MCL R2 ELDERLY

Efficacy of alternating immunochemotherapy consisting of R-CHOP + R-HAD *versus* R-CHOP alone, followed by maintenance therapy consisting of additional lenalidomide with rituximab *versus* rituximab alone for older patients with mantle cell lymphoma

LYSARC

LYSARC: **T**HE **L**YMPHOMA **A**CADEMIC **R**ESEARCH **O**RGANISATION
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Version and date of Protocol: Final version 6.1 – 24/06/2019
EUDRACT Number: 2012-002542-20

CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE PAGE

MCL R2 ELDERLY

EFFICACY OF ALTERNATING IMMUNOCHEMOTHERAPY CONSISTING OF R-CHOP + R-HAD VERSUS R-CHOP ALONE, FOLLOWED BY MAINTENANCE THERAPY CONSISTING OF ADDITIONAL LENALIDOMIDE WITH RITUXIMAB VERSUS RITUXIMAB ALONE FOR OLDER PATIENTS WITH MANTLE CELL LYMPHOMA

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1 SYNOPSIS

Study ID Eudract N°	MCL R2 elderly 2012-002542-20
Title of the study	**Efficacy of alternating immunochemotherapy consisting of R-CHOP + R-HAD versus R-CHOP alone, followed by maintenance therapy consisting of additional lenalidomide with rituximab versus rituximab alone for older patients with mantle cell lymphoma**
Protocol version	Final version n°6.1 – 24/06/2019
Sponsor	**LYSARC**
Coordinating investigator / Co-coordinating investigator	Prof. Dr. M. Dreyling — University Hospital Munich Prof. Dr. J.C. Kluin-Nelemans — University Medical Center Groningen Dr. V. Ribrag — Institut de cancérologie Gustave Roussy
Centers	150 - 200 centres from following study groups may recruit in this study : FIL (Italian Intergroup) (C. Visco, Vincenza/Italy) LYSA (V. Ribrag, Villejuif/France, R. Gressin, Grenoble/France and Marc André Yvoir/Belgium) GLSG (M. Dreyling, W. Hiddemann, Munchen/Germany) HOVON (JK Doorduijn, Rotterdam/Netherlands, JC Kluin-Nelemans, Groningen/Netherlands) GELTAMO (A. Lopez, Barcelona/Spain) PLRG (J. Walewski, M. Szymczyk, Warszawa/Poland) Portugese LSG (M. da Silva, Lisboa/Portugal)
Study Objectives and endpoints	Primary objective: • to evaluate whether the addition of lenalidomide to rituximab-maintenance improves progression free survival (PFS) compared to standard rituximab maintenance after response to induction chemotherapy in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation Primary endpoint: • progression free survival (PFS) from randomization for maintenance to progression or death from any cause Secondary objectives: • to compare efficacy and safety of the maintenance regimens in terms of secondary endpoints • to evaluate whether the introduction of cytarabine into induction improves clinical outcome compared to standard R-CHOP in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation Secondary endpoints: • Time to event :

	- overall survival from induction randomization to death from any cause - overall survival from maintenance randomization to death from any cause - time to treatment failure, progression-free survival from induction randomization, remission duration • PR/CRu to CR and PR to CRu conversion during maintenance • Minimal residual disease (MRD) status and levels in peripheral blood and bone marrow at midterm and at the end of induction, after one and two years from end of induction and during follow-up until progression or up to 2.5 years of follow-up whichever comes first • complete and overall response rates (based on Cheson 1999 criteria) at midterm and end of induction, • safety according to NCI CTCAE (v 4.0) • secondary primary malignancies rates after lenalidomide vs. no lenalidomide • Exploratory : response assessment according to Cheson 2007 criteria including FDG-PET evaluation
Duration of the study	The patients will be recruited over 6 years (5.5 years plus 6 months induction therapy). The final analysis will be performed when 158 events with respect to the primary endpoint have been observed after approximately 2.5 years of follow-up after the last patient randomized for maintenance. All subjects who complete or discontinue the maintenance treatment for any reason will be followed for at least 3 years after his/her last study treatment administration in maintenance period for SPM. A long term follow-up for progression/death will be done up to the end of period of SPM data collection.
Number of patients	Up to 633 patients randomized for induction Up to 443 patients randomized for maintenance
Inclusion and exclusion criteria	**Key Inclusion Criteria** • signed informed consent form • Biopsy-proven mantle cell lymphoma according to WHO classification, including evidence of cyclin D1 overexpression or the translocation t(11;14)(q13;q32), • ≥ 60 years of age and ineligible for autologous transplant • Ann Arbor stage II-IV • previously untreated (except for patients randomized directly for maintenance treatment who will receive 8 RCHOP before registration in the trial) • ECOG performance status ≤ 2 • Male subjects must: - agree to use a condom during sexual contact with a woman of childbearing potential, even if they have had a vasectomy, throughout lenalidomide therapy - agree to not donate semen during lenalidomide therapy. • All subjects must: - have an understanding that the lenalidomide could have a potential teratogenic risk.

- agree to abstain from donating blood while taking lenalidomide therapy
- agree not to share study medication with another person.
- be counselled about pregnancy precautions and risks of foetal exposure.

Key Exclusion Criteria

- Female of child-bearing potential (without natural menopause for at least 24 consecutive months, a hysterectomy or bilateral oophorectomy)
- Any of the following laboratory abnormalities, if not related to lymphoma:
  - Absolute neutrophils count (ANC) <1,000 /mm^3 (1.0 x 10^9/L) if not result of a BM infiltration.
  - Platelet counts < 75,000/mm^3 (75 x 10^9/L) if not result of a BM infiltration.
  - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) >3.0 x upper limit of normal (ULN).
  - Serum total bilirubin > 1.5 ULN (except if due to Gilbert's syndrome)
- Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) < 30 mL /min.
- Central nervous system involvement by lymphoma
- Contraindication for medicamentous DVT prophylaxis for patients at high risk for DVT
- Prior history of malignancies other than MCL unless the subject has been free of the disease for ≥ 5 years (Exceptions: Basal or squamous cell carcinoma of the skin, Carcinoma in situ of the cervix or of the breast, Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient to receive the study medication as planned.
- Poor cardiac function (LVEF < 50%) on echocardiography
- Seropositivity for human immunodeficiency virus (HIV, mandatory test)

  Seropositivity for hepatitis C virus (HCV, mandatory test),

  Active viral infection with hepatitis B virus (HBV, mandatory test):
  - HBsAg positive
  - HBsAg negative, anti-HBs positive and anti-HBc positive

    Patients with prior Hepatitis B must be given antiviral prophylaxis and HBV DNA monitored

    Note: Patients who are HBsAg negative, anti-HBs positive and/or anti-HBc positive but viral DNA negative are eligible.
- Uncontrolled illness including, but not limited to:
  - Active infection requiring parenteral antibiotics
  - Uncontrolled diabetes mellitus
  - Chronic symptomatic congestive heart failure (Class NYHA III or IV).
  - Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months
  - Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia.
- Prior ≥ Grade 3 allergic hypersensitivity to thalidomide.
- Prior ≥ Grade 3 rash or any desquamating (blistering) rash while taking thalidomide.

	• Subjects with ≥ Grade 2 neuropathy. • Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies • Prior use of lenalidomide. • Participation in another clinical trial within three weeks before randomization in this study. **<u>Additional criteria for randomization in maintenance phase :</u>** • Inclusion criteria - CR, CRu or PR after induction treatment, determined as per Cheson 1999 criteria by investigator - During the run-in period of 6 months starting from the date of the first patient randomized in the trial: in case of direct randomization into maintenance phase, patient must have been treated in first line by 6-8 cycles of R-CHOP. • Exclusion criteria - SD or PD after induction treatment determined as per Cheson 1999 criteria assessed by investigator. - Patients who had not received at least 6 cycles of R-CHOP21 or 2 cycles of R-CHOP21 / 2 cycles of R-HAD28 (alternating) - Patients with serious underlying medical conditions, which could impair the ability to receive maintenance treatment - Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) of < 30 mL /min at screening for maintenance. - ANC < 1,000 cells/mm³ (1.0 X 10^9/L) at screening for maintenance; - Platelet count < 50,000 cells/mm³ (50 X 10^9/L) at screening for maintenance.
Benefit/Risk imbalance of treatment program	All study treatments have proven their efficacy in the treatment of MCL. It is expected that patients will achieve a high response rate in each of the induction arms consisting of 8 courses of R-CHOP or alternating 3 courses of R-CHOP and 3 courses of R-HAD. It is hoped that induction with alternating 3 courses of RCHOP and 3 courses of RHAD will improve the outcome. For the maintenance therapy, in patients who initially reach at least a partial response to induction, it is hoped that adding lenalidomide to standard Rituximab maintenance will be beneficial to the patients in term of PFS. It is possible that some patients may not reach a clinical response with the study treatment and will require other treatment outside this protocol. Altogether, in this elderly MCL patient's population, the benefit of this treatment program is expected to be superior to the potential short and long term toxicities. This study will help gain knowledge about this innovative treatment strategy in MCL based on new induction and maintenance strategies.
Design of the trial	phase III randomized trial, international, multicentric, open labeled for induction and maintenance treatment
Study Treatment	***Induction phase*** Patients will be randomized between following induction regimens: • 8 cycles of R-CHOP21 vs.

	• 6 alternating cycles R-CHOP21 and R-HAD28 ***Maintenance phase*** Patients responding to induction with either CR, CRu or PR will be subsequently randomized between : • Subcutaneous rituximab 1400 mg every 8 weeks plus lenalidomide 15 mg (d2-22, repeat d29) up to two years vs • Subcutaneous rituximab 1400 mg every 8 weeks up to 2 years During a run-in period of 6 months starting from the date of the first patient randomized in the trial, patients will be allowed to register after a documented response (CR, CRu or PR) to 6-8 cycles of R-CHOP induction, in order to collect additional data on toxicity and feasibility of the rituximab-lenalidomide (R2) maintenance treatment. As this run-in period is now closed, no direct randomization is allowed. - Subjects who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] will receive a lower starting dose of lenalidomide of 10 mg p.o. once daily on Days 2-22 of every 28-day cycle in Cycle 1 and in Cycle 2. After Cycle 2, if the subject has not experienced any drug-related grade 3 or 4 toxicity for the first 2 cycles, the dose should be increased to 15 mg once daily for 21 days of a 28-day cycle at the discretion of the treating physician. - Patients at high risk for a thromboembolic event (history of a thromboembolic event or a known hypercoagulable state regardless of thromboembolic history will receive prophylactic aspirin (acetylsalicylic acid 100 mg) daily. If ASA is contraindicated, the use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the INR in the range of 2-3 is acceptable. ***Follow-up Phase*** All subjects who complete or discontinue the maintenance treatment for any reason will continue to be followed every 6 months for 2 years then yearly after maintenance and after treatment discontinuation until the end of the study.
Randomization	Patients will first be randomized between two induction regimens. Randomization will be stratified according to country (France, Belgium and Portugal will be considered as one country) and MIPI risk group (High vs Low & Intermediate). Patients responding to induction with either CR, CRu or PR will be subsequently randomized between two maintenance treatment arms, stratified according to country group (Northern countries (Netherlands, Germany, Poland) vs southern countries (France, Belgium, Portugal, Spain, Italy), type of first line induction therapy (R-CHOP vs R-CHOP/R-HAD), response to first line therapy (CR/CRu vs PR) and MIPI risk group (High vs Low & Intermediate) at initial diagnosis. During a run-in period of 6 months starting from the date of the first patient randomized in the trial, patients will be allowed to register at the time of response to R-CHOP induction, and proceed to maintenance randomization to collect additional data on toxicity, feasibility and efficacy of R2 maintenance.
Statistical analysis	<u>Sample size calculation for PFS (primary endpoint):</u> • randomization rate for maintenance 80.5 patients per year, including 10% dropouts • two-sided logrank test, significance level 5% • no interim analysis • 80% power to detect a hazard ratio of 0.64 for PFS after maintenance randomization of lenalidomide+rituximab versus rituximab alone

	• number of events needed: approx. 158 • recruiting period 6 years (5.5 years plus 6 months induction therapy), minimal additional follow-up 2.5 years • Kaplan-Meier estimates from the previous MCL Elderly trial of the European MCL trial (5-years PFS 0.5032 in control arm) • 443 patients with second randomization, including 10% dropouts • 633 patients with first randomization (rate of second randomizations: 70% of first randomizations) All sample size calculations are based on East, version 5. <u>Analysis Plan:</u> The primary endpoint will be analysed according to the two maintenance study arms with an unstratified two-sided log-rank test. Estimates of the treatment effect will be expressed as hazard ratios including two-sided 95% confidence intervals. In addition Kaplan-Meier estimates of median progression-free survival as well as progression-free survival rates at one, two and three, etc. years after randomization for maintenance with 95% confidence intervals will also be reported. <u>Interim Analysis:</u> For the primary objective, no interim analysis will be performed. Interim analyses will be performed to evaluate OS from induction randomization (secondary endpoint) according to induction arms to allow an early closure of the R-CHOP/R-HAD induction arm in case of unexpected inferiority. The sample size determined for the primary objective PFS according to maintenance arms gives a power of 95% to detect a hazard ratio of 0.60 for overall survival between the induction arms (max. 204 events). The OS will be compared between the induction arms, using a group sequential log-rank test corresponding to four analyses (3 interim and one final): an interim at 25% of 204 events or 300 randomized patients, whichever comes first, at 45% of 204 events or 450 randomized patients, whichever comes first, at 60% of 204 events or 530 randomized patients, whichever comes first, and one final at 100% of 204 events. The boundaries evaluation are based on an asymmetric α-spending function of the O'Brien-Fleming type with α=0.025 for each side. The boundary for declaring an inferiority of R-CHOP/R-HAD vs. R-CHOP arm is based on an α-spending function of the O'Brien-Fleming using the Rho method (Rho=3). The boundary for declaring a superiority of R-CHOP/R-HAD vs. R-CHOP arm is based on an α-spending function using the Rho method (Rho=51). The boundaries for superiority will thus be computed in order to keep almost all the alpha for the final analysis. To ensure patients' safety, an Independent Data Monitoring Committee will be established to assess on-going safety data during the course of the study. These interim analyses will be evaluated during these IDMC meeting. All safety concerns will be evaluated during IDMC meetings and according to the results the IDMC would make recommendations on stopping or not the study. The first IDMC review data meeting is planned after the first 25 patients having received lenalidomide maintenance for more than 6 months. At least 3 additional IDMC will occur corresponding to the 3 interim analyses for induction arms. Details on the frequency of IDMC meetings and on the IDMC operation will be provided in the IDMC Charter.
Planned start/end of recruitment	Q4 2013 / Q3 2020

TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
AE	Adverse Event
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
BSA	Body Surface Area
CD20	antigen expressed on the surface of normal and malignant B lymphocytes
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
EC	Ethics Committee
CR	Complete Remission
eCRF	Electronic Case Report Form
CRu	Complete Response unconfirmed
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DVT	Deep Vein Thrombosis
ECOG	Eastern Cooperative Oncology Group
ENT	Ear Nose Throat
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
IDMC	Independent Data Monitoring Committee
LYSA	The Lymphoma Study Association
LYSARC	Lymphoma Academic Research Organisation
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
IMIDs®	Immunomodulatory drug (structural and functional analogues of thalidomide)
IRB	Institutional Review Board
IV	IntraVenous
LDH	Lactic DeHydrogenase
NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada - Clinical Trials Group
NHL	Non-Hodgkin’s Lymphoma
OS	Overall Survival
PD	Progressive Disease
PET	^{18}F-FDG Positon Emission Tomography
PFS	Progression Free Survival
PR	Partial Remission

PS	Performance Status
RR	Response Rate
SAE	Serious Adverse Event
SC	SubCutaneous
SD	Stable Disease
SPM	Second Primary Malignancies
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFR	Tumor flare
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

3 RESPONSIBILITIES

3.1 Title of the trial

Efficacy of alternating immunochemotherapy consisting of R-CHOP + R-HAD versus R-CHOP alone, followed by maintenance therapy consisting of additional lenalidomide with rituximab versus rituximab alone for older patients with mantle cell lymphoma.

3.2 Sponsor

LYSARC : Lymphoma Academic Research Organisation

✉ : Centre Hospitalier Lyon Sud

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The present protocol is supported by a grant from Celgene Corporation and is supported in part by F. Hoffmann-La Roche LTD.

3.3 Coordinating investigators, national reference pathologists biologists and Statistical Advisor at MCL Network

This trial is conducted under the scientific lead of the European Mantle Cell Lymphoma Network and of LYSA Scientific Committee represented by the following persons and institutions.

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3.4 Study management

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3.5 Investigators

All centers of the participating FIL, LYSA, GLSG (German Low-Grade Lymphoma Study group), HOVON, GELTAMO, PLRG and Portugese LSG may include patients in this study.

3.6 Laboratory sites

Laboratories of each study center must provide their normal values and an updated accreditation for quality control.

4 RATIONALE

Mantle cell lymphoma (MCL) is a rare lymphoma subtype that accounts for 5-7% of non-Hodgkin lymphomas in adults {1}.

The diagnosis is based on histological, cytological and cytogenetic examinations. The histological description characterizes different subgroups: small cell, blastoid or pleiomorphic types with a mantle zone pattern, a nodular pattern and a diffuse pattern. The classic MCL immunophenotype shows that lymphoma cells express CD19+, CD20+, CD22+, CD79a+ and the surface IgM and IgD B-cell mature markers but also CD5+ and CD43+. MCL cells are negative for CD10, CD23 and Bcl-6 {1-4}. Some cases may not express CD5 or may be CD23 positive. However, detection of the characteristic cyclin D1 overexpression either by immuno-histochemistry or FISH t(11;14) is generally mandatory to confirm the diagnosis of mantle cell lymphoma {4}.

Few data on prospective studies in more than 50 patients are available in elderly patients with a MCL and aged more than 70. The German Low-Grade Lymphoma Study Group reported a trial including 122 patients (median age 62) randomized between six cycles of CHOP and CHOP plus rituximab (R-CHOP). The overall response rate was higher in the R-CHOP arm (94% versus 75%) with 34% of CR in the R-CHOP arm and only 7% in the CHOP arm (P=.00024) {5} with prolonged time-to-treatment failure after R-CHOP (median 28 vs. 14 months, p=0.0003) and remission duration (29 vs. 18 months, p=0.0052, Update Hoster ASH 2008).

Recently, the European MCL network presented a randomized phase III study including a high number of patients (560 elderly patients). Two induction therapies were compared, 8 cycles of R-CHOP and 6 cycles of R-FC. A second randomization compared rituximab maintenance given every other month to IFN maintenance. Maintenance therapy was continued until progression or recurrence of the lymphoma {6}.

Out of 560 patients, 532 could be analyzed according to intention-to-treat for response, whereas 485 were fully evaluable. Median age was 70 yrs. Although complete remission rates were similar after R-FC *vs* R-CHOP (40% *vs* 34%, p=0.10), progressive disease was more frequent during R-FC (14% *vs* 5%). Four-year overall survival was significantly inferior after R-FC (47% *vs* 62%; p=0.005) with more patients dying in first remission (10% *vs* 4%) {6}.

In 274 of 316 patients randomized for maintenance, rituximab almost doubled the remission duration compared with interferon-alfa (at 4-yr 58% *vs* 29% in remission; hazard ratio 0.55, 95% CI 0.36-0.87; p=0.0109). Rituximab maintenance significantly improved 4-year overall survival up to 87% *vs*. 63% on interferon-alfa (p=0.0051) in patients responding to R-CHOP. This study strongly suggests that 8 cycles of R-CHOP followed by rituximab maintenance could now represent a real standard therapy in elderly patients {6}. Still, the percentage of patients obtaining an initial CR is low. Patients who show early progression do not respond upon salvage therapy and die early. These data ask for further improvement of induction therapy. Furthermore, no plateau in remission duration has been observed, suggesting that maintenance with rituximab is not sufficient.

