Unmet Medical Needs and Latest Multiple Myeloma Treatment

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Disclaimer

- These slides contain data for ixazomib which has not been approved in Taiwan. The information is intended as a source of discussion or presentation at scientific meetings only.

- Currently ixazomib indication had been approved in US for the following:

  Ixazomib is a proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Treatment Goals

• Young Patients (<65 years)
  – Best OS outcome with possibility of cure
  – MRD negative and maintained
  – Is this needed for all patients?

• Old Patients (>70 years)
  – Maximize OS with good quality of life

[Caveat: Cost to achieve these aims]
Treatment of Transplant Eligible NDMM
Phases of Treatment

1. Induction
2. Stem cell Transplant
3. Consolidation
4. Maintenance
Phases of Treatment

- **Induction**
- **Stem cell Transplant**
- **Consolidation**
- **Maintenance**

**Objective**
- Rapid and Deep Response
- Able to harvest
- Minimal toxicity
Significant improvement in post-induction CR/nCR and VGPR rates with bortezomib-based induction regimens

*significant difference between arms

1Harousseau et al. J Clin Oncol 2010; 28(30): 4621-4629
2Einsle et al. Blood 2009; 114(22); Abstract 131 (oral presentation)
3Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)
4Cavo et al. Lancet 2010; 376(9758): 2075-2085
5Rosinol et al. Blood 2010; 116(21); Abstract 307 (oral presentation)
**EVOLUTION Trial: RVdC, RVd, and CyBorD in NDMM**

**Induction 8, 3-week cycles**

- **RVdC (n = 48)**
  - LEN: 15 mg PO; D 1-14
  - BORT: 1.3 mg/m² IV; D 1, 4, 8, 11
  - DEX: 40 mg PO; D 1, 8, 15
  - Cy: 500 mg/m² PO<sup>a</sup>; D 1, 8

- **RVd (n = 42)**
  - LEN: 25 mg PO; D 1-14
  - BORT: 1.3 mg/m² IV; D 1, 4, 8, 11
  - DEX: 40 mg PO; D 1, 8, 15

- **CyBorD (n = 33)**
  - BORT: 1.3 mg/m² IV; D 1, 4, 8, 11
  - DEX: 40 mg PO; D 1, 8, 15
  - Cy: 500 mg/m² PO<sup>a</sup>; D 1, 8

- **CyBorD-mod (n = 17)**
  - BORT: 1.3 mg/m² IV; D 1, 4, 8, 11
  - DEX: 40 mg PO; D 1, 8, 15
  - Cy: 500 mg/m² PO<sup>a</sup>; D 1, 8, 15

**Maintenance 4, 6-week cycles**

- **BORT**
  - 1.3 mg/m² IV; D 1, 8, 15, 22

**Pts could undergo stem cell mobilization and transplant after 2 and 4 induction cycles, respectively**

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<sup>a</sup> Given as a single dose, rounded to the nearest 50 mg.

BORT, bortezomib; CR, complete response; Cy, cyclophosphamide; CyBorD, cyclophosphamide, bortezomib, dexamethasone; CyBorD-mod, cyclophosphamide, bortezomib, dexamethasone with modified cyclophosphamide dosing; DEX, dexamethasone; DOR, duration of response; IV, intravenous; LEN, lenalidomide; LMWH, low molecular weight heparin; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; pt, patient; Rand, randomized; RVd, lenalidomide, bortezomib, and dexamethasone; RVdC, lenalidomide, bortezomib, dexamethasone, and cyclophosphamide; TTP, time to progression; TTR, time to response; VGPR, very good partial response.

## EVOLUTION Trial: Response

<table>
<thead>
<tr>
<th></th>
<th>RVdC (n = 48)</th>
<th>RVd (n = 42)</th>
<th>CyBorD (n = 33)</th>
<th>CyBorD-mod (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient experience on study</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Median follow-up, mos</td>
<td>20</td>
<td>20</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Median cycles, n (range)</td>
<td>5 (1-12)</td>
<td>6 (1-12)</td>
<td>6 (3-12)</td>
<td>6 (3-12)</td>
</tr>
<tr>
<td><strong>Best response across all cycles, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>35 (88)</td>
<td>35 (85)</td>
<td>24 (75)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>CR</td>
<td>10 (25)</td>
<td>10 (24)</td>
<td>7 (22)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>sCR</td>
<td>6 (15)</td>
<td>7 (17)</td>
<td>3 (9)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>23 (58)</td>
<td>21 (51)</td>
<td>13 (41)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Progression</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Best response across all cycles among patients ≤ 65 yrs, n/n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>6/28 (21)</td>
<td>6/28 (21)</td>
<td>2/21 (10)</td>
<td>7/12 (58)</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>15/28 (54)</td>
<td>17/28 (61)</td>
<td>5/21 (24)</td>
<td>8/12 (67)</td>
</tr>
<tr>
<td>ORR (≥ PR)</td>
<td>24/28 (86)</td>
<td>26/28 (93)</td>
<td>14/21 (67)</td>
<td>12/12 (100)</td>
</tr>
</tbody>
</table>

CR, complete response; CyBorD, cyclophosphamide, bortezomib, dexamethasone; CyBorD-mod, cyclophosphamide, bortezomib, dexamethasone with modified cyclophosphamide dosing; ORR, overall response rate; PR, partial response; RVd, lenalidomide, bortezomib, and dexamethasone; RVdC, lenalidomide, bortezomib, dexamethasone, and cyclophosphamide; sCR, stringent complete response; VGPR, very good partial response.

