Making Sense of Treatment
Monday, December 11, 2017

Atlanta, GA
Tonight’s Speakers

Brian GM Durie
Cedars Sinai Medical Center

Joseph Mikhael
Mayo Clinic Scottsdale

Paul Richardson
Dana-Farber Cancer Institute
Tonight’s Topics

• Priorities for early disease
• Frontline options
• Role of ASCT
• Maintenance recommendations
• Early relapse management
• New therapies
Priorities for Early Disease
Abstract #393: MYC Translocations Identified By Sequencing Panel in Smoldering Multiple Myeloma Strongly Predict for Rapid Progression to MM

Niama Keane, MB, MRCP\textsuperscript{a,2}, Caleb K Stein, MS\textsuperscript{3}, Daniel Angelov, MSc, MB\textsuperscript{3}, Shulan Tian\textsuperscript{4}, David Viswanatha, MD\textsuperscript{5}, Shaji K. Kumar, MD\textsuperscript{5}, Angela Dispenzieri, MD\textsuperscript{5}, Veronica Gonzalez De La Calle, MD\textsuperscript{5}, Kristine Misund, PhD\textsuperscript{1,6}, Robert A Kyle, MD\textsuperscript{5}, Michael E O'Dwyer, MD\textsuperscript{2}, Rafael Fonseca, MD\textsuperscript{5}, A. Keith Stewart, MBChB, MBA\textsuperscript{7}, Esteban Braggio, PhD\textsuperscript{8}, Yan Asmann, PhD\textsuperscript{8}, S. Vincent Rajkumar, MD\textsuperscript{2} and P. Leif Berasagel, MD\textsuperscript{8}

Log-rank p-value = 6.18e-13

Events / N
MYC SV 16 / 16
No MYC SV 54 / 80
1-Year Survival
MYC SV 50.0 (30.6, 81.6)
No MYC SV 89.9 (83.8, 96.8)
Peripheral Blood Results with NGF in MGUS & SMM

**MGUS cases**

A

- Time to progression (%)
- ≥0.056 cPC/µL of PB (n=20), 75% TTP: NR
- <0.056 cPC/µL of PB (n=54), 75% TTP: NR
- p=0.003

**SMM cases**

B

- Time to progression (%)
- ≥28.5% cPC/all PBPC (n=14), 75% TTP: 15 months
- <28.5% cPC/all PBPC (n=6), 75% TTP: NR
- p=0.14

15 month median
All Icelanders > 40 years, N=148,000

4,500-5,000 with MGUS/SMM

No further work-up, N=1,500

IMWG Recommendations, N=1,500

Without MGUS/SMM, N=1,500

Intervention arm, N=1,500

iStopMM: largest population-based study

IMWG Recommendations

Intervention arm

iStopMM

R

4500-5000 with MGUS/SMM

All Icelanders > 40 years

Without MGUS/SMM

No further work-up

N=1500

IMWG

Recommendations

N=1500

Intervention arm

N=1500

iStopMM: largest population-based study
What do you foresee will be the best way to diagnose early disease?
Management of High-Risk Smoldering Myeloma
GEM-CESAR: Study Design

