New Treatments in Multiple Myeloma
ASS-FDA SYMPOSIUM 2015
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Rochester, Minnesota
Jacksonville, Florida
Disclosures

No conflicts to disclose
Survival in Myeloma

# Active Drugs in Multiple Myeloma

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<tbody>
<tr>
<td>▪ Alkylators</td>
<td>▪ Bortezomib</td>
<td>▪ Carfilzomib</td>
<td>▪ Ixazomib</td>
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<td>▪ Steroids</td>
<td>▪ Thalidomide</td>
<td>▪ Pomalidomide</td>
<td>▪ Marizomib</td>
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<td>▪ Interferon</td>
<td>▪ Lenalidomide</td>
<td>▪ Panobinostat</td>
<td>▪ Isatuximab</td>
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<td>▪ Anthracyclines</td>
<td>▪ Liposomal doxorubicin</td>
<td>▪ Daratumumab</td>
<td>▪ Dinaciclib</td>
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<td>▪ Ixazomib</td>
<td>▪ Filanesib</td>
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<td>▪ Elotuzumab</td>
<td>▪ LGH447</td>
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<td>▪ ABT-199</td>
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Rajkumar SV. 2015
International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Mdietos A Dimopoulos, Antonio Palumbo, Joao Flimel, Giampaulo Merlini, Maria-Victoria Mateos, Shaji Kumar, Jens Hilgenhaus, Efthimios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dingemans, Brendan Weks, Xavier Lézmi, Sonja Zwengm, Sagar Lonial, Laura Restoli, Elena Zangari, Sandor Jollmann, Orhan Sezer, Sagarstr Y Kudrimoti, Jo Cears, Saad Z. Ustaoni, Juan José Laherre, Hans Erik Johnsen, Merel Balsvo, Michelle Lani, Hartmut Goldschmidt, Evangelos Tarpos, Robert A. Kyle, Kenneth L. Anderson, Brian G.M. Durie, Jesus F. San Miguel

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be
## Revised IMWG Criteria

<table>
<thead>
<tr>
<th>MGUS</th>
<th>SMM</th>
<th>MM</th>
</tr>
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<tbody>
<tr>
<td>• &lt;10% BMPC AND&lt;br&gt;• &lt;3 gm/dL M protein AND&lt;br&gt;• No MDE</td>
<td>• ≥10%-60% BMPC OR&lt;br&gt;• ≥3 gm/dL S. M protein OR&lt;br&gt;• ≥500 mg/24h Ur. M protein AND&lt;br&gt;• No MDE</td>
<td>• PCPD, AND&lt;br&gt;• 1 or more MDE&lt;br&gt;• CRAB&lt;br&gt;• ≥60% BMPC&lt;br&gt;• ≥100 FLC ratio&lt;br&gt;• &gt;1 MRI focal lesion</td>
</tr>
</tbody>
</table>

**MDE**, myeloma-defining events

Molecular Classification of Myeloma

- Trisomies*
  - t(11;14) (CCND1)
  - t(6;14) (CCND3)
- t(4;14) (FGFR3/MMSET)
- t(14;16) (C-MAF)
  - t(14;20) (MAF-B)

*~10% have both trisomies and IgH translocations

# Revised International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Frequency (% of patients)</th>
<th>5-year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum albumin &gt;3.5</td>
<td>28%</td>
<td>82</td>
</tr>
<tr>
<td>• Serum beta-2-microglobulin &lt;3.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No high risk cytogenetics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Normal LDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neither Stage I or III</td>
<td>62%</td>
<td>62</td>
</tr>
<tr>
<td>Stage III</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serum beta-2-microglobulin &gt;5.5 and</td>
<td>10%</td>
<td>40</td>
</tr>
<tr>
<td>• High risk cytogenetics [t(4;14), t(14;16), or del(17p)] or Elevated LDH</td>
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</tbody>
</table>

ECOG E4A03 Trial: Implications for Dex Dosing

![Survival Probability Graph]

**Treatment**
- RD: 35/223 (87%)
- Rd: 10/222 (96%)

**Number at risk**
- RD: 223
- Rd: 221

FIRST Trial: MPT vs Rd18 vs Rd till progression

Kaplan–Meier Estimates of Progression-free Survival and Overall Survival

VISTA Trial: VMP vs MP: Overall Survival

![Graph showing overall survival for Bortezomib and Control groups with P=0.008 and survival data for both groups listed in the table.]

No. at Risk
- Bortezomib: 344, 315, 300, 290, 235, 168, 115, 72, 36, 4
- Control: 338, 320, 301, 280, 220, 157, 116, 69, 29, 7
## MYELOMA THERAPY\(^1-3\)

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.

