New Evidence reports on presentations given at EHA/ICML 2011

Rituximab in the Treatment of Follicular Lymphoma
Report on EHA/ICML 2011 presentations

- Preliminary results of QoL analyses from the intergroup phase III randomized trial of rituximab vs. watch and wait approach in patients with FL (Ardeshna KM, et al. ICML 2011: Abstract 019)


QoL = quality of life; FL = follicular lymphoma; PFS = progression-free survival.
Preliminary results of QoL analyses from the intergroup phase III randomized trial of rituximab vs. watch and wait approach in patients with FL

Ardeshna KM, et al. ICML 2011: Abstract 019
Little is known about the QoL of patients with advanced stage asymptomatic FL who are not treated immediately but rather undergo watchful waiting.

This study by Ardeshna and colleagues was designed to compare immediate treatment with rituximab with watchful waiting. It was powered for both clinical outcome and QoL, and the results were presented at ICML 2011.¹

Study design

- Eligible patients with advanced stage, asymptomatic, non-bulky FL were randomized between watchful waiting, rituximab induction, and rituximab induction followed by rituximab maintenance over two years.

- QoL was assessed before and after randomization. If no new therapies were initiated, QoL was assessed one month after randomization and then every two months for two years, followed by every six months for two years.

QoL = quality of life; FL = follicular lymphoma.
Study design (cont’d)

- QoL questionnaires used were:
  - FACT-G with four additional questions relating to worries about:
    - Their disease becoming more aggressive;
    - Requiring therapy;
    - Being unable to support themselves or their family;
    - Having difficulty planning for the future.


QoL = quality of life; FACT = Functional Assessment of Cancer Therapy.
Study design (cont’d)

- Additional QoL questionnaires used were:
  - HADS
  - Mental Adjustment to Cancer Scale
  - Impact of Event Scale – revised
  - Illness Impact Bank
  - Illness Coping Style


QoL = quality of life; HADS = Hospital Anxiety and Depression Scale.
Study design  *(cont’d)*

- The primary aim was to determine if at seven months after randomization:
  - Immediate treatment with rituximab increased functional wellbeing;
  - Deferring treatment results in increased anxiety and depression;
  - Increased clinic visits and the side effects related to the administration of rituximab negatively impacted wellbeing.

The secondary aims were the same at 13, 25, and 37 months.

Except for HADS subscale, all subscale scores were standardized on a 100-point scale, with 100 indicating perfect health.

A change of five to 10 points was regarded as a minimal clinically important difference, and a p-value of <0.01 was considered to be statistically significant.

At the time of presentation, data had been analyzed for baseline, month 7, and month 13.
Key findings

- Between September 2004 and May 2009, 463 patients were randomized in this study.

- 456 of these patients participated in the QoL portion of this study.

- Baseline QoL was similar between arms: mean scores were 89, 84, 73, and 80 for physical, social/family, emotional, and functional wellbeing, respectively.

- At baseline, 27% of patients had borderline or case anxiety, and 9% had borderline or case depression.

QoL = quality of life.
Key findings (cont’d)

- At months 7 and 13, emotional wellbeing significantly improved in all arms with a mean difference greater than five.
  - The greatest improvement was in rituximab maintenance group.
- Anxiety was unchanged in the watchful waiting and rituximab induction arms, but significantly reduced in the rituximab maintenance arm from 11.0% (baseline) to 6.6% by month 13 ($p = 0.00005$).
- Depression was unchanged from baseline to month 7 or month 13.
Figure 1. Emotional wellbeing

Comparison of change between the arms

<table>
<thead>
<tr>
<th></th>
<th>Baseline to</th>
<th>Baseline to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>month 7</td>
<td>month 13</td>
</tr>
<tr>
<td>Watchful waiting vs. rituximab induction</td>
<td>$p = 0.52$</td>
<td>$p = 0.24$</td>
</tr>
<tr>
<td>Watchful waiting vs. rituximab maintenance</td>
<td>$p = 0.02$</td>
<td>$p = 0.04$</td>
</tr>
<tr>
<td>Rituximab induction vs. rituximab maintenance</td>
<td>$p = 0.27$</td>
<td>$p = 0.64$</td>
</tr>
</tbody>
</table>

