MULTIPLE MYELOMA:
Update from ASH 2014 Meeting
North Texas Myeloma Support Group

January 10, 2015

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Multiple Myeloma and
Stem Cell Transplant Clinic
Multiple Myeloma Classic Triad

- M-Spike
  - Normal Serum Protein Electrophoresis
  - M-Spike

>10% Malignant Clonal Plasma Cells in Bone Marrow

Lytic Bone Lesions
Multiple Myeloma Facts

- 2nd most common Hematologic Malignancy (after NHL)
- ~20,000 people diagnosed with MM each year in US
- ~65,000 people in the US living with myeloma
- > 11,000 MM patients die each year in US
- Still incurable but getting closer to becoming a chronic disease state
- Survival is improving steadily with each decade as new therapies have been emerging, Average survival now estimated around 8-10 years for standard risk
Criteria for Diagnosis of Myeloma

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

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

AND

**Symptomatic Myeloma**
- ≥10% PC
- +/- M-spike

AND

**≥ 1 CRAB:**
- Calcium elevation,
- Renal dysfunction
- Anemia (Hgb <10)
- Bone lesions
Ultra High Risk SMM = Active Myeloma

Not CRAB but now **SLiM CRAB**

- **S** (60% PCs)
- **Li** (Light chains I/U Ratio > 100)
- **M** (MRI > 1 focal lesion)
- **C** (calcium elevation)
- **R** (renal insufficiency)
- **A** (anemia)
- **B** (bone disease)

*Lancet Oncology 11/2014*
<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1962</td>
<td>Melphalan-prednisone (MP)</td>
<td>Introduction of melphalan in the 1960s associated with improved survival. More intense chemotherapy regimens increased response rates, but no improvement in survival compared to MP.</td>
</tr>
<tr>
<td>1996</td>
<td>Autologous SCT</td>
<td>Several randomized trials demonstrated a survival advantage for ASCT compared to conventional chemotherapy (CCT).</td>
</tr>
<tr>
<td>1999</td>
<td>Thalidomide (Thalomid)</td>
<td>Improved response rates and PFS compared to dexamethasone alone. When added to MP, it improves survival compared to MP alone.</td>
</tr>
<tr>
<td>2003</td>
<td>Bortezomib (Velcade)</td>
<td>Bortezomib improves survival compared to high-dose dexamethasone in relapsed myeloma, and VMP improves survival in newly Dx pts compared to MP.</td>
</tr>
<tr>
<td>2003</td>
<td>Tandem Autologous SCT</td>
<td>Tandem SCT improved survival compared with single transplant, but only in those failing to achieve a very good partial response with first transplant.</td>
</tr>
<tr>
<td>2006</td>
<td>Lenalidomide (Revlimid)</td>
<td>Lenalidomide and dex improved survival compared with dex in relapsed myeloma in phase III trials.</td>
</tr>
<tr>
<td>2012</td>
<td>Carfilzomib (Kyprolis)</td>
<td>22% Response rate if refractory to both Vel and Rev.</td>
</tr>
<tr>
<td>2013</td>
<td>Pomalidomide (Pomalyst)</td>
<td>30% Response rate if refractory to both Vel and Rev (7% if no Dex added).</td>
</tr>
</tbody>
</table>
Effect of Novel Agents on Outcome in Newly Diagnosed Myeloma

OS From Diagnosis

Novel Agents + ASCT

ASCT

MM Survival Is Improving With Novel Agents

**Median: 7.3 yrs**

**Follow-up From Diagnosis (Yrs)**

<table>
<thead>
<tr>
<th></th>
<th>≤ 65 Yrs</th>
<th>&gt; 65 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2010</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>2001-2005</td>
<td>63</td>
<td>31</td>
</tr>
</tbody>
</table>

