A PHASE II STUDY OF CHLORAMBUCIL IN COMBINATION WITH SUBCUTANEOUS RITUXIMAB FOLLOWED BY MAINTENANCE THERAPY WITH SUBCUTANEOUS RITUXIMAB IN PATIENTS WITH EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT LYMPHOMA)

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STUDY ACKNOWLEDGEMENT

A signed copy of this page must be sent to the IELSG Central Office before patient enrollment.

Protocol IELSG 38: A phase II study of chlorambucil in combination with subcutaneous rituximab followed by maintenance therapy with subcutaneous rituximab in patients with extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)

As investigator for this study, I understand that this protocol contains information that is confidential and proprietary to IELSG. I have received and read the above mentioned protocol and agree that it contains all necessary details for carrying out the study as described; I will conduct this protocol as outlined therein.

I will provide copies of this protocol and access to all information furnished by IELSG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study. I agree to keep accurate records on all patients information (CRFs and Patients’ informed consent statement) and all other information collected during the study for a minimum period of 10 years.

I agree not to publish all or any part of the results of the study carried out under this protocol, without the prior written consent of IELSG.

All parties agree to ensure direct access to examine, analyze, verify and reproduce source data / documents, and reports from all trial related sites for the purpose of monitoring and auditing, and inspection by domestic and foreign regulatory authorities.

<table>
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* If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s).
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1 BACKGROUND AND STUDY RATIONALE

Extranodal marginal-zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) constitutes approximately 8% of non-Hodgkin’s lymphomas. The stomach is the most frequent site of localization, but MALT lymphomas can arise at any extranodal site [1-2]. Gastric MALT lymphoma is pathogenically linked to chronic Helicobacter Pylori (Hp) gastritis and treatment aimed at eradicating Hp results in lymphoma remission in the majority of patients. Recent data support the hypothesis that other infective agents may be involved in the development of MALT lymphomas arising in different sites. While antibiotics against Hp represent the standard first line treatment for patients with localized gastric MALT lymphoma, their role in the treatment of MALT lymphomas arising in other sites is under investigation. Moreover, despite abundant literature on the histological, clinical and biologic features there is no consensus on the optimal treatment of patients requiring subsequent treatment or those with extensive disease [1-3].

Both radiotherapy as well as systemic treatment modalities with chemotherapy and more recently targeted agents have been tested in patients with MALT lymphoma. Radiotherapy can result in long term disease control for localized lymphoma but is not always feasible [4-5]. Single agent or combination chemotherapy regimens have been also tested. Among trials conducted in the past, oral alkylating and purine analogs as single agents or in combination regimens agents have resulted in high rates of disease control [6-8]. The anti-CD20 monoclonal antibody Rituximab evaluated as single agent showed promising results in a phase II study in 27 patients with gastric MALT lymphoma (25 of them had failed previous treatments) with 77% of patients achieving an objective response [9]. The proteasome inhibitor bortezomib has been evaluated as a targeted treatment but its clinical utility seems limited [10]. More intensive combination regimens such as CHOP are likely active but comparatively toxic and should be limited to patients with histological transformation or with high tumor burden [2,11]. The above reported were however small phase II single arm trials, with short follow up and were not able to establish a commonly accepted standard treatment option for patients with MALT lymphomas.

The International Extranodal Lymphoma Study Group (IELSG) has conducted a randomized phase III study comparing chlorambucil alone versus chlorambucil + rituximab versus rituximab alone. This was the IELSG 19 trial NCT00210353 which is the largest prospective study ever conducted in patients with MALT lymphoma ineligible for or not responding to local treatment. In the first part of this study, conducted from January 2003 to October 2005, patients were randomly assigned in a 1:1 ratio to chlorambucil alone or to the combination of chlorambucil plus rituximab. After the enrollment of the initially planned 252 patients, the study protocol was amended and in October 2006 the trial was re-opened with a three arm design. The novel third arm included the rituximab alone and the randomization ratio was changed to 1:1:6 for a final total sample of 450 patients. The analysis of the first two arms has been recently concluded (Zucca et al, J Clin Oncol in press). Both treatments were well tolerated and no unexpected side effects were recorded. Two hundred and five patients (90%, 95%CI: 86-94%) had an objective response with no significant difference between the two arms (p=0.069). However, the addition of rituximab to chlorambucil resulted in improved remission quality (as measured by complete remission rate). The complete remission (CR) rate was significantly higher (p=0.025) in the combination arm (78%, 95%CI: 69-85%) compared to the chlorambucil only arm (65%, 95%CI: 55-73%). Moreover the combination resulted in a significantly prolonged event free survival (EFS), which was the primary endpoint of the study. In fact the 5 years-EFS in the patients treated with rituximab plus chlorambucil was significantly better (68%, 95%CI: 59-76%) than in those receiving chlorambucil alone (50%, 95% CI:41-60%), with a significant reduction of the risk of EFS events (HR, 0.52, 95%CI:0.34-0.79). The 5 year progression free survival was 67% (95% CI: 59-73) and 71% (95% CI:61-79%) for chlorambucil alone and the combination respectively but did not reach a statistical significance. (p=0.056). The 5 year OS was 89% (95% CI: 83-92%) with no statistical difference between the two treatment arms (p=0.0756).

As expected, the differences in EFS and response rate have not yet translated into improved OS. Both treatments were well tolerated and no unexpected side effects were recorded. In conclusion, the superior efficacy of rituximab in combination with chlorambucil was demonstrated in MALT lymphoma. These data (that will be updated when the third arm follow up is mature) should be taken as preliminary given the long
natural history of this disease. Nevertheless the improved EFS and the trend for an improved PFS with little added toxicity justify the front-line use of this regimen. While final results of this study are awaited with the inclusion of the third arm, a major question that remains open in the first line treatment of MALT lymphomas and has not been addressed in studies conducted so far is the usefulness of maintenance treatment specifically in the context of MALT lymphoma.

Rituximab is an anti-CD20 monoclonal antibody with a well-established efficacy in both aggressive and indolent B-cell non-Hodgkin lymphomas. It has demonstrated clinical benefits in combination with chemotherapy and as single agent, in the first line [12-16] and relapsed setting for induction of remission [17-18] and more recently as maintenance therapy after effective induction [19]. Several phase II or III studies have evaluated the usefulness of maintenance rituximab in patients with indolent lymphomas previously untreated or relapsed after previous treatments [2, 20-26]. While some differences in schedule and duration of maintenance, all these studies confirmed the clinical benefit (statistically significant improvements in EFS and PFS) for the patients that received maintenance therapy in comparison to those that did not. Maintenance rituximab was safe with no added short or long-term major side effects. Additionally, a systematic review and meta-analysis of 5 randomized trials that compared rituximab maintenance therapy with observation or no treatment at relapse comprising 985 adult patients with FL overall and each with adequate OS data [27]. Patients treated with maintenance rituximab had statistically significantly better OS than patients in the observation only arm or patients treated at relapse.

Maintenance rituximab has been now adopted as the standard of care in many institutions for patients with follicular lymphoma which represented the largest population of patients in the above reported trials. The maintenance treatment schedule differed among these trials: weekly for 4 consecutive weeks (four doses) every 6 months, or a single infusion of rituximab was administered every 2 – 3 months. The duration of treatment also varied, from 8 – 9 months to 2 years. Based on the results of the PRIMA study which included the higher number of patients, a 2 year maintenance duration is used in different countries in patients with follicular lymphoma [25].

In the present study a maintenance treatment with rituximab given every two months for two years will be studied specifically for patients with MALT lymphoma after an induction treatment with the combination of chlorambucil plus rituximab which, based on the results of the ILESG-19 trial, represents the standard of care for patients with MALT lymphoma. Additionally a new formulation of subcutaneous rituximab will be used in this study in order to avoid long infusion times and side effects related to the intravenous infusion. This new type of administration could significantly simplify treatment, shorten the administration to less than 10 minutes and improve patient satisfaction.

