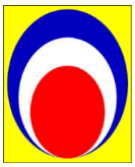

Venetoclax, lenalidomide and rituximab in patients with relapsed/refractory mantle cell lymphoma (VALERIA)

NORDIC LYMPHOMA GROUP
NLG-MCL7 (VALERIA)

EudraCT number: 2017-001060-38

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator	Date
Printed Name of Investigator	

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.

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SYNOPSIS

Total number of patients:

9-24 in phase I portion, +44-47+15

In total: 56-68 pts (3 or 6 patients in phase 1 will be part of the phase 2 cohort)

Expected accrual time:

Jan 2018 – Nov 2021

Study design

A phase I-II, open-label multicenter trial

Primary endpoint

The primary efficacy variable is the evaluation of overall response rate (ORR) at 6 months with lenalidomide-venetoclax and rituximab, in patients with relapsed or refractory mantle cell lymphoma (MCL), using an MRD driven strategy

Secondary endpoints (evaluated at 24 months)

1. ORR in patients previously treated with ibrutinib
2. ORR in patients with *TP53*-mutation and/or 17p deletion
3. Progression-free survival (median)
4. Response duration (median)
5. Molecular remission rate by PCR according to EURO-MRD guidelines
6. Overall survival (median)

7. Health-related quality of life
8. Safety (Grade 3-4 AE according to CTCAE v 4.03)
9. Evaluation of biomarkers for efficacy, by mutational profile and immunohistochemistry

Key criteria for patient selection:

1. Age >18 years
2. Histologically confirmed (according to the WHO classification) MCL stage I-IV
3. Who have received at least 1 prior rituximab-containing chemotherapy regimen, with documented relapse or disease progression following the last anti-MCL treatment

Treatment plan:

Phase 1

The phase 1 will consist of 3 groups with escalating doses of venetoclax and lenalidomide, using an MRD driven strategy.

Definition of dose limiting toxicity

Dose-limiting toxicity (DLT) is defined as a grade 3 or greater non-hematologic toxicity within the first 8 weeks of therapy (exceptions below).

Exceptions

1. Non-hematologic toxicity attributed to rituximab is not counted as DLT.
2. For nausea, vomiting, or diarrhoea, 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. If symptoms indicating DLT is attributed to progressive disease, it will not be counted as a DLT.

Dose finding schedule in phase I

The phase I part of the study will follow a sequential dose escalation, '3 + 3' design. Initially, three subjects are started on treatment with dose regimen A. After the third subject completed 8 weeks of treatment, if no DLT occurred, the next group of three subjects is treated at the next dose level (B). If one of the three initial subjects experienced a DLT, the cohort of subjects will be expanded to six subjects. If less than two out of the six subjects experienced a DLT, then the next higher dose group will be initiated. If two or more (of a cohort of up to six) subjects experienced a DLT, no higher dose levels will be tested and the MTD has been exceeded. Intra-patient dose escalation is not permitted. If two or more subjects, out of 6, in Group A experience a DLT, the next group of 3 patients will be treated in the de-escalation Group X.

The MTD is defined as the highest dose studied for which the incidence of DLT is less than two out of the six subjects during the first 8 weeks of treatment.

Amendment v 1.6

After evaluating 3 patients each in Groups A, B and C, after 8 weeks of treatment, no DLT were encountered in Groups A and B. In Group C, 2 out of 3 patients were hospitalized for grade 3 and 4 infection, and the MTD was considered to have been exceeded. To investigate further dose levels, NLG-MCL Working Group decided to include patients at one more dose level, Group Y (below), before settling on a recommended phase 2 dose.

Dose Escalation Schema

COHORT	Target Venetoclax Dose	Lenalidomide Dose[c]	Rituximab Dose[d]
Group A	400[a]	15	375/1400
Group B	400[a]	20	375/1400
Group Y	600[b]	15	375/1400
Group C	800[b]	20	375/1400
Group X[e]	400[a]	10	375/1400

a. After ramp-up dosing of 20 mg, 50 mg, 100 mg, 200 mg, for one week each

b. After ramp-up dosing of 20 mg, 50 mg, 100 mg, 200 mg, 400 mg for one week each

c. With corresponding dose-reduction, as necessary, for those with impaired renal function

d. 375 mg/m2 IV cycle 1, day 1; 1400 mg sc days 8, 15 and 22 in cycle 1, then day 1 in cycles 3, 5, 7, 9 and 11

e. De-escalation cohort.

Phase 2

Treatment will be given according to dosing below, with an MRD driven strategy.

- Venetoclax, p o. RP2D, with ramp up as above, starting at 20 mg QD days 1-7.
- Lenalidomide: RP2D mg p o, days 1-21
- Rituximab 375 mg/m2 i v Day 1, cycle 1. 1400 mg sc,days 8, 15 and 22 in cycle 1, then day 1 in cycles 3, 5, 7, 9 and 11.

Evaluations during treatment

- Minimal residual disease (MRD) (RQ-PCR of blood according to EURO-MRD guidelines) and computed tomography (CT) is performed every 3 months
- A [18F]fluorodeoxyglucose-positron emission tomography (FDG-PET-CT) is performed after 6 months (for evaluation of primary endpoint)
- When MRD-negative in blood according to EURO-MRD guidelines for deescalating treatment, treatment will continue for another 3 months, when a new evaluation of MRD in blood and bone marrow will be performed. If MRD-negativity is confirmed, treatment is stopped and the patient will be followed with MRD and CT every 3 months for up to 24 months.
- Patients without bone marrow/blood involvement by RQ-PCR at baseline or where a probe for MRD cannot be constructed, are followed by PET-CT every 3 months. When PET-CT is negative (Deauville score 1-2), treatment will continue for another 3 months, when a new PET-CT is performed. If PET-negativity is confirmed, treatment is stopped and the patient will be followed with PET-CT every 3 months for up to 24 months.
- When MRD-positivity occurs, according to EURO-MRD guidelines for escalating treatment, without a clinical relapse: the treatment will be restarted, after CT, bone

marrow and clinical evaluation. If low risk for tumor lysis syndrome, the treatment will be started at full dose, at RP2D. In case of higher tumor burden, Venetoclax (VEN) will be ramped up as above.

- If MRD – negativity is not attained, treatment will continue until clinical progression, for up to 24 months.

GLOSSARY OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ANC	Absolute neutrophil count
β-hCG	Beta-human chorionic gonadotropin hormone
BTK	Bruton tyrosine kinase
CR	Complete remission
CRF	Case report form
CRu	Complete remission, unconfirmed
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
FDG	[18F]fluorodeoxyglucose
GCP	Good Clinical Practice
HRQOL	Health related quality of life
IGHV	Immunoglobulin Heavy Chain Gene Variable Portion
ICH	International Conference on Harmonization
LDH	Lactate dehydrogenase
MCL	Mantle cell lymphoma
MRD	Minimal residual disease
ORR	Overall response rate
OS	Overall survival

PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PR	Partial remission
PQC	Product quality complaint
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SD	Stable disease
SPD	Sum of product of perpendicular diameters
SUSAR	Suspected unexpected serious adverse event
TLS	Tumor lysis syndrome
ULN	Upper limit of normal
VEN	Venetoclax
WBC	White blood cell count

STUDY BACKGROUND AND RATIONALE

Mantle cell lymphoma (MCL) has since its characterization been considered as 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 that 40% of patients still are in a continuous complete remission after 12 years[1].

For patients unable to tolerate myeloablative therapy due to age or comorbidity, there is less consensus on standard therapy. Until recently, the reference treatment for elderly patients with 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 ORR was non-inferior with R-B, but R-B was considerably less toxic, especially with regard to alopecia and infectious complications. In previous trials in patients with relapsed or refractory MCL, the ORR with R-B has been 75-92%, with a median duration of response of 18-19 months [4, 5].

Achievement of a molecular remission is a robust surrogate endpoint for long term PFS in MCL[6]. In the recently presented Nordic MCL3 trial, studying first line therapy in patients with MCL <65 years, a FDG-PET scan was performed after induction chemotherapy. Our data show that a negative PET was an even more sensitive predictor of long term favourable outcome than MRD[7]. In light of these results, FDG-PET is included in the response evaluation in this trial.

In contrast to the trials referenced above – MRD will in the present trial be used as a tool to direct the duration of treatment. In patients without blood/bone marrow involvement, or when a patient specific probe for MRD cannot be constructed, PET-CT will be used instead.

LENALIDOMIDE

Lenalidomide, a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. . In B-cell malignancies, lenalidomide interacts with the ubiquitin E3 ligase cereblon and targets this enzyme to degrade the Ikaros transcription factors IKZF1 (Ikaros)

and IKZF3 (Aiolos), leading to reduced activity of IRF4, a downstream target of cereblon. This leads to proliferation and activation of NK cells, thereby enhancing NK cell–mediated cytotoxicity and antibody-dependent cellular cytotoxicity[8]. It is indicated in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy. .

