Nordic Lymphoma Group

Lenalidomide, bendamustine and rituximab as first-line therapy for patients >65 years with mantle cell lymphoma

– a Nordic Lymphoma Group trial

NLG-MCL4 (LENA-BERIT)

EudraCT number: 2008-007246-60
REVISION HISTORY

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<td>1</td>
<td>2009-04-02</td>
<td>New</td>
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<tr>
<td>2</td>
<td>2009-05-26</td>
<td>The changes involves the following parts of the protocol (changes highlighted in bold type):</td>
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Study synopsis:

Exclusion criteria:

1. Impaired liver function (serum total bilirubin >34 mmol/L, except in case of haemolytic anemia or caused by lymphoma).
2. Absolute neutrophil count (ANC) <1.0x10^9, unless caused by bone marrow infiltration by lymphoma.
3. Platelet count <60 x 10^9, unless caused by bone marrow infiltration by lymphoma.
4. Creatinine clearance below 50 ml/min (Cockcroft-Gault formula).
5. Known HIV positivity.
6. Known seropositivity for HCV, HBsAg, anti-HBc, or other active infection uncontrolled by treatment.
7. Psychiatric illness or condition which could interfere with the subjects’ ability to understand the requirements of the study.
8. Requirement of corticosteroid therapy at a dose >10 mg prednisolone/day.
9. Pregnant or lactating females.

7. Patient registration and selection

Exclusion criteria:

1. Impaired liver function (serum total bilirubin >34 mmol/L, except in case of haemolytic anemia or caused by lymphoma).
2. Absolute neutrophil count (ANC) <1.0x10^9, unless caused by bone marrow infiltration by lymphoma.
3. Platelet count <60 x 10^9, unless caused by bone marrow infiltration by lymphoma.
4. Creatinine clearance below 50 ml/min (Cockcroft-Gault formula).
5. Known HIV positivity
6. Known seropositivity for HCV, HBsAg, anti-HBc, or other active infection uncontrolled by treatment.
7. Psychiatric illness or condition which could interfere with the subjects’ ability to understand the requirements of the study.
8. Requirement of corticosteroid therapy at a dose >10 mg prednisolone/day.
9. Pregnant or lactating females.

**Definition of dose limiting toxicity**

During the phase I portion of the study, dose-limiting toxicity (DLT) is defined as a grade 3 or greater non-hematologic toxicity within the first two cycles of LBR therapy, determined by the Investigator to be related to lenalidomide or bendamustine (exceptions below).

**Exceptions**

1. Non-hematologic toxicity attributed to rituximab is not counted as DLT.
2. For nausea, vomiting, or diarrhea, subjects must have a Grade 3 or 4 event that persists at this level despite the use of optimal symptomatic treatment, in order for these events to be considered a DLT.
3. Grade 3 transaminitis (serum transaminase >5 x and ≤20 x ULN) must be present for ≥ 7 days to be considered a DLT.
4. Grade 3 or 4 venous thromboembolic events are not considered to be DLT.
5. If a DLT is attributed to progressive disease, it will not be counted as a DLT.

14. SUSARs

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs), will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

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<td>3</td>
<td>2009-09-08</td>
<td>Inclusion criteria:</td>
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<tr>
<td></td>
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<td>1. Age &gt;65 years, or age ≤ 65 years unable to tolerate high dose chemotherapy with autologous stem cell support</td>
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<td></td>
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<td>2. Histologically confirmed (according to the WHO classification) mantle cell lymphoma stage II-IV at time of diagnosis, requiring treatment due to at least one of the following symptoms:</td>
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<td></td>
<td>Evaluation of efficacy</td>
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<td>CT-scan and bone marrow examination will be performed before therapy. Evaluation by CT scan is performed after 3, 6, and 13 cycles. If PD – the patient will go off study. After end of therapy, CT is performed every 6 months until 37 months post therapy. A PET scan is recommended before therapy, and is mandatory after 6 and 13 cycles.</td>
</tr>
</tbody>
</table>
Note that response evaluation after 13 cycles is performed 6 weeks after completion of treatment.

Treatment schedule

Six cycles of LBR (lenalidomide-bendamustine-rituximab), cycle duration 28 days, followed by a maximum of seven cycles of L only (total duration 52 weeks). **Rituximab infusion is given before bendamustine, followed by lenalidomide p o.**

Investigations during study

Serum, plasma and whole blood for freezing: additional samples will be collected at visit 15 and 17.

Record retention

All CRFs and other study documents will be maintained by the investigator for at least 15 years after the final presentation of the study.

Participating centers

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   Monica Sender.
   E-mail: monica.sender@vgregion.se

8. Department of Hematology, Karolinska University Hospital, Stockholm
   Eva Kimby
   E-mail: eva@kimby.se

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<tr>
<td>4</td>
<td>2010-11-15</td>
<td>A change in study design in the phase 1 portion</td>
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<tr>
<td></td>
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<td>This implies de-escalation of lenalidomide dose intensity in three steps. A new cohort of 6 patients will be initiated (cohort A). If no DLT occurs in cycles 1-3 in the first three patients, this dose will be regarded as the maximally tolerable dose (MTD) and used in the phase 2 portion. If 1 DLT occurs in the first 3 patients, all 6 patients in this cohort will be evaluated for DLT, and if ≥2 DLT occurs, the next lower cohort will be evaluated. As this is a de-escalation scheme, the next lower cohort will start to include patients as soon as the previous cohort has been included, to avoid interruption in inclusion.</td>
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<td></td>
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<td>Cohort A</td>
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<td>Induction</td>
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Version Date Changes

No lenalidomide in cycle 1
Lenalidomide 10 mg days 1-14 cycles 2-6 (shortened from previously days 1-21)
Bendamustine 90 mg/m2 i v, days 1-2 (cycle 1-6)
Rituximab 375 mg/m2, i v, day 1 (cycle 1-6).

Maintenance
Cycle 7-8 : lenalidomide 10 mg days 1-21
Cycles 9-13: lenalidomide 15 mg days 1-21

**Cohort B**

Induction
No lenalidomide in cycle 1
Lenalidomide 10 mg days 1-14 cycles 2-6
Bendamustine dose reduced to 70 mg/m2 day 1-2 in cycles 2-6
Rituximab 375 mg/m2, i v, day 1 (cycle 1-6).

Maintenance
Cycle 7-8 : lenalidomide 10 mg days 1-21
Cycles 9-13: lenalidomide 15 mg days 1-21

**Cohort C**

Induction
No lenalidomide in cycle 1
Lenalidomide 5 mg days 1-14 cycles 2-6
Bendamustine dose reduced to 70 mg/m2 day 1-2 in cycles 2-6
Rituximab 375 mg/m2, i v, day 1 (cycle 1-6).

Maintenance
Cycle 7-8 : lenalidomide 10 mg days 1-21
Cycles 9-13: lenalidomide 15 mg days 1-21

**Serious adverse event**

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject’s ability to conduct normal life functions)
Version | Date | Changes
---|---|---
| | | • Is a congenital anomaly/birth defect
• Constitutes an important medical event

* Except for hospitalisation caused by neutropenia, thrombopenia and fever, which is considered an expected haematological toxicity

4.1 2011-09-14

Prophylaxis

1. In the first cycle, **all patients** receive prophylactic steroid medication with 4 mg of betamethasone p.o./i.v (or comparable corticosteroid dose), the evening before, and one hour prior to rituximab. All patients receive prophylaxis with paracetamol 1000 mg p.o and antihistamine, according to local routine, prior to rituximab in all cycles.

