Where to go from Here and Future Trials?

Does our understanding of Pathogenesis, Disease management and Novel drugs get us closer to a cure of MM?

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Service des Maladies du Sang
University of Lille
Lille, France
Actions to achieve MM cure

- To better understand MM heterogeneity, to further define high-risk MM

- To improve clinical management; implement new tools for response assessment, investigate treatment of early MM and continuous therapy, improve the outcome of frail patients

- Is MM cure only an issue of new drugs? How many new drug families would be needed to achieve MM cure?
IFM new prognostic model

- del(17p), t(4;14), gain 1q, and β2M

We are seeing considerable improvements in the outcome of standard risk disease subsets

Currently minimal impact on “ultra high risk” subsets of disease

Avet-Loiseau H et al., JCO 2012
Clonal competition with alternating dominance in multiple myeloma

Jonathan J. Keats, Marta Chesi, Jan B. Egan, Victoria M. Garbitt, Stephen E. Palmer, Esteban Braggio, Scott Van Wier, Patrick R. Blackburn, Angela S. Baker, Angela Dispenzieri, Shaji Kumar, S. Vincent Rajkumar, John D. Carpten, Michael Barrett, Rafael Fonseca, A. Keith Stewart and P. Leif Bergsagel

Blood 2012;120:1067-1076
No Heterogeneity
All Myeloma cells are the same

Intraclonal Heterogeneity
Different MM clones sharing features

Interclonal Heterogeneity
Different MM clones NOT sharing features
Heterogeneity of MM
Clonal competition with alternating dominance in MM

JJ Keats et al. Blood 2012;120:1067-1076
Clonal competition with alternating dominance in MM
Potential clinical implications

Keats at al. Blood 2012;120:1067-1076

- **Combination therapies** targeting all coexisting subclones will probably be particularly important for high-risk MM

- **Retreatment** of pts with a regimen on which they have previously progressed is avoided. However, with intervening therapy a sensitive subclone may have re-emerged, and retreatment may be effective
Actions to achieve MM cure

• To better understand MM heterogeneity, to further define high-risk MM

• To improve clinical management; implement new tools for response assessment, investigate treatment of early MM and continuous therapy, improve the outcome of frail patients

• Is MM cure only an issue of new drugs? How many new drug families would be needed to achieve MM cure?
Getting to Minimal Residual Disease (MRD)

Disease burden

Newly diagnosed: $1 \times 10^{12}$

S.S. Patient

CR
Stringent CR

Molecular/Flow CR

Cure?: 0.0

Credit to Sagar Lonial
CR: The IFM experience

With the historical IFM 90: (VAD, Mel140+TBI 8gys)
50% of VGPR and 2% of MRD- were achieved

With the IFM 2008/2009: (VRDx3, Mel200, VRDx2, Rev 1y)
90% of VGPR and 70% of MRD- are achieved

With the ongoing IFM trials, we are trying to improve:
- Induction: CRD, MLN-RD
- High dose regimen: Vel-Mel
- Consolidation: CRD, MLN-RD
- Maintenance: short Rev, MLN, Anti CD38

Thus, 80 to 90% of MRD- can be expected and such a rate will be associated with Cure
**State of the art therapy should go along with state of the art response criteria**

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>2006</th>
<th>2011</th>
<th>2013</th>
<th>2014</th>
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<tbody>
<tr>
<td>Criteria</td>
<td>EBMT (Blade)</td>
<td>IMWG</td>
<td>IMWGv2</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Depth of response</td>
<td>CR</td>
<td>Stringent CR</td>
<td>Flow CR</td>
<td>Molecular CR</td>
<td>Flow CR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NGS CR PET/CT</td>
<td>NGS CR Imaging CR</td>
</tr>
</tbody>
</table>

Credit to Bruno Paiva
Comparison of technologies for MRD assessment

<table>
<thead>
<tr>
<th></th>
<th>Flow Cytometry</th>
<th>ASO PCR</th>
<th>Sequenta LymphoSIGHT™ Sequencing Method*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Universal reagents</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient specific</td>
<td>Assays validated for IGH-VDJ, IGH-DJ, IGK, TRB, TRD, TRG</td>
</tr>
<tr>
<td><strong>Analyte assayed</strong></td>
<td>Cells: Multiple cell surface markers</td>
<td>DNA: 1 clone per patient Not scalable to develop multiple assays per patient</td>
<td>DNA: 2–6 informative receptors each can have multiple clones Universal assay makes it easy to assay more than one receptor for internal control</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>Limited by background: &gt;10⁻⁴</td>
<td>Limited by background: &gt;10⁻⁵</td>
<td>Limited by cell number: &gt;10⁻⁴ Very low intrinsic background</td>
</tr>
<tr>
<td>(cancer cells per leukocyte)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evolution</strong></td>
<td>Cannot be measured</td>
<td>Cannot be measured and can lead to false negatives</td>
<td>Can be measured at diagnosis and during follow up Evolution algorithms developed</td>
</tr>
<tr>
<td><strong>Lab to lab variability</strong></td>
<td>Requires high degree of cross validation and training</td>
<td>Requires high degree of cross validation and training</td>
<td>Universal assay with digital output and low background</td>
</tr>
</tbody>
</table>

*The ClonoSIGHT test is based on the LymphoSIGHT sequencing method.
Prognostic relevance of 18F-FDG PET/CT in MM after ASCT

In multivariate analysis, both severe PET/CT involvement at diagnosis (SUV > 4.2 and/or EMD) and persistence of FDG uptake after ASCT were independent predictors of worst PFS and OS

Implications of MRI and PET scanning for survival of myeloma patients:
ASH 2011
Can we turn MM into CML? 
Can MM management become CML management?

