POST ASCO/EHA/IMWG TELECONFERENCE

Thursday, June 27, 2019
4:00 pm Pacific / 5:00 pm Mountain
6:00 pm Central / 7:00 pm Eastern
Duration: 60 minutes (including Q & A)

myeloma.org

Dr. Brian GM Durie
Chairman of the Board
International Myeloma Foundation
Today’s Featured Speaker

Dr. Durie is

- Chairman of the Board for the IMF
- Scientific Chair of the IMWG and Black Swan Research Initiative
- Co-Chair of the SWOG Myeloma Committee

Brian GM Durie
Cedars-Sinai Medical Center
Recent Abstracts/Presentations/Publications

**ASCO 2019**
- Abstracts: 5,600
- Myeloma-related: 210
- Oral presentations: 8
- Plenary session presentation: 1

**EHA 2019**
- Abstracts: 2,309
- Myeloma-related: 199
- Oral presentations: 13
  (one presidential symp)
- Posters: 182

... plus recent publications
Today’s Topics

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

• Risk classification
  ➢ What is High Risk Smoldering Multiple Myeloma? [HR SMM]

• Treatment strategies
  ➢ Observation
  ➢ Attempt to “prevent” progression to MM
  ➢ Early treatment for myeloma to enhance long term outcomes
Smoldering Multiple Myeloma (SMM)

- Increasing levels of monoclonal protein
- Increasing marrow plasma cell percentage
- Development of End Organ Damage

HR SMM
MDE
CRAB
### 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.
Key Factors for Progression at 2 years

**MDE** *(Myeloma Defining Events)*

- BMPC % = \(\geq 60\%\)
- FLC Ratio = \(\geq 100\)
- MRI = \(\geq 2\) lesions

**HR SMM**

- BMPC % = \(20 - < 60\%\)
- FLC Ratio = \(10 - < 100\)
- [MRI = 0 or 1]
- Serum spike = \(> 1.5\)
- FiSH abnormalities
Risk of Progression at 2 years

For LOW-RISK: 96% prediction of non-progression at 2 years
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 2008 Risk Criteria

Only 14 patients with HR SMM received lenalidomide.
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*

OS = 98%
PFS = 94%

At 30 months

*EHA abstract
Smoldering Multiple Myeloma (SMM)

• Treatment strategies
  ➢ Review carefully
  ➢ Be aware of concerns about using Revlimid as a single agent early (as a “preventative”)
    o Emergence of IMiD resistance
    o Need for ongoing therapy
    o Side effects [51% discontinued therapy]/ costs
      (??? reimbursement for non-FDA approved indication)
    o Second malignancies increased
When Should Treatment Be Initiated?

Potential New Myeloma or Smoldering Myeloma

Any Myeloma Defining Events?
- CRAB,
- >60% PC,
- FLC >100,
- MRI >1 focal

Treat as Myeloma

No Myeloma Defining Events (SMM)

High Risk SMM
(Median TTP ~2 years)
Consider Early Therapy

Intermediate or Low Risk SMM
Clinical Trials
Observation

Adopted 2019
Frontline: Key Question

Can we improve on VRd triplet?

- VRd [VTd]
- KRd
- DRd
- KCd

FORTE Trial
MAIA Trial
TRIPLET

- Dara VRd
- Dara VTd
- Dara KRd

QUADRUPLE
CASSIOPEIA Trial
PHASE 3 RANDOMIZED STUDY OF Dara VTd VERSUS VTd

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

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

**Progression Free Survival**

- D-VTd: 92.7%
- VTd: 84.6%

**Impact of sCR**

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

Number at risk:

- D-VTd: 543, 520, 501, 492, 442, 346, 342, 261, 185, 122, 61, 14, 0
- VTd: 542, 519, 497, 475, 413, 319, 233, 163, 104, 50, 14, 0

Number at risk for sCR:

- D-VTd sCR: 157, 157, 148, 89, 37, 5, 0
- VTd sCR: 110, 110, 100, 57, 27, 6, 0
- D-VTd sCR-: 386, 344, 294, 172, 85, 9, 0
- VTd sCR-: 432, 387, 313, 176, 77, 8, 0

Historical and International Myeloma Foundation Logo
MAIA: PFS by Age Group

- Median follow-up: 28 months (range: 0.0-41.4)

**<75 years**

- Dara Rd
- Median: not reached

**≥75 years**

- Dara Rd
- Median: not reached

**Rd**
- Median: 33.7 mo

**HR, 0.50 (95% CI, 0.35-0.71)**

**HR, 0.63 (95% CI, 0.44-0.92)**

No. at risk:

**Rd**
- 208
- 191
- 175
- 158
- 141
- 132
- 126
- 116
- 86
- 56
- 31
- 11
- 2
- 1
- 0

**D-Rd**
- 208
- 201
- 195
- 186
- 179
- 175
- 170
- 159
- 116
- 83
- 47
- 23
- 7
- 0
- 0

No. at risk:

