Betalutin 
(177Lu-Lilotomab) 

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May 10, 2016
Disclosures of: Arne Kolstad

<table>
<thead>
<tr>
<th>Company name</th>
<th>Research support</th>
<th>Employee</th>
<th>Consultant</th>
<th>Stockholder</th>
<th>Speakers bureau</th>
<th>Advisory board</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordic Nanovector</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
**Background**

- Two anti-CD20 radioimmunotherapy (RIT) agents (Zevalin® and Bexxar®) are currently approved for non-Hodgkin`s lymphoma.

- These drugs are not extensively used in treatment of NHL. Preference for naked anti-CD20 antibody

- They may not be as effective in patients who have been treated with anti-CD20 antibodies.

- A novel RIT agent, Lu177-Lilotomab (Betalutin) is developed at Oslo University Hospital and targets CD37 on B cell NHL.
HH1 (Lilotomab): anti-CD37 antibody

• Developed at the Norwegian Radium Hospital in the mid 1980’s.

• Nordic Nanovektor has obtained exclusive rights.
**CD37 is expressed on the same B-cell subsets as CD20**
Anti-CD37 (Lilotomab) is internalized while anti-CD20 (Rituximab) is not internalized.
**Structure of Betalutin**

**Lilotomab**: antibody that targets the CD37 antigen that is expressed on B-cell lymphocytes and corresponding NHLs.

**Tetraxetan**: Linker that binds to lysine residues on tetulomab and that chelates Lutetium-177.

**Lutetium-177**: Beta-particle emitting radioactive nuclide with 6.7 days half-life.
## Comparison of RIT agents

<table>
<thead>
<tr>
<th></th>
<th>Betalutin™</th>
<th>Zevalin®</th>
<th>Bexxar®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radioisotope</strong></td>
<td>$^{177}$Lu</td>
<td>$^{90}$Y</td>
<td>$^{131}$I</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>6.7 d</td>
<td>✓ 2.7 d</td>
<td>8.0 d</td>
</tr>
<tr>
<td><strong>Mean gamma-energy</strong></td>
<td>0.13 MeV</td>
<td>✓ 0.93 MeV</td>
<td>0.18 MeV</td>
</tr>
<tr>
<td><strong>Mean range in tissue</strong></td>
<td>0.67 mm</td>
<td>✓ 3.6 mm</td>
<td>0.7 mm</td>
</tr>
<tr>
<td><strong>ICRP radiotox.</strong></td>
<td>3 (moderate)</td>
<td>✓ 3 (moderate)</td>
<td>2 (high)</td>
</tr>
<tr>
<td><strong>Y-yield</strong></td>
<td>17 %</td>
<td>0 %</td>
<td>94 %</td>
</tr>
<tr>
<td><strong>Y-energies</strong></td>
<td>110 &amp; 210 keV</td>
<td>Bremsstrahlung</td>
<td>280, 360 &amp; 640 keV</td>
</tr>
<tr>
<td><strong>Imaging possible?</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>CD37</td>
<td>CD20</td>
<td>CD20</td>
</tr>
<tr>
<td><strong>Antibody</strong></td>
<td>tetulomab, murine IgG$_1$</td>
<td>ibritumomab, murine IgG$_1$</td>
<td>tositumomab, murine IgG$_{2a}$</td>
</tr>
<tr>
<td><strong>Pre-treatment</strong></td>
<td>rituximab</td>
<td>rituximab</td>
<td>tositumomab</td>
</tr>
</tbody>
</table>
Radiochemical aspects

• Carrier-free

• "Ready to use" formulation

• Specific activity (100-500MBq/mg)

• Clinical dosage: 10mg/patient
LYMRIT-37-01 phase 1/2 study

• Betalutin as single agent for treatment of relapsed indolent NHL

• A total of 24 patients have been enrolled in to the LYMIRIT-37-01 Phase 1/2 study, including 8 patients in Phase 2. 21 evaluable patients so far.

