Current Management of Relapsed/Refractory Multiple Myeloma

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Disclosures

- Consulting fees from:
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- Stock or stock options from:
  - Acetylon Pharmaceuticals, Inc. and OncoPep
Integration of Novel Therapy Into Myeloma Management

Bortezomib, Lenalidomide, Thalidomide, Doxil, Carfilzomib, Pomalidamide

Target MM in the BM microenvironment to overcome conventional drug resistance in vitro and in vivo

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

Nine FDA approvals and median survival prolonged from 3-4 to 6-7 years, with additional prolongation from maintenance

New approaches needed to treat and ultimately prevent relapse
### Efficacy and Toxicity by Bortezomib schedule

<table>
<thead>
<tr>
<th></th>
<th>VMP* (VISTA)</th>
<th>VMP twice weekly N=63</th>
<th>VMP once weekly N=190</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>30%</td>
<td>27%</td>
<td>23%</td>
</tr>
<tr>
<td>PFS @ 3 years</td>
<td>NA</td>
<td>32%</td>
<td>35%</td>
</tr>
<tr>
<td>Sensory PN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>44%</td>
<td>43%</td>
<td>21%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>13%</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>PN discontinuation</td>
<td>NA</td>
<td>16%</td>
<td>4%</td>
</tr>
<tr>
<td>Total planned dose</td>
<td>67.6</td>
<td>67.6 mg/m²</td>
<td>46.8 mg/m²</td>
</tr>
<tr>
<td>Total delivered dose</td>
<td>NA</td>
<td>41 mg/m²</td>
<td>40 mg/m²</td>
</tr>
</tbody>
</table>

*Mateos et al. J Clin Oncol 2010; PN: peripheral neuropathy

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### SC vs IV Bortezomib for Relapsed/Refractory Myeloma

Moreau et al, ASH 2010 abstr 312

**EQUIVALENT EFFICACY**

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib IV (N=74)</th>
<th>Bortezomib SC (N=149)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PN event, %</td>
<td>53</td>
<td>38</td>
<td>0.04</td>
</tr>
<tr>
<td>Grade ≥2, %</td>
<td>41</td>
<td>24</td>
<td>0.01</td>
</tr>
<tr>
<td>Grade ≥3, %</td>
<td>16</td>
<td>6</td>
<td>0.03</td>
</tr>
<tr>
<td>Risk factors for PN, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 PN at baseline</td>
<td>28</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Exposure to prior neurotoxic agents</td>
<td>85</td>
<td>86</td>
<td></td>
</tr>
</tbody>
</table>

*P-values are based on 2-sided Fisher’s exact test
**Objective:** To determine the efficacy and safety of POM ± LoDEX in RRMM pts

**Primary endpoint:** PFS

**Secondary endpoints:** ORR, safety, time to response, DOR, OS

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**MM-002 Ph2: POM ± LoDEX in RRMM Trial Design**

- **N = 221**
  - Age ≥ 18 y
  - RRMM
  - Prior Tx with LEN and DOR?*
  - Measurable M protein
  - ≥ 2 prior therapies
  - Relapsed after achieving ≥ SD and had PD during or within 60 days of last Tx

* Prior Tx with ≥ 2 cycles of LEN and BORT (separately or in combination). * Patients aged > 15 years had a starting DEX dose of 20 mg/week.

**28-day cycles**

- **Progressive disease**
  - Discontinue and follow up for survival and subsequent treatment

**Option to add LoDEX (40 mg/wk)**

**Progressive disease**

- **28-day cycles**
  - POM (4 mg) D1-21 + LoDEX (40 mg/wk)*
  - (n = 113)

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**MM-002 Ph2: Response by EBMT Criteria**

- **Response rates were higher with POM + LoDEX vs. POM**
  - In pts achieving ≥ PR, median DOR was 8.3 mos for POM + LoDEX vs. 10.7 mos for POM alone (median follow-up: 16.1 and 12.3 mos, respectively)
  - 60% of pts on the POM-alone arm received LoDEX following PD

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**Data cutoff: February 1, 2013; intent-to-treat population.**

MM-002 Ph2: Adverse Events

- Grade 3-4 AEs were primarily hematologic

<table>
<thead>
<tr>
<th>Grade 3-4 Adverse Events ≥ 10% (%)</th>
<th>POM + LoDEX (n = 112)</th>
<th>POM* (n = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Anemia</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Fatigue</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

* Other AEs of clinical interest:
  - Peripheral neuropathy: no grade 3-4
  - DVT: 2% with POM + LoDEX; 3% with POM

* Includes patients who subsequently received LoDEX.

