Overview of Teleconference

2019 treatment algorithms

Active myeloma

Smoldering myeloma

MGUS: early diagnosis
What is MGUS?

- **Monoclonal gammopathy** of undetermined significance

- Monoclonal protein present in serum at low level of <3 Gm/dl (3,000 mg)

- Bone marrow contains <10% plasma cells

- No MDE or CRAB features
IMWG Criteria: MGUS

MGUS

- <10% BMPC AND
- <3 gm/dL M protein AND
- No MDE

SMM

- ≥10%-60% BMPC OR
- ≥3 gm/dL S. M protein OR
- ≥500 mg/24h Ur. M protein AND
- No MDE

MM

- CRAB
  - And/or one or more MDE
    - ≥60% BMPC
    - ≥100 FLC ratio
    - >1 MRI focal lesion

No MDE

MDE

MDE, myeloma-defining events

Progression of MGUS/SMM to Myeloma

Primary Cytogenetic Abnormalities
- t(11;14)
- t(4;14)
- t(6;14)
- t(14;16)
- t(14;20)
- Trisomies

Secondary Cytogenetic Abnormalities
- 1q amp
- Del 17

Secondary Cytogenetic Abnormalities
- Myc translocations
- Del 17
- 1p del

Trisomies/ IgH Translocations
Establishment of the clone

Secondary Cytogenetic Abnormalities
Del(17p), Gain(1q)

Secondary Cytogenetic Abnormalities
Occur with progression

Relapsed Refractory MM
Plasma Cell Leukemia
Extra Medullary Disease

Rajan AM and Rajkumar SV. Blood Cancer J 2015
How common is MGUS?

- 3% of general population >50 years
- 1.7% in 50-59
- >5% in over 70

iStopMM: Iceland Project

Partners
- Sigurdur Kristinsson, University of Iceland
- Binding Site

140,000 adults > Age 40

Screen

What causes myeloma?

Establish criteria for classification/progression

Monitor

Prevent Multiple Myeloma

CURE Trial

HR SMM

CURE!
Key Early Data from Iceland

- Numbers of MGUS/ SMM/ MM

4,000 New MGUS cases

Active disease ... 40 cases/ year

1% per year

- Who gets MGUS?
- What causes MGUS?

- Mutations linked to likelihood?
- New mutations @ MM stage?
- Role of blood test monitoring?
MGUS Follow Up... By the Numbers

Numbers with myeloma

- 20% after 5 years
- 80% after 20 years

Still MGUS!

Multiple myeloma cases

- 200 cases after 5 years
- 400 cases after 10 years
- 600 cases after 15 years
- 800 cases after 20 years

MGUS FOLLOW UP
MGUS always comes before myeloma

Prostate, Lung, Colorectal, and Ovarian (PCLO) Cancer Screening Trial Study

150,000 (age 55-74)

77,469 screened

71 developed MM

MGUS is linked to many outcomes

MGUS

- **Cancers**
  - Myeloma
  - Macroglobulinemia
  - Plasmacytoma

- **Gammopathies**
  - AL Amyloidosis
  - LCDD
  - Cryoglobulinemia

- **Associations**
  - Neuropathy
  - Skin Disorders
  +... increased risk of other disorders
Progression of MGUS to SMM

Important Factors:
- Size and type of spike
- sFLC ratio

Graph showing progression over years with different risk levels:
- High risk
- Low risk

Rajkumar SV. Blood 2005;106:812-817
IMWG Criteria: Smoldering Myeloma (SMM)

- <10% BMPC AND
- <3 gm/dL M protein AND
- No MDE

- ≥10%-60% BMPC OR
- ≥3 gm/dL S. M protein OR
- ≥500 mg/24h Ur. M protein AND
- No MDE

- CRAB
  - And/or one or more MDE
    - ≥60% BMPC
    - ≥100 FLC ratio
    - >1 MRI focal lesion

MDE, myeloma-defining events

Progression to MM
Smoldering Multiple Myeloma

Low-risk SMM: 5%/yr risk of MM

High-Risk SMM

25%/year risk of MM
High Risk SMM: Average progression in 18-24 months

Factors which have been studied

≥10% PCs plus:
- SMM with M protein ≥3 gm/dL or ≥4 gm/dl
- Absence (<5%) of normal PCs by immunophenotyping plus Immunoparesis
- Abnormal FLC ratio 8-100
- Del(17p), t4;14, gain(1q21)/other FiSH abnormalities
- IgA SMM
- Evolving pattern
- Increased circulating plasma cells

Rajkumar SV, Landgren O, Mateos MV. Blood 2015
New Criteria for HR SMM

- M-component level $\geq 2$ gm/dl
- BMPC $\geq 20$
- sFLC ratio (involved/uninvolved) $\geq 20$
- Presence of 1q+ and/or 13q- confers added risk
- Other combinations and new factors being studied

