days 1, 4, 8, 11
- **21-day cycles**

- **Ixazomib**: Days 1, 4, 8, 11
- **Dex**: Days 1, 4, 8, 11

**Notes**

- Phase I: standard 3 + 3 schema, 33% dose increments, based on cycle 1 DLTs
- Phase II: treatment at the RP2D established for ixazomib in phase I (3.0 mg)
- VTE prophylaxis with aspirin 81-325 mg QD or LMWH while receiving Rd
- Stem cell collection allowed after cycle 4, with ASCT deferred until after 8 cycles

Ixazomib Plus RD: ORR Over Course of Treatment

Median DOR 13.8 mos, ranging up to 18.8+ mos

Ixazomib Plus RD: Treatment-Related AEs, All Grades (> 20%)

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Phase I (n = 14)</th>
<th>Phase II (n = 57)</th>
<th>Total (N = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash-related</td>
<td>10 (70)</td>
<td>25 (44)</td>
<td>32 (50)</td>
</tr>
<tr>
<td>PN</td>
<td>9 (64)</td>
<td>30 (53)</td>
<td>34 (53)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (64)</td>
<td>27 (47)</td>
<td>31 (48)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>7 (50)</td>
<td>22 (39)</td>
<td>25 (39)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3 (21)</td>
<td>18 (32)</td>
<td>20 (31)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (36)</td>
<td>17 (30)</td>
<td>19 (30)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (43)</td>
<td>15 (26)</td>
<td>19 (30)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (29)</td>
<td>14 (25)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (29)</td>
<td>15 (26)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (14)</td>
<td>14 (25)</td>
<td>14 (22)</td>
</tr>
</tbody>
</table>

Grade 3 AEs > 5% in total: rash related (16%), hyperglycemia (8%), pneumonia (6%), thrombocytopenia (6%). There were no grade 4 TRAEs. One patient death in phase II from cardiorespiratory arrest characterized as likely related to lenalidomide.

Ixazomib Plus RD: Conclusions

- Twice-weekly oral ixazomib plus lenalidomide/dexamethasone active in patients with newly diagnosed multiple myeloma\(^1\)
- Improved depth of response over course of treatment
- Incidence of dose reductions, rash, and peripheral neuropathy slightly higher with twice-weekly ixazomib dosing vs parallel study with weekly dosing\(^2\)
  - Safety profile from parallel study supports weekly dosing being used in ongoing phase III studies

Summary: Treatment for Patients With Newly Diagnosed Multiple Myeloma

- In phase 3 results from FIRST trial, Rd therapy superior to MPT for PFS and OS with similar safety profiles
- In elderly patients, similar efficacy seen with MPR, CPR, and Rd treatment; MPR AEs worse than CPR and Rd
- Bortezomib-based treatment significantly improved PFS and OS in transplant-eligible NDMM patients vs VAD
- Lenalidomide-based maintenance therapy showed significantly higher PFS vs no maintenance or placebo, but greater risk of grade 3/4 neutropenia, VTE, thrombocytopenia, fatigue, and secondary malignancies
- Twice-wkly oral ixazomib plus lenalidomide/dexamethasone active in patients with NDMM
Relapsed/Refractory Multiple Myeloma
**MM-003 Final Analysis: Pomalidomide/LoDex vs HiDex: PFS and OS**

**PFS**

- **Median PFS, Mos**
  - POM + LoDex (n = 302) 4.0
  - HiDex† (n = 153) 1.9

**OS**

- **Median OS, Mos**
  - POM + LoDex (n = 302) 13.1
  - HiDex† (n = 153) 8.1

*Primary endpoint.
†85 pts (56%) on the HiDex arm received subsequent POM.

