MYELOMA

Treatment and Side Effects Management Update

Supported by grants from Celgene Corporation, Millennium: The Takeda Oncology Company, and Onyx Pharmaceuticals, Inc.
Welcome and Introduction

MABEL MAIA
Senior Manager, Patient Services Programs
The Leukemia & Lymphoma Society
New Advances in the Treatment of MM

Melissa Alsina, MD
May 15, 2012
What is Myeloma?
Epidemiology

- B cell dyscrasia with an *antecedent* premalignant syndrome MGUS
- 2% of all cancers, ~15% hematologic malignancies & 20% of deaths from heme malignancies
- Median Age ~70-with 99% over 40
- Increased incidence in African Americans (2x), men (1.4x), first degree relatives with heme malignancy (3.7x)
- Environmental Risks: ???
  - Pesticides, Organic Solvents, Radiation Exposure, Cosmetics/Hair Dyes, Ground Zero exposures
Age-Specific Incidence Rates for Myeloma, 2003–2007

*<16 cases for this age group.

Diagnosis

• **Presentation:**
  - Anemia (A)
    - (normocytic/chromic)
  - Fatigue
  - Bone Pain
  - Fractures (B)
  - Renal Failure (R)
  - Hypercalcemia (*High*) (C)
  - Infections (*I*)
Diagnosis

- CBC, CMP-Creatinine, calcium & albumin
- Calcium
- LDH
- β2M
- SPEP & SIFE
- 24 Urine TP, UPEP, & UIFE
- Serum Free Light Chains
- Skeletal Survey
- Bone Marrow Biopsy
  - Metaphase Cytogenetics
  - FISH: del 13, del 17, t(4;14), t(11;14), t(14;16) & t(14;20)
    1q21+
    1p32-

SPEP & Immunofixation

- normal
- myeloma
  M-spike
Skeletal Survey
Diagnosis

- **Useful under certain circumstances:**
  - MRI (vertebral fractures)
  - CT (without contrast) +/- PET
  - Tissue biopsy (*solitary plasmacytoma...*)
  - Staining of biopsy of BM, fat pad or other organ site with *Congo Red*
  - Plasma cell labeling index
  - Serum viscosity
  - Bone densitometry
  - HLA Typing
Myeloma Continuum

**MGUS:**
- <3g/dL serum M-Protein
- <10% clonal Plasma Cells in BMBx
- No related organ or tissue impairment/symptoms
  - Hypercalcemia
  - Anemia
  - Renal
  - Boney Lytic lesions

**Smoldering:**
- ≥3g/dL serum M-Protein and/or
- ≥10% clonal Plasma Cells in BMBx
- No related organ or tissue impairment/symptoms
  - Hypercalcemia
  - Anemia
  - Renal
  - Boney Lytic lesions

**Active:**
- Calcium >11.5
- Renal Failure: Cr >2
- Anemia: Hgb <10 or 2gm < than baseline
- Boney lytic lesions
  - Or osteopenic
- Others:
  - Secondary Amyloidosis, hyperviscosity, repeated infections, hypogamma-globulinemia

Durie, et al Leukemia. 2006 Dec;20(12):2220
Staging and Risk Stratification

• **Staging**
  – International Staging System (ISS): *Prognostic*
  – Durie- Salmon Staging System: *Measure of disease burden*

• **Risk Stratification**
  – Cytogenetics: *DNA*
    • Metaphase Cytogenetics
    • FISH: Fluorescence in situ Hybridization
  – Myeloma Personalized Risk Score (MyPRS): *GEP*
### International Staging System (ISS):

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Med OS (mo)</th>
</tr>
</thead>
</table>
| I     | Serum Beta-2 Microglobulin ($\beta$2M) $<$3.5 mg/L  
      | Serum Albumin $>$3.5 g/L | 62          |
| II    | Not Stages I or III* | 44          |
| III   | Serum $\beta$2M $>$5.5 mg/L | 29          |