- Immunophenotypic relapse anticipate clinical relapse
- There is a 9 months lag between molecular CR loss and need for salvage treatment
- Flow cytometry permits the detection of MRD preceding frank relapse
- A dynamic increase in molecular tumor burden detectable by RQ-PCR, predicts late disease relapses several months before clinical recurrence

*Should these patients be re-treated (e.g.: MoAb ± IMiD?)*

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Albert Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Eduardo Olavarría, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.
Figure A: Freedom from progression to symptomatic disease. The graph shows the percentage of patients remaining free from progression as a function of time, with separate curves for the treatment group and the observation group. The hazard ratio for progression is 0.18, with a p-value of less than 0.001. The number of patients at risk in each group at various time points is as follows:

- **Treatment group**: 57, 57, 48, 38, 20, 14, 0
- **Observation group**: 62, 49, 32, 21, 11, 3, 0

Figure B: Overall survival since study inclusion. The graph illustrates the percentage of patients surviving as a function of time, with separate curves for the treatment group and the observation group. The hazard ratio for death is 0.31, with a p-value of 0.03. The number of patients at risk in each group at various time points is as follows:

- **Treatment group**: 57, 57, 55, 48, 26, 17, 0
- **Observation group**: 62, 60, 57, 46, 27, 17, 0
Smoldering Multiple Myeloma

Stratification according to the risk of progression

- **Low risk**
  - Follow-up as MGUS

- **High risk**
  - Close follow-up
  - Candidates to clinical trials to better know the disease

- **Ultra high risk**
  - Treatment as symptomatic MM
Are all 'elderly' people alike?
IMWG consensus statement on the treatment of TNE NDMM patients

Newly diagnosed, symptomatic MM patients NOT eligible for high dose therapy (MEL200) and SCT

Assessment of patient status:
• Presence of comorbidities and/or limits in mental or mobility functions
• Specific index and scores can be used

Very fit

Fit

Unfit

Reduced-intensity ASCT (MEL 100)

MPT
MPV/VMPT-VT
VCD/VRD
MPR-R/Rd

Low-dose MPT/MPV Vd/Rd

MPR-R, melphalan, prednisone, lenalidomide followed by lenalidomide maintenance; MPT, melphalan, prednisone, thalidomide; MPV, bortezomib, melphalan, prednisone; Rd, lenalidomide, low-dose dexamethasone; Vd, bortezomib, low-dose dexamethasone; VMPT-VT, bortezomib, thalidomide, melphalan, prednisone, thalidomide followed by bortezomib plus thalidomide maintenance

Definition and Aims of Consolidation and Maintenance/continuous Therapy

Consolidation

- Increase depth of response (achieve MRD negativity ?)
  - By administration of therapy for limited period of time

Maintenance / Continuous

- Increase response duration, PFS, OS
  - By administration of treatment for a prolonged time period
  - In elderly patients the concept is continuous treatment (especially continuous lenalidomide)

OS, overall survival; PFS, progression-free survival
Consolidation improves response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before</th>
<th>After</th>
</tr>
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<tbody>
<tr>
<td>VTD¹</td>
<td>CR: 15%</td>
<td>49%</td>
</tr>
<tr>
<td>TD²</td>
<td>CR: 40%</td>
<td>47%</td>
</tr>
<tr>
<td>VTD²</td>
<td>CR: 49%</td>
<td>61%</td>
</tr>
<tr>
<td>V³</td>
<td>(n)CR: 20%</td>
<td>45%</td>
</tr>
<tr>
<td>VTD⁴</td>
<td>CR: 33%</td>
<td>52%</td>
</tr>
<tr>
<td>R⁵</td>
<td>≥VGPR: 58%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Before  after

CR: 15% → 49%
CR: 40% → 47%
CR: 49% → 61%
(n)CR: 20% → 45%
CR: 33% → 52%
≥VGPR: 58% → 69%

Courtesy of Dr Antonio Palumbo ASH educational session 2012 – updated in Vienna May 2013

OS: IFM, CALGB and GIMEMA trials

IFM 2005-02: OS from randomization (Nov 2013)  
(Duration of maintenance: 24 mos; follow-up 77 mos)

- LEN (n=307)  
  Median OS: 82 mos
- PBO (n=307)  
  Median OS: 81 mos

P = 0.80

PFS (mos)

CALGB 100104: updated OS (Jan 2013)  
(Median follow-up from ASCT 48 mos)

- LEN  
  Median OS: Not reached
- PBO  
  Median OS: 73 mos

HR = 0.61, P = 0.008

Time since AHCT (mos)