Recent data from the MCL younger trial proved the superiority of alternating R-CHOP with high dose cytarabine (Ara-C) {7}. This study compared, in patient's less than 66 year-old, 6 courses of Rituximab-CHOP followed by myeloablative radiochemotherapy with total body irradiation (TBI) plus cyclophosphamide and ASCT (control arm designed from the first randomized study) to alternating courses of rituximab-CHOP and rituximab-DHAP followed by a high-dose Ara-C-containing myeloablative regimen with TBI and melphalan followed by ASCT (experimental arm). After induction, the overall response rate was similarly high in both arms (90% vs 94%; p=0.19) but the CR and combined CR/CRu rates were significantly higher in the cytarabine-containing arm (26% vs 39%;

p=0.012 and 41% vs 60%; p=0.0003). Time to treatment failure was significantly prolonged in the cytarabine-containing group (hazard ratio 0.68, p=0.0384). This study showed that introducing high-dose cytarabine during induction therapy could lead to a better and longer lasting response in MCL patients, but its use was restricted to younger patients {7}.

4.1 **R-HAD**

Several studies in MCL, including the MCL younger trial, have shown improved outcome of treatment with a regimen incorporating cytarabine. High dose cytarabine has been used for decades in non-Hodgkin's lymphoma, mainly during second line therapy {8}. Safety data were not reported separately in elderly patients, but results of several phase II trials suggested that when doses are adapted to age, no major safety issues are expected in this subgroup of patients {8-10}. Two recent studies investigated the safety and the efficacy of rituximab plus DHAP (dexamethasone, cytarabine and cisplatin) in patients with non-Hodgkin's lymphomas including elderly patients {9, 10}. These reports have included 47 and 53 patients respectively with a median age of 61 and 63 years showing that almost half of the patients were more than 65 year old {9, 10}. Although these two trials did not randomize DHAP versus rituximab plus DHAP no major difference was observed concerning safety when rituximab was incorporated in the treatment. Overall, these data suggested that, even in second line therapy, high dose cytarabine, dexamethasone and rituximab can be administrated safely in patients with a non-Hodgkin's lymphoma. In these two studies reported, treatment related death was observed in two cases, one after cytarabine accidental overdose and one of a fatal infectious complication {9, 10}. Commonly observed grade 3 or 4 toxicities were thrombocytopenia and neutropenia that occurred in most of the patients. Febrile neutropenia occurred in less than 25% of cases {9, 10}.

Therefore, it seems worthwhile to investigate the role of cytarabine in elderly MCL patients.

4.2 **Lenalidomide**

Lenalidomide (revlimid® Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs. It offers potential benefit over the first commercially available IMiD® compound, thalidomide, in terms of both safety and efficacy in patients {11}. Thalidomide has been evaluated in 16 patients with relapsed/refractory mantle cell lymphoma patients for antitumor activity in combination with rituximab. Thirteen patients (81%) experienced objective response and the estimated 3-year overall survival was 75% {12}. The key to the therapeutic potential of lenalidomide lies in the fact that it has multiple mechanisms of action, which act to produce anti-inflammatory, anti-angiogenic, and anti-tumor effects. These effects are thought to be contextual in that they depend on both the cell type and the triggering stimulus. To date, lenalidomide has been associated with TNF-α inhibitory, T-cell co-stimulatory, and anti-angiogenic effects {11}.

Lenalidomide is approved and marketed in multiple countries including the United States, Canada and EU countries for the treatment of patients with previously treated multiple myeloma, in combination with dexamethason. Also, it is approved in some countries for transfusion-dependent anemia due to low- or intermediate-1-risk Myelodysplastic Syndrome (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

4.3 **Rituximab Subcutaneous**

Rituximab is currently administered via the intravenous (IV) route, with infusions typically requiring 3-4h. However, IV administration of rituximab is associated with several drawbacks (such as length of infusion time, side effects associated with rapid tumor lysis or destruction of normal B cells, primarily during the initial cycles of induction, required procedure to establish intravenous access considered as invasive, which is of particular concern to patients with malignant diseases who require repeated intravenous

treatment). In contrast to the IV infusion, the rituximab SC injection takes only 5-6 minutes. It is therefore envisaged that a subcutaneous (SC) formulation of rituximab would bring significant advantages for patients and healthcare providers in terms of comfort and convenience as it is a less invasive route of administration, and can be prepared and administered within minutes. SC administration of rituximab could become a simple alternative to the current practice of IV administration. Improved convenience is particularly important when patients are treated for prolonged periods of time as out-patients, and this may consequently lead to improved compliance.

4.4 Safety of Lenalidomide – rituximab combination

Several studies were reported concerning the safety of the lenalidomide rituximab combination.

Fowler et al {13} reported that among the 110 patients treated with lenalidomide (20 mg daily dose D1-D21 every 28 days cycles), grade > 3 neutropenia occurred in 40% (13% of total cycles) and grade > 3 thrombocytopenia occurred in 4% of patients. The most common grade > 3 non-hematologic toxicities included rash (8 patients), muscle pain (7 patients), fatigue (3 patients) and thrombosis (3 patients). Two episodes of neutropenic fever occurred. Six patients stopped treatment due to adverse events.

Wang et al {14} recently reported their experience on the combination of lenalidomide-rituximab combination in aggressive B-cell lymphomas (DLBCL, transformed B-cell lymphomas and folliclular grade 3). Forty-five patients were treated by lenalidomide with starting dose of 20 mg/day (D1-D21 every 28 days cycle). Twenty six percent of the patients required lenalidomide dose reduction to 15 mg or less. Grade 3 or 4 toxicities were mainly hematologic (neutropenia 53%, thrombocytopenia 36%, febrile neutropenia 11%). Grade 2 or higher rashes were observed in 11%, fatigue in 27% and neuropathy in 18%. No other non-hematological toxicity occurred in more than 5% of cases.

4.5 Clinical Studies of Lenalidomide in Non-Hodgkin's Lymphoma including Mantle Cell Lymphoma

Three phase II studies of single-agent lenalidomide have been conducted in patients with relapsed/refractory non-Hodgkin's Lymphoma (NHL) (CC-5013-NHL-001 in indolent NHL and CC-5013-NHL-002 and NHL-003 in aggressive NHL). The dose/regimen used in these studies was 25 mg qd x 21 days q 28 days for maximum of either 52 weeks (NHL-001 or NHL-002) or until disease progression (NHL-003). Patients with mantle cell lymphoma were included in NHL-002 and NHL-003.

In the two phase II clinical studies including aggressive entities (including MCL, DLBCL, transformed and FL grade 3), the overall response rate (ORR) was 35% in NHL-002 and 36% in NHL-003, respectively {15}. At the time of analysis (31 March 2008) the median progression free survival (PFS) was 3.6 months and the median duration of response was 10.2 months in NHL-002, while in NHL-003 it is still premature to estimate the median PFS and duration of response {15, 16}. In these two studies the most common grade 3/4 adverse events (AEs) were neutropenia (21%) and thrombocytopenia (15%) {15}.

The NHL-002 study was initiated in August 2005. Fifteen of 49 patients had MCL with a median duration of disease of 5.1 years and a median of 4 prior treatments before enrollment {15, 18}. A sub-analysis of the 15 MCL patients in NHL-002 demonstrated an ORR of 53%. At the time of analysis (31 March 2008) the median duration of response was 13.7 months and the median PFS was 5.6 months. Lenalidomide therapy led to complete responses (CR) in 3 patients and partial responses (PR) in 5 patients. Four of 5 patients who relapsed after transplantation and 2 of 5 patients who previously received bortezomib responded to lenalidomide {18}.

Among 15 patients with MCL with a median duration of disease of 5.1 years and a median of 4 prior treatments, 8 had a complete response (CR) or a partial response (PR) for an ORR of 53%. Three

patients (20%) had a CR or unconfirmed CR, and 5 patients (33%) had a PR. The median duration of response was 13.7 months and median PFS was 5.6 months. Four of 5 patients who relapsed after transplantation and 2 of 5 patients who previously received bortezomib responded to lenalidomide. The most common grade 4 adverse event was thrombocytopenia (13%) and the most common grade 3 adverse events were neutropenia (40%), leucopenia (27%), and thrombocytopenia (20%).

In the second study NHL-003 which was initiated in November 2006, 57 of 218 patients enrolled had MCL. As of March 1, 2008, 39 MCL patients were evaluable for response assessment {19}. The median age was 66 (33–82) years and 29 (74%) patients were men. The median time from diagnosis to start of lenalidomide treatment was 3.4 (0.4–9) years. These patients had received a median of 3 (1–8) prior treatments, and 23% (9/39) of patients had received prior bortezomib treatment. The ORR to lenalidomide was 41% (16/39), including 13% (5/39) complete responses (CR/unconfirmed CR), and 28% (11/39) partial responses. Ten (26%) patients had stable disease. As of 1 July 2008, the median duration of response was not reached yet with only 17% events (data in file). The most common grade 3 or 4 adverse events were neutropenia (51%) and thrombocytopenia (25%), anemia (13%), fatigue (10%) and febrile neutropenia (10%). These results suggest that lenalidomide oral monotherapy is effective in the treatment of patients with relapsed or refractory MCL, with manageable side effects {19}.

More recently, Eve et al {20} used lenalidomide at a 15 mg daily dose in the same group of patients. In eleven patients treated at this dose, four patients required dose reduction to 10 mg during the maintenance phase, and two patients required further reduction to 5 mg during the maintenance phase.

The same adaptation was also necessary in the report from Wang {13} suggesting that starting lenalidomide at 15 mg should be safe for the patients.

Recently, in two studies concerning maintenance in multiple myeloma, the recommended dose of lenalidomide was 10 to 15 mg also suggesting that this dose should be the appropriate dose in maintenance with lenalidomide {21; 22}.

4.6 **Conclusions and rationale**

Based on several randomized trials and a systematic Cochrane review {23}, combined immuno-chemotherapy represents the current standard of care in MCL (ESMO guidelines). However, even after immuno-chemotherapy only, a constant relapse pattern has been observed with the majority of patients relapsing within the first 3 years. Based on preliminary results from the recently closed phase III MCL elderly trial performed within the *European MCL Network*, Rituximab maintenance after 8 cycles of R-CHOP induction prolongs remission duration and overall survival and therefore represents the current standard of care for elderly patients with MCL {6}. Still, no plateau has been observed, suggesting that maintenance with rituximab is not sufficient, but can be considered as a standard of care in MCL patients unable to received high-dose therapy with SCT consolidation.

Improving patient's outcome can be reached by improving response rate before maintenance therapy. In younger patients, recent data from the MCL younger trial proved the superiority of alternating R-CHOP with high dose Ara-C when compared to R-CHOP alone {7}. These data suggest that incorporating high-doses cytarabine to induction therapy may improve patients' outcome in patients with MCL.

An international phase II study suggested a longlasting impact of lenalidomide in relapsed MCL {24}. These data suggest that incorporating lenalidomide to maintenance therapy with Rituximab could also improve MCL patients' outcome in patients unfit to receive HDT consolidation therapy.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of the trial is to evaluate whether the addition of lenalidomide to rituximab-maintenance improves progression free survival (PFS) compared to standard rituximab maintenance after response to induction chemotherapy in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation.

5.2 Primary Endpoint

The primary endpoint will be the PFS from randomization for maintenance to progression or death from any cause. For maintenance therapy a significant improvement in remission duration had been observed in the preceding study of the European MCL Network. An improvement of overall survival in the experimental maintenance arm is unlikely to be observed during a reasonable observation time of a single clinical trial.

5.3 Secondary objectives and endpoints

5.3.1 According to maintenance therapy

The secondary efficacy objectives for the maintenance part are:

- To compare the efficacy of maintenance therapy with rituximab plus lenalidomide versus rituximab alone following induction therapy using other parameters of efficacy:
    - Time to event analyses
        - overall survival from maintenance randomization and from induction randomization
        - progression-free survival from induction randomization
    - PR/CRu to CR and PR to CRu conversion during maintenance
    - MRD status and levels in peripheral blood and bone marrow after one and two years from end of induction and during follow-up

The secondary safety objectives are:

- To compare the safety of maintenance therapy with rituximab plus lenalidomide versus rituximab alone following induction therapy using other parameters of efficacy:
    - Toxicity (NCI CTCAE v 4.0)
    - Adverse Events
    - Second primary malignancies rates
- To assess potentially differential effects of maintenance according to induction (pre-defined subgroup analysis of maintenance effects according to induction)

5.3.2 According to induction therapy

The secondary efficacy objectives that will be analyzed according to induction therapy are:

- To evaluate whether the introduction of cytarabine into induction improves clinical outcome compared to standard R-CHOP in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation. This objective will be answered in a confirmatory way with overall survival from induction randomization as primary variable of interest. The previous study in this elderly population did show a significant difference in overall survival for the comparison of R-FC and R-CHOP, while no significant differences were observed for overall response rate, CR rate and time to treatment failure.

- To compare complete and overall response rates (based on Cheson 1999 criteria) at midterm and end of induction, time to treatment failure, and progression-free survival from induction randomization of R-CHOP / R-HAD versus R-CHOP alone
- To compare remission duration and OS from maintenance randomization of R-CHOP / R-HAD versus R-CHOP alone
- To compare MRD status and levels in peripheral blood and bone marrow at midterm and at the end of induction of R-CHOP / R-HAD versus R-CHOP alone
- To compare the safety of the induction therapy with R-CHOP / R-HAD versus R-CHOP alone

5.4 **Exploratory objectives and endpoints**

- To evaluate CR rate after induction / maintenance treatment by 2007 Revised Response Criteria for Malignant Lymphoma incorporating FDG-PET.
- To evaluate PR/CRu to CR and PR to CRu conversion during maintenance according to induction therapy.
- To evaluate MRD status and levels in peripheral blood and bone marrow after one and two years from end of induction and during follow-up according to induction therapy.

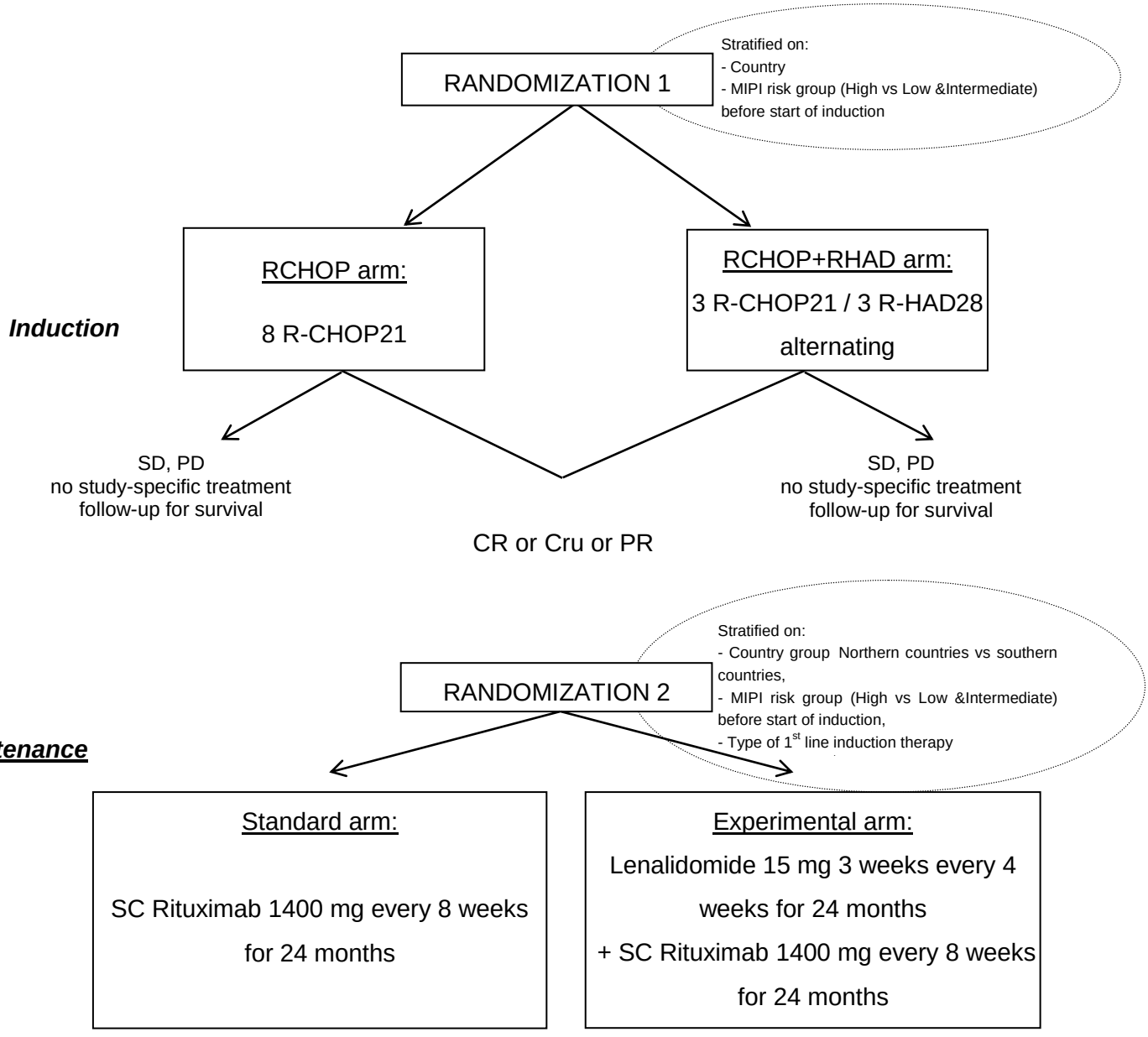
6 STUDY DESIGN

This study is an international, multicentric, open label, randomized phase III trial of 8 cycles of R-CHOP21 versus 3 cycles of R-CHOP21 / 3 cycles of R-HAD28 (alternating) induction treatment in patients aged 60 years and older with previously untreated mantle cell lymphoma followed by a maintenance therapy consisting of rituximab + lenalidomide (revlimid®) versus rituximab alone for patient achieving a CR, CRu or PR after induction. Lenalidomide will be administered at the starting dose of 15 mg daily for patients with normal renal function and 10 mg for patients with moderate renal function from D2 to D22, repeated at day 29 for 24 months or 26 cycles) and rituximab will be administered every 8 weeks for 24 months.

Registration for participating in the study is done according two pathways:

- Previously untreated patients will be registered and randomized for induction before the first cycle of induction treatment. Patients who reached CR, CRu or PR after induction treatment, will have a second randomization for the maintenance treatment.
- During a run-in period of 6 months starting from the date of the first patient randomized in the trial, it was possible to randomize patients directly for maintenance treatment after being treated in first line by 8 cycles of R-CHOP and after having reached CR, CRu or PR (determined as per Cheson 1999 criteria (see Appendix G, {25}). This run-in period was closed in May 2014. In these patients, the data collection regarding the R-CHOP part will be done retrospectively.

Figure 1: Overall study design



Follow-up: for progression death and SPM until the end of the study

Patients will be recruited over 6 years (5.5 years plus 6 months induction therapy).

The duration of the induction is approximately 21 to 24 weeks and duration of the maintenance is 24 months (i.e. maximum 13 cycles of rituximab and 26 cycles of lenalidomide). Randomization for maintenance should occur within 3 months after documentation of a CR/CRu or PR and maintenance treatment should be started within 3 months after end of induction evaluation.

The final analysis will be performed when 158 events with respect to the primary endpoint have been observed. To reach this number of events, all patients will be followed until 2.5 years after the last patient randomized for maintenance. Patients randomized for maintenance will be followed at least until 3 years after his/her last study treatment administration in maintenance period for SPM and for progression/death. All Patients will be followed for death if possible until the end of the study.