*Two potential stage II subcategories exist: 1) serum $\beta$2M $<$3.5 mg/L and serum albumin $<$3.5 g/L or 2) serum $\beta$2M 3.5-5.5 mg/L and any level of serum albumin

JCO. 2005; 23(15):3412
### Durie and Salmon Myeloma Staging System:

<table>
<thead>
<tr>
<th>Stage*</th>
<th>Peripheral Blood Blast (%)</th>
<th>Tumor Burden (x10^{12}/m^2)</th>
</tr>
</thead>
</table>
| I      | **Low M** - Protein levels: IgG <5g/l; IgA <3; Urine Bence Jones Protein <4/gm/24hr  
         - Absent or Solitary Bone Lesion  
         - Normal Hemoglobin, Serum Calcium, Ig levels | 0.6                          |
| II     | Values Between Stages I & III                   | -                           |
| III    | **High M** - Protein levels: IgG >7g/l; IgA >5; Urine Bence Jones Protein > 12/gm/24hr  
         - Advanced or Multiple Bone Lesions  
         - Hemoglobin <8.5, Serum Calcium >12 | 1.2                          |

*Subclassification:  
A: Serum Creatinine <2  
B: Serum Creatinine >2

-Durie & Salmon *Cancer* 1975
# Prognosis

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Proposed Gene Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletion 13 or Aneuploidy by Metaphase Analysis*</td>
<td>Rb</td>
</tr>
<tr>
<td>t(4;14) by FISH</td>
<td>MMSET/FGFR3</td>
</tr>
<tr>
<td>t(14;16) by FISH</td>
<td>c-maf</td>
</tr>
<tr>
<td>t(14;20) by FISH</td>
<td>p53</td>
</tr>
<tr>
<td>Deletion 17p by FISH</td>
<td></td>
</tr>
<tr>
<td>- Hypodiploidy</td>
<td></td>
</tr>
<tr>
<td>Plasma Cell Labeling Index &gt;3.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of unfavorable risk genetics</td>
</tr>
<tr>
<td>Hyperdiploidy by FISH</td>
</tr>
<tr>
<td>t(11;14)</td>
</tr>
<tr>
<td>t(6;14)</td>
</tr>
<tr>
<td>Cyclin D1/CCND1</td>
</tr>
<tr>
<td>Cyclin D3/CCND3</td>
</tr>
</tbody>
</table>

- Patients with t(4;14), β2M<4 mg/l and Hb≥10g/dl may have *intermediate risk* disease; Patients with del13 by FISH and elevated β2M have *unfavorable risk*.

**Metaphase cytogenetics**

**FISH**
Prognosis

Collect Bone Marrow Aspirate

Purify MM Plasma Cells

Stabilize, Enrich and Isolate RNA

Create Biotinylated, Fluorescently Labeled cRNA

MyPRS™ Microarray Analysis

Correlated Risk Level Report Returned to Oncologist

Signal Genetics Customer

GeneChip ID: P1806-02-F495-U133Plus-2 CEL

Patient Accession: demonstration@chipdx.com

Hospital: Memorial Sloan Kettering

Pathologist: Dr Jones

Date of analysis: 3/4/2012 4:06:36 PM

LOW RISK
(MyPRS Plus score<45.2)

73% Probability of being recurrence-free at 5-years.
High probability of favorable prognosis.

