Making Sense of Treatment

Wednesday, June 12, 2019
Today’s Speakers

Brian GM Durie
Cedars Sinai Medical Center

Joseph Mikhael
Translational Genomics Research Institute (TGen)
City of Hope Cancer Center

Philippe Moreau
University of Nantes
Recent Abstracts/Presentations/Publications

**ASCO 2019**
- Abstracts: 5600
- Myeloma-related: 210
- Oral presentations: 8*
- Plenary session presentation: 1

**EHA 2019**
- Abstracts: 2309
- Myeloma-related: 199
- Oral presentations: 13* (one presidential symp)
- Posters: 182*

*With one exception: all represented at EHA*
Today’s Topics

• Smoldering myeloma
• Frontline therapy
• Maintenance
• Relapse therapies
• New agents
Smoldering Myeloma (SMM)

• Risk classification

• Treatment strategies
Smoldering multiple myeloma

Increasing levels of monoclonal protein

Increasing marrow plasma cell percentage

Development of End Organ Damage
### IMWG Project: New SMM Risk Score Tool*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FLC Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-10 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10-25</td>
<td>0.69</td>
<td>1.99 (1.15, 3.45)</td>
<td>0.014</td>
<td>2</td>
</tr>
<tr>
<td>&gt;25-40</td>
<td>0.96</td>
<td>2.61 (1.36, 4.99)</td>
<td>0.004</td>
<td>3</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1.56</td>
<td>4.73 (2.88, 7.77)</td>
<td>&lt;0.0001</td>
<td>5</td>
</tr>
<tr>
<td><strong>M protein (g/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1.5 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1.5-3</td>
<td>0.95</td>
<td>2.59 (1.56, 4.31)</td>
<td>0.0002</td>
<td>3</td>
</tr>
<tr>
<td>&gt;3</td>
<td>1.30</td>
<td>3.65 (2.02, 6.61)</td>
<td>&lt;0.0001</td>
<td>4</td>
</tr>
<tr>
<td><strong>BMPC%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-15 (reference)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>&gt;15-20</td>
<td>0.57</td>
<td>1.77 (1.03, 3.06)</td>
<td>0.04</td>
<td>2</td>
</tr>
<tr>
<td>&gt;20-30</td>
<td>1.01</td>
<td>2.74 (1.6, 4.68)</td>
<td>0.0002</td>
<td>3</td>
</tr>
<tr>
<td>&gt;30-40</td>
<td>1.57</td>
<td>4.82 (2.5, 9.28)</td>
<td>&lt;0.0001</td>
<td>5</td>
</tr>
<tr>
<td>&gt;40</td>
<td>2.00</td>
<td>7.42 (3.23, 17.02)</td>
<td>&lt;0.0001</td>
<td>6</td>
</tr>
<tr>
<td><strong>FiSH abnormality</strong></td>
<td>0.83</td>
<td>2.28 (1.53, 3.42)</td>
<td>&lt;0.0001</td>
<td>2</td>
</tr>
</tbody>
</table>

*689 of the original 2286 had complete data for all risk factors. Logistic regression analyses performed. Principal investigators: Mateos; Kumar; San Miguel; Durie. ASCO abstract #8000; also EHA abstract.
Risk of Progression at 2 years

For **LOW-RISK**: 96% prediction of non-progression at 2 years

<table>
<thead>
<tr>
<th>Risk Stratification Groups</th>
<th>Hazard Ratio (95% CI) Versus Low-risk group (censored 2 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>Reference</td>
</tr>
<tr>
<td>5-8</td>
<td><strong>7.56</strong> (3.77 to 15.2)</td>
</tr>
<tr>
<td>9-12</td>
<td><strong>17.3</strong> (8.63 to 34.8)</td>
</tr>
<tr>
<td>&gt;12</td>
<td><strong>31.9</strong> (15.4 to 66.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Risk score</th>
<th>2 year progression n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>9 / 241 <strong>(3.7%)</strong></td>
</tr>
<tr>
<td>5-8</td>
<td>67 / 264 <strong>(25.4%)</strong></td>
</tr>
<tr>
<td>9-12</td>
<td>65 / 133 <strong>(48.9%)</strong></td>
</tr>
<tr>
<td>&gt;12</td>
<td>37 / 51 <strong>(72.6%)</strong></td>
</tr>
</tbody>
</table>
E3A06: RANDOMIZED PHASE III TRIAL OF LENALIDOMIDE VERSUS OBSERVATION ALONE IN PATIENTS WITH ASYMPTOMATIC HIGH-RISK SMOLDERING MULTIPLE MYELOMA

Sagar Lonial, M.D., Susanna Jacobus, M.Sc., Rafael Fonseca, M.D., Matthias Weiss, M.D., Shaji Kumar, M.D., Robert Z. Orlowski, M.D., Ph.D., Jonathan L. Kaufman, M.D., Abdulraheem M. Yacoub, M.D., Francis K. Buadi, M.D., Timothy O’Brien, M.D., Jeffrey V. Matous, M.D., Daniel M. Anderson, M.D., Robert V. Emmons, M.D., Anuj Mahindra, M.D., Lynne I. Wagner Ph.D., Madhav V. Dhodapkar, M.B.B.S., S. Vincent Rajkumar, M.D.

