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HOVON110/ReBeL Study: Results of the Phase I Part of a Randomized Phase I/II Study of Lenalidomide, Rituximab With or Without Bendamustine in Patients With Relapsed/Refractory Follicular Lymphoma

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Follicular lymphoma (FL), characterized by a t (14;18) (q32;q21), is one of the most common non-Hodgkin lymphomas (NHL). Although FL is sensitive to chemotherapy, immunotherapy and radiotherapy it currently remains an incurable disease. The variable outcome of FL appears to be determined mainly by the tumor-microenvironment and the non-malignant bystander cells.1,2 The immuno-modulatory drug lenalidomide has been shown to modulate the production of various cytokines in the tumor-microenvironment and activates T- and NK-cells.3,4

Impairment of the T-cell immunologic synapse formation in FL seems to be an active immunosuppressive mechanism, which in vitro can be overcome by treatment of FL cells with lenalidomide.5 A synergistic antitumor effect of lenalidomide and rituximab in lymphoma cell killing has been demonstrated in mouse models.2,6,7 Additionally, lenalidomide can have a direct antitumor effect because it inhibits Akt-phosphorylation and increases p21 expression, which are important for tumor cell proliferation and survival. The mechanisms of action of bendamustine include inhibition of the mitotic checkpoints,
induction of mitotic catastrophe, activation of DNA damage stress response, intrinsic apoptosis and base-excision DNA repair mechanisms. Several studies have demonstrated clinical activity of lenalidomide in indolent lymphoma and adding rituximab can improve the response rate with acceptable toxicity. In mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) the combination of lenalidomide, bendamustine and rituximab was found to be effective and feasible in patients in an upfront setting with a high CR rate but also a high rate of infections. To date there are no data on the combination of rituximab, bendamustine and lenalidomide in patients with FL. With this run-in phase I study we aimed to establish the recommended dose level (RDL) of bendamustine and lenalidomide for the triplet combination with rituximab for relapsed or refractory (R/R) FL patients in a subsequent randomized phase II study.

This is a multicenter, phase I/II study sponsored by HOVON (Hemato-Oncologie voor Volwassenen Nederland) (HOVON110; Netherlands Trial Register: Trial NL2882; EudrACT number: 2011-000097-56). The study was approved by the Ethics Committee of the Amsterdam UMC and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

In the ongoing phase II part, patients are randomized between arm A (lenalidomide and rituximab) and arm B (lenalidomide, bendamustine, rituximab). The aim of the phase I part was to determine the dose limiting toxicity (DLT) and RDL of the combination of lenalidomide, rituximab and bendamustine in a 28-day schedule in R/R FL patients. Eligible patients were ≥18 years, and were required to have biopsy proven, CD20 positive stage II-IV R/R FL grade 1–3. Rituximab refractory cases (defined as relapse/progression during or within 6 months after a rituximab containing regimen) were not eligible. The maximum number of prior systemic treatment regimens was five. Prior bendamustine was allowed if it was administered ≥24 months before enrolment and had resulted in at least a partial remission (PR).

A 3+3 dose-escalation design was used. Four carefully designed dose levels were considered: lenalidomide (10 mg, 15 mg or 20 mg) orally, escalating doses of bendamustine (70 mg/m² or 90 mg/m²) IV, combined with a fixed dose of rituximab (375 mg/m²) IV for a total of 6 induction cycles (Table 1). Patients with complete remission (CR) or partial remission (PR) continued with 2 years of rituximab maintenance treatment (8 infusions, every 3 months).

When 3 or 6 patients had been enrolled, inclusion was discontinued until DLT was determined at day 29 of cycle 1. Patients who died of FL within 29 days of starting treatment discontinued until DLT was determined at day 29 of cycle 1.

Results of the phase I part will be presented here. Eighteen patients with R/R FL, from 9 centers in the Netherlands and 1 in Germany, were enrolled between November 2011 and May 2014. Two patients were not evaluable due to a protocol amendment after inclusion, precluding the concurrent use of allopurinol during bendamustine treatment, and one rituximab refractory patient did not fulfill the inclusion criteria, leaving 15 evaluable patients for determination of the DLT and RDL. Median age at baseline was 58 years; 60% were female and the majority of patients had Ann Arbor stage IV disease (73%). The median number of prior treatments was 1 (range 1–3); 2 were rituximab naïve; none of the patients were refractory to their last lymphoma therapy (Table 2).