Additional Result Information:

1. MyPRS Plus Risk Score and Risk Group

P1806-02-F495-U133Plus-2.CEL

Kaplan Meier Analysis of myPRS validation cohort:

- Low Risk: 66/305
- High Risk: 36/46
- Median: 24

P-value < 0.0001, HR 5.16
# Response Criteria:

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sCR</strong>, stringent complete response</td>
<td>CR as defined below plus: Normal free light chain (FLC) ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.</td>
</tr>
<tr>
<td><strong>CR</strong>, complete response</td>
<td>Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow.</td>
</tr>
<tr>
<td><strong>VGPR</strong>, very good partial response</td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level &lt; 100 mg per 24 h.</td>
</tr>
<tr>
<td><strong>PR</strong>, partial response</td>
<td>≥ 50% reduction of serum M-protein and reduction in 24 h urinary M-protein by ≥ 90% or to &lt; 200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.</td>
</tr>
<tr>
<td><strong>SD</strong>, stable disease (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)</td>
<td>Not meeting criteria for CR, VGPR, PR or progressive disease.</td>
</tr>
</tbody>
</table>
Our growing agents in MM

- **Proteosome Inhibitors**
  - Bortezomib (Velcade)
  - Carfilzomib
  - MLN9708
  - Marizomib/NPI-0052

- **IMIDs**
  - Thalidomide
  - Lenalidomide (Revlimid)
  - Pomalidomide

- **Antibodies**
  - Elotuzumab
    - Anti-CS1
  - BT062
    - Anti-CD138-DM4
  - BMS983564
    - Anti-CXCR4

- **HDAC Inhibitors**
  - Vorinostat
  - Panobinostat

- **Cell Signaling Inhibitors**
  - Perifosine
  - AZD6244

- **Microenvironment Inhibitors**
  - CNTO 328
  - AMD3100

- **Traditional Agents**
  - Melphalan
  - Cytoxan
  - Doxorubicin
  - Doxil
  - Dexamethasone
  - Prednisone
  - Bendamustine

- **Old drug new disease**
  - CNTO 328
  - Marizomib/NPI-0052

- **Traditional Agents**
  - Cytoxan
  - Doxorubicin
  - Doxil
  - Dexamethasone
Clinical Trials

• **What is a clinical trial?**
  – A clinical trial is a research study that involves people. It is the final step in a long process that begins with preliminary laboratory research and animal testing.
  – Clinical trials try to **answer specific scientific questions to find better ways to prevent, detect, or treat diseases or to improve care** for people with diseases, such as multiple myeloma.

• **Why is it so important to participate in a clinical trial?**
  – Clinical trials are an important part of the research process.
  – Clinical trials contribute to knowledge of and progress against multiple myeloma and other cancers.
  – Many of today's most effective cancer treatments are based on previous study results.
  – Because of progress made through clinical trials, many people with multiple myeloma are now living longer.
  – The more people who participate in clinical trials, the faster research questions can be answered that will lead to better treatment options for patients with multiple myeloma and other cancers.
Treatment Overview

Induction (Primary Therapy)
- Lenalidomide (Rev)/Dex
- Velcade/Dex
  - VRd
- VelCD/VDC/CyborD (C=Cytoxan)

Consolidation
- Auto SCT
- Allo SCT

Maintenance
- Lenalidomide ?
  - Bortezomib?
Primary Treatment Algorithm

Risk Adapted Therapy
Newly Diagnosed Multiple Myeloma

- Clearly not a transplant candidate
  - High Risk†
    - VRd*, VMP
    - CyBorD
    - Consider Maintenance**
  - Standard Risk
    - Rd
    - VD
    - Consider Maintenance**

- Potential transplant candidate
  - High Risk
    - VRd*
    - CyBorD
  - Standard Risk
    - Rd
    - CyBorD
    - x4 cycles
    - Stem cell harvest
    - ASCT
    - Consider Maintenance**

- Consider VRD for all patients with del17 and CyBorD for patients with other high risk features.
- For patients with high risk disease consider either bortezomib or lenalidomide maintenance.
- Patients who defer/delay transplant initially should be consider at second response.
- Appropriate dose adjustments should be made for co-morbidities.
New Agents & Primary Therapies?
Phase 1/2 Study of Carfilzomib, Lenalidomide (Revlimid), and Low-Dose Dexamethasone (CRd) in Multiple Myeloma (MM)