Risk stratification based upon 421 patients. Follow up for ~3000 patients being finished.
Revlimid (Len) plus dexamethasone (Dex) versus observation randomized trial displaying TTP
Len/Dex versus Observation in High Risk SMM

Overall survival

Hazard ratio for death, 0.31
P=0.03

No. at Risk
Treatment group | 57 | 57 | 55 | 48 | 26 | 17 | 0
Observation group | 62 | 60 | 57 | 46 | 27 | 17 | 0

Treatment of Smoldering Multiple Myeloma

Newly Diagnosed SMM

High Risk
- Evolving, or multiple high risk factors
  - Clinical Trials, or Observation Q3 months
  - Consider Rd, or MM therapy

Low Risk
- Observation

Rajkumar SV, Landgren O, Mateos MV. Blood 2015
SPEP/IFE Negative
Mass Spec negative
$10^{-6}$ negative
$10^{-7/8}$ negative?

Treating HR SMM in clinical trials

CURE Trials
CESAR and ASCENT

Reaching the bottom of the iceberg
European “CURE” Trials: CESAR

Curative Strategy Smoldering Alto Risk

HR SMM

KRd x 6 cycles

ASCT

KRd x 2 cycles

Rd x 2 years

MRD at each phase and best response

ASH abstracts, 2017 & 2018
Overall Outcomes with CESAR Trial*

PFS = 94% at 28 months

*Full updates coming at ASH 2018 (poster)
US “CURE” Trial: ASCENT

Accrual ongoing: ~10 patients

US Sites
- Mayo
- University of Indiana
- University of Maryland
- MDAH
- Swedish Seattle
- Emory
- Chicago
- Cornell
- North Carolina
- Columbia
- Wisconsin
- Kansas

MRD at each phase and best response
Current Expectations

62% Undetected MRD

CESAR KRd

Dara KRd
ASCENT
~75% Undetected MRD
Testing if active myeloma is suspected

1. M-spike (SPEP; UPEP; IFE)
2. Complete blood count
3. Full chemistry panel
4. Freelite
5. Serum $\beta_2$ microglobulin (for ISS staging)
6. Bone marrow (% PC; FiSH)
7. Imaging (X-ray; CT; MRI; PET)
# Baseline Testing Required for Myeloma Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>Smoldering</th>
<th>Early Active</th>
<th>Active Myeloma</th>
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</thead>
<tbody>
<tr>
<td>Spike on SPEP/UPEP</td>
<td></td>
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<tr>
<td>Abnormal Freelite</td>
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<td>Bone Marrow &lt;10% PC</td>
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<td>Spike ≥ 2 G/dl</td>
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<tr>
<td>Freelite ratio ≥ 20%</td>
<td>MGUS</td>
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<tr>
<td>Bone Marrow ≥ 20% PC</td>
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<tr>
<td>Bone Marrow ≥ 60% PC</td>
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<td>1</td>
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<tr>
<td>Freelite Ratio ≥ 100</td>
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<td>2</td>
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<tr>
<td>Creatinine Clearance &lt; 40 mi/min</td>
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<td>3</td>
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<tr>
<td>MRI 2 or more lesions</td>
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<td>4</td>
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<tr>
<td>Calcium Elevation</td>
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<td>C</td>
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<tr>
<td>Renal dysfunction: Creatinine Elevation</td>
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<td>R</td>
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<tr>
<td>Anemia</td>
<td></td>
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<td>A</td>
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<tr>
<td>Bone Lesions:</td>
<td></td>
<td></td>
<td></td>
<td>B</td>
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</table>
Recommended Imaging

**Old**

**Traditional skeletal survey with x-rays**

**New**

- **WBLDCT**
  - Best for early screening for bone disease

- **PET/CT**
  - Response assessment: active residual disease

- **MRI**
  - WB/spine + pelvis
    - Gold standard to assess bone marrow involvement
Staging with FDG-PET/CT and MRI

PET: Focal lesions
Genetic Testing of Bone Marrow Cells

**Fluorescent in Situ Hybridization (FISH)**

High risk FISH
- t(4;14), 17p -, t(14;16), t(14;20), 1q +

**Gene Expression Profiling (GEP)**

High risk GEP
- 70 gene profile
mSMART 3.0: Classification of Newly Diagnosed Active MM

**High Risk**
- High risk genetic abnormalities $^{a,b}$
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del(17p)
  - P53 mutation
  - Gain 1q
- RISS Stage 3
- High plasma cell S-phase $^c$
- GEP: High risk signature
- Double Hit Myeloma: any 2 high risk genetic abnormalities
- Triple Hit Myeloma: 3 or more high risk genetic abnormalities