In a phase II study of patients with relapsed aggressive B-cell lymphoma, 15 patients with MCL were included[9]. Among these, 8 responded to lenalidomide (1 complete remission (CR), 1 complete remission unconfirmed (Cru), 6 partial remission (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 maximum tolerated dose of 20 mg/day, which will be followed by a phase II trial[10]. The most common toxicity was fatigue grade 1-2. In vitro, lenalidomide has shown to increase sensitivity of lymphoma cell lines to rituximab[11].

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[12]. Tumor flare is manageable with nonsteroidal anti-inflammatory drugs[13]. At this point, this has not been reported in other lymphoproliferative disorders.

Lenalidomide is an active drug in MCL, showing response rates of 53%[9]. The most common toxicity was fatigue grade 1-2. Results from a phase II trial with the combination of rituximab and lenalidomide was recently presented, targeting 32 newly diagnosed MCL patients. Efficacy was encouraging, with an ORR of 87%, CR 57% and at 12 months, 93% were free from progression (Ruan et al, ASH 2013).

In the Nordic MCL4 trial, using the combination of lenalidomide, bendamustine and rituximab, as first line therapy for MCL in patients >65 years of age, 51 patients were included. The response rate was 97% after 6 cycles (based on 31 patients). The patients then continued on lenalidomide single agent therapy for another 6 months according to protocol. However, all patients had to stop lenalidomide prematurely, usually after 1-2 cycles of maintenance, due to haematological toxicity. Based on this experience, maintenance therapy with lenalidomide is considered not feasible in this trial on relapsed MCL.

The maximum tolerable dose of lenalidomide in combination with rituximab and ibrutinib was determined in an ongoing phase I trial by the National Cancer Institute, for untreated follicular lymphoma (NCI-2013-00792). In this trial, no dose limiting toxicity was encountered at any dose level up to 20 mg days 1-21, q28d.

RITUXIMAB

Rituximab 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[14].

As the other two agents are given orally, we have chosen the subcutaneous preparation of rituximab, from dose 2 in cycle 1, to obviate the need for intravenous access, although the intravenous preparation may also be used as an option. Biosimilars of rituximab are allowed to be used within this trial. The s c preparation has been shown to be associated with equivalent pharmacokinetic properties and response rates compared to i v rituximab[15].

VENETOCLAX

The generation of a BCL2-selective inhibitor is complicated by the degree of similarity within the BH3-binding domains of BCL2 and BCL-X_L. To circumvent this challenge, a unique BCL2 small molecule co-crystal structure was exploited to guide the rational design of ABT-199 or venetoclax (VEN). VEN has a subnanomolar affinity for BCL2 (Ki < 0.01 nM) and bound over three orders of magnitude less avidly to BCL-XL and BCLw (Ki = 48 nM and 245 nM, respectively), and showed no measurable binding to MCL1. Selectivity has also been proven in vitro, using cell lines dependent on either BCL2 or BCL-XL. VEN was shown to selectively disrupt BCL2–BIM complexes and to induce caspase-dependent cell death. It has been validated in various human lymphoma cell lines, including those derived from diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and MCL, in addition to its activity against acute myelogenous leukemia and acute lymphatic leukemia (ALL) lines. Clinical activity has been most pronounced in CLL and MCL, and is approved in the U.S. for CLL with 17p-deletion. Clinical data in CLL indicate synergism with the anti-CD20 antibody rituximab[16].

The most common adverse effect of VEN is neutropenia, with grade 3-4 neutropenia occurring in 41% of patients. Importantly, tumor lysis syndrome (TLS), including fatal events and renal failure requiring dialysis, has occurred in previously treated CLL patients with high tumor burden treated with VEN, which is the reason for using an initial 5-week ramp-up phase of the dose of VEN. Patients should be assessed for TLS risk, including evaluation of tumor burden and comorbidities, and should receive appropriate prophylaxis for TLS, including hydration. Reduced renal function (CrCl <80 mL/min) further increases the risk. Concomitant use of VEN with strong or moderate CYP3A inhibitors and P-gp inhibitors may increase the risk of TLS at initiation and during the ramp-up phase, and may require dose adjustment. For details about prohibited and cautionary concomitant medications see Appendix 7.

Although based on a small number of patients (n=28), in a phase I trial, VEN has shown a very high rate of response (75%) in relapsed/refractory (R/R) MCL, comparable to the efficacy of Bruton tyrosine kinase (BTK)-inhibitors, and would be an attractive option for this group of patients[17].

RATIONALE FOR THE COMBINATION UNDER STUDY

This is a phase I/II trial, with the aim of evaluating the efficacy of venetoclax to the backbone of rituximab-lenalidomide in patients with relapsed/refractory MCL. A recent substantial step forward in the treatment of MCL has been the introduction of BTK-inhibitors, most notably ibrutinib[18, 19]. Ibrutinib is now an established therapy in R/R MCL, and is undergoing evaluation also in first line. Although 2/3 of patients with R/R MCL respond to ibrutinib, the median response duration with ibrutinib is 17.5 months, and an increasing unmet need is treatment for patients progressing on ibrutinib, for which there is no established effective therapy. Patients progressing on ibrutinib have a very poor outcome, with a median overall survival of 2.9 months[20]. For CLL patients progressing on ibrutinib, encouraging results from salvage treatment with venetoclax has been reported, thus supporting the inclusion of ibrutinib refractory MCL patients in the present trial.

The combination of rituximab and lenalidomide is well- tolerated and effective in R/R MCL (ORR 57%), and has also been studied in untreated patients with MCL, showing even higher efficacy[21]. In this trial proposal, we will add venetoclax to the rituximab/lenalidomide combination, for evaluation of its efficacy and safety in both patients previously treated with ibrutinib and in ibrutinib-naïve patients. In a subset of patients, unable to tolerate chemotherapy, we will also assess efficacy and safety of this combination as first-line therapy.

A phase I trial with a similar combination has recently been initiated, using rituximab i v. Pending the results of this trial, the final recommended phase II dose of lenalidomide and venetoclax has not been determined. In this trial, subcutaneous rituximab is used, and a separate phase I study is included. To minimize costs and treatment-related side effects, duration of treatment will be determined by molecular response, using RQ-PCR on blood samples during therapy and follow-up. This trial will provide a basis for a later phase 3 trial.

BENEFIT-RISK ASSESSMENT

The study population is well defined (subjects with R/R MCL who have received at least 1 rituximab-containing chemotherapy regimen, and currently available treatment options do not offer satisfactory response rates. Therefore, the treatment offered in this study may provide significant clinical benefit. We have chosen not to exclude patients with impaired performance status (<4), as patients with poor performance status due to lymphoma, may still benefit from

active treatment. In addition, there is no need for intravenous access, as these agents are administered orally or as s c injections.

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. Efficacy assessments will occur according to the internationally accepted Lugano Response Criteria for Malignant Lymphoma. Safety assessments will occur through regular clinic visits including laboratory analyses.

The total blood volume to be collected, based on the estimated duration of treatment, is approximately 400 mL, which includes laboratory assessments associated with treatment and biomarker samples. Overall, the volume of blood to be drawn is considered to be acceptable for subjects participating in a cancer clinical study and is deemed reasonable over the timeframe of the study. Overall the benefit-risk assessment for the study is considered positive.

OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

The primary objective is to assess the overall response rate (ORR) at 6 months with lenalidomide-venetoclax and rituximab, in patients with relapsed or refractory mantle cell lymphoma, by use of an MRD driven strategy. ORR includes complete (CR) and partial remissions (PR).

SECONDARY OBJECTIVES

To evaluate, at 24 months:

1. ORR in patients previously treated with ibrutinib
2. ORR in patients with *TP53*-mutation and/or 17p deletion
3. Progression-free survival (median)
4. Response duration (median)
5. Molecular remission rate by PCR according to EURO-MRD guidelines
6. MRD vs PET-CT for correlation with PFS/OS
7. Overall survival (median)
8. Safety (Grade 3-4 AE according to CTCAE v 4.03)

9. Health-related quality of life assessment

10. Evaluation of biomarkers for efficacy, by mutational profile and immunohistochemistry

DIAGNOSIS

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

The paraffin block from diagnosis, and if available, also from time of relapse, will be sent to a national central laboratory for review. 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.

At baseline, blood and bone marrow will be sent to a central laboratory for analysis of immunephenotype and tumor percentage for later MRD assessment. In addition, these samples will undergo targeted next generation sequencing for the most commonly occurring mutations in MCL.

METHODOLOGY

This is a prospective, multicenter, phase I-II clinical trial to determine the efficacy and safety of combining lenalidomide, venetoclax and rituximab in patients with relapsed/refractory mantle cell lymphoma.

EVALUATION OF EFFICACY

CT-scan and bone marrow examination will be performed before start of therapy. Evaluation by CT scan is performed every 3 months. If progressive disease (PD) – the patient will go off study.

A FDG-PET scan is performed after 6 months of therapy, (for evaluation of primary endpoint), and a substitute for MRD in patients without a molecular marker.

