Updates on Diagnostic Criteria and Management of Multiple Myeloma

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Integration of Novel Therapy Into Myeloma Management

Bortezomib, lenalidomide, thalidomide, bortezomib/doxorubicin, carfilzomib, pomalidomide, panobinostat, daratumumab, ixazomib, elotuzumab

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

16 FDA approvals (7 in 2015!) and median patient survival prolonged 3-4 fold

New approaches needed to treat and ultimately prevent relapse
Criteria for Diagnosis of Multiple Myeloma (MM)

**MGUS**
- M spike <3 g
- PC <10%

**Smoldering MM**
- M spike ≥3 g
- OR ≥10% PC

**Active MM**
- ≥10% PC
- M spike +

**AND**

- No anemia, bone lesions, normal calcium and kidney function

**Diagnosis of Active MM In Asymptomatic Patients (IMWG)**

Even without CRAB Features, the following define active MM:
- Bone marrow plasmacytosis > 60% ¹

- Abnormal FLC ratio > 100 (involved kappa) or <0.01 (involved lambda) ²

- Focal bone marrow lesions detected by functional imaging including PET-CT and/or MRI ³, ⁴

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2. Larsen et al Leukemia 2013; 27: 941
4. Hillengass et al Leuk Lymph 2013

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Vaccines Targeting MM Specific Peptides in Smoldering Multiple Myeloma

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 (LLS TAP Program):
Immune responses to vaccine in all patients including tetramer positive cells and type I cytokines

Lenalidomide with vaccine augments these immune response

Lenalidomide and PDL-1, HDAC 6i 241 with vaccine to induce memory Immune response against myeloma

Bae et al., Leukemia 2011; 25:1610-9.
Bae et al., Clin Can Res 2012; 17:4850-60.
Bae et al., Leukemia 2015
Effects of HDACi 241 on MM Specific Cytotoxic T cells (MM CTLs)

- Does not affect viability of CD3, CD4, CD8 T cells
- Does not induce checkpoint inhibitors on MM CTLs
- Increases costimulatory molecules, proliferation, Th-1 cytokine production, and cytotoxicity of MM CTLs
- Increases central and effector memory MM CTL cytotoxicity, costimulatory molecules, and proliferation
- Decreases regulatory T cells

International Staging System (ISS) for Myeloma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>β2m &lt; 3.5 mg/L, albumin &gt; 3.5 g/dL</td>
<td>62</td>
</tr>
<tr>
<td>II*</td>
<td>Not stage I or III</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>β2m &gt; 5.5 mg/L</td>
<td>29</td>
</tr>
</tbody>
</table>

*β2m < 3.5 mg/L and albumin < 3.5 g/dL or β2m 3.5 - < 5.5 mg/dL, any albumin


Revised ISS (R-ISS) incorporates LDH and high risk FISH abnormalities

Palumbo et al J Clin Oncol 2015; 33: 2863-9
Chromosomes and Prognosis in Multiple Myeloma

For conventional low and high dose therapy:

Nonhyperdiploid worse prognosis than hyperdiploid

- t(11;14), hyperdiploidy -standard risk
- t(4;14), t(14;16), t(14;20), del(17p), del(13q14) - high risk

For novel treatments

Bortezomib, but not lenalidomide, can at least partially overcome t(4;14), del(13q14) - del(17p) p53 remains high risk

Increasing Stringency in Defining Complete Response

- CR .................. Negative Immunofixation & < 5% PC in BM

- Stringent CR ...... Normal FLC & no clonal PC by immunohistochemistry (Low sensitivity <10^-2)

- Outside BM ........ Imaging techniques (MRI & CT-PET).

- BM Level ........... Immunophenotypic remission (by multiparametric flow)
  Molecular remission (by sequencing)

* Pitfalls: 1. Pattern of BM infiltration in MM is not uniform... The possibility of residual MM-PC in another territory cannot be excluded (false negative results).
2. Extramedullary relapses.
DEFINITION OF MULTIPLE MYELOMA

Active (Symptomatic) Myeloma2,3

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
And

Any one or more of the following myeloma defining events:
• Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
• Renal insufficiency (creatinine >2 mg/dL [>177 μmol/L] or creatinine clearance <40 mL/min
• Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)
• One or more osteolytic bone lesions on skeletal radiography, CT, or PET-CT
• Clonal bone marrow plasma cells ≥60%
• Abnormal serum FLC ratio ≥100 (involved kappa) or <0.01 (involved lambda)
• >1 focal lesions on MRI studies >5mm

