New Evidence reports on presentations given at EHA/ICML 2011

Bendamustine in the Treatment of Lymphoproliferative Disorders
Report on EHA/ICML 2011 presentations

- Efficacy and safety of bendamustine plus bortezomib in relapsed/refractory multiple myeloma: A phase I/II trial (Berenson JR, et al. ASCO 2011: Abstract 8070)

- Rituximab plus bendamustine in elderly previously untreated patients with indolent, non-follicular NHL: Preliminary data of a single centre study (Pennesse E and Di Renzo N. EHA 2011: Abstract 1440)


NHL = non-Hodgkin lymphoma; RCT = randomized controlled trial.
Efficacy and safety of bendamustine plus bortezomib in relapsed/refractory multiple myeloma: A phase I/II trial

Berenson JR, et al. ASCO 2011: Abstract 8070
Background

- Novel and effective treatment combinations are needed for patients with relapsed/refractory MM.

- Bendamustine is a unique alkylating agent, which is active in MM.

- Bortezomib is approved for the treatment of MM and has previously been shown to be effective in combination with other alkylators such as melphalan and cyclophosphamide.

- Berenson and colleagues presented the results of an open-label, phase I/II study that assessed the efficacy and safety of bendamustine plus bortezomib in relapsed/refractory MM at ASCO 2011.¹

Study design

- Patients older than 18 years, with measurable, relapsed/refractory MM were enrolled in this study.
- Treatment included escalating doses of intravenous bendamustine at 50, 70, or 90 mg/m² plus bortezomib 1.0 mg/m² for up to eight 28-day cycles.
- DLTs were assessed after cycle 1.
- A standard three-plus-three approach was used to determine the MTD, and the MTD cohort was expanded to 40 patients.
- Endpoints included response, duration of response, TTP, and safety.
Key findings

- 38 patients with a median age of 67 years received treatment with this experimental study drug combination and were included in the analysis.
- The patients had received a median of 3.5 prior therapies including bortezomib in 71% and alkylators in 68% of cases.
- A median of three treatment cycles were administered, and study treatment is ongoing in 14 patients (median cycles administered to date is four [range: 1–7 cycles] in these patients).

Key findings (cont’d)

- No DLTs were observed, and bendamustine at a dose of 90 mg/m² plus bortezomib 1.0 mg/m² was designated the MTD.
- Grade 3–4 AEs that occurred in ≥10% of patients included neutropenia, thrombocytopenia, and anemia.
- Grade 3–4 infection occurred in three patients (8%), and grade 3 renal failure was observed in two patients (5%).
Table 1. Grade 3–4 adverse events

<table>
<thead>
<tr>
<th>Grade 3–4 adverse event that occurred in ≥10% of patients</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>13 (34)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>
Key findings (cont’d)

- No grade 3–4 PN was observed but grade 1–2 PN was reported in 10 patients (26%), with eight of these patients having baseline PN at the time of study enrollment.

- In 36 evaluable patients, the ORR was 47%, including one very good partial response, six partial responses, and 10 minimal responses.

- In subgroups of patients, the observed ORR was:
  - 52% in the 90 mg/m^2 cohort (n = 27);
  - 37% in patients with prior bortezomib exposure;
  - 40% in patients with prior alkylator exposure.

PN = peripheral neuropathy; ORR = overall response rate.
**Key findings (cont’d)**

- An additional 17 patients had stable disease.
- Taking all of these results together, the clinical benefit rate (ORR plus stable disease) was 94%.
- The median duration of response and TTP have not been reached.


ORR = overall response rate; TTP = time to progression.
Key conclusions

- Bendamustine 90 mg/m$^2$ plus bortezomib 1.0 mg/m$^2$ is well tolerated.
- Bendamustine plus bortezomib demonstrates promising efficacy in this heavily pretreated population of MM patients.


MM = multiple myeloma.
Rituximab plus bendamustine in elderly previously untreated patients with indolent, non-follicular NHL: Preliminary data of a single centre study

Pennesse E and Di Renzo N. EHA 2011: Abstract 1440
Background

- Bendamustine has shown considerable activity for solid and lymphoid malignancies.
- It has recently become available for clinical use as a first-line treatment for CLL and as salvage therapy after rituximab or rituximab-based regimens for early relapsed or refractory indolent B-cell NHL.
- Recent clinical trials have demonstrated the safety and efficacy of bendamustine in these settings.


CLL = chronic lymphocytic leukemia; NHL = non-Hodgkin lymphoma.
Pennesse and Di Renzo assessed the efficacy and safety of bendamustine in combination with rituximab in elderly previously untreated patients with indolent, non-follicular NHL. The results of this study were presented at EHA 2011.¹

¹ Penesse E and Di Renzo N. EHA 2011: Abstract 1440.
Study design

- Elderly patients with previously untreated indolent, non-follicular NHL were enrolled in this single centre study.
- The study treatment consisted of six to eight 21- to 28-day cycles of rituximab, and bendamustine given intravenously on days 1 and 2.
- Response assessment was planned after the first three cycles were administered and at the end of treatment.
- Supportive therapy with G-CSF and ESA were provided as needed.