AE: adverse event; DVT: deep vein thrombosis; LoDEX: low-dose dexamethasone; POM: pomalidomide.


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Pomalidomide With Low-Dose Dexamethasone Relapsed and Refractory Multiple Myeloma

- POM was effective in heavily pretreated patients who had already received LEN and bortezomib and who progressed on their last line of therapy

  - The combination of POM with LoDEX improves the ORR due to synergy between immunomodulatory agents and glucocorticoids
    - POM + LoDEX, 34%; POM alone, 15%

- Response was durable with POM regardless of the addition of LoDEX
  - POM + LoDEX, 8.3 months; POM alone, 8.8 months

- POM is generally well tolerated, with low rates of discontinuations due to AEs
  - Age had no impact on ORR, DoR, or safety

Pomalidomide plus Low Dose Dex is Active and Well Tolerated in Bortezomib and Lenalidomide Refractory Multiple Myeloma

Table 4
Response rates (ORR, ITT, IRC-based), PFS, and OS in subgroups with adverse prognosis (N = 84)

<table>
<thead>
<tr>
<th>Patients</th>
<th>ORR, N (%)</th>
<th>Median (95% CI)/% at 1 y</th>
<th>Median (95% CI)/% at 1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>29 (34.5)</td>
<td>4.6 (4.7)/25.5</td>
<td>14.9 (11.2)/57</td>
</tr>
<tr>
<td>Refractory to lenalidomide</td>
<td>27 (36)</td>
<td>4.2 (3.6)/23</td>
<td>13.9 (9.1)/54.5</td>
</tr>
<tr>
<td>Refractory to lenalidomide as last line</td>
<td>26 (33)</td>
<td>4.4 (3.9)/22</td>
<td>19.2 (9.7)/63</td>
</tr>
<tr>
<td>Refractory to bortezomib</td>
<td>20 (25)</td>
<td>3.8 (3.6)/24</td>
<td>13.8 (9.1)/54</td>
</tr>
<tr>
<td>Refractory to last line</td>
<td>23 (29)</td>
<td>3.9 (3.7)/25</td>
<td>13.9 (8.5)/55</td>
</tr>
<tr>
<td>Double refractory</td>
<td>20 (24)</td>
<td>3.5 (3.6)/24</td>
<td>13.8 (9.1)/53</td>
</tr>
<tr>
<td>More than 6 lines of therapy</td>
<td>21 (25)</td>
<td>3.2 (3.5)/16</td>
<td>9.2 (3.9)/47</td>
</tr>
<tr>
<td>Del17p and/or tr(14)</td>
<td>21 (25)</td>
<td>2.6 (2.4)/5</td>
<td>5.4 (3.9)/33</td>
</tr>
</tbody>
</table>

Leleu et al Blood 2013

POM + LoDEX vs. HiDEX in RRMM

MM-003 Phase 3—Trial Design

- Primary endpoint: PFS
- Key secondary endpoints: OS, ORR (≥ PR), DOR, safety

28-day cycles
(n = 302)
- POM: 4 mg D1-21
- LoDEX: 40 mg (≤ 75 years) 20 mg (> 75 years) D1, 8, 15, 22

HiDEX: (n = 153)
- 40 mg (≤ 75 years) 20 mg (> 75 years) D1-4, 9-12, 17-20

PD* or intolerable AE
Follow-up for OS and SPM until 5 years post-enrollment
Companion trial MM-003C POM 21/28 days

Thromboprophylaxis was indicated for those receiving POM or with DVT history.

* PD was independently adjudicated in real-time.
AE: adverse event; D: day; DOR: duration of response; DVT: deep vein thrombosis; HiDEX: high-dose dexamethasone; LoDEX: low-dose dexamethasone; MM: multiple myeloma; ORR: overall response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; POM: pomalidomide; PR: partial response; RRMM: relapsed/refractory multiple myeloma; SPM: second primary malignancy.