The anticipated study dates (start / end) are:

1st patient randomized: Q4 2013

Last patient randomized: Q2 2019

Last patient followed for primary analysis: Q4 2021

Final analysis: 2.5 years after the last patient randomized for maintenance.

End of study: 3 years after the last maintenance treatment administration

It is expected that a total of 633 patients will be randomized at 1:1 ratio to receive either R-CHOP/R-HAD or R-CHOP induction treatment and 443 patients will be randomized at 1:1 ratio to receive either experimental or standard maintenance.

7 STUDY POPULATION

Patients must have a histologically proven diagnosis of mantle cell lymphoma, be aged at least 60 years at the time of registration and ineligible for autologous transplant, not previously treated for their lymphoma at randomization for induction and responding (CR, CRu or PR) to induction treatment with 8 cycles of R-CHOP21, 3 R-CHOP21 / 3 R-HAD (alternating) at randomization for maintenance.

During a run-in period of 6 months starting from the date of the first patient randomized in the trial (either to the induction or maintenance phase), patients will be allowed to register after a documented response (CR, CRu or PR) to 6-8 cycles of R-CHOP induction, in order to collect additional data on toxicity and feasibility of the rituximab-lenalidomide (R2) maintenance treatment. As this run-in period is closed in May 2014, no direct randomization is allowed.

7.1 Inclusion/exclusion criteria for randomization 1

7.1.1 Inclusion criteria

Patients must satisfy all the following criteria at study entry to be randomized in the trial:

- signed informed consent form
- Biopsy-proven mantle cell lymphoma according to WHO classification, including evidence of cyclin D1 overexpression or the translocation t(11;14)(q13;q32)
- ≥ 60 years of age and ineligible for autologous transplant
- Ann Arbor stage II-IV
- previously untreated (except for patients randomized directly for maintenance treatment who will receive 8 RCHOP before registration in the trial)
- ECOG performance status ≤ 2
- Male subjects must:

- agree to use a condom during sexual contact with a woman of childbearing potential, even if they have had a vasectomy, throughout lenalidomide therapy
- agree to not donate semen during lenalidomide therapy.

- All subjects must:
  - have an understanding that the lenalidomide could have a potential teratogenic risk.
  - agree to abstain from donating blood while taking lenalidomide therapy
  - agree not to share study medication with another person.
  - be counselled about pregnancy precautions and risks of foetal exposure.

7.1.2 Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

- Female of childbearing potential (i.e. without natural menopause for at least 24 consecutive months, a hysterectomy or bilateral oophorectomy)
- Any of the following laboratory abnormalities at diagnosis, if not related to lymphoma:
  - Absolute neutrophils count <1,000 /mm^3 (1.0 x 10^9/L) if not result of a bone marrow infiltration.
  - Platelet count < 75,000/mm^3 (75 x 10^9/L) if not result of a bone marrow infiltration.
  - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) >3.0 x upper limit of normal (ULN).
  - Serum total bilirubin > 1.5 ULN (except if due to Gilbert's syndrome)
- Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) < 30 mL / min.
- Central Nervous System involvement by lymphoma
- Contraindication for medical DVT prophylaxis for patients at high risk for DVT
- Prior history of malignancies other than MCL unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:
  - Basal cell carcinoma of the skin,
  - Squamous cell carcinoma of the skin,
  - Carcinoma in situ of the cervix,
  - Carcinoma in situ of the breast,
  - Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).
- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient to receive the study medication as planned.
- Poor cardiac function (LVEF < 50%) on echocardiography
- Seropositivity for human immunodeficiency virus (HIV, mandatory test) at study entry
  Seropositivity for hepatitis C virus (HCV, mandatory test) at study entry,
  Active viral infection with hepatitis B virus (HBV, mandatory test) at study entry:
  - HBsAg positive
  - HBsAg negative, anti-HBs positive and anti-HBc positive

    Patients with prior Hepatitis B must be given antiviral prophylaxis and HBV DNA monitored.

    Note: Patients who are HBsAg negative, anti-HBs positive and/or anti-HBc positive but viral DNA negative are eligible.

HIV, HVC and HBV tests are mandatory

- Uncontrolled illness including, but not limited to:
  - Active infection requiring parenteral antibiotics.
  - Uncontrolled diabetes mellitus
  - Chronic symptomatic congestive heart failure (Class NYHA III or IV).
  - Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months
  - Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia.
- Prior ≥ Grade 3 allergic hypersensitivity to thalidomide.
- Prior ≥ Grade 3 rash or any desquamating (blistering) rash while taking thalidomide.
- Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies.
- Subjects with ≥ Grade 2 neuropathy.
- Prior use of lenalidomide
- Participation in another clinical trial within three weeks before randomization in this study

7.2 **Additional Inclusion/exclusion criteria for randomization 2**

To be randomized for maintenance, the patient must satisfy all inclusion / exclusion criteria for randomization 1 and the following criteria:

7.2.1 Inclusion criteria

Patients must satisfy all the inclusion criteria of randomization 1 and the following additional criteria to be randomized for maintenance treatment:

- CR, CRu or PR after induction treatment, determined as per Cheson 1999 criteria (see Appendix G, {20} by investigator even for patients enrolled during the run-in phase.
- During the run-in period of 6 months starting from the date of the first randomization in the trial up to May 2014: in case of direct randomization into maintenance phase, patient must have been treated in first line by 6-8 cycles of R-CHOP.

7.2.2 Exclusion criteria

The presence of any exclusion criteria of randomization 1 or of the following criteria will exclude a subject from enrollment in the maintenance phase:

- SD or PD after induction treatment determined as per Cheson 1999 criteria (see Appendix G, {25} by investigator.
- Patient treated by induction immuno-chemotherapy other than 6-8 cycle of R-CHOP21 or 2-3 cycles of R-CHOP21 / 2-3 cycles of R-HAD28 (alternating)
- Patients with serious underlying medical conditions, which could impair the ability to receive maintenance treatment
- Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) of < 30 mL / min at screening for maintenance.
- ANC is < 1,000 cells/mm³ (1.0 X 10^9/L) at screening for maintenance;
- Platelet count is < 50,000 cells/mm³ (50 X 10^9/L) at screening for maintenance.

8 TREATMENTS

8.1 Drugs description, storage and handling

In this trial, lenalidomide and Rituximab SC are considered as investigational medicinal product (IMP). The other drugs are standard of care.

In Germany, for induction, commercially available of Rituximab IV, cyclophosphamide, doxorubicin, vincristine, cytarabine, prednisone and dexamethasone are also considered as investigational medicinal product (IMP).

In other countries, for induction, commercially available IV formulation of Rituximab and standard of care chemotherapy, i.e. cyclophosphamide, doxorubicin, vincristine and cytarabine will be used. Commercially available prednisone will be used as oral formulation and commercially available dexamethasone will also be used as oral/IV formulation according to marketing authorization.

Standard of care chemotherapy must be available by prescription, generally reimbursed by the health system and used routinely in previously untreated Mantle Cell Lymphoma patients at the center.

Chemotherapy products are to be used according to summary of product characteristics.

8.2 Lenalidomide: description, storage and handling

8.2.1 Description

For maintenance treatment, lenalidomide will be supplied as 5 mg, 10 mg and 15 mg capsules for oral administration, labeled as IMP and are to be used according to Investigator Brochure.

8.2.2 Packaging and labeling

Celgene Corporation will supply lenalidomide capsules in 5 mg, 10 mg and 15 mg, provided in wallets. The packaging containing capsules will be labeled according to the Good Manufacturing Practice guidelines and the local requirements.

8.2.3 Storage conditions

The recommended storage conditions for the lenalidomide drug product are not above +25°C.

8.2.4 Handlings

Lenalidomide capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours have elapsed since missing a dose, the patient can take the dose. If more than 12 hours have elapsed since missing a dose at the normal time, the patient should not take the missed dose, but take the next dose at the normal time on the following day.

For more details, please refer to Investigator's Brochure.

8.3 Rituximab SC: description, storage and handling

8.3.1 Description

Rituximab for SC administration (MabThera SC; Ro 045-2294) contains rituximab with a nominal content of 120 mg/mL rituximab in an 11.7 mL vial and 2,000 U/mL rHuPH20 (manufactured in a Chinese Hamster Ovary [CHO] 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 rituximab SC drug product is a sterile, colorless to yellowish, clear to opalescent liquid supplied in colorless 11.7 mL vials.

The rituximab SC dose will be fixed at 1400 mg for all patients (i.e., independent of the patient's body surface area [BSA]).

8.3.2 Packaging and labeling

Rituximab SC is supplied as a ready-to-use liquid formulation.

The vials containing the investigational product and the packaging containing vials in will be labeled according to Good Manufacturing Practice guidelines and the local requirements.

8.3.3 Storage conditions

The recommended storage conditions for the rituximab SC drug product are between +2°C and +8°C. For additional storage requirements refer to the rituximab SC Investigator's Brochure.

Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2 °C - 8 °C and subsequently for 8 hours at 30°C in diffuse daylight. From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions.In-use storage times and conditions prior to use are the responsibility of the user.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the sponsor upon discovery. For further details, see the rituximab SC Investigator's Brochure.

8.3.4 Handlings

Rituximab for SC administration is supplied as a ready-to-use liquid formulation. The product should be handled gently and foaming avoided. It should not be shaken.

Rituximab SC will be administered at a fixed dose of 1400 mg. 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 SC 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 SC tissue. Study drug 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. A 25 gauge injection needle can also be used, according to local practice.

The injection should be manually pushed at a comfortable flow rate. Administration 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. Rituximab SC may be administered in an inpatient or outpatient setting. Patients should be observed at least 15 minutes following rituximab SC injections. A longer period may be appropriate in patients with an increased risk of hypersensitivity reaction. Patients should be instructed to contact their treating physician immediately if symptoms that are suggestive of severe hypersensitivity reactions or cytokine release syndrome occur at any time after drug administration.

For more details, please refer to Investigator's Brochure.

8.4 Treatment schedule and design

This study involves two randomizations:

- Eligible patients will be registered and have a first randomization to receive R-CHOP or alternating R-CHOP / R-HAD induction treatment.
- Patients exhibiting a CR/CRu or PR after the induction treatment will have a second randomization to either rituximab-lenalidomide or rituximab alone maintenance treatment.

In the run-in period of 6 months, patients without randomization for induction who have reached CR/CRU or PR after an induction treatment with 6-8 cycles of R-CHOP21 given outside the trial, can be randomized directly for maintenance treatment. After this run-in period, no direct randomization will be allowed.

8.4.1 Induction R-CHOP/R-HAD arm

Patients with relevant B-symptoms or raising peripheral lymphocyte counts but incomplete diagnostic reports may receive a pre-phase therapy of one single dose of vincristine (1.4 mg/m2, max. 2 mg) and 100 mg prednisone per day for 1 to 5 days before registration in the study. The pre-phase therapy should not be started before all necessary biopsies were taken. In patients receiving a pre-phase, in further treatment, the vincristine dose in the first cycle should be omitted.

Induction R-CHOP/ R-HAD arm consists in 3 cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) and 3 cycles of R-HAD (rituximab, cytarabine, dexamethasone) alternating. Treatment course is administered in 21-day cycle for R-CHOP and 28-day cycle for R-HAD.

The doses of R-CHOP components are:

R-CHOP	Route	Dose	Days
Rituximab	IV	375 mg/m^2	1
Cyclophosphamide	IV	750 mg/m^2	1
Doxorubicin	IV	50 mg/m^2	1
Vincristine	IV	1.4 mg/m^2 (2mg cap)	1
Prednisone	PO	100 mg/day	1 to 5

The doses of R-HAD components are:

R-HAD	Route	Dose	Days
Rituximab	IV	375 mg/m^2	1 (and 4 only during the first 2 cycles)
Cytarabine	IV	1000 mg/m^2	1 (twice every 12 to 24 hours)
Dexamethasone	PO or IV*	20 mg/day	1 to 4

* The administration route for dexamethasone will be used according to the marketing authorization available in each country for the dose used in the protocol (i.e. oral administration is allowed only in countries where this formulation has a marketing authorization).

R-CHOP and R-HAD will be administered according to the standard preparation and infusion procedures of each investigational site. Therapeutic lumbar puncture will not be recommended in asymptomatic patients. However, therapeutic lumbar puncture may be done according to local standards.

For cycle 2 and 4 (i.e. cycle 1 and 2 of R-HAD), rituximab will be administered at Day 1 and 4 and for the last cycle of R-HAD, rituximab will be administered only at Day 1.

The infusion duration of cytarabine should be 3 hours. For safety reasons, it must not exceed the time of three hours.

Refer to the specific package inserts for preparation, administration, and storage guidelines. At the discretion of the investigator, the vincristine dose should be capped at 2 mg. For subject ≥70 years old, the vincristine dose may be capped at 1.0 mg. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Premedication of Rituximab should be administered (see package insert and protocol Section 8.5).

Rituximab should only be given if circulating lymphocytes are below 50 x 10^9/L, otherwise rituximab will be postponed until lymphocytes are below 50 x 10^9/L. Alternatively, in case of lymphocytosis >50 x 10^9/L, the total dose of rituximab (375 mg/m²) could also be divided in 20% of the total dose of rituximab at D1 of the cycle and 80% of the total dose of rituximab at D2.

8.4.2 Induction R-CHOP arm

Patients with relevant B-symptoms or raising peripheral lymphocyte counts but incomplete diagnostic reports may receive a pre-phase therapy of one single dose of vincristin (1.4 mg/m^2, max. 2 mg) and 100 mg prednisone per day for 1 to 5 days before registration in the study. The pre-phase therapy should not be started before all necessary biopsies were taken. In patients receiving a pre-phase, in further treatment, the vincristin dose in the first cycle should be omitted.

Induction R-CHOP arm consists of 8 cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone). Treatment course is administered in 21-day cycle.

The doses of R-CHOP components are:

R-CHOP	Route	Dose	Days
Rituximab	IV	375 mg/m^2	1
Cyclophosphamide	IV	750 mg/m^2	1
Doxorubicin	IV	50 mg/m^2	1
Vincristine	IV	1.4 mg/m^2 (maximum 2mg)	1
Prednisone	PO	100 mg/day	1 to 5

R-CHOP will be administered according to the standard preparation and infusion procedures of each investigational site. Therapeutic lumbar puncture will not be recommended in asymptomatic patients. However, therapeutic lumbar puncture may be done according to local standards.

Refer to the specific package inserts for preparation, administration, and storage guidelines. The vincristine dose should be capped at 2 mg. For subject ≥70 years old, the vincristine dose may be capped at 1.0 mg at the discretion of the investigator. For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (≥ 10%) leading to changes in BSA.

Premedication of Rituximab should be administered (see package insert and protocol Section 9.3.2).

Rituximab should only be given if circulating lymphocytes are below 50 x 10^9/L, otherwise rituximab will be postponed until lymphocytes are below 50 x 10^9/L. Alternatively, in case of lymphocytosis >50 x 10^9/L,

the total dose of rituximab (375 mg/m²) could also be divided in 20% of the total dose of rituximab at D1 of the cycle and 80% of the total dose of rituximab at D2.

8.4.3 Maintenance experimental Arm: Rituximab + Lenalidomide

Patients randomized to receive rituximab and lenalidomide will receive up to twenty six cycles of lenalidomide 15 mg daily on days 2 to 22 every 4 weeks and up to thirteen injections of rituximab 1400 mg on day 1 every 8 weeks. Treatment is to be continued for a maximum of 2 years or until disease progression or relapse, unacceptable toxicity occurs or voluntary withdrawal.

The schedule of visits will be following:

- one visit every 4 weeks for 16 weeks before starting rituximab administration and/or lenalidomide (this period correspond to cycle 1 to 4 of lenalidomide and cycle 1 and 2 of rituximab).
- From 3rd injection of rituximab, one visit every 8 weeks before starting rituximab administration.

Rituximab SC will be administered at a fixed dose of 1400 mg. For more details regarding rituximab SC injection, please refer 8.3.4 section.

Lenalidomide allocation will be done at each visit, using an IWRS system. The study site will log on the IWRS website before each visit, to receive back the treatment kit number(s) to be dispensed to the patient for the cycle(s).

Lenalidomide dosing will be based on patients creatinine clearance calculated using the Cockcroft-Gault or MDRD formula. Creatinine clearance should be calculated using ideal body weight or actual, whichever is less.

Cockcroft-Gault estimation of creatinine clearance (CrCl):

Serum creatinine units mg/dL => for females, the formula is multiplied by 0.85.

CrCl (mL/min) = [(**140** – **age** (years)) x (**weight** [kg])] / [**72** x (**serum creatinin** [mg/dL])];

Serum creatinine units µmol/L => A = 1.23 for men and A = 1.04 for females.

CrCl (mL/min) = [(**140** – **age** (years)) x (**weight** [kg]) x **A**] / (**serum creatinin** [µmol/L]);

MDRD estimation of glomerular filtration rate (GFR)

Serum creatinin units mg/dL

CrCl (mL/min/1.73 m^2) = 175 x [**Serum creatinin**$^{-1.154}$ x **age**$^{-0.203}$ x 0.742 (if female) x 1.212 (if black)

Serum creatinin units µmol/L

CrCl (mL/min/1.73 m^2) = 30849 x [Serum creatinin-1.154 x age-0.203 x 0.742 (if female) x 1.212 (if black)

Patients who have a creatinine clearance ≥ 60 mL/min or GFR of > 60 mL/min/1.73 m^2 will receive oral lenalidomide 15 mg daily on days 2 to 22 in each 28 day cycle.

Patients who have moderate renal insufficiency (creatinine clearance ≥ 30 mL/min but < 60 mL/min) will receive either a lower starting dose of lenalidomide of 10 mg once daily on Days 2 to 22 of 28-day cycle in Cycle 1 and in Cycle 2. After Cycle 2, if the patient has not experienced any drug-related grade 3 or 4 toxicity, the dose should be increased to 15 mg once daily on Days 2 to 22 of a 28-day cycle at the discretion of the treating physician.

8.4.4 Maintenance standard arm: Rituximab

Patients randomized to receive rituximab will receive up to thirteen injections of rituximab 1400 mg on day 1 every 8 weeks. Treatment is to be continued for a maximum of 2 years or until disease

progression or relapse, unacceptable toxicity occurs or voluntary withdrawal. The schedule of visits will be following:

- One visit every 4 weeks for 16 weeks before starting rituximab administration and 4 weeks after 1rst and 2nd infusions of rituximab.
- From 3rd injection of rituximab, one visit every 8 weeks before starting rituximab administration.

Rituximab SC will be administered at a fixed dose of 1400 mg. For more details regarding rituximab SC injection, please refer 8.3.4 section.

8.4.5 Dose adjustments

8.4.5.1 R-CHOP Modifications

No dose modification will be made in the first cycle. During the next courses, modifications of the treatment schedule will only be made if:

- **Neurotoxicity** (peripheral neuropathy, severe obstipation/paralytic ileus): adapt vincristine according to the discretion of the treating physician.
- **Cardiotoxicity:** A cumulative dose of 400 mg/m^2 of doxorubicin in this study should not be exceeded. Doxorubicin should be discontinued if evidence of left ventricular dysfunction or congestive heart failure develops.
- **Hepatic Toxicity:** If bilirubin level is abnormal, the doxorubicin dose should be reduced to avoid myelotoxicity as outlined below.
  - Serum bilirubin 1.5 – 3.0 mg/dL: Decrease doxorubicin dose to 25 mg/m^2.
    If improvement to < 1.5 mg/dL, resume doxorubicin at 50 mg/m^2.
  - Serum bilirubin > 3.0 mg/dL or severe hepatic impairment:
    Delay doxorubicin for a maximum of 3 weeks.
    If improvement to 1.5 – 3.0 mg/dL, resume doxorubicin at 25 mg/m^2.
    If improvement to < 1.5 mg/dL: resume doxorubicin at 50 mg/m^2.
    If no improvement: discontinue doxorubicin.
- *Myelosuppression*: if neutrophils < 1.5 x 10^9/l or platelets <100 x 10^9/l at the day of the next course, postpone 1 week; if after 1 week insufficient recovery, adapt according to scheme below.

