ReBeL study: a randomized phase I/II trial of lenalidomide and rituximab with or without bendamustine in patients ≥ 18 years with relapsed follicular lymphoma

A HOVON/GLSG/NCRI study

PROTOCOL

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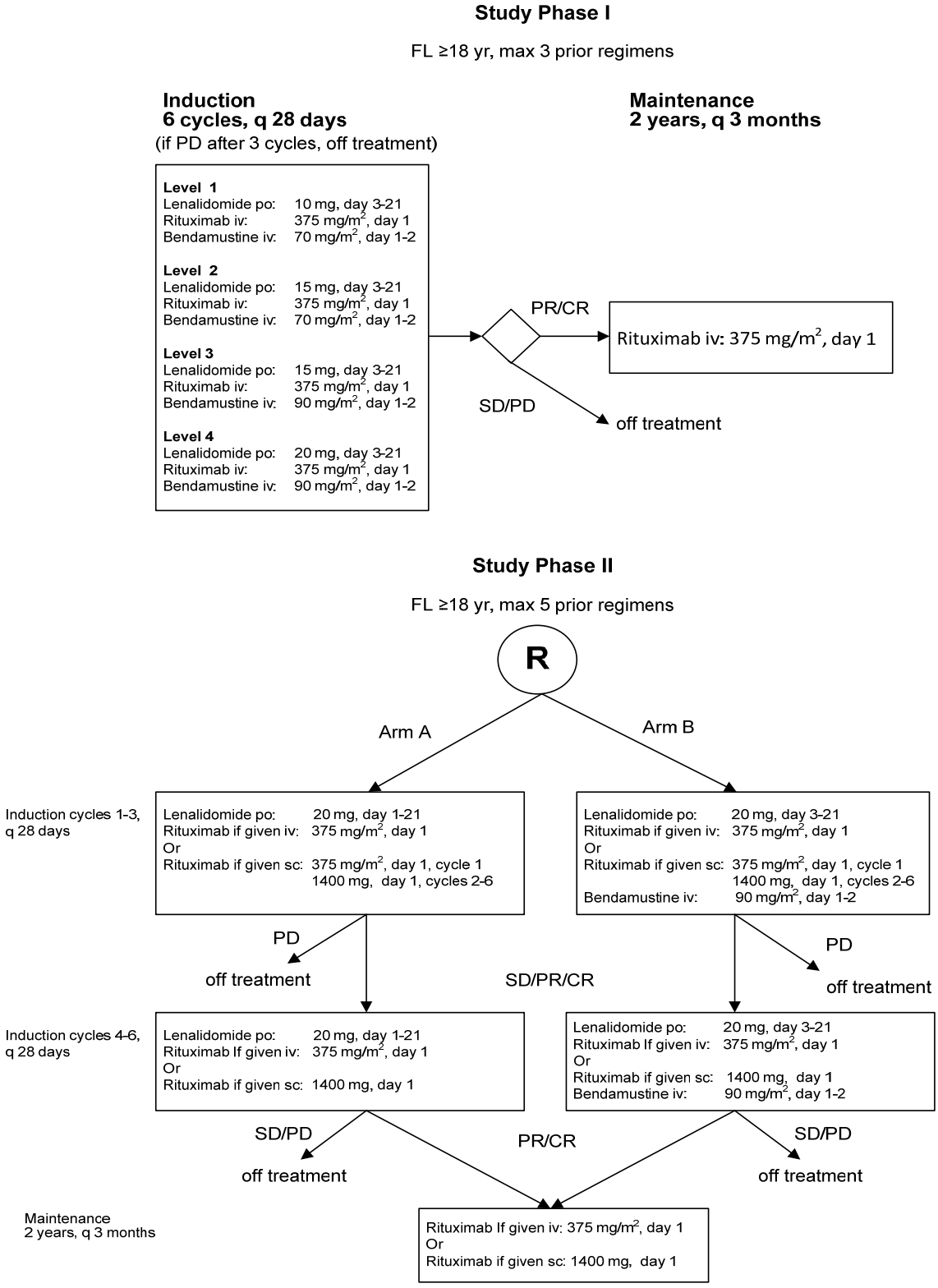
1 Scheme of study



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3 Synopsis

Rationale	Currently, there are no curative options for the treatment of follicular lymphoma (FL). Both lenalidomide and bendamustine show promising activity in FL, and because of limited toxicity, are good candidate drugs to use in combination therapy.
Main study objectives	*For the phase I part of the study:* to determine the dose limiting toxicity (DLT) and recommended dose level (RDL) of lenalidomide and bendamustine given in combination with rituximab for the phase II part of the study *For the phase II of the study:* to determine the efficacy and toxicity of the two arms of the study (arm A: lenalidomide and rituximab, and arm B: lenalidomide, rituximab and bendamustine) in patients with relapsed follicular lymphoma (FL)
Study design	Phase I/II trial; the phase II trial is a multicenter, prospective, randomized phase II trial with two experimental arms
Patient population	Patients aged 18 years or older, with relapsed CD20+ follicular lymphoma, with a maximum of 5 prior systemic regimens
Intervention	All patients will be treated with 6 induction cycles followed by 2 years of maintenance treatment with Rituximab, once every three months. In the induction cycles in the phase I part of the study, lenalidomide, rituximab and bendamustine are given using up to three dose levels of lenalidomide (10, 15 or 20 mg on day 3-21 of a 28-day schedule) with up to two dose levels of bendamustine (70 or 90 mg/m^2 on day 1,2) and rituximab (375 mg/m^2 on day 1). The goal of the phase I part of the study is to establish the RDL of lenalidomide and bendamustine given in combination with rituximab for the phase II of the study.

	In the phase II part of the study, in the induction cycles lenalidomide in combination with rituximab with or without bendamustine is given. Rituximab can be administered either i.v. or s.c..
Duration of treatment	The duration of induction treatment is 6 months, followed by a maximum of 2 years of rituximab maintenance treatment. Subsequently patients will be followed until 8 years after registration.
Target number of patients	Phase I: 15-24 patients Phase II: 150 patients
Expected duration of accrual	3 years
Main study endpoints	**Phase I:** Dose-Limiting toxicity (DLT) and recommended phase II dose (RDL) of lenalidomide and bendamustine given in combination with rituximab **Phase II:** CR rate and severe toxicity during induction treatment
Benefit and nature and extent of the burden and risks associated with participation	Currently, there is no standard treatment for patients with relapsed FL. Lenalidomide, rituximab and bendamustine have shown promising activity in FL, both in first line and in relapse. Since the toxicity of both drugs is relatively minor and in part non-overlapping, combination of these drugs is an attractive option. The hypothesis is that both treatment arms will be effective with acceptable toxicity. Risks for the patient relate to drug specific side-effects, in particular the risk of tumor lysis syndrome, infections and skin toxicity.
Planned interim analysis and DSMB	Several safety analyses are planned during the phase I part of the study and one interim analysis will be performed in the phase II part of the study. Phase I: after every 3 patients who have completed cycle 1 in each dose level a safety analysis will be performed to determine whether patients can be included in the next dose level.