<table>
<thead>
<tr>
<th></th>
<th>RVdC (n = 48)</th>
<th>RVd (n = 42)</th>
<th>CyBorD (n = 33)</th>
<th>CyBorD-mod (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21 (44)</td>
<td>4 (10)</td>
<td>10 (30)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>2 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (15)</td>
<td>5 (12)</td>
<td>4 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (13)</td>
<td>0</td>
<td>3 (9)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (8)</td>
<td>3 (7)</td>
<td>0</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>4 (12)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nonhematologic, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (4)</td>
<td>2 (5)</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>6 (13)</td>
<td>7 (17)</td>
<td>3 (9)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (17)</td>
<td>3 (7)</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CyBorD, cyclophosphamide, bortezomib, dexamethasone; CyBorD-mod, cyclophosphamide, bortezomib, dexamethasone with modified cyclophosphamide dosing; RVd, lenalidomide, bortezomib, and dexamethasone; RVdC, lenalidomide, bortezomib, dexamethasone, and cyclophosphamide.
IFM 2013-04: Phase 3 Trial of CyBorD vs VTD
Study Design

• Transplant-eligible patients with NDMM aged < 66 years
  – Multicenter, prospective, randomized phase 3 trial of induction Tx prior to ASCT

• 170 patients randomized to four 21-day cycles of CyBorD
  – BORT 1.3 mg/m²/d SC days 1, 4, 8 and 11
  – DEX 40 mg/d PO days 1-4 and 9-12
  – Cy 500 mg/m²/d PO days 1, 8, 15

• 170 patients randomized to four 21-day cycles of VTD
  – BORT 1.3 mg/m²/d SC days 1, 4, 8 and 11
  – DEX 40 mg/d PO days 1-4 and 9-12
  – THAL 100 mg/d PO days 1-21

ASCT, autologous stem cell transplant; BORT, bortezomib; Cy, cyclophosphamide; CyBorD, cyclophosphamide, bortezomib, dexamethasone; DEX, dexamethasone; NDMM, newly diagnosed multiple myeloma; PO, by mouth; SC, subcutaneous; THAL, thalidomide; Tx, therapy; VTD, bortezomib, thalidomide, dexamethasone.
IFM 2013-04: Phase 3 Trial of CyBorD vs VTD Results and Authors’ Conclusions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CyBorD (n = 169)</th>
<th>VTD (n = 169)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ CR, %</td>
<td>8.9</td>
<td>13.0</td>
<td>.22</td>
</tr>
<tr>
<td>≥ VGPR, %</td>
<td>56.2</td>
<td>66.3</td>
<td>.05</td>
</tr>
<tr>
<td>≥ PR, %</td>
<td>83.4</td>
<td>92.3</td>
<td>.01</td>
</tr>
<tr>
<td>CD34+ stem cell harvest, 10^6/kg(^b)</td>
<td>9.17</td>
<td>10.68</td>
<td>.05</td>
</tr>
<tr>
<td>Grade 3/4 adverse events, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>33.1</td>
<td>18.9</td>
<td>.003</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10.6</td>
<td>4.7</td>
<td>.04</td>
</tr>
<tr>
<td>Anemia</td>
<td>9.5</td>
<td>4.1</td>
<td>.05</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2.9</td>
<td>7.7</td>
<td>.05</td>
</tr>
</tbody>
</table>

- Patients achieved higher rates of VGPR and PR, greater harvest of stem cells, and less hematologic toxicity with VTD vs CyBorD
  - Supports preferential use of VTD prior to ASCT

\(^a\) Intent-to-treat population.

\(^b\) CyBorD, n = 154; VTD, n = 157.

ASCT, autologous stem cell transplant; CR, complete response; CyBorD, cyclophosphamide, bortezomib, dexamethasone; PR, partial response; SC, subcutaneous; VGPR, very good partial response; VTD, bortezomib, thalidomide, dexamethasone.

Phases of Treatment

- Induction
- Stem cell Transplant
- Consolidation
- Maintenance

**Objective**
- Increase CR rates
Is ASCT still needed in Era of Novel Agents
Significant improvement in post-induction and post-transplant CR/nCR and VGPR rates with bortezomib-based induction regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>post-induction</th>
<th>post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>VD IFM 2005-01</td>
<td>38%</td>
<td>15%</td>
</tr>
<tr>
<td>PAD HOVON/GMMG</td>
<td>42%</td>
<td>35%</td>
</tr>
<tr>
<td>VTD GIMEMA</td>
<td>61%</td>
<td>62%</td>
</tr>
<tr>
<td>VTD PETHEMA/GEM</td>
<td>60%</td>
<td>65%</td>
</tr>
<tr>
<td>vTDS IFM 2007-02</td>
<td>73%</td>
<td>51%</td>
</tr>
</tbody>
</table>

1Harousseau et al. J Clin Oncol 2010; 28(30): 4621-4629
2Sonneveld et al. Blood 2010; 116(21); Abstract 40 (oral presentation)
3Cavo et al. Lancet 2010; 376(9758): 2075-2085
4Rosinol et al. Blood 2010; 116(21); Abstract 307 (oral presentation)
Phase 3: MPR versus tandem ASCT

**Induction**
- n=402
  - Rd (four 28-d cycles)
  - Lenalidomide 25 mg/d, d1-21
  - Low-dose dex 40mg/d, d 1,8,15,22

**Consolidation**
- n=202
  - MPR (six 28-d cycles)
    - Melphalan 0.18 mg/kg/d, d 1-4
    - Prednisone 2 mg/kg/d, d 1-4
    - Len 10 mg/d, d 1-21

**Primary end point: PFS**

**Maintenance**
- No maintenance
- Maintenance
  - Len 10 mg/d, d 1-21
  - 28-d course until relapse

*Palumbo et al. ASH 2011 (Abstract 3069), poster presentation*
# Phase 3 study: MPR versus tandem ASCT

Median follow up 26 months

<table>
<thead>
<tr>
<th></th>
<th>MPR (n=202)</th>
<th>MEL 200 (n=200)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>20%</td>
<td>25%</td>
<td>0.49</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>60%</td>
<td>58%</td>
<td>0.24</td>
</tr>
<tr>
<td>2-year PFS</td>
<td>54%</td>
<td>73%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-year OS</td>
<td>87%</td>
<td>90%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Palumbo et al. ASH 2011 (Abstract 3069), poster presentation*
IFM 2009: Phase 3 Trial of RVd ± ASCT
Study Design

**INDUCTION + CONSOLIDATION**

- **RVd + ASCT**
  - BORT 1.3 mg/m² D1, 4, 8, 11
  - LEN 25 mg PO D1-14
  - DEX 20 mg PO D1, 2, 4, 5, 8, 9, 11, 12
  - 3 × 21-day cycles
  - SC collection with CYC + G-CSF
  - MEL 200 mg/m² + ASCT
  - RVd for 2 × 21-day cycles

- **RVd, no ASCT**
  - BORT 1.3 mg/m² D1, 4, 8, 11
  - LEN 25 mg PO D1-14
  - DEX 40 mg PO D1, 2, 4, 5, 8, 9, 11, 12
  - 3 × 21-day cycles
  - SC collection with CYC + G-CSF
  - RVd for 5 × 21-day cycles

