Myeloma: What do We Know?  
2015: An Update

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Plasma Cell Disorders
- MGUS
- Solitary Plasmacytoma
- Multiple Myeloma
- Waldenström’s Macroglobulinemia
- Amyloidosis
- POEMS Syndrome
- Lymphoplasmacytic lymphoma
Incidence and death in multiple myeloma

Estimates for MM in the United States for 2011

- Accounts for 10% of hematologic cancers in the United States
- Increased incidence in African Americans
- Median age of diagnosis is 70 years


Myeloma Survival by Decade

Improved due to new drugs:

- Auto PSC-T
- Thalidomide
- Lenalidomide
- Bortezomib
Multistep pathogenesis of multiple myeloma

<table>
<thead>
<tr>
<th>Multistep progressive disease</th>
<th>MGUS</th>
<th>Intramedullary multiple myeloma</th>
<th>Extramedullary multiple myeloma</th>
<th>Plasma-cell leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic abnormalities</td>
<td></td>
<td>Secondary translocations</td>
<td></td>
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</tr>
<tr>
<td>Non-hyperdiploidy (50% of patients)</td>
<td>Hyperdiploidy (50% of patients)</td>
<td></td>
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</tr>
<tr>
<td>Increased expression of cyclin D1, D2, and D3</td>
<td>Oncogenic activation of mutation (RAS, FGFR)</td>
<td>Increased expression of cyclin D4</td>
<td>MTC dysregulation, TP53 mutation</td>
<td></td>
</tr>
</tbody>
</table>

MGUS: monoclonal gammopathy of undetermined significance


Presenting Features of MM

<table>
<thead>
<tr>
<th>Feature</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
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</thead>
<tbody>
<tr>
<td>M-protein SIU</td>
<td>97%</td>
<td>73%</td>
<td>66%</td>
<td>58%</td>
<td>19%</td>
<td>13%</td>
<td>11%</td>
<td>4%</td>
<td>4%</td>
<td>3%</td>
<td></td>
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<tr>
<td>Anemia</td>
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<tr>
<td>Lytic Bone Lesions</td>
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<tr>
<td>Bone Pain</td>
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<tr>
<td>Renal Insufficiency</td>
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<tr>
<td>Hypercalcemia</td>
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<tr>
<td>Minor or no abnormalities</td>
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</tr>
<tr>
<td>Hepatomegaly</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
<td>4%</td>
<td></td>
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<tr>
<td>Amyloidosis</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Non-secretory (no SIU M-protein)</td>
<td></td>
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</tr>
</tbody>
</table>

Adapted with permission from Kyle RA et al. Mayo Clin Proc. 2003;78:21
Evaluation for Plasma cell dyscrasia

- CBC, Lytes, Cr, Ca^{2+}, Albumin
- Quantitative immunoglobulins, β2 microglobulin
- SPEP, SIFE, SFLC
- 24 hour urine for TP, UPEP, UIFE
- Skeletal survey, MRI spine or PET/CT
- BMBx: H+E, Flow, cytogenetics, FISH
- Optional: Sequenta
- GENE EXPRESION PROFILE

Gene Expression Microarray Cluster Plot: 70 Genes in ISS Low- to High-Risk Patients

Relative risk

▼ 22 healthy subjects (NPC*), 14 subjects with MGUS, 351 patients with newly diagnosed MM, and 42 HMCL*
## Historical Criteria for Diagnosis of Myeloma

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

**SMM**
- ≥ 3 g/dL M spike
- ≥ 10% plasma cells

**Active MM**
- ≥ 10% plasma cells
- M spike + in serum and/or urine

AND NO CRAB* features or end-organ damage

AND CRAB* features

*CRAB* features
- C: Calcium elevation (> 10.5 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)


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## Monoclonal Gammopathy of Undetermined Significance

Overall 1% progress each yr, correlated with initial paraprotein level, with low risk <1 g/dL, high risk >3 g/dL; P<0.001

![Relative Risk Chart](image)

Adapted with permission from Kyle RA et al. *N Engl J Med.*, 2002;346:564
**MGUS: Walter Reed Study**

*Weiss et al.*

Samples available for 30/90

Median number of samples available 3.5 (1-14)

PPCD detected in 27/30

- +SPEP and/or IFE 21
- + sFLC 6

First detected

- sFLC alone 6
- IFE alone 1
- SPEP + IFE 5
- IFE + sFLC 1
- All three 14

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**Smoldering Multiple Myeloma**

![Graph showing probability of progression over years since diagnosis]

Biomarkers to Predict Risk of Progression

- FLC ratio ≥ 100 predicts risk ($P < .0001$)
- Clonal plasma cells in BM predicts risk ($P < .001$)


Updated IMWG Criteria for Diagnosis of Multiple Myeloma

**MGUS**
- M protein < 3 g/dL
- Clonal plasma cells in BM < 10%
- No myeloma defining events

**Smoldering Myeloma**
- M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
- Clonal plasma cells in BM ≥ 10% to 60%
- No myeloma defining events

**Multiple Myeloma**
- Underlying plasma cell proliferative disorder
- AND 1 or more myeloma defining events
- ≥ 1 CRAB* feature
- Clonal plasma cells in BM ≥ 60%
- Serum free light chain ratio ≥ 100
- > 1 MRI focal lesion