GIMEMA: OS  
(Median follow-up 35 mos)

- LEN  
  5-year OS: 75%
- PBO  
  5-year OS: 58%

HR = 0.62, P = 0.02

Overall survival (%)
**PFS: FIRST and MM-015 Trials**

**FIRST Trial: PFS**
(Median follow-up 37 mos)

- **Rd (n = 535)**: 25.5 mos
- **Rd18 (n = 541)**: 20.7 mos
- **MPT (n = 547)**: 21.2 mos

Hazard ratio:
- Rd vs. MPT: 0.72; \(P = 0.00006\)
- Rd vs. Rd18: 0.70; \(P = 0.00001\)
- Rd18 vs. MPT: 1.03; \(P = 0.70349\)

**MM-015: PFS**
(Median follow-up 30 mos)

- **MPR-R (n = 152)**: 31 mos
- **MPR (n = 153)**: 14 mos
- **MP (n = 154)**: 13 mos

Hazard ratio:
- MPR-R vs. MPR: 0.49; \(P < 0.001\)
- MPR-R vs. MP: 0.40; \(P < 0.001\)

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FIRST Trial: Overall Survival Interim Analysis

574 deaths (35% of ITT)

Patients (%)

Rd  (n= 535)  59.4%
Rd18  (n= 541)  55.7%
MPT  (n= 547)  51.4%

Overall survival (months)

Hazard ratio
Rd vs. MPT: 0.78; \( P = 0.0168 \)
Rd vs. Rd18: 0.90; \( P = 0.307 \)
Rd18 vs. MPT: 0.88; \( P = 0.184 \)

Newly Diagnosed Myeloma

**High Risk**
- VRd
  - Autologous stem cell transplant, if eligible
    - Bortezomib based therapy for minimum of 1 year

**Intermediate Risk**
- VCD (CyBorD)

**Standard Risk**
- Rd or CyBorD
  - Not in VGPR: Lenalidomide maintenance (2 years)
  - VGPR or better: No Maintenance

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• Is MM cure only an issue of new drugs? How many new drug families would be needed to achieve MM cure?
Adapted from Keith Stewart.

Single agent activity (>PR) 39 drugs in multiple myeloma
# Selected Novel Agents Currently Available and/or Under Investigation for RRMM

<table>
<thead>
<tr>
<th>Class</th>
<th>First generation</th>
<th>Next generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunomodulatory drugs</td>
<td>Lenalidomide (p.o.)</td>
<td>Pomalidomide (p.o.)</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>Bortezomib (i.v./s.c.)</td>
<td>Carfilzomib (i.v.)</td>
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<tr>
<td></td>
<td></td>
<td>Marizomib [NPI-0052] (i.v.)</td>
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<tr>
<td></td>
<td></td>
<td>Ixazomib [MLN9708] (p.o.)</td>
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<tr>
<td>Others including:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>Elotuzumab, Daratumumab</td>
<td></td>
</tr>
<tr>
<td>HDAC Inhibitors</td>
<td>Vorinostat, Panobinostat, Romidepsin, AC1215</td>
<td></td>
</tr>
<tr>
<td>Alkylating Agents</td>
<td>Bendamustine, others</td>
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New Proteasome Inhibitors
## RELAPSED AND REFRACTORY MM

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Details</th>
<th>Endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>003-A0 (N=46)</td>
<td>Phase 2</td>
<td>Relapsed from ≥ 2 prior therapies (must include prior Bort and Len or Thal); Refractory to last treatment</td>
<td>1&lt;sup&gt;o&lt;/sup&gt; Endpoint: ORR 2&lt;sup&gt;o&lt;/sup&gt; Endpoints: CBR, DOR, PFS, TTP, safety</td>
<td>Completed</td>
</tr>
<tr>
<td>003-A1 (N=266)</td>
<td>Phase 2</td>
<td>Amendment to 003-A0; 20/27 mg/m&lt;sup&gt;2&lt;/sup&gt; (step up dosing); TLS prophylaxis; Sample size increase to 266</td>
<td></td>
<td>Completed</td>
</tr>
<tr>
<td>005 (N=50)</td>
<td>Phase 2</td>
<td>15/20/27 mg/m&lt;sup&gt;2&lt;/sup&gt;; Relapsed or PD after ≥ 2 prior therapies (achieved ≥MR after ≥1 regimen); 1&lt;sup&gt;o&lt;/sup&gt; Endpoint: PK 2&lt;sup&gt;o&lt;/sup&gt; Endpoint: safety</td>
<td></td>
<td>Completed</td>
</tr>
<tr>
<td>FOCUS (011) (N=302)</td>
<td>Phase 3 CRF vs BSC</td>
<td>≥3 prior therapies; 1&lt;sup&gt;o&lt;/sup&gt; Endpoint: OS 2&lt;sup&gt;o&lt;/sup&gt; Endpoints: PFS, ORR, DCR, DOR, safety</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td>004 (N=164)</td>
<td>Phase 3</td>
<td>1–3 prior regimens, responded to 1&lt;sup&gt;st&lt;/sup&gt; line; BRZ naïve and tx 20 &amp; 20/27 mg/m&lt;sup&gt;2&lt;/sup&gt; 1&lt;sup&gt;o&lt;/sup&gt; Endpoint: ORR 2&lt;sup&gt;o&lt;/sup&gt; Endpoints: CBR, DOR, PFS, TTP, safety</td>
<td>Completed</td>
<td></td>
</tr>
<tr>
<td>006 (N=92)</td>
<td>Phase 1b CRd (6 dose cohorts plus expansion)</td>
<td>1–3 prior therapies; 1&lt;sup&gt;o&lt;/sup&gt; End-point: safety, MTD 2&lt;sup&gt;o&lt;/sup&gt; Endpoints: efficacy, PK</td>
<td>Completed</td>
<td></td>
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<tr>
<td>ASPIRE (009) (N=780)</td>
<td>Phase 3 CRd vs Rd</td>
<td>1–3 prior therapies 1&lt;sup&gt;o&lt;/sup&gt; End-point: PFS 2&lt;sup&gt;o&lt;/sup&gt; Endpoints: OS, ORR, DOR, DCR, TTP, safety, QoL</td>
<td>Completed accrual</td>
<td></td>
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Monoclonal Antibodies