Patients will perform a bone marrow examination at baseline, after 6 months, and 3 months after MRD negativity in blood has been attained.

Assessment of MRD by PCR will be performed on blood and bone marrow before start of therapy, and on blood every 3 months until end of trial. Samples are sent to Rigshospitalet, Copenhagen (Appendix 3).

Health-related quality of life (HRQOL) 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 24 months after start of therapy.

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

PATIENT REGISTRATION AND SELECTION

REGISTRATION AND CRFS

Registration is done by fax or email to the protocol secretariat in Aarhus, Denmark, followed by a fax of the registration page of the CRF.

The secretariat will give you a unique registration number for the patient. After registration of the patient, a receipt will be sent by fax or email.

CONTACT DETAILS:
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Aarhus University Hospital
A-CTO
Palle Juul-Jensens Boulevard 99, C104
DK - 8200 Aarhus N

Phone: +45 7845 5855
Fax: +45 7846 7597

HOW AND WHEN TO SEND CRFS

Data are entered online in the OpenClinica eCRF

INCLUSION CRITERIA

1. Age >18 years
2. Histologically confirmed (according to the WHO 2016 classification) mantle cell lymphoma stage I-IV
3. Who have received at least 1 prior rituximab-containing chemotherapy regimen, with documented relapse or disease progression following the last anti-MCL treatment
4. At least 1 measurable site of disease (>1.5 cm long axis)
5. WHO performance status 0 – 3
6. Written informed consent.
7. Female subjects of childbearing potential must (see page 52 for definition of not fertile):
    a. Understand that the study medication is expected to be teratogenic
    b. Agree to use, and be able to comply with, highly 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.
    c. All fertile women must agree to perform monthly pregnancy tests while on study medication and until 4 weeks after completion of study drug. Tests must have a minimum sensitivity of 25 mIE/ml and be medically witnessed
    d. Highly effective contraception include:
    e. Implant*
    f. Levonorgestrel-releasing intrauterine system (IUS)*
    g. Medroxyprogesterone acetate depot
    h. Tubal sterilisation
    i. Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
    j. Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

       NB! Patients using a hormonal method, must also use a second barrier method.
    k. Sexual abstinence (if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the preferred and usual lifestyle of the subject).

8. 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.
9. 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.

a. Chemotherapy or radiotherapy within 3 weeks

b. Therapeutic antibodies or BTK inhibitors within 4 weeks

c. Radioimmunotherapy within 10 weeks

d. Major surgery within 4 weeks of inclusion in this trial.

2. Previous treatment with venetoclax
3. Impaired liver function: AST and ALT >3.0 × the upper normal limit (ULN) of institution's normal range; Bilirubin > 1.5 × ULN. Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN, per discussion between the investigator and medical monitor. Elevated Bilirubin due to haemolytic anemia or caused by lymphoma, is not an exclusion criterion.
4. Absolute neutrophil count (ANC) <1.0x 10^9, unless caused by bone marrow infiltration by lymphoma.
5. Platelet count <60 x 10^9, unless caused by bone marrow infiltration by lymphoma.
6. Creatinine clearance below 50 ml/min (Cockcroft-Gault)
7. Known CNS lymphoma.
8. Heart failure in NYHA stage IV or other serious CVD

9. Pulmonary failure (ex chronic disease with hypoxemia)
10. Active serious infections such as hepatitis B or C and HIV
11. Conditions with serious immunocompromised state
12. Breastfeeding women must be excluded or stop breastfeeding
13. Other active malignancy.
14. Psychiatric illness or condition which could interfere with the subjects' ability to understand the requirements of the study.
15. Requirement of corticosteroid therapy at a dose >10 mg prednisolone/day.
16. Hypersensitivity to venetoclax, lenalidomide or rituximab, or HACA against rituximab.

TREATMENT

PHASE 1 PORTION

The phase 1 portion will consist of 3 groups with escalating doses of venetoclax and lenalidomide. After all patients in Group C have completed 8 weeks of treatment, data on safety will be reviewed by the NLG MCL Group, to determine the recommended phase 2 dose (RP2D).

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 8 weeks of therapy (exceptions below).

Exceptions:

- Non-hematologic or hematologic toxicity attributed to rituximab is not counted as DLT.
- 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.
- Grade 3 transaminitis (serum transaminase >5 x and $\leqslant$20 x ULN) must be present for $\geqslant$ 7 days to be considered a DLT.
- If a DLT is attributed to progressive disease, it will not be counted as a DLT.

DOSE FINDING SCHEDULE IN PHASE I PORTION

The phase I portion of the study will follow a sequential dose escalation, '3 + 3' design. Initially, three subjects are started on treatment with dose regimen A. After the third subject completed 8 weeks of treatment, if no DLT occurred, then the next group of three subjects are treated at the next dose level (B). 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 will be tested and the maximal tolerable dose (MTD) has been exceeded. Intra-patient dose escalation is not permitted. If two or more subjects, out of 6, in Group A experience a DLT, the next group of 3 patients will be treated in the de-escalation Group X.

The MTD is defined as the highest dose studied for which the incidence of DLT is less than two out of the six subjects during the first 8 weeks of treatment.

Amendment v 1.6

After evaluating 3 patients each in Groups A, B and C, after 8 weeks of treatment, no DLT were encountered in Groups A and B. In Group C, 2 out of 3 patients were hospitalized for grade 3 and 4 infection, and the MTD was considered to have been exceeded. To investigate further dose levels, NLG-MCL Working Group decided to include patients at one more dose level, Group Y (below), before settling on a recommended phase 2 dose.

Dose Escalation Schema

COHORT	Target Venetoclax Dose (mg)	Lenalidomide Dose[c] (mg)	Rituximab Dose[d]
Group A	400[a]	15	375/1400
Group B	400[a]	20	375/1400
Group Y	600[b]	15	375/1400
Group C	800[b]	20	375/1400
Group X[e]	400[a]	10	375/1400

a. After ramp-up dosing of 20 mg, 50 mg, 100 mg, 200 mg, for one week each

b. After ramp-up dosing of 20 mg, 50 mg, 100 mg, 200 mg, 400 mg for one week each

c. With corresponding dose-reduction, as necessary, for patients with impaired renal function

d. 375 mg/m^2 IV cycle 1, day 1; 1400 mg s c days 8, 15 and 22 in cycle 1, then day 1 in cycles 3, 5, 7, 9 and 11

e. De-escalation cohort.

DOSING

GROUP A

- Venetoclax, p o. Days 1-7: 20 mg, Days 8-14: 50 mg, Days 15-21: 100 mg, Days 22-28: 200 mg, Day 29 and onwards: 400 mg daily.
- Lenalidomide: 15 mg p o, days 1-21.
- Rituximab 375 mg/m^2 i v Day 1, cycle 1. 1400 mg s c days 8, 15 and 22 in cycle 1, then every 8 weeks.

GROUP B

- Venetoclax, p o. Days 1-7: 20 mg, Days 8-14: 50 mg, Days 15-21: 100 mg, Days 22-28: 200 mg, Day 29 and onwards: 400 mg.
- Lenalidomide: 20 mg p o, days 1-21.
- Rituximab 375 mg/m^2 i v Day 1, cycle 1. 1400 mg s c days 8, 15 and 22 in cycle 1, then every 8 weeks.

GROUP Y

- *Venetoclax, p o. Days 1-7: 20 mg, Days 8-14: 50 mg, Days 15-21: 100 mg, Days 22-28: 200 mg, Days 29-35: 400 mg, Day 36 and onwards: 600 mg daily.*
- *Lenalidomide: 15 mg p o, days 1-21*
- *Rituximab 375 mg/m^2 i v Day 1, cycle 1. 1400 mg s c days 8, 15 and 22 in cycle 1, then every 8 weeks.*

GROUP C

- Venetoclax, p o. Days 1-7: 20 mg, Days 8-14: 50 mg, Days 15-21: 100 mg, Days 22-28: 200 mg, Days 29-35: 400 mg, Day 36 and onwards: 800 mg daily.
- Lenalidomide: 20 mg p o, days 1-21
- Rituximab 375 mg/m^2 i v Day 1, cycle 1. 1400 mg s c days 8, 15 and 22 in cycle 1, then every 8 weeks.

GROUP X

- Venetoclax, p o. Days 1-7: 20 mg, Days 8-14: 50 mg, Days 15-21: 100 mg, Days 22-28: 200 mg, Day 29 and onwards: 400 mg daily.
- Lenalidomide: 10 mg p o, days 1-21.
- Rituximab 375 mg/m^2 i v Day 1, cycle 1. 1400 mg s c days 8, 15 and 22 in cycle 1, then every 8 weeks.

Phase II cohort

- Venetoclax, p o. Ramp up as above, starting at 20 mg daily days 1-7, until recommended phase II dose (RP2D)
- Lenalidomide: RP2D mg p o, days 1-21
- Rituximab 375 mg/m^2 i v Day 1, cycle 1. 1400 mg sc days 8, 15 and 22 in cycle 1, then every 8 weeks.