NHL = non-Hodgkin lymphoma;
G-CSF = granulocyte colony-stimulating factor;
ESA = erythropoietin-stimulating agents.
Key findings

- Between October 2008 to May 2010, 20 patients with previously untreated indolent, non-follicular NHL were enrolled in the study.
  - The median age was 74 years with 17 patients (85%) being older than 70 years.
  - 11 patients had B-cell CLL or B-CLL/SLL, eight patients had LPL/WM, and one patient had SMZL.
  - Extranodal site involvement was present in one patient and all patients had bone marrow involvement.


NHL = non-Hodgkin lymphoma;
CLL = chronic lymphocytic leukemia;
SLL = small lymphoblastic lymphoma;
LPL = lymphoplasmacytoid lymphoma;
WM = Waldenstrom's macroglobulinemia;
SMZL = splenic marginal zone lymphoma.
Key findings (cont’d)

- 14 patients (70%) had comorbid conditions and 30% had two or more diseases.

- A median of five cycles was delivered and 14 patients (70%) completed the planned treatment.
  - Dose reduction occurred in four patients (20%);
  - Nine patients (45%) received G-CSF as primary (10%) and secondary (25%) prophylaxis;
  - ESA support was required in four patients (22%).


G-CSF = granulocyte colony-stimulating factor; ESA = erythropoietin-stimulating agents.
Key findings (cont’d)

- CR was achieved in 11 patients (55%) and PR in nine patients (45%), resulting in an ORR of 100%.
- 10 of the 11 (91%) patients with B-CLL/SLL achieved CR, while all patients with LPL/WM had a PR. No relapses were observed.
- The median follow-up was 16 months.
- The regimen of rituximab and bendamustine was safe and well tolerated.


CR = complete response; PR = partial response; ORR = overall response rate; B-CLL = B-cell chronic lymphocytic leukemia; SLL = small lymphoblastic lymphoma; LPL = lymphoplasmacytoid lymphoma; WM = Waldenstrom’s macroglobulinemia.
Key findings (cont’d)

- The main AE was neutropenia, which occurred in 39% of patients.
  - Severe neutropenia (grade 3–4) was observed in four patients (20%).
- No non-hematological AEs were observed and there were no deaths related to the study medication.


AE = adverse event.
Key conclusions

- Rituximab and bendamustine is an effective regimen for elderly patients with previously untreated indolent non-follicular NHL including CLL/SLL.
- The treatment is safe, with tolerable toxicities consisting of myelosuppression.
- A longer follow-up period is needed to define response duration and long-term safety.


NHL = non Hodgkin lymphoma; CLL = chronic lymphocytic leukemia; SLL = small lymphoblastic lymphoma.
Bendamustine for patients with indolent lymphoma – a systematic review and meta-analysis of RCTs

Background

- Outcomes of patients with indolent lymphoma have improved in recent decades.
- While it is clear that the addition of rituximab to induction chemotherapy improves survival of these patients, it is unclear what the best chemotherapy partner for rituximab is.
- None of the chemotherapy regimens that have been compared in RCTs were superior in terms of OS.
- A number of RCTs have examined the effect of bendamustine in patients with indolent lymphoma including FL.


RCT = randomized controlled trial; OS = overall survival; FL = follicular lymphoma.
**Background (cont’d)**

- PFS was similar or prolonged with bendamustine compared with other chemotherapy, but an OS benefit has not yet been shown.

- At EHA 2011, Vidal, et al. presented the results of their systematic review and meta-analysis in which they evaluated the effect of bendamustine on the OS of patients with indolent lymphoma.¹

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PFS = progression-free survival; OS = overall survival.
Study design

- RCTs that compared bendamustine to other chemotherapy regimens for patients with indolent lymphoma were included in this meta-analysis.
- The Cochrane Library, MEDLINE, LILACS, references and personal correspondence, conference proceedings from ASH, ASCO, and EHA (2000–2010), and databases of ongoing trials were searched in December 2010.
- Methodological quality assessment was performed using the individual component approach.
- Two reviewers independently assessed the quality of the trials and extracted data.


RCT = randomized controlled trial;
ASH = American Society of Hematology;
ASCO = American Society of Clinical Oncology;
EHA = European Hematology Association.
Study design (cont’d)

- The primary outcome was OS.
- RR with 95% CI was estimated for the individual trials.
- The random-effects model was used to pool the results.