Antibody Therapeutics in Cancer
Mark X. Sliwkowski and Ira Mellman
Science 13 September 2013: 1192-1198
<table>
<thead>
<tr>
<th>Target</th>
<th>mAb</th>
<th>Stage of development</th>
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<tbody>
<tr>
<td><strong>Surface molecules</strong></td>
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<td></td>
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<tr>
<td>CS1</td>
<td>Elotuzumab</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>CD38</td>
<td>Daratumumab, SAR650984, MOR202</td>
<td>Phase 1/2/3, Phase 1/2, Phase 1/2</td>
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<tr>
<td>CD74</td>
<td>Milatuzumab</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>CD40</td>
<td>Dacetuzumab</td>
<td>Phase 1</td>
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<tr>
<td>CD56</td>
<td>Lorvotuzumab mertansine</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CD138</td>
<td>BT062</td>
<td>Phase 1</td>
</tr>
<tr>
<td><strong>Signaling molecules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Siltuximab</td>
<td>Phase 3</td>
</tr>
<tr>
<td>RANKL</td>
<td>Denosumab</td>
<td>Phase 3</td>
</tr>
<tr>
<td>B cell activating factor</td>
<td>Tabalumab</td>
<td>Phase 2/3</td>
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<tr>
<td>(BAFF)</td>
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</tr>
<tr>
<td>VEGF</td>
<td>Bevacizumab, BHQ880</td>
<td>Phase 2, Phase 2</td>
</tr>
</tbody>
</table>

Richardson et al. et al. IMW 2013 (Abstract P-214), poster presentation
Plesner et al. ASH 2013 (Abstract 1987), poster presentation
Martin et al. ASH 2013 (Abstract 284), oral presentation
http://www.clinicaltrials.gov/ct2/show/NCT00421525
http://www.clinicaltrials.gov/ct2/show/NCT00079716
http://www.clinicaltrials.gov/ct2/show/NCT00346255
http://www.clinicaltrials.gov/ct2/show/NCT01001442
Wong et al. ASH 2013 (Abstract 505), oral presentation
Daratumumab single agent: Maximal Change in Paraprotein

- Data at baseline below limits for measurable disease
- Results are before database lock
Personalised Medicine/Targeted treatment of BRAF V600E

Proof of principle experiment

- Shrinkage of large subcutaneous plasmacytoma
- Rapidly decreased measurable M-spike and kappa light chain

Andrulis et al. Cancer Discovery 2013
Targets in MM plasma cells & agents in development

Approved agents

Agents in phase 3 trials

Ocio et al. Leukemia 2013 Nov 20 [Epub]
Never give up!

อย่ายอมแพ้!
Monoclonal antibody-based therapeutic targeting of myeloma

**Antibody-dependent Cellular cytotoxicity (ADCC)**

*Effector cells:*
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb®5592 (HM1.24)

**Complement-dependent Cytotoxicity (CDC)**

*Effector cells:*
- Daratumumab (CD38)

**Apoptosis/growth arrest via targeting signaling pathways**

- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

Tai & Anderson Bone Marrow Research, Volume 2011, Article ID 924058, 14 pages
**PFS and TTP: IFM, CALGB and GIMEMA trials**

**IFM 2005-02: PFS (Nov 2013)**
(Duration of maintenance: 24 mos; follow-up 77 mos)

- **Median PFS**
  - LEN (n=307) 46 mos
  - PBO (n=307) 24 mos

**CALGB 100104: TTP (Jan 2013)**
(Median follow-up from ASCT 48 mos)

- **Median TTP**
  - LEN 50 mos
  - PBO 27 mos

**GIMEMA: PFS**
(Median follow-up 35 mos)

- **Median PFS**
  - LEN 37 mos
  - PBO 26 mos

**References**
- McCarthy P, 14th International Myeloma Workshop 2013; abstract S15-5.
A small proportion of patients have already been cured

- **Allogeneic transplant**: First reports of cure, but still an investigational approach (mortality, age, donor)