MM-003: PFS Based on Cytogenetic Profile

del(17p)/t(4;14)

- Median PFS, Mos
  - POM + LoDex (n = 77): 3.8
  - HiDex (n = 35): 1.1

Standard Risk

- Median PFS, Mos
  - POM + LoDex (n = 148): 4.2
  - HiDex (n = 72): 2.3

HR = 0.44
P < .001

HR = 0.55
P < .001

MM-003: Conclusions

- With extended follow-up, median PFS advantages were maintained for pomalidomide plus low-dose dexamethasone vs high-dose dexamethasone in:
  - Modified high-risk cytogenetics (PFS: 3.8 vs 1.1 mos; HR: 0.46; $P < .001$)
  - Standard-risk cytogenetics (PFS: 4.2 vs 2.3 mos; HR: 0.50; $P < .001$)

Pomalidomide Plus LoDex in RRMM Patients With del(17p) and/or t(4;14)

- Open-label phase II study: interim analysis
- Median TTP (mos): ITT (N = 50), 2.9; del(17p) (n = 20), 7.3; t(4;14) (n = 30), 2.8
- Median OS (mos): ITT (N = 50), 12; del(17p) (n = 20), 12; t(4;14) (n = 30), 9.2
- AEs in 49 pts (98%), 72% hematologic; grade 3/4 AEs in 45 pts (90%)
- SAEs in 32 pts (64%), primarily nonhematologic
- Pomalidomide plus LoDex earlier in RRMM appears to benefit patients with del(17p) but not t(4;14)

Phase II Trial: Carfilzomib/Pomalidomide/Dexamethasone in Patients With RRMM

**Induction**
(cycles 1-6, 28-day cycle)

- **Carfilzomib**
  - 20 mg/m² days 1,2 of cycle 1; 27 mg/m² days 8,9,15,16 cycle 1, all days of following cycles

- **Dexamethasone**
  - 40 mg Days 1, 8, 15, 22

- **Pomalidomide**
  - 4 mg Days 1-21

N = 79

- Maintenance cycles: cycles 7+, 28-day cycle, carfilzomib 27 mg/m² Days 1,2,15,16; dexamethasone and pomalidomide dosing remain unchanged
- Coagulation prophylaxis with aspirin 81 mg QD or LMWH in aspirin-intolerant patients
- Antiviral therapy administered with treatment
- All patients refractory to previous lenalidomide treatment

## Car-Pom-d Outcomes: ORR, DOR, PFS, and OS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Patient Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ VGPR, %</td>
<td>27</td>
</tr>
<tr>
<td>ORR, %</td>
<td>70</td>
</tr>
<tr>
<td>CBR, %</td>
<td>83</td>
</tr>
<tr>
<td>DOR (median), mos</td>
<td>17.7</td>
</tr>
<tr>
<td>PFS (median), mos</td>
<td>9.7</td>
</tr>
<tr>
<td>OS (median), mos</td>
<td>&gt; 18</td>
</tr>
</tbody>
</table>

- Median number prior patient therapy lines: 5
- In patients with high-risk FISH/cytogenetic status (n = 18), the ORR was 78% (n = 14)
- 49% of patients had high- or intermediate-risk status at baseline
- PFS and OS were sustained independent of risk status

# Car-Pom-d Treatment-Related AEs

<table>
<thead>
<tr>
<th>AEs,* n</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>4</td>
<td>17</td>
<td>6</td>
<td>27 (34)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>10</td>
<td>13</td>
<td>1</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>3 (4)</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>20</td>
<td>3</td>
<td>0</td>
<td>33 (42)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>22 (28)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Skin rash, pruritus</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>10 (13)</td>
</tr>
</tbody>
</table>

*2 treatment-related grade 5 events: 1 pneumonia, 1 pulmonary embolism.

Car-Pom-d: Conclusions

- Carfilzomib/pomalidomide/dexamethasone treatment highly active in these lenalidomide-refractory patients
  - 49% pts high- or intermediate-risk cytogenetics at baseline
  - Median number of prior therapy lines per patient: 5
- ORR 70%, ≥ VGPR 27%, median DOR 17.7 mos
- Response rates, PFS, OS preserved independent of risk status
- Hematologic AEs generally manageable and reversible
- Treatment regimen well tolerated