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**Combinations in the Upfront Treatment of MM**

Stewart AK, Richardson PG, San Miguel JF Blood 2009

**RVd versus Rd for Newly Diagnosed MM**

Durie et al, ASH 2015
Bortezomib, lenalidomide and dexamethasone versus Lenalidomide and dexamethasone: Progression Free Survival

Log-rank P value = 0.0018 (one sided)*
HR = 0.712 (0.560, 0.906)*

Durie et al, ASH 2015

Bortezomib, lenalidomide and dexamethasone versus Lenalidomide and dexamethasone: Overall Survival

Log-rank P value = 0.0250 (two sided)*
HR = 0.709 (0.516, 0.973)*

Durie et al, ASH 2015
Phase III Maintenance Studies – Transplant Eligible Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Regimen</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 2005-02</td>
<td>614</td>
<td>Maintenance lenalidomide vs placebo following first or second ASCT</td>
<td>4-yr PFS: 60% vs 33%</td>
</tr>
<tr>
<td>CALGB 100104</td>
<td>460</td>
<td>Maintenance lenalidomide vs placebo after ASCT</td>
<td>Median TTP: 46 vs 27 mos</td>
</tr>
<tr>
<td>RV-MM-PI-209</td>
<td>402</td>
<td>MPR + maintenance lenalidomide vs MPR vs MEL200 + maintenance lenalidomide vs MEL200</td>
<td>Median PFS (R vs no R): 37 vs 26 mos 5-Yr OS (R vs no R): 75 vs 58 mos</td>
</tr>
<tr>
<td>HOVON-65</td>
<td>827</td>
<td>VAD vs PAD followed by HD melphalan and ASCT, then thalidomide or bortezomib as maintenance</td>
<td>Median PFS: 28 vs 35 mos CR/nCR: 15% vs 31%</td>
</tr>
<tr>
<td>Nordic MSG 15</td>
<td>370</td>
<td>Bortezomib x 21 wks vs no maintenance</td>
<td>≥ nCR: 45% vs 35%</td>
</tr>
</tbody>
</table>

### ASCT and Maintenance Improve Outcome

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>noASCT</th>
<th>p.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS, median</strong></td>
<td>59 mos</td>
<td>42 mos</td>
<td>0.01</td>
</tr>
</tbody>
</table>

### ISS I / II STANDARD FISH

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>noASCT</th>
<th>p.</th>
<th>ASCT</th>
<th>noASCT</th>
<th>p.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS, median</strong></td>
<td>60 mos</td>
<td>44 mos</td>
<td>0.05</td>
<td>69 mos</td>
<td>49 mos</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>5-year OS</strong></td>
<td>85%</td>
<td>72%</td>
<td>0.03</td>
<td>84%</td>
<td>72%</td>
<td>0.7</td>
</tr>
</tbody>
</table>

### Maintenance No maintenance

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>noASCT</th>
<th>p.</th>
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</thead>
<tbody>
<tr>
<td><strong>PFS, median</strong></td>
<td>62 mos</td>
<td>41 mos</td>
<td>0.02</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>noASCT</th>
<th></th>
<th>p.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS, median</strong></td>
<td>53 mos</td>
<td>21 mos</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>5-year OS</strong></td>
<td>77%</td>
<td>60%</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Cerrato et al, ASH 2015

### IFM/DFCI 2009 Study (US and France)

Newly Diagnosed MM (N=1,360)

- **RVD x 3**
- **RVD x 2**
- **Lenalidomide**
- **Cy (3g/m2)**
- **Mobilization Goal: 5 x 10⁶ cells/kg**

**Induction**

**Consolidation**

<table>
<thead>
<tr>
<th></th>
<th>Randomize</th>
<th>Calibration</th>
<th>Induction</th>
<th>Collection</th>
<th>MRD</th>
<th>Consolidation</th>
<th>Maintenance</th>
<th>MRD</th>
<th>SCT at relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RVD x 3</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cy (3g/m2)</strong></td>
<td></td>
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<tr>
<td><strong>Mobilization</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Goal: 5 x 10⁶ cells/kg</strong></td>
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<tr>
<td><strong>RVD x 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Richardson et al, ASH 2014