*C*: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
*R*: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
*A*: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
*B*: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

A Multicenter, Randomised, Open-label, Phase III Study of Lenalidomide/Dexamethasone versus Therapeutic Abstention in high-risk Smoldering MM

On behalf of Spanish Myeloma Group (PETHEMA/GEM)

Smoldering Multiple Myeloma: PCs BM infiltration and Serum M-component level

| Group 1: | PCBM ≥ 10% + MC ≥ 3g/dl |
| Group 2: | PCBM ≥ 10% + MC < 3g/dl |
| Group 3: | PCBM < 10% + MC ≥ 3g/dl |

TTP: 2 y
TTP: 8 y
TTP: 19 y

## SMM Trial: High-risk smoldering MM

**PCs BM \( \geq 10\% \) plus M-protein \( \geq 30 \text{ g/L} \)

or

**PCs BM \( \geq 10\% \) or M-protein \( \geq 30 \text{ g/L} \)

but BM aPC/nPC > 95\% plus immunoparesis

*Time elapsed from diagnosis to inclusion not superior to 5 years*

No CRAB (hypercalcemia, anemia, bone lesions, renal impairment) symptoms

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## Schedule of therapy

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction:</strong> Nine 4-wks cycles</td>
<td><strong>Therapeutic Abstention</strong></td>
</tr>
<tr>
<td>Lenalidomide 25 mg/daily during 21d every 28 d</td>
<td>Lenalidomide 10 mg/daily during 21 d every 2 months</td>
</tr>
<tr>
<td>Dexamethasone 20 mg D1-D4 and D12-D15 every 28 d</td>
<td>Therapeutic Abstention</td>
</tr>
</tbody>
</table>

**Maintenance**

| Lenalidomide 10 mg/daily during 21 d every 2 months | Therapeutic Abstention |

Randomization according to: diagnosis in the last 6 months diagnosis more than 6 months
Objectives

**Primary objective**

- Time to progression to symptomatic MM

**Secondary objectives**

- Response rates
- Duration of response
- Progression Free Survival, Overall Survival
- Safety and tolerability

SMM Trial: Time to Progression (n:94)

Median follow-up: 14 m (1-24)

<table>
<thead>
<tr>
<th>No treatment</th>
<th>Lendex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median TTP: 19.3 m</td>
<td></td>
</tr>
</tbody>
</table>

Progressions in abstention arm (n=16)

- 6 pts: lytic lesions
- 3 pts: lytic lesions plus anemia
- 1 pt: lytic lesions renal failure & $\uparrow$Ca2+
- 5 pts: anemia

1 pt: PD due to a rapid increase of BJ prot from 4.5g/24h to 9g/24h in 1 month

$\text{p}<0.0001$
SMM Conclusions

1. Treat Ultra-high risk SMM as MM
2. Follow HR patients closely
3. Consider HR-SMM for Clinical Trial
   ECOG: Rev vs. Observation
   Elotuzumab
   Daratumumab

Natural History of Multiple Myeloma
After the Novel Drugs, what’s next?

Myeloma Treatment: It’s An Art
Initial Approach to Treatment of Myeloma

**Nontransplant Candidate**
(based on age, performance status, and comorbidities)
- Induction treatment
- Maintenance?

**Transplant Candidate**
- Induction treatment (4-6 cycles)
- Stem cell harvest
- Stem cell transplantation
- Consolidation therapy?
- Maintenance?
MM Risk Categories

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Standard Risk (80%) (Expected OS: 6-7 Yrs)</th>
<th>High Risk (20%) (Expected OS: 2-3 Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>t(11;14), t(6;14)</td>
<td>del(17p), t(4;14)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(14;16), +1q21</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Hyperdiploidy</td>
<td>Hypodiploidy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>del(13q)</td>
</tr>
<tr>
<td>β₂-microglobulin*</td>
<td>Low (&lt; 3.5 mg/L)</td>
<td>High (≥ 5.5 mg/L)</td>
</tr>
<tr>
<td>PCLI</td>
<td>&lt; 3%</td>
<td>High (≥ 3%)</td>
</tr>
<tr>
<td>Isotype</td>
<td>--</td>
<td>IgA</td>
</tr>
<tr>
<td>Gene expression profile</td>
<td>Good risk</td>
<td>High risk</td>
</tr>
</tbody>
</table>

*Pts with t(4;14), β₂-microglobulin < 4 mg/L, and Hb ≥ 10 g/dL may have intermediate-risk disease.