**ENDPOINTS**
- Primary: PFS
- Secondary: ORR, TTP, safety, GEP prognostic groups

**MAINTENANCE**

- **LEN**
  - LEN 10 mg PO D1-28
  - If tolerated for 3 months, dose increase to 15 mg is permitted
  - 12 × 28-day cycles

**FOLLOW-UP**

- Up to 4 years
- ASCT at relapse in non-ASCT arm

**Stratification:**
- ISS stage
- Cytogenetic risk

**NDMM 18-65 yrs N = 700**

IFM 2009: Phase 3 Trial of RVd ± ASCT

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>RVd + ASCT (n = 350)</th>
<th>RVd, no ASCT (n = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr PFS, %</td>
<td>61</td>
<td>48</td>
</tr>
<tr>
<td>HR 1.5 (95% CI, 1.2-1.9)</td>
<td>Stratified log-rank $P &lt; .0002$</td>
<td></td>
</tr>
<tr>
<td>3-yr OS, %</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>CR, %</td>
<td>58</td>
<td>46</td>
</tr>
<tr>
<td>$P &lt; 0.01$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPM, n (%)</td>
<td>23 (6.6)</td>
<td>18 (5.1)</td>
</tr>
</tbody>
</table>

- PFS benefit of ASCT was consistent across subgroups including age ($\leq$ or $> 60$ yrs), sex, Ig isotype (IgG or others), ISS stage (I or II or III), cytogenetics (standard or high risk), and response after 3 cycles of RVd (CR or not)

ASCT, autologous stem cell transplant; CR, complete response; HR, hazard ratio; IFM, Intergroupe Francophone du Myelome; Ig, immunoglobulin; ISS, International Staging System; OS, overall survival; PFS, progression-free survival; RVd, lenalidomide, bortezomib, and low-dose dexamethasone; SPM, second primary malignancy.

Phases of Treatment

- Induction
- Stem cell Transplant
- Consolidation
- Maintenance

Objective
- Increase MRD negative rates
MRD Flow Cytometry Helps Predict Outcomes Post Transplant

Progression-Free Survival

- MRD+ not CR
- MRD+ CR
- MRD- not CR
- MRD- CR

$X^2_3 = 27.4757$
$P < .001$

Overall Survival

- MRD+ not CR
- MRD+ CR
- MRD- not CR
- MRD- CR

$X^2_3 = 8.3932$
$P = .0385$

International Myeloma Foundation is leading a multi-center, standardization effort.

MRD by High-Throughput Sequencing Predicts Prognosis in Patients With CR

- Quantitative; with amplification and sequencing of immunoglobulin gene segments using consensus primers for: immunoglobulin heavy-chain locus complete (IGH-VDJH), IGH incomplete (IGH-DJH), and immunoglobulin κ locus (IGK)

![Graph showing TTP (CR Patients) with MRD negative and MRD positive thresholds.](image)

- MRD stratifies the CR population into 2 groups with strikingly different prognosis

How to deepen response - Consolidation

- 2\textsuperscript{nd} Mel 200 ASCT
- 2-4 cycles of consolidation treatment

Ladetto M et al. JCO 2010; 28: 2077-2084
Achieving molecular remission with VTD consolidation following transplant (GIMEMA study)

- n=66 with ≥nCR after ASCT, treated with 2 cycles VTD or TD

<table>
<thead>
<tr>
<th>Efficacy (n=66)</th>
<th>VTD</th>
<th>TD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-consolidation (day 0) PCR negativity</td>
<td>39%</td>
<td>31%</td>
<td>0.062</td>
</tr>
<tr>
<td>Post-consolidation (day +70) PCR negativity</td>
<td>64%</td>
<td>48%</td>
<td>0.007</td>
</tr>
<tr>
<td>Reduction in tumor burden post-consolidation (day +70) (real-time quantitative PCR)</td>
<td>Median 5 log reduction</td>
<td>Median 1 log reduction</td>
<td>0.05</td>
</tr>
</tbody>
</table>

VTD consolidation significantly reduced tumor burden compared to TD as detected by PCR

Terragna et al. Blood 2010; 116(21); Abstract 861 (oral presentation)
Phases of Treatment

**Induction**

**Stem cell Transplant**

**Consolidation**

**Maintenance**

**Objective**
- Maintain deepest response
- Increase OS
- Tolerable with good QoL
## Phase 3 Studies of Thalidomide Maintenance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Details</th>
<th>PFS/OS Increase</th>
<th>Survival post-relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thal/PAM vs PAM vs None&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- 2X +</td>
<td>+ / +</td>
<td>Similar</td>
</tr>
<tr>
<td>Thal/Pred vs Pred&lt;sup&gt;2&lt;/sup&gt;</td>
<td>- 1X +</td>
<td>+ / +</td>
<td>Similar</td>
</tr>
<tr>
<td>Thal vs No Thal&lt;sup&gt;3-5&lt;/sup&gt;</td>
<td>+ 2X +</td>
<td>+ / +</td>
<td>↓ post-Thal</td>
</tr>
<tr>
<td>Thal vs IFN&lt;sup&gt;6&lt;/sup&gt;</td>
<td>+ 1X/2X +</td>
<td>+ / -</td>
<td>↓ post-Thal</td>
</tr>
<tr>
<td>Thal vs None&lt;sup&gt;7&lt;/sup&gt;</td>
<td>+ 1X +</td>
<td>+ / -</td>
<td>↓ post-Thal</td>
</tr>
<tr>
<td>Thal/Pred vs None&lt;sup&gt;8&lt;/sup&gt;</td>
<td>+ 1X +</td>
<td>+ / -</td>
<td>↓ post-Thal</td>
</tr>
</tbody>
</table>

PAM = pamidronate; PD = progressive disease.; Pred = prednisone; Thal = thalidomide.