### Prior Therapies

<table>
<thead>
<tr>
<th></th>
<th>POM + LoDEX (N = 302)</th>
<th>HiDEX (N = 153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median number, n (range)</td>
<td>5 (2–14)</td>
<td>5 (2–17)</td>
</tr>
<tr>
<td>Prior DEX (%)</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>Prior THAL (%)</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Prior ASCT (%)</td>
<td>71</td>
<td>69</td>
</tr>
<tr>
<td>Prior LEN (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Prior BORT (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Prior alkylator (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Refractory disease (%)</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>LEN refractory</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>BORT refractory</td>
<td>79</td>
<td>79</td>
</tr>
<tr>
<td>BORT intolerance</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>LEN and BORT refractory</td>
<td>75</td>
<td>74</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplant; BORT, bortezomib; DEX, dexamethasone; HiDEX, high-dose dexamethasone; LEN, lenalidomide; LoDEX, low-dose dexamethasone; POM, pomalidomide; THAL, thalidomide.


### Response – ITT Population

- Response rate consistent among all subgroups, including LEN and BORT as last prior

<table>
<thead>
<tr>
<th>Responsea</th>
<th>POM + LoDEX (N = 302)</th>
<th>HiDEX (N = 153)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥ PR), n (%)</td>
<td>95 (31)</td>
<td>15 (10)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>sCR/CR</td>
<td>3 (1)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>VGPR</td>
<td>14 (5)</td>
<td>1 (&lt; 1)</td>
<td>—</td>
</tr>
<tr>
<td>PR</td>
<td>78 (26)</td>
<td>14 (9)</td>
<td>—</td>
</tr>
<tr>
<td>MR, n (%)</td>
<td>23 (8)</td>
<td>9 (6)</td>
<td>—</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>129 (43)</td>
<td>70 (46)</td>
<td>—</td>
</tr>
<tr>
<td>Median DOR, b mos (95% CI)</td>
<td>7.0 (6.0–9.0)</td>
<td>6.1 (4.8–8.5)</td>
<td>0.063</td>
</tr>
</tbody>
</table>

ORR: overall response rate; sCR/CR: stringent complete response/complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; DOR: duration of response; CI: confidence interval; POM, pomalidomide; LEN, lenalidomide; BORT, bortezomib; LoDEX, low-dose dexamethasone; MR: minimal response; ORR: overall response rate; PFS, progression-free survival; POM, pomalidomide; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

POM + LoDEX significantly improved PFS vs. HiDEX

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>POM + LoDEX(^a)</th>
<th>HIDEX(^a)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Population</td>
<td>253/302</td>
<td>138/153</td>
<td>0.49 (0.40-0.61)</td>
</tr>
<tr>
<td>del(17p)/t(4;14)</td>
<td>71/77</td>
<td>32/35</td>
<td>0.44 (0.28-0.68)</td>
</tr>
<tr>
<td>Standard-Risk Cytogenetics</td>
<td>126/148</td>
<td>63/72</td>
<td>0.55 (0.40-0.75)</td>
</tr>
</tbody>
</table>

Note: Data shown only for pts with available cytogenetics; totals will not sum.

\(^a\) Number of events/number of patients.

San Miguel JF, et al. ASH 2013 [abstract 686].

Forest Plot of OS Based on Prior Treatment

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>POM + LoDEX(^a)</th>
<th>HIDEX(^a)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Population</td>
<td>176/302</td>
<td>101/153</td>
<td>0.72 (0.56-0.92)</td>
</tr>
<tr>
<td>≤ 3 Prior Tx</td>
<td>41/70</td>
<td>22/33</td>
<td>0.56 (0.33-0.96)</td>
</tr>
<tr>
<td>&gt; 3 Prior Tx</td>
<td>135/232</td>
<td>79/120</td>
<td>0.76 (0.58-1.00)</td>
</tr>
<tr>
<td>Prior THAL</td>
<td>102/173</td>
<td>64/93</td>
<td>0.75 (0.55-1.03)</td>
</tr>
<tr>
<td>No Prior THAL</td>
<td>74/129</td>
<td>37/60</td>
<td>0.66 (0.45-0.99)</td>
</tr>
<tr>
<td>LEN Ref</td>
<td>168/286</td>
<td>94/141</td>
<td>0.70 (0.55-0.90)</td>
</tr>
<tr>
<td>BORT Ref</td>
<td>142/238</td>
<td>79/121</td>
<td>0.77 (0.58-1.01)</td>
</tr>
<tr>
<td>LEN and BORT Ref</td>
<td>135/225</td>
<td>74/113</td>
<td>0.77 (0.58-1.02)</td>
</tr>
<tr>
<td>LEN as Last Prior</td>
<td>47/85</td>
<td>32/49</td>
<td>0.56 (0.36-0.88)</td>
</tr>
<tr>
<td>BORT as Last Prior</td>
<td>76/134</td>
<td>39/66</td>
<td>0.92 (0.63-1.36)</td>
</tr>
</tbody>
</table>

\(^a\) Number of events/number of pts.