1.1 Subcutaneous (SC) Rituximab

1.1.1 SC Rituximab Physicochemical Properties and Clinical Formulation

Rituximab (MabThera®/Rituxan®) is a chimeric murine/human monoclonal antibody that binds to cluster of differentiation 20 (CD20) protein, a hydrophobic transmembrane protein present on the cell surface of pre-B- and mature B-lymphocytes. In particular, CD20 is present on malignant B cells in most patients with mature B-cell lymphoma and leukemia. Rituximab binds to CD20 on B-lymphocytes and eliminates these cells via a number of different possible mechanisms (antibody-dependent cellular cytotoxicity [ADCC], complement dependent cytotoxicity [CDC], apoptosis, and synergism with a variety of chemotherapeutic agents).

Rituximab is a highly purified antibody with an approximate molecular mass of 145 kDa. The chimeric anti-CD20 monoclonal antibody is a glycosylated IgG1-k immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab for SC administration is supplied as a ready-to-use liquid formulation with rituximab at a concentration of 120 mg/mL. The drug product contains 2,000 U/mL recombinant human hyaluronidase (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
IELSG recently on September 16, 2011, and following

However, an independent Data Monitoring Committee (iDMC) is reviewing, at least every 4 months, all intensity (CTC Grade 2). Five percent of events were classified as (Common Toxicity Criteria [CTC] Grade 1). Twenty

The majority of AARs (85%) and of AEs overall (68%) were classified as being of ‘mild’ intensity (Common Toxicity Criteria [CTC] Grade 1). Twenty-seven percent of AEs were classified as ‘moderate’ intensity (CTC Grade 2). Five percent of events were classified as ‘severe’ (CTC Grade 3), all of which resolved. As the clinical part of study BP22333 is still ongoing, safety data from Stage 2 are still accruing. However, an independent Data Monitoring Committee (iDMC) is reviewing, at least every 4 months, all safety data across the three rituximab SC studies in the clinical development plan. This iDMC met most recently on September 16, 2011, and following its safety review concluded that all ongoing SC studies should continue unchanged.

1.1.2 SC Rituximab Clinical Development in Oncology

SC administration of rituximab could become a simple alternative to the current practice of IV administration and is expected to reduce costs associated with IV administration (i.e., nursing costs for IV administration, infusion bed occupation, drug preparation, etc.). 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.

Until now, the standard 375 mg/m2 dose of rituximab in NHL and the 500 mg/m2 dose in CLL could only be administered by IV infusion because the volumes of these doses are too large for SC administration (approximately 70 mL in a 70 kg patient in the case of the 375 mg/m2 dose). Efforts have been made to concentrate the dose of rituximab IV; however, volumes still remain too large to be effectively administered via the SC route.

rHuPH20 is a recombinant human hyaluronidase enzyme that has been shown to increase the dispersion and absorption of co-administered drugs when given via the SC route. rHuPH20 when used as an excipient (permeation enhancer) in the formulation of rituximab, may improve the bioavailability of rituximab following SC administration and/or allow larger volumes to be safely administered via the SC route compared to a SC formulation in the absence of rHuPH20.

A first in human dose finding and pharmacokinetic study (BP22333) of SC rituximab was conducted in patients with FL in the maintenance setting. Based on this study a 1400 mg fixed dose was selected to result in a Ctrough that is not inferior to the 375 mg/m2 IV dose used in FL patients. This dose was confirmed in Stage 2 of the study by demonstrating mean CtroughSC/CtroughIV ratios of 1.24 [1.02;1.51] and 1.12 [0.86;1.45] for the q2m and q3m regimens, respectively. The AUCtauSC/AUCtauIV ratio was 1.35 for both q2m and q3m regimens.

Preliminary safety data from Stage 1 of study BP22333 are available for 108 patients treated with a single SC dose in cohorts B (375 mg/m2 SC, N = 34), C (625 mg/m2 SC, N = 34), and D (800 mg/m2 SC, N = 40). In addition, 16 patients were enrolled in cohort A (375 mg/m2 IV). Rituximab SC was generally well tolerated at all dose levels. No safety signals other than those expected with exposure to rituximab were detected.

As of September 28, 2010, a total of 157 adverse events (AEs) were reported in 65 patients (8/16 patients in cohort A [IV], 17/34 patients in cohort B, 19/34 patients in cohort C, and 21/40 patients in cohort D) [cohort A], hospitalization for transhuminal angioplasty [cohort C], major depression [cohort A, which was subsequently downgraded to a non-serious event] and angina pectoris [cohort D]). All were considered unrelated to study treatment. There have been no reports of serious or severe infections nor of cardiac events. There were no AEs leading to death, withdrawal or treatment discontinuation.

The most commonly documented AE was local ‘Administration-Associated Reactions’ (AARs; N = 30). AARs are all AEs occurring within 24 h of rituximab administration and considered related to study drug. AARs include infusion-related reactions, injection-site reactions, administration site conditions and all symptoms thereof. After AARs, the most common events were mild infections (N = 18) and gastrointestinal disorders (N = 17). The majority of AARs (85%) and of AEs overall (68%) were classified as being of ‘mild’ intensity (Common Toxicity Criteria [CTC] Grade 1). Twenty-seven percent of AEs were classified as ‘moderate’ intensity (CTC Grade 2). Five percent of events were classified as ‘severe’ (CTC Grade 3), all of which resolved. As the clinical part of study BP22333 is still ongoing, safety data from Stage 2 are still accruing. However, an independent Data Monitoring Committee (iDMC) is reviewing, at least every 4 months, all safety data across the three rituximab SC studies in the clinical development plan. This iDMC met most recently on September 16, 2011, and following its safety review concluded that all ongoing SC studies should continue unchanged.

pH 5.5. The drug product is a sterile, colorless to yellowish, clear to opalescent liquid supplied in colorless 10-mL vials (extractable volume 10 mL, 1200 mg antibody) and 15-mL vials (extractable volume 11.7 mL, 1400 mg antibody).

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The clinical development plan for rituximab SC is based on the following rationale: rituximab exerts its anti-lymphoma efficacy through binding to CD20. The specific and saturable interaction of antibodies with their receptor influences the PK disposition. Once target sites are saturated, linear pharmacokinetics are observed [28]. PK of the currently approved IV doses indicates that target sites are saturated [29]. It is expected that maximal clinical benefit is achieved at these concentration levels [30]. Therefore, it is hypothesized that attaining Ctrough with rituximab SC at least as high as with rituximab IV will provide comparable saturation of target sites and thus should result in comparable efficacy. Since rituximab is a life-saving compound with a wide therapeutic window, prevention of underdosing is of upmost importance.

The clinical development plan for rituximab SC is based on two ongoing phase Ib clinical pharmacology studies and an ongoing phase III clinical bridging study. An overview of the clinical development program comprising these four clinical studies is provided below.

1. Clinical pharmacology study (BP22333): an adaptive two-stage study (Stage 1 and Stage 2) for selecting a rituximab SC dose that achieves non-inferior trough concentrations compared to those of rituximab IV, and comparing exposure and safety for the IV and SC formulations in patients with FL (maintenance setting, IV dose: 375 mg/m²).

2. Clinical bridging study (BO22334): a phase III study evaluating efficacy, safety and pharmacokinetics of the SC formulation of rituximab in comparison to standard rituximab IV in patients with previously untreated FL (induction and maintenance setting).

3. Clinical pharmacology study (BO25341): an adaptive two-part phase Ib study (Part 1 and 2) for selecting and confirming a rituximab SC dose that achieves non-inferior trough concentrations to that of rituximab IV in the CLL setting (IV dose: 500 mg/m²).

4. Phase IV randomized clinical study (MO25455) was initiated to evaluate the benefit of maintenance therapy with rituximab SC compared with observation only in patients with relapsed or refractory indolent NHL who completed and responded to rituximab-based immunochemotherapy induction and an initial two years of maintenance therapy with rituximab SC.
2. OBJECTIVES OF THE TRIAL

2.1 Objectives

Aim of the study is to assess the therapeutic safety and activity of the combination of Chlorambucil and Rituximab given for 6 months, followed by 2 years maintenance treatment with subcutaneous Rituximab alone in MALT lymphomas.