- 53 newly diagnosed patients
- Median age was 59 years (range 35–81; 23 pts 65)
- 60% = ISS stage II/III
- 33% had unfavorable cytogenetics

- Responses rapid with 46/49 pts achieving at least PR after 1 cycle, and improved with the duration of treatment
- PR: 100% after 4 cycles; VGPR: 100%; and CR/nCR 79% after 12 cycles
- Responses in pts with unfavorable cytogenetics were similar to response rates in all remaining pts and included a 100% PR in 6 pts with del 17p
MRd: MLN9708- *Oral* Proteasome Inhibitor

- Phase I/II trial of MLN9708 in combination with Lenalidomide and Dex in newly diagnosed myeloma.
  - MLN9708 days 1, 8, and 15 + Len/dex
  - thromboprophylaxis with aspirin or low molecular weight heparin
  - 100% PR, 33% VGPR, 27% CR
  - Response: 14/15 patients PR in the first cycle
  - DLT thrombocytopenia, neutropenia
  - No grade 3/4 neuropathy reported and Gr ½ 11%
  - 2.23 mg/m² for the Phase 2 trial

Berdeja and Richardson ASH 2011 abstract 479 and 301
Treatment Overview

**Induction** (Primary Therapy)
- Len/Dex
- Velcade(Bortez)/Dex
- VRD
- VelCD/VDC/CyborD

**Consolidation**
- Auto SCT
- Allo SCT

**Maintenance**
- Thalidomide ?
- Lenalidomide
- Dexamethasone
- Prednisone
- Bortezomib (Velcade)
What about maintenance therapy?

- No standard maintenance strategy recommended
**Lenalidomide Maintenance: CALGB 100104**

**D-S Stage I-III MM**
- ≤70 years
- ≥2 cycles of induction
- Attained ≥stable disease
- ≤1 year from start of therapy
- ≥2 x 10^6 CD34 cells/kg

**Registration**

**Restaging Days 90-100**

**Mel 200 ASCT**

CR
PR
SD

**Randomization**

Placebo
Lenalidomide 10 mg/day (5-15 mg)

**Primary objective:** Determine the efficacy of lenalidomide in prolonging time to progression (TTP)

**Secondary objectives:** CR rate post-ASCT, overall survival (OS), feasibility of long-term lenalidomide administration

CR = complete response; PR = partial response; SD = stable disease

Lenalidomide Maintenance:
CALGB 100104

Lenalidomide Maintenance

• Concerns Expressed Over Second Malignancies
  – CALGB 100104:
    • 25 new malignancies,
      – 15 occurring among the 231 patients on lenalidomide
      – 6 among the 229 on placebo.
      – 5 cases altogether of acute myeloid leukemia/myelodysplastic syndrome (AML/MDS), 3 in the lenalidomide group (1 in a patient treated for breast cancer), and 2 in the placebo arm.
  
  – IFM 2005-02:
    • 19 new malignancies
      – 10 patients with hematologic malignancies on the lenalidomide arm
      – 2 on the placebo arm
      – non-hematologic cancers have been diagnosed in 6 versus 1 patient, respectively.
Relpased/Refractory MM: General Considerations

- Aggressive versus non aggressive relapse
  • Single agent versus combination therapy
- Individual experience with prior regimens
  • Response quality and duration of response
  • Toxicity
- Limiting comorbidities
  • PN
  • Renal
- Patient preference
  • Oral therapy and distance to center
New Agents & Therapies for Relapsed/Refractory Patients?
Pomalidomide* in patients who have failed Lenalidomide and Bortezomib