- **Autologous stem cell transplant**: 5-10% MM patients remain in CR > 10 y “operationally cured”

- **Novel Drugs**: IMIDS & proteasome inhibitors
  - Refractory patients…….prolong survival
  - Up-front setting…………… survival twice than in 1990s

To consider MM a “truly curable disease” the fraction of patients in cCR should increase to 30-50%?
Analysis of total therapy trials according to high- and low-risk disease status

<table>
<thead>
<tr>
<th></th>
<th>High-risk MM</th>
<th>Low-risk MM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR duration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events / N</td>
<td>UARK 2003–33</td>
<td>UARK 2006–66</td>
</tr>
<tr>
<td>Estimate</td>
<td>13 / 23</td>
<td>8 / 21</td>
</tr>
<tr>
<td></td>
<td>61% (41.81)</td>
<td>66% (44.86)</td>
</tr>
<tr>
<td>Logrank P-value</td>
<td>.04</td>
<td>.72</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>OS</strong></td>
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<tr>
<td>Events / N</td>
<td>UARK 2003–33</td>
<td>UARK 2006–66</td>
</tr>
<tr>
<td>Estimate</td>
<td>14 / 149</td>
<td>5 / 79</td>
</tr>
<tr>
<td></td>
<td>94% (90.98)</td>
<td>92% (95.89)</td>
</tr>
<tr>
<td>Logrank P-value</td>
<td>.15</td>
<td>.95</td>
</tr>
</tbody>
</table>

Patients with low-risk disease derive greater benefit

GEM2000: Pattern of MRD by MFC in BM samples pre- and post-HDT/ASCT

Paiva B et al; Blood. 2008, 112: 4017-4023
FIRST Trial: Study Design

**Randomization 1:1:1**

**Screening**

- **Arm A**
  - Continuous Rd
  - LEN + Lo-DEX Continuously
    - LENALIDOMIDE 25mg D1-21/28
    - Lo-DEX 40mg D1,8,15 & 22/28

- **Arm B**
  - Rd18
  - LEN + Lo-DEX: 18 Cycles (72 wks)
    - LENALIDOMIDE 25mg D1-21/28
    - Lo-DEX 40mg D1,8,15 & 22/28

- **Arm C**
  - MPT
  - MEL + PRED + THAL 12 Cycles¹ (72 wks)
    - MELPHALAN 0.25mg/kg D1-4/42
    - PREDNISONE 2mg/kg D1-4/42
    - THALIDOMIDE 200mg D1-42/42

**Active Treatment + PFS Follow-up Phase**

- PD or Unacceptable Toxicity
- PD, OS and Subsequent anti-MM Tx

**LT Follow-Up**

- Screening LT Follow-Up

**Pts > 75 yrs:** Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL² (100 mg D1-42/42); MEL² 0.2 mg/kg D1-4

- Stratification: age, country and ISS stage

**ISS**, International Staging System; **LT**, long-term; **PD**, progressive disease; **OS**, overall survival


### Activity of MLN9708 in R/R MM (oral admin)

Dose escalation studies in R/R MM after ≥2 prior therapies, which must have included bortezomib, IMiDs, and corticosteroids*

<table>
<thead>
<tr>
<th></th>
<th>Weekly&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Twice-weekly&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>32</td>
<td>56 (26 dose esc. &amp; 30 dose exp)</td>
</tr>
<tr>
<td>Prev. bortezomib</td>
<td>97%</td>
<td>88%</td>
</tr>
<tr>
<td>Prev. NPI0052/CFZ</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>ORR ≥ PR</td>
<td>11% (1 VGPR, 1 PR, 8 SD)</td>
<td>13% (1 CR, 5 PR, 1 MR, 28 SD)</td>
</tr>
<tr>
<td>AEs</td>
<td>Fatigue (30% to 40%)</td>
<td>Thrombocytopenia (30% to 40%)</td>
</tr>
<tr>
<td></td>
<td>Nausea (30%)</td>
<td>Diarrhea (25%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting (20%)</td>
<td>Rash &amp; Neutropenia</td>
</tr>
<tr>
<td>PN</td>
<td>9% G1/2 all of them G1 at entry</td>
<td>11% G1/2 all of them G1 at entry</td>
</tr>
</tbody>
</table>

Gene Expression Profiling (GEP)

Prognostic significance of CNAs

IFM 15 gene-model

Amp(5q), Del(12p), Amp(1q)

Patients at risk
- low-risk: 188 174 152 90 28 1
- high-risk: 62 43 27 17 8 1

Hazard ratio = 6.77 (95% CI: 3.92-11.73) - logrank P < 0.001

0 risk factor (n=54)
1 risk factor (n=80)
2-3 risk factors (n=58)

Decaux et al., JCO 2008;
Avet-Loiseau et al., JCO 2009;27:4585-4590
Impact of post-ASCT PET-CT negativity on clinical outcomes

Complete FDG suppression at PET/CT after ASCT ……Longer PFS & OS

PET-CT is a reliable technique for predicting long-term outcomes

Zamagni et al. Blood 2011;118(23):5989-95
Frailty is stronger predictor of OS than ISS or FISH (GIMEMA)