LEN Maintenance After ASCT in MM: OS Analysis

Studies Included in the Meta-Analysis

**CALGB 100104**

- INDUCTION ASCT
- 1:1 RANDOMIZATION “NO EVIDENCE OF PD”

**IFM 2005-02**

- INDUCTION ASCT
- 1:1 RANDOMIZATION “NO EVIDENCE OF PD”

**GIMEMA (RV-MM-PI-209)**

- 2 × 2 DESIGN
- LEN + DEX × 4 INDUCTION

- ASCT
- MPR: 6 COURSES

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**PLACEBO**
(n = 229)


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**LEN MNTC**
(n = 231)

- Dec 2009
- INTERIM ANALYSIS AND UNBLINDING
- CONTINUED TX
- NO CROSSOVER BEFORE PD ALLOWED
- CROSSED OVER BEFORE PD ALLOWED
- CONTINUED TX

**LENO MNTC**
(n = 307)

- Jan 2010
- CONTINUOUS TX
- NO TX

**LENO MNTC**
(n = 67)

- NO TX

**LENO MNTC**

- CONTINUED TX

**Target population of patients with NDMM who received LEN maintenance or placebo/no maintenance after ASCT**

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Starting dose of 10 mg/day on days 1-28/28 was increased to 15 mg/day if tolerated and continued until PD. Patients received 10 mg/day on days 1-21/28 until PD.

ASCT, autologous stem cell transplant; DEX, dexamethasone; LEN, lenalidomide; MM, multiple myeloma; MNTC, maintenance; MPR, melphalan, prednisone, and lenalidomide; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PD, progressive disease; Tx, treatment.

LEN Maintenance After ASCT in MM: OS Analysis

OS

- 26% reduction in risk of death, with an estimated 2.5-year increase in median survival

<table>
<thead>
<tr>
<th></th>
<th>LEN (NE-NE)</th>
<th>CTL (79.8-96.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, (95% CI), mos</td>
<td>NE</td>
<td>86.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.74 (0.62 - 0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td>P value</td>
<td>.001</td>
<td></td>
</tr>
</tbody>
</table>

Median for LEN treatment arm was extrapolated to be 116 months based on median of the CTL arm and HR (median, 86 months; HR = 0.74).

ASCT, autologous stem cell transplant; CTL, control; HR, hazard ratio; LEN, lenalidomide; MM, multiple myeloma; NE, not estimable; OS, overall survival; pt, patient.

LEN Maintenance After ASCT in MM: OS Analysis

Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LEN</th>
<th>CTL</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt; 60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS stage (I or II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS stage (III)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR after ASCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/VGPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR/SD/PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior induction therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-LEN</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Adverse-risk cytogenetics
  (Yes)                                 |     |     |                      |
| Adverse-risk cytogenetics
  (No)                                  |     |     |                      |
| CrCl post ASCT (< 50 mL/min)            |     |     |                      |
| CrCl post ASCT (≥ 50 mL/min)            |     |     |                      |

---


---

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>LEN</th>
<th>CTL</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt; 60)</td>
<td>372</td>
<td>375</td>
<td>0.68 (0.54-0.86)</td>
</tr>
<tr>
<td>Male</td>
<td>233</td>
<td>229</td>
<td>0.83 (0.63-1.10)</td>
</tr>
<tr>
<td>Female</td>
<td>322</td>
<td>349</td>
<td>0.65 (0.52-0.83)</td>
</tr>
<tr>
<td>ISS stage (I or II)</td>
<td>283</td>
<td>255</td>
<td>0.91 (0.69-1.19)</td>
</tr>
<tr>
<td>ISS stage (III)</td>
<td>411</td>
<td>440</td>
<td>0.65 (0.52-0.81)</td>
</tr>
<tr>
<td>CR after ASCT</td>
<td>113</td>
<td>90</td>
<td>1.04 (0.72-1.51)</td>
</tr>
<tr>
<td>CR/VGPR</td>
<td>66</td>
<td>80</td>
<td>0.63 (0.35-1.16)</td>
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<tr>
<td>PR/SD/PD</td>
<td>320</td>
<td>339</td>
<td>0.70 (0.54-0.90)</td>
</tr>
<tr>
<td>Prior induction therapy</td>
<td>218</td>
<td>210</td>
<td>0.86 (0.65-1.15)</td>
</tr>
<tr>
<td>LEN</td>
<td>147</td>
<td>146</td>
<td>0.48 (0.31-0.75)</td>
</tr>
<tr>
<td>Non-LEN</td>
<td>458</td>
<td>458</td>
<td>0.82 (0.67-1.00)</td>
</tr>
</tbody>
</table>
| Adverse-risk cytogenetics
  (Yes)                                 | 56  | 36  | 1.18 (0.66-2.10)     |
| Adverse-risk cytogenetics
  (No)                                  | 231 | 243 | 0.79 (0.59-1.06)     |
| CrCl post ASCT (< 50 mL/min)            | 33  | 25  | 0.73 (0.33-1.60)     |
| CrCl post ASCT (≥ 50 mL/min)            | 379 | 404 | 0.74 (0.59-0.92)     |

---

*Number of patients. *Cytogenetic data were only available for the IFM and GIMEMA studies. *CrCl post-ASCT data were only available for the CALGB and IFM studies.

ASCT, autologous stem cell transplant; CR, complete response; CrCl, creatinine clearance; CTL, control; HR, hazard ratio; ISS, International Staging System; LEN, lenalidomide; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.
# Secondary Primary Malignancies

<table>
<thead>
<tr>
<th>Study name</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 2005-02</td>
<td>1.640</td>
<td>0.053</td>
</tr>
<tr>
<td>CALGB-100104</td>
<td>2.050</td>
<td>0.031</td>
</tr>
<tr>
<td>MM-015</td>
<td>1.430</td>
<td>0.412</td>
</tr>
<tr>
<td>RV-MM-PI209</td>
<td>0.850</td>
<td>0.798</td>
</tr>
<tr>
<td><strong>Summary estimate</strong></td>
<td><strong>1.62</strong></td>
<td><strong>0.006</strong></td>
</tr>
</tbody>
</table>

- **Outcome**: Odds of developing secondary primary malignancy; LM vs placebo/no maintenance (>1 implies increased risk of secondary primary malignancy with LM)

- **Minimal heterogeneity for estimate of secondary primary malignancy:**
  - Cochran Q = 1.67 (p = 0.644), I² = 0%

Issues Related to Maintenance

- Universal improvement in PFS
- Rarely improve OS
- Quality of life becomes important
- Toxicity related to long-term use of therapeutic agent
STaMINA: Phase III Study Design

Stratified by risk group (high vs standard)

ASCT-eligible pts ≤ 70 yrs with symptomatic MM and ≥ 2 cycles systemic tx initiated in past 12 mos; no prior progression; adequate organ function; (N = 758)

Melphalan 200 mg/m² IV ASCT

Single ASCT
Lenalidomide Maintenance until PD*
10 mg/day for 3 cycles, then 15 mg/day* (n = 257)

Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11
Lenalidomide 15 mg Days 1-15
Dexamethasone 40 mg IV Days 1, 8, 15
Four 28-day cycles (n = 254)

Tandem ASCT
Melphalan 200 mg/m² IV
Second ASCT (n = 247)

Lenalidomide Maintenance until PD
10 mg/day for 3 cycles, then 15 mg/day*

*Originally given for 3 yrs only, but amended to until PD in 2014.

