Bendamustine, bortezomib and dexamethasone (BVD) in elderly patients with relapsed/refractory multiple myeloma: The Intergroupe Francophone du Myélome (IFM) 2009-01 protocol

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## Background

✓ **Progression after 1st line treatment: median survival (months)**

<table>
<thead>
<tr>
<th></th>
<th>MP</th>
<th>MP-T</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFM 99-06 (1)</td>
<td>11.4</td>
<td>13.4</td>
</tr>
<tr>
<td>65-75 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFM 01-01 (2)</td>
<td>9.8</td>
<td>9.3</td>
</tr>
<tr>
<td>&gt;75 yrs</td>
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<td></td>
</tr>
</tbody>
</table>

Bendamustine in multiple myeloma

- Chemotherapeutic agent combining both alkylating agent and purine-analog structures

- Highly active in chronic lymphoproliferative disorders

- Limited data in multiple myeloma:
  * Bendamustine-Prednisone vs Melphalan-Prednisone in newly-diagnosed MM: better CR rate and TTP with similar OS (1)
  * In combination with Thalidomide or Lenalidomide and corticosteroids in relapsed-refractory MM: response rate 26% to 86% (2-5)

References:
(1) Pönisch W: J Cancer Res Clin Oncol 2006;132:205
(2) Lentzsch: Blood 2012 prepublished March 26
(3) Pönisch W: Br J Haematol 2008;143:191
(4) Ramasamy: Br J Haematol 2011;155:620
(5) Grey-Davies: Br J Haematol 2011;156:545
### Bendamustine in multiple myeloma

**In combination with bortezomib and corticosteroids:**

<table>
<thead>
<tr>
<th></th>
<th>N pts</th>
<th>Age</th>
<th>Previous lines</th>
<th>Therapy regimen</th>
<th>Responses (PR+)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>7</td>
<td>63 (51-65)</td>
<td>2 (2-5)</td>
<td>Bort 1.3 mg/m2 d1-4-8-11 Benda 50-100 mg/m2 d1-8 Dex 40 mg d1-4-8-11 Every 21d</td>
<td>57%</td>
<td>ND</td>
</tr>
<tr>
<td>(2)</td>
<td>46</td>
<td>63 (31-77)</td>
<td>2 (1-6)</td>
<td>Bort 1.3 mg/m2 d1-4-8-11 Benda 60-80 mg/m2 d1-2 Pred 100 mg d1-2-4-8-11 Every 21d</td>
<td>60.8%</td>
<td>At 12 months EFS 46% OS 79% if no severe hematological tox EFS 10% OS 22% if tox present</td>
</tr>
<tr>
<td>(3)</td>
<td>40</td>
<td>66 (51-86)</td>
<td>4 (2-10)</td>
<td>Bort 1.3 mg/m2 d1-4-8-11 Benda 60 mg/m2 d1-8 Dex 24 mg d1-2-3-8-9-10 Every 21d</td>
<td>60%</td>
<td>PFS 8 months (responders only)</td>
</tr>
<tr>
<td>(4)</td>
<td>45</td>
<td>64 (40-86)</td>
<td>1-2: 25 pts 3-4: 16 pts &gt; 4: 4 pts</td>
<td>Bort 1.3 mg/m2 d1-4-8-11 Benda 70 mg/m2 d1-4 Dex 20 mg d1-4-8-11 Every 28d</td>
<td>51.5%</td>
<td>PFS 9.4 months</td>
</tr>
</tbody>
</table>

(1) Fenk: Leuk Lymphoma 2007;48:2345  
(2) Pönisch: ASH 2007;2723A  
(3) Hrusovsky: ASH 2007;4851A  
(4) Ludwig: ASH 2011;2928A
Inclusion criteria

- Symptomatic MM according to CRAB criteria before 1\textsuperscript{st} line treatment
- Patient having received conventional chemotherapy in 1\textsuperscript{st} line treatment
- Patient in 1\textsuperscript{st} relapse or refractory to 1\textsuperscript{st} line therapy
- Measurable disease (\(\geq10\text{g/l serum monoclonal gammopathy and/or} \geq 200\text{mg/24h light-chain proteinuria}\))
- ECOG performance status \(\leq 2\) at study entry
- Laboratory test results within these ranges:
  - Absolute neutrophil count \(\geq 1.5 \times 10^9/\text{L}\)
  - Platelet count \(\geq 100 \times 10^9/\text{L}\)
  - Serum creatinine \(\leq 250 \mu\text{mol/l}\)
  - AST (SGOT) and ALT (SGPT) \(\leq 3 \times \text{ULN}\)
Exclusion criteria

- Patients having received more than 1 prior therapy line
- Patients treated with high-dose therapy plus stem cell transplantation in 1st line therapy
- Any prior use of bortezomib or bendamustine
- Active infection or other serious medical condition
- Life expectancy less than 3 months
BVD regimen

- Bendamustine IV: 70 mg/m2 day 1 and 8
- Bortezomib IV: 1.3 mg/m2 day 1, 8, 15 and 22
- Dexamethasone: 20 mg day 1, 8, 15 and 22
Study design

Centralized electrophoresis analysis at inclusion and end of cycle 4

No primary prophylaxis of neutropenia (secondary prophylaxis allowed)
Valacyclovir prophylaxis recommended
No systematic prevention of thrombosis

All data assessed by an external CRO

Pre-study phase

Induction phase
(4 months)
4 consecutives 28-day cycles
B (70mg/m²) : D1 D8
V (1.3mg/m²): D1 D8 D15 D22
D (20mg/d) : D1 D8 D15 D22

