19th Post-ASH : Focus on multiple myeloma

Philip Vlummens
Presentation outline

• Consolidation therapy demystified?
• The role of maintenance therapy
• MRD beyond first line
  – Transplant-ineligible patients (Myeloma XI)
  – Relapse setting (CASTOR/POLLUX)
• New treatment strategies: Venetoclax/Selinexor
EMN02/HOVON95 MM: A Randomized Phase III Study to Compare Bortezomib, Melphalan, Prednisone (VMP) With High-Dose Melphalan Followed by Bortezomib, Lenalidomide, Dexamethasone (RVd) Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Multiple Myeloma
Consolidation therapy

**INDUCTION**
- NDMM
  - N = 1510
- VCD
  - 4 cycles
  - SC collection
- HDM 1/2
- R1

**INTENSIFICATION**
- VMP
  - 4 cycles
- R1

**CONSOLIDATION**
- RVd
  - BORT 1.3 mg/m² IV
    - D1, 4, 8, 11
  - LEN 25 mg PO D1–21
  - DEX 20 mg PO
    - D1, 2, 4, 5, 8, 9, 11, 12
    - 2 × 28-day cycles
  - R2

**MAINTENANCE**
- LEN
  - LEN 10 mg PO
  - Treatment until PD or toxicity

<table>
<thead>
<tr>
<th></th>
<th>No consolidation (444)</th>
<th>VRD (459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>58 (33-66)</td>
<td>57 (29-66)</td>
</tr>
<tr>
<td>Male/female</td>
<td>56/44</td>
<td>57/43</td>
</tr>
<tr>
<td>ISS I, II, III, %</td>
<td>43/40/17</td>
<td>42/37/21</td>
</tr>
</tbody>
</table>
Patient outcome EMN/HOVON trial

- PFS was prolonged with RVd consolidation vs no consolidation (median follow-up 25 mo) from R2
- Benefit in low-risk cytogenetics (HR 0.68, p=0.03), not in high-risk disease (consisting of 25% of patients)
- OS was equal at 86% in both arms
Conclusions

• sCR/CR rate improved following consolidation
• Consolidation therapy with RVd improved PFS when compared to a no consolidation strategy
• Result were independent of ISS stage and were primarily seen in patients without high-risk cytogenetics (planned subgroup-analysis)

However ...
Abstract LBA-1 Stadtmauer et al.

Primary Results From the Randomized Prospective Phase III Trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0702 – STaMINA Trial: Autologous Hematopoietic Cell Transplant (AHCT), With and Without Consolidation With Bortezomib, Lenalidomide (LEN) and Dexamethasone (RVd) and LEN Maintenance vs Tandem AHCT and LEN Maintenance for Up-Front Treatment of Patients With Multiple Myeloma
StaMINA - design

Symptomatic MM
Age ≤ 70 yrs

Induction
Bort/Len/Dex (55,2%)
Cy/Bort/Dex (14,3)
Len/Dex (9,8%)
Bort/Dex (12,1%)
Other (8,6%)

MEL
200 mg/m²
n = 254
4 cycles

RVd
n = 254
4 cycles

LEN Maintenance
n = 257
10 mg/d × 3 cycles
then 15 mg/d

LEN Maintenance
as above

LEN Maintenance
as above

LEN Maintenance
as above

LEN Maintenance
as above
STaMINA – survival data

PFS

38 Month Estimate and 95% CI
Auto/Auto: 56.5 (49.4, 62.9)
Auto/RVD: 56.7 (50.0, 62.8)
Auto/Maint: 52.2 (45.4, 58.6)

OS

38 Month Estimate and 95% CI
Auto/Auto: 82.0 (76.3, 86.5)
Auto/RVD: 85.7 (80.5, 89.5)
Auto/Maint: 83.4 (77.9, 87.7)

PFS high-risk

38 Month Estimate and 95% CI
Auto/Auto: 42.2 (28.8, 55.3)
Auto/RVD: 48.3 (34.9, 60.5)
Auto/Maint: 40.2 (27.1, 53.0)

PFS standard risk

38 Month Estimate and 95% CI
Auto/Auto: 60.9 (52.8, 68.1)
Auto/RVD: 59.5 (51.7, 66.5)
Auto/Maint: 55.9 (48.0, 63.0)
Consolidation therapy

• Consolidation therapy (or a second ASCT) does not seem to provide an incremental outcome benefit in the era of lenalidomide maintenance (EMNO2/HOVON95)

• Results are not uniform between both studies
Abstract 1143 Jackson et al.