Phase II: an interim analysis will be performed after the first 37 patients have been registered and received induction treatment in each arm, or as soon as severe toxicities, as defined in 13.1.2, have been reported in 14 patients among the first 37 registered patients in each treatment arm, whichever comes first.
A DSMB (Data Safety and Monitoring Board) will be installed which will advise the investigators at the end of the phase I part of the study on the determination of the recommended dose level, and will advise about (dis)continuation of each treatment arm at the interim analysis in the phase II of the study.

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5 Introduction and rationale

5.1 Follicular lymphoma

Follicular lymphoma (FL) is the second most frequent type of non-Hodgkin's lymphoma (NHL) and accounts for 20-25% of all lymphomas. In Germany, there are 5000 new cases each year; in the Netherlands approximately 800 new cases are diagnosed yearly[1,2]. The median age at diagnosis is 60 years.

Follicular lymphoma is characterized by a t(14;18)(q32;q21) translocation, which is present in approximately 85% of patients and leads to overexpression of the anti-apoptotic B-cell lymphoma 2 (Bcl-2) protein in the lymphoma cells. Although Bcl-2 is a known oncogene involved in blocking of programmed cell death (apoptosis), the pathogenesis of FL is still incompletely understood, since clearly multiple genetic events are required for the development of FL.

Histologically, FL is defined as a lymphoma of follicle center B cells (centrocytes and centroblasts), which has at least a partially follicular growth pattern. The malignant cells are thought to arise from germinal center B cells and proliferate in a network of non-malignant follicular dendritic cells and T cells. In the revised version of the World Health Organisation (WHO) classification of lymphomas, FL is now divided in cases with few centroblasts (formerly grade 1/2) and cases with increased centroblasts (grade 3), which should be stratified according to the presence (3A) or absence (3B) of residual centrocytes[3]. Grade 3B FL at diagnosis is considered to represent an aggressive form of lymphoma, more resembling diffuse large B cell lymphoma (DLBCL), and is usually treated as such. Histologic transformation of FL to aggressive lymphoma is a common event, ultimately occurring in 30-70% of patients, and is associated with a poor outcome[4].

Bone marrow involvement is common and is often characterized by paratrabecular lymphoid aggregates. The disease course is highly variable, ranging from very indolent waxing and waning lymphadenopathy, justifying a wait-and-see policy in asymptomatic patients, to rapidly progressive disease, requiring immediate treatment. The FLIPI index, based on simple clinical parameters such as age, stage of disease, number of nodal sites, hemoglobin level and LDH (lactate dehydrogenase), is the most commonly used prognostic risk index[6] . Although established in the pre-rituximab era, it has been shown to retain its prognostic significance also in rituximab-treated patients[7], and also predicts progression-free survival (PFS) after first relapse/disease progression[8].

Although FL is exquisitely sensitive to chemotherapy, radiotherapy and immunotherapy, there are currently no curative options. The clinical course of the disease for decades has been characterized by initial responsiveness to single-agent or combination chemotherapy, with excellent response rates but inevitable relapses. Subsequent treatment results in lower response rates and shorter relapse-free survival. The median overall survival (OS) from diagnosis is 8-10 years, after first relapse 4-5 years[9]. However, as a consequence of the introduction of new drugs, such as the monoclonal antibody

rituximab, the OS of patients with FL has improved in recent years[10,11,12]. In first line, immunochemotherapy is now considered standard, with R-CVP and R-CHOP being the most frequently used regimens[13,14]. Upon relapse patients are often treated with fludarabin-containing regimens. The role of maintenance treatment with rituximab has been established for relapsed patients[15,16], and has recently been shown to prolong PFS also in first line[17].
Incorporating novel agents with different mechanisms of action may further improve outcome. Whether or not the quality of the response achieved is important not only for progression free survival (PFS), but also for OS has been debated for a long time. Recent long-term follow-up data from the GELA however clearly demonstrate a significant improvement for OS in patients with a complete response compared to patients with a partial response[18].

5.2 Current treatment for newly diagnosed and relapsed FL patients

Currently, there is no standard treatment for FL, both in first line and in relapse. Treatment options vary from a wait-and-see approach to radiotherapy (which has curative potential in patients with localized disease at presentation), single-agent chemotherapy, combination chemotherapy and stem cell transplantation (SCT). The National LymphoCare Study, a multicenter, longitudinal observational study designed to collect information on treatment regimens and outcomes for patients with newly diagnosed FL in the United States, recently illustrated the lack of a standard approach[19]. The initial therapeutic strategy in 2728 newly diagnosed patients enrolled between 2004 and 2007 was observation in 17.7%, rituximab monotherapy in 13.9%, chemotherapy only in 3.2%, rituximab plus chemotherapy in 51.9% of patients, and radiation therapy in 5.6% of patients. The choice of chemotherapy was CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in 55%, CVP in 23% and fludarabine-based regimens in 15.5% of patients. In large parts of Europe, such as Germany, France and Switzerland, R-CHOP is considered standard treatment, whereas in other countries, such as the Netherlands and the United Kingdom, R-CVP is most frequently prescribed in first line. Consequently, because the choice of second-line treatment depends on the choice of and response to first-line treatment, there is also no standard second-line treatment. Both R-CHOP (in patients not previously treated with R-CHOP) and fludarabine-based regimens (R-FC or R-fludarabine) are effective and can lead to prolonged PFS. Fludarabine-containing regimens have not been tested in phase III trials in relapsed patients; in first line fludarabine was shown not to be superior to CVP in terms of PFS.[20]
Recently, a subcutaneous formulation of rituximab has been registered for patients with FL, which has a major advantage of reducing the time of administration to only 5-6 minutes (see paragraph 5.9).