### Table 1

<p>| Dose Levels of Lenalidomide/Rituximab/Bendamustine for Each Cycle, in Total 6 Induction Cycles. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Agent</th>
<th>Level 1 (N = 3)</th>
<th>Level 2 (N = 3)</th>
<th>Level 3 (N = 3)</th>
<th>Level 4 (N = 6)</th>
<th>Route of administration and days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>10 mg o.d.</td>
<td>15 mg o.d.</td>
<td>15 mg o.d.</td>
<td>20 mg o.d.</td>
<td>p.o. day 3-21</td>
</tr>
<tr>
<td>(max 800 mg)</td>
<td>(max 800 mg)</td>
<td>(max 800 mg)</td>
<td>(max 800 mg)</td>
<td>(max 800 mg)</td>
<td>i.v. day 1</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>375 mg/m²</td>
<td>375 mg/m²</td>
<td>375 mg/m²</td>
<td>i.v. day 1</td>
</tr>
<tr>
<td>(max 375 mg/m²)</td>
<td>(max 375 mg/m²)</td>
<td>(max 375 mg/m²)</td>
<td>(max 375 mg/m²)</td>
<td>(max 375 mg/m²)</td>
<td></td>
</tr>
<tr>
<td>Bendamustine</td>
<td>70 mg/m²</td>
<td>70 mg/m²</td>
<td>90 mg/m²</td>
<td>90 mg/m²</td>
<td>i.v. day 1–2</td>
</tr>
<tr>
<td>(max 150 mg/day)</td>
<td>(max 150 mg/day)</td>
<td>(max 150 mg/day)</td>
<td>(max 150 mg/day)</td>
<td>(max 150 mg/day)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

Demographic and Disease Characteristics of the 15 Patients Enrolled in the Phase I Study.

<table>
<thead>
<tr>
<th>性别</th>
<th>年龄</th>
<th>性别</th>
<th>年龄</th>
<th>性别</th>
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<tbody>
<tr>
<td>女性</td>
<td>9</td>
<td>女性</td>
<td>9</td>
<td>女性</td>
<td>9</td>
</tr>
</tbody>
</table>

Patients could have had more than 1 systemic regimen prior to start of the study.
Among all 15 eligible patients only 1 DLT occurred before day 29 of cycle 1. This event, a grade 3 allergic reaction probably due to bendamustine, occurred at dose level 4 (the highest dose level). One other patient discontinued the study after cycle 4, because of an allergic reaction to rituximab. Despite recommendations against the use of allopurinol, two patients, in dose level 2 and 1 in dose level 3, used allopurinol; none of them experienced any signs of Stevens-Johnson syndrome.

All patients experienced at least 1 AE grade 2–4, in total 57 AEs were reported; 65% (n = 37 grade 2, 24% (n = 14) grade 3 and 10% (n = 6) grade 4. The most common AEs of any grade were: neutropenia, leucocytopenia, gastrointestinal disorders, infections, and abnormal laboratory results (Table 3). Six patients (40%) experienced a total of 13 SAEs; 3 pneumonias, 2 allergic reactions and 5 second primary malignancies; 3 basal cell carcinoma, 1 Merkel cell carcinoma, and 1 lung cancer. The lung cancer was only located in the lung and treated with curative intended radiotherapy. The other SAEs occurred only once; fever, knee pain and thrombocytopenia. Eight were classified as SAEs due to hospitalization, all 13 SAE’s resolved completely.

This first clinical study investigating the combination of lenalidomide, bendamustine and rituximab in R/R FL showed an acceptable safety and tolerability profile. Only one DLT was reported and most AEs were grade 2. Hematological toxicity was mostly seen at dose level 4 without severe consequences. The secondary primary malignancies were considered possibly related, but the patients had received prior therapy that could have contributed. We concluded that dose level 4 (lenalidomide 20mg dag 3–21 day, bendamustine 90mg/m² dag 1–3, combined with rituximab 375mg/m² day 1) is feasible for R/R FL patients. This dose level is currently being studied further in the randomized phase II part of the study for efficacy and toxicity in comparison with 6 cycles of lenalidomide 20mg dag 1 to 21 day and rituximab 375mg/m² day 1.

### Acknowledgments

The authors acknowledge the HDC trial team (HOVON Data Center) for trial coordination and central data management and Roberto Liu, Amsterdam UMC, location AMC for trial coordination.

### References