2.2 Endpoints

2.2.1 Primary Endpoint (on which the sample size is calculated)

Complete Remission rate at 6 months.

2.2.2 Secondary Endpoints

- Response rate (Complete and partial remission rates) for all patients;
- Progression-free-survival (PFS) (any case)
- Event-free-survival (EFS) at 5 years for all patients;
- Overall survival for all patients;
- Response duration for responder patients;
- Acute and long-term toxicity
3 TRIAL DESIGN

**SCREENING AND REGISTRATION**

**PART A (Induction phase I)**

**Chlorambucil** 6 mg/m² daily p.o for 42 consecutive days (weeks 1-6)

**Rituximab** 375 mg/m² iv on days 1, 8, 15 and 22 (day 1 of weeks 1, 2, 3, 4)

**RESTAGING** (week 7-8)

**RESPONDER PATIENTS - CR, PR, SD**

**OFF TRIAL**

Follow up for survival data

**PART B (Induction phase II)**

Starting d56

**Chlorambucil** 6 mg/m² daily p.o for 14 consecutive days (d1-14) every 28 days 4 cycles

**Rituximab** 1400 mg sc on day 1 every 28 days for 4 cycles (4 doses on days 56, 84, 112 and 140)

**RESTAGING** (week 25)

**RESPONDER PATIENTS - CR, PR, SD**

**OFF TRIAL**

Follow up for survival data

**PART C (Maintenance phase)**

Starting 8-12 weeks from the completion of part B

**Rituximab** 1400 mg sc every 2 months for 6 injections (1 year)

**RESTAGING** (after 1 year)

**RESPONDER PATIENTS - CR, PR, SD**

**OFF TRIAL**

Follow up for survival data

**FINAL RESTAGING**

**RESPONDER PATIENTS - CR, PR, SD**

Follow-up every 4 months for 2 years, then every 6 months for 3 years and then annually for 10 years from study entry
4. TRIAL DURATION AND TERMINATION TIMELINES

The inclusion of patients is planned to start in Q4 2012 and will stop after the inclusion of 112 patients, which is expected in Q4 2014. End of trial treatment (last patient, last visit) is expected for Q4 2019. All patients will be followed up for 10 years from study entry.
5. **PATIENT SELECTION CRITERIA**

5.1 **Inclusion Criteria**

To be eligible for inclusion in this trial, patients **must fulfill all the following criteria:**

1. Histologically proven diagnosis of CD20-positive marginal zone B-cell lymphoma of MALT type either de novo, or relapsed following **local** therapy (including surgery, radiotherapy and antibiotics for H. pylori-positive gastric lymphoma) arisen at any extranodal site

1.1 The following patients with gastric MALT Lymphoma can be entered:
   
   a. H. pylori-negative cases, either de novo (non pre-treated) or at relapse following local therapy (i.e., surgery, radiotherapy or antibiotics).
   b. H. pylori-positive cases at diagnosis, who failed antibiotic therapy, including
      * Patients with clinical (endoscopic) and histological evidence of disease progression at any time post H. pylori eradication
      * Stable disease with persistent lymphoma at ≥ 1 year post H. pylori eradication
      * Relapse (without H. pylori re-infection), after a remission
      * Patients who failed either first line antibiotics or further local treatment (surgery or radiotherapy)

1.2 Similar consideration may be applied to patients with ocular adnexal lymphoma treated with antibiotics.

2. Measurable or evaluable disease. Measurable disease in at least two perpendicular dimensions on an imaging scan is defined as: lymph node or nodal mass bi-dimensional measurement with > 1.5 cm in longest transverse diameter or the short diameter must measure > 10 mm regardless of the longest transverse diameter.

3. Any stage (Ann Arbor I-IV) (see Appendix A)

4. Age ≥ 18

5. Life expectancy of at least 1 year

6. ECOG performance status 0-2 (see Appendix B)

7. Adequate bone marrow function (WBC >3.0x10^9/L, ANC >1.5x10^9/L, PLT >100x10^9/L), unless due to lymphoma involvement

8. Adequate kidney (serum creatinine <1,5x upper normal) and liver function (ASAT/ALAT <2,5 upper normal, total bilirubin <2,5x upper normal), unless due to lymphoma involvement

9. For women of childbearing potential only: negative serum pregnancy test done within 7 days prior to study drugs administration or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first study drugs administration

10. Fertile male or female patients of childbearing potential and their partners must use two forms of contraception during the study and for at least 12 months after the last dose of subcutaneous rituximab.

   For appropriate methods of contraception considered acceptable, see Appendix C. Should a woman become pregnant or suspect she is pregnant while she or her partner are participating in this study and for 12 months after study participation, the patient should inform the treating physician immediately.

Female patients of **childbearing potential** are defined as follows:

* Pre-menopausal women (patients with regular menstruation, patients after menarche with amenorrhea or irregular cycles, patients using a contraceptive method that precludes withdrawal bleeding
* Women who have had tubal ligation
Female patients may be considered to NOT be of childbearing potential for the following reasons:

- The patient has undergone total abdominal hysterectomy with bilateral salpingo-oophorectomy or bilateral oophorectomy
- The patient is medically confirmed to be menopausal (no menstrual period) for 24 consecutive months

11. Ability to understand and the willingness to sign a written informed consent document

5.2 Exclusion Criteria

1. Evidence of histologic transformation to a high grade lymphoma
2. Prior diagnosis of neoplasm within 5 years, except cervical intraepithelial neoplasia type 1 (CIN1) or localized non-melanomatous skin cancer
3. Prior chemotherapy
4. Prior immunotherapy with any anti-CD20 monoclonal antibody
5. Prior radiotherapy in the last 6 weeks
6. Use of corticosteroids during the last 28 days, unless prednisone chronically administered at a dose <20 mg/day for indications other than lymphoma or lymphoma-related symptoms
7. Evidence of clinically significant cardiac disease, as defined by history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within 12 months before study entry
8. Evidence of symptomatic central nervous system (CNS) disease
9. Evidence of active opportunistic infections
10. Known HIV infection
11. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBCab positive (regardless of HBsAb status), a HBV DNA test will be performed and if positive the subject will be excluded
12. Positive serology for hepatitis C (HC) defined as a positive test for HCAb, confirmed by HC RIBA immunoblot assay on the same sample.
13. Pregnant or lactating status
14. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
15. Fertile men or women of childbearing potential who do not agree to use a highly effective measure of contraception (such as oral contraceptives, intrauterine device or barrier method of contraception in conjunction with spermicidal jelly or surgically sterile) throughout the study and for at least 12 months after the last dose of subcutaneous rituximab
6. REGISTRATION PROCEDURE

Patients fulfilling the eligibility criteria and that have signed the informed consent will be centrally registered at the following website:

https://openclinica.eoc.ch/OpenClinica

Treatment should start within 7 days from registration.
7 TREATMENT PLAN

7.1 Treatment Plan

The study consists in three parts. In Part A (induction phase I) patients will be treated with Chlorambucil 6 mg/m² daily p.o for 42 consecutive days (weeks 1-6) in combination with intravenous Rituximab 375 mg/m² on days 1, 8, 15 and 22 (day 1 of weeks 1, 2, 3 and 4). After restaging (to be performed during weeks 7-8, i.e. between d42 and d55), responding patients (CR, PR) and those with stable disease will be treated in part B (induction phase II). In part B, starting from d56, (month 3) patients will receive Chlorambucil 6 mg/m² daily p.o for 14 consecutive days (d1-14) every 28 days for 4 cycles in combination with subcutaneous Rituximab 1400 mg on day 1 of each 28-day cycle. After restaging (to be performed at the end of month 6, week 25) responding patients and those with stable disease will be treated in part C. In Part C (maintenance phase) patients will be treated with subcutaneous Rituximab 1400 mg every two months for 2 years (in total 12 injections). During maintenance phase, CT scans will be performed every 12 months and patients responding or with stable disease will stay on treatment for a total of two years as above reported.