Novel Induction Regimens
Continuous Improvement of Responses

Overview of Updates in Newly Diagnosed Multiple Myeloma

- FIRST: effect of age on lenalidomide/dexamethasone vs MPT in transplantation-ineligible pts
- Weekly vs twice weekly carfilzomib in combination with cyclophosphamide/dexamethasone
- Ixazomib/lenalidomide/ dexamethasone induction and maintenance
Overview of Updates in Relapsed/Refractory Multiple Myeloma

- ASPIRE: addition of carfilzomib to Lenalidomide/dex

- Monoclonal antibodies in combination with Lenalidomide/dex
  - SAR650984 (anti–CD38 mAb)
  - Daratumumab (anti–CD38 mAb)
  - Elotuzumab (anti–SLAMF7/CS1 mAb)
Therapeutic algorithms for newly diagnosed patients with plasma cell myeloma

**Front line treatment**

**Induction**
- Rev/Dex, Vel/Dex
- RVD, VCD
- CTD, VTD, VDD, MPT, MPV, MPR

**Consolidation**

**Maintenance**
- None
- Rev
- Velcade
- Clinical Trial

**Auto-SCT**

**Relapsed**

**Salvage**
- Whatever worked before or haven’t tried
Newly Diagnosed
Multiple Myeloma
FIRST: Lenalidomide/Dexamethasone vs MPT in NDMM SCT-Ineligible Pts

**Active treatment + PFS follow-up phase**

- **Arm A**: Continuous Rd + Lenalidomide + LoDex Continuously until Progression
- **Arm B**: Rd18 + Lenalidomide + Low dose Dex 18 cycles (72 wks)
- **Arm C**: MPT + Mel + Pred + Thalidomide 12 cycles[^2] (72 wks = 18 mo)

**Phase III** (N = 1623)

PD or unacceptable toxicity → PD, OS, and subsequent anti-MM Tx

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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: PFS by Age Stratification

Aged 75 Yrs or Younger
- Median, Mos
  - Rd: 27.4
  - Rd18: 21.3
  - MPT: 21.8

Aged Older Than 75 Yrs
- Median, Mos
  - Rd: 21.2
  - Rd18: 19.4
  - MPT: 19.2

### 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

- Continuous Rd (Rev/dex) improved PFS compared to MPT or 18 cycles of Rd for newly diagnosed MM regardless of age
  - Median and 3-yr PFS both extended with continuous Rd vs MPT or Rd18 whether pts were younger or older than 75 yrs of age
  - 3-yr OS extended with continuous Rd vs MPT whether pts were younger or older than 75 yrs of age
- Toxicity profile of Continuous Rd similar among pts younger or older than 75 yrs of age

Weekly Carfilzomib (Kyprolis) in Combo With Cyclophosphamide/Dex in NDMM

- Phase I/II trial to assess feasibility of reduction of carfilzomib dosing from twice weekly to once weekly (in combination with cyclophosphamide + dexamethasone in elderly pts with NDMM)
  - Carfilzomib given weekly using standard 3+3 phase I dose-escalation (starting at 45 mg/m², increasing to 56 or 70 mg/m²)
- Phase I data (n = 12) identified MTD as 70 mg/m²
- Phase II cohort currently enrolling
  - 18 pts included in current analysis

Weekly Carfilzomib + Cytoxan/Dex: Preliminary Efficacy

At Least nCR

<table>
<thead>
<tr>
<th>Cycle 4</th>
<th>Cycle 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>41</td>
</tr>
<tr>
<td>24</td>
<td>47</td>
</tr>
</tbody>
</table>

At Least VGPR

<table>
<thead>
<tr>
<th>Cycle 4</th>
<th>Cycle 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>57</td>
<td>77</td>
</tr>
</tbody>
</table>

- Once weekly\(^1\)
- Twice weekly\(^2\)

Weekly Carfilzomib + Cytoxan/Dex: Conclusions

- Weekly Car appeared safe and effective in combo with weekly cytoxan/dex in newly diagnosed, elderly pts with MM
  - MTD of weekly Carfilzomib: 70 mg/m$^2$
  - Not more toxic than current standard 27mg/m$^2$ twice weekly
  - 89% of pts achieved deep response (at least VGPR) with weekly dosing after only 4 cycles
  - Responses improved over time; 41% of pts achieved ≥ nCR after 9 cycles vs 30% after 4 cycles