Risk-Adapted Therapy for Myeloma:

- **M-SMART**

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH</td>
<td>FISH</td>
<td>All others including:</td>
</tr>
<tr>
<td>Del 17p</td>
<td>t(4;14)</td>
<td>FISH</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>Cytogenetic del 13</td>
<td>t(11;14)</td>
</tr>
<tr>
<td>t(14;20)</td>
<td>Hypodiploidy</td>
<td>t(6;14)</td>
</tr>
<tr>
<td>GEP High risk signature</td>
<td>PCLI</td>
<td>hyperdiploid</td>
</tr>
</tbody>
</table>
Risk-Adapted Therapy for Myeloma:

<table>
<thead>
<tr>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Standard risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Cycles of VRd</td>
<td>4 Cycles of CyBarD</td>
<td>4 Cycles of Rd or CyBarD</td>
</tr>
<tr>
<td>Collect stem cells</td>
<td>Collect stem cells</td>
<td>Collect stem cells</td>
</tr>
<tr>
<td>Autologous stem cell transplant (especially if not in CR)</td>
<td>Autologous stem cell transplant</td>
<td>Autologous stem cell transplant</td>
</tr>
<tr>
<td>VRd for a minimum of 1 year</td>
<td>Bortezomib-based therapy for a minimum of 1 year</td>
<td>Consider lenalidomide maintenance</td>
</tr>
</tbody>
</table>

3 yr  | 4-5 yr  | 8-10 yr  | OS (Mikhail et al. MCP 2013)

Current OS and High Risk Myeloma

A good risk stratification system should allow identification of this ~25% patients
Does Response Matter? Cure vs. Control

Depth and TTP

PCR, MRI, Flow-cytometry

INDUCTION: Blockbuster Agents

- Proteasome Inhibitors
  - Bortezomib (Velcade)
  - Carfilzomib (Kyprolis)
  - Ixazomib (MLN 9708), (an oral PI)

- IMiDs
  - Lenalidomide (Revlimid)
  - Thalidomide (Thalomid)
  - Pomalidomide (Pomalyst)
Goals of Induction Therapy

- High response rate; rapid response
- Depth of response (MRD?)
- Improve performance status and quality of life
- Not limit PBSC mobilization (for younger pts)
- Current issues:
  - Role of transplant
  - Optimal duration of therapy

How deep of a response should we aim for?

Achieving ≥ VGPR or CR Should Be the Goal of Therapy

Phase III Trials: Induction Regimens for Transplantation-Eligible Pts

Cavo     PETHEMA/GEM     IFM 2005-01     HOVON-65     GMMG-HD4     E4A03

Pts Achieving ≥ VGPR (%)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>18-mo PFS</th>
<th>18-mo OS</th>
<th>12-mo PFS</th>
<th>24-mo PFS</th>
<th>3-yr PFS</th>
<th>3-yr OS</th>
<th>5-yr PFS</th>
<th>5-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/lenalidomide/dexamethasone (RVD)</td>
<td>75%</td>
<td>97%</td>
<td>97%</td>
<td>92%</td>
<td>79%</td>
<td>96%</td>
<td>42%</td>
<td>70%</td>
</tr>
<tr>
<td>Carfilzomib/lenalidomide/dexamethasone (KRd)</td>
<td>12-mo</td>
<td>24-mo</td>
<td>3-yr</td>
<td>3-yr</td>
<td>3-yr</td>
<td>3-yr</td>
<td>5-yr</td>
<td>5-yr</td>
</tr>
<tr>
<td>Carfilzomib/thalidomide/dexamethasone (KTd)</td>
<td>72%</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Bortezomib/cyclophosphamide/dexamethasone (CyBorD)</td>
<td>42%</td>
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</tr>
<tr>
<td>Ixazomib/lenalidomide/dexamethasone</td>
<td>88%</td>
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</tbody>
</table>

Earlier Phase Studies: Induction Regimens for Transplantation-Eligible Pts

Pts Achieving ≥ VGPR (%)

EVOLUTION Trial: Combinations of VD With Cyclophosphamide or Lenalidomide

- Randomized phase II trial of VDC vs VDR vs VDCR in previously untreated MM

![Graph showing PFS and OS for different combinations of VD with cyclophosphamide or lenalidomide.](image)


High-Dose Mel + ASCT vs MPR in NDMM

- A randomized, controlled phase III trial exploring utility of transplant in NDMM (N = 273)

![Graph showing probability of PFS and OS for different treatment regimens.](image)

**IFM/DFCI2009: Conventional Dose RVD to High-Dose Treatment With ASCT**

- Randomized, open-label phase III trial
- Primary endpoint: PFS
- Secondary endpoints: RR, TTP, safety

Pts with previously untreated MM; measurable disease; between age 18-65; ECOG PS 0-2 (planned N = 700)

- Collection of PBSCs using cyclophosphamide and GCSF

ClinicalTrials.gov: NCT01191060.

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**Phases of Therapy: Transplant Ineligible**

- **Transplant ineligible**
  - Induction chemotherapy
    - 8-12+ cycles
  - Maintenance therapy
    - 1+ years
  - Supportive Care
    - Biphosphonates
    - Vitamins

- Relapse
- Salvage therapy

**Goals**

- Control disease (PR/CR)
- Improve PFS/OS
- Limited toxicity
- QUALITY of LIFE
**FIRST: Lenalidomide/Dexamethasone vs MPT in NDMM SCT-Ineligible Pts**

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

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Continuous Rd</th>
<th>Len + LoDex</th>
<th>Continuously</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lenalidomide</td>
<td>25 mg Days 1-21/28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LoDex</td>
<td>40 mg Days 1, 8, 15, 22/28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B</th>
<th>Rd18</th>
<th>Len + LoDex</th>
<th>18 cycles (72 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lenalidomide</td>
<td>25 mg Days 1-21/28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LoDex</td>
<td>40 mg Days 1, 8, 15, 22/28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm C</th>
<th>MPT</th>
<th>Mel + Pred + Thal</th>
<th>12 cycles (72 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Melphalan</td>
<td>0.25 mg/kg Days 1-4/42</td>
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<tr>
<td></td>
<td></td>
<td>Prednisone</td>
<td>2 mg/kg Days 1-4/42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thalidomide</td>
<td>200 mg Days 1-4/42</td>
</tr>
</tbody>
</table>

Len dose adjusted based on creatinine clearance.
Pts aged older than 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.
Stratified by age, country, and ISS stage.