### Table 1. HADS – anxiety

<table>
<thead>
<tr>
<th></th>
<th>Baseline (%)</th>
<th>Month 7 (%)</th>
<th>Month 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Watchful waiting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>71.3</td>
<td>76.5</td>
<td>77.4</td>
</tr>
<tr>
<td>Borderline anxiety</td>
<td>10.8</td>
<td>10.6</td>
<td>13.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17.8</td>
<td>12.9</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>p = 0.8238</strong></td>
<td></td>
<td><strong>p = 0.301</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rituximab induction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>79.2</td>
<td>75.4</td>
<td>77.8</td>
</tr>
<tr>
<td>Borderline anxiety</td>
<td>11.7</td>
<td>15.8</td>
<td>13.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9.1</td>
<td>8.8</td>
<td>9.3</td>
</tr>
<tr>
<td><strong>p = 0.9999</strong></td>
<td></td>
<td><strong>p = 0.9999</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rituximab maintenance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>71.1</td>
<td>79.0</td>
<td>86.1</td>
</tr>
<tr>
<td>Borderline anxiety</td>
<td>17.9</td>
<td>12.3</td>
<td>7.2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.0</td>
<td>8.8</td>
<td>6.6</td>
</tr>
<tr>
<td><strong>p = 0.1496</strong></td>
<td></td>
<td><strong>p = 0.0000535</strong></td>
<td></td>
</tr>
</tbody>
</table>
Key findings (cont’d)

- Mental adjustment to cancer improved significantly from baseline to month 7 or month 13 in the rituximab maintenance arm and patients felt more in control of their situation, but this was not observed in the rituximab induction or watchful waiting arms.

- There was a trend for patients receiving rituximab maintenance to be less worried about their disease becoming more aggressive at month 7 and this trend became highly significant at month 13.

- At month 7, patients in the watchful waiting arm were more likely to be worrying about requiring treatment (or more treatment) than patients receiving rituximab maintenance.

Table 2. Mental adjustment to cancer

<table>
<thead>
<tr>
<th></th>
<th>Change from baseline to month 7</th>
<th>Change from baseline to month 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful waiting</td>
<td>-3.49</td>
<td>+1.56</td>
</tr>
<tr>
<td></td>
<td>p = 0.17</td>
<td>p = 0.50</td>
</tr>
<tr>
<td>Rituximab induction</td>
<td>-0.79</td>
<td>-0.22</td>
</tr>
<tr>
<td></td>
<td>p = 0.78</td>
<td>p = 0.94</td>
</tr>
<tr>
<td>Rituximab maintenance</td>
<td>+8.53</td>
<td>+9.06</td>
</tr>
<tr>
<td></td>
<td>p &lt;0.0001</td>
<td>p &lt;0.0001</td>
</tr>
</tbody>
</table>
Key findings (cont’d)

- Patients receiving rituximab maintenance were significantly less worried about supporting themselves or their family by month 13 than patients in watchful waiting.

- In terms of difficulty in planning for the future, there were some improvements in all treatment arms from baseline to month 7 or month 13, but these were not significant.

Key conclusions

- At baseline, the physical, social, and functional wellbeing is high in all patients, while emotional wellbeing is relatively reduced.

- There is an increase in case anxiety relative to the normal population, the cause of which was likely worry about the disease becoming more aggressive and the need for treatment.

- There is also an increase in case depression relative to the normal population.

- The negative impact of the diagnosis of FL lessens with time.

Key conclusions *(cont’d)*

- Emotional wellbeing and additional concerns improved, and this was greater in the rituximab maintenance group compared with watchful waiting. Patients on watchful waiting were more likely that patients on rituximab maintenance to:
  - Be worried about the disease becoming more aggressive;
  - Be worried about the need for therapy;
  - Be worried about their ability to support themselves or their family;
  - Not feel in control of their situation;
  - Have negative associations with hospital visits;
  - Avoid thinking about or learning about their illness;
  - Have reduced improvement in emotional wellbeing.

Key conclusions (cont’d)

- None of the QoL scales used in this study showed a benefit for watchful waiting over rituximab induction or rituximab maintenance.