Neutrophils x 10^9/l	Platelets x 10^9/l	Cyclo-phosphamide	Doxorubicin	Vincristine	Prednisone	Rituximab
≥1.5	>100	100%	100%	100%	100%	100%
<1.5 - 1.0	>100	75%	75%	100%	100%	100%
<1.0 - 0.5	50-100	50%	50%	100%	100%	100%
<0.5	<50	0%	0%	100%	100%	100%

Dose reduction will be calculated according to the doses given at the previous cycle. In case of severe myelosuppression with neutrophils counts < 1.0 x 10^9/l and/or platelet counts < 50 x 10^9/l as assessed on two consecutive days but recovery to neutrophils > 1.5 x 10^9/l after 3 weeks, it is strongly advised to reduce the dose of R-CHOP to 75% in cyclophosphamide and 75% in doxorubicin in subsequent cycles.

This reduction of dose can be omitted if the severe myelosuppression can be assumed to be the result of an initial significant bone marrow involvement.

In case of any > grade 3 non-hematological toxicity despite optimized supportive care (except alopecia and nausea) dose modifications should be discussed with the study coordinators.

8.4.5.2 R-CHOP / R-HAD Modifications

No dose modification will be made for R-CHOP in the first course. During the next courses, modifications of the treatment schedule will be made according to 8.4.5.1.

For R-HAD, before each treatment cycle the following laboratory values are required:

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L if not result of leukemic MCL
- Platelets ≥ 100 x 10^9/L if not result of leukemic MCL
- Creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 50 mL/min.

Modifications of the treatment schedule will be made if myelosuppression occurs:

- if neutrophils < 1.5 x 10^9/l or platelets < 100 x 10^9/l after 3 weeks, postpone up to 2 weeks after R-CHOP;
- if 5 weeks after R-CHOP, insufficient recovery or ongoing hematological grade III/IV toxicities, adapt according to scheme below.

Neutrophils x 10^9/l	Platelets (x 10^9/l)	Cytarabine
≥1.5	>100	100%
<1.5 - 1.0	75 – 100	75%
<1.0 - 0.5	50 – 75	50%
<0.5	<50	0%

In case of any ≥ grade 3 non-hematological toxicity despite optimized supportive care (except alopecia and nausea) dose modifications should be discussed with the study coordinators.

8.4.5.3 Rituximab SC Dose Modifications

No dose modification should be made for rituximab SC.

8.4.5.4 Lenalidomide Dose Modifications

Patients will be evaluated for AEs at each visit with the NCI CTCAE v4.0 used as a guide for the grading of severity.

The lenalidomide dose for each subject will be interrupted and/or modified by following the toxicity rules as described in table 1 and table 2.

Basically, if a significant toxicity, defined as dose-limiting toxicity in Table 2, occurs on or after day 15 of the cycle, treatment will be held (interrupted) until the end of the cycle and the dose will then be reduced by a step (dose level -1) at the subsequent cycle.

If toxicity occurs before day 15 of the cycle, treatment will be held until recovery to a grade 1 and restarted without dose reduction for the rest of the cycle (continue until day 22; missed doses will not be made up).

The next cycle will resume at reduced dose (dose level -1) in subsequent cycles. In those instances where in the opinion of the investigator re-challenge at the same dose level poses an unacceptable risk to the patient, treatment will be held (interrupted) until the end of the cycle and the dose will be reduced by a step at the subsequent cycle.

In case of recurrence of an event during the same cycle, lenalidomide will be held until the next cycle.

Doses that were missed, due to toxicity or any other reasons, will not be rescheduled. If a dose is reduced, re-escalation is not permitted.

There will be no dose adjustment for rituximab. In case of cycle delay due to lenalidomide induced toxicity, rituximab of the next cycle will also be postponed until AE has resolved and recycling is allowed.

Resumption of dosing (if dose interrupted prior to day 15 and day 1 of next cycle) may begin if:

- The ANC is ≥ 1,000 cells/mm³ (1.0 X 10^9/L);
- The platelet count is ≥ 50,000 cells/mm³ (50 X 10^9/L);
- Lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1 severity;
- Any other lenalidomide-related AE not requiring discontinuation has resolved to ≤ Grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated once every seven days and a new cycle of treatment with lenalidomide will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for more than 28 days, the Project Manager and the Coordinating Investigators must be notified.

Table 1: Lenalidomide Dose Modification Rules

NCI CTCAE **Toxicity Grade**	**Action Required**
Grade 3 neutropenia (one time reading)	Follow CBC at least every seven days.
Neutropenia Sustained (≥ 7 days) Grade 3 OR ≥ Grade 3 associated with fever (temperature ≥ 38.5º C) OR Grade 4	• If neutropenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If neutropenia has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • Use of G-CSF is recommended if the ANC is below 500 during a cycle as per ASCO and ESMO guidelines. Treatment with G-CSF up to 3 days is allowed to reach ANC required to give the next cycle • In both cases, restart subsequent cycle at next lower dose Growth factors (G-CSF) will be administered for 3 days whenever neutrophils count drops below 500/mm^3

Thrombocytopenia ≥ Grade 3 (platelet count < 50,000 cells/mm³ [50x10^9/L])	• If thrombocytopenia has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow CBC every seven days • If thrombocytopenia has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Rash Grade 2 or grade 3 without desquamating Desquamating (blistering) ≥Grade 3 or Non-desquamating Grade 4	• Hold (interrupt dose). Please contact the Project Manager and the Coordinating Investigator to discuss any further steroid prophylaxis. When resolved (grade ≤1), restart at the same dose level, a consultation in dermatology is strongly recommended in case of grade 3 or higher. • Permanently discontinue lenalidomide
Allergic reaction or hypersensitivity Grade 2 Grade 3-4	• If allergic reaction has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If allergic reaction has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose and please contact the Project Manager and the Coordinating Investigator to discuss any further steroid prophylaxis. • Permanently discontinue lenalidomide
Constipation Grade 1-2 ≥ Grade 3	• Initiate bowel regimen and maintain dose level • If constipation has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If constipation has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Venous thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation; restart at Investigator's discretion (maintain dose level)
Peripheral neuropathy Newly developed ≥ Grade 3 (applies only to those neuropathies which begin or worsen while on study)	• If neuropathy has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If neuropathy has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose

Tumor Flare Reaction (TFR)*	• Continue lenalidomide, maintain dose level
Grade 1-2	• At the investigator's discretion may initiate therapy with NSAIDs, limited duration corticosteroids, and/or narcotics
Grade 3-4	• Initiate therapy with NSAIDs, corticosteroids, and/or narcotics • If TFR has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle, and follow at least every seven days • If TFR has occurred before day 15 and resolved to ≤ Grade 1 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose
Other lenalidomide related non-hematologic AEs ≥ Grade 3	• If AE has occurred on or after day 15 hold (interrupt dose) for the rest of the cycle and follow at least every seven days • If AE has occurred before day 15 and resolved to ≤ Grade 2 restart at same dose level for the rest of the cycle • In both cases, restart subsequent cycle at next lower dose

*AEs are graded using the NCI CTCAE v 4.0; however TFR and rash will be graded using NCI CTCAE v 3.0 as subsequent versions do not contain a provision for TFR.
Please note that leucopenia and lymphopenia are not part of dose modification rules, only neutropenia grade 3 or 4 requires dose modification.

Table 2: Lenalidomide Dose Modification Rules For Abnormal Liver Function*

DLT, based on NCI CTCAE Toxicity Grade	Action Required
ALT grade 2 (>3 - 5 x UNL) **and** Total bilirubin grade 1 (> ULN - 1.5 x ULN)	• Continue lenalidomide: re-test at next scheduled visit • No dose modification
ALT ≥ grade 3 (>5 x ULN) **or** Total bilirubin ≥ grade 2 (> 1.5 x ULN)	• hold (interrupt dose) for the rest of the cycle and follow weekly ALT and total bilirubin until return to baseline • Resume the same dose of lenalidomide if recovery (return to baseline) from the event is ≤ 14 days. • If recovery is prolonged beyond 14 days, weekly testing of liver functions should occur during that cycle and then the lenalidomide dose should be decreased by one level at the start of the next cycle.

*For patients with Gilberts Syndrome or liver involvement by lymphoma, dose reductions should be made in consultation with the principal investigator.

8.4.5.5 Lenalidomide Dose Reductions Levels

The daily dose of lenalidomide may be reduced successively by one level from the starting dose. There will be no more than one dose level reduction per cycle. Once a subject's dose has been reduced, dose re-escalation will not be permitted. Patients who cannot tolerate the lowest applicable dose level will permanently stop lenalidomide and continue rituximab SC up to the end of the 2 years of maintenance. Refer to table 3 for lenalidomide level doses.

Patients who have moderate renal insufficiency [creatinine clearance ≥ 30 mL/min but < 60 mL/min] will receive a lower starting dose of lenalidomide of 10 mg p.o. once daily in Cycle 1 and Cycle 2 Days 2-22 for 28-days. Refer to dose reduction steps table 4 below.

Table 3: Dose Reduction Steps For Adverse Events Related To Lenalidomide for Patients Initiating Treatment at 15 Mg Daily on Days 2-22, every 28 Days

Dose	**Once Daily on Days 2-22, Every 28 Day Cycles**
Starting dose	15 mg daily on Days 2-22, every 28 days
Level -1[a]	10 mg daily on Days 2-22, every 28 days
Level -2[a]	5 mg daily on Days 2-22, every 28 days
Level -3[a,b]	5 mg every other day daily on Days 2-22, every 28 days

a Once a patient's dose has been reduced, no dose re-escalation is permitted.

b Patients who cannot tolerate Dose Level -3 will permanently stop lenalidomide and continue rituximab SC up to the end of the 2 years of maintenance.

Table 4: Dose Modification Steps for Patients Initiating Treatment at 10 Mg Daily on Days 2-22, every 28 Days

Dose	**Once Daily on Days 2-22, Every 28 Days**
Starting dose [a,b,c]	10 mg daily on Days 2-22, every 28 days
Level A Dose [a, b]	15 mg daily on Days 2-22, every 28 days
Level -1 [c]	5 mg on days on Days 2-22, every 28 days
Level -2 [c,d]	5 mg every other day daily on Days 2-22, every 28 days

a If the patient has not experienced any drug-related grade 3 or 4 toxicity for the first 2 cycles, the dose should be increased to 15 mg p.o. once daily on Days 2-22 of each 28 day cycle at the discretion of the treating physician.

b Once the dose is escalated to 15 mg once daily for 21 days every 28 day, dose may be reduced successively by 1 level, ie, to 10 mg.

c Once a patient's dose has been reduced, no dose re-escalation is permitted.

d Patients who cannot tolerate Dose Level -2 will permanently stop lenalidomide and continue rituximab SC up to the end of the 2 years of maintenance.

8.4.5.6 Potential risk of Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML occurred in patients treated with anti-CD 20 including Rituximab. PML is a destructive infection of oligodendrocytes of the Central Nervous System (CNS) white matter, leading to neurologic deficits associated with demyelination. Death of oligodendrocytes leads to focal loss of myelin and dysfunction of associated myelinated tracts involving the cerebral hemispheres, cerebellum, or brainstem.

The symptoms of PML are unspecific, appear gradually, and can vary depending on the location of brain lesions. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as "cortical" (eg, aphasia or visual-spatial

disorientation) occur because the pathology of PML is typically immediately subcortical in the white matter, undermining the cortex referable to the clinical syndrome.

In this context, a clinical neurological examination must be performed at each clinical examination planned in the study protocol during treatment and follow up periods. The LYSARC would like to focus on the importance of investigating further any unexplained neurological symptoms identified during the study.

The diagnosis of PML should be considered in any patient presenting with new-onset neurological manifestations or symptoms like weakness or paralysis, vision loss, impaired speech and cognitive deterioration, and not only the possible cerebral relapse of patient lymphoma. Exploration of PML includes, but is not limited to, consultation with a neurologist, brain MRI and a lumbar puncture for JC virus detection by PCR in CerebroSpinal Fluid (CSF). PCR analysis of CSF for JC virus is the best test to confirm PML (the other parameters of spinal fluid are typically normal).

The therapy with anti-CD 20 antibodies (rituximab) should be discontinued during the investigations of a potential PML and permanently stopped if the diagnosis of PML is confirmed.

Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the adequate monitoring and treatment of PML.

8.4.5.7 Recommandations related to the management of skin reactions (Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome)

Severe skin reactions such as Toxic Epidermal Necrolysis and Stevens−Johnson Syndrome, some with fatal outcome, have been reported. In case of such an event with a suspected relationship to MabThera/Rituxan, treatment should be permanently discontinued.

8.4.5.8 Hepatitis B Infections

Cases of hepatitis B reactivation, including reports of fulminant hepatitis, some of which were fatal, have been reported in subjects receiving rituximab IV, although the majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera/Rituxan as per local guidelines. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation. A systematic prophylaxis should be given to patients with HBcAg positive or HBsAg positive (according to current practice of the sites). Prophylactic treatment should be given up to 1 year after the last cycle of Rituximab. For patient at risk of reactivation (HBcAg positive or HBsAg positive), DNA load should be performed and be negative at time of study entry and DNA load be monitored on a regular basis during the trial (according to current practice of the sites).

8.4.5.9 Recommandations related to the management of Drug reaction with eosinophilia and systemic symptoms (DRESS)

Drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported with lenalidomide. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis); eosinophilia; fever; and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events are extremely rare and have the potential to be fatal. Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash.

Lenalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS is suspected, and must not be resumed following discontinuation for these reactions.

Discontinuation of lenalidomide should be considered if skin rash ≥ Grade 2 is exfoliative or bullous or if Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS is suspected. Lenalidomide should not be resumed following discontinuation for these reactions.

8.4.5.10 Recommandations in case of hypothyroidism and hyperthyroidism

As hypothyroidism and hyperthyroidism have been reported in patients treated with lenalidomide, thyroid function monitoring is recommended before the start of lenalidomide and during treatment according to clinical routine of the sites.

8.5 Drug Dispensation and accountability

8.5.1 Responsibilities

All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the packaging is not to be used. Damaged packaging is to be reported to the sponsor and stored until instructions have been given.

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product (lenalidomide and SC rituximab) will be responsible for ensuring that the Investigational Products used in the clinical trial are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements. All Investigational Medical Products must be stored in accordance with labeling and shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained. Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure. Under no circumstances will the Investigator supply Investigational Product to a third party, allows the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

8.5.2 Retrieval or destruction

All unused and undelivered treatments will be destroyed by the Investigator (or the pharmacist) after the Sponsor provides a written authorization. All treatments returned by the patients will be destroyed by the Investigator (or the pharmacist) after the Sponsor validates the accountability log. All partially used disposable treatments will be immediately destroyed by the investigator (or the pharmacist). All destroyed treatments have to be documented by the pharmacist on a Certificate.

In case of a potential defect in the quality of Investigational Product, the Sponsor may initiate a recall procedure. In this case, the investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

8.5.3 Accountability and compliance

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed and used for each patient. The study monitor will periodically check the supplies of investigational products held by the investigator or pharmacist to verify accountability of all investigational products used. All unused investigational products and all medication containers will be destroyed by the study sites. The Sponsor will verify that a final report of drug accountability to the unit

dose level is prepared and maintained in the investigator study file. Administration of the study treatment will be supervised by the investigator or sub-investigator.

8.6 Concomitant treatment restrictions

Concomitant use of other anti-cancer therapy while the patient is in the study is considered as protocol violation and needs to be reported.

Doses of steroids (defined as ≤ 20 mg per day) are allowed during the study. Doses beyond 20 mg per day are not allowed during the study or during the 28-day screening period except when necessary for short duration. The steroid dosage and the allowable treatment period will be determined by the investigator on a case by case basis upon discussion with the medical monitor.

No other investigational therapies or non-drug therapies to treat MCL shall be initiated while the patient is on the study except upon discussion with the coordinating investigator.

8.7 Prophylactic measures

8.7.1 Permitted Concomitant Medications and Procedures

Therapies considered necessary for the subject's well-being may be administered at the discretion of the Investigator. All medications (prescription and non-prescription), growth factors, transfusions, treatments and therapies taken from 28 days prior to start of maintenance through the last dose of maintenance therapy, must be recorded on the appropriate page of the eCRF.

8.7.2 Rituximab premedication

In order to reduce the incidence and severity of infusion- or injection-related reactions, it is recommended that all patients receive the following premedication administered 30-60 minutes prior to each rituximab IV or SC administration:

- paracetamol (acetaminophen)
- diphenhydramine hydrochloride or alternative antihistamine.

Steroids used in CHOP should be administered before the start of the rituximab infusion and only optional during the maintenance phase.

8.7.3 Growth Factors

Growth factors during induction treatment (e.g. G-CSF, GM-CSF, erythropoietin, etc.) may be prescribed by the Investigator for rescue from severe hematologic events and should be used in accordance with the American Society of Clinical Oncology's (ASCO) guidelines or the European Society for Medical Oncology (ESMO) guidelines.

8.7.4 Tumor flare Treatment - Maintenance phase

TFR is unlikely to happen in the maintenance setting as only patient achieving a CR, CRu or PR after induction can be randomized in maintenance phase.

Treatment of TFR is up to the discretion of the investigator depending upon the severity and clinical situation. It is suggested that Grades 1 and 2 TFR be treated with non-steroidal anti-inflammatory drugs (NSAIDs) [i.e. ibuprofen 400-600 mg orally every 4-6 hours as needed], corticosteroids, and/or narcotic analgesics for pain management. Refer to table 1 for further instructions and dose modifications for Grade 3 and 4 TFR.

In mild to moderate cases, it is suggested that lenalidomide should be continued along with symptomatic treatment as above. In more severe cases, lenalidomide should be interrupted, as indicated in Table 1.

During the Maintenance Phase, emergency use of corticosteroids at any dose to treat TFR symptoms is allowed at the Investigator's discretion.

8.7.5 Thromboembolism Prophylaxis - Maintenance phase

It is recommended that patients in the lenalidomide arm who are at high risk for a thromboembolic event (high risk is defined as history of a thromboembolic event and/or taking a concomitant medication associated with an increased risk for a thromboembolic event and/or a known hypercoagulable state regardless of thromboembolic history) receive prophylactic aspirin (100 mg) daily unless contraindicated. If aspirin is contraindicated, use of low molecular weight heparin or warfarin (or equivalent Vitamin K antagonist) to keep the international normalized ratio (INR) in the range of 2-3, or use of other anti-thrombotic therapy according to hospital guidelines, or physician preference, is acceptable. However, the choice of anticoagulant for prophylaxis for VTE relies upon the investigator's discretion and should be tailored to the subject's individual risk/benefit profile by taking into account the individual thrombotic risk (e.g., history of venous thrombosis), bleeding risk, and the quality of compliance with antithrombotic treatment.

9 STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

9.1 Study flow chart

See on Appendix A.