2. **In cycle 2, all patients will receive oral prednisolone 20 mg x 2 days 1-14, then taper in one week. Corticosteroids are allowed, at the discretion of the investigator, also in the following cycles.**

Monitoring

Independent staff from another institution or CRO company, not involved in the study, will perform monitoring of the study. Inclusion criteria, endpoints and all the test results according to the assessment schedule will be monitored to assure data quality. **The monitoring will take place when the patient has completed the study.**

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator ___________________________ Date ___________________________
By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and local regulations governing the conduct of clinical studies.
Protocol secretariat and registration

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Study synopsis

Lenalidomide, bendamustine and rituximab as first-line therapy for patients >65 years with mantle cell lymphoma – a Nordic Lymphoma Group trial (LENA-BERIT)

Total number of patients:

60

Expected accrual time:

Aug 2009 – Aug 2011

Study design

A phase I- II, non-randomised, open-label multicenter trial.

Objective of study:

Primary endpoint:

- Phase I portion: Establishing MTD for lenalidomide in combination with BR
- Phase II portion: Progression-free survival

Secondary endpoints:

1. Response duration
2. Overall response rate with and without PET
3. Complete remission rate with and without PET
4. Health-related quality of life
5. Molecular remission rate by PCR
6. Overall survival
7. Safety
8. Evaluation of biomarkers for efficacy
Criteria for patient selection:

**Inclusion criteria:**

1. Age >65 years, or age ≤ 65 years unable to tolerate high dose chemotherapy with autologous stem cell support
2. Histologically confirmed (according to the WHO classification) mantle cell lymphoma stage II-IV, requiring treatment due to at least one of the following symptoms:
   a. Bulky disease: nodal or extranodal mass > 7cm in its greater diameter
   b. B symptoms
   c. Elevated serum LDH
   d. Involvement of at least 3 nodal sites (each with a diameter greater than 3 cm)
   e. Symptomatic splenic enlargement
   f. Compressive syndrome
   g. Pleural/peritoneal effusion
3. No previous treatment for lymphoma except radiotherapy or one cycle of any chemotherapy regimen for lymphoma.
4. WHO performance status 0 – 3
5. Written informed consent.
6. Female subjects of childbearing potential† must:
   a. Understand that the study medication is expected to have a teratogenic risk
   b. Agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study drug, throughout study drug therapy (including dose interruptions) and for 4 weeks after the end of study drug therapy, even if she has amenorrhoea. This applies unless the subject commits to absolute and continued abstinence confirmed on a monthly basis. The following are effective methods of contraception*
      i. Implant**
      ii. Levonorgestrel-releasing intrauterine system (IUS)**
      iii. Medroxyprogesterone acetate depot
      iv. Tubal sterilisation
      v. Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
      vi. Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

* Combined oral contraceptive pills are not recommended. If a subject was using combined oral contraception, she must switch to one of the methods above. The increased risk of VTE continues for 4 to 6 weeks after stopping combined oral contraception.

** Prophylactic antibiotics should be considered at the time of insertion particularly in patients with neutropenia due to risk of infection.

† A female subject or a female partner of a male subject is considered to have childbearing potential unless she meets at least one of the following criteria: Age ≥50 years and naturally amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy does not rule out childbearing potential), premature ovarian failure confirmed by a specialist gynaecologist, previous bilateral salpingo-oophorectomy or hysterectomy, XY genotype, Turner syndrome or uterine agenesis.
Copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

a. Understand that even if she has amenorrhea, she must follow all the advice on effective contraception.

b. She understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.

c. Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml not more than 3 days before the start of study medication once the subject has been on effective contraception for at least 4 weeks. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.

d. Agree to have a medically supervised pregnancy test every 4 weeks including 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These tests should be performed not more than 3 days before the start of next treatment. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.

7. Male subjects must

a. Agree to use condoms throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy if their partner is of childbearing potential and has no contraception.

b. Agree not to donate semen during study drug therapy and for one week after end of study drug therapy.

8. All subjects must

a. Agree to abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.

b. Agree not to share study medication with another person and to return all unused study drug to the investigator.

Exclusion criteria:

1. Impaired liver function (serum total bilirubin >34 mmol/L, except in case of haemolytic anemia or caused by lymphoma).

2. Absolute neutrophil count (ANC) <1.0x 10^9, unless caused by bone marrow infiltration by lymphoma.

3. Platelet count <60 x 10^9, unless caused by bone marrow infiltration by lymphoma.

4. Creatinine clearance below 50 ml/min (Cockcroft-Gault)

5. Known HIV positivity.

6. Known seropositivity for HCV, HBsAg, anti-HBc, or other active infection uncontrolled by treatment.

7. Psychiatric illness or condition which could interfere with the subjects’ ability to understand the requirements of the study.

8. Requirement of corticosteroid therapy at a dose >10 mg prednisolone/day.

9. Pregnant or lactating females.
Treatment plan:

Six cycles of LBR (lenalidomide-bendamustine-rituximab), cycle duration 28 days, followed by a maximum of seven cycles of L only (total duration 52 weeks).

- L: p o  days 1-14 in cycle 2-6, days 1-21 in cycles 7-13.
  - Phase I: Planned dose levels of L are 10 and 5 mg/day during cycles 2-6. In cycles 7-8, all patients will receive an initial dose of 10 mg/day, in cycles 9-13 15 mg/day.
  - Phase II: L is used at MTD level from the phase I portion during cycles 2-6. In cycles 7-8, the dose is 10 mg/day, in cycles 9-13 15 mg/day.

- B: 90-70 mg/m2 i v, days 1-2 (cycle 1-6)

- R: 375 mg/m2, i v, day 1, (cycle 1-6).

Setting for study:

Phase I-II, non-randomized, open-label, multicenter trial in Sweden, Norway, Finland and Denmark.
## Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation or Specialist Term</th>
<th>Explanation</th>
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<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ANC</td>
<td>Absolute neutrophil count</td>
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<td>ASCT</td>
<td>Autologous stem cell transplantation</td>
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<td>β-hCG</td>
<td>Beta-human chorionic gonadotropin hormone</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CR</td>
<td>Complete remission</td>
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<tr>
<td>CRF</td>
<td>Case report form</td>
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<tr>
<td>CRu</td>
<td>Complete remission, unconfirmed</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>CTC</td>
<td>Common toxicity criteria</td>
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<tr>
<td>DLT</td>
<td>Dose-limiting toxicity</td>
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<tr>
<td>FCBP</td>
<td>Female of child bearing potential</td>
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<tr>
<td>FDG [18F]fluorodeoxyglucose,</td>
<td></td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
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<tr>
<td>IMiD</td>
<td>Immunomodulatory drug</td>
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<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<tr>
<td>MCL</td>
<td>Mantle cell lymphoma</td>
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<td>MRD</td>
<td>Minimal residual disease</td>
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<tr>
<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>PD</td>
<td>Progressive disease</td>
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<td>PET</td>
<td>Positron emission tomography</td>
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<td>PFS</td>
<td>Progression free survival</td>
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<tr>
<td>PR</td>
<td>Partial remission</td>
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<tr>
<td>SAE</td>
<td>Serious adverse event</td>
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<tr>
<td>SD</td>
<td>Stable disease</td>
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<tr>
<td>SPD</td>
<td>Sum of product of perpendicular diameters</td>
</tr>
<tr>
<td>TLS</td>
<td>Tumor lysis syndrome</td>
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<td>WBC</td>
<td>White blood cell count</td>
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2. Study background and rationale

Mantle cell lymphoma has since its characterization been considered to be a chemotherapy resistant, incurable lymphoma. It often presents with disseminated disease including bone marrow and gastro-intestinal tract involvement. A characteristic cytogenetic aberration is detectable in most patients, the t(11;14) by which the cyclin D1 gene on chromosome 11 is translocated to the enhancer of the IgH gene on chromosome 14, leading to cyclin D1 protein overexpression.