Ixazomib Plus RD: ORR Over Course of Treatment

(MLN9708) + Rev/dex (Oral Triple Drug Therapy)

Median DOR 13.8 mos, ranging up to 18.8+ mos

Ixazomib Plus Rev/Dex: Conclusions

- Oral ixazomib plus lenalidomide/ dex active in patients with newly diagnosed multiple myeloma\cite{1}
- 90% of pts had PR or better
- 48% of pts had deepening of response with Ixazomib maintenance
- Incidence of dose reductions, rash, and peripheral neuropathy slightly higher with twice-weekly ixazomib dosing vs weekly dosing\cite{2}
  - Weekly dosing being used in ongoing phase III studies (Very low Neuropathy with weekly dosing, ASH 2012)

Summary: Treatment for Patients With Newly Diagnosed Multiple Myeloma

- In phase 3 FIRST trial, Continuous Rd therapy superior to MPT for PFS and OS with similar safety profiles and good effect regardless of age.
- Once weekly Carfilzomib MTD 70 mg/m2 combined with weekly Cytoxan and Dex, at least as effective as twice weekly historical data and not more toxic.
- Weekly oral Ixazomib (MLN9708) plus lenalidomide/dex active in patients with NDMM and has minimal neuropathy though some seen with twice weekly.
- Responses improve over time with maintenance Ixazomib.
Relapsed/Refractory Multiple Myeloma
ASPIRE: Phase III Trial Comparing Len/Dexamethasone ± Carfilzomib in R/R MM

- Randomized, open-label, multicenter phase III trial

Stratified by β₂-microglobulin, prior bortezomib, and prior lenalidomide

**KRd** (n = 396)
- Carfilzomib 27 mg/m² IV
- Days 1, 2, 8, 9, 15, 16 (20 mg/m² days 1, 2, cycle 1 only)
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40 mg Days 1, 8, 15, 22

**Rd** (n = 396)
- Lenalidomide 25 mg Days 1-21
- Dexamethasone 40 mg Days 1, 8, 15, 22

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

ASPIRE: PFS in ITT Population (Primary Endpoint)

**Proportion Surviving Without Progression**

- **KRD** (n = 396)
- **Rd** (n = 396)

**Median PFS, mos**
- **KRD**: 26.3
- **Rd**: 17.6

**HR (KRD/Rd) (95% CI)**
- **KRD**: 0.69 (0.57-0.83)
- **Rd**: < .0001

**P value (1 sided)**
- **KRD**: < .0001
- **Rd**: < .0001

**Risk Group by FISH**

<table>
<thead>
<tr>
<th>Risk Group by FISH</th>
<th>KRd (n = 396)</th>
<th>Rd (n = 396)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td><strong>Median PFS, Mos</strong></td>
<td><strong>n</strong></td>
<td><strong>Median PFS, Mos</strong></td>
<td><strong>HR</strong></td>
</tr>
<tr>
<td>High</td>
<td>48</td>
<td>23.1</td>
<td>52</td>
<td>13.9</td>
</tr>
<tr>
<td>Standard</td>
<td>147</td>
<td>29.6</td>
<td>170</td>
<td>19.5</td>
</tr>
</tbody>
</table>

ASPIRE: Interim OS Analysis

- Median follow-up: 32 mos
- Median OS was not reached; results did not meet prespecified statistical boundary ($P = .005$) at interim analysis.