9.2 Baseline examination

The patients will be required to give written informed consent to participate in this study before any non-routine baseline evaluations are conducted.
The histological examination of representative diagnostic material (lymph node, other involved soft tissue or bone marrow only if lymph node material is not available) must be performed within 6 months prior to therapy onset.
The subject's eligibility has to be evaluated during the baseline period prior to randomization and administration of the first cycle of chemotherapy.
In the population randomized directly in maintenance, initial staging and MIPI assessment has to be performed before R-CHOP and eligibility has to be re-evaluated prior to randomization for the maintenance phase.
The assessments are to be conducted within 28 days before administration of the study treatment, physical examination and basic laboratory examination within 2 weeks:

- Demographic data including age, gender, weight, height
- Physical examination including general physical examination, disease related symptoms, consultation ENT specialist upon indication, blood pressure, heart rate, ECOG Performance Status (see Appendix E)
- Staging (see Appendix C)
- Relevant medical history and history of the NHL
- Complete blood cell count,
- Biochemical tests: beta-2-microglobuline, Lactate dehydrogenase (LDH, along with upper limit of the normal range, ULN), ALT (SGOT), AST (SGPT), bilirubine, creatinine
- HIV, HBV and HCV serologies (mandatory for the first randomization and are to be performed 6 weeks before enrolment)

- Cervical region (neck), chest, abdominal and pelvis CT scan (with IV contrast in absence of contraindication)
- Optional PET scan
- Endoscopy or other investigations for extranodal localisations, if clinically indicated
- Chest X-ray
- Bone marrow biopsy for cytology, histology and optional immunophenotyping (CD20/CD5 staining aspirate; CD20 and cyclin D1 biopsy)
- ECG, Echocardiography (or isotopic method to determine resting ejection fraction)
- Sample for MRD studies: blood and bone marrow (cf. Appendix K)

9.3 Evaluation during induction treatment

Before each cycle, the following items need to be checked:

- Physical examination, including disease related symptoms, vital signs and ECOG performance status (see Appendix E)
- Complete blood cell counts
- Adverse events reporting / concomitant treatment

Any patient presenting with progressive disease during initial chemotherapy therapy should not receive further study-specific therapy. After complete documentation of progression, these patients need to be followed for survival.

9.4 Midterm and end of induction treatments evaluations

After 4 cycles of induction treatment and at the end of induction within 3 – 6 weeks after D1 of the last cycle of induction treatment, the response of the patient should be evaluated by the following evaluations using the Cheson 1999 criteria (see Appendix G).

- Physical examination including disease related symptoms, vital signs, ECOG Performance Status.
- Complete blood cell count
- Biochemical tests: LDH, ALT (SGOT), AST (SGPT), creatinine
- Bone marrow biopsy if positive before induction.
- CT scan of involved nodal area, especially assessment of measurable lesions.
- PET scan (optional)
- Endoscopy or other investigations for extranodal localizations, if clinically indicated
- Any other evaluations or procedures performed at baseline for evaluation of the disease response.
- Adverse events reporting / concomitant treatment
- Samples for MRD studies: peripheral blood at midterm, peripheral blood and bone marrow at end of induction (cf. Appendix K).

9.5 Evaluation before starting maintenance treatment

Patient with complete (CR, CRu) or partial remission after chemotherapy induction are eligible for second randomization.

9.6 Evaluation during maintenance treatment

For all patients, maintenance visits must be performed every 4 weeks during 16 weeks then every 8 weeks up to 2 years.

For all patients, the following assessments must be conducted:

- Physical examination, including disease related symptoms; vital signs and ECOG performance status [see Appendix A] at each maintenance visit, prior each rituximab infusion or starting of lenalidomide.
- Toxicity assessment must be performed every 4 weeks, during maintenance phase. In order to monitor toxicity every 4 weeks, for both maintenance arm, the investigator will contact the patient by phone 4 weeks after every maintenance visits when visits are performed every 8 weeks.
- Complete blood cell counts at Day 1, 8, 15 and 22 of 1rst cycle of maintenance (rituximab +/- lenalidomide), then 15 days during 8 weeks (i.e. at day 1 and 15 of cycles 2 and 3 of lenalidomide for maintenance experimental arm or day 29 and 43 of cycle 1 of rituximab and day 1 and 15 of cycle 2 of rituximab in maintenance standard arm), and every 4 weeks thereafter (i.e. at day 1 of next cycles of lenalidomide in maintenance experimental arm or at Day 1 and 29 of next cycles of rituximab in maintenance standard arm) unless clinically indicated.
- Biochemical tests: creatinine, ALT, total bilirubin at Day 1 of 1rst cycle of rituximab +/- lenalidomide, then every 4 weeks during 16 weeks (i.e. at day 1 of cycle 2 to 5 of lenalidomide for rituximab + lenalidomide arm or at Day 29 of cycle 1 of rituximab, Day 1 and 29 of cycle 2 and day 1 of cycle 3 in rituximab alone arm), and every 12 weeks thereafter (i.e. at day 1 of cycle 8, 11, 14, 17, 20, 23 and 26 of lenalidomide in maintenance experimental arm or at Day 29 of cycle 4, 7, 10 and 13 of rituximab, Day 1 of cycle 6, 9 and 12 of rituximab in maintenance standard arm).
- Adverse events reporting / concomitant treatment / SPM

9.7 Response evaluation during maintenance treatment

Response evaluations will be performed using the Cheson 1999 criteria (see Appendix G):

- after 6 months of maintenance ,
- after 12 months of maintenance and
- after 18 months of maintenance

The following items need to be checked:

- Physical examination including disease related symptoms, vital signs, ECOG Performance Status.
- Complete blood cell count
- Biochemical tests: LDH
- Bone marrow biopsy / cytology if clinically indicated.
- CT scan of involved nodal area
- PET scan (optional)
- Adverse events reporting / concomitant treatment
- Samples for MRD studies: peripheral blood each 6 month and bone marrow once a year (cf. Appendix K).

In case of suspicion of progression, additional CT scans will be allowed if clinically indicated.

9.8 End of maintenance evaluation / early discontinuation evaluation

The following assessment must be conducted within the 2 months (60 days) after day 1 of last cycle. Response is determined as per Cheson 1999 criteria (see Appendix G).

- Physical examination including disease related symptoms, vital signs, ECOG Performance Status.
- Complete blood cell counts with differential and platelet count
- Biochemical tests: LDH
- Bone marrow biopsy / cytology if lymphoma involvement at start of maintenance
- CT scan of involved nodal area
- PET scan (optional)
- Any other evaluations or procedures for evaluation of the treatment response
- Adverse events reporting / concomitant treatment
- Samples for MRD studies: peripheral blood and bone marrow (cf. Appendix K).

In case of premature withdrawal during the maintenance period, the evaluation should be performed within 2 months after Day 1 of the last cycle or before any new treatment.

9.9 Follow-up assessments

All subjects, including patients who withdraw from study treatment, patients not randomized for or not treated with maintenance, or patients with stop of maintenance, will be followed every 6 months for 2 years and yearly thereafter until 2.5 years after the last patient randomized for maintenance.

Response is determined as per Cheson 1999 criteria (see Appendix G, {25}).

The following assessments must be conducted at each follow up visit:

- Physical examination
- Complete blood cell counts
- Biochemical tests: LDH
- ECOG Performance Status (see Appendix E)
- Neck, Thoracic and abdominal CT scan for evaluation of progression every 6 months during the 1st 24 months after completion of treatment, and every year thereafter.
- Any other evaluations or procedures for evaluation of the treatment response
- Samples for MRD studies: peripheral blood each 6 month and bone marrow once a year (cf. Appendix K).

All patients, including patients who withdraw from the study treatment, or patients who progress / receive new treatment after treatment period, or patients not responding to induction, patients not randomized for or not treated with maintenance or patients with stop of maintenance will be followed for death once yearly until the end of the trial. Data regarding any new anti-lymphoma therapy will be collected.

All subjects who complete or discontinue the maintenance treatment for any reason will be followed for at least 3 years after his/her last study treatment administration in maintenance period for SPM. A long term follow-up for progression/death will be done up to the end of period of SPM data collection.

9.10 Progression/relapse

Relapse/progression will be determined as per Cheson 1999 criteria (see Appendix G, {25}).

Progressive disease should be based on CT scan.

A pathological confirmation by biopsy of the lesion should be done if possible.

New anti-lymphoma therapy and response to salvage therapy will be collected in eCRF.

10 STUDY PROCEDURES

10.1 Informed consent

Written informed consent approved in compliance with local regulatory authority will be obtained from each patient prior to being randomized the trial.

The informed consent for the collection of biological samples and for genetic study studies should be signed before sampling for minimal residual disease (MRD) analysis.

The patient and the investigator will date and sign the informed consent form.

The investigator shall provide an original copy of the signed consent to the study patient; an original copy shall be maintained in the investigator's study file.

10.2 Pathological diagnosis

Inclusion of the patient in the trial will be based on local pathological assessment.

Histopathology central review process has become in the last years a common and prerequisite procedure for clinical trials in the field of lymphomas. It requires both a histopathological and immunohistochemical approach using an appropriate panel of antibodies according to the morphological pattern and, in some instances, further molecular or genetic analysis.

A mandatory pathological review will be organized for all patients included in the trial at diagnosis. The goal of this central review will be to confirm the diagnosis and to classify precisely the malignancy according to the WHO classification 2008. The pathological review will be centralized nationally in each participating countries in their national reference laboratory (cf. section 3.3).

The review will be done without knowledge of patient outcome and will comprise the confirmation of the diagnosis of mantle cell lymphoma (both by morphology and immunophenotyping including CD5, CD10, CD20, CD23, BCL2 and Cyclin D1), and recording of the morphological variants including prognostic factors such as Ki67 expression.

Therefore for each patient, the investigator will be requested to submit a registration form along with a copy of the histopathological report and bone marrow report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified.

All the requested tumor paraffin embedded blocks from the formalin fixed sample (that was used for diagnosis), or 10 unstained slides, will be sent to the designated national pathology platform according to the process described in Appendix J.

In absence of tumor samples, when bone marrow samples of good quality are available, patient can be included and bone marrow fixed sample can be sent for pathological review.

At reception, routinely stained sections will be assessed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized, and a consensus diagnosis will be established. When the diagnosis has been revised the clinician and the initial pathologist will be informed.

Initial tumor block will also be used to make tissue microarray (TMA) and tissue core for DNA extraction; both will be used to study the expression of markers which may influence the prognosis of mantle cell lymphoma

At the end of the inclusion, frozen tumor tissue will be requested and organized by the designated national pathological platform. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of mantle cell lymphoma patients.

10.3 Randomization procedure for induction and maintenance

A patient will be randomized after verification of eligibility directly on IWRS (Interactive Web Response System) by the investigators through the internet network with the address below. To access the interactive randomization system, the investigator needs to record a username and a password.

IWRS: https://www.clininfohosting.com/specif/MCLR2_ELDERLY

First randomization should be done before the start of the induction treatment. The study site will receive back the randomization number and arm for the induction phase.

The LYSARC coordination center will be the contact by phone for any request: **+ 33 4 72 66 93 33**.
The investigator should fax or send as an electronic attachment to the coordination center (LYSARC: +**33 4 26 07 40 13**) a copy of the pathology report.

After completion of induction treatment, if patient reach a CR/CRu or a PR, the second randomization should be done before the start of maintenance treatment. In the run-in period of 6 months, patients without randomization for induction who have reached CR/CRU or PR after an induction treatment with 6-8 cycles of R-CHOP21 given outside the trial can be randomized directly for maintenance treatment. In both cases, randomization should occur within 3 months after documentation of a CR/CRu or PR. The study site will receive back the arm for maintenance phase.

Stratification:

First randomization (for induction) will be stratified according to country (France, Belgium and Portugal will be considered as one country) and MIPI risk group (high vs intermediate/low risk) at study entry.

For second randomization (i.e. for maintenance), randomization will be stratified according to country group (Northern countries (Netherlands, Germany, Poland) vs southern countries (France, Belgium, Portugal, Spain, Italy), MIPI risk group (high vs intermediate/low risk) before start of induction, type of first line induction therapy (R-CHOP vs R-CHOP/R-HAD) and response to first line therapy (CR/CRu vs PR).

10.4 Minimal Residual Disease (MRD) analysis

The objectives of minimal residual disease (MRD) analysis are:

- to evaluate MRD level at diagnosis, at the end of induction, during maintenance and at all the planned molecular time points;

- to evaluate the relative activity of the two induction and maintenance regimens on MRD kinetics assessed in terms of rate of conversion to molecular remission, rate of molecular relapse, quantitative increase of tumor burden in the bone marrow and peripheral blood.

- to assess the prognostic impact of molecular response, molecular relapse and disease kinetics assessed by real time PCR at various time points (both on peripheral blood and bone marrow) on PFS.

Investigation of potential predictive markers of prognosis as well as the biological effects of induction and maintenance treatment on minimal residual disease will be examined as described below. Patient participation in these exploratory correlative science sub-studies is strongly encouraged.

10.4.1 Minimal Residual Disease Status

MRD detection in MCL has been evaluated in several publications for both staging and follow-up {27-30}.The EU MCL network is developing guidelines for standardization both the technology and the reporting of MRD in MCL and other hematological diseases.

In this trial, we will use the expertise of the EU MCL network to assess MRD status using allele-specific quantitative PCR (RQ-PCR) to determine each individual patient's MRD status. Allele-specific quantitative PCR is currently the most sensitive, specific and standardized method for MRD assessment in MCL and has been successfully used in multicenter clinical trials for the treatment of MCL.

For RQ-PCR, it will be necessary to determine an individual clonal marker by DNA sequencing of the individual lymphoma clone from each patient. This will be possible from diagnostic peripheral blood and bone marrow analysis prior to any treatment. A prerequisite for establishment of an individual MRD assay is the determination of lymphoma cell infiltration in the diagnostic peripheral blood or bone marrow samples based on flow-cytometry. Only exceptionally DNA from diagnostic tumor tissue (formalin fixed paraffin embedded tumor block) will be used.

In both induction arms, peripheral blood will be collected at diagnosis, midterm and end of induction treatment and bone marrow at diagnosis and end of induction treatment. For patients randomized directly in maintenance phase, no sample collection is requested as no sample will be available for diagnosis. During maintenance, peripheral blood will be collected every 6 months and bone marrow once a year.

For each time point, peripheral blood and bone marrow samples (see Appendix K for description of the samples required for each time point) will be sent to the national reference biology laboratories listed in section 3.3 of the protocol. MRD analysis will be done in the each national reference laboratory.

10.4.2 Assessment of the Molecular and Acquired Changes in Genes Involved in Lymphomagenesis in initial tumor block

MCL is a heterogeneous disease with several prognostic subtypes, previously reported, based on molecular genetics and gene expression. Tumor samples from patients prior to lenalidomide treatment will be used to evaluate potential molecular subclasses that may be associated with clinical response to lenalidomide treatment. The microenvironment as well as tumor cell profiles will be evaluated, as the mechanism of action of lenalidomide in MCL is most likely to involve both components of the tumor.

Pretreatment initial tumor blocks will be evaluated for MCL characteristics including but not limited to profiling of acquired changes in chromosome or DNA of the tumor cells, protein and gene expression. If possible, tissue cores will be processed from individual initial tumor blocks into a tissue array for the immunostaining. Paraffin sections or excised cores will also be prepared from these initial tumor blocks and used for RNA and DNA extraction. Biological markers to be examined may include immunohistochemistry for cyclin D proteins, SPARC, Ki67, p21, pAkt and other indicators of oncogenic pathway activation, markers of angiogenesis and types of infiltrating immune cells. Gene expression, microRNA expression and common genetic alterations in MCL will also be examined in RNA and DNA extracted from the tumor. The cyclin D1-IgH translocation occurring at t(11;14)(q13;q32) as well as additional acquired genetic changes (e.g., loss-of-heterozygosity at 8p21.3) may be examined. When possible, RNA may be used to measure global gene expression or micro RNAs. Collectively, the chromosomal changes, gene and protein expression will provide a detailed molecular analysis of

individual tumors. These tumor properties, in turn, may provide important insights into specific characteristics related to individual patient responses to lenalidomide treatment.

11 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

11.1 Premature withdrawal from trial intervention

Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate eCRF page.

Criteria for subject withdrawal include (but are not limited to) death, toxicity, lymphoma progression, concomitant disease, noncompliance (including loss of subject to follow-up), consent withdrawal, and major protocol violation, including initiation of alternate anti-neoplasic therapy.

Patients should however remain in the trial for the purposes of follow-up and data analysis.

11.2 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states their wish not to contribute further data to the study, the relevant LYSARC contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study.

11.3 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time there must be documented attempts to contact the patient either by phone or letter.

11.4 Premature discontinuation of the study

The sponsor reserves the right to stop the trial at any time. The investigators will be informed of this decision in writing.

The same applies to any investigator wanting to discontinue his/her participation to the trial. The investigator must immediately inform the sponsor in writing of this decision.

12 SAFETY PARAMETERS

12.1 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 eCRF rather than the individual signs or symptoms of the diagnosis or syndrome according to general AE/SAE reporting rules (see below).

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.

Table 5: General AE/SAE reporting rules:

	Induction	**Maintenance**
AE	Any episode of any grade of toxicities, related to a Serious Adverse Event (SAE) will be recorded by the Investigator as Adverse Event (AE) from the time the subject signs informed consent to 28 days after the last dose of induction treatment. During induction treatment, non-serious AE of grade 3-5 related to treatment occurring from start of induction treatment are to be reported as "toxicity".	Any episode of any grade of toxicities, related to a Serious Adverse Event (SAE) will be recorded by the Investigator as Adverse Event (AE) from the time the subject signs informed consent to 28 days after the last dose of maintenance treatment AE of grade 2-5 for infections and neurological toxicities and AE of grade 3-5 for other toxicities (CTCAE – version 4.03) must be reported as "AE" from the time the subject signs informed consent to 28 days after the last dose of maintenance treatment. In experimental maintenance arm (ie lenalidomide + rituximab arm), any AE leading to the doses modification and whatever their grade should be reported as "AE"
SAE	Hematological toxicities (anemia, thrombocytopenia, leucopenia, and neutropenia), febrile neutropenia, and nausea, requiring hospitalization less than 8 days, are not to be reported as SAE (life-threatening and fatal events should be reported as SAE regardless the duration of hospitalization).	

AEs will be considered ended (recovered without sequelae) when recovered to a grade 0 or grade baseline.

At baseline, any abnormal medical condition which is not reported in laboratory tests (biochemistry, hematology) should be declared on medical history page, whether due to lymphoma or not.

This medical condition should be followed at each clinical examination: if it worsts in maintenance phase (transition to grade ≥ 3 or ≥ 2 for infections and neurological toxicities), it should be declared as an AE which will be resolved when returned to the grade observed at baseline.

AEs and serious adverse events will be recorded on the AE page of the eCRF and in the subject's source documents. All SAEs must be reported to LYSARC Pharmacovigilance Department, within 24 hours of the Investigator's knowledge of the event by facsimile using the MCLR2 LYSARC SAE Report Form.

12.2 Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

12.2.1 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 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 regardless of the treatment arm the subject is in. This includes any SPM, regardless of causal relationship to maintenance treatment, occurring at any time for the duration of the study, from the time of signing the ICD up to 3 years after the last dose of maintenance treatment.

Events of SPM 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 eCRF and subject's source documents. Documentation on the diagnosis of the SPM 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.).

Events **not considered** to be SAEs are hospitalizations for:

- 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.

- A procedure or hospitalization for progression/relapse investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling).

- 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 eCRF.
  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.

- Sign, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as “Serious Adverse Event” nor AE.

- “Alopecia” toxicity (any grade) will never be reported as “Serious Adverse Event” nor AE.

- Serious adverse events will not be recorded after the start of a new chemotherapy treatment, with the exception of SPM or if it is related to lenalidomide as assessed by the investigator.

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

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

12.2.2 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);

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

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*

Specific NCI Working Group or other criteria pertinent to the indication may also be used as applicable.

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.

