INTERNATIONAL MYELOMA FOUNDATION presents

IMWG CONFERENCE SERIES

“Making Sense of Treatment”

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IMWGconferenceseries.myloma.org

WEDNESDAY JUNE 21 2017

Watch the LIVESTREAM: 3:00 AM PST/5:00 AM CT/6:00 AM ET
(replay will also be available)
Questions for Today’s Conference Series

• What is ideal imaging in 2017?
• How will new agents impact frontline therapy?
• Can MRD testing in trials guide decisions?
• Are you proactive about risk assessment?
• Which new therapies will make an impact?
• How important is cost?
What is ideal imaging in 2017
SLiM + CRAB

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

## Baseline Testing Required 2017

<table>
<thead>
<tr>
<th>MGUS</th>
<th>Smoldering</th>
<th>Early Active</th>
<th>Active Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spike on SPEP/UPEP</td>
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<tr>
<td>Abnormal Freelite</td>
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<tr>
<td>Bone Marrow &lt;10% PC</td>
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<tr>
<td>Bone Marrow &gt;10% PC</td>
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<tr>
<td>Bone Marrow ≥ 60% PC</td>
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<tr>
<td>Freelite Ratio ≥ 100</td>
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<tr>
<td>Creatinine Clearance &lt; 40 ml/min</td>
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<tr>
<td>MRI 2 or more lesions</td>
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<tr>
<td>Calcium Elevation</td>
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<td>C</td>
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<tr>
<td>R Creatinine Elevation</td>
<td></td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Bone Lesions on:</td>
<td></td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>X-ray</td>
<td></td>
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<tr>
<td>LD WB CT</td>
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<td></td>
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<tr>
<td>PET/CT or MRI</td>
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</tbody>
</table>

- MDE
  - 1
  - 2
  - 3
  - 4
• **Do you still use x-rays** which miss 20% of lesions?

• **Is your first or next step:**
  - WBLD CT?
  - or
  - MRI of spine/pelvis?
  - or
  - WB PET/CT?
Do you foresee other tests to predict or confirm active disease?
How will new agents impact frontline therapy?
SWOG S0777 Study Design: VRd versus Rd

Randomization  
N = 525

Stratification:  
• ISS (I, II, III)  
• Intent to transplant @ progression (yes/no)

Eight 21-day Cycles of VRd

- **Bortezomib** 1.3/mg² IV  
  Days 1, 4, 8, and 11  
- **Lenalidomide** 25 mg/day PO  
  Days 1-14  
- **Dexamethasone** 20 mg/day PO  
  Days 1, 2, 4, 5, 8, 9, 11, 12

Six 28-day Cycles of Rd

- **Lenalidomide** 25 mg/day PO  
  Days 1-21  
- **Dexamethasone** 40 mg/day PO  
  Days 1, 8, 15, 22
Progression-Free Survival By Assigned Treatment Arm

Log-rank P value = 0.0018 (one sided)*

*Stratified

HR = 0.712 (0.560, 0.906)*

Log-rank P value = 0.0018 (one sided)*

Events / N in Months
VRd 137 / 242 43 (39, 52)
Rd 166 / 229 30 (25, 39)
Overall Survival By Assigned Treatment Arm

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

Medians in months:
- VRd: 76 (66, 93)
- Rd: 100 (56, .)

Deaths:
- VRd: 76
- Rd: 100

*Stratified
IFM 2009: Impact of MRD Negative

PFS

No. at Risk

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<thead>
<tr>
<th></th>
<th>0</th>
<th>136</th>
<th>145</th>
<th>115</th>
<th>28</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD Arm – MRD Negative</td>
<td>0</td>
<td>171</td>
<td>202</td>
<td>155</td>
<td>45</td>
</tr>
<tr>
<td>Transplantation Arm – MRD Negative</td>
<td>350</td>
<td>158</td>
<td>83</td>
<td>42</td>
<td>4</td>
</tr>
<tr>
<td>RVD Arm – MRD Positive</td>
<td>350</td>
<td>137</td>
<td>62</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td>Transplantation Arm – MRD Positive</td>
<td>350</td>
<td>137</td>
<td>62</td>
<td>41</td>
<td>5</td>
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P<0.001
New Combos