San Miguel JF, et al. ASH 2013 [abstract 686].
Safety Profile – Grade 3/4 AEs in ≥20%

<table>
<thead>
<tr>
<th>Grade 3/4 hematologic AEs (%)</th>
<th>POM + LoDEX (n = 300)</th>
<th>HIDEX (n = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51</td>
<td>28</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>30</td>
<td>9</td>
</tr>
</tbody>
</table>

Grade 3/4 non-hematologic AEs (%)

<table>
<thead>
<tr>
<th>Grade 3/4 non-hematologic AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Dyspnea</td>
</tr>
</tbody>
</table>

AE: adverse event; HIDEX: high-dose dexamethasone; LoDEX: low-dose dexamethasone; POM: pomalidomide.


Study Design

Richardson et al ASH 2013

- MM-005 is a phase 1, multicenter, open-label, dose-escalation study (Figure 1)
- In April 2013, the study was amended to allow 6 patients to receive SC BORT

Figure 1. MM-005 Study Design: POM + BORT + LoDEX
### Pom low dose dex and bortezomib in relapsed MM

#### Table 4. Summary of Best Response (IMWG) in Intravenous BORT Cohorts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cohort 1 (n = 3)</th>
<th>Cohort 2 (n = 3)</th>
<th>Cohort 3 (n = 3)</th>
<th>Cohort 4 (n = 3)</th>
<th>Cohort 5 + Exp Cohort (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response, n (%)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>6 (67)</td>
</tr>
<tr>
<td>sCR/CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (11)</td>
</tr>
<tr>
<td>VGPR</td>
<td>1 (33)</td>
<td>0</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>4 (44)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (33)</td>
<td>2 (67)</td>
<td>0</td>
<td>0</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Median cycles received (range)</td>
<td>5 (4-16)</td>
<td>6 (4-18)</td>
<td>16 (5-20)</td>
<td>10 (4-13)</td>
<td>11 (6-15)</td>
</tr>
</tbody>
</table>

*8 of 9 patients were evaluable for response; one patient discontinued study treatment in cycle 2 due to treatment-unrelated metastatic pancreatic cancer.

CR, complete response; Exp, expansion; IMWG, International Myeloma Working Group; PR, partial response; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Richardson et al, ASH 2013

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### Carfilzomib: A Novel Proteasome (Chymotryptic) Inhibitor

- Novel chemical class with highly selective and irreversible proteasome binding
- Improved antitumor activity with consecutive day dosing
- No neurotoxicity in animals
- 23% Responses lasting 7.8 months with survival 15.4 months in relapsed and relapsed/refractory MM w/o

Demo et al Cancer Res 2007; 67:6383
Integrated Safety Profile of Single-Agent Carfilzomib: Experience from 526 Patients

- 4 phase II studies (PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005).

- Adverse events of any grade: fatigue (55.5%), anemia (46.8%), and nausea (44.9%), 22.1% cardiac (7.2% cardiac failure), 69.0% respiratory (42.2% dyspnea), and 33.1% renal impairment adverse event (24.1% increased serum creatinine), febrile neutropenia (1.1%). peripheral neuropathy (13.9%).

- The tolerable safety profile allows for administration of full-dose carfilzomib with low discontinuation rates.


CRd in Relapsed and Upfront MM

- Response to CRd therapy in RRMM was high, with an ORR of 78%
  - 41% VGPR or better

- CRd well-tolerated with durable responses

- ASPIRE phase 3 open-label, international, multicenter trial comparing CRd to Rd in R/R MM fully enrolled.