5.3 Follicular lymphoma: the role of the microenvironment

The highly variable outcome of follicular lymphoma appears to be determined for a large part by the tumor microenvironment: nonmalignant bystander cells, such as T cells, monocytes/macrophages and stromal cells play a key role in the establishment and proliferation of the tumor[21,22]. Both genetic and immunologic data support a model for the development of FL as a disease of functional B cells in which specific molecular alterations infer intrinsic growth properties of the tumor cells, as well as dictate a specific functional cross talk with the immunologic regulatory network resulting in extrinsic growth support. Recent gene-expression data lend support to the crucial role of the immunologic context in the development and clinical behavior of FL, with a focus on the role of T cells and accessory cells[23,24]. FL with a poor response to anti-CD20 therapy (rituximab), as well as poor prognosis FL transforming to DLBCL within 3 years both have gene-expression signatures that are more similar to normal activated lymphoid tissue[25,26]. Specifically, genes related to the functional status of follicular dendritic cells (FDCs) are relatively overexpressed in poor prognosis as compared to good-prognosis FL (eg, CCL19, CCL20, CCR1) and the T-cell repertoire seems to be skewed toward T-helper1 functions. In contrast, in the ‘‘good prognosis’’ group, terminal B cell differentiation prevails in the context of a similarly dense, but non-activated T-cell population. Upon transformation, there is a dramatic drop in absolute T-cell numbers that, however, retain their activated T-helper1 phenotype in the context of immature dendritic cell (DC) features (CCR1,CCL3, CCL5). Although the results of gene-expression studies all point in a similar direction with regard to the role of the immune microenvironment in FL, the results of immunohistochemical studies on specific T-cell subsets and accessory cells are often contradictory. Specific cell populations, such as tumor associated macrophages, significantly correlate with poor prognosis in some series[27], but with good prognosis or without any significant impact in others[28]. In general, these studies are all well performed. Some of the contradictive results may be explained by technical variations caused by staining and/or scoring variation, but the explanation may be mostly directed by diversity of the clinical characteristics of the patients and variation in treatment. The impact of the microenvironment on response to treatment and/or prognosis may be partly dependent on specific treatment protocols (e.g. fludarabine versus alkylating agents; ‘’aggressive’’ treatment versus more "indolent" treatment; treatment with or without monoclonal antibodies)[29,30]

Our current study, making use of the advantage of having two treatment arms with a possibly differential effect on the microenvironment, therefore among others aims to investigate the pre-treatment composition of the immune microenvironment in FL and to monitor changes induced by different treatment modalities by serial fine needle aspirations and tumor biopsies of easily accessible FL localizations during treatment.

5.4 Lenalidomide

Lenalidomide (REVLIMID®; Celgene Corp., NJ, USA) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs). It was structurally designed to enhance the immunomodulatory and antitumor activity of its predecessor thalidomide, and is much less neurotoxic and in general well tolerated[31]. The key to its therapeutic potential lies in the fact that it has multiple mechanisms of action, which include both immunomodulatory and non-immunomodulatory antiproliferative effects. Lenalidomide has been associated with TNF-α inhibitory, T cell costimulatory, and anti-angiogenic activities.

Lenalidomide is marketed in the United States for the treatment of patients with transfusion- dependent anaemia due to low- or intermediate-1-risk Myelodysplastic Syndrome (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities[32], and in the United States and the European Union in combination with dexamethasone for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy[33,34].

Lenalidomide is currently being investigated as treatment for various oncologic indications, including NHL, Hodgkin's lymphoma (HL), chronic lymphocytic leukemia (CLL) and solid tumours.

5.5 Background and rationale for the use of lenalidomide in NHL

The current knowledge on mechanisms of action of lenalidomide in NHL has been reviewed by Chanan-Khan[35]. Lenalidomide has been shown to modulate the production of various cytokines in the tumor microenvironment, e.g. by downregulation of prosurvival cytokines such as TNF-a, IL6, IL8 and VEGF. In addition, lenalidomide inhibits Akt-phosphorylation, and increases p21 expression. The PI3-kinase/Akt signalling pathway is important for proliferation and survival of tumor cells, among others because it is involved in VEGF signaling. Lenalidomide also has an effect on the immune cellular compartment, by activating T and NK cells. T-cell proliferation is stimulated, and production of IL2 and IFNγ are increased through T cell receptor activation. In addition, NK cell proliferation and activation has been demonstrated, and lenalidomide enhances NK-cell-mediated antibody-dependent cellular cytotoxicity (ADCC) induced by rituximab in vitro. Both in vitro and in in vivo mouse models, synergistic antitumor effects of lenalidomide and rituximab on lymphoma cells have been demonstrated[36,37,38]. In one study lenalidomide was also shown to downregulate CD20 expression in CLL cells, suggesting a possible antagonism between these two agents[39]. This finding may however represent an artefact caused by capping of CD20. Furthermore, upregulation of costimulatory molecules such as CD80, CD86 and CD40, thus increasing the antigen-presenting cell capacity, as well as upregulation of Fas ligand (CD95) have been demonstrated on tumor cells. Taken together, these phenotypic changes in tumor cells and immune cells may result in an immune-mediated antitumor response.

Recently, both in CLL and in FL it has been shown that impairment of the T-cell immunologic synapse formation is an active immunosuppressive mechanism. For FL, a significant reduction in formation of the F-actin immune synapse was shown in tumor-infiltrating T cells from lymph nodes and in peripheral blood T cells from patients with a leukemic phase of the disease. Interestingly, in vitro, treatment of both the FL cells and T cells with lenalidomide has been shown to overcome this impaired T-cell immunologic synapse formation[40].

Despite these recent observations, the exact mechanism of action of lenalidomide in NHL remains highly uncertain. It is possible that the antitumor activity of lenalidomide is mediated through multiple, possibly mutually exclusive processes that primarily depend on the type of tumor cells and their microenvironment. Additional work to better elucidate lenalidomide's mechanism of action in NHL and its ability to modulate the cellular interplay between the microenvironment and the malignant lymphoma cells will be part of the current study.

5.6 Clinical studies with lenalidomide in NHL

Following demonstration of activity in MM and CLL, lenalidomide has been shown to have considerable single agent clinical activity in NHL: overall response rates in patients with relapsed/refractory indolent lymphoma are 25-35%[41,42], whereas the first results of small studies combining lenalidomide with rituximab show an overall response rate of 75-80%[43,44].

Witzig et al. performed a mutlicenter phase II study in 43 patients with relapsed and/or refractory indolent NHL[41]. Patients received up to 12 cycles of oral lenalidomide, 25 mg on a 21/28 day schedule. The median number of prior regimens was 3. The overall response rate (ORR) was 27% in patients with FL. The median duration of response was not reached, but exceeded 16.5 months. The most common adverse events were hematologic events, fatigue, gastrointestinal complaints, and rash. Four patients had a tumor flare reaction (TFR) grade 1 or 2, 3 of whom had CLL and 1 had FL (1/22 patients with FL).

In a phase II study with lenalidomide and rituximab in relapsed/refractory indolent NHL (30 patients, 22with FL) patients received lenalidomide, (25 mg d1-21 on a 28 day schedule), with 4 administrations of rituximab.[43] After 2 out of the 4 first patients developed grade 3 tumor lysis syndrome (TLS), the protocol was amended to reduce the lenalidomide starting dose to 20 mg and to institute allopurinol as TLS prophylaxis. The ORR was 74%, including 44% CR (5 patients), with a median PFS of 12,4 months.