Lenalidomide Is a Highly Effective Maintenance Therapy in Myeloma Patients of All Ages: Results of the Phase III Myeloma XI Study
Myeloma XI overview

Intensive Pathway

Randomise 1:1

CTD  RCD

Assess Response

NC + PD  CR + VGPR  PR + MR

CVD  Assess Response

CVD  Assess Response

High Dose Melphalan & ASCT

Maintenance Randomisation**

No maintenance  Lenalidomide 10mg maintenance  Lenalidomide 10mg + Vorinostat 300mg maintenance

Non-Intensive Pathway

Randomise 1:1

CTDa  RCDa

Assess Response

NC + PD  CR + VGPR  PR + MR

Randomise

CVD  Assess Response

Nothing  CVD  Assess Response

CVD  Assess Response

Maintenance Randomisation

No maintenance  Lenalidomide 10mg maintenance  Lenalidomide 10mg + Vorinostat 300mg maintenance

**Patients entered into the RCD arm and assessed as NC or PD at the end of RCD induction are not eligible for the maintenance randomisation
Myeloma XI: Len maintenance

NDMM
TE and TNE pts
Treated on Myeloma XI
induction protocols
N = 1551

RANDOMIZATION 1:1

LEN Maintenance
LEN 10 mg d1–21
28-day cycles

Treatment until PD

No Maintenance

Primary endpoints: PFS and OS
N = 1551 with 828 TE and 723 NTE > 857 maintenance and 694 no maint.
Median age maintenance/no maintenance: 68 (29-89) vs 68 (30-90)
Equal distribution of ISS and cytogenetics between groups
Median follow-up was 27 mo
Len maintenance : Results

PFS TE

PFS TNE

PFS overall

PFS according to treatment duration (other than progression)
Myeloma XI : Len maintenance

- Maintenance with lenalidomide until progression resulted in a significant PFS improvement
- Longer treatment reduced risk of relapse
- OS data are not available yet
- SPM data:
  - 72 SPMs observed (48 vs 24)
  - No clinically significant increase in invasive SPMs
Abstract 245 de Tute et al.

Impact of minimal residual disease in transplant ineligible myeloma patients: results of from the UK NCRI Myeloma XI trial.
MRD in transplant-ineligible patients

- MRD ...
  - Independent prediction of outcome
  - Demonstrable quantitative effect
  - Impact is independent of the therapy received
  - Applicable to high- and standard-risk patients
  - But majority of data available in ASCT-based therapies
Myeloma XI – transplant ineligible patients

- Induction 1
  - CTD
  - CRD
  - Max. response
    - PD
    - SD
    - MR
    - PR
    - VGPR
    - CR

- Induction 2
  - CVD
  - No CVD

- Maintenance
  - Lenalidomide
  - Observation

- MRD
  - 6-colour flow-cytometry

- N=297/1852
  - Median age 74.0 yrs (56-87)
  - 62.8% male
  - IgG 60.5%
  - ISS III 34.2%
Results

- Overall 41/297 patients (13.8%) achieved MRD-negativity
- No difference between induction therapy was seen
- MRD-status withheld using multivariate analysis
MRD is correlated with PFS
Myeloma XI - MRD

- Feasible using flowcytometry
- Qualitative and continuous variable
- Is a meaningful endpoint/therapeutic goal in transplant-ineligible patients
- Improvement of PFS
Evaluation of Minimal Residual Disease (MRD) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Treated With Daratumumab in Combination With Lenalidomide Plus Dexamethasone or Bortezomib Plus Dexamethasone
CASTOR & POLLUX

- Multicenter, randomized (1:1), open-label, active-controlled, phase 3 studies in ≥1 prior line of therapy for MM

**POLLUX**

**DRd (n = 286)**
- D 16 mg/kg IV
  - Every week: Cycles 1-2
  - Every 2 weeks: Cycles 3-6
  - Every 4 weeks until PD
- R 25 mg PO (similar to Rd alone)
- d 40 mg

**Rd (n = 283)**
- R 25 mg PO
  - Days 1-21 of each cycle until PD
- d 40 mg weekly until PD

**CASTOR**

**DVd (n = 251)**
- D 16 mg/kg IV
  - Every week: Cycles 1-3
  - Every 3 weeks: Cycles 4-8
  - Every 4 weeks: Cycles 9+
- V 1.3 mg/m² SC (similar to Vd alone)
- d 20 mg