- Remarkable extent and frequency of response to CRd upfront in ND MM (94% ORR, with 80% CR,nCR after 12 cycles in a subset of pts)

Wang et al ASCO 2011; Jakubowiak et al, Blood 2012
Carfilzomib Pomalidomide Low dose Dex

- Median of 5 prior lines of therapy; 49% of patients had high/intermediate risk cytogenetics at baseline

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ VGPR</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>CBR</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>DOR (median)</td>
<td>17.7 months</td>
<td></td>
</tr>
<tr>
<td>PFS (median)</td>
<td>9.7 months</td>
<td></td>
</tr>
<tr>
<td>OS (median)</td>
<td>&gt; 18 months</td>
<td></td>
</tr>
</tbody>
</table>

- Response rates, PFS, and OS were preserved independent of FISH/cytogenetic risk status
- Well tolerated with no unexpected toxicities

Shah et al ASH 2013

MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)

- Effector cells:
  - ADCC

Complement-dependent Cytotoxicity (CDC)

- CDC
  - C1q

Apoptosis/growth arrest via targeting signaling pathways

- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)

Tai & Anderson Bone Marrow Research 2011
**Elotuzumab Clinical Overview**

- Elotuzumab in phase I/II studies in patients with relapsed/refractory MM
- Elotuzumab was generally well tolerated; incidence and severity of infusion reactions were mitigated by a premedication regimen
- Phase III trials of elotuzumab in combination with lenalidomide/dexamethasone are ongoing in front-line and relapsed/refractory MM

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>Efficacy, %</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1701</td>
<td>I</td>
<td>Elotuzumab monotherapy</td>
<td>SD = 26.5</td>
<td>--</td>
</tr>
<tr>
<td>1702</td>
<td>I</td>
<td>Elotuzumab + bortezomib</td>
<td>ORR = 48</td>
<td>9.5 months</td>
</tr>
<tr>
<td>1703</td>
<td>I</td>
<td>Elotuzumab + lenalidomide/dexamethasone</td>
<td>ORR = 82</td>
<td>NR (median follow-up 16.4 months)</td>
</tr>
<tr>
<td>1703</td>
<td>II</td>
<td>Elotuzumab + lenalidomide/dexamethasone</td>
<td>ORR = 84</td>
<td>10 mg/kg: 33 months 20 mg/kg: 18.6 months</td>
</tr>
</tbody>
</table>

NR, not reached

**Phase III Trial in Patients With Relapsed or Refractory MM (ELOQUENT-2)**

- Enroll N = 320
- Stratify/Randomize
- 28-day cycles:
  - 25 mg of oral lenalidomide on days 1-21
  - 40 mg of oral dexamethasone on days 1, 8, 15, and 22
- 10 mg/kg elotuzumab weekly on days 1, 8, 15, and 22 during the first two 28-day cycles and on days 1 and 15 of subsequent cycles
- 25 mg of oral lenalidomide on days 1-21 of every 28-day cycle
- 40 mg oral dexamethasone in weeks without elotuzumab
- 28 mg oral and 8 mg IV dexamethasone in weeks with elotuzumab

Daratumumab Anti-CD 38 MoAb

18 of 29 patients in phase I benefit (5PR,4MR,9SD)

DARA: Response

**Efficacy**

- All patients followed up for at least 2 weeks
- Marked decrease in M-protein
- PR or better: 15/20 patients
- 3 CR, 6 VGPR
- Median time to response: 4.3 weeks (2.1-11.3)


**SAR650984: Maximal Change in Paraprotein**

*Myeloma Patients Treated at Doses of 1 mg/kg Q2W or Higher*

One patient at 3.0 mg/kg and 20 mg/kg with 0% change; One patient at 20 mg/kg not evaluable

A Phase Ib Dose-Escalation trial of SAR650984 (Anti-CD38 mAb) in Combination With Lenalidomide and Dexamethasone in Relapsed/Refractory Multiple Myeloma: Response Summary (IMWG Criteria) (Martin et al, ASCO 2014)

<table>
<thead>
<tr>
<th>Number of Patients (%)</th>
<th>All (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>18 (58)</td>
</tr>
<tr>
<td>VGPR</td>
<td>7 (23)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (35)</td>
</tr>
<tr>
<td>MR</td>
<td>2 (6)</td>
</tr>
<tr>
<td>CBR (MR or better)</td>
<td>20 (65)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (10)</td>
</tr>
<tr>
<td>PD</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>


BT062: Indatuximab Ravtansine

- A potent Antibody-Drug Conjugate (ADC) developed by Biotest for the treatment of CD138-expressing tumors
- Designed to deliver the maytansinoid cytotoxic agent, DM4, specifically to CD138-expressing tumor cells
- CD138 is highly expressed on multiple myeloma (MM) cells