RR = relative risk; OS = overall survival; CI = confidence interval.
Key findings

- Four trials were identified for inclusion in this meta-analysis.
  - They were conducted between the years 1994 and 2010 and published between 2006 and 2010.
  - The studies randomized a total of 1,251 adult patients with a mean or median age of 58 to 68 years.

- The rate of patients with FL ranged between 40% to 52%, and mantle cell lymphoma 20% to 21% in the three trials that included patients with those types of lymphomas.

- One trial included only patients with CLL.


FL = follicular lymphoma; CLL = chronic lymphocytic leukemia.
Key findings (cont’d)

- The comparisons were between:
  - Bendamustine, vincristine, prednisone to COP;
  - Bendamustine-rituximab to R-CHOP;
  - Bendamustine-rituximab to fludarabine-rituximab;
  - Bendamustine to chlorambucil.


COP = cyclophosphamide, vincristine, prednisone;
R-CHOP = rituximab, cyclophosphamide, adriamycin,
vincristine, prednisone.
<table>
<thead>
<tr>
<th>Study</th>
<th>Herold 2006</th>
<th>Rummel 2009</th>
<th>Rummel 2010</th>
<th>Knauf 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>164</td>
<td>549</td>
<td>219</td>
<td>319</td>
</tr>
<tr>
<td>Mean/median age (years)</td>
<td>58</td>
<td>64</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>FL (40%), MCL (21%), other</td>
<td>FL (52%), MCL (20%), other</td>
<td>FL (46%), MCL (20%), other</td>
<td>CLL</td>
</tr>
<tr>
<td>Bendamustine regimen</td>
<td>Bendamustine, vincristine, prednisone</td>
<td>Rituximab, bendamustine</td>
<td>Rituximab, bendamustine</td>
<td>Bendamustine</td>
</tr>
<tr>
<td>Comparator</td>
<td>COP</td>
<td>R-CHOP</td>
<td>R-fludarabine</td>
<td>Chlorambucil</td>
</tr>
</tbody>
</table>

*CLL = Chronic lymphocytic lymphoma; COP = cyclophosphamide, vincristine, prednisone; FL = follicular lymphoma; MCL = mantle cell lymphoma; R-CHOP = rituximab, cyclophosphamide, adriamycin, vincristine, prednisone*
Key findings (cont’d)

- Patients treated with bendamustine had an improved OS compared with controls and the RR for death was 0.80 (95% CI: 0.67–0.97, I^2 = 0).

- After excluding the trial with only CLL patients, the RR for death became 0.82 (95% CI: 0.67 –1.01).

- PFS was improved with bendamustine, with a HR of 0.47 (95% CI: 0.39–0.57).


OS = overall survival; RR = relative risk; CI = confidence interval; CLL = chronic lymphocytic leukemia; PFS = progression-free survival; HR = hazard ratio.
Figure 1. All cause mortality in patients with indolent lymphoma treated with bendamustine compared to other chemotherapy

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bendamustine</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Indolent lymphomas (FL, MCL, others)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herold 2006</td>
<td>32</td>
<td>82</td>
<td>43</td>
</tr>
<tr>
<td>Rummel 2009</td>
<td>34</td>
<td>260</td>
<td>33</td>
</tr>
<tr>
<td>Rummel 2010</td>
<td>42</td>
<td>109</td>
<td>46</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>451</strong></td>
<td><strong>432</strong></td>
<td><strong>80.0%</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>108</td>
<td>122</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau* = 0.00; Chi* = 1.32, df = 2 (p = 0.52); I* = 0%

Test for overall effect: Z = 1.87 (p = 0.06)

CLL patients only

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Bendamustine</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Knauf 2009</td>
<td>31</td>
<td>162</td>
<td>41</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>162</strong></td>
<td><strong>157</strong></td>
<td><strong>20.0%</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>108</td>
<td>41</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>613</td>
<td>589</td>
<td>100%</td>
<td>0.80 (0.67–0.97)</td>
</tr>
</tbody>
</table>

**Total events**

| 139    | 163   |        |                      |

Heterogeneity: Tau* = 0.00; Chi* = 1.54, df = 3 (p = 0.67); I* = 0%

Test for overall effect: Z = 2.33 (p = 0.02)

Test for subgroup differences: Chi* = 0.24, df = 1 (p= 0.62), I* = 0%

95% CI = 95% confidence interval; CLL = Chronic lymphocytic lymphoma; FL = follicular lymphoma; MCL = mantle cell lymphoma

Key findings (cont’d)

- Complete remission rates improved with bendamustine compared with controls, with an RR of 2.31 (95% CI: 1.07–4.96, random effects model, I² = 88%).

- The rate of grade 3–4 adverse events was unaffected, with an RR of 1.21 (95% CI: 0.99–1.48).