Overall Survival

Multivariate Analysis

- Unfit vs Fit: HR = 1.24 (0.74, 2.08)
- Frail vs Fit: HR = 3.11 (1.97, 4.90)
- ISS 3 vs ISS 1-2: HR = 1.77 (1.23, 2.54)
- HR vs SR Fish: HR = 1.83 (1.26, 2.63)
- ECOG 2-3 vs 0-1: HR = 1.19 (0.81, 1.76)

Lower risk Death
- FIT
- ISS 1-2
- FISH neg

Higher risk Death
- FRAIL
- ISS 3
- FISH pos

Fit defined as: score=0  Unfit defined as: score=1  Frail defined as: score>2

* Fit defined as: score=0  Unfit defined as: score=1  Frail defined as: score=2

Smoldering Multiple Myeloma

- SMM definition should be revisited
- Risk stratification at diagnosis is mandatory
- High risk/ultra high risk SMM benefit from early treatment with Len-dex: benefit in TTP to active disease and also in OS
- Numerous clinical trials with several drugs are currently ongoing in this group of patients

These results support to change the current treatment paradigm for this patient population

Early treatment in Early MM patients
Continued Improvement in Survival Since the Introduction of Novel Agents

- 1,056 patients grouped into 2001–2005 and 2006–2010 cohorts
- Survival improved over time, particularly in patients aged > 65 years (p = 0.001)


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, years</td>
<td>4.6</td>
<td>NR</td>
<td>0.001</td>
</tr>
<tr>
<td>1-year survival, %</td>
<td>83</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>5-year estimated OS, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>48</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>&gt; 65 years</td>
<td>31</td>
<td>56</td>
<td>0.001</td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>63</td>
<td>73</td>
<td>NS</td>
</tr>
</tbody>
</table>
The definition of CR requires further improvements

- CR ……………….. Negative Immunofixation & < 5% PC in BM

- Stringent CR……Normal FLC & No clonal PC by immunohistochemistry (Low sensitivity <10⁻²)

- **Immunophenotypic** CR (by multiparametric flow) **Molecular** CR (by RT-PCR): (Sensitivity 10⁻⁴ - 10⁻⁶) *

- Outside BM ……..Imaging techniques (MRI & CT-PET)

* Pitfalls: 1. Pattern of BM infiltration in MM is not uniform... The possibility of residual MM-PC in another territory cannot be excluded (false negative results).

2. Extramedullary relapses.
Selected induction regimens and response in MM

<table>
<thead>
<tr>
<th>Induction regimen</th>
<th>Patients responding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAD</td>
<td>40</td>
</tr>
<tr>
<td>TAD</td>
<td>50</td>
</tr>
<tr>
<td>TD</td>
<td>60</td>
</tr>
<tr>
<td>VD</td>
<td>70</td>
</tr>
<tr>
<td>RD</td>
<td>80</td>
</tr>
<tr>
<td>Rd</td>
<td>90</td>
</tr>
<tr>
<td>PAD</td>
<td>100</td>
</tr>
<tr>
<td>VTD</td>
<td>100</td>
</tr>
<tr>
<td>CyVD</td>
<td>100</td>
</tr>
<tr>
<td>RVD</td>
<td>100</td>
</tr>
<tr>
<td>CarRD</td>
<td>100</td>
</tr>
<tr>
<td>CarCyD</td>
<td>100</td>
</tr>
<tr>
<td>IRD</td>
<td>100</td>
</tr>
<tr>
<td>CyVRD</td>
<td>100</td>
</tr>
</tbody>
</table>

Adapted, Stewart et al Blood 2009
Courtesy of Dr. P. McCarthy. ASH Educational 2013

Can we turn myeloma into CML?

- Immunophenotypic relapse anticipate clinical relapse \(^1\)
- There is a 9 months lag between molecular CR loss and need for salvage treatment \(^2\)
- Flow cytometry permits the detection of MRD preceding frank relapse \(^3\)
- A dynamic increase in molecular tumor burden detectable by RQ-PCR, predicts late disease relapses several months before clinical recurrence \(^4\)

**Should these patients be re-treated (e.g.: MoAb ± IMiD?)**

- 31 patients in CR + Flow CR after up-front treatment
  - MRD monitoring during f/up
  - MRD positive: 85% clinical relapse
  - Flow CR: 39% clinical relapse
  - \(P = .01\)

What would the most clinically optimal follow-up procedures be?

Induction → HDT/ASCT → Consolidation → Maintenance

Preventive treatment → F/up

Salvage treatment

Relapse

Pretreatment prognostic factors → MRD
Double vs single ASCT after bortezomib-based induction

PFS and OS in patients with 2 adverse variables (ISS3, high-risk CG, failure to achieve CR after induction)

<table>
<thead>
<tr>
<th></th>
<th>Double ASCT</th>
<th>Single ASCT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>41 months</td>
<td>20 months</td>
<td>0.003</td>
</tr>
<tr>
<td>OS</td>
<td>67 months</td>
<td>31.5 months</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

PFS and OS for pts with high-risk cytogenetics and who failed CR after bortezomib-based induction regimens

Cavo et al. ASH 2013 (Abstract 767), oral presentation
Actions to achieve MM cure

• To better understand MM heterogeneity, to further define high-risk MM

• To improve clinical management in both high-risk (implement new tools for response assessment, investigational drugs) and low-risk MM (avoid over treatment)

• Is MM cure only an issue of new drugs? How many new drug families would be needed to achieve MM cure?
## Complete Responses: are they all the same?