In younger patients, the benefit of myeloablative approaches is by many investigators considered to be clear, exemplified by the results from the Nordic Lymphoma Group MCL2-protocol, where patients <65 years, received a sequential treatment including dose-escalated CHOP, high dose cytarabine and rituximab as induction, followed by high dose chemotherapy with stem cell support. The results are very promising, showing a plateau of 66% progression-free survival at 6 years, which may indicate that a fraction of patients with MCL may achieve long term remissions and even cure[1].

For patients unable to tolerate myeloablative therapy due to age or comorbidity, there is less consensus about standard therapy. Until recently, the standard treatment for elderly patients with mantle cell lymphoma (MCL) has been CHOP+ rituximab (R-CHOP)[2]. However, the German STIL Group recently presented preliminary data from a phase III trial of 483 patients where R-CHOP was compared to the combination of rituximab and bendamustine (R-B) as first-line treatment in follicular lymphoma and MCL (100 patients) [3]. The overall response rate was non-inferior with R-B, but R-B was associated with considerably less toxicity, especially with regard to alopecia and infectious complications. In previous trials in patients with relapsed or refractory MCL, the overall response rate with R-B has been 75-92%, with a median duration of response of 18-19 months [4,5].

These findings have prompted us to develop the R-B regimen further. Lenalidomide is an active drug in MCL, showing response rates of 53%[6]. It has been combined with rituximab in a phase I trial, showing a maximally tolerated dose of 20 mg/day, which will be followed by a phase II trial[7]. The most common toxicity was fatigue grade 1-2.

In vitro, lenalidomide has shown to increase sensitivity of lymphoma cell lines to rituximab[8]. An attractive option would be to combine R-B with lenalidomide. In the present study, the overall response rate, complete remission rate, remission duration and progression-free survival will be compared to that of the R-B arm of the German STIL Study.

Lenalidomide

Lenalidomide (Revlimid®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. It is indicated in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy. It is rapidly absorbed following oral administration with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. Co-administration with food does not alter the extent of absorption (AUC). In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%.

The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours.
In a phase II study of patients with relapsed aggressive B-cell lymphoma, 15 patients with MCL were included[6]. Among these, 8 responded to lenalidomide (1 CR, 1 CRu, 6 PR), i.e. an ORR rate of 53%. The most common grade 4 adverse events were neutropenia (8.2%) and thrombocytopenia (8.2%); the most common grade 3 adverse events were neutropenia (24.5%), leukopenia (14.3%), and thrombocytopenia (12.2%). Lenalidomide has been combined with rituximab in a phase I trial, showing a maximally tolerated dose of 20 mg/day, which will be followed by a phase II trial[7]. The most common toxicity was fatigue grade 1-2. In vitro, lenalidomide has shown to increase sensitivity of lymphoma cell lines to rituximab[8].

In patients with chronic lymphatic leukaemia (CLL), lenalidomide has been associated with serious complications – in the form of tumor lysis syndrome, and tumor flare, characterized by dramatic and painful lymph node enlargement[9]. Tumor flare has been reported to be manageable with nonsteroidal anti-inflammatory drugs[10]. At this point, this has not been reported in other lymphoproliferative disorders.

Bendamustine

Bendamustine, originally developed in the German Democratic Republic in the 1970s, is a chemotherapy agent consisting of a mechlorethamine (nitrogen mustard) group, a benzimidazole ring, and a butyric acid side chain. In vitro studies demonstrate rapid production of DNA crosslinks and strand breaks after bendamustine exposure. In addition to direct DNA damage and apoptosis, other mechanisms include inhibition of mitotic checkpoints and induction of mitotic catastrophe. These characteristics may explain the activity of bendamustine in drug-resistant cancer cells and refractory lymphoma patients. Benzimidazole acts as a purine antagonist in experimental models; the contribution of this structure to the overall antitumor activity of bendamustine is unknown. In vitro testing in CD20-positive lymphoma cell lines has demonstrated synergy between bendamustine and rituximab, evidenced by a reduction in the bendamustine concentration required to induce apoptosis in 50% of tumor cells after the addition of rituximab[11].

In patients with relapsed or refractory MCL, the overall response rate with the combination of rituximab and bendamustine (R-B) has been 75-92%, with a median duration of response of 18-19 months[4,5]. The primary toxicity was reversible myelosuppression; grade 3 or 4 neutropenia was reported in 36%. Other grade 3 or 4 hematologic toxicities included thrombocytopenia (3-9%) and anemia (1-2%). Nonhematologic toxicity was generally mild and consisted of grade 1-2 events. Adverse events attributed to bendamustine included (all grades) nausea (70%), infection (64%), fatigue (59%), constipation (44%), diarrhea (36%), headache (36%), and vomiting (29%).

Rituximab

Rituximab (Mabthera®) is a chimeric anti-CD20 antibody, with clinical activity in all B-cell lymphomas, most notably in combination with chemotherapy in diffuse large B-cell lymphoma and follicular lymphoma, or as a single agent in follicular lymphoma. In MCL, the addition of rituximab to CHOP (R-CHOP) has been shown to be superior in terms of response and time to treatment failure (21 vs 14 months) [2]. The Nordic Lymphoma Group MCL2 protocol, where rituximab and cytarabine was added, similarly showed a marked prolongation progression-free and overall survival compared to the previous MCL1 protocol[1].
3. Objectives of the study

Primary objectives

♦ Phase I: Establishing maximally tolerable dose (MTD) of lenalidomide in combination with bendamustine and rituximab

♦ Phase II: The primary efficacy variable is the evaluation of progression-free survival with lenalidomide, bendamustine and rituximab as frontline therapy in mantle cell lymphoma patients

Secondary objectives

• Overall response rate with and without PET
• Complete remission rate with and without PET
• Health-related quality of life
• Molecular remission rate by PCR
• Overall survival
• Safety
• Evaluation of biomarkers for efficacy

4. Diagnosis

A histological diagnosis of mantle cell lymphoma is established by the local pathologist of each participating centre. The diagnosis has to be confirmed by expression of CD5, CD20 and cyclin-D1 or demonstration of a t(11;14).

In all cases, a paraffin block will be sent to a central laboratory for revision. New stainings for cyclin D1, CD20, CD5, CD23, Ki67 and SOX11 will be performed centrally, and a tissue microarray will be performed for future studies of biomarkers. Level of Ki67 expression will be assessed at the central laboratory.

5. Methodology

This is a prospective, multicenter, phase I-II clinical trial to determine the efficacy and safety of combining lenalidomide, bendamustine and rituximab as primary treatment in patients >65 years with mantle cell lymphoma.

6. Evaluation of efficacy

CT-scan and bone marrow examination will be performed before therapy. Evaluation by CT scan is performed after 3, 6, and 13 cycles. If PD – the patient will go off study. After end of therapy, CT is performed every 6 months until 37 months post therapy.

A PET scan is recommended before therapy, and after 6 and 13 cycles. Note that response evaluation after 13 cycles is performed 6 weeks after completion of treatment.

All patients will perform a new bone marrow examination after 3, 6 and 13 cycles of therapy.
Assessment of Minimal Residual Disease (MRD) by PCR will be performed on blood and bone marrow specimens before therapy, and after 6 and 13 cycles. Samples are sent to Rigshospitalet, Copenhagen (Appendix 5).