*IFM vs. US: 1yr vs. Continuous
## 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></td>
</tr>
<tr>
<td>VGPR</td>
<td>29%</td>
<td>29%</td>
<td>0.02</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</td>
<td>228 (65%)</td>
<td>280 (80%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Attal et al, ASH 2015


![Graph showing PFS (Progression-Free Survival) comparison between HDT and no HDT groups.](image)

N at risk
- HDT: 350, 309, 261, 153, 27
- no HDT: 350, 296, 228, 128, 24

P<0.001

Attal et al, ASH 2015
Sequencing Distinguishes Outcome in FDM Negative Patients

Avet-Loiseau et al, ASH 2015

Phase 1/2 Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

Sequencing Distinguishes Outcome in FDM Negative Patients

Avet-Loiseau et al, ASH 2015

Phase 1/2 Study of Carfilzomib, Lenalidomide, and Dexamethasone (CRd)

ISS Stage | Cytogenetics | Carfilzomib Dosage
---|---|---
| | Normal or Favorable (n=33) | Unfavorable (n=16) | 20 mg/m² | 27 mg/m² | 36 mg/m² |
| | | | | | |
| I (n=20) | 97 | 100 | 100 | 100 | 88 |
| II/III (n=29) | 91 | 100 | 100 | 100 | 88 |
| Unfavorable (n=16) | 61 | 75 | 100 | 100 | 47 |

- Generally well tolerated and manageable side effects
- Grade 3/4 adverse events in ≥10% of pts
  - Hematologic: anemia, neutropenia, thrombocytopenia
  - Non-hematologic: hyperglycemia, dyspnea/CHF, HTN, deep vein thrombosis/ pulmonary embolism, renal dysfunction

Best Response to Ixazomib Len Dex and Ixazomib maintenance

![Graph showing response rates to Ixazomib Len Dex and Ixazomib maintenance.]

10 (48%) pts improved their response during maintenance:
- 2 VGPR to nCR, 5 VGPR to CR, 1 VGPR to sCR, and 2 CR to sCR

Kumar et al ASH 2014

Lenalidomide Bortezomib Dexamethasone Panobinostat

- The combination of lenalidomide 25 mg, subcutaneous bortezomib 1.3 mg/m², dexamethasone, and panobinostat 10 mg in newly diagnosed myeloma

≥ ORR 94%
≥ VGPR 67%
CR/nCR 46%
MRD negative 54% (n=26)

- No effect of panobinostat on stem cell collection/mobilization or quality of graft.
- Randomized phase II study of RVD +/- panobinostat planned

Shah et al, ASH 2015
VTD with or without daratumumab in transplant eligible NDMM – IFM2015/HOVON131

Induction 4 cycles
VTD + Dara
VTD

Consolidation 2 cycles
VTD + Dara
HDM ASCT

Maintenance 2 yrs
Dara
Observation

Endpoints:
- sCR
- PFS, OS

Molecular profiling of MM

Stratify by dara treatment, response, MRD status

MRD by flow & NGS

Erasmus MC

VTD + R HDM ASCT

MM/DC Vaccination following Autologous PBSCT for Myeloma


Ongoing CTN randomized trial of lenalidomide with or without vaccine posttransplant Avigan et al
Bone marrow mononuclear cells

\[ ACY241 (0.5 \mu M) \]
\[ \text{PD-L1 Ab (1ug/ml)} \]

\[ \text{pt.1, pt.2, pt.3, pt.4, pt.5} \]

% increase specific cytotoxicity

\[ \text{ACY} \]
\[ \text{PD-L1} \]
\[ \text{ACY+ PD-L1} \]

Autologous MM Cytotoxicity is Enhanced by ACY 241 + PD-L1 Ab

Bae et al, 2016

MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

**Primary Therapy for Non-Transplant Candidates**

(Assess for response after 2 cycles)

**Preferred Regimens:**
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)
- Melphalan/prednisone/bortezomib (MPB) (category 1)
- Melphalan/prednisone/lenalidomide (MPL) (category 1)
- Melphalan/prednisone/thalidomide (MPT) (category 1)