- Primary endpoint: PFS at 38 mos
- Secondary endpoints: OS, ORR, CR conversion rate, safety, infections, tx-related mortality, QoL


Slide credit: clinicaloptions.com
STaMINA: PFS and OS for Overall Population

**PFS (Primary Endpoint)**

- **38-Mo Estimate (95% CI)**
  - Tandem ASCT: 56.5 (49.4-62.9)
  - RVD consolidation: 56.7 (50.0-62.8)
  - Single ASCT: 52.2 (45.4-58.6)

**Pts at Risk, n**
- Tandem ASCT 247
- RVD consolidation 254
- Single ASCT 257

**Mos From Randomization**

**OS**

- **38-Mo Estimate (95% CI)**
  - Tandem ASCT: 82.0 (76.3-86.5)
  - RVD consolidation: 85.7 (80.5-89.5)
  - Single ASCT: 83.4 (77.9-87.7)

**Pts at Risk, n**
- Tandem ASCT 247
- RVD consolidation 254
- Single ASCT 257

STaMINA: PFS and OS for Pts With High Risk

**PFS**

<table>
<thead>
<tr>
<th>Pts at Risk, n</th>
<th>Mos From Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tandem ASCT 57</td>
<td>42 28 14</td>
</tr>
<tr>
<td>RVD consolidation 65</td>
<td>25 38 18</td>
</tr>
<tr>
<td>Single ASCT 59</td>
<td>47 33 16</td>
</tr>
</tbody>
</table>

38-Mo Estimate (95% CI)
- Tandem ASCT: 42.2 (28.5-55.3)
- RVD consolidation: 48.3 (34.9-60.5)
- Single ASCT: 40.2 (27.1-53.0)

**OS**

<table>
<thead>
<tr>
<th>Pts at Risk, n</th>
<th>Mos From Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tandem ASCT 57</td>
<td>55 46 32</td>
</tr>
<tr>
<td>RVD consolidation 65</td>
<td>61 55 36</td>
</tr>
<tr>
<td>Single ASCT 59</td>
<td>56 54 32</td>
</tr>
</tbody>
</table>

38-Mo Estimate (95% CI)
- Tandem ASCT: 79.3 (66.1-88.2)
- RVD consolidation: 77.5 (64.3-86.4)
- Single ASCT: 79.5 (65.8-88.1)


Slide credit: clinicaloptions.com
Summary for Approach to Transplant Eligible patients

- Triplet induction
- Velcade based [VRD/KRD for HR patients]
- Transplant still needed [Double transplant for HR patients]
- Consider further consolidation for patient with suboptimal response
- Maintenance may prolong OS
Treatment of NDMM in transplant Ineligible Patients
Thalidomide-based treatment for elderly pts with newly diagnosed MM

- **MPT vs MP (6 randomized phase III trials)**
  - 4/6 studies: PFS benefit
  - 3/6 studies: OS benefit
  - Meta-analyses and systematic review
    - MPT superior to MP for ORR, CR, PFS, EFS: not OS

- **CTDa vs MP (phase III MRC Myeloma IX trial)**
  - CTDa superior for ORR and CR: not PFS or OS
  - Thal maintenance increased PFS: not OS

- **Thal/Dex vs MP (phase III trial)**
  - Thal/dex superior for ORR and \( \geq VGPR \): not PFS or OS
  - Thal/IFN maintenance improved PFS: not OS over IFN

---

7. Waage et al. ASCO 2010 (abstract 8130); EHA 2010 (abstract 567)
10. Morgan et al. ASH 2009 (abstract 352), oral presentation
11. Morgan et al. ASH 2010 (abstract 623), oral presentation
Len + high-dose Dex vs Len + low-dose Dex in patients with newly diagnosed myeloma

ECOG-E4A03 trial design

Patients with newly diagnosed MM (n = 445)

- Len + high-dose Dex, 4 cycles, cycle length 28 days
  - Len 25 mg/day, days 1–21
  - Dex 40 mg/day, days 1–4, 9–12, 17–20

- Len + low dose Dex, 4 cycles
  - Len 25 mg/day, days 1–21
  - Dex 40 mg/day, days 1, 8, 15, 22

Primary end-point: response rate and adverse events

FIRST (MM-020): Final Survival Analysis
Study Design\textsuperscript{1,2}

- Stratification: Age (\(\leq 75\) vs \(> 75\) yrs), country, and ISS stage (I/II vs III)
- Thromboprophylaxis was mandatory
- Data cutoff: January 21, 2016

\textsuperscript{1} Facon T, et al. Final Analysis of Overall Survival From the FIRST Trial. ASH 2016, abstract 241
FIRST (MM-020): Final Survival Analysis

**Progression-Free Survival**

- Updated PFS was prolonged with Rd continuous
  - Results remain consistent nearly 3 years after the original PFS analysis

### Progression-Free Survival (Months)

<table>
<thead>
<tr>
<th></th>
<th>Median PFS, mos</th>
<th>4-year PFS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>26.0</td>
<td>32.6</td>
</tr>
<tr>
<td>Rd18</td>
<td>21.0</td>
<td>14.3</td>
</tr>
<tr>
<td>MPT</td>
<td>21.9</td>
<td>13.6</td>
</tr>
</tbody>
</table>

\[ HR (95\% CI) \]

**Rd continuous vs MPT:**

- Rd continuous: 13.6%
- MPT: 14.3%
- 4-year PFS: 32.6%

- 0.69 (0.59-0.79), \( P < .00001 \)

**Note:**

PFS is based on investigator assessment of IMWG criteria; Data cutoff: January 21, 2016.
FIRST, Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide; HR, hazard ratio; IMWG, International Myeloma Working Group; MPT, melphalan, prednisone, thalidomide; PFS, progression-free survival; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

FIRST (MM-020): Final Survival Analysis

**Overall Survival**

- The pre-specified final OS analysis for the primary comparison showed that Rd continuous significantly extended OS vs MPT.