Fowler et al. studied the combination lenalidomide and rituximab in previously untreated patients with indolent B cell NHL[44]. Among 46 evaluable patients with FL treated with 6 cycles of lenalidomide (20 mg d1-21 of a 28-day cycle) and rituximab, 375 mg/m^2 on day 1, 45 patients responded and 40 (87%) had a complete response. Rash was seen in 58% of patients, but was generally mild and self-limited, and did not occur on re-exposure to the drug.

Several studies are underway combining lenalidomide with CVP or CHOP, which seems feasible[45]. In a phase I/II trial of R2CHOP in newly diagnosed patients with DLBCL or FL grade 3, there were no DLT's when lenalidomide was given at a dose of 15, 20 or 25 mg on day 1-10 of a standard R-CHOP21 schedule. All patients received 6 mg pegfilgrastim. The addition of lenalidomide did not affect hematologic recovery and did not result in treatment delays. The 25 mg/day dose of lenalidomide was taken forward to a phase II trial. In a similar phase I/II trial reported by Vitolo et al, the MTD was 15 mg when given on day 1-14[46].

5.7 Bendamustine

In the last few years, interesting results have been presented for the use of bendamustine (Levact®, Treanda®, Ribomustin®) in FL, showing a favorable toxicity profile and considerable activity in FL in relapse (reviewed by Cheson and Rummel)[47]. In the USA and large parts of Europe, it has now been approved for use in rituximab-refractory indolent NHL. In vitro testing in CD20-positive lymphoma cell lines has demonstrated synergy between bendamustine and rituximab, with a significant reduction of the bendamustine concentration required to induce apoptosis in 50% of the tumor cells after the addition of rituximab[48].

The chemical structure of bendamustine (γ-[1-methyl-5-bis(β-chloro-ethyl)-amino-benzimidazolyl-2]-butyric acid hydrochloride) consists of 3 major groups which account for its molecular properties. The alkylating group (2-chloroethylamine) is seen in other nitrogen mustard agents, such as cyclophosphamide, chlorambucil and melphalan; the butyric acid chain is also present in chlorambucil, and the benzimidazole ring (unique to bendamustine) provides its antimetabolite, nucleoside-like properties. The mechanisms of action include inhibition of mitotic checkpoints, induction of mitotic catastrophe, activation of the DNA damage stress response, intrinsic apoptosis and base-excision DNA repair mechanisms[49]. Bendamustine differs from other alkylating agents in that it creates more durable and extensive dsDNA breaks and activates base-excision DNA repair pathways rather than alkyltransferase DNA repair mechanisms, and exhibits incomplete resistance with other alkylating agents.

Bendamustine is used intravenously, and is infused over 30-60 minutes. It is highly protein bound and primarily metabolized by the liver via hydrolysis to mostly inactive metabolites, and excreted primarily by the kidney, with a highly variable amount ultimately detected in the urine[50]. Bendamustine is currently not FDA approved for patients with a creatinine clearance <40 ml/min, and should also be used with caution in patients with hepatic impairment.

Thusfar, multiple doses and schedules have been used, with a dose between 60 and 120 mg/m^2 on 2 consecutive days every 3-4 weeks being most frequently used. The dose limiting toxicity at higher doses is thrombocytopenia and, at a single dose of 280 mg/m^2, cardiotoxicity. Recently, a consensus meeting was held to develop recommendations including dose and schedule for the various clinical

indications, both as single agent and in combination therapy, and to provide guidance for supportive measures[51]. For initial therapy and for relapsed patients, the recommended dose when combined with rituximab is 90 mg/m^2. These recommendations are based on the following trials.

An early trial performed in Germany used bendamustine at 120 mg/m^2 on days 1 and 2 of a 21 day schedule in 58 patients with relapsed or refractory indolent lymphomas, with an ORR of 73%, including 6 CRs in 52 evaluable patients[52]. The median duration of response was 16 months. Friedberg[53] and Kahl[54] both performed similar phase II studies with a similar dosing schedule in relapsed indolent NHL in the US. In a pooled analysis of these two studies, the ORR in 161 evaluable patients was 76% with 23% CR(u), and a PFS of 9 months[55]. The toxicity of bendamustine was mostly hematologic (neutropenia and thrombocytopenia). The most common nonhematologic toxicities are rash, nausea, fatigue, vomiting, fever, diarrhea and constipation, mostly of mild severity. An infusion reaction has been described consisting of fever, hypotension, back and muscle pain, chills and rigors, which occurs within 24 hours of administration of the drug, and can occur up to the third cycle. This syndrome resolved with discontinuation of the drug and/or the use of corticosteroids. Opportunistic infections have been reported, including herpes zoster, herpes simplex, candidiasis, cytomegaloviral infection, Pneumocystis jiroveci pneumonia, atypical mycobacterial infection, and tuberculosis. Therefore, physicians should be highly vigilant and screen for opportunistic infections in case of (persistent) fever. Currently, no standard antibiotic prophylaxis is advised. Secondary malignancies have been reported in 6 patients out of 176 patients treated in the US studies: 3 MDS, 1 CMML, 1 squamous cell carcinoma, and 1 AML.

Bendamustine has been combined with other cytostatic agents and with rituximab. The combination of bendamustine at a dose of 90 mg/m^2 with rituximab was studied in 2 phase II trials. Rummel showed a high ORR of 90% with 60% CR in 63 patients with relapsed indolent NHL or mantle cell lymphoma (MCL), and a median PFS of 24 months[56]. Robinson showed almost identical results in 66 patients: 92% ORR, 55% CR[57]. An ongoing trial shows promising results of the combination of rituximab, bendamustine and bortezomib (VERTICAL trial)[5].

A phase III randomized trial of R-bendamustine versus R-CHOP in first line in patients with FL, mantle cell lymphoma, Waldenstrom's macroglobulinemia and marginal zone lymphoma favoured R-bendamustine, although this trial was designed as a non-inferiority trial. PFS was longer, 69 vs 31 months, and toxicity was lower (less myelosuppression, neurotoxicity and no alopecia in the experimental arm)[59]. However, there is no sign of a plateau in the PFS curves, indicating that there is room for improvement, especially in high-risk patients. Because bendamustine is only mildly myelosuppressive, it is an attractive agent to combine with other agents.

Retreatment with bendamustine is feasible and effective. In 88 patients with CLL or indolent lymphoma, who had received one or two prior treatments with bendamustine, and were retreated with a bendamustine containing regimen, the ORR was 76%, with 6% . The main toxicity was myelosuppression (grade 3+4 36% in CLL patients and 43% in NHL patients), and there was no

unexpected major non-haematologic toxicity. 5 patients had to be hospitalised; there was no treatment-related mortality.[60] In addition, more than 50 patients were retreated with bendamustine following treatment in the StIL study protocols, with no major unexpected toxicity (M. Rummel, personal communication). These data demonstrate that even using a more myelosuppressive regimen such as the BMR regimen, retreatment with bendamustine is feasible.