Health-related quality of life will be assessed by use of the EORTC QLQ-C30 questionnaire, handed to patients and filled in at home, before therapy, after 6 and 13 cycles, and one year after end of therapy.

The safety and tolerability will be assessed by way of clinical investigation and relevant laboratory parameters at restaging visits.

7. Patient registration and selection

Registration and CRFs

Registration is done by a telephone call to the protocol secretariat, phone no: +46 46 17 70 34, followed by a fax of the registration page of the CRF to +46 46 17 60 23. The secretariat will give you a unique registration number for the patient. After registration of the patient, a receipt will be sent by fax.

How and when to send CRFs

Send in CRFs as soon as they are completed. This is especially important in the phase I part of the study. If the CRFs are not received by the secretariat in time, a reminder will be sent. The CRF page is faxed to the protocol secretariat, and the original is kept at the study site. The completed HRQOL questionnaires are similarly faxed, and the original is kept in the CRF locally. At monitoring, the originals are replaced by a copy, and the originals are transferred to the protocol secretariat.

Inclusion criteria

1. Age >65 years, or age ≤65 years unable to tolerate high dose chemotherapy with autologous stem cell support
2. Histologically confirmed (according to the WHO classification) mantle cell lymphoma, stage II-IV, in need of treatment due to at least one of the following symptoms:
   a. Bulky disease: nodal or extranodal mass > 7cm in its greater diameter
   b. B symptoms
   c. Elevated serum LDH
   d. involvement of at least 3 nodal sites (each with a diameter greater than 3 cm)
   e. symptomatic nodal or splenic enlargement
   f. compressive syndrome
   g. pleural/peritoneal effusion
   h. anemia (<12), thrombocytopenia (< 100) or neutropenia (<1.5) caused by bone marrow infiltration of lymphoma
3. No previous treatment for lymphoma except radiotherapy or one cycle of any chemotherapy regimen for lymphoma.
4. WHO performance status 0 – 3
5. Written informed consent.
6. Female subjects of childbearing potential† must:
   a. Understand that the study medication is expected to have a teratogenic risk
   b. Agree to use, and be able to comply with, effective contraception without interruption, 4 weeks before starting study drug, throughout study drug therapy (including dose interruptions) and for 4 weeks after the end of study drug therapy, even if she has amenorrhoea. This applies unless the subject commits to absolute and continued abstinence confirmed on a monthly basis. The following are effective methods of contraception*
      i. Implant**
      ii. Levonorgestrel-releasing intrauterine system (IUS)**
      iii. Medroxyprogesterone acetate depot
      iv. Tubal sterilisation
      v. Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
      vi. Ovulation inhibitory progesterone-only pills (i.e., desogestrel)
   c. Understand that even if she has amenorrhea, she must follow all the advice on effective contraception.
   d. She understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
   e. Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml on the day of the study visit or in the 3 days prior to the study visit once the subject has been on effective contraception for at least 4 weeks. This requirement also applies to women of childbearing potential who practice complete and continued abstinence. The test should ensure the subject is not pregnant when she starts treatment.
   f. Agree to have a medically supervised pregnancy test every 4 weeks including 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These pregnancy tests should be performed on the day of the study visit or in the 3 days prior to the study visit. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.

7. Male subjects must

† A female subject or a female partner of a male subject is considered to have childbearing potential unless she meets at least one of the following criteria: Age \( \geq 50 \) years and naturally amenorrhoeic for \( \geq 1 \) year (amenorrhoea following cancer therapy does not rule out childbearing potential), premature ovarian failure confirmed by a specialist gynaecologist, previous bilateral salpingo-oophorectomy or hysterectomy, XY genotype, Turner syndrome or uterine agenesis.

* Combined oral contraceptive pills are not recommended. If a subject was using combined oral contraception, she must switch to one of the methods above. The increased risk of VTE continues for 4 to 6 weeks after stopping combined oral contraception.

**Prophylactic antibiotics should be considered at the time of insertion particularly in patients with neutropenia due to risk of infection. Copper releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.
a. Agree to use condoms throughout study drug therapy, during any dose interruption and for one week after cessation of study therapy if their partner is of childbearing potential and has no contraception.

b. Agree not to donate semen during study drug therapy and for one week after end of study drug therapy.

8. All subjects must

a. Agree to abstain from donating blood while taking study drug therapy and for one week following discontinuation of study drug therapy.

b. Agree not to share study medication with another person and to return all unused study drug to the investigator or pharmacist.

Exclusion criteria

1. Impaired liver function (serum total bilirubin >34 mmol/L, except in case of haemolytic anemia or caused by lymphoma).

2. Absolute neutrophil count (ANC) <1.0x 10^9, unless caused by bone marrow infiltration by lymphoma.

3. Platelet count <60 x 10^9, unless caused by bone marrow infiltration by lymphoma.

4. Creatinine clearance below 50 ml/min (Cockcroft-Gault formula).

5. Known HIV positivity

6. Known seropositivity for HCV, HBsAg, anti-HBc, or other active infection uncontrolled by treatment.

7. Psychiatric illness or condition which could interfere with the subjects’ ability to understand the requirements of the study.

8. Requirement of corticosteroid therapy at a dose >10 mg prednisolone/day.

9. Pregnant or lactating females.

8. Treatment

Treatment schedule

Six cycles of LBR (lenalidomide-bendamustine-rituximab), cycle duration 28 days, followed by a maximum of seven cycles of L only (total duration 52 weeks). Rituximab infusion is preferably given before bendamustine, followed by lenalidomide p.o.

L: p.o days 1-14 in cycle 2-6. Planned dose levels of L are 5 and 10 mg/day in cycles 2-6. In cycles 7-8, all patients will receive an initial dose of 10 mg/day, days 1-21, and in cycles 9-13 the dose is 15 mg/day days 1-21.

B: 90 mg/m2 i.v, days 1-2 (cycle 1-6) as a 60 min infusion. In the Phase I portion, the dose in Cohort B and C is reduced to 70 mg/m2 i.v, days 1-2 in cycles 2-6.

R: 375 mg/m2, i.v, day 1, (cycle 1-6). The dose is adjusted to the nearest multiple of 100 mg. Infusion time according to local guidelines for rituximab.
NOTE: At cycle 1, when lymphocytosis is often present, the rituximab schedule may be modified at the discretion of the investigator in order to minimize infusion related reactions. The rituximab dose may then be divided into two days, such as the administration of 100 mg day 1 and the remaining dose day 2.

**Definition of dose limiting toxicity**

During the phase I portion of the study, dose-limiting toxicity (DLT) is defined as a grade 3 or greater non-hematologic toxicity within the first two cycles of LBR therapy (exceptions below).

**Exceptions**

1. Non-hematologic toxicity attributed to rituximab is not counted as DLT.
2. For nausea, vomiting, or diarrhea, subjects must have a Grade 3 or 4 event that persists at this level despite the use of optimal symptomatic treatment, in order for these events to be considered a DLT.
3. Grade 3 transaminitis (serum transaminase >5 x and ≤20 x ULN) must be present for ≥7 days to be considered a DLT.
4. Grade 3 or 4 venous thromboembolic events are not considered to be DLT.
5. If a DLT is attributed to progressive disease, it will not be counted as a DLT.