<table>
<thead>
<tr>
<th></th>
<th>Median OS, mos</th>
<th>4-yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd continuous</td>
<td>59.1</td>
<td>59.0</td>
</tr>
<tr>
<td>Rd18</td>
<td>62.3</td>
<td>58.0</td>
</tr>
<tr>
<td>MPT</td>
<td>49.1</td>
<td>51.7</td>
</tr>
</tbody>
</table>

HR (95% CI) 
Rd continuous vs MPT: 
0.78 (0.67-0.92), *P* = .0023
Phase III Study Schema

N = 459, 82 centers in Europe, Australia, and Israel

**RANDOMISATION**

**MPR-R**
- M: 0.18 mg/kg, days 1-4
- P: 2 mg/kg, days 1-4
- R: 10 mg/day po, days 1-21

**MPR**
- M: 0.18 mg/kg, days 1-4
- P: 2 mg/kg, days 1-4
- R: 10 mg/day po, days 1-21

**MP**
- M: 0.18 mg/kg, days 1-4
- P: 2 mg/kg, days 1-4
- PBO: days 1-21

**Continuous Lenalidomide Treatment**
- 10 mg/day days 1-21

**Disease Progression**

**Open-Label Extension Phase**

**Lenalidomide (25 mg/day) +/− Dexamethasone**

Stratified by age (≤ 75 vs > 75 years) and stage (ISS I/II vs III)

M, melphalan; P, prednisone; R, lenalidomide; PBO, placebo; po, orally; ISS, International Staging System.
Progression-Free Survival*
All Patients
60% Reduced Risk of Progression

Median PFS

- MPR-R: 31 months
- MPR: 14 months
- MP: 13 months

HR 0.398
$P < .0000001$

HR 0.804
$P = .153$

Median follow-up 25 months

*Analysis based on data up to May 2010
Landmark Analysis
69% Reduced Risk of Progression

MPR
Lenalidomide Continuous Therapy

HR 0.314
P < .001
Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma


<table>
<thead>
<tr>
<th>Table 2. Response rates and times to response on protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate, N (%)</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>VGPR</td>
</tr>
<tr>
<td>PR</td>
</tr>
<tr>
<td>≥ VGPR</td>
</tr>
<tr>
<td>Overall response on protocol (≥ PR)</td>
</tr>
<tr>
<td>Median time to response (in months, range)</td>
</tr>
<tr>
<td>Median time to maximum response (in months, range)</td>
</tr>
</tbody>
</table>
Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma

A. Keith Stewart,1 Susanna Jacobus,2 Rafael Fonseca,1 Matthias Weiss,3 Natalie S. Callander,4 Asher A. Chanan-Khan,5 and S. Vincent Rajkumar6

1Division of Hematology, Mayo Clinic Arizona, Scottsdale, AZ; 2Dana-Farber Cancer Institute, Boston, MA; 3Marshfield Clinic, Marshfield, WI; 4University of Wisconsin, Madison, WI; 5Division of Hematology, Mayo Clinic, Jacksonville, FL; and 6Division of Hematology, Mayo Clinic, Rochester, MN
VISTA: Bortezomib as Initial Standard Therapy in MM

Assessment with melphalan and prednisone

MPV
Cycles 1–4
Bortezomib 1.3 mg/m² i.v. days 1, 4, 8, 11, 22, 25, 29, 32
Melphalan 9 mg/m² and prednisone 60 mg/m² days 1–4

Cycles 5–9
Bortezomib 1.3 mg/m² i.v. days 1, 8, 22, 29
Melphalan 9 mg/m² and prednisone 60 mg/m² days 1–4

9 × 6-week cycles (54 weeks) in both arms

MP
Cycles 1–9
Melphalan 9 mg/m² and prednisone 60 mg/m² days 1–4

Primary end-point: TTP

SWOG S0777: RVd vs Rd With Rd Maintenance Phase 3 Study Design

INDUCTION

**RVd**
- LEN 25 mg PO d1–14
- DEX 20 mg PO D1, 2, 4, 5, 8, 9, 11, 12
- BORT 1.3 mg/m² IV D1, 4, 8, 11
- 8 × 21-day cycles (n = 242)

**Rd**
- LEN 25 mg PO d1–21
- DEX 40 mg PO d1, 8, 15, 22
- 6 × 28-day cycles (n = 232)

Stratified by ISS stage and intent to SCT

ENDPOINTS

**Primary:** PFS
**Secondary:** ORR, OS, safety

MAINTENANCE

**Rd**
- LEN 25 mg PO d1–21
- DEX 40 mg PO d1, 8, 15, 22
- 28-day cycles until PD, unacceptable toxicity, or withdrawal of consent

FOLLOW-UP

Follow-up for 6 years for OS

- All pts received aspirin 325 mg/day
- RVd pts received HSV prophylaxis per institutional standard

BORT, bortezomib; D, day; DEX, dexamethasone; HSV, herpes simplex virus; ISS, International Staging System; LEN, lenalidomide; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral administration; pt, patient; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone; SCT, stem cell transplant.

SWOG S0777: RVd vs Rd With Rd Maintenance Survival Analyses

<table>
<thead>
<tr>
<th></th>
<th>RVd (n = 242)</th>
<th>Rd (n = 232)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI), mos</td>
<td>43 (39-51)</td>
<td>31 (26-40)</td>
</tr>
<tr>
<td>HR (96% Wald CI)</td>
<td>0.742 (0.579-0.951)</td>
<td></td>
</tr>
<tr>
<td>1-sided stratified log-rank P value</td>
<td>.0066&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Median OS (95% CI), mos</td>
<td>NR</td>
<td>63 (55-69)</td>
</tr>
<tr>
<td>HR</td>
<td>0.666</td>
<td></td>
</tr>
<tr>
<td>2-sided log-rank P value</td>
<td>.0114</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> This analysis reached the prespecified significance level of .02.

HR, hazard ratio; Rd, lenalidomide and low-dose dexamethasone; NR, not reached; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide and low-dose dexamethasone; RVd, bortezomib, lenalidomide, and low-dose dexamethasone.