Acknowledgement: This study was coordinated by the ECOG-ACRIN Cancer Research Group (Peter J. O’Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under the following award numbers: CA180820, CA180794, CA180790, CA180853, CA180858, CA180864, CA189805, CA189863, CA189870, CA180888, CA180826, (IF QOL: CA189828). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, nor does mention of Co-authors, study sponsor, etc.
Phase III PFS by Mayo 2018 Risk Criteria

High Risk

Intermediate Risk

Low Risk
CURATIVE STRATEGY (GEM-CESAR) FOR HIGH-RISK SMOLDERING MYELOMA

CARFILZOMIB, LENALIDOMIDE AND DEXAMETHASONE (KRD) AS INDUCTION FOLLOWED BY HDT-ASCT, CONSOLIDATION WITH KRD AND MAINTENANCE WITH RD*

100%
90%
50%

OS = 98%
PFS = 94%

At 30 months

*EHA abstract
Smoldering Myeloma (SMM)

- Risk classification
- Treatment strategies
Frontline Therapy

- CASSIOPEIA: Dara VTd versus VTd
- MAIA: Dara len/dex versus len/dex
- SQ Dara
- Forte: KRd ± ASCT
- t(11;14) impact
PHASE 3 RANDOMIZED STUDY OF Dara VTd VERSUS VTd

TRANSPLANT ELIGIBLE NEWLY DIAGNOSED MULTIPLE MYELOMA: PART 1 CASSIOPEIA RESULTS*

MRD negative: 33.7% versus 19.9%
PHASE 3 RANDOMIZED STUDY OF Dara VTd VERSUS VTd

**Progression Free Survival**

Hazard ratio for disease progression or death, 0.47 (95% CI 0.33-0.67); p<0.0001

**Impact of sCR**

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>D-VTd sCR</th>
<th>VTd sCR</th>
<th>D-VTd sCR-</th>
<th>VTd sCR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>157</td>
<td>157</td>
<td>148</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>110</td>
<td>110</td>
<td>100</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>386</td>
<td>344</td>
<td>294</td>
<td>172</td>
</tr>
<tr>
<td></td>
<td>432</td>
<td>387</td>
<td>313</td>
<td>176</td>
</tr>
</tbody>
</table>

INTERNATIONAL MYELOMA FOUNDATION
Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma* (MAIA)

*NEJM May 2019: 380; 22 pp 2104-2115
PHASE 3 STUDY OF SUBCUTANEOUS (SC) VERSUS INTRAVENOUS (IV) DARATUMUMAB ADMINISTRATION

PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA: COLUMBA

Dara SQ equivalent and SAFE

*ASCO abstract #8005; EHA abstract also
CARFILZOMIB LENALIDOMIDE DEXAMETHASONE (KRD) WITH OR WITHOUT TRANSPLANTATION

NEWLY DIAGNOSED MYELOMA (FORTE TRIAL): EFFICACY ACCORDING TO RISK STATUS

<table>
<thead>
<tr>
<th></th>
<th>Table 1A: Overall population</th>
<th>Table 1B: Subgroup analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>44%</td>
<td>43%</td>
</tr>
<tr>
<td>≥CR</td>
<td>60%</td>
<td>61%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>89%</td>
<td>87%</td>
</tr>
<tr>
<td>MRD negative</td>
<td>58%</td>
<td>54%</td>
</tr>
</tbody>
</table>

*ASCO abstract #8002; EHA abstract also

KRd + ASCT and KRd 12 cycles are equivalent!
Outcomes of patients with t(11;14) multiple myeloma: An International Myeloma Working Group*

*ASCO: abstract #8015; also EHA abstract
• CASSIOPEIA: dara VTd versus VTd

• MAIA: dara len/dex versus len/dex

• SQ dara

• Forte: KRd ± ASCT

• t(11;14) impact
DEEPENING RESPONSES SEEN WITH IXAZOMIB MAINTENANCE POST-AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT)

PROLONGED PROGRESSION-FREE SURVIVAL - ANALYSIS FROM THE TOURMALINE-MM3 STUDY*

Deepening best response PR/VGPR at entry

*EHA abstract: PS1382
Maintenance

• Ixazomib
Relapse Therapies

- Isatuximab Pd versus Pd
- Dara Kd
- K in frail patients
- Elo Pd
- Selinexor/dara
A phase III randomized, open label, multicenter study comparing isatuximab, pomalidomide, and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone.