**Rd**
- 161
- 141
- 132
- 122
- 113
- 104
- 93
- 84
- 63
- 38
- 19
- 7
- 1
- 1
- 0

**D-Rd**
- 160
- 146
- 140
- 134
- 130
- 125
- 120
- 112
- 87
- 63
- 39
- 12
- 4
- 1
- 0

**Median PFS was significantly prolonged for D-Rd versus Rd in both age groups**

Usmani SZ, et al., ASCO 2019; abstract 8035, oral presentation
Overview of mPFS in recent phase 3 trials in NSCT NDMM

Direct comparison between trials is not intended and should not be inferred. HR, hazard ratio; NR, not reached; NSCT, non-stem cell transplant; PFS, progression-free survival; Rd, lenalidomide, low-dose dexamethasone; RdD, daratumumab, lenalidomide, dexamethasone; RVd, lenalidomide, bortezomib and dexamethasone; VMP; bortezomib, melphalan, prednisone.

CARFILZOMIB LENALIDOMIDE DEXAMETHASONE (KRD) WITH OR WITHOUT TRANSPLANTATION

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

<table>
<thead>
<tr>
<th>Table 1A: Overall population</th>
<th>Table 1B: Subgroup analysis</th>
</tr>
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<tbody>
<tr>
<td>KRd_ASCT_KRd12</td>
<td>R-ISS 1</td>
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<tr>
<td>N=158</td>
<td>N=157</td>
</tr>
<tr>
<td>sCR</td>
<td>44%</td>
</tr>
<tr>
<td>≥CR</td>
<td>60%</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>89%</td>
</tr>
<tr>
<td>MRD negative</td>
<td>58%</td>
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</table>

*ASCO abstract #8002; EHA abstract also

**KRd + ASCT and KRd 12 cycles are equivalent!**
Myeloma: Frontline Treatment

**Not Transplant Candidate**
- VRd x 8-12 cycles;†
  - Len maintenance or
  - DRd until progression

**Frail Patients**
- Rd x 1 year;
  - Len maintenance until progression

**Transplant Candidate**
- VRd‡ x 3-4 cycles or Dara-based quadruplet in selected high risk patients

**Auto SCT Maintenance**
- (Len for std risk; Bortez for high risk)

**VRd x4 cycles**
- Len Maintenance Delayed Transplant

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*Based on CALGB 100104, S0777, IFM-2009, CTN 0702, HOVON, MAIA, CASSIOPEIA
†VTD/VCd if VRd not available

Rajkumar SV © 2019
• Ixazomib: new data at EHA
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
Relapse Therapies: New Data

- Elotuzumab Pd
- Isatuximab Pd versus Pd
- Dara Kd
- K in frail patients
- Selinexor/dara
- Venetoclax update [EHA: LBA]
Elotuzumab-Pd vs Pd (PFS)

Isatuximab-Pd versus Pd

HR = 0.596 (95% CI, 0.436 to 0.814)

p = 0.001

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Isa-Pd</th>
<th>Pd</th>
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<tbody>
<tr>
<td>Months</td>
<td>154</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>129</td>
<td>105</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>1</td>
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</tr>
</tbody>
</table>

Data cut-off 11 Oct, 2018

CI, confidence interval; d, dexamethasone; HR, Hazard ratio; IRC, Independent Review Committee; Isa, isatuximab; mos, months; PFS, progression-free survival; P, pomalidomide

Richardson PG et al. ASCO 2019
Daratumumab Plus Carfilzomib and Dexamethasone

ORR = 84%
≥CR: 33%
≥VGPR: 71%
18.3
37.8
13.4

ORR = 79%
≥CR: 29%
≥VGPR: 69%
18.8
39.6
10.4

ORR = 90%
≥CR: 37%
≥VGPR: 73%
20
36.7
16.7

≥ VGPR ~70%

*Blood May 21, 2019: online
Once-Weekly Carfilzomib in Frail Patients

SUBGROUP ANALYSIS FROM THE PHASE 3 A.R.R.O.W. STUDY

*ASCO: abstract #8027; also EHA abstract

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

First Relapse

- Not Refractory to Lenalidomide*
  - DRd
  - Alternatives: KRd, IRd, ERd

- Refractory to Lenalidomide
  - DVd or DPd
  - Alternatives: EPd, VCd, KPd, IPd, Pd

*Relapse occurring while off all therapy, or while on small doses of single-agent lenalidomide, or on bortezomib maintenance