• The latest trial data were presented at the AACR congress in April 2016
**Major inclusion criteria**

1. Histologically confirmed (by WHO classification) **relapsed** incurable non-Hodgkin B-cell lymphoma of following subtypes; follicular grade I-IIIA, marginal zone, small lymphocytic, lymphoplasmacytic and mantle cell

2. Age > 18 years

3. A pre-study WHO performance status of 0-1

4. Life expectancy should be ≥ 3 months

5. <25% tumour cells in bone marrow biopsy

6. CD37+, re-biopsy or test on existing tumour material if not known

7. Measurable disease by radiological methods
**Major exclusion criteria**

1. Medical contraindications, including uncontrolled infection, severe cardiac, pulmonary, neurologic, psychiatric or metabolic disease, steroid requiring asthma/allergy, known HIV positive

2. Laboratory values:
   a. Absolute Neutrophil Counts ≤ 1.5 x 10^9 /l
   b. Platelet count ≤ 150 x 10^9 /l
   c. Total bilirubin ≥ 30 mmol/l
   d. ALP and ALAT ≥ 4x normal level
   e. Creatinine ≥ 110 µmol/l (men), 90 µmol/l (women)
   f. IgG ≤ 3 gr/l

3. Known CNS involvement of lymphoma
Treatment schedule. In Arm 1 patients received rituximab (375 mg/m²) on day -28 and -21 to deplete circulating B cells. On day 0 pre-dosing with 50 mg HH1 (cold CD37 antibody) was administered before Betalutin injection. In Arm 2 Betalutin was administered without HH1 pre-dosing on day 0. The first patient received 250 mg/m² rituximab on day -7 and day 0 prior to Betalutin and was included in Arm 2 in the presented poster.
Betalutin’s clinical development plan - Targeting approval in third line for follicular lymphoma

**LYMRIT 37-01 – Phase 1/2 trial**

- **Phase 1**
  - Arm 1 (closed)
    - 10MBq (- HH1 R0) N=1
    - 10MBq (+ HH1 50mg) N=3
    - 20MBq (+ HH1 50mg) N=3
  - Arm 2 (closed)
    - 15MBq (+ HH1 50mg) N=6
  - Arm 3
    - 15MBq (- HH1 R0) N=3 to 6
  - Arm 4
    - 15MBq (+ high dose HH1) N=3 to 6

- **Phase 2**
  - 15MBq (+ HH1 50mg) N=9
  - 10MBq (- HH1) N=2
  - 17.5MBq or 20MBq* (- HH1 – R0) N=3 to 6
  - 17.5MBq or 20MBq* (+ high dose HH1) N=3 to 6

**Pivotal Phase 2 PARADIGME trial**

- **First Patient:** 2H 2017
- **Dose TBD N=85**
- **Last Patient:** 2H 2018
- **Regulatory submission:** 1H 2019

**PARADIGME dose decision:** Q1 2017

*Dose decision based on safety data and Safety Review Board’s recommendation.
FL = follicular lymphoma.

**Summary of demographics and baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Phase 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose level</strong></td>
<td>10 MBq/kg N=3</td>
<td>15 MBq/kg N=6</td>
<td>20 MBq/kg N=3</td>
<td>10 MBq/kg N=2*</td>
</tr>
<tr>
<td><strong>Median age (years)</strong></td>
<td>68 50-69</td>
<td>66.5 49-78</td>
<td>68 41-69</td>
<td>63 58-68</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>3 (100%)</td>
<td>5 (83%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>0</td>
<td>1 (17%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td><strong>Primary diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- FL</td>
<td>3 (100%)</td>
<td>5 (83%)</td>
<td>2 (100%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>- MCL</td>
<td>0</td>
<td>1 (17%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Prior treatments, range</strong></td>
<td>1-8</td>
<td>1-5</td>
<td>2-2</td>
<td>2-2</td>
</tr>
</tbody>
</table>

*First patient received 250 mg/m² rituximab on day -7 and day 0 prior to Betalutin and is included in this group.

FL = follicular lymphoma, MBq = megabecquerel, MCL = mantle cell lymphoma.
**Imaging schedule**

FDG PET/CT = fluorodeoxyglucose positron emission tomography-computer tomography.