PART A: Induction phase I

Chlorambucil 6 mg/m² daily p.o for 42 consecutive days (weeks 1-6) in combination with Rituximab 375 mg/m² iv on day 1, 8, 15, 22 during the first month (4 weekly doses).

PART B: Induction phase II

Following restaging after induction phase I (to be performed in weeks 7-8), responder patients (CR, PR) and those with stable disease will be treated in induction phase II and will receive:

Chlorambucil 6 mg/m² daily p.o for 14 consecutive days every 28 days for 4 cycles (weeks 9-10, 13-14, 17-18, 21-22) in combination with subcutaneous Rituximab 1400 mg on day 1 of each 28-day cycle (day 1 of w9, w13, w17 and w21).
PART C: Maintenance phase

1 injection every 2 months for 2 years (total 12 injections)

After restaging (to be performed at the end of month 6, w25) responding patients and those with stable disease will be treated with subcutaneous Rituximab 1400mg every two months for 2 years (in total 12 injections). Maintenance must start 8-12 weeks after the completion of the induction phase II. During maintenance phase, CT scans will be performed every 12 months and patients responding or with stable disease will stay on treatment for a total of two years as above reported.

7.2 Criteria for Withdrawal from Study

Patients will be withdrawn from the study when any of the criteria listed below applies and will be transferred to the follow-up phase:

• progressive disease
• symptomatic deterioration
• unacceptable toxicity
• patient refusal
• General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
• protocol treatment has to be delayed for more than 2 weeks during part A and B and for more than 4 weeks during part C of the study
• patient becomes pregnant

Patients removed from the study for progressive disease will be followed up for survival data and for information on further therapies. No trial-specific assessments will be performed after progression.

7.3 Concomitant Medications and Not Permitted Treatments

Supportive therapy

Use of G-CSF is recommended in case of Grade 3-4 neutropenia. Antimicrobial prophylaxis including the administration of antibiotics, antiviral, antifungine, and/or anti-pneumocystic drugs is allowed and should follow institutional guidelines.

Not permitted treatments

The following treatments are prohibited during study treatment:

• Investigational or unlicensed/unapproved agents of any type;
• Other concomitant anti-tumour agents not defined in this protocol as study treatment, including lymphoma-therapeutic doses of glucocorticosteroids.

Patients receiving any of the prohibited therapies will be discontinued and followed for survival. Patients should not receive long-term treatment (> 1 month) with corticosteroids other than intermittent dexamethasone to control or prevent nausea or vomiting, or corticosteroids for non-infective exacerbations of asthma or respiratory disease. Non-steroidal hormones administered for non-lymphoma-related conditions (e.g. insulin for diabetes) are permitted.

It is recommended that any course of immunization for patients should be completed at least 4 weeks before starting rituximab Induction and patients should not receive any vaccinations that contain live or attenuated organisms during the study.
8 STUDY DRUGS

8.1 Drug Supply

Chlorambucil is considered standard treatment, it is commercially available worldwide and will be provided by each participating institute. The lot number of chlorambucil used in the study must be documented in the CRFs.

Rituximab (Mabthera®) intravenous and subcutaneous will be supplied by F.Hoffmann La Roche Ltd. Vials and the packaging containing vials will be labeled according to the Good Manufacturing Guidelines and local requirements.

8.2 Preparation and Administration

8.2.1 Chlorambucil

Chlorambucil comes as a tablet of 2mg to take by mouth. It should be taken at the same time every day on an empty stomach. The number of tablets will be calculated on the dose of 6 mg/m² rounded to nearest 2 mg.

8.2.2 Intravenous Rituximab

The qualified individual responsible for dispensing the study drug will prepare the correct dose. This individual will write the date dispensed and patient number on the study drug vial label and on the Drug Accountability Record. This individual will also record the study drug batch or lot number received by each patient during the study.

Patients receiving IV rituximab will be administered a dose of 375 mg/m². The appropriate amount of solution to be withdrawn from the vial will be calculated as follows: Volume (mL) = BSA (m²) x dose (375 mg/m²) / concentration of reconstituted solution mg/mL (100 mg/10 mL and/or 500 mg/50 mL)

See table below for recommended rate of administration of the first and subsequent infusions of intravenous Rituximab.

The prepared IV rituximab solution should be administered as an IV infusion through a dedicated line. It should not be administered as an IV push or bolus. Patients should be closely monitored for the onset of cytokine release syndrome. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have the infusion interrupted immediately. Patients should then be evaluated for evidence of TLS including appropriate laboratory tests and for pulmonary infiltration with a chest x-ray. In all patients, the infusion should not be restarted until complete resolution of all symptoms and normalization of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate IRRs usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms. Rituximab will be administered  IV in an outpatient setting if possible.
### Administration of first and subsequent infusions of intravenous Rituximab

This table represents a guideline that can be used for the first and subsequent infusion of intravenous rituximab. However institutional policies may be used if slightly different form the table below.

<table>
<thead>
<tr>
<th>First infusion</th>
<th>Subsequent infusions</th>
</tr>
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<tbody>
<tr>
<td>• Begin infusion at an initial rate of 50 mg/hr.</td>
<td>• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/hr and follow instructions for the first infusion.</td>
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<tr>
<td>• If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.</td>
<td>• If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hr), begin the infusion at a rate of 100 mg/hr.</td>
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<tr>
<td>• If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).</td>
<td>• If no infusion reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.</td>
</tr>
<tr>
<td>If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).</td>
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### Premedication before each administration of rituximab

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

- 1000 mg of paracetamol (acetaminophen)
- 50-100 mg diphenhydramine hydrochloride or alternative antihistamine.

Institutions should follow their standard premedication procedures regarding anti-emetics and hydration.

### 8.2.3 Subcutaneous Rituximab

Patients receiving SC rituximab 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 (a 25 gauge injection needle can also be used, according to local practice) will be inserted using sterile technique in the subcutaneous 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 subcutaneous 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.

The injection should be manually pushed at a flow rate of approximately 2 mL/min, therefore an administration volume of 11.7 mL should take approximately 5-6 minutes. If there is a request by the patient to interrupt the injection, the pressure on the syringe should initially be eased to alleviate the pain. If the pain is not alleviated the injection should be stopped and the patient should be asked when they are comfortable to resume the injection. The remaining content of the syringe should be administered at the same injection site.
**Premedication before each administration of rituximab**
In order to reduce the incidence and severity of infusion/injection-related reactions, it is recommended that all patients receive the following oral premedication administered 30-60 minutes prior to each rituximab administration:
- 1000 mg of paracetamol (acetaminophen)
- 50-100 mg diphenhydramine hydrochloride or alternative antihistamine.
Institutions should follow their standard premedication procedures regarding anti-emetics and hydration.

**8.3 Formulation, Packaging and Labeling**

**8.3.1 Intravenous Rituximab**
Rituximab for the IV administration will be provided as 500 mg/50 mL liquid filled vials with a nominal content of 10 mg/mL rituximab. The drug product contains sodium acetate (buffer), sodium chloride (tonicity adjustment), and polysorbate 80 (surfactant) in water for injection at a pH of 6.5. The drug product is a sterile, colourless to pale yellow liquid.

**8.3.2 Subcutaneous Rituximab**
Rituximab for the subcutaneous administration is supplied as a ready to use liquid formulation with a nominal content of 120 mg/mL rituximab in an 11.7 mL vial and must not be diluted prior to administration. The drug product contains 2,000 U/mL rHuPH20 (manufactured in a 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 drug product is a sterile, colorless to yellowish, clear to opalescent liquid in colourless 11.7 mL vials.

**8.4 Expected toxicity**

**8.4.1 Expected Adverse Events with Chlorambucil**
The main side effect of Chlorambucil is myelosuppression, usually reversible; gastrointestinal toxicity is observed rarely with nausea, diarrhoea and stomatitis.

Lung fibrosis (generally reversible), liver toxicity with jaundice and irreversible pancytopenias have been reported usually in association with drug overdose. Skin reactions (rash) have been reported, too.