**Dose finding schedule in phase I portion**

*Initial schedule*

The phase I portion of the study followed a sequential dose escalation, '3 + 3' design. Initially, three subjects were started on treatment with dose regimen 1. After the third subject completed two cycles (8 weeks) of treatment, if no DLT occurred, then the next group of three subjects were treated at the next dose level of lenalidomide. If one of the three initial subjects experienced a DLT, the cohort of subjects was expanded to six subjects. If less than two out of the six subjects experienced a DLT, then the next higher dose group was initiated. If two or more (of a cohort of up to six) subjects experienced a DLT, no higher dose levels were be tested and the MTD had been exceeded. Intra-patient dose escalation was not permitted.

The MTD was defined as the highest dose studied for which the incidence of DLT is less than two out of the six subjects during the first cycle of LBR therapy.

Due to unexpected toxicity in the initial 12 patients with this schedule, especially during cycle 1, this has been modified as below.

*Schedule in Amendment 4 (Protocol Final Version 4.0 2010-11-15)*

This implies de-escalation of dose intensity in three steps. A new cohort of 6 patients will be initiated (cohort A). If no DLT occurs in cycles 1-3 in the first three patients, this dose will be regarded as the maximally tolerable dose (MTD) and used in the phase 2 portion.

If 1 DLT occurs in the first 3 patients, all 6 patients in this cohort will be evaluated for DLT, and if ≥2 DLT occurs, the next lower cohort will be evaluated. As this is a de-escalation scheme, the
next lower cohort will start to include patients as soon as the previous cohort has been included, to avoid interruption in inclusion.

**Phase II portion**

Additional patients are enrolled at the MTD on the phase II portion of the trial, making a total number of 60 patients.

During the maintenance phase, the lenalidomide dose will be the same for all patients (10 mg/day) day 1-21 in cycles 7-8, and 15 mg/day in cycles 9-13, whether in the phase I or in the phase II portion of the study.

**Prophylaxis**

1. In the first cycle, *all patients* receive prophylactic steroid medication with 4 mg of betamethasone p o / i v (or comparable corticosteroid dose), the evening before, and one hour prior to rituximab. All patients receive prophylaxis with paracetamol 1000 mg p o and antihistamine, according to local routine, prior to rituximab in all cycles.

2. In cycle 2, all patients will receive oral prednisolone 20 mg x 2 days 1-14, then taper in one week. Corticosteroids are allowed, at the discretion of the investigator, also in the following cycles.

3. The use of G-CSF, such as inj pegfilgrastim 6 mg s c day 3, is *mandatory* after LBR in cycles 1-6.

4. Antibiotic prophylaxis is not routinely administered.

5. *All patients* receive allopurinol 300 mg/day p o days 1-3 cycle 1, and are encouraged to keep well hydrated during the first cycle of LBR due to potential risk of tumor lysis syndrome. *Allopurinol should not be continued further due to risk of cutaneous reactions in combination with bendamustine.*

6. *All patients* receive thrombosis prophylaxis with aspirine (acetyl salicylic acid, ASA) 75 mg/day during the treatment phase, unless contraindicated.

7. Patients with a history of a thromboembolic event and/or a known hypercoagulable state, or patients in whom ASA is contraindicated, should instead receive prophylaxis with low molecular weight heparin (LMWH), at the discretion of the investigator.

**Blood counts**

A blood count, including B-hemoglobin, WBC, differential count, and platelets, is performed at days 1, 7, 14, 21 (+/- 1 day) in cycles 1-2, and days 1 and 14 (+/- 1 day) in cycles 2-13.
**Bendamustine**

<table>
<thead>
<tr>
<th>Initial dose</th>
<th>90 mg/m² days 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction Step 1</td>
<td>70 mg/m² days 1 and 2</td>
</tr>
<tr>
<td>Reduction Step 2</td>
<td>60 mg/m² days 1 and 2</td>
</tr>
<tr>
<td>Reduction Step 3</td>
<td>50 mg/m² days 1 and 2</td>
</tr>
</tbody>
</table>

Except if due to extensive bone marrow involvement by MCL, recovery to absolute neutrophil count ≥1,0 x 10⁹/L and platelet count ≥100 x 10⁹/L is required before starting the second and subsequent cycles. If not, the following cycle is postponed until haematological recovery. The dose of bendamustine should be kept at 90 mg/m² days 1 and 2, and instead lenalidomide should be reduced as shown below.

Only when lenalidomide has been terminated due to hematological toxicity and if neutrophil and platelet counts still have not recovered to the levels above, should the dose of bendamustine be reduced to 70 mg/m² days 1+2, **(reduction step 1)** in the following cycles.

The bendamustine dose will be reduced further, to 60 mg/m² days 1+2 **(reduction step 2)** if neutrophil and platelet count have not recovered to levels above in spite of reduction to step 1 at start of the subsequent cycle.

The bendamustine dose will be reduced to **reduction step 3** (50 mg/m² days 1+2) if neutrophil and platelet count have not recovered to levels above in spite of reduction to step 2 at start of the subsequent cycle.

After a grade IV neutropenic infection (in patients already receiving G-CSF), or thrombocytopenia grade IV, the lenalidomide should stopped temporarily and then reduced to the next lower level in the subsequent cycles.

**Rituximab**

There will be no reductions of the rituximab dose. If an infusion-related or hypersensitivity reaction to rituximab is seen, the infusion is temporarily stopped, and the rate of drug administration is altered according to local routine. The total dose administered remains the same in such cases. In case of a serious or life threatening reaction, the infusion should be terminated and such adverse event reported.

**Lenalidomide**

**Induction (cycles 2-6)**

- Phase I and II-portion

In case of a dose-limiting toxicity (above), determined to be related to lenalidomide, or haematological toxicity grade III-IV (not DLT), lenalidomide will be stopped, and the dose will be reduced to the next lower level at the start of the following cycle.
<table>
<thead>
<tr>
<th>Maximum dose</th>
<th>10 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction Step 1</td>
<td>5 mg/day</td>
</tr>
</tbody>
</table>

**Maintenance (cycles 7-13)**

**Thrombocytopenia**

<table>
<thead>
<tr>
<th>Thrombocyte count</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goes below &lt; 25 x 10⁹/l, for the first time</td>
<td>Stop lenalidomide</td>
</tr>
<tr>
<td>At return to ≥ 25 x 10⁹/l</td>
<td>Restart lenalidomide at next lower level</td>
</tr>
</tbody>
</table>

At subsequent cycles with <25 x 10⁹/l

<table>
<thead>
<tr>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop lenalidomide</td>
</tr>
</tbody>
</table>

At return to ≥ 25 x 10⁹/l

<table>
<thead>
<tr>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restart lenalidomide at next lower level (10 or 5 mg/day). Do not use a dose below 5 mg/day</td>
</tr>
</tbody>
</table>

**Neutropenia**

<table>
<thead>
<tr>
<th>Neutrophil count</th>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goes below &lt; 0,5 x 10⁹/l, for the first time</td>
<td>Stop lenalidomide</td>
</tr>
</tbody>
</table>

At return to ≥ 0,5 x 10⁹/l without other toxicity

<table>
<thead>
<tr>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restart lenalidomide at the current level.</td>
</tr>
</tbody>
</table>

At return to ≥ 0,5 x 10⁹/l with other hematological toxicity

<table>
<thead>
<tr>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restart lenalidomide at next lower level</td>
</tr>
</tbody>
</table>

At subsequent cycles with < 0,5 x 10⁹/l

<table>
<thead>
<tr>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop lenalidomide</td>
</tr>
</tbody>
</table>

At return to ≥ 0,5 x 10⁹/l

<table>
<thead>
<tr>
<th>Action taken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restart lenalidomide at next lower level (10 or 5 mg/day). Do not use a dose below 5 mg/day</td>
</tr>
</tbody>
</table>

**Suppliers**

Celgene Corporation will supply lenalidomide (Revlimid®), and Mundipharma will supply bendamustine, free of charge during the study. Rituximab (Mabthera®) will be supplied according to standard health care procedures from the pharmacy, as the trial is conducted within its approved indication.