Ixazomib in Patients With RRMM Not Refractory to Bortezomib

Phase II Trial
N = 32

- Ixazomib 5.5 mg
  Days 1, 8, 15
  28-day cycle
  2-4 cycles

- ≤ MR by 2 cycles or ≤ PR by 4 cycles or PD anytime

- ≥ MR by 2 cycles or ≥ PR by 4 cycles

- Add 40 mg/wk dexamethasone

- Continue treatment until progression

- Continue treatment until progression

- Patients receive standard supportive care, including antiemetics
- Key exclusions: grade ≥ 3 neuropathy (or grade 2 with pain); previous proteasome inhibitor therapy except bortezomib

# Responses to Ixazomib With or Without Dexamethasone

<table>
<thead>
<tr>
<th>Response Category, n</th>
<th>Single-Agent Response</th>
<th>Upgraded Response With Dex</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ PR</td>
<td>5</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>≥ MR</td>
<td>8</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>sCR</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>VGPR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>3</td>
<td>6 (2 MR, 4 SD)*</td>
<td>9</td>
</tr>
<tr>
<td>MR</td>
<td>3</td>
<td>3 (2 SD, 1 PD)*</td>
<td>4</td>
</tr>
<tr>
<td>SD</td>
<td>16</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>PD</td>
<td>4</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>NA</td>
<td>4</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

*Responses in parentheses prior to adding dexamethasone.

Adverse Events With Ixazomib Plus Dexamethasone

Thrombocytopenia
Fatigue
Nausea
Diarrhea
Constipation
Vomiting
PSN
Neutropenia
Cognitive disturbance
Rash
Lymphopenia
Anemia
Leukopenia
Edema, Limbs
Insomnia
Creatinine Increased

Ixazomib: Conclusions

- Single-agent treatment with ixazomib shows activity with deep responses in some patients
- Adding dexamethasone in patients with poor response improves response
- With dexamethasone added as needed, overall response rate with ixazomib treatments is 34%
- Ixazomib combination treatment at doses of 4 mg and 5.5 mg is subject of ongoing phase II trial

Oral HDAC-6 Inhibitor ACY-1215 Combination Therapy With Bortezomib

- ACY-1215 is a selective HDAC-6 inhibitor
- Study patients had RRMM with prior proteasome inhibitor and/or immunomodulatory agent therapy
- Phase Ib dose-escalation patients (N = 22) received ACY-1215 (40, 80, 160, 240 mg) Days 1-5, 8-12 + IV bortezomib (1.0, 1.3 mg/m²) Days 1, 4, 8, and 11 with dexamethasone PO 20 mg Days 1, 2, 4, 5, and 8, 9, 11, 12 in 21-day cycle
- ACY-1215 combination therapy well tolerated up to 240 mg QD (Days 1-5, 8-12) and 160 mg BID
- Grade 3/4 GI AEs were rare with manageable hematologic AEs
- 25% response rate and 60% clinical benefit rate observed, including in patients refractory to bortezomib

KSP Inhibitor ARRY-520 (Filanesib) in RRMM Patients With Low AAG Levels

- ARRY-520 (filanesib) is a kinesin spindle protein inhibitor
- α-1 acid glycoprotein is a potential selection marker for ARRY-520

Study design:
- Cohort 1: filanesib 1.5 mg/m² Q2W (n = 32)
  - ≥ 2 previous Tx regimens, including bortezomib and an immunomodulatory agent
- Cohort 2: filanesib 1.5 mg/m² Q2W + dexamethasone 40 mg PO wkly (n = 55)
  - ≥ 2 previous Tx regimens, including ≥ 2 cycles of lenalidomide and/or bortezomib

Impact of α-1 Acid Glycoprotein Levels on Filanesib Treatment

*Low AAG is associated with longer survival.