<table>
<thead>
<tr>
<th>PFS (Mos)</th>
<th>Pts (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>18</td>
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<tr>
<td>18</td>
<td>24</td>
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<td>24</td>
<td>30</td>
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<td>30</td>
<td>36</td>
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<td>36</td>
<td>42</td>
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<tr>
<td>42</td>
<td>48</td>
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<tr>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>54</td>
<td>60</td>
</tr>
</tbody>
</table>

**Median PFS, Mos**

- Rd (n = 535): 25.5
- Rd18 (n = 541): 20.7
- MPT (n = 547): 21.2

**HR (P Value)**

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

**4-Yr OS, %**

- Rd (n = 535): 59.4
- Rd18 (n = 541): 55.7
- MPT (n = 547): 51.4

**HR (P Value)**

- Rd vs MPT: 0.78 (.0168)
- Rd vs Rd18: 0.90 (.307)
- Rd18 vs MPT: 0.88 (.184)

**FIRST Trial: Efficacy Analysis of Len/Dex vs MPT in SCT-Ineligible Pts With MM**

- Overall response (continuous Rd vs MTP): 75% vs 62% (P < .00001)
- Similar, tolerable safety profiles between treatment groups; incidence of secondary primary malignancies 0.4% in Rd arm vs. 2.2% in MPT

**MM-015: Study Design**

- Primary endpoint: PFS
- Secondary endpoint: OS, ORR, TTR, DOR, safety


**MM-015: MPR With Maintenance R Efficacy Analysis**

**PFS**

- **MPR-R** (n = 152)
  - M: 0.18 mg/kg Days 1-4
  - P: 2 mg/kg Days 1-4
  - R: 10 mg/day PO Days 1-21

- **MPR** (n = 153)
  - M: 0.18 mg/kg Days 1-4
  - P: 2 mg/kg Days 1-4
  - R: 10 mg/day PO Days 1-21

- **MP** (n = 154)
  - M: 0.18 mg/kg Days 1-4
  - P: 2 mg/kg Days 1-4
  - Pbo: Days 1-21

<table>
<thead>
<tr>
<th>Cycles 1-9 (28-day cycle)</th>
<th>Cycles ≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Len 10 mg/day Days 1-21</td>
<td>Maintenance Placebo Days 1-21</td>
</tr>
</tbody>
</table>

- **Median PFS**
  - MPR-R (n = 152): 31 mos
  - MPR (n = 153): 14 mos
  - MP (n = 154): 13 mos

- **MPR-R vs MPR** (HR: 0.49; P < .001)
- **MPR-R vs MP** (HR: 0.40; P < .001)

**Updated OS**

- **Median OS**
  - MPR-R (n = 152): 56 mos
  - MPR (n = 153): 52 mos
  - MP (n = 154): 54 mos

- **MPR-R vs MPR** (HR: 0.88; P < .43)
- **MPR-R vs MP** (HR: 0.95; P < .74)

CRd Treatment Schema

Carfilzomib, Lenalidomide and low dose Dexamethasone

Transplant-eligible and transplant-ineligible patients

CRd Induction

CRd Cycles 1–4

CRd Cycles 5–8

CRd Cycles 9–24

LEN Cycles 25+

Lenalidomide (off protocol)

Transplant-eligible

≥PR

ASCT

Until disease progression or unacceptable toxicity

≥PR

ASCT

Stem cell collection

• Assessments on D1 and 15 of C1 and D1 thereafter using modified IMWG Criteria with nCR

Cycles 1–8

• CFZ 20-27-36 mg/m² Days 1–2, 8–9, 15–16

• LEN 25 mg Days 1–21

• DEX 40 mg weekly Cycles 1-4, 20 mg weekly Cycles 5–8

Cycles 9–24

• CFZ on Days 1–2 and 15–16 only

• CFZ, LEN, DEX at last best tolerated doses

Cycles 25+

• LEN at last best tolerated dose

CRd Best Response

Median 12 cycles (range 1–25)

Age >65 y/o

≥PR 87

≥VGPR 83

≥nCR 61

sCR

N=25

Overall

≥PR 98

≥VGPR 81

≥nCR 62

sCR 42

N=53
Initial Therapy: What is SOC?