**Dosage form**

Lenalidomide will be supplied as 5 and 10 mg capsules for oral administration. Bendamustine will be supplied as vials each containing 55 mg lyophilized powder for solution for infusion contains 25 mg bendamustine hydrochloride and as vials each containing 220 mg powder for solution for infusion contains 100 mg bendamustine hydrochloride. The vials are opened and reconstituted as close to the time of patient administration as possible. The product is reconstituted with 40 ml (for the 100 mg presentation) or 10 ml (for the 25 mg presentation) of
Sterile Water for Injection. The reconstituted product is further diluted into 500 ml, q.s., 0.9% Sodium Chloride for Injection. **The product should then be delivered to the patient as soon as possible.** The route of administration is by intravenous infusion over 60 minutes. Rituximab is contained in 100 and 500 mg vials for dilution to 1-4 mg/ml in 0.9% Sodium Chloride for injection. The route of administration is by intravenous infusion over 1.5-4 hours.

**Packaging**

Lenalidomide will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain sufficient drug to last for 21 days of dosing. Study drug must be dispensed in the original packaging with the label clearly visible. Only one 21 day supply may be provided to the patient each cycle. Bendamustine will be shipped to pharmacy in vials containing 100 and 25 mg bendamustine hydrochloride for reconstitution.

**Labeling**

Lenalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. Bendamustine is labeled by pharmacy and administered at study sites.

**Receipt of study drug**

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to the suppliers.

**Storage**

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

**Unused study drug supplies**

Investigator or designee will return unused study drugs to pharmacy for destruction. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty bottles or unused capsules.

**10. Tests performed at diagnosis:**

- Clinical examination and complete medical history
- Assessment of WHO Performance Status
- Full blood count, biochemistry (urea, creatinine, bilirubin, ALAT, ALP, albumin, LDH)
- Bone marrow biopsy for morphology and immunochemistry and aspiration for flow cytometry
- Blood and bone marrow for MRD, to Copenhagen
- CT of thorax, abdomen/pelvis and neck
- PET (not mandatory)
- Health-related quality of life assessment (HRQOL), by EORTC QLQ-C30.
11. Tests performed at response evaluation:
- Clinical examination and complete medical history
- Blood tests as above
- Bone marrow biopsy and flow cytometry.
- Blood and bone marrow for MRD, to Copenhagen
- CT of thorax, abdomen/pelvis and neck
- PET, after 6 and 13 cycles (not mandatory)
- HRQOL assessment
- Serum, plasma and whole blood for freezing
- Flow cytometry of lymphocyte populations

12. Criteria for evaluation and endpoint

Response criteria I (Cheson et al. 1999[12]) – using CT only

♦ Complete remission (CR)
Disappearance of all disease-related symptoms and measurable lesions, including normalisation of other abnormal initial parameters (if any) such as biochemical abnormalities definitely assignable to MCL (e.g. S-LDH), X-rays and bone marrow. All lymph nodes must have regressed to < 1.5 cm in their largest transverse diameter and to ≤1.0 cm for those nodes which were 1.1 to 1.5 cm before treatment.

♦ Complete remission unconfirmed (CRu)
The criteria of a CR are fulfilled, except that residual lymph node(s) mass greater than 1.5 cm have regressed by more than 75% in the sum of the products of the two largest perpendicular diameter(s) (SPD). A CRu should when possible be assigned to a CR or PR by histological examination.

♦ Partial remission (PR)
Decrease of at least 50% in the sum of the product of the two largest perpendicular diameters in all measurable and evaluable lesions and disappearance of disease-related symptoms with no lesion increasing 25% or more in size and without any new lesions appearing.

♦ Stable disease (SD)
The patient does not qualify for complete or partial remission or progressive disease.

♦ Progressive disease (PD)
Increase in size of 25% or more of the product of the two largest perpendicular diameters of one or more measurable and evaluable lesions during treatment or the occurrence of new lesions.

Response criteria II – using CT and PET (Cheson 2007)[13]

♦ Complete remission (CR)
Disappearance of all evidence of disease
  o Nodal Masses:
    ▪ (a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative.
    ▪ (b) Variably FDG-avid or PET negative; regression to normal size on CT
  o Bone marrow: Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

♦ Partial remission (PR)
  Regression of measurable disease and no new sites
  o Nodal Masses: 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes.
  o FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site
  o Variably FDG-avid or PET negative; regression on CT
  o Bone marrow: Irrelevant if positive prior to therapy; cell type should be specified

♦ Stable disease (SD)
  Failure to attain CR/PR or PD
  o Nodal Masses:
    ▪ (a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET
    ▪ (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT

♦ Progressive disease (PD)
  o Any new lesion or increase by 50% of previously involved sites from nadir
  o Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis
  o Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy

Relapse
During follow-up the occurrence of relapse in patients previously registered as being in CR will be registered. The following data will be registered:

1. Relapse yes/no
   if yes:
2. Date of relapse
3. Site of relapse

At relapse, every centre is free to initiate further treatment according to local guidelines. At this point the patient will exit the study, although centres are encouraged to keep sending in follow-up forms to allow establishing the overall survival time.

Endpoint criteria

Progression-free survival
This is the primary endpoint of the phase II study. It is defined as the interval between registration date and date of documented progression or lack of response, first relapse, or death of any cause. [13]. Otherwise, patients will be censored at the last date they were known to be alive. For patients not responding at any time point on study treatment, PFS is defined as 1 day.

**Overall survival**
This is defined as time from registration to death of any cause. Patients still alive or lost to follow-up are censored at the last date they were known to be alive.

**Cause of death**
During the study and after its completion the cause of death will be registered according to the following cause-of-death criteria:

1. Lymphoma
2. Treatment toxicity
3. Secondary malignancy
4. Other disease not related to 1, 2 or 3
5. Other cause

**Response duration**
Response duration is from the time when criteria for response (i.e., CR, CRu or PR) are met, to the first documentation of relapse or progression.

13. Reporting adverse events

**Adverse Event**
An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject’s health, including laboratory test values, regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.

All AEs will be recorded by the Investigator(s) from the time of signing the informed consent through the end of the designated follow-up period.

**Serious adverse event**
A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability/incapacity (a substantial disruption of the subject’s ability to conduct normal life functions)
• Is a congenital anomaly/birth defect
• Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

**Classification of severity**

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The severity of adverse events (AEs) will be graded on a scale of 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE). The NCI CTCAE V3.0 can be viewed on-line at the following NCI web site: [http://ctep.cancer.gov/reporting/ctc.html](http://ctep.cancer.gov/reporting/ctc.html). If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Mild</strong> Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities</td>
</tr>
<tr>
<td>2</td>
<td><strong>Moderate</strong> Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres</td>
</tr>
<tr>
<td>3</td>
<td><strong>Severe</strong> Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required</td>
</tr>
<tr>
<td>4</td>
<td><strong>Life-threatening</strong> Immediate risk of death; requires hospitalization and clinical intervention.</td>
</tr>
<tr>
<td>5</td>
<td><strong>Death</strong></td>
</tr>
</tbody>
</table>
Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Serious Adverse Event (SAE) Reporting

Reporting to Regulatory Authorities and the Ethics Committee

The sponsor will inform relevant Regulatory Authorities and the Ethics Committee:

- of all relevant information about serious unexpected adverse events suspected to be related to the study medication that are fatal or life threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.