QoL = quality of life.
Bortezomib-rituximab results in improved PFS and response rates vs. Rituximab, and quality of response is associated with improved outcomes, in patients with relapsed FL

Background

- Outcomes in patients with FL have improved in recent years because of the introduction of new therapies, and the quality of response to first-line therapy is associated with improved survival.\(^1\)

- Rituximab is approved for relapsed/refractory FL and it is a widely used treatment in newly diagnosed and relapsed FL.\(^2\)

- Bortezomib has shown activity as a single agent in heavily pre-treated indolent lymphoma patients.\(^3\)

- In combination with rituximab, bortezomib has shown activity in a randomized phase II study in FL and other non-Hodgkin lymphoma subtypes.\(^4,5\)


FL = follicular lymphoma.
Background *(cont’d)*

- In this study, Coiffier and colleagues report on the overall efficacy and safety results of the international, multicentre, phase III LYM3001 study that compared bortezomib-rituximab with rituximab alone in patients with relapsed or refractory rituximab-naïve or rituximab-sensitive FL.

- Additionally, analyses were conducted to determine the impact of quality of response to treatment on outcomes. The results were presented at EHA 2011.⁶

Study design

- Patients with grade 1 or 2 measurable, relapsed FL with a TTP of six or more months for prior rituximab-containing therapy were enrolled.

- Patients were randomized in a one-to-one ratio to receive five five-week treatment cycles consisting of bortezomib plus rituximab, or rituximab alone on the same schedule.

- The primary endpoint was PFS.

- Secondary endpoints included ORR, CR/CRu rates, DOR, TTP, and one-year OS, as well as safety and tolerability.


FL = follicular lymphoma.; TTP = time to progression; PFS = progression-free survival; ORR = overall response rate; CR = complete response; CRu = unconfirmed CR; DOR = duration of response; OS = overall survival.
Key findings

- A total of 676 patients were enrolled to receive bortezomib-rituximab (n = 336) or rituximab alone (n = 340).
- The baseline characteristics were generally well balanced between the study arms.
  - The median age was 57 years in the bortezomib-rituximab arm (range: 24–83 years) and 57 years in the rituximab arm (range: 21–84 years).
  - 43% and 44% had received prior rituximab, respectively.

### Key findings (cont’d)

- Patients in both arms received a median of five cycles of therapy (range: 1–5 cycles).
  - 71% and 72% of the patients in the bortezomib-rituximab and rituximab arms, respectively, completed all five cycles.
  - 17% and 23% of patients, respectively, discontinued study therapy prior to completing all five cycles due to disease progression.

**Efficacy**

- After a median follow-up of 33.9 months, the median PFS was 12.8 months for bortezomib-rituximab vs. 11.0 months with rituximab.


PFS = progression-free survival.
Figure 1. Progression-free survival

Median PFS (95% CI)
- Rituximab: 11.0 months (9.1–12.0)
- Bortezomib-rituximab: 12.8 months (11.5–15.0)

HR: 0.822 (0.681–0.991)
p = 0.039

Patients at risk:
- R only: 340 267 216 171 120 94 76 60 46 35 27 17 9 5 2 1
- Btz-R: 336 265 229 197 142 115 97 80 62 46 33 23 15 11 6 2

95% CI = 95% confidence interval

Key findings (cont’d)

- PFS had the greatest clinical benefit in patients younger than 65 years, those receiving second- or third-line therapy, those who were rituximab-naive, those who had more than one year since their last therapy, and those with adverse prognostic factors.

- The ORR (CR/CRu+PR) was 63% vs. 49% ($p < 0.001$) in the bortezomib-rituximab and rituximab arms, respectively, including 25% vs. 18% CR/CRu ($p = 0.035$).

- Median DOR was 16.0 and 13.8 months, with 50% and 32% of patients in the bortezomib-rituximab arm and 38% and 23% in the rituximab arm having durable responses for six and 12 months, respectively.


PFS = progression-free survival; ORR = overall response rate; CR = complete response; CRu = unconfirmed CR; DOR = duration of response; PR = partial response.
Table 1. Response rates and durability of response

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib-rituximab (n = 315)</th>
<th>Rixuximab (n = 324)</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>63</td>
<td>49</td>
<td>0.569 (0.415–0.780)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>25</td>
<td>18</td>
<td>0.665 (0.455–0.973)</td>
<td>0.035</td>
</tr>
<tr>
<td>PR</td>
<td>38</td>
<td>31</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stable disease</td>
<td>25</td>
<td>37</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>12</td>
<td>14</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>16.0 (12.6–20.9)</td>
<td>13.8 (11.8–16.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Median DOR (CR/CRu)</td>
<td>28.6 (21.6–NE)</td>
<td>30.9 (14.2–NE)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Durable response (≥6 months) rate, %</td>
<td>50</td>
<td>38</td>
<td>0.608 (0.444–0.833)</td>
<td>0.002</td>
</tr>
<tr>
<td>Durable (≥6 months) CR/CRu</td>
<td>24</td>
<td>17</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Durable response (≥12 months) rate, %</td>
<td>32</td>
<td>23</td>
<td>0.636 (0.448–0.904)</td>
<td>0.012</td>
</tr>
<tr>
<td>Durable (≥12 months) CR/CRu</td>
<td>18</td>
<td>13</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval; CR = complete response; CRu = unconfirmed complete response; DOR = duration of response; NE = not evaluable; ORR = overall response rate; PR = partial response