Akt Inhibitor Afuresertib in Combination With Bortezomib and Dexamethasone

Phase I (n = 15), dose escalation
Phase II (n = 40), safety expansion
cycles 1-8, 21-day cycles

- **Afuresertib**
  - Dose escalation, 75-175 mg
  - Days 1-21

- **Dexamethasone**
  - 20, 40 mg
  - Days 1, 4, 8, 11

- **Bortezomib, IV or SQ**
  - 1.0, 1.3 mg/m²
  - Days 1, 4, 8, 11

- Phase I: modified 3 + 3 schema; < 5 PRs, stop; ≥ 5 PRs, expand
- Phase I and II: cycle 9 and beyond, afuresertib monotherapy daily

# Afuresertib MTD, AEs, and ORR

<table>
<thead>
<tr>
<th>Afuresertib, mg</th>
<th>Bortezomib, mg/m²</th>
<th>Dex, mg</th>
<th>DLT, n/N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>1.0</td>
<td>20</td>
<td>0/4</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>1.3</td>
<td>20</td>
<td>1/6</td>
<td>ALT elevation, grade 2</td>
</tr>
<tr>
<td>125</td>
<td>1.3</td>
<td>20</td>
<td>1/6</td>
<td>Erythema multiforme, grade 3</td>
</tr>
<tr>
<td>150</td>
<td>1.3</td>
<td>20</td>
<td>0/6</td>
<td></td>
</tr>
<tr>
<td>175</td>
<td>1.3</td>
<td>20</td>
<td>2/6</td>
<td>Rash, grade 3 (n = 2), diarrhea, grade 3 (n = 1), thrombocytopenia, grade 3 (n = 1)</td>
</tr>
</tbody>
</table>

- Maximum tolerated dose

- Most common AEs:
  - Hematologic: thrombocytopenia, anemia, neutropenia
  - Nonhematologic: fatigue, diarrhea, nausea, constipation, dyspepsia

- ORR (≥ PR): part 1, 50%; part 2, 65%

Afuresertib: Conclusions

- Afuresertib can be safely administered as part of an afuresertib/bortezomib/dexamethasone regimen in patients with RRMM
- MTD for afuresertib as part of regimen: 150 mg/day
- Most common adverse events gastrointestinal
- Bortezomib-refractory patients responded to afuresertib combination therapy

Monoclonal Antibody Daratumumab With Lenalidomide and Dexamethasone

- Phase I/II, open-label, multicenter study in small population (N = 12) of daratumumab, an IgG1κ monoclonal antibody targeting CD38-expressing tumor cells, in combination with lenalidomide and dexamethasone

- 3 + 3 dose-escalation design

- Daratumumab doses from 2, 4, 8, or 16 mg/kg/wk for 8 wks, 2 x mo for 16 wks, 1 x mo until disease progression, unmanageable toxicity or up to maximum 24 mos

- Lenalidomide administered according to label

- Dex administered 1 x wk

## Daratumumab Regimen: Overall Response Rate and Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>2 mg/kg (n = 3)</th>
<th>4 mg/kg (n = 3)</th>
<th>8 mg/kg (n = 3)</th>
<th>16 mg/kg (n = 2)</th>
<th>Total (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>VGPR</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
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<td>2</td>
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</tr>
<tr>
<td>MR</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Most common AEs: neutropenia, diarrhea, constipation, nausea, fatigue

**Daratumumab: Conclusions**

- Daratumumab well tolerated in doses up to 16 mg/kg in combination with lenalidomide and dexamethasone
- Regimen provides reduction in M protein; 8 of 11 patients achieved partial response or higher
- MTD not yet reached
- Manageable AEs suggest that further study of daratumumab/lenalidomide/dexamethasone is warranted

Indatuximab Ravitansine With Lenalidomide and Low-Dose Dexamethasone

- Phase I/IIa study of indatuximab ravitansine, an antibody-drug conjugate targeting CD138-expressing tumor cells, in combination with lenalidomide and dexamethasone in patients with RRMM

- Phase I: 3 + 3 dose escalation (80, 100, and 120 mg/m²) to determine DLT and MTD

- Phase IIa: MTD cohort expansion to a total of 37 patients to describe response rates

- Treatment regimen: 28-day cycle:
  - Indatuximab ravitansine: Days 1, 8, 15
  - Lenalidomide: 25 mg/day for 21 days
  - Low dexamethasone: 40 mg/day Days 1, 8, 15, 22
  - Treatment cycles repeated until DP or unacceptable toxicity