EVALUATION AND MRD

- MRD (RQ-PCR of blood according to EURO-MRD guidelines) and CT is performed every 3 months
- A FDG-PET-CT is performed after 6 months (for evaluation of primary endpoint). PET-CT is also used to substitute for MRD evaluation in patients without a molecular marker.
- When MRD-negative in blood, treatment will continue for another 3 months, when a new evaluation of MRD in blood and bone marrow will be performed. If MRD negativity is confirmed, treatment is stopped and the patient will be followed with MRD and CT.
- When MRD+ (positive), no clinical relapse: the treatment will be restarted, after CT, bone marrow and clinical evaluation. If low risk for tumor lysis syndrome, the treatment will be started at full dose, 800 mg VEN, 20 mg LEN. In case of higher tumor burden (e.g., any

lymph node with a diameter ⩾5 cm or high absolute lymphocyte count [ALC ⩾25 x 10^9/L]), VEN will be ramped up as above.

- If MRD–negativity (or PET-negativity if the patient is without baseline bone marrow/blood involvement) is not attained, treatment will continue until clinical progression or for a maximum of 24 months.

RITUXIMAB

The first dose in cycle 1 is given intravenously according to local routine, 375 mg/m^2. For the first infusion, 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. The following doses may be given subcutaneously (s c). Biosimilars of rituximab are also allowed.

Rituximab for s c administration is supplied as a ready to use liquid formulation with a nominal content of 120 mg/mL rituximab in an 11.7 mL vial and must not be diluted prior to administration. Furthermore, rituximab s c contains rHuPH20 as an excipient at a concentration of 2000 U/mL (manufactured in a Chinese Hamster Ovary cell line) acting as a permeation enhancer, histidine/histidine-HCl (buffer), α,α-trehalose (bulking agent), methionine (stabilizer), and polysorbate 80 (surfactant) in water for injection at a pH of 5.5. The drug product is a sterile, colourless to yellowish, clear to opalescent liquid. The rituximab s c dose is 1400 mg for all patients, independent of patient body-surface area. This translates into an injection volume of 11.7 mL.

For each injection, 11.7 mL of the solution should be withdrawn from the vial. The 27 gauge injection needle will be inserted using sterile technique in the s c tissue of the abdomen. The needle should be fully inserted, being careful that the tip of the needle is deeper than the dermis but not as deep as the underlying muscle. The goal of the placement angle and needle depth is to achieve uniform placement into every patient's s c tissue. It should not be injected into moles, scars, or bruises. The skin should be pinched and needle inserted before the skin is released and the pressure on the syringe can be applied.

The injection should be manually pushed at a flow rate of approximately 2 mL/min, therefore an administration volume of 11.7 mL should take approximately 5-6 minutes. If there is a request by the patient to interrupt the injection, the pressure on the syringe should initially be eased to alleviate the pain. If the pain is not alleviated the injection should be stopped and the patient should be asked when they are comfortable to resume the injection.

There is no specific recommendation regarding the observation period after rituximab s c injections; medical judgment should be utilized.

VENETOCLAX

Venetoclax will be administered orally with water within 30 minutes of a meal at approximately the same time each day, once daily, beginning on day 1 of cycle 1.

LENALIDOMIDE

Lenalidomide will be administered orally, once daily on days 1-21 of each 28-day cycle.
Treatment will be repeated every 28 days provided that any occurring toxicities have recovered to ≤ grade 1.

TUMOR LYSIS SYNDROME PROPHYLAXIS

Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumour burden (e.g., any lymph node with a diameter $\geqslant$5 cm or high absolute lymphocyte count [ALC $\geqslant$25 x 10^9/L]) are at greater risk of TLS when initiating venetoclax. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk. The risk may decrease as tumour burden decreases with venetoclax treatment.

Prior to initiating venetoclax, blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed and pre-existing abnormalities corrected. The prophylaxis measures listed below should be followed. More intensive measures should be employed as overall risk increases.

HYDRATION

Patients should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink plenty of water daily starting 2 days before and throughout the dose-titration phase. Patients should be particularly instructed to drink 1.5-2.0 L daily, 2 days prior to and the days of dosing at initiation and each subsequent dose increase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.

ANTI-HYPERURICAEMIC AGENTS

Anti-hyperuricaemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax in patients with high uric acid levels or at risk of TLS and may be continued through the titration phase. This should be given in the form of T Allopurinol 300 mg x 1 , or in case of hypersensitivity to allopurinol, febuxostat 120 mg x 1, or rasburicase according to local guidelines.

LABORATORY ASSESSMENTS

Pre-dose (up to 48 hours before): For all patients, blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed prior to the initial dose to evaluate

kidney function and correct pre-existing abnormalities. Blood chemistries should be reassessed prior to each subsequent dose increase during the titration phase.

Post-dose: For patients at risk of TLS, blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine) should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax. Electrolyte abnormalities should be corrected promptly. The next venetoclax dose should not be administered until the 24-hour blood chemistry results have been evaluated.
NOTE: The same monitoring schedule should be followed at the start of the 50 mg dose and then for patients who continue to be at risk, at subsequent dose increases.

HOSPITALISATION

Based on physician assessment, some patients, especially those at greater risk of TLS, may require hospitalisation on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours. Hospitalisation should be considered for subsequent dose increases based on reassessment of risk.

DOSE MODIFICATIONS FOR TUMOUR LYSIS SYNDROME

If a patient experiences blood chemistry changes suggestive of TLS, the following day's venetoclax dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with venetoclax can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see dose reduction schema). When resuming treatment after interruption due to TLS, the instructions for prevention of TLS should be followed (see "Prevention of tumour lysis syndrome" above).

RECOMMENDATIONS REGARDING RISK-STRATIFIED HYDRATION AND ANTIHYPERURICEMIC THERAPY

- Low risk (all lymph nodes <5 cm and absolute lymphocyte count [ALC] <25,000/mm^3): Outpatient: Hydrate with 1.5 to 2 L of oral hydration per day and administer allopurinol (beginning 2 to 3 days prior to venetoclax initiation). Administer i v hydration for patients unable to tolerate oral hydration.

- Medium risk (any lymph node 5 to <10 cm or ALC $\geqslant$25,000/mm^3): Outpatient: Hydrate with 1.5 to 2 L of oral hydration per day (administer i v hydration for patients unable to tolerate oral hydration; consider additional i v hydration) and administer allopurinol (beginning 2 to 3 days prior to venetoclax initiation).

- High risk (any lymph node ⩾10 cm OR ALC ⩾25,000/mm^3 and any lymph node ⩾5 cm): Hydrate with 1.5 to 2 L of oral hydration (administer i v hydration for patients unable to tolerate oral hydration) and 150 to 200 mL/hour i v hydration as tolerated; administer allopurinol (beginning 2 to 3 days prior to venetoclax initiation); consider rasburicase if baseline uric acid is elevated.

Note: elective hospitalization should be considered, at the discretion of the treating investigator, for any patient with diminished renal and/or cardiac function.

OTHER PROPHYLAXIS

1. In the first cycle, *all patients* receive prophylactic steroid medication with 4 mg of betamethasone p o / i v (or comparable other corticosteroid dose), the evening before, and one hour prior to rituximab day 1. All patients receive prophylaxis with paracetamol 1000 mg p o and antihistamine, according to local routine, prior to rituximab day 1 in cycle 1, and every following cycle if i v rituximab is used. Premedication prior to the following s c rituximab injections will be given according to local routine.

2. Filgrastim or appropriate substitute is to be administered during the last 7 days of each cycle during the time of lenalidomide interruption, except for patients with a day 22 ANC > 10 x 10^9/L. This medication can be used concurrently during the treatment cycle if non-febrile neutropenia is noted.

3. Due to the possibility of an increased risk for Pneumocystis pneumonia, trimethoprim/sulfamethoxazole according to local guidelines, should be administered from the start of treatment until at least three months after finishing protocol therapy. An alternative for patients with contraindications to trimethoprim-sulfa is dapson.

   All patients on lenalidomide are recommended to use: aspirin (ASA), LMWH or NoAC for thrombosis prophylaxis, and in case of prior history of DVT, PE or arterial thrombosis: LMWH or NoAC.

TOXICITY, TREATMENT MODIFICATIONS AND INVESTIGATIONAL DRUGS

BLOOD COUNTS

A blood count, including B-hemoglobin, WBC, differential count, and platelets, is performed at days 1, 8, 15, 22 (+/- 1 day) in cycles 1-2, and days 1 and 15 (+/- 1 day) in cycles 2-12, and at day 1 during the following cycles .

Except if due to extensive bone marrow involvement by MCL, recovery to absolute neutrophil count $\geqslant 1.0 \times 10^9$/L and platelet count $\geqslant 100 \times 10^9$/L is required before starting the second and subsequent cycles. If not, the following cycle is postponed until hematological recovery. G-CSF may be used at the discretion of the investigator, in addition to day 22-28, which is according to protocol.