- Multicenter, open-label, randomized phase II trial

### Induction
6 x 28-day cycles

- **Carfilzomib** i.v. 20/36 mg/m²
  - Days 1, 2, 8, 9, 15, 16

- **Lenalidomide** 25 mg
  - Days 1–21

- **Dexa** 40 mg
  - Days 1, 8, 15 & 22

### High-dose Melphalan [200 mg/m²] Followed by ASCT

- **Carfilzomib** i.v. 20/36 mg/m²
  - Days 1, 2, 8, 9, 15, 16

- **Lenalidomide** 25 mg
  - Days 1–21

- **Dexa** 40 mg
  - Days 1, 8, 15 & 22

### Consolidation
2 x 28-day cycles

- **Carfilzomib** i.v. 20/36 mg/m²
  - Days 1, 2, 8, 9, 15, 16

- **Lenalidomide** 25 mg
  - Days 1–21

- **Dexa** 40 mg
  - Days 1, 8, 15 & 22

### Maintenance
24 x 28-day cycles

- **Lenalidomide** 10 mg
  - Days 1–21

- **Dexamethasone** 20 mg
  - Days 1, 8, 15 & 22

**High-risk was defined according to the Mayo and/or Spanish models**

- Patients with any one or more of the biomarkers predicting imminent risk of progression to MM were allowed to be included but...
- New imaging assessments were mandatory at screening and if bone disease was detected in the CT or PET-CT, patients were excluded
<table>
<thead>
<tr>
<th></th>
<th>Induction (KRdx6) N = 35</th>
<th>HDT/ASCT N = 35</th>
<th>Consolidation (KRdx2) N = 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥CR</td>
<td>49%</td>
<td>62%</td>
<td>74%</td>
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<tr>
<td>VGPR</td>
<td>37%</td>
<td>23%</td>
<td>20%</td>
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<tr>
<td>PR</td>
<td>14%</td>
<td>14%</td>
<td>6%</td>
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<tr>
<td>MRD-negative</td>
<td>26%</td>
<td>47%</td>
<td>62%</td>
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</table>
Two patients experienced relapse from CR before the end of induction and they proceeded to subsequent therapy.

Two deaths: one patient who relapsed from CR and was refractory and died due to disease progression; other patient due to massive ischemic stroke during induction.
And the more gentle approach...
Daratumumab Monotherapy in SMM

1:1:1 RANDOMIZATION

Arm A (16 mg/kg IV; 8-week cycles); Long Intense (max 3 years)
- Cycle 1: QW
- Cycles 2 & 3: Q2W
- Cycles 4-7: Q4W
- Cycles 8-20: Q8W

Arm B (16 mg/kg IV; 8-week cycles); Intermediate (max 3 years)
- Cycle 1: Q2W
- Cycles 2-20: Q8W

Arm C (16 mg/kg IV; one 8-week cycle); Short Intense
- Cycle 1: QW

n = 41

Following until PD or end of study (4 years from LPFD)

Primary endpoints:
- CR
- % patients with PD or death per patient-year

As defined by 2014 IMWG criteria for SMM.

Daratumumab single agent shows activity in SMM
- Co-primary endpoint of median PFS $\geq 24$ months was met
- Co-primary endpoint of CR ($>15\%$) was not met

ORR, overall response rate; PR, partial response; VGPR, very good partial response; PFS, progression-free survival.
Extended daratumumab dosing prolongs biochemical/diagnostic PFS

There are these two approaches to early/smoldering disease:
  • Attempted “Cure”
  • Control

Which do you favor?
Frontline Options
First in the non-transplant setting
**ALCYONE Study Design**

**Key eligibility criteria:**
- Transplant-ineligible NDMM
- ECOG 0-2
- Creatinine clearance ≥40 mL/min
- No peripheral neuropathy grade ≥2

**Stratification factors**
- ISS (I vs II vs III)
- Region (EU vs other)
- Age (<75 vs ≥75 years)

**VMP × 9 cycles (n = 356)**
- Bortezomib: 1.3 mg/m² SC
  - Cycle 1: twice weekly
  - Cycles 2-9: once weekly
- Melphalan: 9 mg/m² PO on Days 1-4
- Prednisone: 60 mg/m² PO on Days 1-4
- Same VMP schedule

**D-VMP × 9 cycles (n = 350)**
- Daratumumab: 16 mg/kg IV
  - Cycle 1: once weekly
  - Cycles 2-9: every 3 weeks
- Cycles 1-9: 6-week cycles
- Cycles 10+: 4-week cycles

**D-Cycles 10+**
- 16 mg/kg IV
- Every 4 weeks: until PD

**Follow-up for PD and survival**

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- ORR
- ≥VGPR rate
- ≥CR rate
- MRD (NGS; 10⁻⁵)
- OS
- Safety

**Statistical analyses**
- 360 PFS events: 85% power for 8-month PFS improvement
- Interim analysis: ~216 PFS events

NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; EU, European Union; VMP, bortezomib/melphalan/prednisone; SC, subcutaneously; PO, orally; D, daratumumab; IV, intravenously; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; OS, overall survival.
Efficacy: PFS

50% reduction in the risk of progression or death in patients receiving D-VMP

PFS, progression-free survival; VMP, bortezomib/melphalan/prednisone; D, daratumumab; HR, hazard ratio; CI, confidence interval.

- Median (range) follow-up: 16.5 (0.1-28.1) months
- Consistent PFS treatment benefit across subgroups

Kaplan-Meier estimate.
Significantly higher ORR, ≥VGPR, and ≥CR with D-VMP
>3-fold higher MRD-negativity rate with D-VMP
Will Dara VMP be new standard of care?