<table>
<thead>
<tr>
<th>Response Criteria</th>
<th>Tumor gene copy number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>25,000 - 500,000</td>
</tr>
<tr>
<td>PR</td>
<td>5,000 – 100,000</td>
</tr>
<tr>
<td>VGPR</td>
<td>1,500 – 20,000</td>
</tr>
<tr>
<td>Immunofixation-negative CR</td>
<td>1,000 – 10,000</td>
</tr>
<tr>
<td>Immunophenotypic CR*</td>
<td>10 – 100</td>
</tr>
<tr>
<td>Molecular CR^</td>
<td>5 – 20</td>
</tr>
</tbody>
</table>

QuiRedex: Study Design

- Multicenter, open-label, randomized phase III trial in high-risk SMM

### Induction
- 9 x 28-day cycles
  - **Lenalidomide** 25 mg/day on Days 1-21 +
  - **Dexamethasone** 20 mg/day on Days 1-4, 12-15

### Maintenance
- 28-day cycles
  - **Lenalidomide** 10 mg/day on Days 1-21
    - (Low-dose dexamethasone added at time of biologic progression)

Patients with high-risk smoldering MM (N = 125)

In both arms, blood counts, biochemical analysis (including creatinine and calcium) and serum/urine levels of MC were performed monthly. Skeletal survey was performed during the screening phase and thereafter only if clinical symptoms emerged.

Amendment in August 2011: Stop treatment after 2 years

Induction 6 cycles of CRd

ASCT (melphalan 200)

Consolidation (2 cycles of CRd) (6 cycles of EloRd)

Maintenance (Len-dex+Elotuzumab)

Primary objective: To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

Hypothesis: At least 50% of patients will achieve the objective
VTD Consolidation: Long-Term Follow-Up

- Impact of MRD detection by RQ-PCR on late recurrences and OS
- Median follow-up: 65 months; n = 39

**Probability of PFS**
- SMR: Standard molecular remission (MRD negativity on two consecutive samples by RQ-PCR)
- No patient with full molecular remission or SMR has died
- Dynamic increase in molecular tumor burden predicts late disease relapses before clinical recurrence

**Probability of OS**
- 5-year OS 100% vs 74%, \( P = .012 \)

Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma

Michel Attal, M.D., Valerie Lauwers-Cances, M.D., Gerald Marit, M.D., Denis Caillot, M.D., Philippe Moreau, M.D., Thierry Facon, M.D., Anne Marie Stoppa, M.D., Cyrille Hulin, M.D., Lofti Benboubker, M.D., Laurent Garderet, M.D., Olivier Decaux, M.D., Serge Leyvraz, M.D., Marie-Christiane Vekemans, M.D., Laurent Voillat, M.D., Mauricette Michallet, M.D., Brigitte Pegourie, M.D., Charles Dumontet, M.D., Murielle Roussel, M.D., Xavier Leleu, M.D., Claire Mathiot, M.D., Catherine Payen, M.D., Hervé Avet-Loiseau, M.D., and Jean-Luc Harousseau, M.D., for the IFM Investigators

Figure 1. Kaplan–Meier Curves for Progression-free Survival and Overall Survival in the Intention-to-Treat Population, According to Study Group, at Study Unblinding (July 2010).

Panel A shows progression-free survival, with median rates of 41 months in the lenalidomide group as compared with 23 months in the placebo group (hazard ratio, 0.50; P < 0.001). Panel B shows overall survival. At 3 years after randomization, overall survival was similar in the two groups (hazard ratio, 1.25; P = 0.29).
Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma

Philip L. McCarthy, M.D., Kouros Owzar, Ph.D., Craig C. Hofmeister, M.D.,
David D. Hurd, M.D., Hani Hassoun, M.D., Paul G. Richardson, M.D.,
Sergio Giralt, M.D., Edward A. Stadtmauer, M.D., Daniel J. Weisdorf, M.D.,
Ravi Vij, M.D., Jan S. Moreb, M.D., Natalie Scott Callander, M.D.,
Koen Van Besien, M.D., Teresa Gentile, M.D., Ph.D., Luis Isola, M.D.,
Richard T. Maziarz, M.D., Don A. Gabriel, M.D., Ph.D., Asad Bashey, M.D., Ph.D.,
Heather Landau, M.D., Thomas Martin, M.D., Muzaffar H. Qazilbash, M.D.,
Denise Levitan, M.D., Brian McClune, M.D., Robert Schlossman, M.D.,
Vera Hars, M.S., John Postiglione, B.A., Chen Jiang, Ph.D., Elizabeth Bennett, B.H.E.,
Susan Barry, B.A., Linda Bressler, Pharm.D., Michael Kelly, M.A., Michele Seiler, M.S.,
Cara Rosenbaum, M.D., Parameswaran Hari, M.D., Marcelo C. Pasquini, M.D.,
Mary M. Horowitz, M.D., Thomas C. Shea, M.D., Steven M. Devine, M.D.,
Kenneth C. Anderson, M.D., and Charles Linker, M.D.