DOSE REDUCTION, LENALIDOMIDE AND VENETOCLAX

Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

DOSE LEVELS FOR DOSE REDUCTION

- Venetoclax: 200 mg, 400 mg, 600 mg and 800 mg
- Lenalidomide: 5 mg, 10 mg, 15 mg and 20 mg

Hematological Toxicity Dose Reductions for Venetoclax		
ANC at start of cycle	Platelets at start of cycle	Action
$\geqslant$1,000µL or	>50,000/µL	None.

500-999/μL with fever or infection or	<50,000-25,000/μL with concurrent grade ⩾2 bleeding	-*1st Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. If noted during the venetoclax ramp up, consideration for starting at the same dose level can be considered per discussion with PI. -*2nd Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. Restart at the next lowest dose level. -*3rd Occurrence*: Discontinue protocol therapy.
<500/μL lasting > 14 days or with fever or infection or	<25,000/μL lasting > 7 days or noted with concurrent grade ⩾2 bleeding	-*1st Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. If noted during the venetoclax ramp up, consideration for starting at the same dose level can be considered per discussion with PI. -*2nd Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. Restart at the next lowest dose level. -*3rd Occurrence*: Discontinue protocol therapy.
Note: G-CSF (Filgrastim) may be given for up to 14 days for neutropenia in the absence of fever. Can be given concurrently and continuously with treatment at treating physician's discretions to prevent neutropenia.		

Hematological Toxicity Dose Reductions for Lenalidomide		
ANC at start of cycle	Platelets at start of cycle	Action
⩾1,000/μL or	>50,000/μL	None.

500-999/μL with fever or infection or	<50,000-25,000/μL with concurrent grade ⩾2 bleeding	*-1st Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. Resume treatment at 5 mg below previous dose; do not dose below 5 mg daily. *-2nd Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. Resume treatment at 5 mg below previous dose; do not dose below 5 mg daily. *-3rd Occurrence*: Discontinue protocol therapy.
<500/μL lasting > 14 days or with fever or infection or	<25,000/μL lasting > 7 days or noted with concurrent grade ⩾2 bleeding	*-1st Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. Resume treatment at 5 mg below previous dose; do not dose below 5 mg daily. *-2nd Occurrence*: Hold current dose until ANC ⩾ 1,000/μL and platelets ⩾ 50,000/μL. Do not replace missed doses. Resume treatment at 5 mg below previous dose; do not dose below 5 mg daily. *-3rd Occurrence*: Discontinue protocol therapy.
[1]Note: G-CSF (Filgrastim) may be given for up to 14 days for neutropenia in the absence of fever. Can be given concurrently with treatment at treating physician's discretions to prevent neutropenia.		

Following haematological recovery, the doses of lenalidomide or venetoclax may be re-escalated at the discretion of the investigator.

Non-Hematological Toxicity Dose Reductions			
CTCAE Grade	Venetoclax	Lenalidomide	Rituximab
0-2	No change from original starting dose.	No change from original starting dose.	No change from original starting dose.
3 that persists for ⩾7 days except	Hold until resolved to ≤ Grade 2, then reduce to	Hold until resolved to ≤ Grade 2, then reduce	No change from original starting dose (unless

Grade 3 vomiting which should lead to dose modification if symptom persists for ⩾ 2 days following appropriate supportive care.	the next lowest dose level upon resolution.	dose by 5 mg upon resolution, do not dose below 5 mg daily.	noted to be an infusion reaction at which time consider stopping therapy)
Second episode of grade 3 as described above or 1st episode 4 toxicity	Hold until resolved to ≤ Grade 2, then reduce to the next lowest dose level upon resolution.	Hold until resolved to ≤ Grade 2, then reduce dose by 5 mg upon resolution, do not dose below 5 mg daily.	**Do not administer any further doses on study.**
Third episode of grade 3 or 2nd episode 4 toxicity	**Remove subject from trial**	**Remove subject from trial**	**Do not administer any further doses on study.**

DOSE MODIFICATION OF LENALIDOMIDE DUE TO RENAL INSUFFICIENCY

In case of deterioration of renal function during trial, lenalidomide may need to be reduced.

- Creatinine clearance 30-50 mL/min: reduce to 10 mg/day
- Creatinine clearance <30 mL/min: stop lenalidomide, until recovery

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. If the full dose of rituximab at day 1, cycle 1 can be given, the following doses will be given subcutaneously. In the case of a severe infusion reaction at that point, the following dose will also be administered intravenously according to local routine, 375 mg/m^2.

CONCOMITANT MEDICATIONS

PERMITTED CONCOMITANT MEDICATIONS

Blood and platelet transfusions and supportive medications (such as for emesis, diarrhea,etc.) in accordance with standard practice are permitted.

ASA or appropriate alternative anticoagulant should be administered as long as patients remain on lenalidomide.

Short courses of corticosteroids (< 14 days) for non-cancer-related medical reasons (eg, treatment for rash, arthritis, asthma, autoimmune disorders) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Patients who receive concomitant medication that could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. Replace prior vitamin K antagonist therapy with low-molecular-weight heparin (LMWH) or NOAC prior to Day 1 of Cycle 1.

Hematopoietic growth factors are allowed as directed per protocol and if clinically indicated and used in accordance with the prescribing information. G-CSF may be administered in each cycle of therapy as primary prophylaxis for neutropenia, per American Society of Clinical Oncology (ASCO), EORTC, and European Society for Medical Oncology (ESMO) guidelines [22] or per each site's institutional standards.

Prophylactic treatment with antibiotics should be administered as per standard practice. Cotrimoxazole prophylaxis is mandatory. Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards.

PROHIBITED CONCOMITANT MEDICATIONS

Use of the following therapies (excluding protocol-specified treatments) is prohibited during the study:

- Any anti-cancer therapy
- Hormonal therapy other than contraceptives, stable hormone-replacement therapy, or megestrol acetate

- Biologic agents other than G-CSF and/or EPO

Use of the following concomitant medications is prohibited within 7 days before the first

dose and during the study (see also Appendix 6):

- Steroid therapy for antineoplastic intent
- Moderate/strong CYP3A4 inhibitors such as fluconazole, ketoconazole, and clarithromycin with use of venetoclax, during the ramp-up phase
- Moderate/strong CYP3A4 inducers such as rifampicin, carbamazepine, phenytoin, and St. John's wort with use of venetoclax

Note: After definition of RP2D, for those subjects in whom moderate/strong CYP3A4 inhibitor use is essential, venetoclax may be continued at a reduced dose at the discretion of the investigator.

Appendix 7 gives details on which drugs should be avoided

PROHIBITED FOODS

Use of the following foods is prohibited during the study and for at least 3 days before initiation of study treatment:

- Grapefruit
- Grapefruit juice
- Products that contain grapefruit
- Seville oranges (including marmalade that contains Seville oranges)
- Star fruit

SUPPLIERS

Celgene Corporation will supply lenalidomide, and Abbvie will supply venetoclax, free of charge during the study. Rituximab 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. Venetoclax will be supplied as 10, 50 and 100 mg tablets for oral administration. 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. For subcutaneous use, Rituximab is contained in 1400 mg vials for s c injection, and is injected in abdominal subcutaneous fat as an injection over 5 minutes.

PACKAGING

Lenalidomide will be shipped to the pharmacy at the study site in individual blisters. Blisters 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.

Venetoclax will be shipped to the pharmacy at the study site packaged in individual bottles or blisters with quantities sufficient to accommodate study design. Study drug must be dispensed in the original packaging with the label clearly visible.

LABELING

Lenalidomide and venetoclax investigational supplies are dispensed to the patients in individual blisters or bottles of capsules or tablets. Each blister or bottle will identify the contents as study medication. Each blister or bottle will be labeled per local requirements and this label must remain affixed to the kit.

STORAGE

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Upon receipt, study drug will be stored as specified on the label and kept in a secure location.

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.

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 blisters or bottles or unused capsules/tablets.

TESTS PERFORMED AT BASELINE (FOR TIME LIMITS, SEE FLOW SHEET):

- Clinical examination and complete medical history
- Assessment of WHO Performance Status
- Full blood count, biochemistry (creatinine, bilirubin, ALAT, ALP, albumin, LDH)
- Bone marrow biopsy for morphology and immunochemistry and aspiration for flow cytometry
- Blood and bone marrow for identification of patient specific IGHV rearrangement/t(11;14) to Copenhagen (Appendix 3)
- Sending ten unstained sections from diagnostic biopsy to Copenhagen for DNA extraction (Appendix 4)
- PET + CT of thorax, abdomen/pelvis and neck
- Health-related quality of life assessment (HRQOL), by EORTC QLQ-C30.
- Flow cytometry of normal lymphocyte populations in peripheral blood (CD19/CD3/CD4/CD8/CD56)
- Serology for HIV, HBV, HCV
- Serum, plasma and whole blood for freezing in -70 C, for biobanking, locally
- Plasma for cell free DNA, 40 ml in STRECK tubes
- Sending a formalin-fixed tissue sample for central review and TMA (Appendix 2)
- Immunoglobulin levels
- Creatinine clearance

BLOOD, BONE MARROW AND TUMOR SECTIONS TO COPENHAGEN - MRD

This material will be used for identification of patient specific IGHV rearrangement/t(11;14) and MRD according to EURO-MRD criteria. In addition, lymphocyte fraction from full blood (lymphoprep/Ficoll prep + viable freezing of cell suspension, and from bone marrow (BM) aspirates will be used for targeted NGS sequencing, including *TP53,* epigenetics, and isolation (through FACS) of tumor and immune cell populations in blood and BM (diagnostic samples) + blood (progression) for subsequent gene expression/RNAseq analysis, preferentially on a single-cell basis, and for PDX mouse models.