12.2.3 Causality

The Investigator must determine the relationship between the administration of Rituximab sub cutaneous and Lenalidomide (if applicable) and the occurrence of an AE/SAE as Not Related or Related as defined below:

Not related:	A causal relationship is **unlikely or remote** between the adverse event and study drug administration and other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Related:	A causal relationship is **possible** between the adverse event and study drug administration and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

For Germany, the Investigator must also determine the relationship between the administration of Rituximab IV, cyclophosphamide, doxorubicin, vincristine, prednisone as well as cytarabine and dexamethasone if applicable and the occurrence of an AE/SAE as Not Related or Related as defined above.

12.2.4 Duration

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

12.2.5 Action Taken

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

12.2.6 Outcome

The investigator will report the outcome of the event for both AEs and 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).

12.3 **Reporting of Serious Adverse Events**

All events that meet one or more criteria of seriousness (see Section 12.2.1.) that occurred **from the time of signing the ICF up to 28 days after the last study drug administration,** regardless the relationship to the study treatment requires the completion of an SAE Report Form in addition to being recorded on the AE page of the eCRF.

A Serious Adverse Event that occurs after this time, including during the follow-up period, **if considered related to the study medication**, will be reported regardless of the time between the last drug administration and the event onset.

All SAEs must be reported to LYSARC Pharmacovigilance Department (i.e., within 24 hours of the Investigator's knowledge of the event) by facsimile, or other appropriate method, using the SAE Report Form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to study drugs) that occur during the study (from the time the patient signs informed consent to 28 days after the last dose of study drug(s)), and those made known to the Investigator at anytime thereafter that are related of being related to study drugs. SAEs occurring prior to treatment will be captured.

12.3.1 Obligations of the Investigator

In a case of serious adverse event**, the Investigator must immediately SEND (preferably by fax) the SAE pages to:**

LYSARC Pharmacovigilance department:

FAX: +33 (0) 3 59 11 01 86

All SAE forms must be dated and signed by the responsible Investigator or one of his/her authorized staff Members.

- The SAE report should provide a detailed description of the SAE specifying the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all serious adverse events and his opinion as to whether the serious adverse event can be related to the study drugs. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis.
- Attach the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical study are properly mentioned on any copy of source document. For laboratory results, include the laboratory normal ranges.
- Follow up of any Serious Adverse Event that is fatal or life threatening should be provided within one calendar week. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent as soon as these become available.

Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to LYSARC Pharmacovigilance Department.

Safety Queries

Queries pertaining to SAEs will be communicated from LYSARC Pharmacovigilance Department to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days.

Where required by local legislation, the Investigator is responsible for informing the IRB/EC of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with LYSARC and the IRB/EC.

12.3.2 Obligations of the sponsor

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and suspected to be related to study drugs, to the Health Authorities, Ethic Committees in each country in accordance with international and local regulations, and to the Investigators:

- within 7 days after knowledge of such a case for fatal or life-threatening events. Relevant follow-up information for these cases will be subsequently submitted within an additional eight days
- and within 15 days of first knowledge by the investigator for other serious adverse events.

The expectedness of an adverse reaction will be determined by the Sponsor according to the reference safety information (Investigator's Brochures) of lenalidomide and rituximab SC.

The LYSARC Pharmacovigilance department will be responsible for expedited reporting (SUSAR, New Safety Issues, Annual safety Reports) to the relevant Health Authorities and to the Ethics Committee according to the local regulation.

12.4 **Pregnancy**

Females of childbearing potential are excluded of this study.

If a female partner of a male patient becomes pregnant, the male patient 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 LYSARC and allow the pregnancy related event to be followed up to completion.

The Sponsor will inform Celgene immediately, using the Pregnancy Reporting Form provided by LYSARC, 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 lenalidomide or within 28 days of the Patients' last dose of lenalidomide.

13 BENEFIT/RISK IMBALANCE OF TREATMENT PROGRAM

All study treatments have proven their efficacy in the treatment of MCL. It is expected that patients will achieve a high response rate in each of the induction arms consisting of 8 courses of R-CHOP or alternating 3 courses of R-CHOP and 3 courses of R-HAD. It is hoped that induction with alternating 3 courses of RCHOP and 3 courses of RHAD will improve the outcome. For the maintenance therapy, in patients who initially reach at least a partial response to induction, it is hoped that adding lenalidomide to standard rituximab maintenance will be beneficial to the patients in term of PFS It is possible that some patients may not reach a clinical response with the study treatment and will require other treatment outside this protocol.

Altogether, in this elderly MCL patient's population, the benefit of this treatment program is expected to be superior to the potential short and long term toxicities. This study will help gain knowledge about this innovative treatment strategy in MCL based on new induction and maintenance strategies.

A possible increased of risk of developing new malignancies is associated to lenalidomide intake. Patients in maintenance experimental arm, receiving lenalidomide will be closely monitored (every 6 months for 3 years after the last lenalidomide intake) for the development of new cancers and SPM will be reported as serious adverse events regardless of the treatment arm the subject is in. All SPM occurred in this study will be reviewed by IDMC members every 6 months.

14 STATISTICAL CONSIDERATIONS

14.1 Study design

The primary objective of the trial is to evaluate whether the addition of lenalidomide to rituximab-maintenance improves progression free survival (PFS) compared to standard rituximab maintenance after response to induction chemotherapy in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation.

Secondary objectives are

- to compare efficacy and safety of the maintenance regimens in terms of secondary endpoints
- to evaluate whether the introduction of cytarabine into induction improves clinical outcome compared to standard R-CHOP in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation. This objective will be answered in a confirmatory way with overall survival as primary variable of interest.
- to compare efficacy and safety of the induction regimens in terms of other secondary endpoints

14.2 Primary Endpoint

The primary endpoint is the progression free survival after randomization for maintenance.

Progression free survival (PFS) after randomization for maintenance is defined as the period from the date of maintenance randomization until the date of progression or death from any cause. For patients who have not progressed or died at the time of analysis, PFS will be censored on the date of latest tumor assessment. If no tumor assessments were performed after the maintenance randomization, PFS will be censored at the time of randomization for maintenance.

14.3 Secondary Endpoints

14.3.1 Efficacy Endpoints

The following secondary efficacy endpoints will be evaluated:

- ***Overall Survival (OS)***

Overall survival from induction randomization is defined as the period from induction randomization to death from any cause.

Overall survival from maintenance randomization is defined as the period from maintenance randomization to death from any cause.

Patients who have not died until the time of the analysis will be censored at their last contact date.

Additionally, overall survival from start of treatment to death from any cause may be analyzed.

- ***Time to treatment failure (TTF)***

Time to treatment failure (TTF) is defined as the time from start of induction to stable disease, progression or death from any cause. Patients alive without treatment failure will be censored at the latest tumor assessment date. TTF may also be calculated from induction randomization.

- ***Progression-free survival (PFS) from induction randomization***

Progression-free survival (PFS) from induction randomization is defined as the period from induction randomization to progression or death from any cause. Patients alive without progression at the time of analysis will be censored at the latest tumor assessment date.

- ***Remission duration (RD)***

Remission duration will be calculated in patients with response (CR, CRu, PR) to induction from end of induction to the date of progression, relapse or death from any cause. Patients alive without progression and relapse will be censored at the latest tumor assessment date.

- ***PR/CRu to CR and PR to CRu conversion*** during maintenance

- ***Minimal residual disease (MRD)***

MRD status and levels in peripheral blood and bone marrow at midterm and at the end of induction, after one and two years from end of induction and during follow-up until progression or up to 2.5 years of follow-up whichever comes first.

- ***Response rates***

The complete response rates (CR including or excluding CRu) and overall response (CR, CRu, PR) rates are evaluated at midterm and after the end of induction treatment.

14.3.2 Safety Endpoints

The following secondary safety endpoints will be evaluated:

- **Adverse events** graded for worst level according to the NCI-CTCAE (Version 4.0)
- **SAEs** (Verbatim descriptions, MedDRA-Preferred Term, System Organ Class)
- **Rates of second primary malignancies**
- **Vital sign measurements, clinical laboratory measurements.**

14.3.3 Exploratory Endpoints

The following exploratory efficacy endpoint will be evaluated:

- CR rate after induction / maintenance treatment according to Cheson 2007 criteria including FDG-PET evaluation.

14.4 Analysis populations

14.4.1 Induction Intention-to-treat (ITT) population

The induction intention-to-treat (ITT) population includes all patients randomized for induction regardless of study drug being received or not or other protocol violations. According to the ITT, patients from the induction ITT population will be analyzed based on assigned treatment group per induction randomization. Patients without staging during induction will be excluded for the evaluation of remission rates.

14.4.2 Maintenance Intention-to-treat (ITT) population

The maintenance intention-to-treat (ITT) population includes all patients randomized for maintenance regardless of study drug being received or not or other protocol violations. According to the ITT, patients from the maintenance ITT population will be analyzed based on assigned treatment group per maintenance randomization. For time-to-event endpoints, no censoring rules due to protocol violations will be applied.

14.4.3 Modified induction intention-to-treat (mITT) population

The modified induction ITT (mITT) population includes patients from induction ITT population with stage II-IV MCL for whom induction treatment was started in accordance with the induction randomization

result. According to the mITT, for patients with response to induction (CR, CRu, PR), in whom an anti-lymphoma treatment is started without progression and not according to the protocol, time-to-event endpoints will be censored at start of the new therapy.

14.4.4 Modified maintenance intention-to-treat (mITT) population

The modified maintenance ITT (mITT) population includes patients from maintenance ITT population with stage II-IV MCL for whom maintenance was started in accordance with the maintenance randomization result. According to the mITT, for patients with response to induction (CR, CRu, PR), in whom an anti-lymphoma treatment is started without progression and not according to the protocol, time-to-event endpoints will be censored at start of the new therapy.

14.4.5 Induction safety population

Induction safety population includes all registered patients who have received at least one component of the planned induction treatment. Patients will be analyzed according to the induction therapy actually received.

14.4.6 Maintenance safety population

Maintenance safety population includes all registered patients who have received at least one component of the planned maintenance treatment. Patients will be analyzed according to the maintenance therapy actually received.

14.5 **Statistical Methods**

14.5.1 General

Continuous variables will be summarized, also according to treatment arms, in tables displaying sample size, median, range; quartiles will also be presented when considered relevant.

Categorical data will be described, also according to treatment arms, in counts and percentages of non-missing data. Comparison will be performed if relevant by means of two-sided Chi square or exact Fisher tests.

Censored data will be presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for probability rates at fixed time points, with 95% confidence intervals. Estimates of the treatment effects will be expressed as hazard ratios including 95% confidence limits using an unstratified Cox proportional-hazards analysis.

Graphical display of Kaplan-Meier curves will be provided to help data interpretation visually. The median time to event will be calculated (if reached). Time-to-event endpoints will be compared by means of log-rank tests, unstratified and also stratified according to the randomization stratification factors. All efficacy analyses will be performed according to the ITT and, as supportive analyses, according to the modified ITT.

Multivariable logistic or Cox regression models will be applied including the treatment arms, potential confounders (e.g. MIPI, response, induction treatment), and, for maintenance effects, the interaction term of induction and maintenance (pre-specified subgroup analysis).

Exploratory subgroup analyses according to MIPI and, for maintenance, according to response will also be performed by interaction terms within multivariable regression.

14.5.2 Primary efficacy endpoint

The primary analysis between the two study arms in the maintenance phase will be an unstratified two-sided log-rank test. The primary analysis will be conducted based on the maintenance-ITT population. Estimates of the treatment effect will be expressed as hazard ratios including two-sided 95% confidence intervals. In addition Kaplan-Meier estimates of median progression-free survival as well as progression-free survival rates at one, two and three… etc years after randomization with 95% confidence intervals will also be reported.

A log-rank test stratified on the maintenance randomization factors will also be performed. In addition the same analyses as described above will be performed on the maintenance modified ITT. The stratified log rank test and the analyses on the mITT population will be considered as supportive analyses.

14.5.3 Secondary efficacy endpoints

Except for overall survival according to induction arms, all secondary endpoints will be analyzed in a descriptive way. Overall survival will be compared between induction arms with a confirmatory statistical test as described in the interim analyses section.

14.5.4 Safety endpoints

Safety analyses will be performed on safety population and according to the treatment actually received (as treated).

All adverse events will be tabulated and graded for worst level according to the NCI-CTCAE (Version 4.0) for each patient. When applicable, summary of safety data will also be performed by cycle. Verbatim descriptions of SAEs reported during the study period will be mapped to MedDRA-Preferred Term and System Organ Class. All SAEs, study drug related events, AEs leading to death will be listed and summarized in frequency tables. All deaths will be listed and also summarized by cause of death.

Listing of patients with SPM will be provided. SPM rates will be estimated as cumulative incidence rates adjusting for death without SPM as competing event (competing risk survival analysis).

14.6 **Hypothesis testing**

A two-sided unstratified log-rank test will be used for testing the difference in progression-free survival between the two treatment groups. The significance level for the final analysis will be 0.05.

The null (H_0) and alternative hypothesis (H_A) will be:

H_0: PFS (Experimental arm) = PFS (Standard arm)

H_A: PFS (Experimental arm) $\neq$ PFS (Standard arm), where PFS denotes the probability distribution of progression free survival after randomization for maintenance.

The significance level of the statistical test is set to 0.05. The null hypothesis of equal distributions of progression free survival after randomization for maintenance will be rejected, if the two-sided p-value from the unstratified fixed sample log-rank test is ≤ 0.05.

14.7 **Sample size calculation**

The trial is powered to detect a hazard ratio of 0.64 for PFS after randomization for maintenance comparing experimental versus standard arm with a power of 80%. As a reference, the trial would also have a power of 95% to detect a hazard ratio of 0.56 as observed in the previous MCL Elderly trial of the

European MCL Network for rituximab-maintenance versus interferon maintenance. The number of events needed to detect such a difference is calculated to 158.

For the calculation of patient numbers needed, the following assumptions are used:

- rate of first randomizations: 115 per year
- rate of second randomizations (70% of first randomizations): 80.5 per year, including 10% dropouts.
- recruiting time 6 years (5.5 years plus 6 months induction therapy), additional follow-up 2.5 years
- Kaplan-Meier estimates from the previous MCL Elderly trial of the European MCL trial

Table 6 describes the following numbers of events which will be observed with these assumptions if the alternative hypothesis is true.

Table 6: Number of event estimated

Years	Probability event free	Events cum, HR 0.64	Patients 2nd randomization (excl. drop-outs)	Patients 2nd randomization (incl. drop-outs)
0	1	0	0	0
0.5	0.9650	0.00	36.37	40.25
1	0.8918	1.40	72.74	80.5
1.5	0.8138	5.80	109.11	120.75
2	0.7568	12.73	145.48	161
2.5	0.7047	20.64	181.85	201.25
3	0.6834	29.66	218.22	241.5
3.5	0.6560	39.35	254.59	281.75
4	0.5964	51.81	290.96	322
4.5	0.5591	65.48	327.33	362.25
5	0.5032	80.98	363.7	402.5
5.5	0.4838	96.59	400.07	442.75
6	0.4529	113.25	400.07	442.75
6.5	0.424	129.53	400.07	442.75
7	0.3969	143.75	400.07	442.75
7.5	0.3716	156.36	400.07	442.75
8	0.3478	168.83	400.07	442.75

Thus, a sample size of 443 randomized patients for maintenance is needed and sufficient to answer the primary objective. To achieve such a number for maintenance, 633 patients need to be randomized for induction.

14.8 **Interim analysis**

14.8.1 Interim analysis for secondary induction question

A secondary question of the study is to evaluate whether the introduction of cytarabine into induction improves clinical outcome compared to standard R-CHOP. A two-sided unstratified log-rank test will be used for testing the difference in overall survival between the two induction arms in a confirmatory way. For security reasons, interim analyses will be performed to allow an early closure of the R-CHOP/R-HAD arm if an unexpected inferiority of the R-CHOP/R-HAD arm with respect to overall survival has been observed. As we are more interested in detecting a superiority of the R-CHOP/R-HAD arm at the end of the study than early in the trial we decided to use a methodology that allow us to keep most of the

significance for the final analysis and less for interim analysis. We thus decided to use an asymmetric alpha-spending method of the O'Brien and Fleming.

14.8.1.1 Power calculation

In the previous MCL Elderly trial of the European MCL Network {6} the percentage of survival at 4 years in the R-CHOP arm has been estimated at 64.5%.

Taking into account the same survival distribution than for the previous study described below, a total of 223 deaths would be expected in the two arms at 8 years if the hazard ratio for R-CHOP/R-HAD vs. R-CHOP is 0.6 (see Figure 2 & Table 7).

In a fixed sample test of survival curves with an OS hazard ratio of 0.60, a log rank test at the 0.05 two-sided level performed when there are around 200 deaths across all arms would have power of 95%.

Figure 2: Events (hazard ratio 0.6) /Accrual according to time (in years)

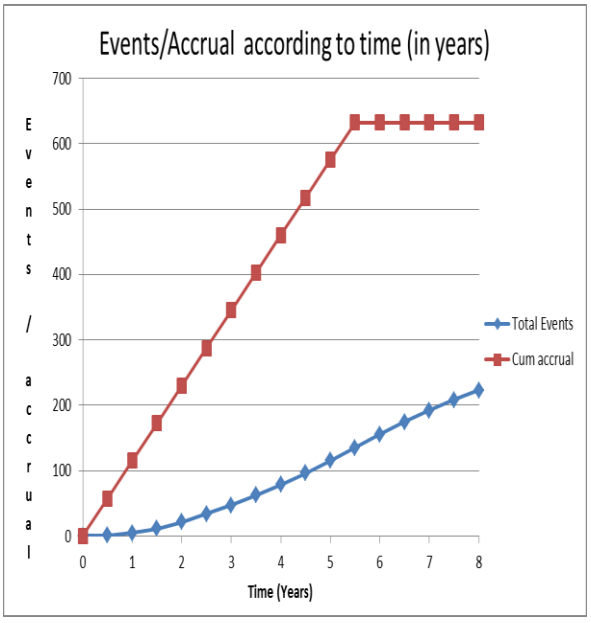


Table 7: Number of events estimated (hazard ratio 0.6)

Years	Total Events	Cum accrual
0	0	0
0.5	1.21	57.5
1	4.85	115
1.5	11.41	172.5
2	21.36	230
2.5	33.68	287.5
3	47.29	345
3.5	62.2	402.5
4	78.43	460
4.5	95.97	517.5
5	114.84	575
5.5	135.05	632.5
6	155.4	632.5
6.5	174.68	632.5
7	192.41	632.5
7.5	208.14	632.5
8	222.9	632.5

14.8.1.2 Interim analysis design

The OS will be compared between the induction arms, using a group sequential log-rank test corresponding to four analyses (3 interim and one final). A maximum number of 204 events will be required for this analysis.

The interim analyses will occur at the following times: an interim at 25% of 204 events or at the latest with 300 randomized patients, at 45% of 204 events or at the latest with 450 randomized patients, at 60% of 204 events or at the latest with 530 randomized patients, and one final at 100% of 204 events.

To ensure patients' safety, an Independent Data Safety Monitoring Committee will be established to assess on-going safety data during the course of the study. These interim analyses will be evaluated during these IDMC meeting. Details of the IDMC operation will be provided in the IDMC Charter.

The boundaries evaluation are based on an asymmetric α-spending function of the O'Brien-Fleming type with α=0.025 for each side. The boundary for declaring an inferiority of R-CHOP/R-HAD vs. R-CHOP

arm is based on an α-spending function of the O'Brien-Fleming type using the Rho method (Rho=3). The boundary for declaring a superiority of R-CHOP/R-HAD vs. R-CHOP arm is based on a α-spending function using the Rho method (Rho=51). The boundaries for superiority will thus be computed in order to keep almost all the alpha for the final analysis.