1. Binding to CD138
2. Receptor (CD138) mediated internalization
3. Lysosomal processing of SPDB linker leads to lipophilic DM4 metabolites (DM4 + S-methyl-DM4)
4. Inhibition of tubulin polymerisation
5. Cell cycle arrest and apoptosis
6. Bystander killing of neighbouring cells

Kelley et al ASH 2013
Summary

- BT062 administration on days 1, 8, 15 of 28-day cycle in combination with Lenalidomide and low dose dexamethasone
  - Phase I completed, MTD defined as 100 mg/m²
  - 21 patients treated in one of the 3 dose levels (80, 100, 120 mg/m²)
  - 13 patients are receiving ongoing treatment
  - Treatment duration of up to about 1 year
  - MAD reached at 120 mg/m² with mucositis and anemia reported as dose-limiting toxicities (DLT)
  - Stable disease or better was observed in 100% of the 15 evaluated patients, including 2 CRs, 4 VGPR, 5 PR (ORR=73%)
  - ≥PR was observed in 6 out of 8 Len/Dex refractory patients (ORR=75%)
  - ≥PR was observed in 8 out of 9 patients treated at MTD (ORR=89%)

ORR=Objective Response Rate (≥PR)  Kelly et al ASH 2013

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Proteasome: Present and Future Therapies

Deubiquitylating Enzymes (DUBs)
- Targeting USP-7
- USP14/UCHL 15

ATPases/Cdc48

Immuno-proteasome

Potential Therapeutic Targets

- ATPases/Cdc48
- Six Protease activities
  - \( \beta_5 \), \( \beta_5i \)
  - \( \beta_1 \), \( \beta_1i \)
  - \( \beta_2 \), \( \beta_2i \)

26S PROTEASOME

Free for re-cycling

Degraded protein

Bortezomib, Carfilzomib, CEP-18770, ONYX-0912, MLN 2238, NPI-0052: \( \beta_5 \), \( \beta_1 \), \( \beta_2 \)
b-AP15, a Novel USP14/UCHL5 Inhibitor, Induces Polyubiquitination Without Blocking Proteasome Catalytic Activities

Tian et al. Blood 2014; 123: 706-16

b-AP15 Inhibits Tumor Growth and Prolongs Survival Clinical Trial Ongoing

Tian et al. Blood 2014; 123: 706-16
MLN2238/9708 Oral Chymotryptic Inhibitor More Potently Blocks MM Cell Growth \textit{In Vivo} than Bortezomib

Chauhan et al., Clin Cancer Res 2011; 17: 5311-21.

Weekly MLN9708 (Ixazomib) in Relapsed/Refractory MM: Phase I Study

- Single-agent oral MLN9708 MTD 2.97 mg/m² on a weekly (days 1, 8, and 15 every 28 days) schedule

- Oral MLN9708 generally well tolerated
  - hematologic and gastrointestinal events generally manageable, low rate of discontinuations
  - Infrequent PN, only 1 grade 3 PN

- Pharmacokinetic profile supports weekly oral dosing

- Relapsed and/or refractory MM patients (median 4 prior lines of therapy)
  - ORR (≥PR) of 18%, plus 2% MR and 30% SD, including relapse post Bortezomib

Kumar ASCO 2013
MLN9708 in Relapsed and/or Refractory MM: Expansion Cohorts of a Phase 1 Dose-Escalation study
Richardson et al ASH 2011

- 46 pts evaluable for response
  - 21 in dose-escalation cohorts
  - 30 in expansion cohorts (including 6 from dose-escalation cohorts)
- 6 pts have achieved ≥PR
  - 1 CR, confirmed by bone marrow (Pl-naïve expansion cohort)
  - 5 PRs (1 each at 1.2 and 2.23 mg/m² in dose-escalation cohorts; 1 in RRMM and 2 in bortezomib-relapsed expansion cohorts)
- 1 pt achieved MR (bortezomib-relapsed expansion cohort; 40% M-protein reduction)
- All 7 pts remain in response, with duration of disease control of up to 15.9 months
- 28 pts have achieved SD
  - 14 in dose-escalation cohorts
  - 9, 5, and 2 in RRMM, bortezomib-relapsed, and Pl-naïve expansion cohorts
  - Durable, with disease stabilization for up to 12.9 months

Ixazomib lenalidomide dexamethasone in newly diagnosed multiple myeloma
Richardson et al ASH 2013