<table>
<thead>
<tr>
<th></th>
<th>Mayo 1</th>
<th>MM002 2</th>
<th>IFM2009-02 3**</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>70 (35 /35)</td>
<td>221</td>
<td>83 (40 /43)</td>
</tr>
<tr>
<td>No prior Rx</td>
<td>6</td>
<td>5</td>
<td>4 (1-8)</td>
</tr>
<tr>
<td>ORR</td>
<td>26 / 29%</td>
<td>13/34% (PR)</td>
<td>42 / 39%</td>
</tr>
<tr>
<td>TTP</td>
<td>6.4 /3.3 mo</td>
<td>2.7/4.7</td>
<td>9.7 / 7 mo</td>
</tr>
<tr>
<td>OS</td>
<td>78% at 6 mo</td>
<td>14/16.9 mo</td>
<td>13.4</td>
</tr>
<tr>
<td>Gr ¾ ANC</td>
<td>37 / 55%</td>
<td>42%</td>
<td>23-26 heme</td>
</tr>
</tbody>
</table>

- Pom 2 mg qd + dex then Pom 4 mg qd +Dex
- Pom 4 mg 21/28 +/- Dex
- Dex Pom 4 mg qd or 21/28

1\(^{st}\) Lacy et al. Blood 2011, 2\(^{nd}\) Richardson et al. ASH 2011; 3\(^{rd}\) Leuleu et al. ASH 2011

**Pomalidomide 1-21 superior to 28/28 with less toxicity.
Pomalidomide + other agents

• Phase I/II: Pomalidomide, Cytoxan, and Prednisone
  – 41 patients median age of 69 years
  – Pom 2.5mg PO daily with cytoxan & Pred (PO 50mg QOD/28)
  – 32 evaluable patients: 59% ≥ PR, 37.5% PR, 16% VGPR, 6% CR
  – 15 Len refractory: 73% ≥ PR, 53% PR, 13% VGPR, 7% CR
  – Grade 4 hematologic toxicities neutropenia (9%) & thrombocytopenia (9%). Grade 3-4 non-hematologic infection (9%), rash (9%), neurologic (6%) & hepatic (3%) toxicities. Thromboembolism occurred in 1 patient.

• Phase I/II: Pomalidomide, Cytoxan, and Dex- MCC16705
  – Pom 4mg PO days 1-21, cytoxan escalating dose, dex 40mg 1-4, 15-19

Palumbo ASH 2011, abstract 632
## Carfilzomib*

<table>
<thead>
<tr>
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<th>PX171-003</th>
<th>PX171-004</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>266 (257)</td>
<td>59/66</td>
</tr>
<tr>
<td>Prior Therapy Lenalidomide Btz refractory</td>
<td>Btz, IMID, alkylator 94% 65%</td>
<td>1-3 prior 46 / 71% 0</td>
</tr>
<tr>
<td>Existing PN</td>
<td>77%</td>
<td>71 / 67%</td>
</tr>
<tr>
<td>ORR (PR+), %</td>
<td>24%</td>
<td>42 / 53%</td>
</tr>
<tr>
<td>MR Btz refractory</td>
<td>10% 17%</td>
<td>17 / 9% 0</td>
</tr>
<tr>
<td>PFS, median</td>
<td>3.6 months</td>
<td>8.3 mo</td>
</tr>
<tr>
<td>DOR, median</td>
<td>7.4 months</td>
<td>13 mo</td>
</tr>
<tr>
<td>Gr ¾ ANC</td>
<td>8%</td>
<td>12 / 12%</td>
</tr>
<tr>
<td>Gr ¾ plt</td>
<td>22%</td>
<td>14 / 9 %</td>
</tr>
<tr>
<td>Gr 3 PN</td>
<td>(NR=2) 0.8%</td>
<td>1 patient (transient)</td>
</tr>
</tbody>
</table>

1-Siegel et al. ASH 2011  
2-Vij et al. ASH 2011 abstract 813
MLN9708 - Oral Proteosome Inhibitor*

- Phase I/II trial of MLN9708 single agent relapsed/refractory myeloma.
  - MLN9708: 0.24 mg/m² to 2.23 mg/m² on days 1, 4, 8, and 11 of a 21-day cycle (56 pts)
  - 13% ≥PR partial response, 2% CR, & 61% SD
  - MTD 2.0 mg/m² biweekly