OR

- Dara Rd
- Dara Vd
- Dara VRd (lite)
- Dara KRd
- Other
What about frontline in the transplant setting?
Importance of MRD sensitivity in IFM 2009 Trial VRd ± ASCT

**Graph:**
- **Positive MRD** vs. **Negative MRD**
- **Patients (%)** over time since MRD assessment
- **Time since MRD assessment:**
  - Positive MRD: > 10^{-6}
  - Negative MRD: < 10^{-6}
- **At risk:**
  - Positive MRD: 146
  - Negative MRD: 87

**Statistical Significance:**
- \( P < 0.001 \)

**Legend:**
- **Positive MRD**
- **Negative MRD**
Impact of treatment arm?

P < 0.001

Patients (%)

Time since MRD assessment

N at risk
positive MRD-Transplant 68
positive MRD-RVD 66
negative MRD_Transp 50
negative MRD_RVD 40

P < 0.001
Impact on OS

![Graph showing the impact on OS](image)

- MRD negative
- MRD positive

<table>
<thead>
<tr>
<th>Time since MRD assessment (months)</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
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<tbody>
<tr>
<td>Patients (%)</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>P-value</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
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</table>

No. at Risk
- MRD negative: 90, 90, 89, 85, 54, 8
- MRD positive: 276, 268, 255, 237, 142, 21
A Phase I/II Trial of Carfilzomib/ Lenalidomide/ Dexamethasone With Lenalidomide Extension in Patients With Newly Diagnosed Multiple Myeloma (n=53)

Overall CR rate (n=53) = 42% (sCR)
MRD by Flow: Most negative
Phase II trial of Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Newly Diagnosed Multiple Myeloma (n=45)

Overall CR rate 56%*
MRD by NGS negative in ~2/3 of CR

* VRd in IFM 2009: 48%
mSMART - Off-Study
Transplant Eligible

Standard-Risk: t(11;14), t(6;14), Trisomies
Intermediate-Risk: t(4;14)
High-Risk: Del 17p, t(14;16), t(14;20)

VRd

mSMART – Off-Study
Transplant Eligible

msmart.org

• Dara-KRd: safe and effective
Abstract #3110: Daratumumab (DARA) in Combination with Carfilzomib, Lenalidomide, and Dexamethasone (KRd) in Patients with Newly Diagnosed Multiple Myeloma (MMY1001): Updated Results from an Open-Label, Phase 1b Study

Figure. Best confirmed response rates with DARA+KRd

After 4 cycles (n = 21)
- ≥PR: 100%
- ≥VGPR: 71%
- ≥CR: 14%
- sCR: 14%

After 8 cycles* (n = 15)
- ≥PR: 100%
- ≥VGPR: 87%
- ≥CR: 27%
- sCR: 27%

Best Response (n = 21)
- ≥PR: 100%
- ≥VGPR: 91%
- ≥CR: 57%
- sCR: 43%

*5 patients who proceeded to ASCT before Cycle 8 and 1 patient who discontinued due to progressive disease at Cycle 7 were excluded.
How do you select frontline therapy in the ASCT setting?
Maintenance Recommendations
Abstract #904: Minimal Residual Disease in the Maintenance Setting in Myeloma: Prognostic Significance and Impact of Lenalidomide

Figure 1 (a). Impact of MRD result for patients with an informative sample at six months post maintenance randomisation. Progression-free survival is greatly superior in the MRD-negative patients (>50 months vs 20 months, p<0.0001, HR 0.2, 95% CI 0.11-0.37).
GEM2014MAIN: role of MRD in optimizing duration of maintenance

Protocol Example

GEM2014MAIN

2-years

Ixazomib-Rd

Rd

MRD monitoring

3-years

MRD monitoring

MRD+ 

Rd

MRD monitoring

MRD- 

No maintenance

MRD monitoring
Is maintenance “standard of care” now?