RR = relative risk; CI = confidence interval.
Key conclusions

- This meta-analysis shows for the first time that bendamustine improves OS and PFS in patients with indolent lymphoma and CLL compared with other chemotherapy regimens.

- These results should be interpreted cautiously due to the wide clinical heterogeneity of patients and treatments.

- Further trials of a more homogenous group should be performed to explore the role of bendamustine in various lymphoproliferative neoplasms.


OS = overall survival; PFS = progression-free survival; CLL = chronic lymphocytic leukemia.
Bendamustine in combination with fludarabine and rituximab: A phase I-II novel non-myeloablative conditioning for AST in patients with lymphoid malignancies

Khouri IF, et al. ICML 2011: Abstract 042
Background

- It has previously been reported that fludarabine, rituximab, and cyclophosphamide have been used as nonmyeloablative conditioning therapy.\(^1\)

- Based on bendamustine’s efficacy in a number of different types of lymphoma, it is hypothesized that in the setting of nonmyeloablative allogeneic allografting, it can induce remission and stabilize disease with low toxicity.

- In order to improve outcomes in allogeneic stem cell transplantation, Khouri and colleagues studied the impact of substituting cyclophosphamide with bendamustine in conditioning.

- The results of this study were presented at ICML 2011.\(^2\)

Patients with relapsed CD20-positive NHL or CLL were included in this study.

Bendamustine was given intravenously in an escalated dose of 70, 90, 110, and 130 mg/m$^2$ daily three and five days prior to transplantation.

Fludarabine at a dose of 30 mg/m$^2$ was given on the same days.

Rituximab was given at a dose of 375 mg/m$^2$ 13 days prior to transplant and at a dose of 1,000 mg/m$^2$ on six days prior, and one and eight days after transplant.


NHL = non-Hodgkin lymphoma; CLL = chronic lymphocytic leukemia.
Tacrolimus and methotrexate were used for GVHD prophylaxis.

Thymoglobulin 1 mg/kg was given one and two days prior to transplant to patients who were being transplanted from an unrelated donor.

The primary endpoints were engraftment and DLTs.

The secondary endpoints were response rates and occurrence of GVHD.

GVHD = graft versus host disease; DLT = dose-limiting toxicity.
Key findings

- The study included 23 patients: nine with MCL, four with FL, six with CLL, and four with DLBCL.
- Median age was 60 years (range: 30–70 years).
- Median prior treatments was two and three patients had prior transplant.
- At the time of transplant, 18 patients (78%) were relapsed and sensitive to induction while four (22%) were refractory or had primary induction failure.
- 15 patients received their transplants from related donors and eight from matched unrelated donors.


MCL = mantle cell lymphoma; FL = follicular lymphoma; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma.
Key findings (cont’d)

- The number of patients who received the 70, 90, 110, and 130 mg/m\(^2\) daily doses of bendamustine were two, three, three, and 15, respectively.
- One patient had a secondary rejection of stem cells from an unrelated donor (low stem cell dose).
- 14 patients (61%) did not nadir to an ANC <500 and 19 (83%) did not experience a platelet count <20,000/mm\(^3\).
- The median donor T-cell chimerism at day 30 was 93%.


ANC = absolute neutrophil count.
Key findings (cont’d)

- One patient developed acute GVHD (grade 3) and one of 21 evaluable patients developed chronic GVHD.
- With a median follow-up time of eight months, the OS and PFS rates were 92% and 79%, respectively.
- Complete remission was observed in 18 patients (78%) and partial remission in three (13%) patients.
- Fungal infection was the cause of the only death observed and that patient also experienced grade 4 gastrointestinal and neurologic AEs.


GVHD = graft versus host disease; OS = overall survival; PFS progression-free survival; AE = adverse event.
Figure 1. Bendamustine-based allogeneic nonmyeloablative conditioning survival

OS = overall survival; PFS = progression-free survival

Figure 2. Bendamustine-based allogeneic nonmyeloablative conditioning response

- Median follow-up = 8 months (3–25 months)

CR – complete response; PR – partial response; SD – stable disease

The maximal grade of other observed toxicities was 3 and these included 11 grade 3 infections and two grade 3 cardiovascular AEs.

No DLT was observed.


AE = adverse event; DLT = dose-limiting toxicity.
Key conclusions

- This study is the first report to suggest that combining bendamustine at a dose of up to 130 mg/m² daily for three days with fludarabine and rituximab is safe and constitutes a well-tolerated conditioning treatment for nonmyeloablative allogeneic stem cell transplantation.

- Immunosuppression without myelosuppression was achievable and the toxicities were minimal, with no DLT and low rates of acute GVHD.

- Currently, patients are being treated with this regimen in an outpatient setting and the study is ongoing to verify the safety and efficacy of bendamustine, fludarabine, and rituximab.


GVHD = graft versus host disease; DLT = dose-limiting toxicity.