As the lymphoma cell content in bone marrow may be low, it is often necessary to construct a DNA primer for MRD from material from the diagnostic surgical biopsy. This is the reason why unstained sections from the biopsy are sent at baseline to the MRD lab.

LYMPH NODE BIOPSIES

In case of lymph node/tumour biopsies at base-line or relapse, sample material will be used for translational research projects, including DNA- and RNA- sequencing, and for PDX mouse models.

IMMUNOPROFILING OF SERUM SAMPLES

The serum samples are used to profile immune-related proteins using the IMMRay or similar platforms developed at the Department of Immunotechnology, Lund University. The technology allows the simultanous measurement of > 150 different proteins in one analysis.

TESTS PERFORMED BEFORE EACH CYCLE OF INDUCTION OR MAINTENANCE

- Clinical examination and complete medical history
- Assessment of WHO Performance Status
- Full blood count, biochemistry (creatinine, bilirubin, ALAT, ALP, albumin, LDH)

TESTS PERFORMED AT RESPONSE EVALUATION – EVERY 3 CYCLES

- Clinical examination and complete medical history
- Blood tests as above
- Blood for MRD, to Copenhagen (Appendix 3) (substituted by PET in patients without a molecular marker for MRD)
- CT of thorax, abdomen/pelvis and neck
- PET is performed after 6 cycles. Should be assessed using the 5-point, Deauville score
- HRQOL assessment

- Serum, plasma and whole blood for freezing
- Plasma for cell free DNA, 40 ml in STRECK tubes
- Flow cytometry of normal lymphocyte populations in peripheral blood

  (CD19/CD3/CD4/CD8/CD56)

ADDITIONAL TESTS PERFORMED AT RELAPSE

- Serum, plasma and whole blood for freezing
- Bone marrow
- Lymph node including single cell suspension
- Flow cytometry of normal lymphocyte populations in peripheral blood (CD19/CD3/CD4/CD8/CD56)
- Plasma for cell free DNA, 40 ml in STRECK tubes

Investigations as above are performed until clinical progression, for a maximum of 24 months after start of treatment. Study subjects are followed every 3 months for overall survival for 24 months after documented progression or end of therapy.

Patients still on treatment after 24 months, when the study ends, may continue therapy outside trial.

When MRD-negative in blood, treatment will continue for another 3 months, when a new evaluation of MRD in blood and bone marrow will be performed. If MRD negativity is confirmed, treatment is stopped and the patient will be followed with MRD and CT, every 3 months up to a maximum of 24 months.

TESTS PERFORMED AT MOLECULAR RELAPSE

At time of molecular relapse, but without clinical relapse, CT, bone marrow and clinical evaluation will be performed to evaluate the risk for tumor lysis syndrome, before restarting treatment.

CRITERIA FOR EVALUATION AND ENDPOINT

RESPONSE CRITERIA – USING CT AND PET (LUGANO-CRITERIA)[23]

Note that the following text only provides a short summary of the Lugano criteria. Evaluation of PET is performed according to the 5-point scale (Deauville)[24], see Appendix 4. The score is recorded in the CRF. A score of 1-3 is considered negative, and a score of 4-5 as positive.

- **Complete remission (CR)**

  Disappearance of all evidence of disease

  - Nodal Masses: mass of any size permitted if FDG-PET is negative.
  - 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

  - Nodal Masses: 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes.
  - One or more PET positive at previously involved site
  - Bone marrow: Irrelevant if positive prior to therapy

- **Stable disease (SD)**

  Failure to attain CR/PR or PD

  - Nodal Masses: PET positive at prior sites of disease and no new sites on CT or PET

- **Progressive disease (PD)**

  - Any new lesion or increase by 50% of previously involved sites from nadir

- 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
- Lesions PET positive if proven to be due to MCL

♦ Overall response rate (ORR) –primary endpoint – is the sum of CR and PR

RELAPSE/PROGRESSION

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
2. Date of relapse
3. Site of relapse
4. Info regarding further treatment

In patients in PR or SD during treatment, progression will be registered.

The following data will be registered:

1. Progression yes/no
2. Date of progression
3. Site of progression
4. Info regarding further treatment

At relapse or progression, 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 defined as the interval between registration date and date of documented progression or lack of response, first relapse, or death of any cause. [25]. Otherwise, patients will be censored at the last date they were known to be alive. For patients with PD as best response, 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 or PR) are met, to the first documentation of relapse or progression.

ADVERSE EVENTS

MONITORING, RECORDING AND REPORTING OF ADVERSE EVENTS

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence 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 (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on

the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome. Disease progression is not to be reported as an adverse event.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent to 28 days after the last dose of study drug. *Grade 1-2 hematological toxicity is an exception and does not need to be reported.*

AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to the Sponsor within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

Causality will be assessed independently for each drug, using a 2-point scale (yes/no).

Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (i.e., in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires unplanned inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- 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.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to study drugs, occurring at any time for the duration of the study, from the time of signing the informed consent up to the end of follow-up. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation of the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drugs or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.
- Disease progression should not be recorded as an adverse event or serious adverse event; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

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

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

SEVERITY / INTENSITY

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03);

AEs that are not defined in the NCI CTCAE should be evaluated for severity / intensity according to the following scale:

- *Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required*
- *Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required*
- *Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible*
- *Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable*
- *Grade 5 = Death - the event results in death*

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

CAUSALITY

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: A causal relationship of the adverse event to IP administration is unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: There is a reasonable possibility that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

DURATION

For SAEs, the Investigator will provide a record of the start and stop dates of the event.

ACTION TAKEN

The Investigator will report the action taken with the study drugs as a result of an AE or SAE, as applicable (e.g., discontinuation or reduction of study drugs, as appropriate) and report if concomitant and/or additional treatments were given for the event.

OUTCOME

The investigator will report the outcome of the event for SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause) or death (due to the SAE).

ABNORMAL LABORATORY VALUES

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;

- requires treatment, modification/ interruption of study drug dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

PROCEDURES

All initial PQCs for venetoclax must be reported to Abbvie by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to Abbvie according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested.

PREGNANCY

FEMALES OF CHILDBEARING POTENTIAL:

Lenalidomide is structurally to thalidomide, which is known to be teratogenic. A strict definition of fertility is necessary:

Definition of not fertile:

1. Age > 50 years and amenorea for > 1 year
2. Premature ovarial failure confirmed by specialist in gynecology
3. Bilateral salpingo-ooferectomi or hysterectomy
4. Genotype XY, Turners syndrome, uterusagenesia

Fertile women must be informed about and understand the teratogenic risk of study medication and the need for effective prevention against pregnancy and monthly pregnancy tests during

study, even if she has amenorea. In case of suspected pregnancy she should consult a physician without delay.

Male patients who have fertile partners must be informed about the potential teratogenic risks of intercourse with a fertile or pregnant woman and therefor the obligation to use a condom (even after vasectomy). If partner suspects pregnancy she should consult a physician with experience in teratology without delay.

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 immediately reportable events. 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 the Sponsor who will inform Abbvie immediately using a Pregnancy Reporting Form. The exposure of any pregnant female (e.g., caregiver or pharmacist) to lenalidomide is also an immediately reportable event.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify the Sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

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 suspects is related to the in utero exposure to the study drugs should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study drugs should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

If a pregnancy related event is reported in a female partner of a male subject, the investigator should ask if the female partner is willing to share information with sponsor and allow the pregnancy related event to be followed up to completion.

The Sponsor will inform Celgene and Abbvie immediately, using the Pregnancy Reporting Form, of any information related to pregnancies or suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring in partner of Patients while the Patients are still treated with the study drugs or within 28 days of the Patients' last dose of study drug.

Expedited Reporting of Adverse Events

Reporting to Regulatory Authorities and the Ethics Committee

The Sponsor will inform relevant Regulatory Authorities and Ethics Committees;

- Of all relevant information about serious unexpected adverse events suspected to be related to the study drugs 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 be subsequently be submitted within an additional eight days
- Of all other serious unexpected events suspected to be related to the study drugs 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 to Celgene and Abbvie

The investigator will inform the Sponsor of all SAEs (by fax) within 24 hours in order that the sponsor can fulfill their regulatory reporting obligations within the required timeframes.