**Vd (n = 247)**
- V 1.3 mg/m² SC on Days 1, 4, 8, and 11
  - for 8 cycles
- d 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 for 8 cycles

**MRD assessments**
- At suspected CR
- 3 & 6 months after CR

**Patient characteristics**
- Median (range) prior lines: 1 (1-11)
- Prior V: 84%
- Prior R: 18%

**MRD assessments**
- At suspected CR
- 6 & 12 months after first study dose

**Patient characteristics**
- Median (range) prior lines: 2 (1-10)
- Prior V: 66%
- Prior R: 42%
CASTOR & POLLUX

POLLUX

18-month PFS

- Patients surviving without progression, %
- Median PFS
  - DRd: not reached; Rd: 17.5 months
  - HR: 0.37 (95% CI, 0.28-0.50; \( P < 0.0001 \))

CASTOR

12-month PFS

- Patients surviving without progression, %
- Median PFS
  - DVd: not reached; Vd: 7.1 months
  - HR: 0.33 (95% CI, 0.26-0.43; \( P < 0.0001 \))

<table>
<thead>
<tr>
<th>Response Level</th>
<th>DRd (%)</th>
<th>Rd (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>CR</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>VGPR</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>PR</td>
<td>15</td>
<td>32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response Level</th>
<th>DVd (%)</th>
<th>Vd (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>CR</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>VGPR</td>
<td>35</td>
<td>19</td>
</tr>
<tr>
<td>PR</td>
<td>22</td>
<td>34</td>
</tr>
</tbody>
</table>

Median (range) follow-up:
- POLLUX: 17.3 (0-24.5) months
- CASTOR: 13.0 (0-21.3) months
MRD-negativity in CR patients

- Daratumumab in combination with standard of care significantly improved MRD-negative rates at all thresholds.

**P <0.005.**

*** P <0.0001.
- Lower risk of progression in MRD-negative patients (ITT analysis)
- PFS benefit in MRD-positive patients who received daratumumab-containing regimens versus standard of care
Conclusions

• MRD-negativity is associated with a lower risk of progression in relapsed patients
• Daratumumab induced MRD-negativity in over 4 times as many CR patients as standard of care regimens
• Addition of Daratumumab prolongs PFS even when MRD-positive
• The higher rate of MRD-negativity and deep clinical responses may lead to improved OS (data not mature)
Abstract 488 Kumar et al.

Venetoclax monotherapy for relapsed/refractory multiple myeloma: Safety and efficacy results from a phase I study
Characteristics

- Phase 1, open-label multicenter study of venetoclax, a BCL-2 inhibitor, in RRMM.

- Patients were treated on a 21-day cycle with daily venetoclax.

- Patients who progressed on monotherapy could have dexamethasone added.
## Patient characteristics and adverse events

### Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), years</td>
<td>63 (31-79)</td>
</tr>
<tr>
<td>ISS</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>24 (38)</td>
</tr>
<tr>
<td>II/III</td>
<td>39 (62)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td></td>
</tr>
<tr>
<td>t(11;14)</td>
<td>30 (46)</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>del(17p)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>del(13q)</td>
<td>32 (48)</td>
</tr>
<tr>
<td>Hyperdiploid</td>
<td>27 (41)</td>
</tr>
<tr>
<td>No. of prior lines of therapy, median (range)</td>
<td>5 (1-15)</td>
</tr>
<tr>
<td>ASCT, n (%)</td>
<td>50 (76)</td>
</tr>
<tr>
<td>Bortezomib/refractory, n (%)</td>
<td>62 (94) / 46 (70)</td>
</tr>
<tr>
<td>Lenalidomide/refractory, n (%)</td>
<td>62 (94) / 51 (77)</td>
</tr>
<tr>
<td>Bortezomib and lenalidomide refractory, n (%)</td>
<td>40 (61)</td>
</tr>
<tr>
<td>Refractory to last prior therapy, n(%)</td>
<td>52 (79)</td>
</tr>
</tbody>
</table>

### Adverse events

<table>
<thead>
<tr>
<th>AE</th>
<th>Any grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>66 (100)</td>
<td>45 (68)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21 (32)</td>
<td>17 (26)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18 (27)</td>
<td>14 (21)</td>
</tr>
<tr>
<td>Anemia</td>
<td>15 (23)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>15 (23)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12 (18)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Non-hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (47)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (36)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18 (27)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>14 (21)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (21)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