5.8 Combination of lenalidomide and bendamustine

In patients with MM, the combination of bendamustine with lenalidomide has been tested in a phase I/II dose escalation study. The MTD has been determined as bendamustine 75 mg/m^2 day 1,2) and lenalidomide 10 mg (day 1-21)[61]. Cheson and Crawford reported a phase I study on the combinatioen of bendamustine, lenalidomide and rituximab (BLR). Patients with NHL or HL failing standard therapies received bendamustine (90 mg/m^2 days 1, 2 every 28 days), and lenalidomide (escalating from 5 mg 21/28 days) for six cycles, followed by 6 months of lenalidomide. When lenalidomide 20 mg was reached, rituximab 375 mg/m^2 on day one of each cycle was added for patients with B-NHL. Histologies included diffuse large B-cell lymphoma (DLBCL, 11), marginal zone lymphoma (3), HL (2), and one each of transformed follicular lymphoma, Sézary syndrome, Waldenström macroglobulinaemia and mantle cell lymphoma. No patients with follicular lymphoma were included. Neutropenia was the most common grade 3 and 4 toxicity, but no maximum tolerated dose was identified. [62]

A phase I/II study performed by the Nordic Lymphoma Group in elderly patients with MCL has demonstrated a high ORR (97%), with a CR rate of 64%. After a median follow-up of 31 months, the median PFS was 42 months, and the 3-year OS was 73%%. Infection was the most common non-hematological grade 3-5 event and occurred in 21 (42%) patients. Opportunistic infections occurred in three patients; 2 PCP and 1 CMV retinitis. Second primary malignancies (SPM) were observed in eight patients (16%). There were 3 treatment related deaths in the phase I part, after which the lenalidomide was omitted in cycle 1. The authors concluded that lenalidomide in combination with R-bendamustine is feasible as first-line therapy in older patients with MCL, and is associated with a high CR rate, but that there was a high degree of severe infections [63] .

5.9 The subcutaneous use of rituximab

5.9.1 The subcutaneous use of rituximab

In contrast to the i.v. infusion, rituximab s.c. injection takes only 5-6 minutes. The simple s.c. injection could thus significantly reduce the time a patient spends in the hospital and eliminate hospital burden associated with i.v. administration (e.g., nursing time for i.v. dosing, occupation of beds at the day care facility). Previously, the relatively large volume of the established rituximab i.v. dose has hindered the s.c. administration of rituximab, but this hurdle has been overcome by concentrating the i.v. rituximab

formulation 12-fold and by adding recombinant human hyaluronidase (rHuPH20) as an excipient and a permeation enhancer. rHuPH20 hydrolyses hyaluronic acid fibers of the interstitial matrix allowing the installation of volumes larger than 2-3 mL and increasing the dispersion of locally injected drugs across a broad range of molecular weights without tissue distortion. rHuPH20 improves the PK profiles of large biopharmaceuticals administered via the interstitial route and drives the PK profile towards an i.v. administration profile. rHuPH20 was approved by the US Food and Drug Administration in 2005. The approved indication includes 'hypodermoclysis', i.e. s.c. injection/infusion of fluid in large volume. Preclinical, clinical and extensive post-marketing experience with the rHuPH20 excipient used in the rituximab s.c. formulation has shown the component to be well-tolerated.

5.9.2 Clinical trials with rituximab s.c.

Recently, results have become available of stage 1 of the phase III "**SABRINA**" study in which patients treated with follicular lymphoma treated with R-CHOP/R-CVP in first line were randomized between i.v. and s.c. administration of rituximab[64]. The primary endpoint was met, with a C_{trough} ratio (rituximab s.c. versus i.v.) of 1.62 (90% CI: 1.36–1.94) exceeding the noninferiority threshold of 0.8. The AUC ratio of 1.38 (90% CI: 1.24–1.53) (secondary endpoint) also indicated noninferiority. Furthermore, response rates indicated that s.c. administration did not compromise the efficacy of rituximab (s.c., ORR 90.5%, CR 46.0%; i.v. ORR 84.4%, CR 29.7%). After a median follow-up of 9 months, there were no new or unexpected safety signals for rituximab s.c.. Grade 3/4 AEs were reported in 47% of patients (s.c.) and 46% (i.v.). The only grade 3/4 AE occurring in > 10% of patients was neutropenia (26% in the s.c. arm, 22% in the i.v. arm). Administration-related reactions (ARRs) were more frequent in the rituximab s.c. arm (50% versus 32%). The majority of these were grade 1/2 (94.5% versus 97.8%), and no grade 4 ARRs were reported.

In a second study (''SparkThera'') maintenance therapy with rituximab delivered subcutaneously or intravenously in previously untreated or relapsed FL[65] was investigated, and also in this study the primary endpoint (C_{trough} serum level ratio) was met: the lower limits of 90% CIs exceeded the noninferiority threshold (0.8) for 2-monthly (1.02) and 3-monthly (0.86) dosing of rituximab s.c.. Therefore, 1400 mg of rituximab s.c. was concluded to be noninferior to intravenous administration of 375 mg/m^2 rituximab. The safety profile in both arms was consistent with the established safety profile of rituximab. Grade 3/4 AEs occurred in 18% and 17% of patients (s.c. versus i.v.). Grade 3/4 AEs occurring in more than one patient in either arm were neutropenia (two in each arm) and arthralgia (two in the i.v. arm). The most frequent AEs were ARRs. The incidence of these was higher in the rituximab SC arm (31% versus 4%) and most were local reactions.

In conclusion, in both studies noninferiority of the 1400 mg rituximab s.c. dosing was demonstrated, compared with intravenous administration of 375 mg/m^2, when given as maintenance therapy every 2 months or every 3 months.

5.10 The role of PET-CT in patients with FL

Positron emission tomography (PET) using [^{18}F]fluorodeoxyglucose (FDG) has emerged as a powerful functional imaging tool for staging, restaging and response assessment of DLBCL and HL. Its role in indolent, incurable FDG-avid lymphomas such as FL is currently unclear. Furthermore, false-positive results post-treatment can occur because of infection and inflammation. In the revised Cheson criteria, FDG-PET (pretreatment and post-treatment) is recommended in FL in clinical trials if ORR/CR is the primary endpoint.[66] Recently, an analysis was presented of a subset of 160 patients from the PRIMA trial[17], in whom 277 PET-CT scans were performed. The PET-CT was shown to be positive in 99% of the patients at diagnosis. A significant correlation between post-treatment PET-CT results and PFS and OS was found.[67]Taken together, these data support the use of FDG-PET scanning in this trial.