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
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<tbody>
<tr>
<td><strong>Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)</strong></td>
<td><strong>Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)</strong></td>
</tr>
<tr>
<td>• Bortezomib/dexamethasone (category 1)</td>
<td>• Dexamethasone (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dexamethasone</td>
<td>• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/doxorubicin/dexamethasone (category 1)</td>
<td>• Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide(^4)/dexamethasone</td>
<td>• Melphalan/prednisone (MP)</td>
</tr>
<tr>
<td>• Bortezomib/thalidomide/dexamethasone (category 1)</td>
<td>• Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>• Lenalidomide(^4)/dexamethasone (category 1)</td>
<td>• Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)</td>
</tr>
</tbody>
</table>

\(^1\)Kassim JM, Gribben JG. Cancer. 2016;137(6):535-547.
Bortezomib, Lenalidomide and Dexamethasone vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma Without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777

Brian G.M. Durie, MD, Antje Hoering, PhD, S. Vincent Rajkumar, MD, Muneer H. Abidi, MD, Joshua Epstein, DSc, Stephen P. Kahanic, MD, Mohan Thakuri, MD, Frederic Reu, MD, Christopher M. Reynolds, MD, Rachael Sexton, MS, Robert Z. Orlowski, MD, PhD, Bart Barlogie, MD, PhD, Angela Dispenzieri, MD
Overall Survival By Assigned Treatment Arm

Log-rank P value = 0.0125 (one sided)*

HR = 0.709 (0.516, 0.973)*

Stratified

Deaths / N
VRd  76 / 242
Rd   100 / 229

Median in Months
VRd  75 (66, .).
Rd   64 (56, .)

*Stratified
Leading cancer research. Together.
Initial Treatment of Myeloma

Newly Diagnosed MM

Not Transplant Candidate
- VRd
- Rd (if frail, age ≥75)*

Transplant Candidate
- VRd x 4 cycles
  - Auto SCT +/- Maintenance
    (Len for std risk; bortez for high risk)
  - VRd x 4 cycles
    Len maintenance
    Delayed Transplant

IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)

Randomize

RVDx3

CY (3g/m2)
MOBILIZATION
Goal: 5 x10^6 cells/kg

Melphalan
200mg/m^2 * +
ASCT

RVD x 2

Lenalidomide x 12 months

RVDx3

CY (3g/m2)
MOBILIZATION
Goal: 5 x10^6 cells/kg

RVD x 5

Lenalidomide x 12 months

ASCT at relapse
MEL 200 mg/m2 if <65 yrs,
>65 yrs 140mg/m2
Upfront versus Delayed Transplantation

**MAG study**

**SWOG study**

IFM/DFCI 2009 Study
Newly Diagnosed MM Pts (SCT candidates)

Randomize

RVDx3

CY (3g/m2) MOBILIZATION
Goal: 5 x 10^6 cells/kg

Melphalan 200mg/m^2* + ASCT

RVD x 2

Len until progression

RVD x 3

CY (3g/m2) MOBILIZATION
Goal: 5 x 10^6 cells/kg

RVD x 5

Len until progression

ASCT at relapse
MEL 200 mg/m^2 if <65 yrs ,
>65 yrs 140mg/m^2
INCORPORATING NEW TREATMENTS
CLINICAL PRACTICE
Bortezomib Maintenance

HOVON trial: OS according to Arm and del(17p)

Sonneveld P et al. JCO 2012;30:2946-2955
Maintenance Therapy

Standard-Risk
- t(11;14), t(6;14), Trisomies

Intermediate-Risk
- t(4;14)

High-Risk
- Del 17p, t(14;16), t(14;20)

Initial Therapy or Autologous stem cell transplant

Lenalidomide maintenance

Bortezomib-based maintenance
  - Ixazomib-based maintenance
  - Addition of monoclonal antibodies

CLINICAL TRIALS
Clinical Trials

• Frontline phase III trials
  • Ixazomib (IRd vs Rd)
  • Elotuzumab (Elo-Rd vs Rd)
  • Daratumumab (Dara-Rd vs Rd)

• Maintenance
  • Ixazomib
  • Elotuzumab (planned)
Len/Dex versus Observation in High Risk SMM: OS

B

Overall Survival since Study Inclusion (%)

Hazard ratio for death, 0.31
P = 0.03

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Treatment group</th>
<th>Observation group</th>
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<tr>
<td>Months</td>
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<td>10</td>
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<td></td>
<td>20</td>
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<tr>
<td>No. at Risk</td>
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FAQs

• Previously untreated patients: Should we add bortezomib to Rd based on S0777?

• Previously treated patients: Should we add ixazomib or elotuzumab to Rd?

• Should we add daratumumab to frontline regimens?
THE FUTURE