- Phase I/II trial of weekly MLN9708
  - MLN9708: 0.24 mg/m² to 3.95 mg/m² on days 1, 8, and 15 of a 28-day cycle
  - 18/32 patients evaluated: ORR 11%-1 VGPR & 1 PR; 8 SD (44%).
  - 69 with disease progression
  - MTD 2.95mg/m² weekly

Richardson ASH 2011 abstract 479 & Kumar ASH 2011 abst 816
Marizomib/NPI0052

- Phase I: Clinical Evaluation of Twice-Weekly Marizomib (NPI-0052) in Patients with Relapsed/Refractory Multiple Myeloma (MM)
  - 71% prior exposure to Velcade & 41% resistant to Velcade
  - Dosing on D1,4,8,11 of a 21 day cycle
  - RP2D 0.5 mg/m2 IV over 2h
  - Toxicity: fatigue, anorexia, nausea, headache, mild cognitive deficit
  - Response: ≥PR in 19% (17% of bortezomib refractory & 29% Len refractory patients)
  - Fatigue, nausea, vomiting, headache, and fever, additionally hallucinations, loss of balance, and cognitive changes

Richardson et al. ASH 2011 abstract 302
**HuLuc63/Elotuzumab-Anti-CS1 antibody***

- Randomized phase II: Len/dex + 10 or 20 mg/kg Elotuzumab.
  - 73 Relapsed/Refractory (36 & 37)
  - weekly for 2 cycles then QOW
  - Premedication: dex 8 mg, benadryl, zantac, tylenol
  - 3% grade 3 infusion reactions
  - ORR 80% (92% at 10 and 73% at 20 mg/kg)
    - For patients with 1 prior line, ORR 100% for 10mg & 82% for 20 mg/kg
  - 14.1 mf/u → no mPFS
  - Compares very favorably with MM009-010

Lonial et al. ASH 2011 abstract 303

ELOQUENT I (NDMM) and ELOQUENT II (R/RMM) randomized phase III studies (10mg/kg)
BT062- Anti-CD138-DM4 Antibody

- Phase I/II trial with single agent BT062 and anti-CD138 (IgG4) + DM4 (maytasinoid) toxin IV q 3 weeks in relapsed/refractory myeloma
  - First in human study
  - N=32, 100% prior bortezomib and 87% prior lenalidomide
  - MTD 160 mg/m2
  - DLT: hand foot and mucositis
  - Grade 3/4: myelosuppression mucosal inflammation including eye irritation.
  - Response: 1 PR (4%), 2 MR (7%), 11 SD (39%)
  - Question: End of dose failure and need for more frequent dosing given $t_{1/2}$ was 2 days

Jagannath, et al. ASH 2011 abstract 305
Vorinostat: VANTAGEs

- **VANTAGE 095** (bortezomib refractory patients): ORR 17%, ≥MR 31%,
- **Median PFS 3.1 months, median OS 11.2 months**
- **VANTAGE 088** (1-3 prior lines, Btz sensitive)

<table>
<thead>
<tr>
<th></th>
<th>Btz SAHA n=317</th>
<th>Btz placebo n=320</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>56%</td>
<td>41%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>7.63m</td>
<td>6.83m (p=0.01)</td>
</tr>
<tr>
<td>Gr3/4 Platelets</td>
<td>45%</td>
<td>24%</td>
</tr>
<tr>
<td>Gr3/4 diarrhea</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Prior Btz</td>
<td>25%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Siegel / Dimopoulos et al. ASH abstract 811 and 480
Panobinostat*: PANORAMA 2

- Phase II study of Bortezomib + LBH590/Panobinostat + Dex
  - 55 Bortezomib Refractory patients with a median 2 prior regimens including IMID.
  - Phase 1 consisted of 8 three-week cycles of oral panobinostat (20 mg days 1, 3, 5, 8, 10, 12), +IV Bortez and Dex/21 days.
  - Phase 2
    - ORR 29%, MR+ 49%
    - Gr ¾ platelets 53%, fatigue 16%, diarrhea in 14%; no Grade ¾ PN.