**Standard Risk$^a$**
- All others including:
  - Trisomies
  - t(11;14)$^d$
  - t(6;14)

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$^a$Trisomies may ameliorate. $^b$By FISH or equivalent method. $^c$Cut-offs vary. $^d$t(11;14) may be associated with plasma cell leukemia

mSMART – Off-Study*

Transplant Ineligible

**t(11;14), t(6;14), Trisomies**

- VRd for ~12 months;
  - If frail: Rd

- Rd for at least 1 year

**t(4;14), t(14;16), t(14;20), Del 17p**

- VRd for ~12 months

- Bortezomib-based maintenance till progression

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*a In patients treated initially with Rd, continuing treatment until progression is an option for patients responding well with low toxicities;

*b Dex is usually discontinued after first year

*c Duration based on tolerance; consider risks and benefits for treatment beyond 3 years

---

*This general treatment approach is presented here (mSMART – off-study); however, clinical trials must be considered and are preferred at every level (mSMART – on-study).

mSMART – Off-Study*  
**Transplant Eligible**

- **t(11;14), t(6;14), Trisomies**
  - 4 cycles of VRd
  - Collect Stem Cells $^a$
  - Autologous stem cell transplant (preferred)
  - Len maintenance for at least 2 years $^b$
  - Rd until progression $^c$

- **Del 17p**
  - 4 cycles of VRd or KRd
  - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
  - Carfilzomib or Bortezomib-based maintenance till progression $^b$

- **t(4;14), t(14;16), t(14;20), Double or Triple Hit Myeloma**
  - 4 cycles of KRd
  - Autologous Stem Cell Transplant (ASCT); Consider tandem ASCT
  - Carfilzomib or Bortezomib-based maintenance till progression $^b$

---

*This general treatment approach is presented here (mSMART – off-study); however, clinical trials must be considered and are preferred at every level (mSMART – on-study).*

2018 Update: Overall survival with frontline VRd (N=460)

- VRd: 55% OS at 7 years
- SWOG 0777

Deaths / N in Months
- Rd: 125 / 225
- VRd: 102 / 235

Median in Months
- Rd: 69 (59, 88)
- VRd: NR

*P-value = 0.0114

Months from Registration

0 24 48 72 96 120
SWOG 0777: OS landmarked at 12 months (N = 357)

*P-value < 0.0001

<table>
<thead>
<tr>
<th>Response</th>
<th>Deaths / N</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>52/81</td>
<td>49.90 (36.82, 61.72)</td>
</tr>
<tr>
<td>SD</td>
<td>26/41</td>
<td>38.14 (23.84, 67.90)</td>
</tr>
<tr>
<td>VGPR+</td>
<td>95/239</td>
<td>76.38 (76.38, 76.38)</td>
</tr>
</tbody>
</table>

VGPR 60% at 8 years
## Adding in ASCT

### Frontline VRd* + ASCT: Spanish Trial

<table>
<thead>
<tr>
<th></th>
<th>Induction (VRDx6)</th>
<th>HDT/ASCT</th>
<th>Consolidation (VRDx2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRD Undetected (negative)</td>
<td>35%</td>
<td>54%</td>
<td><strong>58%</strong> Negative at $10^{-6}$</td>
</tr>
<tr>
<td>MRD Detected (positive)</td>
<td>65%</td>
<td>46%</td>
<td>42%</td>
</tr>
</tbody>
</table>
VRd + ASCT: Spanish Trial

Progression-free survival (%)

<table>
<thead>
<tr>
<th>MRD+ ( \geq 10^{-4} )</th>
<th>MRD+ ( \geq 10^{-5} ) to ( &lt;10^{-4} )</th>
<th>MRD+ ( \geq 2 \times 10^{-6} ) to ( &lt;10^{-5} )</th>
<th>MRD-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>26</td>
<td>NR</td>
<td>40</td>
</tr>
</tbody>
</table>

- HR (95% CI) = 0.4 (0.3 – 0.5); \( P < .001 \)

NEG \( @ 10^{-6} \)
### Current Therapies

#### Frontline
- Rd: Revlimid dex
- Vd: Velcade dex
- VRd: Velcade Revlimid dex
- KRd: Kyprolis Revlimid dex
- ASCT: autologous stem cell transplant

#### Maintenance
- Revlimid ± Proteasome Inhibitor

#### Relapse
- Dara
- Kyprolis
- Pomalidomide
- Elotuzumab
- Ixazomib
- Panobinostat
- Cyclophosphamide
- VDT-PACE

#### Plus new agents in trials
The Future of Myeloma Therapy

MGUS
- Low risk MGUS
- High risk MGUS

HR SMM
- Low risk SMM
- New HR SMM

MM
- Ultra high risk
- New

2/20/20
- MDE
- CRAB
- BR*

*BR = biochemical relapse

Monitor

Treat as MM