One patient had confirmed transformed lymphoma at 3 months. Tumour response was assessed according to Cheson criteria 2007. ORR = Overall response rate, CR = Complete response, PR = Partial response, SD = Stable disease, PD = Progressive disease.

**Maximum tumour volume reduction**

Maximum change in the sum of products of the diameters (SPD) of up to six of the largest tumour nodules for each patient from baseline.

*Patient with transformed disease.

Duration of response

Duration of response of all patients with response assessment (12/21). Triangles represent start of response (partial and complete).

MBq = megabecquerel.

### Incidence of grade 3 (>2 weeks) and grade 4 (>1 week) hematological adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Phase 2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose levels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 MBq/kg N=3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>15 MBq/kg N=6</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>20 MBq/kg N=3</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10 MBq/kg N=2*</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15 MBq/kg N=2</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>3</td>
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<tr>
<td>15 MBq/kg N=5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N=21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTCAE grade**</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Platelet count decrease</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Neutrophil count decrease</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>N=21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>4</td>
<td></td>
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</tr>
</tbody>
</table>

*First patient received 250 mg/m² rituximab on day -7 and day 0 prior to Betalutin and is included in this group. **CTCAE grade version 4.

SAEs rated as possibly or probably related to Betalutin: epistaxis, pulmonary infection and febrile neutropenia were reported in one patient each and two cases of atrial fibrillation.

**MBq = megabecquerel.**

Hematological toxicity phase 1

**Figures:**
- Platelets Arm 1 and 2
- Neutrophils Arm 1 and 2

**Haematology data.** Platelet counts and neutrophil counts of all patients in arm 1 and 2 of phase 1. The phase 2 patients were not included in these plots.
**Imaging results: FDG PET/CT scan**

Complete metabolic response (FDG PET/CT) at 3 months in patient with follicular lymphoma at 20 MBq/kg

Complete metabolic response (FDG PET/CT) at 6 months in patient with follicular lymphoma at 15 MBq/kg

Patient is still in complete remission 24 months after Betalutin treatment

Patient is still in complete remission 24 months after Betalutin treatment

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FDG PET CT = fluorodeoxyglucose positron emission tomography-computer tomography; MBq = megabecquerel; SPECT = single-photon emission computerized tomography.
**Summary**

- Betalutin, a single dose, *ready-to-use formulation*, that binds to a novel target, CD37 for the treatment of NHL.

- Most AEs were hematological (thrombocytopenia and neutropenia), all transient and reversible.

- Promising efficacy and durable responses have been observed.

- Betalutin as single agent may become a good alternative for patients with indolent NHL, relapsed/refractory to anti-CD20 therapy and chemotherapy.
Participating centres

**Phase I & II – 11 centers**
- Norway
  - Oslo – Dr Kolstad
  - Trondheim - Dr. Fagerli
  - Bergen – Prof Bjørn
- Croatia
  - Zagreb – Dr. Aurer
- Italy
  - Bologna - Prof. Zinzani
  - Milan – Dr. Ciceri
- Poland
  - Warsaw – Dr Walewski
- Spain
  - Madrid - Dr Provencio Pulla
  - Salamanca - Dr Garcia-Sancho
- Sweden
  - Umeå - Dr. Erlansson
- UK
  - Manchester - Prof. Illidge

**Phase II – 14 centres**
- Austria
  - Innsbruck - Dr. Willenbacher
  - Linz - Dr. Welterman
  - Vienna - Prof. Raderer
- Czech Republic
  - Ostrava - Prof. Hajek
  - Olomouc - Prof. Papajik
  - Prague - Prof. Trnéný
- Italy
  - Firenze - Prof. Bosi
- Poland
  - Kraków - Prof. Jurczak
  - Warsaw - Prof. Jedrzejczak
- Sweden
  - Linköping - Dr. Lagerløf
  - Borås - Dr. Andersson
- UK
  - Poole - Dr. Bayne
  - Glasgow - Dr. O’Rourke
  - Bristol - Dr. Beasley