Rare cases of secondary myeloid leukemia have been reported in patients treated with continuous long-term administration of the compound.

**8.4.2 Expected Adverse Events with Rituximab**
The main side effects of the drug could be the following.

**Likely**
- Fever > 38.5 °C
- Rigors, which can be severe
- Hypotension
- Bone and joint pain
Rare
• Allergic reactions, evolving in rare cases to anaphylactic shock
• Bronchospasm
• Tumor lysis syndrome with acute renal failure, particularly in patients with a WBC > 25 x 109/L
• Acute cardiac failure, particularly in patients with a previous history of cardiac disease
• Cytokine release syndrome with dyspnea

Rituximab has been associated with the following risks:

a. Infusion-Related Reactions
Patients treated with rituximab in combination with chemotherapy are at risk for IRRs. Fatal infusion reactions within 24 hours of rituximab infusion can occur; approximately 80% of fatal reactions occurred with the first infusion. Severe reactions to rituximab typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

b. Tumor Lysis Syndrome
Patients may be at risk for tumor lysis syndrome. With rituximab treatment, acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of rituximab in patients with NHL. A high number of circulating malignant cells (³ 25,000/mm3) or high tumor burden confers a greater risk of tumor lysis syndrome. For patients with evidence of tumor lysis syndrome, rituximab should be discontinued and the patient treated as clinically indicated.

c. Hepatitis B Exposure
Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of rituximab treatment and approximately 1 month after the last dose. Patients with chronic hepatitis B (hepatitis B surface antigen [HBsAg] positive) viral infection are at risk for reactivation and will be excluded from the study.

d. Progressive Multifocal Leukoencephalopathy
Rare cases of PML have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications. In a review of patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem-cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is extremely rare but should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem-cell transplant. Most cases of PML were diagnosed within 12 months of the patients’ last infusion of rituximab.

e. Cardiac Toxicity
Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life threatening.

f. Infection
Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following the completion of rituximab-based therapy. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, Varicella zoster virus, West Nile virus, and hepatitis B and C.

g. Severe Mucocutaneous Reactions
Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.
h. **Bowel Obstruction and Perforation**

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. In post-marketing reports of rituximab, the mean time to documented gastrointestinal perforation was 6 days (range, 1–77) in patients with NHL.

Safety data collected for patients exposed to rituximab SC during study BP22333 revealed no safety signals other than those expected with exposure to rituximab IV. The most commonly documented AE was local ‘Administration-Associated Reactions’ (AARs; N = 30). AARs are all AEs occurring within 24 h of rituximab administration and considered related to study drug. AARs include infusion related reactions, injection-site reactions, administration site conditions and all symptoms thereof.

**8.5 Dose Modifications**

Additional cycles of therapy may be administered provided that the patient meets the following criteria on Day 1 of each cycle:

- ANC > 1x10^9/L
- Platelets > 100x10^9/L
- Non-hematologic toxicity recovered to < grade 1 (or tolerable grade 2)
- No evidence of progressive disease

**Chlorambucil:** If any hematological toxicity of grade 3-4 occurs during the initial 6-week cycle of Chlorambucil or during the successive 2-week cycle, then the following cycle will be given with a 33% reduction of the dose (i.e. at 4 mg/m^2/d). If tolerated, subsequent dose increase (up to the prescribed dose) is recommended.

The administration of Chlorambucil should be delayed (1 week) in case of non-complete recovery from hematological toxicity of the previous course (i.e., ANC <1.0 G/l, PLT<100 G/l).

**Rituximab:** No dose reduction is allowed for Rituximab. If Chlorambucil has to be delayed (see above) then also Rituximab will be delayed to keep its administration on day 1 of each Chlorambucil cycle.
9 ADVERSE EVENTS (AE)

9.1 Definition of Adverse Event

Patients will be instructed by the investigator to report the occurrence of any adverse event.

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment.

An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

9.1.1 Drug – Adverse Event Relationship

The causality relationship of study drug to the adverse event will be assessed by the Investigator as either Yes or No.

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, the drug-event relationship should be assessed as Yes and the AE is defined as Adverse Reaction (AR).

The following criteria should be considered in order to assess the relationship as Yes:

• Reasonable temporal association with drug administration
• It may or may not have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
• Known response pattern to suspected drug
• Disappears or decreases on cessation or reduction in dose
• Reappears on re-challenge

The following criteria should be considered in order to assess the relationship as No:

• It does not follow a reasonable temporal sequence from administration of the drug
• It may readily have been produced by the patient’s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient
• It does not follow a known pattern of response to the suspected drug
• It does not reappear or worsen when the drug is re-administered
9.2 Definition of Serious Adverse Event

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:
• Results in death.
• Is life-threatening (Grade 4 according to CTCAE). Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form. (Exceptions: Grade 4 AEs not to be reported as SAEs: hematological toxicity and mucositis).
• Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
• Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons’ ability to conduct normal life functions.
• Is a congenital anomaly/birth defect.
• Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs (e.g., any new malignancy other than a relapse of the current tumor need to be reported as SAE).

9.2.1 Pregnancy and Exposure in Utero

In the case of pregnancy occurring during the course of the trial or within 90 days of discontinuing the study drug, the investigator must report the event to the IELSG operation office within the same timelines as a SAE and classify it as an ‘other medically significant condition’ on the SAE form.

This must be done irrespective or whether an adverse event has occurred and within 24 hours of awareness of pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induce termination of pregnancy).

The investigator will follow the subject until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify the IELSG Operation Office of the outcome within 5 days. The investigator will provide this information as a follow up. The reason(s) for an induced abortion must be specified. If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow up procedures for reporting serious adverse events and report the event to the IELSG Operation Office. In the case of a live birth, the “normality” of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of presumably normal infant must pass before an Exposure in Utero can be completed). The “normality” of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory finding are suggestive of a congenital abnormality.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:
• “Spontaneous abortion” includes miscarriage and missed abortion.
• All neonatal death that occurs within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational medication should also be reported.
9.2.2 Exposure During Lactation

An exposure during lactation occurs if an infant or child may have been exposed through breast milk to the study drug during breastfeeding by a female taking the study drug. Information regarding exposure during lactation is submitted to the IELSG Operation Office on a SAE Report Form within 24 hours of awareness of the exposure. Appropriate follow-up is required to determine the occurrence an outcome of any adverse event in the infant.

9.2.3 Serious Adverse Drug Reactions (SADRs)

All SAEs suspected to be related (see above 9.1.1) to the trial treatment are defined as Serious Adverse Drug Reactions (SADRs).

9.2.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All SAE that are:
• suspected related to the study drug (therefore SADRs) AND
• not described in the protocol or in reference documents (e.g. Investigators’ Brochure, Product Information/Summary of product characteristics) are defined as Suspected Unexpected Serious Adverse Reactions (SUSARs) and qualify for expedited reporting (see 9.3).

9.3 Procedures for AE, SAE and SUSAR Reporting

Patients will be instructed by the investigator to report the occurrence of any AE. The investigator assesses and records all AEs observed during the AE reporting period (i.e. from inclusion until 30 days after end of treatment).

AEs are coded with the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (see appendix D), and assigned a grade (from 1 = mild to 5 = death related to AE) as well as a relationship (suspected vs. not suspected) to trial treatment.

Any SAE must be reported within 24 hours (working days) by completing the “SAE Report form” of electronic CRFs (eCRFs).

eCRFs website: https://openclinica.eoc.ch/OpenClinica

SAE reporting period is from inclusion until 30 days after end of treatment.

The SAE outcome must be reported within 2 weeks after definitive assessment by completing the outcome section of the “SAE form”, (see eCRFs).

The physician responsible for patient care should organize any supplementary investigation of serious adverse events based on the clinical judgment on the likely causing factors. This means seeking a further opinion from a specialist in the field of the adverse event. If a patient dies, any post mortem finding including histopathology must be provided.