- Durvalumab + Rd (Lonial et al: Abstract #TPS 8055)
- Elotuzumab + VRd (Laubach et al: Abstract #8002)
- KRd versus KCd: ≥VGPR 74% versus 61% (Gay et al: Abstract #8003)
- Dara + KRd (Jakubowiak et al: Abstract #8000)
What is the future of frontline therapy?

• **When** ≥ triple therapy feasible
  - VRd or VTD + Dara or ? + ?

• **Then**
  - Upfront ASCT whenever possible?
  - or
  - New novel combo without ASCT?
Can MRD testing in trials guide decisions?
Value of Lenalidomide Maintenance Post-ASCT

Meta-analysis of overall survival*

• 3 randomized trials: 1,209 patients
• Median follow up 6.6 years
• Median overall survival: 86 months v. not reached: P = 0.001
• At 5 years 66% v. 71%
  6 years 58% v. 65%
  7 years 50% v. 62%
• Benefit for ≤ PR as well as VGPR/CR patients

*ASCO Attal et al 2016
Can MRD testing solve our maintenance problems?

1-2 years

A

MRD

- Stop

MRD

+ Continue or change

B
Are you proactive about risk assessment?
mSMART 2.0: Classification of Active MM

### High-Risk 20%
- **FISH**
  - Del 17p
  - t(14;16)
  - t(14;20)
- **GEP**
  - High risk signature

### Intermediate-Risk 20%
- **FISH**
  - t(4;14)*
- **Cytogenetic**
  - Deletion 13 or hypodiploidy
- **PCLI >3%**

### Standard-Risk 60%
- All others including:
  - Hyperdiploid
  - t(11;14)
  - t(6;14)

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Risk</td>
<td>3 years</td>
</tr>
<tr>
<td>Intermediate-Risk</td>
<td>4-5 years</td>
</tr>
<tr>
<td>Standard-Risk</td>
<td>8-10 years</td>
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</tbody>
</table>

mSMART – Off-Study
Transplant Eligible

Standard-Risk

- Trisomies only
  - 4 cycles of Rd
  - Collect Stem Cells
  - Continue Rd

Intermediate-Risk

- t 11;14, t 6;14, Trisomies + IgH
  - 4 cycles CyBorD
  - Autologous stem cell transplant

- t 4;14
  - 4 cycles of CyBorD
  - Bor based therapy for minimum of 1 year

High-Risk

- Del 17p, t14;16, t14;20
  - 4 cycles of VRd
  - Autologous stem cell transplant, especially if not in CR

- Trisomies + IgH
  - Collect Stem Cells

**Standard-Risk**

- 4 cycles of Rd
- Collect Stem Cells
- Continue Rd

**Intermediate-Risk**

- t 11;14, t 6;14, Trisomies + IgH
  - 4 cycles CyBorD
  - Autologous stem cell transplant
- t 4;14
  - 4 cycles of CyBorD
  - Bor based therapy for minimum of 1 year

**High-Risk**

- Del 17p, t14;16, t14;20
  - 4 cycles of VRd
  - Autologous stem cell transplant, especially if not in CR
- Trisomies + IgH
  - Collect Stem Cells

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*a Bortezomib containing regimens preferred in renal failure or if rapid response needed
* If age >65 or > 4 cycles of Rd Consider G-CSF plus cytoxan or plerixafor
* Continuing Rd for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year
* Consider risks and benefits; If used, consider limited duration 12-24 months

**Collect Stem Cells**

- 2 cycles of Rd consolidation; then Len maintenance if not in VGPR but Len responsive*

**Continue Rd**

- 2 cycles of Rd consolidation; then Len maintenance if not in VGPR but Len responsive*