Key findings (cont’d)

- In both arms, PFS was significantly longer in patients who achieved CR/CRu vs. PR vs. NR.
  - In the bortezomib-rituximab arm the median PFS was 32.6, 13.6, and 4.5 months, respectively;
  - In the rituximab arm the median PFS was 33.1, 14.1, and 4.7 months ($p \leq 0.01$ for all comparisons).

PFS = progression-free survival; CR = complete response; CRu = unconfirmed CR; PR = partial response; NR = no response.
Figure 2. Progression-free survival by treatment arm and response to treatment

Similarly, higher quality of response was associated with longer TTP, TTNT and TFI in both treatment arms.

The median TTP was 13.3 vs. 11.3 months, the median TTNT was 23.0 vs. 17.7 months and the median TFI was 17.7 vs. 13.0 months in the bortezomib-rituximab and rituximab arms, respectively.

The one year OS rates were 90.1% and 90.5% with bortezomib-rituximab vs. rituximab, respectively.
<table>
<thead>
<tr>
<th>Table 2. Outcomes by treatment arm: overall and by response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Bortezomib-rituximab</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Median TTP – ITT, months (95% CI)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>TTP, patients with CR/CRu</strong></td>
</tr>
<tr>
<td><strong>TTP, patients with PR</strong></td>
</tr>
<tr>
<td><strong>TTP, patients with NR</strong></td>
</tr>
<tr>
<td><strong>Median TTNT – ITT, months (95% CI)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>TTNT, patients with CR/CRu</strong></td>
</tr>
<tr>
<td><strong>TTNT, patients with PR</strong></td>
</tr>
<tr>
<td><strong>TTNT, patients with NR</strong></td>
</tr>
<tr>
<td><strong>Median TFI – ITT, months (95% CI)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>TFI, patients with CR/CRu</strong></td>
</tr>
<tr>
<td><strong>TFI, patients with PR</strong></td>
</tr>
<tr>
<td><strong>TFI, patients with NR</strong></td>
</tr>
<tr>
<td><strong>1-year OS rate – ITT, % (95% CI)</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

*HR for OS between arms

95% CI = 95% confidence interval; CR = complete response; CRu = unconfirmed complete response; HR = hazard ratio; ITT = intent to treat; NE = not evaluable; NR = no response; OS = overall survival; PR = partial response; TFI = treatment-free interval; TTNT = time to next treatment; TTP = time to progression
Key findings (cont’d)

Safety

- The rates of AEs, grade ≥3 AEs, serious SAEs, dose reductions, and treatment withdrawals were higher in the bortezomib-rituximab arm than in the rituximab arm.

- In the bortezomib-rituximab and rituximab arms, 46% and 21% of patients had grade ≥3 AEs, 18% and 11% had SAEs, and 16% and 1% had PN, most of which were reversible.

AEs = adverse events; SAEs = serious adverse events; PN = peripheral neuropathy.
Key conclusions

- Bortezomib-rituximab resulted in improvements in PFS, ORR, CR/CRu rates, DOR, and other outcomes compared with rituximab alone.

- The toxicity of the treatment was acceptable and though AE rates were higher with bortezomib-rituximab than with rituximab alone, this did not affect the feasibility of treatment.

- Achievement of CR/CRu vs. PR vs. NR was associated with greater clinical benefit in both arms.


PFS = progression-free survival; ORR = overall response rate; CR = complete response; CRu = unconfirmed CR; DOR = duration of response; AE = adverse event; PR = partial response; NR = no response.
Key conclusions (cont’d)

- The longer PFS and TTNT in the bortezomib-rituximab arm were driven by the additional responses with bortezomib-rituximab vs. rituximab, notably higher rates of durable response, CR/CRu, and durable CR/CRu.

- Further studies have begun to build on the bortezomib-rituximab combination.

PFS = progression-free survival; CR = complete response; CRu = unconfirmed CR; TTNT = time to next treatment.