Indatuximab Ravtansine: Conclusions

- Indatuximab ravtansine with lenalidomide and low-dose dexamethasone achieved responses (including CR) at MTD and below, suggesting the combination is active at well-tolerated doses
- MTD defined as 100 mg/m²
- MAD at 120 mg/m²; anemia and mucositis reported as dose-limiting toxicities
- 100% of evaluated patients (n = 15) achieved SD or better, including 2 CRs, 4 VGPRs, 5 PRs (ORR 73%)
  - ≥ PR in 6 of 8 Len/Dex refractory patients (ORR 75%)
  - ≥ PR in 8 out of 9 patients treated at MTD (ORR 89%)

**CD38 Monoclonal Antibody SAR650984**

- Phase I dose-escalation study, SAR650984 targeting selected CD38+ hematological malignancies; primary objective, MTD/MAD
- SAR650984 administered weekly or every 2 wks to 34 myeloma patients
- MTD not reached with weekly or biweekly schedule
- **Overall response rate (CR + PR)**
  - Dosing cohorts ≥ 1 mg/kg = 25%; ≥ 10 mg/kg = 31%
- **Clinical benefit rate (CR + PR + MR)**
  - Dosing cohorts ≥ 1 mg/kg = 33%; ≥ 10 mg/kg = 38%
- **Time to initial response (CR, PR, MR, median)** 6.1 wks (range: 3.4-12.3)
- Shows favorable safety profile in hematological malignancies
- Clinical response correlated with bone marrow plasma cell clearance

Summary: Treatment of Patients With Relapsed/Refractory Multiple Myeloma

- Pomalidomide in combination with low-dose dexamethasone with or without carfilzomib showed activity in RR patients with a good safety profile
- Ixazomib, an oral proteasome inhibitor, showed activity used alone as well as in combination with dexamethasone
- Oral HDAC-6 inhibitor ACY-1215 showed clinical benefit in patients refractory to proteasome inhibitor and/or immunomodulatory agents, including bortezomib
- KSP inhibitor ARRY-520 (filanesib) showed higher OS in pts with lower α-1 acid glycoprotein levels
- Bortezomib-refractory patients responded to novel Akt inhibitor afuresertib combination therapy
Summary: Treatment of Patients With RRMM

- Monoclonal antibody daratumumab well tolerated in combination with lenalidomide and dexamethasone

- Antibody-drug conjugate indatuximab ravidansine with lenalidomide and low-dose dexamethasone achieved responses (including CR) at MTD

- CD38 monoclonal antibody SAR650984 showed clinical response that correlated with bone marrow plasma cell clearance
Treatment of Multiple Myeloma: Conclusions

- Lenalidomide and dexamethasone until DP is standard of care for nontransplant patients with NDMM

- In NDMM transplant candidates, 3-drug regimens using immunomodulatory drugs and proteasome inhibitors pre- and posttransplant can prolong PFS and OS

- Lenalidomide maintenance until DP prolongs PFS and OS, with increased risk of secondary cancers in patients who received MP or high-dose therapy and ASCT
Treatment of Multiple Myeloma: Conclusions

- Pomalidomide with low-dose dexamethasone is active in RRMM (including 17p deletion)
- Carfilzomib/pomalidomide/low-dose dexamethasone increases response and is tolerated in RRMM
- Novel agents, including oral proteasome inhibitors, monoclonal antibodies/immunotoxins, KSP inhibitors, Akt inhibitors, and HDAC-6 inhibitors, demonstrate promising activity in RRMM
- 2 vs 3 drugs in early relapse setting will be addressed in coming mos with results from ongoing phase 3 trials
- Incorporation of novel therapies at all stages of disease is improving patient outcome in MM
Survival after Transplants for Multiple Myeloma, 2001-2011

- Autologous (N=30,709)
- Sibling donor (N=528)
- Unrelated donor (N=140)

P < 0.001

By Donor Type
MYELOMA AWARENESS MONTH