Summary of Approach to Transplant Ineligible Patients

- MP is no longer good enough
- MPR is not a good regimen
- MPT, Rd, VMP are all active
- VRd better than Rd
- Continuous treatment prolongs PFS
Management of Relapse Disease
Relapse situations

Two clear scenarios

Slow, asymptomatic relapse
- No symptoms
- Slowly progressing disease
- Low tumor burden
- Cytogenetic low risk
- Good performance status

Fast, symptomatic relapse
- Symptoms
- Rapidly progressing disease
- High tumor burden
- Organ involvement
- Cytogenetic high risk
- Poor performance status

The challenge: Identify appropriate time to initiate treatment for situations ‘in between’
How Does the Timing of Relapse Influence Treatment Decisions?

- **Early relapse: within < 1 year**
  - May indicate resistant disease
  - Change from initial treatment
  - Incorporate novel agent, if not previously used

- **Late relapse: after > 2 years**
  - Consider rechallenge with initial therapy
  - If previous therapy was effective
  - If previous therapy was given for a short, defined duration
    - Consider addition of another agent
Can treatment be individualized at relapse?

Decisions based on relapse characteristics & co-morbidities

- Agressive vs non-aggressive............ 3 vs 2 drug combination
- Peripheral Neuropathy.................... Lenalidomide
- Renal impairment.......................... Bortezomib (Thal, Len)
- Venous Thrombosis.......................... Bortezomib (Thal, Len)
- Low BM reserve............................. Bortezomib or Thalidomide
- Hospital’ distance.......................... Lenalidomide or Thalidomide
Multiple factors drive treatment choice in relapsed/refractory MM

- Tolerance to prior therapies
- Prior therapies received†
- Time interval since last therapy
- Subtype e.g. t(4;14)
- Age
- Previous SCT
- Performance status
- Treatment availability
- Pre-existing toxicities e.g. PN
- Side effects
- Comorbidity e.g. renal impairment*
- Influential factors*
Options

- Thalidomide based
- Revlimid based (include retreatment)
- Velcade based (include retreatment)
- Triplet better than doublet
- Combination Chemotherapy (DT-PACE, DCEP) – Especially if extramedullary disease
- Transplant (including AlloSCT)
Emerging Therapies

1. New Generation Proteasome Inhibitor
   a) Carfilzomib (Onyx) – Aspire, Endeavour
   b) Ixazomib (Millenium) - Tourmaline

2. New Generation Imids
   a) Pomalidomide (Celgene) – MM003

3. Histone Deacetylase Inhibitor
   a) Panobinostat (Novartis) - Panorama

4. Monoclonal Antibodies
   a) Daratumumab (Anti-CD38) – Sirius, Pollux, Castor
   b) Elotuzumab (Anti-CS1) - Eloquent

5. CDK4/6 Inhibitor

6. Venetoclax (BCL2)

7. Selinexor

8. Immunotherapies
## Trials in Relapse MM (1-3 prior lines)

<table>
<thead>
<tr>
<th></th>
<th>Panorama</th>
<th>Endeavour</th>
<th>Castor</th>
<th>Aspire</th>
<th>Eloquant-2</th>
<th>Tourmaline-1</th>
<th>Pollux</th>
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<tbody>
<tr>
<td></td>
<td>VD</td>
<td>PVD</td>
<td>VD</td>
<td>KD</td>
<td>VD</td>
<td>DVD</td>
<td>RD</td>
</tr>
<tr>
<td>ORR(%)</td>
<td>55</td>
<td>61</td>
<td>63</td>
<td>77</td>
<td>63</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>≥CR (%)</td>
<td>6</td>
<td>11</td>
<td>6</td>
<td>13</td>
<td>9</td>
<td>19</td>
<td>9</td>
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<tr>
<td>sCR (%)</td>
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<tr>
<td>PFS/mths</td>
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<td>9.4</td>
<td>18.7</td>
<td>7.2</td>
<td>NR</td>
<td>17.6</td>
</tr>
<tr>
<td>HR</td>
<td>0.63</td>
<td>0.53</td>
<td>0.39</td>
<td>0.69</td>
<td>0.7</td>
<td>0.7</td>
<td>0.74</td>
</tr>
</tbody>
</table>

|                | VD       | PVD       | VD     | KD     | VD         | DVD          | RD     |
|                | 87       | 66        | 79     | 72     | 78         | 76           | 93     |
|                | 32       | 4         | 7      | 7      | 12         | 19           | 43     |
|                | NR       | NR        | 4      | 14     | NR         | NR           | 7      |
|                | NR       | NR        | NR     | NR     | NR         | NR           | 10     |
|                | 26.3     | 14.9      | 19.4   | 14.7   | 20.6       | 18.4         | NR     |
|                | 0.69     | 0.7       | 0.74   | 0.37   |            |              |        |
TOURMALINE-MM1: Phase 3 study of weekly oral ixazomib plus lenalidomide-dexamethasone

Global, double-blind, randomized, placebo-controlled study design

Randomization

Ixazomib + Lenalidomide + Dexamethasone
Ixazomib: 4 mg on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22
Repeat every 28 days until progression, or unacceptable toxicity

Placebo + Lenalidomide + Dexamethasone
Placebo: on days 1, 8, and 15
Lenalidomide: 25 mg* on days 1-21
Dexamethasone: 40 mg on days 1, 8, 15, 22

N=722

Stratification:
- Prior therapy: 1 vs 2 or 3
- ISS: I or II vs III
- PI exposure: yes vs no

Primary endpoint:
- PFS

Key secondary endpoints:
- OS
- OS in patients with del(17p)

Response and progression (IMWG 2011 criteria\(^1\)) assessed by an independent review committee (IRC) blinded to both treatment and investigator assessment

*10 mg for patients with creatinine clearance ≤60 or ≤50 mL/min, depending on local label/practice

Outcomes by cytogenetic risk group

<table>
<thead>
<tr>
<th></th>
<th>ORR, %</th>
<th>≥VGPR, %</th>
<th>≥CR, %</th>
<th>Median PFS, months</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRd</td>
<td>Placebo -Rd</td>
<td>IRd</td>
<td>Placebo -Rd</td>
<td>IRd Placebo -Rd HR</td>
</tr>
<tr>
<td>All patients</td>
<td>78.3*</td>
<td>71.5</td>
<td>48.1*</td>
<td>39</td>
<td>20.6 14.7 0.742*</td>
</tr>
<tr>
<td>Standard-risk patients</td>
<td>80</td>
<td>73</td>
<td>51</td>
<td>44</td>
<td>20.6 15.6 0.640*</td>
</tr>
<tr>
<td>All high-risk patients</td>
<td>79*</td>
<td>60</td>
<td>45*</td>
<td>21</td>
<td>21.4 9.7 0.543</td>
</tr>
<tr>
<td>Patients with del(17p)†</td>
<td>72</td>
<td>48</td>
<td>39</td>
<td>15</td>
<td>21.4 9.7 0.596</td>
</tr>
<tr>
<td>Patients with t(4;14) alone</td>
<td>89</td>
<td>76</td>
<td>53</td>
<td>28</td>
<td>18.5 12.0 0.645</td>
</tr>
</tbody>
</table>

*p<0.05 for comparison between regimens. †Alone or in combination with t(4;14 or t(14;16).
Data not included on patients with t(14:16) alone due to small numbers (n=7).