ASPIRE: Response Rates

- AEs consistent with previous studies; no unexpected toxicities observed

ASPIRE: Conclusions

- PFS significantly improved by 9 mos in pts treated with KRd vs Rd relapsed/refractory MM ($P < .0001$)
  - Median PFS of 26.3 mos with triplet combination unprecedented in this setting
- Interim OS analysis reveals trend favoring KRd
- Increased ORR with KRd vs Rd: 87.1% vs 66.7%
  - More pts achieved CR or better with triplet: 31.8% with KRd vs 9.3% with Rd
- Acceptable safety profile observed with KRd
- KRd potentially new SOC for treatment of relapsed MM

Phase I Trial: SAR650984 in Combination With Len/Dex in Relapsed/Refractory MM

- DoR: 9.13 mo (range: 1.2-15.2)

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Total (N = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>sCR</td>
</tr>
<tr>
<td></td>
<td>VGPR</td>
</tr>
<tr>
<td></td>
<td>PR</td>
</tr>
<tr>
<td>CBR</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>MR</td>
</tr>
<tr>
<td>SD</td>
<td>19</td>
</tr>
<tr>
<td>PD</td>
<td>13</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3</td>
</tr>
</tbody>
</table>

- SAR650984 is a humanized IgG1 mAb to the CD38 receptor

SAR650984 + Len/Dex: Conclusions

- Combination SAR650984 with len/dex appears safe and effective in heavily pretreated pts with relapsed/refractory MM
  - ORR was 58%; 63% at the SAR650984 10 mg/kg dose level
  - Manageable safety profile, consistent with those of individual agents
  - At 9-mo follow-up, overall median PFS was 6.2 mos

Phase I Trial: Daratumumab in Combo w/ Len/Dex in Rel/Ref MM

- Phase I/II dose-escalation trial of daratumumab in combination with len/dex in rel/ref MM (safety cohort: n = 45; efficacy cohort: n = 43)
  - Daratumumab is a human mAb targeting CD38-expressing cells
  - Dose escalation: daratumumab 2-16 mg/kg/wk for 8 wks, twice monthly for 16 wks, then once monthly for 24 mos in total or until PD, unmanageable AE
  - Lenalidomide 25 mg on Days 1-21 of each 28-day cycle
  - Dexamethasone 40 mg/wk for of each 28-day cycle

- Median prior lines of therapy: 2 (range: 1-4); most with prior exposure to IMiDs and/or a proteasome inhibitor; 3 pts refractory to len

- MTD: daratumumab 16 mg/kg + len 25 mg and dex 40 mg/wk

Daratumumab in Combination With Len/Dex: Overall Best Response

**Overall Best Response**

- **Part 1**
  - 100 Patients
  - CR 31%
  - VGPR 46%
  - PR 23%

- **Part 2**
  - 86.7 Patients
  - CR 6.7%
  - VGPR 43%
  - PR 37%

**VGPR or Better Response by Cycles of Treatment (Part 2)**

- **≥ 2 Cycles (n = 30)**
  - 50.0 Patients
  - CR 6.7%
  - VGPR 43.3%

- **≥ 4 Cycles (n = 25)**
  - 60 Patients
  - CR 8.0%
  - VGPR 52%

- **≥ 6 Cycles (n = 7)**
  - 64.7 Patients
  - CR 11.8%
  - VGPR 52.9%

- Mean follow-up: 12.9 mos (Part 1); 5.6 mos (Part 2)
- Median time to response: 1 mo for 16 mg/kg in Part 2; median time to CR: 4.9 mos in Part 2

Combination daratumumab with len/dex appears safe and effective in heavily pretreated pts with relapsed/refractory MM

- ORR: 100% in Part 1; 87% in Part 2
- Favorable safety profile with manageable toxicities
- Accelerated infusion tolerable but associated with higher incidence of infusion reactions

Phase III trials of daratumumab + len/dex ongoing

- MMY3003 (relapsed/refractory), enrolling
- MMY3008 (frontline), enrollment to start early 2015

Phase I Trial: Elotuzumab in Combo With Len/Dex in Rel/Ref MM

- Phase Ib/II trial of elotuzumab + len/dex in relapsed/refractory MM
  - Elotuzumab is a humanized IgG1 mAb targeting SLAMF7 (CS1), a glycoprotein highly expressed on myeloma and NK cells
  - Elotuzumab 10 or 20 mg/kg on Days 1, 8, 15, 22 for cycles 1-2; Days 1, 15 for subsequent cycles
  - Lenalidomide 25 mg on Days 1-21 of each 28-day cycle
  - Dexamethasone 40 mg/wk