### Transplant Eligible
- RD (<6 cycles)
- V(D)
- RVD
- VCD
- 4-Drug
  - VTCD
  - VRCD

### Non-Transplant
- RD
- V(D)
- VCD
- RVD
- BiRD
- MP + T or R or V

Suggested Empiric Age-Adjusted Dose Reduction in Pts With Myeloma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Younger Than 65 Yrs</th>
<th>65-75 Yrs</th>
<th>Older Than 75 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>40 mg/day Days 1-4, 15-18 q4w or Days 1, 8, 15, 22 q4w</td>
<td>40 mg/day Days 1, 8, 15, 22 q4w</td>
<td>20 mg/day Days 1, 8, 15, 22 q4w</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.25 mg/kg Days 1-4 q6w</td>
<td>0.25 mg/kg Days 1-4 q6w or 0.18 mg/kg Days 1-4 q4w</td>
<td>0.18 mg/kg Days 1-4 q6w or 0.13 mg/kg Days 1-4 q4w</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>300 mg/day Days 1, 8, 15, 22 q4w</td>
<td>300 mg/day Days 1, 8, 15 q4w or 50 mg/day Days 1-21 q4w</td>
<td>50 mg/day Days 1-21 q4w or 50 mg/day QOD Days 1-21 q4w</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>200 mg/day</td>
<td>100 mg/day or 200 mg/day</td>
<td>50 mg/day to 100 mg/day</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg/day Days 1-21 q4w</td>
<td>15-25 mg/day Days 1-21 q4w</td>
<td>10-25 mg/day Days 1-21 q4w</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² bolus Days 1, 4, 8, 11 q3w</td>
<td>1.3 mg/m² bolus Days 1, 4, 8, 11 q3w or Days 1, 8, 15, 22 q5w</td>
<td>1.0-1.3 mg/m² bolus Days 1, 8, 15, 22 q5w</td>
</tr>
</tbody>
</table>

Getting to Minimal Residual Disease: New Definitions for CR

- Newly diagnosed: $1 \times 10^{12}$
- CR
- Stringent CR
- Molecular/flow CR
- Cure?

Disease burden: $1 \times 10^{8}$

Bortezomib Lenalidomide Antibodies

Methods for Assessing Minimal Residual Disease to Predict Outcome

8-Color Flow$^{[1]}$  Next-Gen Sequencing$^{[2]}$  PET/CT$^{[3,4]}$

<table>
<thead>
<tr>
<th>PFS (Proportion)</th>
<th>Mos</th>
<th>PFS (Proportion)</th>
<th>Mos</th>
<th>PFS (Proportion)</th>
<th>Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>6</td>
<td>0.8</td>
<td>12</td>
<td>0.6</td>
<td>18</td>
</tr>
<tr>
<td>0.8</td>
<td>12</td>
<td>0.6</td>
<td>24</td>
<td>0.4</td>
<td>30</td>
</tr>
<tr>
<td>0.6</td>
<td>24</td>
<td>0.4</td>
<td>36</td>
<td>0.2</td>
<td>42</td>
</tr>
<tr>
<td>0.4</td>
<td>36</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TTP (CR Pts)

- MRD-  - MRD+
- Overall

<table>
<thead>
<tr>
<th>PFS (Proportion)</th>
<th>Mos</th>
<th>TTP (CR Pts)</th>
<th>Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td></td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

PET CR

- Median: 90 mos

NO PET CR

- Median: 50 mos

PFS (CR Pts After First-line Therapy)

<table>
<thead>
<tr>
<th>PFS (Proportion)</th>
<th>Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

PET CR

- Median: 90 mos

NO PET CR

- Median: 50 mos

P = .001  n = 26  P = .010  n = 36

**Maintenance in Myeloma**

- PFS advantage\(^{[1-3]}\)
- OS improvements?\(^{[2]}\)
- Toxicities of treatment
  - Myelosuppression\(^{[3]}\)
  - Second primary malignancies\(^{[3,4]}\)
  - Quality of life
- Unclear whether all pts benefit from maintenance
- Unclear which agent and duration of therapy

---

**IFM 2005-02: Lenalidomide vs Placebo Maintenance After ASCT for Myeloma**

- Phase III study in pts < 65 yrs after ASCT in first line (N = 459)*
  - Consolidation: Len 25 mg/day PO Days 1-21 every 28 days for 2 mos; maintenance: randomize to Len 10-15 mg/day or placebo until relapse
- 5-yr PFS (primary endpoint) superior with Len: 42% vs 18% with placebo (\(P < .0001\))
  - PFS benefit independent of subgroup (eg, \(\beta_2\)-M, ORR)
  - Median EFS: 40 mos with Len vs 23 mos for placebo
  - **Median OS: similar (> 80 mos)**
  - Grade 3/4 PN: similar in both groups

---

CALGB 100104: Lenalidomide vs Placebo Maintenance Following ASCT for Myeloma

- Phase III trial with D-S stage 1-3 pts; < 71 yrs and > 2 cycles of induction with SD or better (N = 460)
- PFS: ITT analysis with median follow-up from transplant of 34 mos
  - Estimated HR: 0.48 (95% CI: 0.36-0.63); median TTP: 46 vs 27 mos
- OS: 35 deaths with lenalidomide and 53 deaths with placebo
  - 3-yr OS 88% vs 80%, HR 0.62 or a 38% reduction in death with the cross over


HOVON-65/GMMG-HD4: Bortezomib Induction, Maintenance in NDMM

- Pts with newly diagnosed MM (N = 827)
  - VAD* (n = 414)
  - PAD† (n = 413)
- HDM‡ ASCT
- HDM‡ ASCT
- Thalidomide 50 mg QD for 2 yrs
- Bortezomib 1.3 mg/m² 1x/2 wks for 2 yrs