- 56 pts treated at the RP2D were evaluable for response (7 phase 1, 49 phase 2)
- 61% of pts had 100% decreases in M-protein or serum free light chain from baseline
Marizomib: A Non-Peptide Proteasome Inhibitor Induces Rapid, Broad and Prolonged Inhibition

Marizomib (NPI-0052)

• Exhibits high levels of proteasome inhibition without toxicities associated with bortezomib
• Active in bortezomib and IMiD resistant myeloma preclinically

Responses to Marizomib +/- Dexamethasone in Evaluable Pts at Full Dose [ >0.4 mg/m²]† Twice Weekly (n=21**)
Richardson et al ASH 2011

<table>
<thead>
<tr>
<th></th>
<th>All Pts</th>
<th>Pts Refractory to Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EBMT</td>
<td>Pts Refractory to Bortezomib</td>
</tr>
<tr>
<td>≥ SD</td>
<td>11/20</td>
<td>8/12</td>
</tr>
<tr>
<td>MR + PR</td>
<td>3/20</td>
<td>2/12</td>
</tr>
<tr>
<td>Uniform Criteria</td>
<td>12/21</td>
<td>8/12</td>
</tr>
<tr>
<td></td>
<td>PR + VGPR</td>
<td>4/21</td>
</tr>
<tr>
<td></td>
<td>PR + VGPR</td>
<td>2/12</td>
</tr>
</tbody>
</table>

Median Duration of Response (all Pts) = 133 days (~ 5 mos)

<table>
<thead>
<tr>
<th></th>
<th>EBMT</th>
<th>Pts Refractory to Lenalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ SD</td>
<td>11/19</td>
<td>8/13</td>
</tr>
<tr>
<td>MR + PR</td>
<td>3/19</td>
<td>3/13</td>
</tr>
<tr>
<td>Uniform Criteria</td>
<td>11/19</td>
<td>9/14</td>
</tr>
<tr>
<td></td>
<td>PR + VGPR</td>
<td>4/14</td>
</tr>
</tbody>
</table>

• Response criteria defined with baseline SPEP ≥ 0.5 g/dL or UPEP ≥ 200 mg/24h with at least 2 assessments after treatment Day 1 for EBMT, also by free lite for UC**.
• Refractory defined as having PD during or within 60 days of last regimen.
Development of Rationally-Based Combination Therapies (HDAC and Proteasome Inhibitors)


VANTAGE 088: An International, Multicenter, Randomized, Double-Blind Study of Vorinostat or Placebo with Bortezomib in Relapsed MM

- The combination of vorinostat + bortezomib is active in patients with relapsed and refractory MM
  - Significant improvement in response rate
  - ORR 54% vs 41% ($P<0.0001$); CBR 71% vs 53% ($P<0.0001$)

- PFS and TTP were prolonged in the combination arm compared with bortezomib alone
  - PFS hazard ratio reduction of 23% ($P=0.01$): 7.63 months (6.9–8.4) versus 6.83 months (5.7–7.7)

- Diarrhea, fatigue, and thrombocytopenia limited tolerability.

**PANORAMA 1 Study Design**

*Randomized, Double-Blind, Phase 3 Study in Relapsed or Relapsed and Refractory MM*

**Treatment Phase 1**
- Eight 21d cycles (24 wks)
- Panobinostat + bortezomib + dexamethasone
- Placebo + bortezomib + dexamethasone

**Treatment Phase 2**
- Four 42d cycles (24 wks)
- Panobinostat + bortezomib + dexamethasone
- Placebo + bortezomib + dexamethasone

**Follow-up**
- Pts with clinical benefit * in Treatment Phase I can proceed to Treatment Phase II

**Pts (N = 768)**
- Rel or Rel/Ref MM (BTZ-ref excluded)
- 1-3 prior lines of therapy
- Stratification factors:
  - Prior lines of therapy
  - Prior BTZ

**Primary endpoint:** PFS (per modified EBMT criteria; confirmed by IRC)¹,²
**Key secondary endpoint:** OS
**Other secondary endpoints:** ORR, nCR/CR rate, DOR, TTR, TTP, QoL, and safety

*Study conducted at 215 centers across 34 countries*

¹ Achieving ≥ no change according to modified EBMT criteria (SD or better)
² Study conducted at 215 centers across 34 countries

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**PANORAMA 1: A Randomized, Double-Blind, Phase 3 Study of Panobinostat or Placebo Plus Bortezomib and Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma**