At each interim analysis, boundaries for the normalized log-rank test statistic will be calculated and the statistical test will reject the null hypothesis, if the normalized log-rank statistic exceeds the calculated boundaries.

Table 6 gives the nominal alpha levels and boundaries for rejecting the null hypothesis corresponding to the O'Brien-Fleming boundaries (Jennison and Turnbull, 2000) for the comparison between the induction arms.

These limits are approximate and will be recalculated based on the amount of information (i.e. number of deaths) available from the two arms when the interim analysis will be actually performed and with the full information defined as a total of 204 events from the two arms at the final analysis.

Table 6:* Boundaries for Rejecting Null Hypothesis on normalized z-scale – *computed with East 5.4 (Rho method[(1)], Rho=3 for lower boundary and Rho=51 for the upper boundary)

Information Fraction	Cumulative Events	Sides	Alpha Spent	Nominal Alpha	Boundary to Reject H0	
					H0-	H0+
0.250	50.860	one-sided	0.00039	0.00039	-3.35935	
0.450	91.547	one-sided	0.00228	0.00204	-2.87141	+8.87648
0.600	122.063	one-sided	0.00540	0.00433	-2.62510	+7.31466
1.000	203.438	two-sided	0.02500	0.02279/0.025	-1.99927	+1.95996

(1) Jennison and Turnbull 2000, Group Sequential Methods with Applications to Clinical Trials, New York: Chapman & Hall, p. 148.

For example, if at the second interim analysis with 45% events, the normalized test statistic from the log-rank test is lower than -2.87141, then the independent IDMC could consider recommending to stop the induction randomization in favor of inferiority of R-CHOP/R-HAD arm. However, the final decision of stopping/unblinding the induction randomization at the time of the interim analyses lies with the sponsor of the study, taking the recommendation from the IDMC into account. In the case of stopping the induction randomization, recruitment to the trial and randomization for maintenance will be continued assigning all further patients to the induction arm with superior overall survival.

At the final analysis, the alternative hypothesis of inferior R-CHOP/R-HAD arm will be accepted, if the normalized normalized test statistic from the log-rank test is smaller than -1.99927. The alternative hypothesis of superior R-CHOP/R-HAD arm will be accepted, if the normalized test statistic from the log-rank test is greater than 1.95996. Otherwise, the null hypothesis will not be rejected.

14.8.2 Interim analysis for primary maintenance question

No interim analyses will be performed for the primary objective.

15 STUDY COMMITTEE

15.1 Independent Data Monitoring Committee

An independent external Data Safety Monitoring Committee (IDMC) will review ongoing safety data throughout the study. The IDMC will include at least three independent members (2 experts in MCL and one statistician). The first IDMC is planned to occur after 25 patients have completed 6 months of rituximab-lenalidomide maintenance. At least 3 additional IDMC will occur corresponding to the 3 interim analyses for induction arms.

All SPM occurred in this study will be sent to IDMC member every 6 months.

Details on the frequency of IDMC meetings and on the IDMC operation will be provided in the IDMC Charter. All data presented at the meeting will be considered confidential. Following each meeting the IDMC will prepare a report and may recommend changes in the conduct of the trial.

16 STUDY MONITORING

16.1 Investigators Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. The sponsor staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all patients who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

16.2 Sponsor Responsibilities

The sponsor (LYSARC) or an authorized representative of this study has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, study adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the project leader and of his clinical research support team is to help the investigator maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team to review study progress, investigator and subject adherence to study requirements and any emergent problems.

During monitoring visits, the following points will be scrutinized with the investigator: subject informed consent, inclusion and exclusion criteria, subject recruitment and follow-up, subject compliance to the study treatment, study treatment accountability (if applicable), concomitant therapy use, evaluations of

response, serious/non serious adverse event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected on a visit per visit basis.

16.3 Source document requirements

According to the guidelines on Good Clinical Practice, the study monitor has to check the case report form entries against the source documents. The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to source data which supports data on the case report forms (e.g. patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

16.4 Use and completion of the case report forms (eCRF)

An electronic case report form will be completed for each study patient. It is the responsibility of the investigator to ensure the accuracy, completeness, legibility and timeliness of the data reported in the patient's eCRF which have been designed by the sponsor to record all observations and other pertinent data to the clinical investigation.

Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events and patient status.

The investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action.

16.5 Study Drug Monitoring

Accountability for the study drugs (lenalidomide and rituximab SC) at the clinical site is the responsibility of the investigator. The investigator will ensure that the study drugs are used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual.

Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, or disposal of the drug will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

All unused lenalidomide and used vial of rituximab SC will be retained at the site until they are inventoried by the monitor. All used, unused or expired study drugs and all material containing study drugs will be treated and disposed by the study site of as hazardous waste in accordance with governing regulations.

17 ETHICAL AND REGULATORY STANDARDS

17.1 Ethical principles

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983) and the 41st (Hong Kong, 1989), the 48th (Somerset West, 1996), the 52nd (Edinburg, 2000) World Medical

Assemblies, notes for clarification added by the WMA General Assembly on paragraph 29 (Washington 2002) and on Paragraph 30 (Tokyo 2004) and amendment laid down by the 59th (Seoul, October 2008) and 64th (Fortaleza, October, 2013) World Medical Assemblies.

17.2 **Laws and regulations**

This study is also in accordance with laws and regulations of the country(ies) in which the trial is performed, as well as any applicable guidelines.

17.3 **Informed consent**

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each subject prior to any study related procedures or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining subject's informed consent must be reviewed and approved by LYSARC prior to Ethics Review Committee submission.

The investigator must explain to potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it may entail. Patients will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date.

An original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and an original copy given to the study subject. When allowed by local regulation, an original copy will be recovered by the LYSARC or representative sponsor in a sealed envelope after last patient randomized in the trial.

In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study patients participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

17.4 **Ethics Review Committee and competent authorities submission**

The sponsor must submit this study to country central ethics review committee, and to competent authorities and it is required to forward a copy of written approvals / advices signed to the investigators.

18 ADMINISTRATIVE PROCEDURES

18.1 **Curriculum vitae**

An updated copy of the curriculum vitae of each investigator and sub-investigator will be provided the LYSARC prior to the beginning of the study.

18.2 Secrecy agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of LYSARC.

They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of LYSARC.

It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

18.3 Record retention in investigating center(s)

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.

However national regulations should be taken into account, the longest time having to be considered.

For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

Any center will notify the sponsor before destroying any data or records.

18.4 Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

18.5 Publication

The results of the trial will be published after complete data collection and evaluation. Partial or preliminary results can be published beforehand. Publication is to be initiated by the coordinating investigators and approved by LYSA Scientific Committee.

Any publication in the form of a lecture, poster or article must be basically approved by LYSA Scientific Committee and the European MCL Network.

The authors will be proposed by the coordinating investigators and finally decided by Steering Committee and the European MCL Network.

All study data and publications are the property of LYSARC and the European MCL Network.

18.6 Insurance compensation

The sponsor certifies having taken out a liability insurance policy which covers the investigator and his co-workers and which is in accordance with the local laws and requirements. Specific statements will be contained in appendix where is needed.

A certificate of insurance will be provided to the investigator in countries in which this document is required.

18.7 Company audits and inspections by regulatory agencies

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it may be necessary to conduct a site audit or an inspection.

By signing this study, the investigator agrees to allow LYSARC and its representative, and drug regulatory agencies to have direct access to his study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in eCRF, review of documentation required to be maintained, and checks on drug accountability.

The sponsor will in all cases help the investigator prepare for an inspection by any regulatory agency.

18.8 Clinical study report

The sponsor will inform of the end of the trial the Competent Authorities and Ethics Committees within 3 months following the end of the study. A study report will be prepared under the responsibility of the sponsor and approved by the European MCL Network, less than one year after the end of the study and forwarded to the Competent Authorities and Ethics Committees

18.9 Study amendments

It is specified that the appendices attached to this study and referred to in the main text of this study, form an integral part of the study.

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the European MCL Network and LYSARC.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the coordinating investigators and by the sponsor and the signed amendment will be appended to this protocol.

Approval / advice of amendments by Ethics Review Committee and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

Prior to initiating the changes, study amendment must be submitted to regulatory agencies, where applicable, except under emergency conditions.

18.10 Closure of the Study

The sponsor reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/EC, regulatory authorities, etc...).

In addition, the Investigator or the sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

19 REFERENCES

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2. Zelenetz AD, Abramson JS, Advani RH, at al. NCCN clinical practice guidelines in oncology, Non-hodgkin's lymphomas. *J Natl Compr Canc Netw*. 2010;8(3):288-334.

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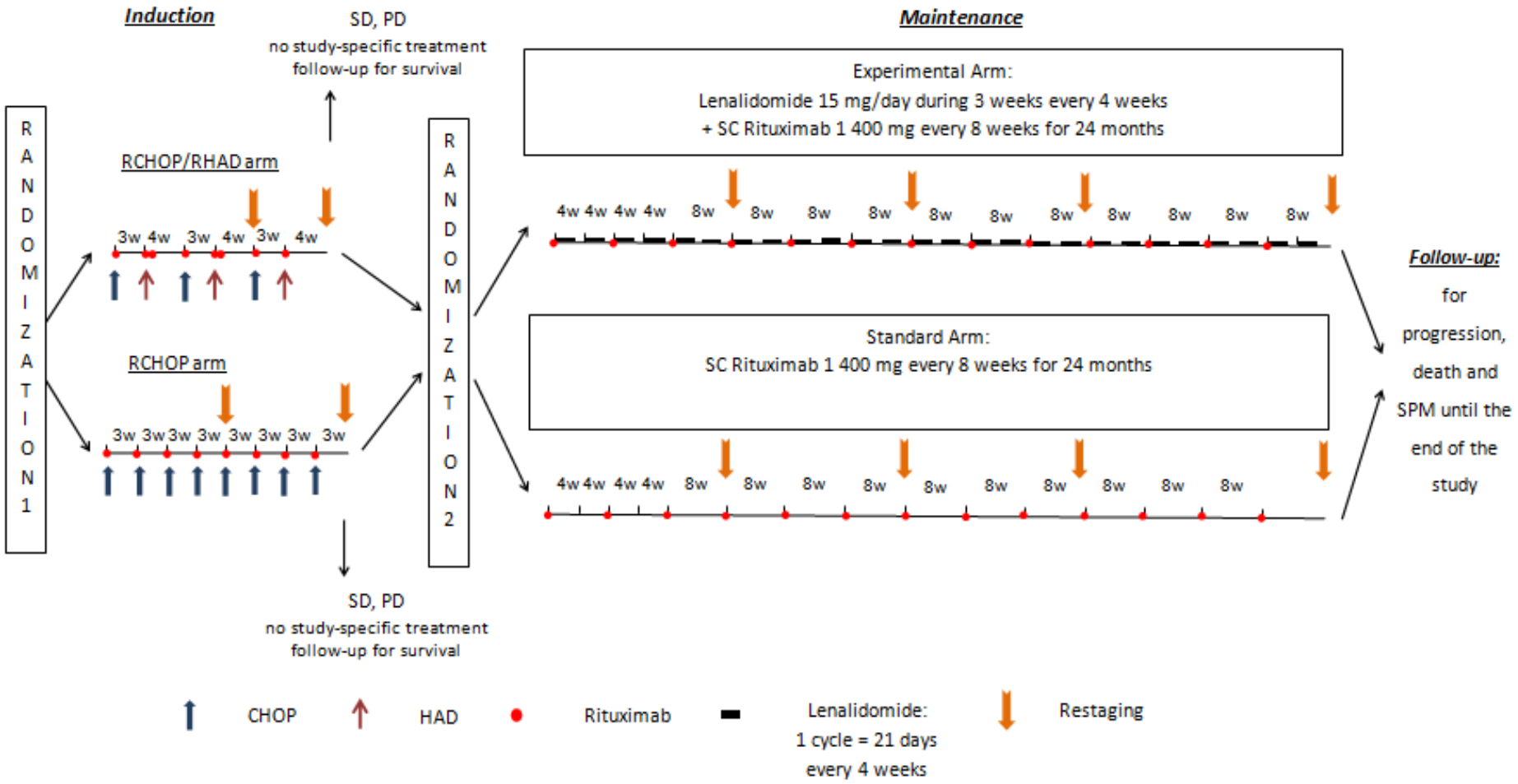
20 APPENDIXES

20.1 Appendix A: Study Flow Chart



20.2 Appendix B: Schedule of Evaluations

	Treatment									**Follow-up**
	Baseline	During induction	Response evaluation at midterm of induction treatment	Response evaluation at end of induction treatment	Randomization for maintenance treatment	**During maintenance treatment : 2 years, 13 cycles of rituximab +/- 26 cycles of lenalidomide** Rituximab Arm (= R arm): Rituximab SC: D1 every 8 weeks - repeat D57 (D57=D1 of next rituximab cycle) Rituximab + Lenalidomide Arm (= R2 arm): Rituximab SC: D1 every 8 weeks - repeat D57 + Lenalidomide D2-22 repeat D29 (D29=D1 of next lenalidomide cycle)			Response evaluation during maintenance and at end of maintenance treatment	
Date (weeks or months)	Within 28 days before C1 D1	D1 prior each cycle	After C4, prior C5 D1	3-6 weeks after treatment or at premature withdrawal	Within 3 months after end of induction evaluation and before D1 C1, within 28 days from D1 C1 (j)	R arm: Prior each Rituximab injection R2 arm: Prior Rituximab injection and starting Lenalidomide R arm: C1, 2: D1, D29 C3 to 13: D1 R2 arm: C1 to 4: D1 C5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25: D1	R arm: C1: D1, D8, D15, D22, D29, D43 C2: D1, D15, D29 C3 to 13: D1, D29 R2 arm: C1: D1, D8, D15, D22 C2, 3: D1, D15 C4 to 26: D1	R arm: C1, 2: D1, D29 C3, 6, 9, 12: D1 C4, 7, 10, 13: D29 R2 arm: C1 to 5: D1 C8, 11, 14, 17, 20, 23, 26: D1	Every 6 months; within 60 days after D1 of last cycle and prior starting any new treatment	Every 6 months for 2 years then once a year until progression yearly follow-up for death until the end of the study in all patients
Randomization	X				X					
Written informed consent (a)	X				X (j)					
Demographic data (b)	X				X (j)					
Inclusion / exclusion criteria	X				X					
Clinical examination (c)	X (within 14 days before C1 D1)	X	X	X	X (j, within 14 days before C1 D1)	X			X	X
ECG, Echocardiography	X									
Chest X Ray	X									
Blood cell counts (d)	X (within 14 days before C1 D1)	X	X	X	X (j, within 14 days before C1 D1)		X		X	X
Biochemical tests (e)	X (within 14 days before C1 D1)		X	X	X (j, within 14 days before C1 D1)			X	X	X
HIV, HBV, HCV serologies (f)	X (within 6 weeks prior 1rst randomization)				X (j, within 6 weeks prior 1rst randomization)					
Sample for MRD (g)	X		X	X					X	X
Neck, Thoracic and abdominal CT scan	X		X	X					X	X
Optional : PET Scan	*X*		*X*	*X*					*X*	
Bone marrow biopsy & aspirate (h)	X		X (if clinically indicated)	X (if clinically indicated)					X (if clinically indicated)	
Assessment of Second Primary Malignancy (i)	Continuous report									X
Toxicities	Continuous report									

(a) : Written information consents (for clinical trial, for collection of biological samples) have to be signed before randomization in the trial. In case of direct randomization for maintenance, informed consents have to be signed before randomization for maintenance and performing any procedure specific for MCL-R2 Elderly trial.

(b) : Age, gender, weight, height, relevant medical history, history of the NHL. Demographic data at baseline will be collected retrospectively for patients randomized directly in maintenance phase.

(c) : General physical examination, ENT upon indication, blood pressure, heart rate, ECOG Performance Status.
Examination has to be performed within 2 weeks before administration of first cycle of induction in case of randomization for induction or within 2 weeks before administration of first cycle of maintenance in case of direct randomization in maintenance.

(d) : Leucocytes, hemoglobin, neutrophils, lymphocytes and platelets.
Blood cell count has to be performed within 2 weeks before administration of first cycle of induction in case of randomization for induction or before administration of first maintenance cycle in case of direct randomization in maintenance.
For maintenance phase, blood cell count have to be performed at D1, D8 and D15 for first cycle of maintenance, then every 2 weeks for 8 weeks and every 4 weeks thereafter.

(e): LDH, β2-microglobuline, ALT, AST, Bilirubine, Creatinine at baseline within 2 weeks before administration of first cycle of induction in case of randomization for induction or within 2 weeks before administration of first maintenance cycle in case of direct randomization in maintenance.
LDH, ALT, AST, Creatinine for midterm and end of induction evaluations;
Creatinine and creatinine clearance before randomization for maintenance;
ALT, total bilirubin, creatinin at Day 1 of cycle 1, then every 4 weeks for 16 weeks, then every 12 weeks thereafter.
LDH has to be performed for each response evaluation and for each follow-up visits.

(f): Within 6 weeks before randomization (i.e. before randomization for induction or before direct randomization for maintenance).

(g): No sample for MRD evaluation has to be sent to reference biologist before signature of specific informed consent.
A baseline: peripheral blood (PB) and bone marrow (BM) aspirate. Bone marrow sampling is not mandatory for MRD purpose only: If a bone marrow aspirate for staging has been performed before signature of informed consent specific for MRD sample collection and analyses, only blood for MRD will be collected, and a new bone marrow aspiration is not necessary specifically for MRD analyses.
Induction at midterm evaluation: PB.
Induction at end of induction evaluation: PB and BM.
During maintenance and follow-up: PB every 6 months and bone marrow in yearly intervals until 36 months of follow-up or progression.

(h): Mandatory at baseline then if clinically indicated

(i): SPM will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. 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 and including the follow-up period of 3 years. Events of SPM 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 eCRF and subject’s source documents. Documentation on 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.).

(j): these examinations concerned only patients randomized directly for maintenance treatment from 04/11/2013 to 04/05/2018 when they achieved partial response after 6 to 8 cycles of RCHOP given outside the protocol

20.3 **Appendix C: Ann Arbor staging**

- **Stage I:**
  - I: Involvement of a single lymph node region
  - IE: Localized involvement of a single extra-lymphatic organ or site.
- **Stage II:**
  - II: Involvement of 2 or more lymph node regions on the same side of the diaphragm
  - IIE: Localized involvement of a single associated extra-lymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm
- **Stage III:**
  - III: Involvement of lymph node regions on both sides of the diaphragm
  - IIIE: Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site
  - IIIS: Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen
  - IIIS+E: Both IIIS+IIIE
- **Stage IV:**
  - IV: Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement

    IVE: Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Source: American Joint Committee on Cancer. Non-Hodgkin's lymphoma. In: AJCC Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997:289-294.

20.4 **Appendix D: Body Surface Area calculation**

The algorithm to be used in this study is Mosteller formula (1987):

BSA = √ [(Height (cm) x Weight (kg))/3600]

Source: Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med. 1987 Oct 22; 317(17):1098

20.5 **Appendix E: Performance Status Criteria**

The following table presents the ECOG performance status scale:

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

20.6 **Appendix F: MIPI**

MIPI Score = 0.03535 X age (years)

+ 0.6978 (if ECOG > 1, otherwise 0)

+ 1.367 X $\log_{10}$(LDH/ULN)

+ 0.9393 X $\log_{10}$(WBC count per 10^{-6} L)

ECOG: ECOG performance status (see Appendix E), LDH: lactate dehydrogenase, $\log_{10}$: logarithm with respect to base 10, MIPI: Mantle Cell Lymphoma International Prognostic Index, ULN: upper limit of the normal range, LDH/ULN: LDH divided by ULN, WBC: white blood cell.