The sponsor (IELSG) shall be responsible for ensuring that any SAEs are appropriately reported to the relevant health authorities according to applicable laws and regulations in each country where the Study will be conducted and to perform any additional activities.
Reporting of SUSAR (suspected unexpected serious adverse reactions)

Events that fall into this category must be reported within 24 hours of occurrence using the SAE Report Form (see above) in the first instance. Then the reporter PI will be asked to fill in the appropriate CIOMS form (provided upon occurrence by IELSG Operation office).

It is the legal requirement of the sponsor to report SUSARs to the Competent Authorities and Ethics Committees (fatal or life-threatening within 7 days, nonfatal and non life-threatening within 15 days).
10  CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

10.1 Before Treatment Start

- Baseline (pre-study) evaluations are to be conducted within 7 days prior to start of protocol therapy. Imaging studies and endoscopic (and/or echoendoscopic examination when required) must be done ≤4 weeks prior to the start of therapy.
- In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.
- History, complete physical examination and vital signs (blood pressure, height, weight, resting heart rate) with measurement of all palpable disease.
- Bone marrow aspirate and biopsy recommended but not mandatory.
- Complete blood count (CBC) with differential white count.
- Serum creatinine, glucose, Na, K, ASAT, ALAT, alkaline phosphatase, gamma GT, total bilirubin, uric acid, LDH, beta2-microglobulin, and serum protein electrophoresis.
- HBV and HCV, serology.
- HIV serology.
- For women of childbearing potential only: pregnancy test within 7 days prior to study drugs administration (or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first study drugs administration).
- Baseline radiologic evaluation, within 1 month prior to start therapy (CT/MRI; Staging PET/CT is allowed in addition to CT scan).
- Endoscopic and/or echoendoscopic examination when required (e.g., stomach, intestine or lung localizations) with multiple random biopsies.
- Electrocardiogram (ECG).

10.2 During Treatment

- Full blood count with differential white count on weeks 1, 2, 3, 4, 6, 7 or 8 (interim restaging), 9, 11, 13, 15, 17, 19, 21, 23, 25 (end of induction). Every 2 months during the maintenance phase.
- Biochemistry: creatinine, uric acid, gamma GT, ASAT and ALAT on weeks 3, 5, 9, 13, 17, 21, and every 2 months during maintenance phase.
- Biochemistry at restaging (weeks 7-8, 25, after 1 year of maintenance, after 2 year of maintenance): creatinine, uric acid, gamma GT, ASAT and ALAT. LDH, beta2-microglobulin, serum protein electrophoresis (if abnormal before treatment) during weeks 7-8 (interim restaging), 25 (end of induction) and at the end of treatment.
- Repeat imaging studies of all disease parameters on weeks 7-8, 25, after 1 year of maintenance, after 2 year of maintenance.
- Repeat endoscopic examinations and biopsy (if disease parameters) on weeks 7-8, 25, after 1 year of maintenance, after 2 year of maintenance.
- Electrocardiogram (ECG), week 7 or 8, week 25, at the end of the first year of maintenance.
10.3 After the End of Treatment (Follow-up)

The follow-up controls should be assessed every 4 months for the first 2 years, then every 6 months for 3 years and then annually for 10 years from study entry and should include:

- Complete physical examination and vital signs (blood pressure, height, weight, resting heart rate) with measurement of all palpable disease.
- Full blood count with differential white count, serum creatinine, ASAT, ALAT, alkaline phosphatase, LDH, beta2-microglobulin, and serum protein electrophoresis.
- Imaging (eg. CT scan, chest X ray, abdominal ultrasound) and endoscopy as clinically indicated
- Repeat bone marrow aspirate and biopsy if involved at diagnosis
- Report on Adverse events if applicable
<table>
<thead>
<tr>
<th>SCREENING week</th>
<th>PART A - INDUCTION PHASE I week</th>
<th>PART B - INDUCTION PHASE II week</th>
<th>PART C - MAINTENANCE PHASE month</th>
<th>FOLLOW UP</th>
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</tr>
<tr>
<td>Adverse events reporting© X X X X X X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
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</tbody>
</table>

a. For women of childbearing potential only: pregnancy test within 7 days prior to study drugs administration (or within 14 days if with a confirmatory urine pregnancy test within 7 days prior to the first study drugs administration)
b. PE: Physical examination including vital signs (blood pressure, height, weight, resting heart rate) with measurement of all palpable disease.
c. Blood count with differential white count: hemoglobin, platelet count, white blood cell (WBC) count, neutrophils and lymphocytes percent differential count
d. Biochemistry:
   (X1) at baseline: serum glucose, creatinine, Na, K, uric acid, ASAT, ALAT, alkaline phosphatase, gamma-GT, total bilirubin, LDH, beta2-microglobulin, serum protein electrophoresis.
   (X2) on treatment: repeat only creatinine, uric acid, ASAT, ALAT, gamma-GT.
   (X3) at resting and on follow up: creatinine, uric acid, gamma GT, ASAT and ALAT. LDH, beta2-microglobulin, serum protein electrophoresis (if abnormal before treatment)
e. Standard HIV, HBV, HCV serology.
f. Bone marrow examination (recommended but not mandatory): including bone marrow biopsy and aspirate with immunophenotypic analysis. To be repeated at resting and during follow up if involved at diagnosis.
g. Imaging Baseline radiologic evaluation, within 1 month prior to start therapy (CT/MRI, Staging PET/CT is allowed in addition to CT scan, XRAY). Chest, abdomen and pelvis imaging are mandatory, head and neck when required. Other imaging examinations (echography, scintigraphic imaging) when required for special clinical conditions. Imaging studies of all disease parameters are to be repeated on weeks 7-8, 25, after 1 year of maintenance, after 2 year of maintenance; during follow up as clinically indicated.
h. Endoscopy: endoscopy or echoendoscopy examination when required, with multiple random biopsies. To be repeated on weeks 7-8, 25, after 1 year of maintenance, after 2 year of maintenance if disease parameter and as clinically indicated during follow-up
i. Adverse events must be collected from the time of informed consent signature, throughout the treatment period and up to and including 30 days post-study follow-up period. After discontinuation from treatment patients must be followed-up for any new adverse event for 30 calendar days. All SAEs must be reported within 24 hours. All AEs must be followed up until resolution unless in the opinion of the investigator the condition is unlikely to resolve due to the patient’s underlying disease.

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11  EFFICACY ASSESSMENTS

11.1 Definition of Efficacy Parameters

Complete response rate (CR) at the end of induction phase, defined according to the Cheson criteria [31] (Appendix E). For patients with gastric lymphomas histological response is evaluated according to GELA scoring system [32] (Appendix F)

12  STATISTICAL METHODS

12.1 Sample Size Calculation

This is a phase II, single arm, multicentric trial. Primary endpoint (on which the sample size is calculated) is the Complete Remission rate for all enrolled patients at the end of the induction phase II. Patients discontinuing the study at, or prior to, the end of induction phase I will be included in the analysis as non-responders. Based on the results of IELSG19 trial the complete remission rate in the Chlorambucil arm was 68% (95%CI:55%-73%) in comparison to 78% (95%CI:69%-85%) in the Chlorambucil + intravenous Rituximab arm.

In this trial we want to explore the combination of Chlorambucil with a different administration (subcutaneous) of Rituximab aiming to show that this new combination results in a complete remission rate that is higher than that of Chlorambucil alone and is at least as high as in the combination arm of the previous trial (that is therefore close to 78%). Therefore, we set a null hypothesis H0=65% and an alternate hypothesis H1=78%. A one sided test with α=0.05 would permit to reject the null hypothesis if the complete remission rate is higher than 74% with a power of 90%. The sample size required to test this hypothesis is 112 patients.

This sample size will also permit us to compare time related endpoints with the ones obtained in the IELSG 19 trial, thus providing information on the usefulness of maintenance with subcutaneous Rituximab. For instance, a 5yr-EFS of 68% (95% CI 59-76%) was observed in the combination arm of the IELSG 19 trial and if we were to show an improvement of 5yr-EFS to 85%, a two sided test with power 90% and a=0.05 would require a sample size of 66 patients.

This will be the first specifically dedicated study to MALT lymphoma addressing the maintenance treatment with rituximab.