**Other Regimens:**
- Dexamethasone (category 2B)
- Ixazomib/lenalidomide/dexamethasone
- Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)
- Melphalan/prednisone (MP)
- Thalidomide/dexamethasone (category 2B)
- Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)

**MYEL-D**
Impact of Novel Agents in the Treatment of Elderly Patients with Newly Diagnosed MM

Substantial improvements in PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>Median PFS (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP&lt;sup&gt;1&lt;/sup&gt;-&lt;sup&gt;8&lt;/sup&gt;</td>
<td>11–20</td>
<td>29.1–49.4</td>
</tr>
<tr>
<td>MPT&lt;sup&gt;1&lt;/sup&gt;-&lt;sup&gt;6&lt;/sup&gt;</td>
<td>15–27.5</td>
<td>29–51.6</td>
</tr>
<tr>
<td>VMP&lt;sup&gt;7&lt;/sup&gt;,&lt;sup&gt;8&lt;/sup&gt;,&lt;sup&gt;11&lt;/sup&gt;</td>
<td>21.7–27.4</td>
<td>68.5% (3-yr OS)*</td>
</tr>
<tr>
<td>MPR-R&lt;sup&gt;3&lt;/sup&gt;</td>
<td>31</td>
<td>N/A</td>
</tr>
<tr>
<td>VMP-VT/VP&lt;sup&gt;10&lt;/sup&gt;</td>
<td>34</td>
<td>74% (3-yr OS)*</td>
</tr>
<tr>
<td>VMPVT-VT&lt;sup&gt;11&lt;/sup&gt;</td>
<td>37.2</td>
<td>85% (3-yr OS)*</td>
</tr>
</tbody>
</table>

*Median OS not reached
N/A: not available

1Palumbo et al. Blood 2008; 112:3107–3114
4Waage et al. Blood 2010; 116:1405-12
10Palumbo et al. ASH 2010 (Abstract 622)
11Palumbo et al. ASH 2010 (Abstract 620)

FIRST Trial: Len/Dex versus MPT in Newly Diagnosed Non Transplant Candidates

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Continuous Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN + Lo-DEX Continuously</td>
<td>LENALIDOMIDE 25mg D1-21/28 Lo-DEX 40mg D1,8,15 &amp; 22/28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B</th>
<th>Rd18</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN + Lo-DEX: 18 Cycles (72 wks)</td>
<td>LENALIDOMIDE 25mg D1-21/28 Lo-DEX 40mg D1,8,15 &amp; 22/28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm C</th>
<th>MPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEL + PRED + THAL 12 Cycles (72 wks)</td>
<td>MELPHALAN 0.25mg/kg D1-4/42 PREDNISONE 2mg/kg D1-4/42 THALIDOMIDE 200mg D1-22/28</td>
</tr>
</tbody>
</table>

Pls > 75 yrs: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL<sup>2</sup> (100 mg D1-22/28); MEL<sup>2</sup> 0.2 mg/kg D1-4

• Stratification: age, country and ISS stage

**FIRST Trial: Conclusions**

Continuous Rd significantly extended PFS, with an OS benefit vs. MPT

**PFS:**
- HR = 0.72 (P = 0.00006)
- Consistent benefit across most subgroups
- Rd better than Rd18 (HR = 0.70, P = 0.00001)
- 3 yr PFS: 42% Rd vs. 23% Rd18 and MPT
- Planned interim OS: HR = 0.78 (P = 0.0168)
- Rd was superior to MPT across all other efficacy secondary endpoints

**Safety profile with continuous Rd was manageable**

- Hematological and non-hematological AEs were as expected for Rd and MPT
- Incidence of hematological SPM was lower with continuous Rd vs. MPT

In NDMM transplant-ineligible patients, the FIRST Trial establishes continuous Rd as a new standard of care


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**When to Consider Retreatment**

- Differences between biochemical relapse and symptomatic relapse need to be considered
- Patients with asymptomatic rise in M-protein can be observed to determine the rate of rise and nature of the relapse
  - **Caveat:** patients with known aggressive or high-risk disease should be considered for salvage even in the setting of biochemical relapse
- CRAB criteria are still listed as the indication to treat in the relapsed setting—however, in patients with progression, treatment can avoid CRAB
  - **C**: Calcium elevation (> 11.5 mg/L or ULN)
  - **R**: Renal dysfunction (serum creatinine > 2 mg/dL)
  - **A**: Anemia (Hb < 10 g/dL or 2 g < normal)
  - **B**: Bone disease (lytic lesions or osteoporosis)
## MYELOMA THERAPY

Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem-cell reserve prior to stem-cell harvest in patients who may be candidates for transplants.