5.11 Rationale of the study

There are currently no data on the combination of bendamustine with lenalidomide in patients with FL. Both drugs are very promising agents for the treatment of this disease, both from a clinical and from a research viewpoint. The combination of lenalidomide with rituximab seems especially advantageous as it can provide an effective chemotherapy-free regimen for (elderly or frail) NHL patients. On the other hand, combination with chemotherapy (i.e. bendamustine) might provide a more effective regimen. Therefore, we propose to perform, after a short run-in phase to establish the RDL for the combination of lenalidomide, rituximab, and bendamustine, a randomized phase II study in FL to identify the most promising of these two experimental regimens to use in a subsequent randomized phase III study.
In the phase I part of the study the combination of lenalidomide, rituximab and bendamustine will be tested at a maximum of four carefully selected dose levels (three different doses of lenalidomide, and two different doses of bendamustine).
In the phase II part of the study, we have built in an interim analysis to shield patients from an ineffective or toxic treatment by requiring early termination of one or both treatment arms if the CR rate during/after induction treatment is poor or the severe toxicity rate is high.

6 Study objectives

For the phase I part of the study:

- To determine the feasibility and recommended dose level (RDL) of the combination of lenalidomide, rituximab, and bendamustine in a 28 day schedule

For the phase II part of the study:

- To study the efficacy and toxicity of the two arms of the study (LR: lenalidomide and rituximab, and LRB: lenalidomide, rituximab, and bendamustine) in patients with relapsed follicular lymphoma, and to identify the most promising of these two treatment arms.
- To determine the value of PET-CT scanning in response assessment of FL patients
- To identify predictive factors for response. For this purpose, in the non-chemotherapy-based lenalidomide-rituximab regimen and in the chemotherapy-based lenalidomide-rituximab-bendamustine regimen, various tissue–associated markers will be explored both on tumor cells and on non-malignant cells of the tumor microenvironment using tissue microarrays or primary lymphoma biopsy samples. These studies will be supported by gene expression profiling in a selection of the patients. Results will be correlated to clinical outcome as well as PET-CT results and circulating subsets of T cells and NK cells. An exploratory analysis will be performed to identify putative covariates that might indicate which patient populations would benefit most from treatment with the non-chemotherapy-based lenalidomide-rituximab regimen or from the chemotherapy-based lenalidomide-rituximab-bendamustine regimen.
- To specifically explore treatment-induced alterations in non-malignant immune cell populations. For this purpose, alterations during treatment in these populations in the peripheral blood and at the tissue level of involved lymph nodes will be performed. For the latter analysis sequential fine needle aspirations and biopsies will be performed in a selection of patients. The sequential biopsies will also be used to study the biological mechanisms of tumor cell kill.

7 Study design

This study is a prospective, multicenter, open label, randomized phase I/II trial consisting of two parts: a short non-randomized phase I, with15-24 patients, to establish the recommended dose level for arm B of the phase II trial, and a randomized phase II part (with two experimental arms) with 150 patients. The most promising of these two treatment arms will subsequently be taken forward to a large randomized phase III trial.

7.1 Phase I

The study will begin with a feasibility part, in which the combination of lenalidomide, rituximab and bendamustine followed by rituximab maintenance will be tested at 4 carefully selected dose levels, with the goal to establish the recommended dose level of the study. A '3+3' dose escalation scheme, as illustrated in the figure on the next page, is used. Decisions regarding feasibility and dose escalation to the next cohort, continuation or stopping are based on the dose limiting toxicity (described in paragraph 13.1).

Enrollment at each dose level will consist of a minimum of 3 patients and a maximum of 6 patients. When 3 or 6 patients have been entered, inclusion will be discontinued until DLT has been determined at day 29 after start of cycle I for these patients. Patients who die of lymphoma within 29 days after start of cycle I, but without a DLT, will be considered to be non-evaluable, and will be replaced by other patients.

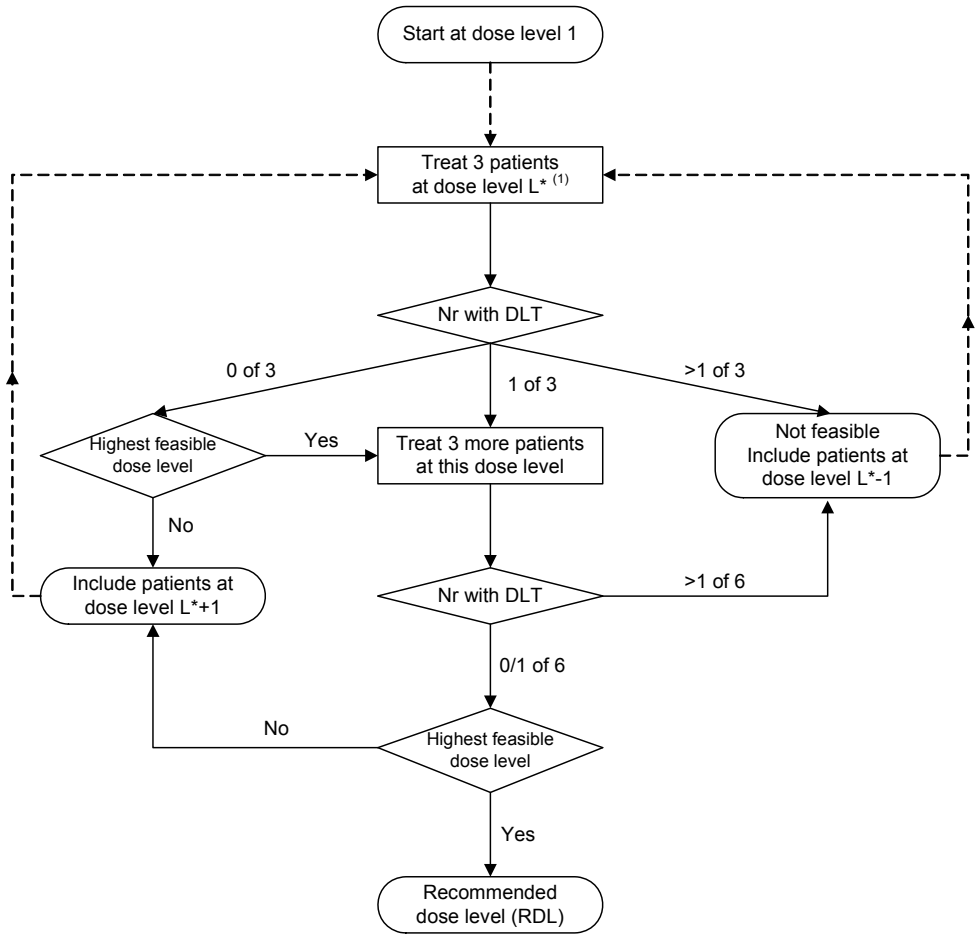
The dose escalation stops as soon as at least two patients experience a DLT, either in the first cohort of three patients treated at that dose level, or in the two cohorts of three patients treated at that dose level or, alternatively, when the highest planned dose level has been reached. Before opening the next higher dose level the dose limiting toxicity information at the preceding dose level will be reviewed and expansion or escalation will be undertaken as appropriate.