Figure 1. Kaplan-Meier Estimates of Progression-free and Overall Survival. HSCT denotes hematopoietic stem-cell transplantation.
Achievement of plateau with alloSCT

**EFS**

- Autograft–allograft group
- Double-autologous-transplant group

**OS**

- Autograft–allograft group
- Double-autologous-transplant group

*But: due to high treatment-related morbidity and mortality use outside clinical trials not recommended*

IFM 2009/DFCI trial

VRD × 3

SC collection

VRD × 5

Lenalidomide 1yr

(HDM + ASCT at relapse)

MEL200 + ASCT

VRD × 2

Lenalidomide 1yr

DFCI = Dana Farber Cancer Institute. ClinicalTrials.gov: NCT01208662.
Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma

Antonio Palumbo, M.D., Roman Hajek, M.D., Ph.D., Michel Delforge, M.D., Ph.D., Martin Kropff, M.D., Maria Teresa Petrucci, M.D., John Catalano, M.B., B.S., Heinz Gisslinger, M.D., Wiesław Wiktor-Jędrzejczak, M.D., Ph.D., Mamia Zodelava, M.D., Ph.D., Katja Weisel, M.D., Nicola Cascavilla, M.D., Genadi Iosava, M.D., Michele Cavo, M.D., Janusz Kloczko, M.D., Ph.D., Joan Bladé, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Ph.D., Torben Plesner, M.D., Joergen Radke, M.D., Christian Langer, M.D., Dina Ben Yehuda, M.D., Alessandro Corso, M.D., Lindsay Herbein, B.S., Zhinuan Yu, Ph.D., Jay Mei, M.D., Ph.D., Christian Jacques, M.D., and Meletios A. Dimopoulos, M.D., for the MM-015 Investigators*
Figure 2. Survival Outcomes in the Intention-to-Treat Population.

Panel A shows the Kaplan–Meier estimates of median progression-free survival (MPR-R group, 31 months; MPR group, 14 months; and MP group, 13 months). Panel B shows the effect of maintenance therapy on progression-free survival from the start of maintenance in patients who had received MPR induction therapy (landmark analysis; median progression-free survival from maintenance initiation, 26 months in the MPR-R group and 7 months in the MPR group). Panel C shows the median overall survival among all patients (MPR-R group, 45.2 months; MPR group, not reached; and MP group, not reached).
Achievement of plateau with Total Therapy 3 in patients with GEP-defined low-risk disease

High 4-yr CR duration of 89% consistent with a cure estimate of 55%

EFS

OS

Other variables to keep in mind…

<table>
<thead>
<tr>
<th></th>
<th>Multidimensional (≥8-color) FC</th>
<th>Molecular ASO-PCR</th>
<th>High-throughput sequencing</th>
<th>PET-CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time</strong></td>
<td>2-hours</td>
<td>5 days</td>
<td>7 days</td>
<td>2-hours</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>High</td>
<td>Intermediate</td>
<td>?</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>~150 euros</td>
<td>~450 euros</td>
<td>??</td>
<td>High</td>
</tr>
<tr>
<td><strong>Standardization</strong></td>
<td>In process (EuroFlow)</td>
<td>Yes (Biomed)</td>
<td>Yes (Sequenta)?</td>
<td>?</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>$10^{-5}$</td>
<td>$10^{-5} - 10^{-6}$</td>
<td>$10^{-6}$</td>
<td>High (?)</td>
</tr>
</tbody>
</table>
### Lenalidomide as the backbone of therapy in elderly patients

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Combinations and Phases</th>
</tr>
</thead>
</table>
| **Proteasome inhibitors** | • Rd + **carfilzomib** in RRMM, phase 3 (US/EU), phase 1/2 (US)  
• Rd + **MLN9708** in RRMM: phase 3 (USA, Canada, EU)  
• Rd + **MLN9708** in NDMM: phase 3 (USA, Canada, France, Belgium, Japan) |
| **HDAC inhibitors** | • Rd + **vorinostat** in RRMM: multiple phase 1/2 (US, EU), 1 phase 3 (USA)  
• Rd + **panobinostat** in RRMM: 2 phase1/2 (USA, Australia, EU)  
• Rd + **ACY-1215** in RRMM: phase 1 (USA) |
| **Monoclonal antibodies** | • Rd + **elotuzumab** in RRMM: multiple phase 1/2 (EU, USA, Japan), 1 phase 3 (ELOQUENT-2)  
• Rd + **elotuzumab** in NDMM: phase 3 (ELOQUENT-1)  
• Rd + **daratumumab** in RRMM: 2 phase 1/2 (USA, Canada, EU)  
• Rd + **SAR650984** in RRMM: phase 1 (USA)  
• Rd + **IPH2101** in RRMM: phase 1 (USA) |