Consolidation phase
(2 months)
2 consecutives 28-day cycles
B (70mg/m²) : D1 D8
V (1.3mg/m²): D1 D8 D15 D22
D (20mg/d) : D1 D8 D15 D22

Maintenance phase
(12 months)
6 28-day cycles every 2 months
B (70mg/m²) : D1 D8
V (1.3mg/m²): D1 D8 D15 D22
D (20mg/d) : D1 D8 D15 D22

Response evaluation every 2 months*

Response evaluation
Less than PR: study end
Loss of response: study end

Phase 2 study
Objectives

✓ **Primary objective:**
  * response at end of cycle 4

✓ **Secondary objectives:**
  * overall response rate
  * response after consolidation and maintenance phases
  * time to best response
  * progression-free survival
  * overall survival
  * toxicity
Baseline characteristics

- From 03/2010 to 07/2011: 83 patients screened in 27 IFM centers
  - 5 screening failures
  - 4 did not receive treatment (comorbidity)
  - 1 not fulfilling inclusion criteria

- 73 patients analyzed

- Median time from diagnosis: 29 months (range 5-88)
Baseline characteristics

Median age 75.8 years (range 66-86)
80 years or older 19 patients (26%)

Male 38 patients – Female 35 patients

Performance status ECOG
0: 16 patients (21.9%)
1: 35 patients (47.9%)
2: 22 patients (30.1%)
ND: 1 patient (1.3%)

Creatinine level ≥ 150 mcmol/l 11 patients (15.3%)

Beta 2 microglobulin level > 3.5 mg/l 49 patients (67.1%)

Preexisting neuropathy 24 patients (32.8%) – 23 pretreated with Thalidomide
Grade 1: 19 patients
Grade 2: 5 patients
Baseline characteristics

✓ Cytogenetic study by FISH analysis (centralized in Nantes laboratory)
  * Informative in 58 patients
  * t(4;14): 9 patients (15.5%)
  * del17p: 5 patients (8.6%)

✓ Prior therapies: 1 line in 73 patients (100%)
  * Melphalan - Prednisone: 12 patients
  * Melphalan - Prednisone - Thalidomide: 44 patients
  * Lenalidomide - Dexamethasone: 14 patients
  * Others: 3 patients (MPR: 1, Thal-Dex: 1, MCDex-Thal: 1)
Centralized electrophoresis analysis at inclusion and end of cycle 4

No primary prophylaxis of neutropenia (secondary prophylaxis allowed)
Valacyclovir prophylaxis recommended
No systematic prevention of thrombosis

All data assessed by an external CRO

Present analysis restricted to first 4 cycles
Results

✓ Response at end of cycle 4: 42 patients (57.5%)

<table>
<thead>
<tr>
<th>Response</th>
<th>n pts</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>8</td>
<td>10.9</td>
</tr>
<tr>
<td>VGPR</td>
<td>9</td>
<td>12.3</td>
</tr>
<tr>
<td>PR</td>
<td>25</td>
<td>34.2</td>
</tr>
<tr>
<td>SD</td>
<td>10</td>
<td>13.6</td>
</tr>
<tr>
<td>Progression</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Premature withdrawal</td>
<td>10</td>
<td>13.6</td>
</tr>
</tbody>
</table>

✓ Among 10 premature withdrawals: 1 in VGPR, 6 in PR

✓ Overall response: 49 patients (67.1%) + 6 minor responses
Results

Survival at 4 months:

- Deaths: 11 patients (15%)
  - Multiple myeloma: 6 patients (8.2%)
  - Sepsis: 4 patients (5.4%)
  - Renal failure: 1 patient (1.3%)

- Progression free survival at 4 months: 77.2%
- Overall survival at 4 months: 85%
Prognostic factors

<table>
<thead>
<tr>
<th></th>
<th>Responses</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta 2 microglobulin</strong></td>
<td>≤ 3.5 mg/l</td>
<td>18/24 pts (75%)</td>
</tr>
<tr>
<td></td>
<td>&gt;3.5 mg/l</td>
<td>24/49 pts (49%)</td>
</tr>
<tr>
<td><strong>IMiD in 1st line</strong></td>
<td>No</td>
<td>10/12 pts (83.3%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>32/61 pts (52.5%)</td>
</tr>
<tr>
<td><strong>Del17p</strong></td>
<td>Absent</td>
<td>33/53 pts (62.2%)</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>1/5 pts (20%)</td>
</tr>
</tbody>
</table>

Age 80y+, creatinine level ≥ 150 mcmol/l, t(4;14), prior alkylating treatment, refractory to 1st line: ns
Toxicity

☑ Adverse events grade 3-4:
  * Neutropenia: 16 pts (21.9%), thrombocytopenia: 7 pts (9.5%)
  * Sepsis: 12 pts (16.4%)
  * Gastro-intestinal: 8 pts (10.9%)
  * Anaphylaxis: 1 pt (1.3%)

☑ Deep vein thrombosis: 2 patients (2.7%)

☑ Peripheral neuropathy grade > 1: 9 patients (12.3%)
  * all grade 2
  * preexisting in 5 pts

☑ Treatment stopped in 20 patients (27.3%)
  * lack of efficacy: 11 pts (15%)
  * toxicity: 9 pts (12.3%)
In this elderly population, the BVD combination shows promising results (57.5% response rate at end of cycle 4, 67.1% overall response rate)

A longer follow-up is necessary to assess durability of response and survival

BVD combination demonstrates a good safety profile. Weekly administration of bortezomib results in a low rate of peripheral neuropathy