Primary endpoint: PFS adjusted for ISS stage
Secondary endpoints: response, PFSₐ, PFS/PFSₐ from last HDM, OS, safety, toxicity

*VAD: 3 cycles of vincristine 0.4 mg IV QD, Days 1-4; doxorubicin 9 mg/m² QD, Days 1-4; dexamethasone 40 mg oral QD, Days 1-4, 9-12, 17-20, every 28 days.
†PAD: 3 cycles of bortezomib 1.3 mg/m² QD, Days 1, 4, 8, 11; doxorubicin 9 mg/m² QD, Days 1-4; and dexamethasone 40 mg oral QD, Days 1-4, 9-12, 17-20, every 28 days.
‡HOVON, single cycle; GMMG 2 cycles.
HOVON-65: Bortezomib in Induction and Maintenance for Newly Diagnosed MM

- CR/nCR superior with PAD induction (30% vs 15% with VAD) and by best response (35% vs 49% with VAD) \( (P < .001 \text{ for both})^{[1]} \)
- PFS and OS superior with bortezomib-based treatment regimen\(^{[1]}\)

\[
\begin{align*}
\text{HR: 0.76 (95\% CI: 0.64-0.90; } P = .001) \\
\text{HR: 0.78 (95\% CI: 0.64-0.90; } P = .01) \\
\end{align*}
\]

- Bortezomib significantly improved OS for pts presenting with renal failure \( (P < .001)^{[2]} \)


Cumulative Incidence of Secondary Primary Malignancies by Treatment

\[
\begin{align*}
\text{Cum Incidence, } & \% \\
\text{3 Yrs} & \text{5 Yrs} & \text{3 Yrs} & \text{5 Yrs} \\
\text{Len + Mel} & 2.7 & 4.4 & 1.8 & 3.9 \\
\text{Len + Cyclo} & 3.5 & \text{NE} & 0.3 & \text{NE} \\
\text{Len + Dex} & 2.2 & 2.6 & 0.3 & 1.3 \\
\text{No Len} & 2.9 & 3.4 & 0.4 & 1.4 \\
\end{align*}
\]

Options for Relapsed/Refractory Disease

Initial Therapy

- Relapse
- No Response/Relapse

>6 months

- Repeat initial therapy
- Clinical trial

≤6 months

- Revlimid® + dex
- Velcade® + dex
- Velcade® + Doxil®
- SCT
- Clinical trial

Additional combinations e.g., RVD

Relapse after Revlimid® and Velcade®

- Kyprolis®
- Pomalyst® + dex
- SCT
- Clinical trial

SCT=Stem cell transplant
RVD=Revlimid, Velcade, dexamethasone

Myeloma Therapeutics Over Time

1992 2002 2012
New Drugs in Multiple Myeloma

- Proteasome Inhibitors – 2nd generation/oral
- Immunomodulatory drugs – 3rd generation
- Monoclonal antibodies
- Inhibitors of proliferation and apoptosis
  - AKT inh, mTOR inh, Pim kinase inh
- Inhibitors of protein homeostasis
- Novel pathways
  - Selective inhibitor of nuclear export
  - Kinesin spindle protein inhibitor
Monoclonal Antibody Based Therapy
Current Agents in Clinical Trials

- **Antibody**
  - Elotuzumab
  - Dara, SAR650984, Mor202
  - B-B4, nBT062–>
  - MK-3475, BMS-936559
  - IPH 2101
  - Lucatuzumab
  - AVE1642

Target
- SlamF7
- CD38
- CD138
- KIR
- CD40
- IGF-1

Antibodies: Multiple Mechanisms to Kill Cancer Cells

1. Delivery of poison payload (ADC), direct cellular cytotoxicity
2. Antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP)
3. Complement-dependent lysis (CDC)
4. Direct cellular signaling (apoptosis)

CD38 enzymatic activity inhibition

| 0. T-cell signals |
| Cancer Cell membrane |
| Antibody Fc Receptor |
| Complement |
| NAD |
| sADPR |
| X |
| ? |
Monoclonal antibodies: Elotuzumab (anti-SlamF7):

Elotuzumab + Len + LoDex in relapsed/refractory MM (Len naïve)

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Elotuzumab 10 mg/kg</th>
<th>Elotuzumab 10 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR (≥PR), n (%)</td>
<td>36 (92)</td>
<td>37 (76)</td>
<td>73</td>
</tr>
<tr>
<td>CR/stringent CR, n (%)</td>
<td>5 (14)</td>
<td>4 (11)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>VGPR, n (%)</td>
<td>17 (47)</td>
<td>14 (38)</td>
<td>31 (43)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>11 (31)</td>
<td>10 (27)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>&lt;PR, n (%)</td>
<td>3 (8)</td>
<td>9 (24)</td>
<td>12 (16)</td>
</tr>
</tbody>
</table>

- Little difference in response, regardless of poor cytogenetics
  - ORR 80% and 84%, high-risk and standard-risk, respectively
  - PFS in 10 mg/kg cohort ~33 months

- Two Large Phase III Trials Comparing Len/LoDex vs ELO/Len/LoDex


Monoclonal antibodies: Elotuzumab

PFS with Elotuzumab + Len + LoDex

- At a median follow-up of 20.8 months, median PFS has not been reached in the 10 mg/kg arm