12.2 Study Population

Three populations will be considered for the analysis, as follows:

- The Safety Evaluable (SE) population defined as all treated patients (i.e. eligible as decided at the time of registration that receives at least 1 dose of study treatment combination). An incorrect treatment schedule or drug administration or an early termination of treatment does not result in exclusion of patients from this population. Patients with major deviations from the eligibility criteria affecting safety or from the treatment schedule at cycle 1 for reasons other than toxicity may be presented in separate tables/listings.

- The Intention to Treat (ITT) population defined as the SE population (i.e. eligible as decided at the time of registration that receives at least 1 dose of study treatment). An incorrect treatment schedule or drug administration or an early termination of treatment does not result in exclusion of patients from this population. Patients with major deviations from the eligibility criteria affecting safety or from the treatment schedule at cycle 1 for reasons other than toxicity may be presented in separate tables/listings.
• The Efficacy Evaluable (EE) population defined as all treated patients, with no major deviations from the eligibility criteria affecting efficacy evaluation, for whom the tumor response could be evaluated at least once while on treatment. These patients should have received at least 2 cycles after treatment starts, unless disease progression occurs at cycle 1.

12.3 Analysis

All patients who receive at least one dose of any of the study drugs will be included in summary statistics, except for the analysis of study conduct and subject disposition for which all patients enrolled in the study will be displayed, even if not treated. Information will be provided concerning patient demographics, including baseline performance status, age and prior treatments.

12.3.1 Study Conduct and Subject Disposition

Patients satisfying the definition of the study populations will be tabulated and listed. The number of patients withdrawing from the study, not meeting the eligibility criteria, and who are considered protocol violators will also be described. Reasons why patients are excluded from any study population will be listed.

12.3.2 Baseline Characteristics and Treatment Group Comparability

Patient characteristics at study entry will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables.

12.3.3 Treatment Analysis

The number of cycles administered, actual and total doses administered, absolute and relative dose intensity, dose modifications, delays and omissions, as well as reasons for deviation from planned therapy and overall duration of treatment will be described.

12.3.4 Safety Analysis

Safety and tolerability analysis will be applied on the SE population.

Adverse events physical examination, vital signs, concomitant medication, laboratory and instrumental data will be considered for the safety analyses. Descriptive statistics will be provided for these variables.

Adverse events will be coded using MedDRA dictionary at the lowest level term and their severity graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4. Descriptive statistics will be provided. The analysis will focus on the events reported after the start of treatment (treatment emergent adverse events); the incidence of adverse event by treatment period (i.e. cycle1 and whole study period) will be calculated on a patient basis (i.e counting the number of patients). In this analysis, patients/cycles will be classified according to the worst severity grade experienced during the analyzed time-window. Drug related adverse events will be evaluated in the same way.

Specific subsets of AEs, such as serious AEs, AEs leading to treatment discontinuation, AEs leading to treatment modification/schedule change will be identified in patients data listings

Hematological and biochemical toxicity will be graded according to the NCI CTCAE v4 and will be described by means of shift tables, reporting the worst grade observed during the analyzed time-window (cycle1, all cycles) vs. baseline grade.
Nadir/Zenith values, time to nadir/zenith and time to recovery may be explored for selected haematological/biochemical variables. Summary statistics will be presented by study period (cycle1, cycles > 1, all cycles).

Previous and concomitant medication will be tabulated while other relevant safety data will be reported in listings

12.3.5 Efficacy Analysis

The main endpoint will be the complete remission rate (CRR).

**Complete Remission Rate (CRR)** Complete response rate (CR) at the end of induction phase, defined according to the Cheson criteria [31] (Appendix E). For patients with gastric lymphomas histological response is evaluated according to GELA scoring system [32] (Appendix F). A patient with unknown or missing response will be treated as a non-responder, i.e., the patient will be included in the denominator when calculating the percentage. Exact methods for calculated confidence intervals will be utilized.

**Duration of Response** is defined, for the subset of patients with a CR or PR, as the time from when criteria for response are first met until first documented relapse or progression or death due to any cause. If sample size permits, duration of response will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of patients who show a CR or PR are included in this summary.

**Time to Next Treatment** is defined as the time from the end of primary treatment until the institution of the next therapy. Time to Next Treatment will be summarized descriptively using Kaplan-Meier medians and quartiles.

**Event Free Survival**, for all patients, is defined as the interval between the time of entry onto trial and failure or death from any cause.

**Progression Free Survival** is defined as the time from the first treatment administration to documentation of disease progression, start of a new antitumor therapy or death (for any cause). Patients not known to have progressed or started a new antitumor therapy or died (for any cause) will be censored for PFS at the time of last tumor assessment.

**Overall Survival**, for all patients, is measured from entry onto trial until death from any cause.
13. ETHICAL

The IELSG will act as sponsor of this international multi-centre trial which will be conducted in accordance with the Declaration of Helsinki, the Guidelines of Good Clinical Practice issued by the International Conference on Harmonisation (ICH) and the appropriate regulatory requirement(s).

The IRB/EC of each participating center will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites with IRB/EC approval and competent authority acceptance.

Therefore before planning to enter any patients into this trial, the investigator has to make sure that his center has been authorized/activated. Copies of the approval letters will keep on file at the IELSG.

The investigator is responsible for ensuring that the clinical study is conducted in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

The patient’s consent to participate in the study must be obtained for all cases, after a written full explanation has been given of the treatment and before performance of any study-related activity. Patient Information Form and Informed Consent Forms must be approved by IELSG and must be finalized by the principal investigator in each country/institution following the requirements of the local Regulatory Authorities and ECs.

The right of a patient to refuse to participate without giving reasons must be respected.

After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol at any stage if it is felt to be in the patient’s best interests. The reason for giving such alternative treatment should be recorded and the patient should remain in the study for the purposes of follow-up and data analysis.

Similarly, the patient must remain free to withdraw consent at any time without giving reasons and without prejudicing further treatment.
14. QUALITY CONTROL AND QUALITY ASSURANCE

Several procedures guarantee quality of trial conduct:

• Reviews of protocol and forms according to standard operating procedures
• Requirements for principal investigators for participation: signed and dated CV and trial-specific agreement
• Validation of database and statistical analysis
• CRFs will be checked; queries will be issued in case of inconsistencies.
• Data review by the trial chair or a delegated person (all CRFs will be reviewed and checked on medical content)
• Safety monitoring
• An authorization list must be kept at the center
• Accountability of trial drugs
• The trial will be monitored
• Internal audit of the trial

Direct access to the original data

The investigator/institution should make available for direct access all requested trial-related records and should permit monitoring and auditing by the sponsor, and inspection by ethics committees and the appropriate regulatory authority(ies).

Monitoring

All source data must be accessible for auditing and monitoring. The trial will be monitored by personnel designated by the IELSG.

For this trial the expected average monitoring visit frequency is one visit for each site and one additional visit for selected centers depending on accrual. Usually before enrollment of the first patient, a trial initiation visit will take place. The objective of this visit is to train the local staff involved in the conduct of the trial (including sub-investigators, research nurse, clinical research coordinator, pharmacist), to describe the main features of the protocol, the use of the CRFs, the practicalities of the trial and to set up the trial-specific trial master file (TMF).

In case of queries, inadequate data quality or changes in staff, additional visits will be performed for further patients until acceptable data quality is again obtained.

Auditing and inspecting

IELSG can perform audits, as part of implementing quality assurance. The appointed auditor is independent of the clinical trials/systems.

Authorities have the right to perform inspections, and the IELSG has the right to perform on-site auditing during working hours upon reasonable prior notice.

Data protection and archiving

Patient confidentiality will be maintained according to applicable legislation. Patients must be informed of, and agree to, data transfer and handling, in accordance with data protection law.

Patient data will be pseudonymised: each patient in the study will be uniquely identified by a code which is a combination of 2-digit trial number, followed by 3-digit center number and 3-digit subject number.
The trial and the center numbers are assigned by IELSG Operation Office. Upon signing the informed consent form, a patient number is assigned to every single patient by the PI, using consecutive numbers (e.g. 001, 002, 003,...).