Richardson, Alsina et al. ASH 2011 abstract 814

-PANORAMA 1: phase III study of panobinostat/placebo + bortezomib + dexamethasone in patients with relapsed MM.- on going

-PANORAMA 3: Randomized phase II Pano + IV vs SC Bortezomib + Dex –pending
Perifosine*/KRX 0401

- Phase I/II study of Perifosine, Bortezomib and Dex
  - Phase I: MTD 50 mg PO daily
  - N=84, median 2 prior lines of Bortez
  - Response:
    - 3-CR/nCR, 13- PR, 14-MR (ORR 19%, ≥MR 36%)
    - mPFS 6.4 months; mOS 25 months (22.5 Bortez refractory)
    - Gr ¾ plt 23%, ANC 15%

Richardson et al ASH 2011 abstract 815

A phase III trial is underway comparing perifosine–bortezomib plus dexamethasone with bortezomib–dexamethasone in patients with relapsed/refractory MM previously treated with bortezomib.
• Smoldering myeloma is observed and treatment deferred until symptoms develop; however, management of High Risk SMM one may consider initiating therapy.

• The optimal choice of induction therapy includes a novel agent. While 3 drug therapy might increase response rates and PFS, it is associated with greater toxicity, it remains unclear if it increases survival. Four drug therapy remains a question.

• The proteosome inhibitors Carfilzomib and MLN9708 may significantly impact on our choices of upfront therapy in combination with Len/dex.

• Pomalidomide and Carfilzomib show single agent activity in relapsed and refractory myeloma as well as in combination with tradition and novel agents.
Take Home Message(s)

- Lenalidomide is an intriguing option for maintenance therapy post-transplant, but carries unclear risks for side effects and second primary malignancies.

- **Pomalidomide** and **Carfilzomib** show single agent activity in relapsed and refractory myeloma as well as in combination with traditional and novel agents.

- A host of **new therapeutics** lead by Carfilzomib, Pomalidomide, Panobinostat, and Elotuzumab are promising in the setting of relapsed/refractory disease.

- Subcutaneous Bortezomib is FDA approved for relapsed/refractory and newly diagnosed setting; however, there is no data in upfront setting or in combination with anything other than dex.

- **Clinical trial participation** should be considered at all times.
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Management of Myeloma Symptoms and Side Effects

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Myelosuppression
Peripheral Neuropathy
Deep Vein Thrombosis
Bone Pain
Fatigue and Survivorship
Myelosuppression

- Low White Blood Cells
- Low Red Blood Cells
- Low Platelets

A CBC is a blood test that measures white blood cells, red blood cells, and platelets
Treatment Related Myelosuppression

**Novel Agents and Chemotherapies**

- Velcade
- Revlimid
- Cytoxan
- Melphalan
- DCEP
- VTDPACE
- CVAD

Steroids may cause immunosuppression, but will not lower WBC’s

- Dexamethasone
- Prednisone
Low White Blood Cells (Neutropenia)

Neutrophils are a WBC that fight off infections.

If Absolute Neutrophil Count (ANC) is <1000 you are at a very high risk for infection

If ANC is <1000 Neupogen (GCSF) may be given to stimulate production of white blood cells
Infection Prevention

- Hand-washing
- Avoid crowds
- Stay away from people who are sick
- Your doctor may prescribe an antibiotic to prevent infections
- Do not take tylenol if you run a fever, Call your doctor
Low Platelet Count (Thrombocytopenia)

You have a high risk of bleeding if your platelet count is <10,000

Signs that your platelets are low:
- Bruising easily
- Nose bleeds
- Increased bleeding from Gums

Notify your doctor if you notice any of the symptoms above

** If you are on Aspirin, your doctor may stop it temporarily until your platelets return to a normal level
Low Red Blood Cells (Anemia)

If you have low red blood cells you may experience fatigue and shortness of breath with activity.