Daratumumab: A Novel anti-CD38 MoAB

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n/N</th>
<th>Max reduction in M-component</th>
<th>Max reduction of plasma cells in BM smear</th>
<th>Responses according to Rajkumarb</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/kg</td>
<td>6/6</td>
<td>Serum %</td>
<td>Unire %</td>
<td>Reduction %</td>
</tr>
<tr>
<td>0.5 mg/kg</td>
<td>6/6</td>
<td>12</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>3/3</td>
<td>24</td>
<td>9</td>
<td>84</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>1/1</td>
<td>67</td>
<td>55</td>
<td>16</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>3/3</td>
<td>49</td>
<td>87</td>
<td>97</td>
</tr>
<tr>
<td>8 mg/kg</td>
<td>3/3</td>
<td>82</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>16 mg/kg</td>
<td>2/2</td>
<td>50</td>
<td>33</td>
<td>100</td>
</tr>
</tbody>
</table>

* Not measurable at baseline
* Normal at baseline
* FLC only measurable
* Evaluation based on maximal reduction in M-component or FLC according to consensus of uniform reporting of clinical trials (Rajkumar. Blood 2011;117:4691-5)
* Based on only one measurement (no consecutive measurements); SD stable disease; MR minimal response; PR partial response

Plesner et al, ASH 2012: Abstr 73

Maximal Reduction of Serum M-Component

Dose 4 -24 mg/kg
Qwk ORR~42%

Plesner et al, ASH 2012: Abstr 73
**Daratumumab: Single Agent in Relapse MM**

**Part II: Optimizing dose and infusion times**

<table>
<thead>
<tr>
<th>Weekly dosing</th>
<th>A: Dara 8 mg/kg</th>
<th>B: Dara 8 mg/kg</th>
<th>C: Dara 8 mg/kg</th>
<th>D: Dara 16 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion time</td>
<td>4</td>
<td>6</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>n</td>
<td>16</td>
<td>8</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td># priors</td>
<td>4</td>
<td>6.5</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>ORR</td>
<td>8%</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best responses</td>
<td>PR's</td>
<td></td>
<td>2CR 1 PR</td>
<td></td>
</tr>
</tbody>
</table>

Lockhorst et al, ASCO 2014: Abstr 8513

**SAR650984: Phase I Studies**

- **Single Agent: TED10893**

<table>
<thead>
<tr>
<th>Accelerated escalation</th>
<th>1 patient/cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>0.001 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>0.01 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>0.03 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>0.1 mg/kg q2W</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basic escalation</th>
<th>3–6 patients/cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>1 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>3 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>5 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg q1W</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg q2W</td>
<td></td>
</tr>
<tr>
<td>20 mg/kg q1W</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expansion Cohorts (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At recommended Phase 2 dose in patients with MM Standard Risk High-risk</td>
</tr>
</tbody>
</table>

**Response/clinical benefit rate**

- **ORR=32%**
- **CBR 37%**

Martin et al, ASCO 2014
SAR650984 Phase I Studies

SAR650984 /Len /LoDex
- Adults with RRMM
- At least 2 prior therapies
  - Prior IMiD therapy permitted
  - Refractory to IMiD OK

STUDY Population
- Median 6 prior regimens†
- 81% IMiD refractory
- 52% Bortezomib refractory
- 48% Carfilzomib refractory

Standard dose escalation (3 + 3 design)
3–6 patients per cohort

SAR650984 iv, Days 1 and 15 per 28 day cycle
- Cohort 1: 3 mg/kg
- Cohort 2: 5 mg/kg
- Cohort 3: 10 mg/kg

Expansion cohort
18 patients
- 10 mg/kg†
- Lenalidomide 25 mg on days 1–21 per 28-day cycle
- Dexamethasone 40 mg Qw (Days 1, 8, 15 and 22)

*MTD not reached

Martin et al. ASCO 2014

SAR650984 Phase I Studies

Phase I: SAR/ Len/LoDex

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>All (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>18 (58)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Partial response</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Minimal response</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Clinical benefit (MR or better) 20 (65)
Stable disease 3 (10)
Progressive disease 7 (23)
Not evaluable 1 (3)

Martin et al. ASCO 2014
SAR650984 Phase I: Clinical Results

SAR650984+Len/LoDex: Response according to prior therapy

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide refractory (n=25)</td>
<td>48%</td>
</tr>
<tr>
<td>Lenalidomide non-refractory (n=6)</td>
<td>100%</td>
</tr>
<tr>
<td>Pomalidomide refractory (n=9)</td>
<td>33%</td>
</tr>
<tr>
<td>Bortezomib refractory (n=16)</td>
<td>40%</td>
</tr>
<tr>
<td>Carfilzomib refractory (n=15)</td>
<td>100%</td>
</tr>
</tbody>
</table>

ARRY-520: Targeting KSP

- **ARRY-520**
  - A targeted Kinesin Spindle Protein (KSP) inhibitor
  - Novel MOA critical to the function of proliferating cells
  - Little cross-resistance to other drugs

- **Phase II** *(Lonial et al ASH 2013)*
  - RRMM: >2 priors
  - With or without Dex

- **Phase I** *(Shah et al EHA 2013)*
  - With Carfilzomib
  - RRMM
**ARRAY-520-212– Phase 2 Study Design**