Patients with relapsed/refractory multiple myeloma (RRMM)

<table>
<thead>
<tr>
<th></th>
<th>Isa Pd</th>
<th>Pd alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>11.5 months</td>
<td>6.5 months</td>
</tr>
<tr>
<td>ORR</td>
<td>60.4%</td>
<td>35.3%</td>
</tr>
<tr>
<td>VGPR</td>
<td>31.8%</td>
<td>8.5%</td>
</tr>
<tr>
<td>MRD negative (10^{-5})</td>
<td>5.2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*ASCO: abstract #8004; also EHA abstract
Daratumumab Plus Carfilzomib and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma*

*Blood May 21, 2019: online

≥ VGPR
~70%
SUBGROUP ANALYSIS FROM THE PHASE 3 A.R.R.O.W. STUDY

<table>
<thead>
<tr>
<th>Grade ≥3 TEAEs of interest,* n</th>
<th>Fit</th>
<th>Intermediate</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once-weekly Kd70, n=60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twice-weekly Kd27, n=66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0</td>
<td>3 (5)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Once-weekly Kd70, n=79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twice-weekly Kd27, n=60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Standardized MedDRA Queries – Narrow

- Once weekly tolerated in frail patients
- Also true in Endeavor and Aspire subgroup analysis (IFM)

*ASCO: abstract #8027; also EHA abstract
ELOTUZUMAB PLUS POMALIDOMIDE AND DEXAMETHASONE FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA

EFFICACY RESULTS AFTER ADDITIONAL FOLLOW-UP OF THE PHASE 2, RANDOMIZED ELOQUENT-3 STUDY

Overall survival (all randomized patients)

Probability of survival

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

Time (months)

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

HR 0.54 (95% CI 0.30–0.96)

79% (versus 68%)

68% (versus 49%)

Patients at risk

EPd 60 58 54 53 48 46 43 41 39 34 30 17 11 3 1 0

Pd 57 51 47 43 38 35 34 32 27 23 18 10 6 3 1 0
How do you select and sequence?
New Agents

- CAR T
- AMG 420 BiTE
- CELMOD (CC220)
Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma*

*NEJM May 2, 2019: pp 1726-1737
IMPROVED EFFICACY AND SAFETY OF A DUAL-TARGET CAR-T CELL THERAPY

TARGETING BCMA AND CD38 FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA FROM A PHASE I STUDY
EVALUATION OF AMG 420, AN ANTI-BCMA BISPECIFIC T-CELL ENGAGER (BITE®) IMMUNOTHERAPY

R/R MULTIPLE MYELOMA (MM) PATIENTS: UPDATED RESULTS OF A FIRST-IN-HUMAN (FIH) PHASE 1 DOSE ESCALATION STUDY

Patients with R/R MM responding to the anti-BCMA BiTE® AMG 420 as of Feb 2019

- 6.5 µg/d
- 50 µg/d
- 100 µg/d
- 200 µg/d
- 400 µg/d
- 800 µg/d

Post EOT 10.3 m: sCR
Post EOT 7.2 m: VGPR
Post EOT 8.6 m: CR

Cycle
Month (approx)
0  1.5  3  4.5  6  7.5  9  10.5  12  13.5  15

PD  PR  Very Good PR  CR  MRD negative sCR

Time post EOT
Treatment ongoing
# A CELMOD, IN COMBINATION WITH DEXAMETHASONE IN PATIENTS WITH RELAPSED/REFRACTORY MULTIPLE MYELOMA

## Table 1. Responses in evaluable patients

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>IBER dose 0.3–1.2 mg + DEX (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good partial response</td>
<td>1</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>15</td>
</tr>
<tr>
<td>Minimal response (MR)</td>
<td>10</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>19</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6</td>
</tr>
<tr>
<td><strong>Overall response (≥PR, %)</strong></td>
<td><strong>16 (31)</strong></td>
</tr>
<tr>
<td>Clinical benefit (≥MR, %)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Disease control (≥SD, %)</td>
<td>45 (88)</td>
</tr>
</tbody>
</table>

DEX, dexamethasone; IBER, iberdomide
• Selinexor 100 mg weekly combined with standard dara well-tolerated

• ORR = 77% without prior Selinexor or dara

Also: ASCO #2014 STORM trial update
• What is your perspective on new therapies?

➢ Which are top priority?

➢ Which are promising?

➢ Can any be offered in frontline or early disease?
Other Interesting Abstracts

Examples

• ASCO #8020: BCMA as a biomarker
• ASCO #8023: Prognosis of 1q+ patients
• ASCO #8031: Importance of circulating plasma cells
• ASCO #8036: DNA mutations in blood
• ASCO #8053: Update on GSK 2857916
What are key next trials or studies?
THANK YOU!

• Experts
• Audience
• Sponsors
• Until next time!
Thank you to our sponsors!