### Therapy for Previously Treated Multiple Myeloma

**Preferred Regimens:**

1. Repeat primary induction therapy (if relapse at >6 mo)
2. Bortezomib (category 1)
3. Bortezomib/dexamethasone
4. Bortezomib/cyclophosphamide/dexamethasone
5. Bortezomib/lenalidomide/dexamethasone
6. Bortezomib/ibposomal doxorubicin (category 1)
7. Bortezomib/thalidomide/dexamethasone
8. Carfilzomib
9. Carfilzomib/dexamethasone
10. Carfilzomib/lenalidomide/dexamethasone (category 1)
11. Cyclophosphamide/lenalidomide/dexamethasone
12. Daratumumab
13. Dexamethasone/cyclophosphamide/doxorubicin/cisplatin (DCEP)
14. Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)
15. Elotuzumab/lenalidomide/dexamethasone (category 1)
16. Ixazomib
17. Ixazomib/dexamethasone
18. Ixazomib/lenalidomide/dexamethasone (category 1)
19. High-dose cyclophosphamide
20. Lenalidomide/dexamethasone (category 1)
21. Panobinostat/bortezomib/dexamethasone (category 1)
22. Pomalidomide/dexamethasone (category 1)
23. Thalidomide/dexamethasone

### Other Regimens:

- Bendamustine
- Bortezomib/vorinostat
- Lenalidomide/bendamustine/dexamethasone
- Panobinostat/carfilzomib

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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


POM + LoDEX significantly improved PFS vs HiDEX

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>POM + LoDEX</th>
<th>HiDEX</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>

### ASPIRE: Carfilzomib, Lenalidomide, and Dexamethasone (KRd) vs Lenalidomide and Dexamethasone (Rd)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of neuropathy at baseline, %</td>
<td>36.4</td>
<td>34.6</td>
</tr>
<tr>
<td>Number of prior regimens, median (range)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Prior therapies, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>54.8</td>
<td>57.8</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>65.9</td>
<td>65.7</td>
</tr>
<tr>
<td>Non-responsive to prior bortezomib*</td>
<td>15.2</td>
<td>14.6</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>19.9</td>
<td>19.7</td>
</tr>
<tr>
<td>Any IMiD</td>
<td>58.8</td>
<td>57.8</td>
</tr>
<tr>
<td>Refractory to prior IMiD in any prior regimen</td>
<td>21.5</td>
<td>22.2</td>
</tr>
<tr>
<td>Bortezomib and IMiD</td>
<td>36.9</td>
<td>35.1</td>
</tr>
<tr>
<td>Non-responsive to prior bortezomib* and refractory to prior IMiD</td>
<td>6.1</td>
<td>6.8</td>
</tr>
</tbody>
</table>


### PFS by Risk Group

<table>
<thead>
<tr>
<th>Risk Group by FISH</th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
<th>HR (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median, months</td>
<td>N</td>
</tr>
<tr>
<td>High</td>
<td>48</td>
<td>23.1</td>
<td>52</td>
</tr>
<tr>
<td>Standard</td>
<td>147</td>
<td>29.6</td>
<td>170</td>
</tr>
</tbody>
</table>

Primary End Point: Progression-Free Survival
Intent-to-Treat Population (N=929)

- Median follow-up: 11.2 months

Dimopoulos et al, ASCO 2015

Carfilzomib Pomalidomide Low dose Dex

- Median of 5 prior lines of therapy; 49% of patients had high/intermediate risk cytogentic risk status at baseline
  - ≥ VGPR 27%
  - ORR 70%
  - CBR 83%
  - DOR (median) 17.7 months
  - PFS (median) 9.7 months
  - OS (median) > 18 months

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

Shah et al ASH 2013
**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 3/4 diarrhea (25.5% vs 8%), fatigue (23.0% vs 11.9%), thrombocytopenia (67.4% vs 31.4%), and leukopenia (34.5% vs 11.4%), discontinuation due to AE (33.6% vs 17.3%).