The Sponsor will supply Celgene and Abbvie with a copy of all SAEs which involve *exposure* to their respective product 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 Abbvie with a copy of the annual periodic safety report e.g. Development Update Safety Report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committee.

Contact details for Sponsor

Nordic Lymphoma Group

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Aarhus University Hospital
A-CTO
Palle Juul-Jensens Boulevard 99, C104
DK - 8200 Aarhus N, Denmark
Phone: +45 7845 5855
Fax: +45 7846 7597

Contact details for Drug Safety Abbvie:

Denmark
dksafety@abbvie.com

Sweden
medinfosafety@abbvie.com

Norway
drugsafety.norway@abbvie.com

Finland

Investigator reports adverse events that occur during the course of the Study directly to the Finnish Medicines Agency (FIMEA), as required by and in accordance with the applicable Law.

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.

STUDY DURATION

The protocol aims to begin in q1 2018, and the inclusion is estimated to end in third quarter of 2021.

Patients will be followed for safety until 28 days after end of study treatment, for a maximum of 24 months from inclusion.

Patients still on treatment after 24 months after inclusion, without disease progression when the study ends, may continue on therapy outside trial, or, depending on national regulations, in an extension clinical trial.

Patients will be followed for overall survival for 24 months after finishing study treatment.

End of trial is defined as the last visit for the last subject participating in the trial.

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 patient's own wish to terminate study treatment
- If the responsible physician thinks a change of therapy would be in the best interest of the patient.

STUDY TERMINATION

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the sponsor. If a study is suspended or terminated for safety reasons, the sponsor will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. The sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of an investigational site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator

STATISTICAL ANALYSIS PLAN

The following assumptions were used to estimate the sample size and the trial duration:

- Inclusion period up to 2 years
- Additional follow-up period up to 2 years
- Inclusion rate, 30 per year
- Drop-out rate, 10% of included patients
- Power 80% to detect an ORR superiority of venetoclax+lenalidomide+rituximab vs. the historical control of lenalidomide+rituximab (77% vs. 57%)[26]. For this purpose, 44 patients would need to be recruited.

Analysis cohort

The analysis of the primary objective will be performed according to the intention to treat. Thus, all included patients will be included in the primary analysis irrespective of eligibility. No exclusion or censoring will be done in case of protocol violations. The analysis for the primary endpoint will be performed for 50 patients with relapsed/refractory (R/R) MCL. As a preplanned analysis, overall response rate for patients previously treated with ibrutinib will be assessed.

As an exploratory substudy, 15 patients with untreated MCL, ineligible for combination chemotherapy were planned to be enrolled. However, due to competing trials in the Nordic area, no patients in this population were found to be eligible, and a decision was made by the Nordic Lymphoma MCL Group, on 04-NOV-2020, to omit this cohort from the study.

Statistical Analysis Methods

The primary endpoint, ORR will be calculated after 6 months of treatment, based on CT, PET and bone marrow examination according to the Lugano criteria[27].

Statistical Analysis of Secondary Objectives

OS is the time to death from any cause, and will be censored at the latest follow-up date in patients alive. OS will be calculated from inclusion in the trial.

PFS is the time to progression or death from any cause. Patients alive without progression at latest follow-up will be censored at the latest tumour assessment date. PFS will be calculated from study inclusion.

Secondary efficacy analyses will be performed according to the intention-to-treat without exclusion or censoring for protocol violations.

Time-to-event endpoints will be described using Kaplan-Meier estimates and compared between groups using log-rank tests. This refers to groups based on MIPI category, age, gender, mutational profile, previous ibrutinib exposure and number of previous line of treatment.

Categorical endpoints will be described by absolute and relative frequencies and compared between groups by Fisher's exact tests.

For efficacy endpoints we will perform multivariable regression models to adjust treatment effects for potential confounders, such as MIPI, Ki-67 index, and mutational profile. All secondary objectives will be analysed in a descriptive way without correction for multiple testing.

Statistical Analysis of Exploratory Objectives

Time-to-event endpoints will be described using Kaplan-Meier estimates and compared between groups using log-rank tests. Categorical endpoints will be described by absolute and relative frequencies and compared between groups by Fisher's exact tests. Multivariable regression models will be performed to identify clinical and biological prognostic or predictive factors. All exploratory objectives will be analysed in a descriptive way without correction for multiple testing.

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 person 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 response and safety data from the phase 1 portion.

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 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 by the subject's dated signature.

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 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. Monitors (as well as auditors and inspectors) will be provided with direct access to source documentation (patients' records).

FINANCING

The study will be financed by the Nordic Lymphoma Group. Abbvie will contribute with a research grant. Abbvie will provide venetoclax and Celgene will provide lenalidomide as study drug.

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26. Wang M, Fayad L, Wagner-Bartak N, Zhang L, Hagemeister F, Neelapu SS, Samaniego F, McLaughlin P, Fanale M, Younes A *et al*: Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. *Lancet Oncol* 2012, 13(7):716-723.
27. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA, Alliance AL, Lymphoma G, Eastern Cooperative Oncology G *et al*: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014, 32(27):3059-3068.

APPENDIX 1 FLOWSHEET

PROTOCOL: NLG-MCL7 (VALERIA)

PATIENT NAME:

	Before therapy		Treatment phase – until MRD negative confirmed or up to 24 months.																Relapse
Weeks	Within 4 weeks	Within 2 weeks	0	4	8	10	12	16	20	22	24	28	32	34	36 etc	40 etc	44 etc	46 etc.	
Cycle			1	2	3		4	5	6		7	8	9		10	11	12		
Date																			
Medical history		x																	
Adverse events			x	x	x		x	x	x		x	x	x		x	x	x		
Physical examination, weight, WHO Performance		x	x	x	x		x	x	x		x	x	x		x	x	x		
Complete blood count#		x	x	x	x		x	x	x		x	x	x		x	x	x		
Tumor lysis samples* - K, P, Ca, Creatinine, uric acid		x	x*	x*	x*														
Creatinine, ALAT, ALP, LDH, Bilirubin. Albumin		x	x	x	x		x	x	x		x	x	x		x	x	x		
Creatinine clearance	x																		
HIV, HBV, HCV serology	x																		
CT neck, thorax, abdomen, pelvis with contrast	x					x				x				x				x	
PET	x[2]									x									
Bone marrow biopsy	x																		
Bone marrow and blood flow cytometry	x										x[c]				x[c]			x[c]	x
MRD blood	x						x				x				x			x	
MRD bone marrow	x						x				x[c]				x[c]			x[c]	
EORTC QLQ-C30		x					x				x				x				
Serum, plasma and whole blood for freezing	x						x				x				x				x
Plasma for cell free DNA, 40 ml in STRECK tubes	x						x				x				x				x
Lymphocyte subsets		x					x				x				x				x
Immunoglobulin levels		x					x				x				x				
Pregnancy Test[1]	x		x	x	x		x	x	x		x	x	x		x	x	x		
Venetoclax + Rituximab+ Lenalidomide			x[a]	x[b]	x		x[b]	x	x[b]		x	x[b]	x		x[b]	x	x[b]		

#A blood count, including B-hemoglobin, WBC, differential count, and platelets, is performed at days 1, 7, 14, and 21 (+/- 1 day) in cycles 1-2 and days 1 and 14 in cycles 2-12, and at day 1 during the following cycles.

* TLS specific blood chemistries are obtained before start of venetoclax, before every elevation of dose level, and 6-8 and 24 hours after every elevation of dose level in the ramp up phase.

[1]For women of child-bearing potential.

[2]Mandatory at baseline, and to confirm molecular remission prior to stopping treatment in patients without an MRD marker

[a]Rituximab given days 1, 8, 15 and 22 in cycle 1.

[b]No rituximab in this cycle.

[c]Only bone marrow to confirm molecular remission prior to stopping treatment.

If a lymph node / tumor biopsy is performed at either base line and/or relapse, fresh frozen material should be stored at -80 degrees.

APPENDIX 2 PATHOLOGY FORM

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

Klaus Beiske, Dept of Pathology, Rikshospitalet, Oslo, Norway. Email: Klaus.beiske@medisin.uio.no

Erik Clasen-Linde, Dept of Pathology, Rigshospitalet, DK 2100 Copenhagen, Denmark.

E-mail: erik.clasen-linde@regionh.dk

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

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:……..

Study number:……

Who is being treated according to the Seventh Nordic MCL Protocol (VALERIA)

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

Original access number:

Sincerely,

Signature:……Hospital:……Country…….

APPENDIX 3 MOLECULAR STUDIES (MRD)

Use a copy of this form whenever molecular samples are submitted to Copenhagen. Please e-mail the completed form to the lab (e-mail below) and include the form in the shipment.