The decryption key ("subject identification log") must be kept in a safe place by the investigator, at the trial centre, and only made accessible to authorised and authenticated persons.

No tissue and/or blood samples will be sent abroad within this trial.

All information collected during the trial project must be stored correctly and for the appropriate length of time (at least 10 years).

**Patient diaries**

Patient diaries for Chlorambucil will be used during part A and B (induction phase I and II) of the trial. Investigators will check the entries in diaries for compliance and side effects in each visit. The diaries will be collected by the Investigator and will be archived at the end of part B.
15. PUBLICATION POLICY

The results of this study will be submitted for publication in peer reviewed journals and for presentation at appropriate scientific meetings.

IELSG wants to recognize the contributions of all individuals who take part in the preparation of the study, the analysis of data, including patients.

The study chair on the basis of the statistical analysis will write the final publication of the trial results.

The study chair should make the final decision regarding authorship and order of authors on a manuscript; this authors’ list should be approved by the Director of the IELSG Operation Office and by the President of the IELSG Board of Directors.

In principle, the study chair will be the first/last author of any publication and other contributors will be included as authors according to their input into the study:

• the investigators who have included more than 5% of the eligible patients in the trial by order of inclusion;
• the study statistician
• additional members who contribute significantly to study design, analysis, management of data, trial coordination, manuscript writing
• representatives of other disciplines (e.g., pathologists, molecular biologists and others)
• ideally, each otherwise unrepresented country or co-operative group, which have enrolled patients, should have the opportunity to include one author (this may be dealt with highly accruing sites)
• additional authors can be added (e.g., representatives of centers contributing significantly to the patient population of the study).

Anyhow, all the contributors who do not meet the criteria for authorship should be listed in an appendix to the manuscript or in the acknowledgments.

The acknowledgments’ list will include the names of all participating institutions together with the corresponding names of the principal investigators.

No publication can occur without agreement of the study chair, IELSG Operation Office, and Board of Directors. Case reports on therapeutic features involving patients registered in a IELSG trial are strongly discouraged. However, participating investigators may report their own experience on patients registered in this trial at scientific meetings or journals with permission of the IELSG and of the study chair without disclosing the overall results of the study. If this is foreseen, the investigator agrees to submit all their abstracts or manuscripts to the study chair and to the IELSG Operation Office prior to submission. This allows the sponsor and the study chair to ascertain that the communication will not undermine the value of the whole study and to provide comments based on information that may not be yet available to all the investigators; a written reply will then be sent by the study coordinator to the investigators, within 2 weeks.
16 REFERENCES


5. Thieblemont C, Berger F, Dumontet C, et al: Mucosa associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 95:802-6,


APPENDIX A

Ann Arbor staging - Cotswolds recommendations

Stage I: involvement of a single lymphatic region (I), or localized involvement of a single extralymphatic organ or site (IE).

Stage II: involvement of two or more lymphatic regions on the same side of diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions the same side of diaphragm (IIE).

Stage III: involvement of two or more lymphatic regions on both sides of diaphragm (III) which may also be accompanied either by localized involvement of an extralymphatic organ or site (IIIIE), or by involvement of the spleen (IIIS).

Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs or tissue, with or without associated lymph node involvement.

Bone marrow or liver involvement will always be considered as stage IV.

Lymphatic structures include lymph nodes, spleen, thymus, Waldeyer’s ring including tonsils. The lymphatic regions are defined according to Ann Arbor as (a) clinical enlargement of a node when alternative pathology may reasonably be ruled out (suspicious nodes should always be biopsied if treatment decisions are based on their involvement) ; and (b) enlargement on plain radiograph, CT scan, or lymphography.

Localized involvement of an extralymphatic site (extranodal site or E-lesion) is diagnosed when the involvement is small enough to be in principle accessible for curative radiotherapy (thereby excluding diffuse organ involvement corresponding to stage IV).

Criteria for “B” symptoms

The presence of (a) unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation and/or (b) unexplained, persistent, or recurrent fever with temperatures above 38°C during the previous month and/or (c) recurrent drenching night sweats during the previous months is denoted by the suffix letter ‘B’. ‘A’ indicates the absence of these symptoms.

Criteria for bulk disease

The bulk of palpable lymph nodes will be defined by the largest dimension (cm) of the single largest lymph node or conglomerate node mass in each region of involvement. A node or nodal mass must be 10 cm or greater to be recorded as "bulky".

A mediastinal mass will be defined as "bulky" on a postero-anterior chest radiograph, when the maximum width is equal or greater than one-third of the internal transverse diameter of the thorax at the T5-T6 level. The chest radiography should be taken with maximal inspiration in the upright position at a source-skin distance of 2 m.
**APPENDIX B**

**ECOG Performance Status Scale**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of working hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of working hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
Acceptable and Unacceptable Forms of Contraception for Women of Childbearing Potential

Women of childbearing potential are required to use two forms of acceptable contraception, including one barrier method starting 4 weeks prior to study entry, during participation in the study and for the 3 months following the last dose.

Female patients of childbearing age are defined as follows:

- Patients with regular menses
- Patients, after menarche with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had tubal ligation

Female patients may be considered to NOT be of childbearing potential for the following reasons:

- The patient has undergone total abdominal hysterectomy with bilateral salpingooophorectomy or bilateral oophorectomy
- The patient is medically confirmed to be menopausal (no menstrual period) for 24 consecutive months

Acceptable forms of contraception for women of childbearing potential:

**Primary Forms**
- Tubal ligation
- Partner’s vasectomy
- Intrauterine device
- Hormonal (combination birth control pills, skin patches, injections, implants, or vaginal ring)
- Barrier forms (always used with spermicide)

**Secondary Forms**
- Diaphragm
- Cervical cap
- Barrier form (used with or without spermicide)
- Male latex condom
- Vaginal sponge (contains spermicide)

Unacceptable forms of contraception for women of childbearing potential:

- Birth control pills without estrogen
- IUD progesterone T
- Female condom
- Natural family planning (i.e., rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Male patients must use a latex condom every time they have sex with a woman of child-bearing potential.
APPENDIX D

Common Terminology Criteria for Adverse Events (CTCAE)

VERSION 4.03

Toxicity Criteria

In the present study, toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Response definitions for clinical trial according to Cheson

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative</td>
<td>Not palpable, nodules disappeared</td>
<td>Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Variably FDG-avid or PET negative; regression to normal size on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes</td>
<td>≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Variably FDG-avid or PET negative; regression on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed</td>
<td>Any new lesion or increase by ≥ 50% of previously involved sites from nadir</td>
<td>Appearance of a new lesion(s) &gt; 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node &gt; 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy</td>
<td>&gt; 50% increase from nadir in the SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
<tr>
<td>disease or PD</td>
<td></td>
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Abbreviations: CR, complete remission; FDG, [18F] fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease
# GELA histological grading system for post-treatment evaluation of gastric MALT lymphoma

<table>
<thead>
<tr>
<th>Score</th>
<th>Lymphoid infiltrate</th>
<th>LEL</th>
<th>Stromal changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (complete histological remission)</td>
<td>Absent or scattered plasma cells and small lymphoid cells in the LP</td>
<td>Absent</td>
<td>Normal or empty LP and/or fibrosis</td>
</tr>
<tr>
<td>pMRD (probable minimal residual disease)</td>
<td>Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM</td>
<td>Absent</td>
<td>Empty LP and/or fibrosis</td>
</tr>
<tr>
<td>rRD (responding residual disease)</td>
<td>Dense, diffuse, or nodular extending around glands in the LP</td>
<td>Focal LEL or absent</td>
<td>Focal empty LP and/or fibrosis</td>
</tr>
<tr>
<td>NC (no change)</td>
<td>Dense, diffuse, or nodular</td>
<td>Present, “may be absent”</td>
<td>No changes</td>
</tr>
</tbody>
</table>

MM, muscularis mucosa; LP, lamina propria; SM, submucosa; LEL, lymphoepithelial lesions