- of all other serious unexpected events suspected to be related to the study medication as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

Immediate reporting by Investigator to Sponsor and Sponsor reporting to Companies

The investigator will inform the sponsor of all SAEs within 24 hours in order that the sponsor can fulfil his regulatory reporting obligations within the required timeframes. In circumstances where it is not possible to submit a complete report, an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 14 calendar days and sent to the national coordinator. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorised staff members.

The sponsor will supply Celgene and Norpharma A/S with a copy of all SAEs (for Norpharma only SAEs with relationship to bendamustine, classified as possible or higher) within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g IB, SmPC).

The sponsor will provide Celgene and Norpharma A/S with a copy of the annual safety report at the time of the submission to the regulatory authority and the Ethics Committee.
Contact details for Sponsor:

Clinical Research Unit
Department of Oncology
Lund University Hospital
SE-221 85 Lund
Sweden
Phone   +46 46 17 70 34
Fax       +46 46 17 60 23
Email:   jan.sundberg@skane.se

Contact details for Drug Safety Celgene Nordics:

Celgene AB
Kista Science Tower
164 51 Kista
Sweden
Phone:  +46 8 703 16 31
Fax:    +46 8 703 16 03
E-mail: drugsafety-nordic@celgene.com

Contact details for Drug Safety Norpharma a/s for Nordics:

Pharmacovigilance Manager
Napp Pharmaceuticals Ltd
Science Park
Milton Road
Cambridge
CB4 0GW
United Kingdom

Phone: +44 1223 42 4444
Fax: +44 1223 42 6002
e-mail: drugsafetyuk@napp.co.uk

Pregnancies

Female of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug, or within 28 days of the subject’s last dose of study drug, are considered events to be reported immediately to Sponsor and Celgene and Norpharma. If the subject is on study drug, the study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Sponsor who will inform Celgene and Norpharma immediately by facsimile using an SAE Report Form.
The female should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify the Sponsor and Celgene and Norpharma of the outcome of the pregnancy within 5 days or as specified below. The Investigator will provide this information as a follow-up to the initial pregnancy report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted foetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted foetus]), the Investigator should follow the procedures for reporting SAEs.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspect is related to the in utero exposure to the study drug should also be reported.

Male Subject:

Female partners of males taking investigational product should be advised to call their healthcare provider immediately if they get pregnant. The male subject should notify the Investigator of his partner’s pregnancy and her healthcare provider information. The Investigator will then provide this information to the Sponsor and Celgene and Norpharma for follow-up as necessary.

Adverse event updates

Celgene and Norpharma shall notify the principle investigator/sponsor of the following information:

1. Any AE associated with the use of study drug or in other studies that is both serious and unexpected.
2. Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The principle investigator/sponsor will forward this information to other investigators involved in the trial.

The sponsor shall notify the EC and the relevant regulatory authorities of any new significant risks to subjects as required.

All adverse events occurring during the treatment period and until the end of the last treatment administration will be reported in the treatment evaluation form.

14. SUSARs

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs), will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

15. Study duration:
The protocol aims to begin in the second half of 2009, and the inclusion is estimated to end in second half of 2011. Patients will be followed for 36 months post therapy.

16. Criteria for study discontinuation

In absence of unacceptable toxicity or other cause for discontinuation (see below), patients will receive study treatment as outlined above. The following events are deemed sufficient cause to terminate study treatment.

- Progressive disease
- Severe (grade 4) non-haematologic toxicity except alopecia
- The patients own wish to terminate study treatment
- If the responsible physician thinks a change of therapy would be in the best interest of the patient

17. Statistical considerations

This is an exploratory study of toxicity (maximally tolerable dose) of lenalidomide in combination with rituximab-bendamustine in the phase I portion, and progression free survival (PFS) in the phase II portion of the study. A prolongation of median PFS with 6 months compared to the R-B arm in the STiL study[3] is considered clinically significant, meriting further study of the LBR regimen in a phase III setting. In a preliminary analysis of the STiL study, the median PFS for patients with MCL in the R-B arm is 30 months, indicating that a median PFS of \( \geq 36 \) months with the LBR regimen would be considered a clinically significant improvement.

Assuming the PFS times follow an exponential distribution, the SE of the estimated median survival, on a logarithmic scale, is \( 1/\sqrt{D} \), where \( D \) is the total number of observations. Hence converting this to a multiplicative factor times the anticipated median survival of 36, gives a width of 23.1 months for the 95% confidence interval based on 40 observations.

The total patient sample size is 60, including the phase I portion of the study. Based on Danish population-based studies[14], the annual incidence of MCL in the Nordic countries is 0.9/100,000/year, with a median age of 66 years. With the inclusion also of some younger patients with poor performance status, 100 Nordic patients will be eligible. We estimate to include 30% in this trial, i.e., 60 in two years.

Patients who are prematurely withdrawn from the study will not be replaced.

18. Publication rules

Manuscripts based on this protocol will be made according to the Vancouver System: Uniform Requirements for Manuscripts Submitted to Medical Journals (latest updated version 2008: www.icmje.org). Authorship is based on important contributions to:
- Idea, planning or modifying the protocol, collection, analysis or interpretation of data
- Writing or critically revising the manuscript
- Acceptance of the final manuscript.
All three aspects must be covered.
The chairman of the writing committee is the main responsible for accomplishing the goals of the protocol, and will also be responsible for writing the manuscript. In that case he will be 1st author. If important contributions from members of the study group warrant separate publications, the contributor in question will be first author on that article. Members of the writing committee are expected to fulfil the above criteria and to be co-authors.

All manuscripts will be distributed to the contributors prior to submission for publication. In addition, the companies providing financial support are able to review the manuscript at least 30 days before submission.

Preliminary results from the study are to be subject to presentation at international and national meetings. This includes a presentation of study design at time of initiation of the study, and presentation of the data from the phase I portion and response data on the induction therapy.

19. Ethical aspects

Patient protection

The responsible investigator will ensure that this study is conducted in agreement with the declaration of Helsinki, Tokyo, Venice and Hong Kong amendments (14), and the laws and the regulations of the country. The protocol has been written, and the study will be conducted according to the guidelines for Good Clinical Practice, issued by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). As a pre-requirement for implementation, the protocol will have to be approved by the local, regional or national Ethical Review Boards according to the existing national and local regulatory requirements.

Informed consent

All patients will be informed of the aims of the study, including the possible adverse events, the procedures involved and the possible hazards to which he/she will be exposed. They will be informed as to the strict confidentiality of their data, but that their medical records will be reviewed for trial purposes by authorised individuals other than their treating physician. It will be emphasised that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered. In accordance with the guidelines of Good Clinical Practice the “consent must be documented either by the subject’s dated signature or by the signature of an independent witness who records the subject’s assent”.

Protocol modifications

Any amendments to this protocol that seems appropriate, as the study progresses (e.g. affects safety or efficacy) will be agreed upon between the coordination and/or principal investigator. Amendments will be submitted to the Ethics Committee (IECs) and the Regulatory Authority for written approval before the implementation of the amended version.

Record retention
All CRFs and other study documents will be maintained by the investigator for at least 15 years after the final presentation of the study.

**Monitoring**

Independent staff from another institution or CRO company, not involved in the study, will perform monitoring of the study. Inclusion criteria, endpoints and all the test results according to the assessment schedule will be monitored to assure data quality.