**Bor or CyBorD for minimum of 1 year**

Are you proactive about risk status
or
Wait for relapse?
Which new therapies will make an impact?
Approved Treatment Options 2017

- **1958**: Melphalan
- **1960**: Melphalan
- **1962**: Prednisone
- **1966**: High-Dose Dex
- **1968**: Auto Transplantation
- **1986**: High-Dose Dex
- **1986**: Hematopoietic Growth Factors
- **1986**: Intake of Food
- **1992**: Lenalidomide
- **1993**: Velcade
- **1998**: Thalidomide
- **2000**: Bortezomib
- **2003**: Bortezomib
- **2005**: Pomalidomide
- **2006**: Lenalidomide
- **2007**: Doxorubicin
- **2009**: ELT(Nova), Lenalidomide
- **2010**: Carfilzomib
- **2012**: Pomalidomide
- **2013**: Velcade, Pomalidomide
- **2015**: Daratumumab, Ixazomib, Elotuzumab, Panobinostat

**Auto** = Autologous; **Dex** = Dexamethasone
Relapse Therapy: ASCO 2017

• **Dara updates**
  - CASTOR: Dara Vd (Lentzsch et al: Abstract #8036)
    MRD at $10^{-5}$: 10% v 2%
  - Pollux: Dara Rd (Bahlis et al: Abstract #8025)
    MRD at $10^{-5}$: 25% v 6%

• **Isatuximab** + Pom/Dex (Mikhael et al: Abstract #8007)
  +/- Pom/Dex (Richardson et al: Abstract #8057)

• **Checkpoint**  Atezo + Len/Dara (Cho et al: Abstract #8053)
  Durvalumab + Dara (Richardson et al: Abstract #8054)
  Nivolumab + Pom/Dex ± Elo (Lonial et al: Abstract #8052)
  [CheckMate 602]
Trial Design for Nelfinavir Study

- Prospective, single-arm, multi-center, open-label phase II

**Cycle 1-6** (21 days)

- **Nelfinavir** 2x 2500 mg p.o. days 1 – 14
- **Bortezomib** 1.3 mg/m² i.v. or s.c. days 1, 4, 8, 11
- **Dexamethasone** 20 mg p.o. days 1-2, 4-5, 8-9, 11-12
- Follow-up until start of new myeloma therapy or death

- Simon’s two stage design, n=34
  - ≤ 15% response rate uninteresting, ≥ 30% response rate promising
  - power=80%, alpha=5%

- Completion after cycle 6 (18 weeks maximum trial therapy)
- Academic trial without industry (finance/drug) support
Best responses

Maximum relative change in serum M-protein or serum free light chain concentration in individual evaluable patients.
Question

Which new therapies have an impact in the frontline setting?
How Good are the “New” Novel Therapies?

- **CAR-T**
  - Efficacy
  - Toxicities: “cytokine storm”; immune deficiency...
  - Cure potential ??
- **Checkpoint inhibitors**
  - Efficacy in combo
  - Immune toxicities
  - Early use a concern?
- **Other agents**
  - Selinexor
  - Nelfinavir
  - New IMiD beyond Pom
How important is cost?
Increasing depth of response in myeloma with newer drugs

At least VGPR after 4 cycles induction in newly diagnosed MM

RD or CyBorD
$100,000 per year

VRD or KRD
$250,000 per year

KRD - Dytfield Haematologica 99(9) e162-4 2014
KCD – Bringhen Blood 124(1) 63-69 2014
VCD – Khan Br J Haematol 156(3) 326-333 2012
VRD – Roussel J Clin Oncol 32(25) 2712-2717
2014
TD & VTD – Cavo Blood 2012
RD – Rajkumar Lancet Oncol 11(1) 29-37

K – Carfilzomib
C – Cyclophosphamide
V – Bortezomib
R – Lenalidomide
A – Doxorubicin
D – Dexamethasone
How much does cost truly impact access; choices; outcomes?

- A few patients?
- Many patients?
- All patients?
Thank you for your support!