- Improvement in median PFS of 4 mos w/o difference in ORR or OS
- Two-fold increase in nCR/CR rate (28% vs 16%)
- Higher rate of Grade ≥3 diarrhea (25.5% vs 8%), fatigue (23.0% vs 11.9%), thrombocytopenia (67.4% vs 31.4%), and leucopenia (34.5% vs 11.4%), discontinuation due to AE (33.6% vs 17.3%).
- Confirms the efficacy of PAN-BTZ-Dex observed in heavily pretreated, BTZ-refractory pts (PANORAMA 2): ORR: 34.5%; CBR: 52.7%; median PFS: 5.4 mos; median OS: 17.5 mos¹,²
- Need for less toxic more selective HDACi that can be given with PI to exploit synergistic cytotoxicity.


Richardson et al ASCO 2014
ACY1215 Alone and With Bortezomib in Relapsed/Refractory MM

- **Monotherapy**
  - 6/15 patients had stable disease (SD) as their best response.

- **Combination with bortezomib and dexamethasone**
  - 20/22 were evaluable for response assessment in six combination cohorts
    - Overall response rate (≥PR): 25% in heavily pretreated patients
    - 5 patients withdrew after one cycle and 3 had progressive disease after 2 cycles
    - Clinical benefit rate (≥SD): 60%
    - 6/10 patients refractory to bortezomib had ≥SD (1 VGPR, 1 MR, 4 SD)
    - Responding patients have been on study 2 to 16 cycles
    - All 3 patients treated 240 mg QD cohort had MR or better

Raje et al, ASH 2013

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Background: Targeting KSP with ARRY-520 (Filanesib)

- **Filanesib** is a targeted Kinesin Spindle Protein (KSP) inhibitor
  - KSP is a microtubule motor protein critical to the function of proliferating cells

- KSP inhibition induces aberrant mitotic arrest and rapid cell death
  - Novel mechanism of action for MM
  - Preferentially acts on MCL-1 dependent cells including MM
  - Not expected to be cross-resistant with other drugs

Lonial et al ASH 2013
Low AAG is Associated with Higher ORR

<table>
<thead>
<tr>
<th></th>
<th>Filanesib Single-agent</th>
<th>Filanesib + Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Pts&lt;sup&gt;1&lt;/sup&gt;</td>
<td>AAG-High AAG-Low</td>
</tr>
<tr>
<td>n</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>5 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CBR (≥ MR)</td>
<td>7 (22%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Duration of Response (months)</td>
<td>8.6</td>
<td>-</td>
</tr>
<tr>
<td>Time to Next Treatment (months)</td>
<td>3.7</td>
<td>2.6</td>
</tr>
<tr>
<td>OS (months)</td>
<td>19.0</td>
<td>4.5</td>
</tr>
</tbody>
</table>

<sup>1</sup> 4 patients did not have a baseline AAG measurement, including 1 responder

Additional Targets in Development

- BTK inhibitors
- KSP inhibitors (Array 520)
- AKT inhibitor
- Nuclear transport inhibitors (KPT)
- CDK inhibitors
- Bromodomain inhibitors
**Mutations in Myeloma**

19 patients each with newly diagnosed and relapsed MM

- **Protein homeostasis:** 42% including FAM46C, RPL10, RPS6KA1, EIF3B, XBPI, LRRK2

- **NF-κB signaling:** 10 point mutations, 4 additional structural rearrangements affecting coding
  Confers bortezomib sensitivity

- **Histone methylating enzymes:** WHSC1, UTX, MLL

- **BRAF:** 4% activating Single patient MM response

**PSMB5 β5** proteasome subunit mutation confers proteasome inhibitor resistance in laboratory, not identified in clinic

Lichter et al Blood 2012; 120: 4513-16.

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**Summary and Conclusions**

- Pomalidomide low dose dex is active in relapsed refractory MM (including 17p deletion)
- Bortezomib or carfilzomib and pomalidomide low dose dex increases response and is tolerated in relapsed refractory MM
- Novel agents include inhibitors of KSP, BTK, Akt, nuclear transport, CDK, and bromodomains.
- Novel agents including oral proteasome inhibitor ixazomib, monoclonal antibodies elotuzumab and daratumumab, immunotoxin indatuximab and HDAC6 inhibitor ricolinostat demonstrate promising activity in relapsed refractory MM and in combination with lenalidomide/dex