†Consider salvage auto transplant in eligible patients

Rajkumar SV © 2019

How do you select and sequence?
### Active Drugs in Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Alkylators</td>
<td>Bortezomib</td>
<td>Carfilzomib</td>
<td>GSK 2857916</td>
</tr>
<tr>
<td>Steroids</td>
<td>Thalidomide</td>
<td>Pomalidomide</td>
<td>AMG 420</td>
</tr>
<tr>
<td>Interferon</td>
<td>Lenalidomide</td>
<td>Panobinostat</td>
<td>CAR-Ts</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Liposomal doxorubicin</td>
<td>Ixazomib</td>
<td>Isatuximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daratumumab</td>
<td>Selinexor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elotuzumab</td>
<td>Venetoclax</td>
</tr>
</tbody>
</table>

Rajkumar SV. 2019

**Future Drugs**
- BiTEs [AMG 701 / EM 801 / JNJ 64007957]
- Anti CD 46 and 74
- CelMODs [220/ 9284]
- DTP 3
- BION 1301
- JNJ 42756493
New Agent: Updates

• GSK 2857916
• AMG 420 BiTE
• CAR T
• CELMOD (CC220)
• Selinexor
• Venetoclax

Major target BCMA
GSK-ADC: DREAMM1 Phase 2 Part 2

- Results at 3.4 mg/kg IV Q3 Wk

89% Double refractory;
34% double + Dara refractory
29% Cyto High-risk

Trudel et al. Ash 2017


Updated Results

- ORR 60%
- 2 sCR
- 3 CR
- 14 VGPR
- 2 PR

- PFS: 12 months
- DOR: 14.3 months

- D/PI/IMiD refractory
  - PFS 6.2 m
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
**BiTE® FORMATS IN DEVELOPMENT**

<table>
<thead>
<tr>
<th>First-Generation</th>
<th>Half-Life Extended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD3</td>
<td>Molecule incorporates CD3 and Target Antigen Binding Regions; addition of HLE domain prolongs in vivo half-life</td>
</tr>
<tr>
<td>VH2/VL2</td>
<td>Modeled in vivo Half-Life: Approximately 7 days</td>
</tr>
<tr>
<td>VH1/VL1</td>
<td>Dosing: Weekly infusion</td>
</tr>
<tr>
<td>Anti-Tumor</td>
<td>Dosing: Continuous infusion</td>
</tr>
</tbody>
</table>

Molecule incorporates CD3 and Target Antigen Binding Regions; addition of HLE domain prolongs in vivo half-life. Modeled in vivo Half-Life: Approximately 7 days.


CD = cluster of differentiation; VH = variable domain, heavy chain; VL = variable domain, light chain.
Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma*

*NEJM May 2, 2019: pp 1726-1737
How Does BCMA Therapy Measure Up?

- In what order should we give these therapies?
- What line of therapy should we target?
- Will sequential BCMA therapies be possible
- Will CAR T cell therapy replace autoSCTx?

<table>
<thead>
<tr>
<th></th>
<th>GSK2857916</th>
<th>bb2121 (≥150 x 10⁶ CAR T cells)</th>
<th>AMG-420</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>Escalation Group: 21</td>
<td>N = 42</td>
</tr>
<tr>
<td>Median Prior Lines of Therapy</td>
<td>57% ≥ 5 prior lines</td>
<td>7 regimens (3 – 14)</td>
<td>PLT. 4 (2-13)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>12 months</td>
<td>11.8 months (17.7 months for MRD- pts)</td>
<td>PFS – NR</td>
</tr>
<tr>
<td>ORR CR/sCR VGPR PR</td>
<td>60% 9% 43% 9%</td>
<td>95.5% 50.0% 36.4% 9.1%</td>
<td>ORR 70% 5 CR - 1 VGPR - 1 PR</td>
</tr>
</tbody>
</table>

GSK2857916: BCMA mAb Drug Conjugate
Vs
bb2121: BCMA CAR T Cell Therapy
Vs.
Bispecific – AMG-420

Trudel S et al. ASH 2017.
Raje N et al. ASCO 2018.
FIRST CLINICAL (PHASE 1B/2A) STUDY OF IBERDOMIDE (CC-220; IBER)
SAFETY AND EFFICACY OF COMBINATION OF SELINEXOR, DARATUMUMAB, AND DEXAMETHASONE (SDD) IN PATIENTS WITH MULTIPLE MYELOMA (MM) PREVIOUSLY EXPOSED TO PROTEASOME INHIBITORS AND IMMUNOMODULATORY DRUGS

• Selinexor 100 mg weekly combined with standard dara well-tolerated

• ORR = 77% without prior Selinexor or dara

Also: ASCO #2014 STORM trial update
Venetoclax Update

• Anti-BCl-2 therapy
• **BELLINI Trial**: 41/194 patients in Venetoclax Vd died: 13 linked to therapy plus infection and progression
• Both PFS and OS benefit in patients with t(11;14): EHA 2019

**CANOVA Trial** for t(11;14) patients
**Re-opened**: Venetoclax/dex vs Pom/dex
New Therapies

• What is the current perspective?
  ➢ Which are top priority?
  ➢ Which are promising?
  ➢ Can any be offered in frontline or early disease?
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