*Lonial et al. ASH 2013*

**Cohort 1: ARRY-520 Single Agent**

ARRY-520  1.5 mg/m² q 2 weeks

1 2 1 2

G-CSF  G-CSF  2-stage, single-arm study

**Cohort 2: ARRY-520 + Dexamethasone Combination**

ARRY-520  1.5 mg/m² q 2 weeks

1 2 1 2

G-CSF  G-CSF

Dexamethasone  40 mg PO weekly  2-stage, single-arm study

---

**ARRAY-520-212 Pre-Dose AAG Levels Correlate with Clinical Outcome**

- AAG Cutoff ≥ 1.1 g/L in Array ELISA was qualitatively assigned
- Absolute value of cutoff is likely to change in final assay

- "High" [AAG] Partial Response
- Minimal Response

Lonial et al ASH 2013
ARRAY-520-212

Low AAG is Associated with Higher ORR

<table>
<thead>
<tr>
<th></th>
<th>ARRY-520 Single Agent</th>
<th>ARRY-520 + dex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Pts(^1)</td>
<td>AAG-High</td>
</tr>
<tr>
<td>n</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>5 (16%)</td>
<td>0 (%)</td>
</tr>
<tr>
<td>CBR (≥ MR)</td>
<td>6 (19%)</td>
<td>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>

5 patients did not have a baseline AAG measurement
4 patients did not have a baseline AAG measurement, including 1 responder

Novel Drugs: Nuclear Export Inh.

- Cancer cells over express XPO1
- TSP’s assess DNA damage/cell fate
- SINE compounds inhibit XPO1-

Nuclear localization and activation of multiple TSPs

Reduces Oncoproteins MYC, BCL2/BCL6, CycD1, Inhibits NF-κB

Courtesy of KaryoPharm
### SINE Inhibitor: Phase 1 Trial in Advanced Hematologic Malignancies – Focus on Multiple Myeloma

*(EHA Update – Data through June 2014)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>CBR (24%)</th>
<th>ORR</th>
<th>sCR</th>
<th>PR (24%)</th>
<th>MR</th>
<th>SD (18%)</th>
<th>PD (12%)</th>
<th>NE (12%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selinexor Low Dose</td>
<td>17</td>
<td>4</td>
<td>--</td>
<td>--</td>
<td>4 (24%)</td>
<td>8</td>
<td>3 (18%)</td>
<td>2 (12%)</td>
<td></td>
</tr>
<tr>
<td>Selinexor High Dose</td>
<td>17</td>
<td>2 (12%)</td>
<td>1 (6%)</td>
<td>--</td>
<td>1 (6%)</td>
<td>1</td>
<td>8 (47%)</td>
<td>3 (18%)</td>
<td>4 (24%)</td>
</tr>
<tr>
<td>Selinexor + Low Dex</td>
<td>8</td>
<td>6 (75%)</td>
<td>4 (50%)</td>
<td>1 (12%)</td>
<td>3 (38%)</td>
<td>2</td>
<td>1 (12%)</td>
<td>1 (12%)</td>
<td></td>
</tr>
</tbody>
</table>

CBR=Clinical Benefit Response (MR+PR+sCR), ORR=Overall Response Rate (sCR+PR), sCR=Stringent Complete Response, PR=Partial Response, MR=Minor Response, SD=Stable Disease, PD=Progressive Disease, NE=Non-Evaluable

### Novel drugs in clinical trials for MM

- **Immunotherapy**
  - Checkpoint inhibitors
  - CAR-T cells
- **Protein Metabolism**
  - HDAC Inhibitors
  - P97 inhibitor
- **Other - cell cycle, etc.**
  - CDK inhibitors
  - PIM Kinase inhibitors
  - Bromodomain inhibitors
- **Targeted Therapies**
  - B-RAF inh
    - vemurafenib
  - MEK inh.
    - trametinib
  - FRFR3 Inh
    - Dovitinib, su5402
    - Mab’s
Conclusions

- Many promising agents
  - Blockbusters: anti-CD38 mAb's
  - Potential Blockbusters: ARRY520, other mAb’s
  - SINE inh, ACY1215, PIM Inh, Bromodomain inh.

- Future efforts should focus on:
  - Identifying biomarkers for response
  - Optimizing combinations and dosing strategies
  - Using genomic data to help select targets/therapy

- All patients are appropriate for Clinical Trials
Current Management of Bone Disease

- Treat the myeloma
- Novel therapies have benefits
  - Direct effect on inflammatory cytokines
  - Inhibition of bone resorption
  - Osteoclast stimulation
- Bisphosphonates
  - Pamidronate
  - Zoledronic acid
- Supplement with calcium and vitamin D3 to maintain calcium homeostasis
- Radiotherapy (low dose)
  - Impending fracture
  - Cord compression
  - Plasmaclymas
- Vertebroplasty/kyphoplasty
- Orthopedic consultation
  - Impending or actual long-bone fractures
  - Bony compression of spinal cord
  - Vertebral column instability


Bisphosphonates and Osteonecrosis

- Uncommon complication causing avascular necrosis of maxilla or mandible
- Suspect with tooth or jaw pain or exposed bone
- May be related to duration of therapy
- Incidence between 3% and 4% with zoledronic acid or pamidronate