- Median OS was not reached in either arm
- In the IRd arm, median PFS in high-risk patients was similar to that in the overall patient population and in patients with standard-risk cytogenetics
Different Ixazomib Trials

- C16010 (Tourmaline 1) – 5 patients
- C16013 – Asia Phase 1 – 11 patients
- C16019 – Phase 3 maintenance in post-transplant patients – 10 patients
- C16021 – Phase 3 maintenance in non-transplant eligible – 8 patients (Ongoing)
Pharmacokinetics and safety of ixazomib plus lenalidomide–dexamethasone in Asian patients with relapsed/refractory myeloma: a phase 1 study

Neeraj Gupta1*, Yeow Tee Goh2, Chang-Ki Min3, Jae Hoon Lee4, Kihyun Kim5, Raymond S. M. Wong6, Chor Sang Chim7, Michael J. Hanley7, Huyuan Yang8, Karthik Venkatakrisnan1, Ai-Min Hui9, Dixie-Lee Esseltine9 and Wee Joo Chng10,11

Abstract

Background: The oral proteasome inhibitor ixazomib is under phase 3 clinical investigation in multiple myeloma (MM) in combination with lenalidomide–dexamethasone. This study was conducted to investigate the pharmacokinetic and safety profiles of ixazomib, administered with lenalidomide–dexamethasone, in East Asian patients with relapsed/refractory MM.

Methods: Adult patients with measurable disease who had received 1–3 prior lines of therapy received oral ixazomib on days 1, 8, and 15, lenalidomide (25 mg) on days 1–21, and dexamethasone (40 mg) on days 1, 8, 15, and 22, in 28-day cycles. Primary objectives were to characterize ixazomib plasma pharmacokinetics, determine the recommended phase 2/3 dose, and evaluate safety and tolerability.

Results: Forty-three patients were enrolled. No dose-limiting toxicities were reported for the first six patients receiving ixazomib (4.0 mg), confirming this as the recommended phase 2/3 dose. Ixazomib was rapidly absorbed with a median $T_{\text{max}}$ of 1.5 h on day 1 and 2.0 h on day 15 of cycle 1 and had a geometric mean terminal half-life of 61 days. Twenty-one (49 %) patients had at least one drug-related grade ≥3 adverse event (AE); the most common were neutropenia (19 %), diarrhea (14 %), and thrombocytopenia (12 %). Twenty-eight of 43 (65 %) response-evaluable patients had at least a partial response. The recommended phase 2/3 dose for ixazomib was determined to be 4.0 mg.

Conclusions: The all-oral combination of ixazomib plus lenalidomide–dexamethasone appeared active and well tolerated at 4.0 mg. Consequently, East Asian patients enrolled in phase 3 studies are receiving the same ixazomib dose as patients in other regions.

Trial registration: This study is registered at NCT01645930.

Keywords: Multiple myeloma, Ixazomib, Ethnicity, East Asian, Pharmacokinetics
Fig. 1 Mean plasma concentration–time profiles of ixazomib in combination with lenalidomide–dexamethasone on a day 1 and b day 15 of cycle 1 (safety population)
### Table 4 Most common any grade (>10% of patients) and grade ≥3 (>1 patient) drug-related AEs

<table>
<thead>
<tr>
<th>Any grade AE, n (%)</th>
<th>Chinese (n = 20)</th>
<th>Korean (n = 16)</th>
<th>Other (n = 7)</th>
<th>Overall (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin/subcutaneous tissue disorders&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10 (50)</td>
<td>4 (25)</td>
<td>7 (100)</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10 (50)</td>
<td>4 (25)</td>
<td>3 (43)</td>
<td>17 (40)</td>
</tr>
<tr>
<td>PN NEC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4 (20)</td>
<td>3 (19)</td>
<td>4 (57)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (20)</td>
<td>3 (19)</td>
<td>2 (29)</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (15)</td>
<td>4 (25)</td>
<td>1 (14)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (10)</td>
<td>4 (25)</td>
<td>2 (29)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (25)</td>
<td>0</td>
<td>3 (43)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (10)</td>
<td>1 (6)</td>
<td>4 (57)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (10)</td>
<td>4 (25)</td>
<td>1 (14)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>3 (15)</td>
<td>2 (13)</td>
<td>0</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (15)</td>
<td>0</td>
<td>2 (29)</td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade ≥3 AE, n (%)</th>
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<th>Korean (n = 16)</th>
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<th>Overall (N = 43)</th>
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<tbody>
<tr>
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<td>4 (25)</td>
<td>1 (14)</td>
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<td>Thrombocytopenia</td>
<td>1 (10)</td>
<td>2 (25)</td>
<td>2 (29)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>4 (25)</td>
<td>2 (29)</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (5)</td>
<td>1 (6)</td>
<td>2 (29)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (5)</td>
<td>0</td>
<td>2 (29)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>1 (5)</td>
<td>0</td>
<td>2 (29)</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> System organ class, includes the preferred terms dry skin, macular rash, pruritus, skin hyperpigmentation (each n = 4), generalized pruritus, pruritic rash (each n = 3), maculopapular rash, skin exfoliation (each n = 2), skin discoloration, dermatitis aceneiform, night sweats, drug eruption, papular rash, pigmentation disorder, and abnormal hair growth (each n = 1)

<sup>b</sup> Higher level term, includes the preferred terms peripheral neuropathy (n = 9) and peripheral sensory neuropathy (n = 2)
Considerations in Making Choices

• Efficacy
• Toxicities
• Access / Cost
• Route of administration / Schedule / Logistics
Unmet Needs

• Treatment of HR disease
  – Incl extramedullary disease, PCL

• Cost of Drugs and Drug Access

• Predictive Marker – Choice of Drugs and combinations
Thank you for your attention

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