The Hematology Laboratory 4041, Attention Lone Bredo Pedersen
Entrance 4, 4th. floor
Leukemia Lab. 4041, rum 4142/44
Rigshospitalet
9 Blegdamsvej
2100 Copenhagen
Denmark

Phone +45 3545 1844 Leukemia Lab.

Fax +45 3545 4283 (Clinical Trial Unit) attention Leukemia Lab

Email: haem-cll.rigshospitalet@regionh.dk

Please find enclosed samples from our patient:

Patient study ID number: VALERIA-……-……

Who is being treated according to the NLG-MCL7 Protocol (VALERIA)

Samples are taken date:……time……., corresponding to Cycle……., Day……..

and consist of:

- ☐ 15 ml bone-marrow aspirate, Medium
- ☐ 50 ml blood, anticoagulated EDTA
- ☐ 40 ml blood in STRECK tubes
- ☐ Optional: fresh frozen lymph node/tumor biopsy

Has the patient previously been treated in a NLG MCL trial? ☐ Yes No ☐

If yes, which trial:…… patient ID number…….

Sincerely,

Signature:……

Name: ……Hospital:……Country……

To be completed by the Laboratory:		
Date of Tube's reception: ___/___/___	Date of Tube's Manipulation: ___/___/___	Deadline of Reception : ___ hours
☐ DNA extraction: ___/___/___	☐ Immunophenotyping at Baseline: ___/___/___	☐ Freezing cells at Baseline: ___/___/___

Handling of biological material

50 ml of peripheral venous blood (EDTA) and 15 ml of bone marrow aspirate (medium) should be collected in a sterile tube.

Base line sample

Should be sent ***by courier***, to arrive in Copenhagen within 24 hours. Bone marrow should be dissolved in cell medium (as for cytogenetic studies).

Follow-up samples

The sample should be sent by courier to Copenhagen for arrival within 24 hours. To avoid samples arriving in weekends, please collect and ship only Monday through Wednesday. Please label all tubes.

Lymph node / tumor samples

Whenever a lymph node / tumor biopsy is performed at base line or relapse, fresh frozen sample material should be sent to Copenhagen, kept at -80 degrees (no time limit) and sent on dry ice by courier.

STRECK tubes

40 ml of peripheral venous blood should be collected in 4 x 10 ml STRECK tubes.

The tubes should be held in room temperature and sent directly (the same day) to the central biobank in Copenhagen by regular mail, for arrival in less than 48 hours. To avoid samples arriving in weekends, please collect and ship only Monday through Wednesday. Please label all tubes.

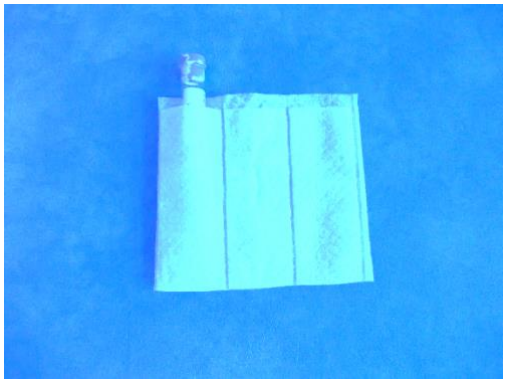
In Copenhagen, separation and storage of plasma should be performed as soon as possible, but no later than seven days from sampling.

- These tubes should be drawn as the last ones during the sampling.
- Venous puncture should performed in the same way for each patient, i.e. always in a peripheral vein or always in a subcutaneous venous port.
- Prevent back flow since the tube contains chemical additives.
- Release tourniquet once blood starts to flow in the tube. Fill tube completely.
- Mix by gentle inversion 8 to 10 times. One inversion is a complete turn of the wrist, 180 degrees, and back.

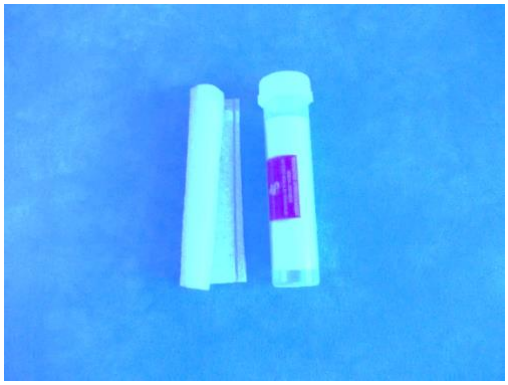
The lab should be informed by email at the time of shipment, or before (address as above).

Instructions for shipment of STRECK tubes

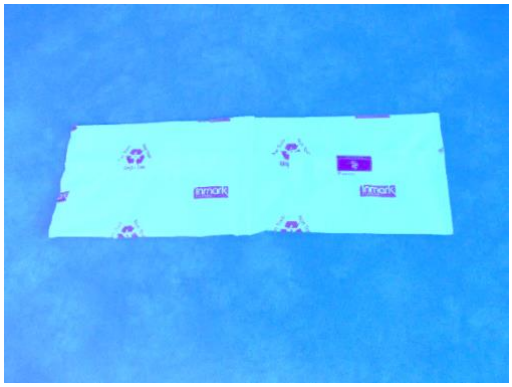
Please note, that the Streck tubes should be kept in room temperature (15°-30° C).
Do not centrifuge the tubes.



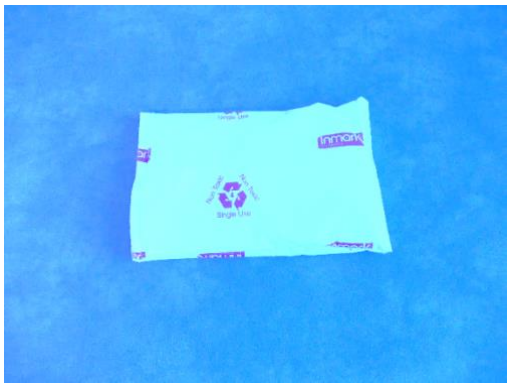
Mark the Streck tube with site number and subject number with the labels provided. Put the tube in the protective foil.



Put the tube into the transport tube.



Place the transport tube on the gelpack medium.



Fold the gel pack medium on the middle.

Place the gel pack with the Streck tube into the zip lock plastic bag.

Put the plastic bag into the pre labelled envelope, and send it by ordinary mail. Please remember to attach the blood sampling sheet.

APPENDIX 4 SECTIONS FROM DIAGNOSTIC BIOPSY FOR MRD

Use a copy of this form when tissue sections are submitted to Copenhagen.

The Hematology Laboratory 4041, Attention Lone Bredo Pedersen/Anne Margrete Svendsen

Entrance 4, 4th. floor

Leukemia Lab, room 4141

Rigshospitalet

9 Blegdamsvej

2100 Copenhagen

Denmark

Phone +45 3545 1844 Leukemia Lab.

Fax +45 3545 4283 (Clinical Trial Unit) attention Leukemia Lab

Email: haem-cll.rigshospitalet@regionh.dk

Please find enclosed samples from our patient:

Patient initials and study number:……

Who is being treated according to the NLG-MCL7 Protocol (VALERIA)

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

- Ten 10 μm sections from formalin fixed tissue from diagnostic lymph node/tumor biopsy
- Each section is put into an Eppendorf tube or similar container

Sincerely,

Signature:……

Name: ……Hospital:……Country……

APPENDIX 5 SCORING OF PET ACCORDING TO THE 5-POINT (DEAUVILLE) SCORE

1. no FDG uptake above background

2. FDG uptake ⩽ mediastinum

3. FDG uptake > mediastinum but ⩽ liver

4. FDG uptake moderately > liver

5. FDG uptake markedly higher than liver and/or new lesions

APPENDIX 6 HIGHLY EFFECTIVE METHODS OF CONTRACEPTION FOR FERTILE WOMEN WITHIN THE TRIAL

1. Implant*
2. Levonorgestrel-releasing intrauterine system (IUS)*
3. Medroxyprogesterone acetate depot
4. Tubal sterilisation
5. Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
6. Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

NB! Patients using a hormonal method (1-3 or 6), must also use a second barrier method.

Comments

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.

Combined oral contraceptive pills are not recommended due to a potentially increased risk of thromboembolism with lenalidomide. 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.

APPENDIX 7 SAMPLE LIST OF EXCLUDED AND CAUTIONARY MEDICATIONS

Excluded

Strong CYP3A inducers - avasimibe,carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort

Moderate CYP3A inducers - bosentan, efavirenz, etravirine, modafinil, nafcillin,

Strong CYP3A inhibitors - boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, paritaprevir/ritonavir combinations, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole

Moderate CYP3A inhibitors - amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem[1], erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil

Cautionary

Warfarin and coumarin derivatives**

P-gp substrates
Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan*

BCRP substrates
Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan*

OATP1B1/1B3 substrates
Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan

P-gp inhibitors
Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor

BCRP inhibitors
Geftinib*

Note that this is not an exhaustive list. For an updated list, see the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruits.

* These are anticancer agents.

** Closely monitor the international normalized ratio (INR).

[1] Moderate CYP3A inhibitor per venetoclax FDA USPI.