- Confirms PAN-BTZ-Dex in BTZ-refractory pts (PANORAMA 2): ORR: 34.5%; CBR: 52.7%; median PFS: 5.4 mos; median OS: 17.5 mos

- FDA approved for relapsed refractory MM exposed to bortezomib and IMiD

- Need for less toxic more selective HDACi that can be given with PI to exploit synergistic cytotoxicity.

  *San Miguel J, et al. Lancet Oncol. 2014*

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**Ricolinostat (ACY 1215) Selective Histone Deacetylase 6 Inhibitor**

- Synthesized and validated at DFCI

- Angel investor company has advanced to phase II-III clinical trials-LLS TAP Program

- Well tolerated daily oral medication

- Achieves 50% responses when combined with either bortezomib, lenalidomide or pomalidomide in relapsed refractory myeloma
Phase 3 study of weekly oral ixazomib plus lenalidomide-dex: final PFS analysis

- 35% improvement in PFS with IRd vs Rd (data cut-off 30 October 2014)

A subsequent exploratory analysis of PFS was conducted (median follow-up 23.3 and 22.9 months in the IRd and Rd arms); median PFS 20 vs 15.9 months

Response rates and TTP improved and responses durable with IRd

<table>
<thead>
<tr>
<th>Response rates, %</th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (≥PR)</td>
<td>78.3</td>
<td>71.5</td>
<td>p=0.035</td>
</tr>
<tr>
<td>CR+VGPR</td>
<td>48.1</td>
<td>39.0</td>
<td>p=0.014</td>
</tr>
</tbody>
</table>

Response categories

<table>
<thead>
<tr>
<th>CR</th>
<th>IRd (N=360)</th>
<th>Placebo-Rd (N=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>66.7</td>
<td>64.9</td>
<td>–</td>
</tr>
<tr>
<td>VGPR</td>
<td>36.4</td>
<td>32.3</td>
<td>–</td>
</tr>
</tbody>
</table>

Median time to response, mos* | IRd 1.1 | Placebo-Rd 1.9 | –       |

Median duration of response, mos | IRd 20.5 | Placebo-Rd 15.0 | –       |

- Significant improvements in different response categories
  - Conservative assessment of best response – derived up until the end of treatment
  - Independently determined by IRC assessment of blinded central laboratory data, rigorously following IMWG 2011 criteria

- PFS benefit confirmed by time to progression (TTP) analysis: median 21.4 months versus 15.7 months with IRd versus Rd, HR 0.712; p=0.007

Moreau et al ASH 2015
Monoclonal Antibody Based Therapeutic Targeting of Multiple Myeloma

Antibody-dependent Complement-dependent Cellular Cytotoxicity (ADCC) vs. CDC

**Antibody-dependent Cytotoxicity (ADCC)**
- Effector cells: NK cell, macrophage, neutrophil.
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (SLAMF7)
- Daratumumab (CD38)
- XmAb5592 (HM1.24)
- SAR650984 (CD38)

**Complement-dependent Cytotoxicity (CDC)**
- Effector cells: C1q
- Daratumumab (CD38)
- SAR650984 (CD38)

Apoptosis/growth arrest via intracellular signaling pathways

**Progression-Free Survival**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Progression-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (months)</td>
<td>19.4</td>
</tr>
<tr>
<td>1-year PFS (%)</td>
<td>68</td>
</tr>
<tr>
<td>2-year PFS (%)</td>
<td>41</td>
</tr>
<tr>
<td>3-year PFS (%)</td>
<td>26</td>
</tr>
<tr>
<td>1-year follow-up PFS (%)</td>
<td>57</td>
</tr>
<tr>
<td>2-year follow-up PFS (%)</td>
<td>28</td>
</tr>
<tr>
<td>3-year follow-up PFS (%)</td>
<td>18</td>
</tr>
</tbody>
</table>

**Relative difference (%)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>E-Ld</th>
<th>Ld</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative difference (%)</td>
<td>19</td>
<td>52</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.70 (0.57, 0.85)</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.73 (0.60, 0.89)</td>
<td></td>
</tr>
</tbody>
</table>

Dimopoulos et al ASH 2015
Prespecified interim analysis for overall survival indicates a strong trend (p=0.0257) with early separation sustained over time for E-Ld vs Ld.