Although expansion or escalation will be based on DLT after cycle I only, feasibility of each dose level will be based on DLT observed during cycles I and II.

The RDL for the phase II part of the study is defined as the highest dose level with 0 or 1 DLTs observed during cycles I and II among 6 patients. Therefore, if for example in level L+1 , 2 or more DLTs have been observed, and only 3 patients have been included in level L, then another 3 patients will have to be included in level L, to ensure that there are fewer than two DLTs among 6 patients treated at that dose level. If the maximum dose level is reached with 3 patients, an additional 3 patients will be treated at that dose level. Due to the 3+3 dose-escalation scheme, if all dose levels are used, a minimum of 15 and a maximum of 24 evaluable patients will be entered in the phase I part of the study. Intra-patient dose escalation is not permitted.

The DSMB will advise the principal investigator and the study coordinators on the determination of the recommended dose level.

Figure 2: Flow chart phase I part of the study



(1) L* should be read as `1', `2', `3', or `4', whichever applicable

7.2 Randomized phase II part of the trial

After completion of the phase I part and final selection of the recommended dose level, the protocol has been amended, describing the RDL for arm B of the phase II part of the study. The RDL for the combination of lenalidomide, rituximab and bendamustine is lenalidomide 20 mg (flat dose) on day 3-21 of each cycle, rituximab 375 mg/m^2 on day 1 of each cycle and bendamustine 90 mg/m^2 on day 1 and 2 of each cycle.

The phase II part is designed as a randomized study. All eligible patients will be randomized to one of two arms: arm A, LR: lenalidomide in combination with rituximab, or arm B, LRB: lenalidomide in combination with rituximab and bendamustine, at the recommended dose level established in the phase I part of the study. Restaging is performed after 3 cycles. Patients with SD, PR or CR will continue with another 3 cycles. Patients with PR or CR after 6 cycles will receive rituximab

maintenance treatment for a maximum of 2 years (both arms). Both experimental arms will be evaluated for efficacy and toxicity separately, and a formal comparison between the two treatment arms will not be performed.
In the phase II part of the study, we have built in an interim analysis after recruitment of half of the patients in each arm, to shield patients from an ineffective or toxic treatment by requiring early termination of the trial if the CR rate during/after induction treatment is poor or the severe toxicity rate is too high. (The definition of severe toxicity is given in par 9.1.2.)
Details of all treatments (dose and schedule) are given in paragraph 9.
A scheme of the study is given in paragraph 1.

8 Study population

8.1 Eligibility for registration/randomization

All patients must be registered/ randomized before start of treatment and must meet all of the following eligibility criteria.

8.1.1 Inclusion criteria

- Relapsed FL grade 1, 2, 3a, see appendix A;
- Ann Arbor stage II-IV at relapse, see appendix B;
- A biopsy or FNA to show CD20 postivity is required. A biopsy/FNA performed at any time since the most recent therapy is acceptable as long as this shows FL and there is no clinical concern for transformation at the time of study entry. In case clinically transformation is suspected, a biopsy should be obtained at the time of study entry to exclude transformation;
- A maximum of five prior systemic treatment regimens (patients who have had a prior allogeneic SCT are excluded; prior autologous SCT (if > 1 year ago) is allowed);
- Prior bendamustine is allowed, under the following conditions:
    - Only one prior treatment (with a maximum of 6 cycles) with bendamustine is allowed
    - Patients must have had a PR or CR following prior use of bendamustine
    - Prior treatment with bendamustine must have taken place ≥24 months ago (measured from the start of prior bendamustine treatment, i.e. approximately 18 months from the end of prior bendamustine treatment)
- Subjects must have an indication for treatment based on one or more of the following criteria:
    - Involvement of at least 3 nodal sites, each with a diameter > 3 cm
    - Symptomatic splenomegaly

- Bulky disease at study entry according to the GELF criteria[68] nodal or extranodal mass (except spleen) > 7 cm in its greatest diameter
- B-symptoms (absence or presence of fever and/or night sweats and/or unexplained loss of 10% of body weight or more in the 6 months preceding diagnosis)
- Hb < 10 g/dl (6.2 mmol/l) (if caused by bone marrow infiltration and not otherwise explained)
- Thrombocytopenia: platelets < $100x10^9$/l caused by bone marrow infiltration
- Organ compression syndrome (e.g. hydronephrosis caused by lymphadenopathy)
- Pleural/peritoneal effusion
- Symptomatic extranodal manifestations;

♦ Measurable disease as defined in appendix C (patients with only bone marrow involvement are therefore not eligible);

♦ Age ≥ 18 years;

♦ Able to adhere to the study visit schedule and other protocol requirements;

♦ WHO performance status of 0-2;

♦ Laboratory test results within these ranges: absolute neutrophil count ≥ $1.5x\ 10^9$/l (unless bone marrow infiltration), platelet count ≥ $100x\ 10^9$/l (unless bone marrow infiltration), creatinine clearance ≥ 50 ml/min, total bilirubin ≤ 30 µmol/l (1,75 mg/dl), AST & ALT ≤ 3x ULN;

♦ Females of childbearing potential must have a negative serum or urine pregnancy test within 10 - 14 days prior to and again within 24 hours of starting lenalidomide treatment;

♦ Patients must be willing and capable to use adequate contraception during and after the therapy (all men, all pre-menopausal women; see 10.2 and 12.5). Patients must be able to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan;

♦ Written informed consent.

8.1.2 Exclusion criteria

♦ Rituximab-refractory patients (definition: progression during or within 6 months after rituximab containing immunochemotherapy. Patients relapsing under rituximab maintenance treatment are eligible, if at biopsy or FNA CD20 positivity is confirmed);

♦ Clinical or histologic signs of transformation. Patients with a prior transformed phase of FL are eligible IF there are currently no signs of transformation and there is histologic proof that the current phase is not transformed AND the transformed phase occurred >2 years ago;

♦ Prior allogeneic SCT;

♦ Prior autologous SCT less than one year ago;