Your doctor may prescribe an injection that will stimulate the production of your red blood cells

- Aranesp
- Procrit
Peripheral Neuropathy

Peripheral Neuropathy is damage to the peripheral nervous system. It usually affects the hands and feet.

Symptoms include:
- Burning
- Tingling
- Numbness
- Pain
Myeloma Medications Causing Peripheral Neuropathy

• Thalidomide
• Velcade
• Revlimid (Rare)
Symptom Management of Peripheral Neuropathy

Make sure to inform your doctor or nurse if you experience symptoms of peripheral neuropathy.

#1 Way to Manage Neuropathy:
Schedule and/or dosage changes in treatment.

Possible Treatments
- Topical comfort measures
- Vitamins
- Prescription Medications
Deep Vein Thrombosis (DVT)

A DVT is a blood clot that can form in the arm or leg.

A DVT can be caused by Multiple Myeloma or its treatments:
- Thalidomide/Dexamethasone
- Revlimid/Dexamethasone
- Combination Chemotherapy
- Epogen or Procrit

Signs of a DVT may include swelling in one arm or leg. It may or may not include warmth, redness, or tenderness.
DVT Prevention

- Take a baby aspirin (81 mg) daily if ok with your doctor
- Full dose coumadin or lovenox may be needed – depending on risk factors; ie; history of clots
- Change positions frequently
- Get out of the car and move around every 1-2 hours when taking a trip
- Move around every hour if allowed when flying on an airplane
- Call your doctor if you notice any swelling in an arm or leg
Bone pain is a common symptom of Multiple Myeloma

Bone pain can decrease quality of life:
- Decreased activity
- Sleep disturbance
- Fatigue
- Delayed healing
- Stress
- Depression
Treatment for Bone Pain

- Pain medications
- Radiation Therapy
- Kyphoplasty (for compression fractures in your back)
- Bisphosphonates (Aredia and Zometa)
Side Effects of Bisphosphonates

- Increased serum creatinine (kidney function test)
  - Have a serum creatinine blood test before each dose of Zometa/Aredia

- Osteonecrosis of the jaw - exposed bone in the oral cavity
  - Maintain good oral hygiene
  - Routine dental exams
  - Stop Zometa/Aredia at least 1 month before any invasive dental work (do not restart until area is completely healed)
Fatigue and Survivorship

- Fatigue is the #1 issue affecting quality of everyday life
- Causes are multifactorial
  - Symptoms of Myeloma
  - Side effects of treatment
Factors Contributing to Fatigue and Management Suggestions

- **Decreased Activity**
  - Energy conservation, exercise

- **Dehydration**
  - Drink, drink, drink

- **Poor Nutrition**
  - Balanced diet, multivitamin, small frequent meals, nutritionist

- **Treatments and Medications**
  - Keep your physician informed of symptom changes, keep an accurate list of medications

- **Sleep Disturbances**
  - Correct the underlying cause, medications

- **Depression and Stress**
  - Meditation, prayer, relaxation, support groups, medications
Living a Healthy Life with Myeloma

- Myeloma is manageable
- Patients are living twice as long
- Continue to have regular screenings with your primary doctor
Today there is more than HOPE for Myeloma patients and their families.
Question and Answer Session
The Leukemia & Lymphoma Society’s (LLS) Co-Pay Assistance Program offers financial assistance to qualified myeloma patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE:** [www.LLS.org/copay](http://www.LLS.org/copay)
- **TOLL-FREE PHONE:** (877) LLS-COPAY

For more information about myeloma and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE:** (800) 955-4572
- **EMAIL:** infocenter@LLS.org