- Two patients had dose-limiting toxicities of abdominal pain and nausea at 600 mg
- No events of TLS
- Serious AEs: pneumonia (8%), sepsis (5%), pain, pyrexia, cough and hypotension (3% each)

AEs for 20% or more of patients for any grade AE or for 10% or more with grade 3 or 4.
Response and time to progression

15 patients received add-on dexamethasone.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active, n (%)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Discontinued, n (%)</td>
<td>55 (83)</td>
</tr>
<tr>
<td>Progression</td>
<td>41 (62)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>8 (12)</td>
</tr>
</tbody>
</table>

Response rates:
- **sCR**: 3%
- **CR**: 4%
- **VGPR**: 8%
- **PR**: 6%
Conclusions

• Data suggests Venetoclax monotherapy is safe
• An ORR of 21% was seen in all patients
• In patients with t(11;14), a higher ORR (40% vs 6%) was seen
• Other treatment combinations (Bort) are being actively investigated based on pre-clinical data (Moreau et al., abstract 975) and show promising results
Abstract 491 Vogl et al.

Selinexor and low dose dexamethasone (Sd) in patients with lenalidomide, pomalidomide, bortezomib, carfilzomib and anti-CD38 ab refractory multiple myeloma (MM): STORM study.
Mechanism of Selinexor

- Exportin 1 (XPO1) is the nuclear exporter for tumor suppressor proteins and the glucocorticoid receptor
- Inhibition of XPO1 induces retention of these proteins
- Suppression of oncprotein expression
STORM-trial

• Patients refractory to
  – Bort, Carf, Len, Pom = quad-refractory
  – Also refractory to anti-CD38 = penta-refractory

Selinexor 80 mg and dexamethasone 20 mg
Twice weekly

6 doses per 28 days
(3 weeks on, 1 week off)

8 doses per 28 days
(continuously)

* Dose modification for toxicity possible
### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Quad-refractory</th>
<th>Penta-refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>62 (41-78)</td>
<td>68 (31-78)</td>
</tr>
<tr>
<td><strong>Males : females</strong></td>
<td>24 (50%) : 24 (50%)</td>
<td>13 (42%) : 18 (58%)</td>
</tr>
<tr>
<td><strong>Median prior regimens (range)</strong></td>
<td>7 (3-16)</td>
<td>7 (5-17)</td>
</tr>
<tr>
<td><strong>Median years from diagnosis (range)</strong></td>
<td>4 (1-16)</td>
<td>4 (1-35)</td>
</tr>
<tr>
<td><strong>Prior therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>48 (100%)</td>
<td>31 (100%)</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>47 (98%)</td>
<td>30 (97%)</td>
</tr>
<tr>
<td>Stem cell transplant</td>
<td>37 (77%)</td>
<td>24 (77%)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>20 (42%)</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Treatment 6 doses : 8 doses/cycle</td>
<td>40 (83%) : 8 (17%)</td>
<td>11 (35%) : 20 (65%)</td>
</tr>
</tbody>
</table>
STORM results

- At time of analysis 70 patients (%) had discontinued treatment
  - Progression (70%)
  - Adverse events (17%)

<table>
<thead>
<tr>
<th>Most frequent 3/4 AEs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trombocytopenia</td>
<td>59%</td>
</tr>
<tr>
<td>Anemia</td>
<td>28%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>22%</td>
</tr>
</tbody>
</table>

Dose interruptions: 52%
Dose reductions: 37%
Discontinuation: 18% (14 pt)

Using supportive care:
- Anti-emetics
- Growth factors
- Salt supplementation
STORM results

- ORR 20 – 21% (6-8/mo no diff)
- CR?
- Med. time to response : 1 mo
- Med. duration response : 5 mo

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>MR or better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>9,3 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Median PFS</td>
<td>2,3 mo</td>
<td>5,5 mo</td>
</tr>
</tbody>
</table>
Conclusions

• The results suggest that Sd displays anti-tumor activity in heavily pretreated patients
• An ORR of 20 – 21% is seen and responses are associated with a benefit in PFS and OS
Key points

• The exact role of consolidation therapy, especially in the era of lenalidomide maintenance, remains unclear.

• Maintenance therapy with IMiDs is well tolerated and should be considered in the future treatment of MM patients if available.

• MRD is an important marker of response and leads to prolonged PFS, even in elderly and RRMM patients.

• The interplay between MRD and OS looks promising and will hopefully be elucidated in the near future.

• Agents such as Selinexor and Venetoclax exhibit noteworthy activity in RRMM patients.