- Current analysis on phase II data to assess efficacy and safety of combination

Elotuzumab in Combination With Len/Dex: Final Efficacy Results

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Elotuzumab 10 mg/kg (n = 36)</th>
<th>Elotuzumab 20 mg/kg (n = 36)</th>
<th>Total (N = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>92</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>- sCR</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>- CR</td>
<td>11</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>- VGPR</td>
<td>47</td>
<td>38</td>
<td>43</td>
</tr>
<tr>
<td>- PR</td>
<td>28</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>SD</td>
<td>8</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Time to first response, mos</td>
<td>1.0</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Median DoR, mos</td>
<td>23.0</td>
<td>18.0</td>
<td>20.8</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>32.5</td>
<td>25.1</td>
<td>28.6</td>
</tr>
</tbody>
</table>

Elotuzumab in Combination With Len/Dex: Conclusions

- Combination elotuzumab with len/dex appears safe and effective in heavily pretreated pts with relapsed/refractory MM
  - ORR: 92% with 10 mg/kg elotuzumab
  - Median PFS: 32.5 mos with 10 mg/kg
- Favorable safety profile; most common treatment-related AEs included diarrhea, fatigue, muscle spasms, constipation (From Revlimid)
- Accelerated infusion well tolerated and pretreatment regimen decreased rate of infusion reactions
- Phase III trials with elotuzumab + len/dex in newly diagnosed MM and relapsed/refractory MM currently ongoing

Most Promising New Therapies in Relapsed/Refractory Myeloma

- Daratumumab (monoclonal antibody targeting CD38)
- SAR650984 (monoclonal antibody targeting CD38)
- Elotuzumab (Anti-CS1 monoclonal Ab)
- ACY-1215 (Oral HDAC-6 Inhibitor) combo w/ Vel
- Ixazomib (Oral Proteasome inhibitor)
- ARRY-520 (filanesib)(Kinesin Spindle Protein inhibitor)
- Afuresertib (Akt Inhibitor) in combo w/ Vel/Dex (65% ORR even if refractory to Vel)
- Chimeric antigen Receptor (CAR) Gene modified T Cell therapy (mostly for Lymphoma/Leukemia so far but being modified for Myeloma and very exciting)
Hot Topic in Myeloma: MRD

- Clonal Heterogeneity causes different response to classes of drugs over the course of myeloma

- Lack of Minimal Residual disease by high sensitivity flow cytometry or by molecular PCR testing confirms not all Complete Remissions are the same

- Can we use molecular testing to decide when to stop maintenance therapy or when to add additional therapy to try to achieve MRD negative status?

- Ongoing trials such as the BMT-CTN Dana Farber study are using molecular testing for MRD to help determine the effect of this finding
Is treating to a CR enough?

Current MM Trials at UT Southwestern

- Phase I study of oral HDAC6 inhibitor (Ricolinostat) in combination with Pomalidomide and Dex (triple oral therapy) for Relapsed MM
- Phase I study of anti-BCMA monoclonal antibody (first in human) (plasma cell specific)
- Phase I study of Ibrutinib (oral btk inhibitor) in combination with Carfilzomib and Dexamethasone for relapsed Myeloma
- Phase II randomized study of Carfilzomib +/- Arry520 (2:1)(can cross over to get Arry520 if progressing on Car)
- Phase II study of Arry520 (iv every other wk Kinesin spindle inhibitor)
- Phase III MM007 study of velcade/dex +/- Pomalidomide for rel MM
- Phase III study of Rev/dex +/- Daratumumab for relapsed MM
- BMT/CTN Dana Farber DETERMINATION study of early vs delayed stem cell transplant in newly Dx MM <65 y/o
- ECOG study of Rev vs Observation for high risk Smoldering MM
- MMRF Compass study (tissue bank and database for newly Dx MM)
Questions?