If so: with what?
Early Relapse Management
Abstract #743: Final Analysis from the Randomized Phase 3 Aspire Trial

A. Keith Stewart, MBChB, MBA1, David Siegel, MD, PhD2, Heinz Ludwig, MD3, Thierry Facon, MD4, Hartmut Goldschmidt, MD5, Andrzej J. Jakubowiak, MD6, Jesus F. San Miguel, MD7, Mihaela Obreja8, Julie Blaede8 and Meletios A. Dimopoulos9

Figure. OS KM Curve From the ITT

<table>
<thead>
<tr>
<th></th>
<th>KRd (N=396)</th>
<th>Rd (N=396)</th>
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<tbody>
<tr>
<td>Death, n (%)</td>
<td>246 (62.1%)</td>
<td>267 (67.4%)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>48.3</td>
<td>40.4</td>
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<tr>
<td>HR (KRd/Rd) (95% CI)</td>
<td>0.794 (0.667, 0.945)</td>
<td>0.0045</td>
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<tr>
<td>p-value (1-sided)</td>
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Medians were estimated using the Kaplan-Meier method. Hazard ratio and p-value were obtained from the stratified Cox regression and the stratified log-rank test, respectively.
Abstract #739: Updated Efficacy and Safety Analysis of Pollux

Meletios A. Dimopoulos1, Darrell J. White, MD2, Lofti Benboubker, MD3*, Gordon Cook, MD, PhD4*, Merav Leiba5*, James Morton5*, P. Joy Ho, MBBS, DPhil, FRACP, FRCPA, FTSc(RCPA)7*, Kihyun Kim8*, Naoki Takezako, MD, PhD9, Sonali Trivedi10, Kaida Wu10, Tineke Casnault11, Christopher Chiu10, Jordan Schecter12* and Philippe Moreau13*

Figure 1: (A) Progression-free survival and (B) overall response rate with DRd vs Rd

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Rd</th>
<th>246</th>
<th>249</th>
<th>266</th>
<th>186</th>
<th>146</th>
<th>86</th>
<th>23</th>
<th>2</th>
<th>0</th>
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<tbody>
<tr>
<td>HR</td>
<td>0.41</td>
<td>0.31</td>
<td>0.33</td>
<td>P &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NR</td>
<td>17.5 mo</td>
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DRd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; HR, hazard ratio; CI, confidence interval; NR, not reached; CR, complete response; VGPR, very good partial response; PR, partial response; sCR, stringent complete response.

*ITT population.

ASH 2017
How do you select therapy for early relapse (1-3 prior regimens)?

What are your “go to” options?
New Therapies
Venetoclax Monotherapy (N=66)

Venetoclax + Bortezomib/Dex

Moreau, P et al. ASH Abstract # 975, 2016.
Published Blood: 30: 2392-2400, November 30, 2017
Selective Inhibitor of Nuclear Export®
Phase II STORM Trial: Selinexor + Dex in R/R MM

Vogl, DT et al. ASH Abstract # 491, 2016.
Isatuximab (TCD14079): Anti-CD38 MoAb

Response Summary (IMWG Criteria): Evaluable Patients

Five patients with high-risk cytogenetics (del17p or t(4;14)): 1 attained VGPR, 1 PR, and 1 minimal response

Patients who were Len, PI, or IMiD and PI refractory had an ORR of 60%, 50%, and 47%, respectively

Data cut-off March 01, 2017. *Data represent dose escalation cohort (n=9) and expansion cohort (n=3) combined. CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response
Anti-BCMA CAR T cell therapy: abstract #740*

- Dose escalation; phase 1
- Refractory disease ≥ 3 prior therapies (3-14)
- Fludara/Cyclo “prep”
- 21 evaluable patients
- At > 50 x 10^6 bb2121 CAR T cells
  - ≥ CR = 56%
  - ≥ VGPR = 89%
- PFS: 71% at 9 months
- Cytokine release syndrome (CRS): 71%: 2 Gd3

*Berdeja: ASH 2017 et al (Bluebird/Celgene/NCI)
GSK 2857916: Anti-BCMA Mab/drug conjugate: abstract #741

- Humanized IgG1 anti-BCMA MoAb + auristatin-F
- Phase 1 study, Part 2 (expansion phase)
- 35 patients: ORR = 21/35 (60%)
- 6s CRs; 2 CR and 15 VGPR
<table>
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<tr>
<th>MAbs</th>
<th>Immuno-modulatory Agents</th>
<th>Proteasome Inhibitors</th>
<th>Cytotoxic CT</th>
<th>HDAC inhibitors</th>
<th>BCL2 inhibitor</th>
<th>Other</th>
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<tr>
<td>Daratumumab</td>
<td>Thalidomide</td>
<td>Bortezomib</td>
<td>Melphalan</td>
<td>Vorinostat</td>
<td>Venetoclax</td>
<td>Selinexor</td>
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<td>Atezolizumab</td>
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<td>Benda-mustine</td>
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Classes of Drugs With Anti-MM Activity
What do you feel are the most promising new therapies?