**Financing**

The study will be financed by the Nordic Lymphoma Group. Celgene, Norpharma (DK), Mundipharma (NO, FI, SE) and Roche will each contribute with a research grant.
References


### Appendix 1

**WHO Performance Status Scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair</td>
</tr>
</tbody>
</table>
### Protocol: NLG-MCL4 (LENA-BERIT)

**Patient name:**

**Lenalidomide, bendamustine and rituximab as first-line therapy for patients >65 years with mantle cell lymphoma**

#### Flow sheet 1

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Before therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Within 4</td>
</tr>
<tr>
<td><strong>Visit number</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Date</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Hb, WBC with diff count, Thromb</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Creatinine, ASAT, ALAT, ALP, LDH, Bilirubin, Albumin,</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Creatinine clearance</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>HIV, HBV, HCV serology</strong></td>
<td></td>
</tr>
<tr>
<td><strong>CT neck, thorax, abdomen, pelvis with contrast</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>PET</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Bone marrow biopsy</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Bone marrow and blood flow cytometry</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>MRD blood/bone marrow to Copenhagen</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>EORTC QLQ-C30</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Serum, plasma and whole blood for freezing</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Lymphocyte subsets</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Immunoglobulin levels</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Pregnancy Test</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Bendamustin + Rituximab+ Lenalidomide</strong></td>
<td>x</td>
</tr>
<tr>
<td><strong>Lenalidomide alone</strong></td>
<td>x</td>
</tr>
</tbody>
</table>

*A blood count, including B-hemoglobin, WBC, neutrophil count, and platelets, is performed at days 1, 7, 14, and 21 (+/- 1 day) in cycles 1-2, and days 1, 14 in cycles 3-13. ** Not mandatory. ***For women of child-bearing potential.*
Protocol: NLG-MCL4 (LENA-BERIT)

Patient name:

**Lenalidomide, bendamustine and rituximab as first-line therapy for patients >65 years with mantle cell lymphoma**

**Flow sheet 2**

<table>
<thead>
<tr>
<th>Week</th>
<th>40</th>
<th>44</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months after completion of therapy</td>
<td></td>
<td></td>
<td>1.5 7 13 19 25 31 37</td>
</tr>
<tr>
<td>Visit number</td>
<td>12 13 14 15 16 17 18 19 20 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb, WBC with diff count, Thromb*</td>
<td>x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, ASAT, ALAT, ALP, LDH, Bilirubin, Albumin,</td>
<td>x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT neck, thorax, abdomen, pelvis with contrast</td>
<td>x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET**</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ-C30</td>
<td>x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum, plasma and whole blood for freezing</td>
<td>x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow and blood flow cytometry</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD blood/bone marrow to Copenhagen</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin levels</td>
<td>x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test***</td>
<td>x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide alone</td>
<td>x x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*A blood count, including B-hemoglobin, WBC, neutrophil count, and platelets, is performed at days 1, 7, 14, and 21 (+/- 1 day) in cycles 1-2, and days 1, 14 in cycles 3-13. ** Not mandatory. ***For women of child-bearing potential.*

40
Appendix 3

Participating centers

SWEDEN

1. Department of Oncology, Lund University Hospital, SE 22185 Lund, Sweden
   Mats Jerkeman.
   E-mail: mats.jerkeman@med.lu.se

2. Department of Oncology, Uppsala University Hospital, SE 751 85 Uppsala, Sweden.
   Anna Laurell.
   E-mail: anna.laurell@akademiska.se

3. Department of Hematology, Sahlgrenska University Hospital, Göteborg, Sweden
   Monica Sender.
   E-mail: monica.sender@vgregion.se

4. Department of Oncology, University Hospital of Norrland, SE 981 85 Umeå, Sweden
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   E-mail: martin.erlanson@onkologi.umu.se

5. Department of Medicine, Sunderbyn Hospital, Luleå, Sweden
   Lena Brändefors
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6. Department of Hematology, Karolinska University Hospital, Stockholm
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13. Department of Oncology, University Hospital of Tromsø, N-9038 Tromsø, Norway.  
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14. Department of Haematology and Oncology, University Hospital of Stavanger, N-4068 Stavanger, Norway.  
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15. Department of Hematology, Rigshospitalet, Copenhagen, Denmark  
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16. Department of Hematology, Herlev Hospital, Copenhagen, Denmark  
Michael Pedersen  
E-mail: micped06/her@exchange.ka

17. Department of Hematology, Århus University Hospital, Århus, Denmark  
Hans Herluf Bentzen  
E-mail: hanbe@as.aaa.dk

FINLAND

19. Department of Hematology, Helsinki University Hospital, Helsinki  
Riikka Räty  
Email: riikka.raty@hus.fi

20. Department of Hematology Oulu University Hospital  
Outi Kuittinen  
Email: outi.kuittinen@ppshp.fi

21. Department of Oncology, Turku University Central Hospital  
Sirkku Jyrkkio  
Email: sirkku.jyrkkio@tyks.fi
22. Department of Oncology, Kuopio University Hospital
   Esa Jantunen
   Email: esa.jantunen@kys.fi

23. Department of Hematology, Mikkeli Central Hospital
   Maija Mikkola
   Email: maija.mikkola@esshp.fi
24. Appendix 4

Pathology Form

Use a copy of this form when an original paraffin block is shipped to one of the reference pathologists below:

Elisabeth Ralfkiaer, Dept of Pathology, Rigshospitalet, DK 2100 Copenhagen, Denmark. E-mail: elisabeth.ralfkiaer@rh.hosp.dk

Marja-Liisa Karjalainen-Lindsberg, Dept of Pathology, Helsinki University Central Hospital, Fin 00290, Helsinki, Finland. E-mail: Marja-Liisa.Karjalainen-Lindsberg@hus.fi

Jan Delabie, Dept of Pathology, The Norwegian Radium Hospital, 0310 Oslo, Norway. E-mail: jan.delabie@labmed.uio.no

Christer Sundstrom, Dept of Pathology, Uppsala University Hospital, SE-75185 Uppsala, Sweden. E-mail: christer.sundstrom@akademiska.se

Mats Ehinger, Department of Pathology/Cytology, Lund University Hospital, SE-223 55 Lund, Sweden. E-mail: mats.ehinger@skane.se

Please find enclosed samples from our patient:

Patient initials, date of birth and study number:…………………

Who is being treated according to the Fourth Nordic MCL Protocol

Samples are taken date:………………….. and consist of a paraffin block:

Original access number:

Sincerely,

Signature:…………………………….Hospital:………………………..Country……………….
Appendix 5

**Molecular studies**

Use a copy of this form whenever molecular samples are submitted to Copenhagen.

To:
The Hematology Laboratory 4041  
Leukemia and Lymphoma Marker Section  
Rigshospitalet  
DK Copenhagen  
Denmark

Attention Lone Pedersen  
Phone +45 3545 4045 Fax +45 3545 4841

Please find enclosed samples from our patient:

Patient initials and study number:………………….

Who is being treated according to the NLG-MCL4 Protocol (LENA-BERIT)

Samples are taken date:………………….. and consist of:

☐ 10 ml bone-marrow aspirate, anticoagulated  
☐ 50 ml blood, anticoagulated

Sincerely,

Signature:………………………………Hospital:………………………Country…………

**Handling of biological material**  
50 ml of peripheral venous blood and 10 ml of bone marrow aspirate should be collected in a sterile tube containing EDTA as an anticoagulant. The sample should be sent by mail to Copenhagen for arrival in less than 72 hours. Please label the tubes, and avoid shipment that will arrive at week-ends

Remember to fax a copy of this form at the day of shipment.