All parameters are evaluated at baseline, i.e. after diagnosis and before randomization for induction.

Risk groups are defined by:

MIPI risk group	**MIPI score**
Low risk	< 5.7
Intermediate risk	≥ 5.7 and < 6.2
High risk	≥ 6.2

Source: Hoster E, Dreyling M, Klapper W, Gisselbrecht C, Van Hoof A, Kluin-Nelemans HC, Pfreundschuh M, Reiser M, Metzner B, Einsele H, Peter N, Jung W, Wörmann B, Ludwig WD, Dührsen U, Eimermacher H, Wandt H, Hasford J, Hiddemann W, and Unterhalt M. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008; 111:558-565

20.7 **Appendix G: IWG Response criteria for NHL (Cheson 1999)**

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	**Normal**	**Normal**	**Normal**	**Normal**
CRu	**Normal**	**Normal**	**Normal**	**Indeterminate**
	Normal	**Normal**	**>75% decrease**	**Normal or indeterminate**
PR	**Normal**	**Normal**	**Normal**	**Positive**
	Normal	**≥50% decrease**	**≥50% decrease**	**Irrelevant**
	Decrease in liver/spleen	**≥50% decrease**	**≥50% decrease**	**Irrelevant**
Relapse/PD	**Enlarging liver/spleen; new sites**	**New or increased**	**New or increased**	**Reappearance**

CR = complete remission; CRu = complete remission unconfirmed; PR = partial remission; PD = progressive disease

Stable Disease (SD)

Stable disease is defined as less than a PR but not progressive disease.

20.8 Appendix I: Lenalidomide Pregnancy Prevention Plan for subjects in Clinical Trials

The Pregnancy Prevention Plan (PPP) applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1. The Lenalidomide Risks of Foetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 2) provides the following information:

- Potential risks to the foetus associated with lenalidomide exposure
- Definition of female of childbearing potential (FCBP)/female not of childbearing potential (FNCBP)
- Requirements for counseling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
- Acceptable birth control methods for male subjects receiving lenalidomide in the study

2. The Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 3 and Section 4 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject records for each dispensation.

3. The Lenalidomide Information Sheet (Section 5) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

2. LENALIDOMIDE RISKS OF FOETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

2.1. Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo-foetal development study in animals indicated that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

2.1.1. Definition of Females of Childbearing Potential

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

FCBP are excluded from this protocol.

2.1.2. Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

2.2. Counseling

2.2.1. Females Not of Childbearing Potential

For a FNCBP, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

2.2.2. Males

Traces of lenalidomide have been found in semen. Male subjects taking lenalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

2.3. Contraception

2.3.1. Male Subjects:

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.4. Pregnancy Precautions for Lenalidomide Use

2.4.1. Before Starting Lenalidomide

2.4.1.1. Male Subjects:

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

2.4.2. During and After Study Participation

2.4.2.1. Male Subjects:

- Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg

calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide, the Investigator must be notified immediately.

2.4.3. Additional precautions

- Subjects should be instructed to never give lenalidomide to another person
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide.

3. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR FEMALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/ mm /yyyy)

Check one risk category:

☐ Not FCBP (Female not of childbearing potential): a female who: 1) has undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has been naturally postmenopausal for at least 24 consecutive months

FCBP are excluded from this protocol.

3.1. Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled subject regarding the following:

☐ Potential risk of foetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.

☐ The subject has not and will never share lenalidomide with anyone else.

☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____ (dd/mm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

4. LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT FOR MALE SUBJECTS

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/ mm /yyyy)

1. I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.

- ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

- ☐ The subject confirmed that he has not impregnated his female partner while in the study.

- ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.

- ☐ The subject has not and will never share lenalidomide with anyone else.

- ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking lenalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of lenalidomide.

- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.

- ☐ The subject has not and will not break, chew, or open lenalidomide capsules at any point.

- ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject.

Do Not Dispense Lenalidomide if:

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

5. Lenalidomide Information Sheet

For subjects enrolled in clinical research studies

Please read this lenalidomide information sheet before you start taking study drug and each time you get a new supply. This lenalidomide information sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about lenalidomide?

1. **Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to lenalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

A small amount of lenalidomide is found in human semen. The risk to an unborn baby in females whose male partner is receiving lenalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking lenalidomide
    - During breaks (dose interruptions) of lenalidomide
    - For at least 28 days after the last dose of lenalidomide
- **Male subjects should not donate sperm or semen** while taking lenalidomide during breaks (dose interruptions) and for at least 28 days the last dose of lenalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. **All subjects:**

- **Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take lenalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of lenalidomide.
- **Do not break, chew, or open lenalidomide capsules at any point.**
- You will get no more than a 28-day supply of lenalidomide at one time.
- Return unused lenalidomidecapsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

20.9 **Appendix J: Review of Pathological Samples**

General principles and organization of the pathological review:

The MCL R2 elderly study requires a histological review of all cases included in the trial at diagnosis. Histological criteria of inclusion and exclusion have been detailed in the current protocol. Histological review requires both morphology and immuno-histochemistry. In addition, a tissue collection will be organized to allow production of tissue-arrays and to optimize collection and conservation of frozen tissue.
The review process will be by the national reference pathology institute. Each centre should send the material (paraffin blocks and/ or slides) of their cases directly to the national reference pathology institute.

Practical aspects of the pathology review:

- Information on patient randomization

At patient enrollment, the investigator is requested to fax to LYSARC registration centre a pathological form with a copy of the histopathological report on which the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as the bone marrow report when possible. In the case where no histopathological report is available, the pathological form with the name and address of the pathologist can be faxed. This procedure is set up to optimize tracing of the samples.

At reception, the LYSARC registration center will fax the inclusion form with the pathological reports to the designated national pathological coordinator.

- Sample request

At reception of the pathological report and inclusion form, the designated pathological coordinator will contact the initial pathologist and send:

- a copy of the pathological form or the histo-pathological report
- an explanatory letter describing the importance of the ancillary genomic and tissue micro-arrays projects and requesting:
  - the paraffin block from the formalin fixed tumor sample that was used to set the diagnosis. In cases where the block no longer contains tumor material, 10 unstained Superfrost+ slides or stained slides could be sent to the Institute (stained slides will be returned as soon as the review is completed.)
  - a copy of the pathological report if it was not obtained before
  - a copy of the bone marrow pathological report.
  - to notify the Institute of the presence of frozen tissue from this tumor.

All these requirements (excluding frozen tissue) will be sent to the national pathology institutes (see table in section 3.3).

Tissue microarray (TMA) construction: For tissue microarray construction, a slide stained with hematoxylin and eosin will be prepared from each formalin-fixed paraffin donor block, and two or three tissue cylinders representative of tumor regions will be punched and transferred into a recipient paraffin block following a defined design. Reactive lymphoid tissues will be also included in the TMA blocks, as controls.

Review: For the review process, routinely stained sections will be obtained and an appropriate panel of antibodies according to morphological aspects will be applied. A review of all the national cases will be organized by the national reference pathologist or a designated substitute.

Diagnosis will be assigned to each case according to the WHO-classification from 2008. In addition a joint review by all national reference pathologists will be performed on a yearly basis. The following cases will be included in the joint review:

- Diagnosis other than MCL according to national reference pathologists review.
- Uncertain diagnosis for any reason according to national reference pathologists review.
- Rare variants of MCL (e.g. Sox11 negative MCL, cyclin D1 negative MCL) according to national reference pathologists review.

Reporting and bio-banking: The review pathologists for MCL R2 elderly Study will send to the study site clinician and the initial pathologist that submitted the case for review its review conclusions.

In addition, results of all the national reference reviews will be sent to the study pathologist coordinator and to the sponsor on a yearly basis in tabular format. The results of the yearly joint meeting will also be reported to the sponsor and – if deviating from the national pathologist results also to study site pathologist and pathology centre that submitted the case for review.

The block will be returned to the pathologist upon request by the site pathologist and/or according to national law. In any other case, the block remains at the national reference pathologist with the initial pathologist who could at any time ask for this block to be returned. In some cases, it might be possible that the block could be returned to a partner center from LYSA, in agreement with the initial pathologist who could at any time ask for this block to be returned.

20.10 Appendix K: MRD studies

The results of MRD will be not incorporated into the response evaluation nor influence the management of the patient.

CLINCAL AND TECHNICAL BACKGROUND

MRD detection by PCR-based amplification of antigen receptor rearrangements is an established tool for disease monitoring in ALL. Moreover it proved to be an effective outcome predictor also in mature B-cell tumors and particularly in MCL. The achievement of PCR-negativity in increasing proportions of patients heralded the clinical successes observed in the treatment of this neoplasm following the introduction of Rituximab and high-dose Ara-C containing programs. More importantly, several studies have clearly demonstrated that achievement of PCR-negativity confers significant PFS advantages to MCL patients {28, 33-35}. The results of these analyses are in line with the most recent study from the European Mantle Cell lymphoma Network reporting the largest MRD analysis so far conducted in MCL. This analysis included patients involved in two large trials of the European Mantle Cell Lymphoma Network including 259 patients {29}. The results from this large analysis clearly indicate that molecular remission achievement acts as a major independent predictor of superior outcome in MCL. Based on the high predictive value of MRD, most current lymphoma trials now include PCR-analysis as additional outcome parameter.

MRD determination is usually performed using the IgH rearrangement and the t(11;14). Both these rearrangements provide stable and reliable tumour markers. Based on the published experience it is possible to obtain a molecular marker using the t(11;14) in approximately 30% of patients while the rate of success with the IgH rearrangement is greater than 80% {29}. Based on the combined used of these two methods the vast majority of patients (approximately 90%) can currently obtain a molecular marker suitable for MRD determination if an adequate diagnostic tissue is provided. In recent years to validate the MRD approach in MCL, the Euro-MRD group (previously known as European Study Group for Minimal Residual Disease) has conducted a multi-laboratory standardization process which has involved 11 laboratories across Europe {37}. This effort had led to the development of common guidelines for the conduction of the experiments and the interpretation of results ensuring the achievement of excellent levels of reliability and reproducibility among the participating labs. Thus MRD detection in MCL performed by a trained laboratory in accordance to the Euro-MRD indications might be considered a validated and standardized highly reproducible tool, perfectly suitable for application in the context of large international Phase III trials.

MRD PROCEDURE

The sample collection will be centralised and organised by the defined national referent biologist. For all patients bone marrow and peripheral samples will be obtained at diagnosis and at 11 subsequent time points in order to verify the impact of different therapeutic options on disease

clearance. Please note that bone marrow sampling at baseline is not mandatory for MRD purpose only: If a bone marrow aspirate for staging has been performed before signature of informed consent specific for MRD sample collection and analyses, only blood for MRD will be collected, and a new bone marrow aspiration is not necessary specifically for MRD analyses.

All patients will be screened for both IgH rearrangement and the t(11;14) according to published methods {27,38} in order to identify a patient-specific clonal marker by DNA sequencing of the individual lymphoma clone. Patient-specific primers and probes will be then generated for RQ-PCR-based MRD determination using diagnostic peripheral blood and bone marrow analysis prior to any treatment. If both markers will be obtained they will be both monitored. In this trial, the MRD status will be assessed using allele-specific quantitative PCR (RQ-PCR) according to the Euro-MRD Guidelines {37}. A prerequisite for establishment of an individual MRD assay is the flow-cytometric determination of lymphoma cell infiltration in the diagnostic peripheral blood or bone marrow samples or alternatively the availability of CD19 purified tumor cells at diagnosis. Only exceptionally DNA from diagnostic tumor tissue (formalin fixed paraffin embedded tumor block) will be used.

PERIPHERAL BLOOD AND BONE MARROW SAMPLES COLLECTION

Time points for sample collection for MRD analysis are:

	TIME POINTS	SAMPLES
INDUCTION PHASE	Prior treatment: for all patients before any treatment	30 ml EDTA Blood
		3-5 ml EDTA Bone marrow
	Midterm staging: after 4 cycle of induction	30 ml EDTA Blood
	End of induction treatment	30 ml EDTA Blood
		3-5 ml EDTA Bone marrow
MAINTENANCE PHASE	6 months of treatment	30 ml EDTA Blood
	12 months of treatment	30 ml EDTA Blood
		3-5 ml EDTA Bone marrow
	18 months of treatment	30 ml EDTA Blood
	End of maintenance treatment	30 ml EDTA Blood
		3-5 ml EDTA Bone marrow
FOLLOW-UP PHASE	6 months of follow-up	30 ml EDTA Blood
	12 months of follow-up	30 ml EDTA Blood
		3-5 ml EDTA Bone marrow
	18 months of follow-up	30 ml EDTA Blood
	24 months of follow-up	30 ml EDTA Blood
		3-5 ml EDTA Bone marrow
	36 months of follow-up	30 ml EDTA Blood

No samples will be sent after disease progression.

For Belgian centers, *8.5 mL blood and 3 to 5 mL bone marrow will be sent on Paxgene tube.*

20.11 **Appendix L: Safety reporting in the Netherlands**

This appendix is an addition to the procedures regarding safety reporting, as described in protocol chapter 12.

The appendix is only applicable to safety reporting in The Netherlands.

The appendix constitutes the following:

- Where reporting of SAE's to the Ethics Committee is required by national laws or regulations or by the procedures of the Ethics Committee, the HOVON Data Center will report those SAE's by means of a six-monthly SAE line listing.
- SUSAR reporting will continue as described in the protocol. The HOVON Data Center will report SUSARs to the Dutch Ethics Committee and Competent Authority through the "Toetsing online" web portal in compliance with national regulations.

Administrative note: after approval this document is to be filed with the protocol in the Trial Master File of the sponsor and with the protocol in the Investigator Trial File of sites in the Netherlands.

Certificat de signature

Identifiant d'enveloppe: C93D670FC66D45D69EB43DEDAE6F900B

État: Complété

Objet: Please sign with DocuSign : MCL_R2_elderly_protocol v6.1_20190624.pdf

Enveloppe source:

Nombres de pages du document: 93

Signatures: 4

Émetteur de l'enveloppe:

Nombre de pages du certificat: 5

Paraphe: 0

Emma Van Agthoven

LYSARC Centre Hospitalier Lyon Sud

Signature dirigée: Activé

Pavillon 6D Secteur Sainte Eugénie

Horodatage de l'enveloppe: Activé

Pierre-Benite, 69 69495

Fuseau horaire: (UTC+01:00) Bruxelles, Copenhague, Madrid, Paris

emma.van-agthoven@lysarc.org

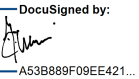
Adresse IP: 176.147.143.194

Suivi de dossier

État: Original
03/07/2019 15:02:13

Titulaire: Emma Van Agthoven
emma.van-agthoven@lysarc.org

Lieu: DocuSign

Événements de signataire	Signature	Horodatage
BILBAULT Pascal Pascal.Bilbault@lysarc.org Niveau de sécurité: E-mail, Authentification de compte (aucune)	DocuSigned by:  82549D050143400...	Envoyée: 03/07/2019 15:12:02 Consultée: 04/07/2019 15:55:02 Signée: 04/07/2019 15:55:50
	Sélection d'une signature : Style présélectionné En utilisant l'adresse IP: 195.28.207.50	
Divulgation relative aux Signatures et aux Dossiers électroniques: Accepté: 05/06/2019 16:42:36 ID: 3a6b3520-962b-4b35-a0ec-6830fe5d11cb		
Hanneke Kluin-Nelemans j.c.kluin@umcg.nl Niveau de sécurité: E-mail, Authentification de compte (aucune)	DocuSigned by:  A53B889F09EE421...	Envoyée: 03/07/2019 15:12:01 Consultée: 04/07/2019 22:23:47 Signée: 04/07/2019 22:25:06
	Sélection d'une signature : Écrit sur un appareil En utilisant l'adresse IP: 188.206.78.104 Signé à l'aide d'un périphérique mobile	
Divulgation relative aux Signatures et aux Dossiers électroniques: Accepté: 04/07/2019 22:23:47 ID: 6b3742a7-e65c-4130-ab7e-de937abe8c79		
Martin Dreyling Martin.Dreyling@med.uni-muenchen.de Niveau de sécurité: E-mail, Authentification de compte (aucune)	DocuSigned by:  9BE829AC54BA403...	Envoyée: 03/07/2019 15:12:01 Consultée: 04/07/2019 18:50:53 Signée: 04/07/2019 18:51:25
	Sélection d'une signature : Style présélectionné En utilisant l'adresse IP: 138.245.1.1	
Divulgation relative aux Signatures et aux Dossiers électroniques: Accepté: 04/07/2019 18:50:53 ID: 6218a113-3966-4008-8c7b-9121d89434da		

Événements de signataire	Signature	Horodatage
Vincent Ribrag vincent.ribrag@gustaveroussy.fr Niveau de sécurité: E-mail, Authentification de compte (aucune)	DocuSigned by: Vincent Ribrag 75B83D610D7148D... Sélection d'une signature : Style présélectionné En utilisant l'adresse IP: 194.167.111.61	Envoyée: 03/07/2019 15:12:01 Consultée: 03/07/2019 16:37:51 Signée: 03/07/2019 16:38:01

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Accepté: 03/07/2019 16:37:51
ID: bf899c15-ae26-4f71-8f87-0cd0f923eb9b

Evénements de signataire en personne	Signature	Horodatage

Événements de livraison de l'éditeur	État	Horodatage

Événements de livraison de l'agent	État	Horodatage

Événements de livraison intermédiaire	État	Horodatage

Événements de livraison certifiée	État	Horodatage

Événements de copie conforme	État	Horodatage
Christine Stephan christine.stephan@lysarc.org Niveau de sécurité: E-mail, Authentification de compte (aucune)	Copié	Envoyée: 03/07/2019 15:12:02
Jessica Batout jessica.batout.ext@lysarc.org Niveau de sécurité: E-mail, Authentification de compte (aucune)	Copié	Envoyée: 03/07/2019 15:12:02

Divulgation relative aux Signatures et aux Dossiers électroniques:
Non offert par DocuSign

Divulgation relative aux Signatures et aux Dossiers électroniques:
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Événements de témoins	Signature	Horodatage

Événements de notaire	Signature	Horodatage

Événements de résumé de l'enveloppe	État	Horodatages
Enveloppe envoyée	Haché/crypté	03/07/2019 15:12:02
Certifié livré	Sécurité vérifiée	04/07/2019 22:23:47
Signature finalisée	Sécurité vérifiée	04/07/2019 22:25:06
Complété	Sécurité vérifiée	04/07/2019 22:25:06

Événements de paiement	État	Horodatages

Divulgation relative aux Signatures et aux Dossiers électroniques

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electronically from us.

How to contact LYSARC:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

To contact us by email send messages to: marion.coadic@lysarc.org

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To let us know of a change in your e-mail address where we should send notices and disclosures electronically to you, you must send an email message to us at marion.coadic@lysarc.org and in the body of such request you must state: your previous e-mail address, your new e-mail address. We do not require any other information from you to change your email address..

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ii. send us an e-mail to marion.coadic@lysarc.org and in the body of such request you must state your e-mail, full name, US Postal Address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

Operating Systems:	Windows® 2000, Windows® XP, Windows Vista®; Mac OS® X
Browsers:	Final release versions of Internet Explorer® 6.0 or above (Windows only); Mozilla Firefox 2.0 or above (Windows and Mac); Safari™ 3.0 or above (Mac only)
PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	800 x 600 minimum
Enabled Security Settings:	Allow per session cookies

** These minimum requirements are subject to change. If these requirements change, you will be asked to re-accept the disclosure. Pre-release (e.g. beta) versions of operating systems and browsers are not supported.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please verify that you were able to read this electronic disclosure and that you also were able to print on paper or electronically save this page for your future reference and access or that you were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format on the terms and conditions described above, please let us know by clicking the 'I agree' button below.
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