Dimopoulos et al ASH 2015

Phase 2 Study of Daratumumab (DARA) in Patients with ≥3 Lines of Prior Therapy or Double Refractory Multiple Myeloma: 54767414MMY2002 (Sirius)

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

Lonial et al ASCO 2015
Overall Response Rate: Daratumumab + Len/Dex

<table>
<thead>
<tr>
<th></th>
<th>N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>26 (81)</td>
</tr>
<tr>
<td>95% CI</td>
<td>63.6-92.8</td>
</tr>
</tbody>
</table>

Best response

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>8 (25)</td>
<td>11.5-43.4</td>
</tr>
<tr>
<td>CR</td>
<td>9 (28)</td>
<td>2.0-25.0</td>
</tr>
<tr>
<td>VGPR</td>
<td>9 (28)</td>
<td>13.7-46.7</td>
</tr>
<tr>
<td>PR</td>
<td>6 (19)</td>
<td>7.2-36.4</td>
</tr>
</tbody>
</table>

VGPR or better

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR+CR+VGPR+PR</td>
<td>20 (63)</td>
<td>43.7-78.9</td>
</tr>
</tbody>
</table>

CR or better (sCR+CR)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR+CR</td>
<td>11 (34)</td>
<td>18.6-63.2</td>
</tr>
</tbody>
</table>

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

Plesner et al ASH 2015

Immune Suppressive Microenvironment in MM

Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity

Effector: Autologous effector cells (CD3T cells, NK cells)
Target: CD138+ MM cells from Rel/Ref MM-BM

* p<0.05


Lenalidomide Enhances Checkpoint Blockade Induced Cytotoxicity Against MM cells

Phase 1 Trial of Pembrolizumab + Lenalidomide and Low Dose Dexamethasone in RRMM

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Total N = 17</th>
<th>Len Refractory* N = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>13 (76)</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Very Good Partial Response</td>
<td>4 (24)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>9 (53)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Disease Control Rate†</td>
<td>15 (88)</td>
<td>7 (78)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>3 (18)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>1 (6)</td>
<td>1 (11)</td>
</tr>
</tbody>
</table>

*3 patients double refractory and 1 triple refractory (Len/Bor +Pom)
†Disease Control Rate = CR + VGPR + PR + SD >12 weeks.
Data cutoff date: September 22, 2015

San Miguel et al ASH 2015

Immune Effects of HDACi 241 in MM Therapy

Augments PD-L1 expression on MM cells

Augments MM cell line cytotoxicity, which is enhanced with pomalidomide, CD38Ab, and/or PD-1/PD-L1 Abs

Augments and autologous MM cell cytotoxicity, which is enhanced by CD38 Ab and/or PD-1/PD-L1 Abs

Enhances MM cytotoxicity alone and with PD-1/PD-L1Abs, even in the presence of pDCs

Augments NK cell function, alone and with PD-L1 Ab
Myeloma CAR therapy

- Multiple promising targets:
  - CD19, CD138, CD38, CD56, kappa, Lewis Y, CD44v6, CS1, 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 underway
  - Anecdotal prolonged responses but no robust efficacy data available yet

- Many questions remain about CAR design:
  - optimal co-stimulatory domains
  - optimal vector
  - optimal dose and schedule
  - need for chemotherapy
  - Perhaps ‘cocktails’ of multiple CARs or CARs + chemotherapy will be required for best outcomes

Stadtmauer et al, 2015

MM Patient #1: Response to CD19 CAR Therapy

sCR, MRD neg
Now d +307
TTP after ASCT #1 d190
Remission inversion

Garfall et al, NEJM 2015; 373: 1040-7
Summary and Conclusions

• Broader population of patients now eligible for therapy: 60% BM plasma cells; kappa:lambda>100; bone disease on MRI or PET/CT

• In newly diagnosed transplant candidates, three drug regimens incorporating immunomodulatory drugs and proteasome inhibitors before and after transplant prolong PFS and OS.

• MRD portends for better patient outcome and is a goal of therapy

Summary and Conclusions

• Relapse therapies now include bortezomib, lenalidomide/dex, bortezomib/pegylated doxorubicin, pomalidomide/dex, carfilzomib, bortezomib/panobinostat, elotuzumab len dex, daratumumab, and ixazomib.

• Novel targeted and immune therapies are showing great promise.

• Incorporation of novel therapies at all stages of disease is further improving patient outcome in MM