- Any prior use of an immunomodulatory agents such as lenalidomide, pomalidomide or CC-122;
- Concurrent use of other anti-cancer agents or treatments;
- The use of prednisolone for any other indication than lymphoma treatment is allowed at a maximum dose of or equivalent to 20 mg prednisolone;
- Concurrent use of allopurinol, e.g. because of gout. Patients with gout are advised to switch to another anti-gout medication, because of the risk of Stevens-Johnson Syndrome observed in patients using bendamustine and allopurinol;
- Use of any other experimental drug or therapy within 28 days of baseline;
- Hepatitis B (including HBcAb) positive, Hepatitis C positive and/or HIV positive patients;
- Patients with uncontrolled autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP);
- Active fungal, bacterial, and/or viral infection;
- Recent vaccination for yellow fever (within 4 weeks before registration)
- Pregnant or breast-feeding females (lactating females must agree not to breast feed while taking lenalidomide);
- Known hypersensitivity and/or serious adverse reactions to lenalidomide or similar drugs;
- Intolerance of exogenous protein administration, or known allergy to murine products;
- Uncontrolled hyperthyroidism or hypothyroidism;
- Neuropathy ≥ grade 2 at time of inclusion;
- Clinically symptomatic severe cardiac dysfunction (NYHA III-IV, see appendix G);
- Clinically symptomatic severe pulmonary dysfunction;
- Severe neurologic or psychiatric diseases;
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection);
- History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast, prostate cancer (TNM stage of T1a or T1b);
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

9 Treatment

9.1 Induction in the phase I part of the study: lenalidomide, rituximab and bendamustine

9.1.1 Treatment schedule

Treatment will be administerd according to the schedule below.

The patient will be treated at the dose level assigned at registration.

(More information about assigning dose levels is given in paragraph 7.1)

Dose level 1

Agent	Dose/day	Route of administration	Days
Lenalidomide	10 mg o.d.	p.o.	3-21
Rituximab	375 mg/m^2 (max 800 mg) o.d.	i.v.	1
Bendamustine	70 mg/m^2 (max 150 mg/day) o.d.	i.v.	1,2

The next cycle will start at day 29 if the criteria given in 9.2.2 are met.

o.d.: once daily

Dose level 2

Agent	Dose/day	Route of administration	Days
Lenalidomide	15 mg o.d.	p.o.	3-21
Rituximab	375 mg/m^2 (max 800 mg) o.d.	i.v.	1
Bendamustine	70 mg/m^2 (max 150 mg/day) o.d.	i.v.	1,2

The next cycle will start at day 29 if the criteria given in 9.2.2 are met.

o.d.: once daily

Dose level 3

Agent	Dose/day	Route of administration	Days
Lenalidomide	15 mg o.d.	p.o.	3-21
Rituximab	375 mg/m^2 (max 800 mg) o.d.	i.v.	1
Bendamustine	90 mg/m^2 (max 200 mg/day) o.d.	i.v.	1,2

The next cycle will start at day 29 if the criteria given in 9.2.2 are met.

o.d.: once daily

Dose level 4

Agent	Dose/day	Route of administration	Days
Lenalidomide	20 mg o.d.	p.o.	3-21
Rituximab	375 mg/m^2 (max 800 mg) o.d.	i.v.	1
Bendamustine	90 mg/m^2 (max 200 mg/day) o.d.	i.v.	1,2

The next cycle will start at day 29 if the criteria given in 9.2.2 are met.
o.d.: once daily

The Complete blood count (CBC) should be checked at least weekly for the first cycle, and every two weeks during all subsequent cycles, or more frequently if clinically indicated.
During induction treatment, especially during the first two cycles, it is important to check serum chemistry frequently (especially tumor lysis parameters, as described in paragraph 10).
For dose delays and dose adjustments, see paragraph 9.2.2. If treatment is required to be held for toxicity for >28 days, the patient should go off protocol treatment.

Rituximab should be administered according to standard institutional practices, taking into account the special precautions given in paragraph 9.2.3. If applicable, rounding of the calculated dose to the nearest 100 mg (dose banding) is allowed. In patients in whom no adverse events are seen during the first rituximab administration, subsequent administrations can be done according to the rapid infusion schedule.
Bendamustine should be dissolved in NaCl 0.9%, 500 ml, and can be administered as an intravenous infusion over one hour. Bendamustine should be administered preferrably as soon as possible after preparation, but always within 3.5 hours after preparation of the solution if kept at room temperature, or within 48 hours after preparation if kept refrigerated. Dose banding of bendamustine is allowed as per local guidelines.

Patients will receive induction therapy for 3 cycles, every 28 days, after which restaging using conventional CT scanning is performed. Patients who have progressive disease proven by CT-scan following 3 cycles of induction treatment will go off protocol. All other patients (patients with CR, PR or SD) will receive another 3 cycles of induction treatment, every 28 days.
Patients who are in PR or CR based on results of the CT scan (in the phase I part a PET scan is not required nor is it reimbursed) after 6 cycles of induction treatment, will receive rituximab maintenance treatment. Patients who for whatever reasons cannot continue with lenalidomide and/or lenalidomide/bendamustine after 4 or 5 induction cycles are allowed to continue with rituximab

maintenance treatment if they are in PR or CR. Patients who are not in PR/CR after 4, 5 or 6 induction cycles, go off protocol treatment.
Further information about maintenance treatment is given in paragraph 9.3.

9.1.2 Dose adjustments during the phase I part of the study

For dose delays and dose adjustments, see paragraph 9.2.2.

9.1.3 Special precautions and supportive care

For special precautions and supportive care, see paragraph 9.2.3.

9.2 Induction in the phase II part of the study

9.2.1 Treatment schedule

Treatment will be administerd according to the schedule of the assigned treatment arm, given below.

Arm A: lenalidomide and rituximab (LR)

Agent	**Dose/day**	**Route of administration**	**Days**
Lenalidomide	20 mg o.d.	p.o.	1-21
Rituximab if given i.v.	375 mg/m^2 (max. 800 mg) o.d.	i.v.	1
Rituximab if given s.c.*	375 mg/m^2 (max. 800 mg) o.d. 1400 mg fixed dose o.d.	i.v. s.c.	Day 1 cycle 1 Day 1 cycle 2-6

The next cycle will start at day 29 if the criteria given in 9.2.2 are met.
o.d.: once daily

Arm B: lenalidomide, rituximab and bendamustine (LRB)

Agent	Dose/day	Route of administration	Days
Lenalidomide	RDL (20 mg) o.d.	p.o.	3-21
Rituximab if given i.v.	375 mg/m^2 (max. 800 mg) o.d.	i.v.	1
Rituximab if given s.c.*	375 mg/m^2 (max. 800 mg) o.d. 1400 mg fixed dose o.d.	i.v. s.c.	Day 1 cycle 1 Day 1 cycle 2-6
Bendamustine	RDL (90 mg/m^2 (max. 200 mg)) o.d.	i.v	1,2

The next cycle will start at day 29 if the criteria given in 9.2.2 are met.
o.d.: once daily
*The first dose of rituximab (day 1 cycle 1) is always given i.v.; subsequent doses can be given either i.v. at a dose of 375 mg/m2 or s.c. at a fixed dose of 1400 mg s.c. (see below for details)

The dose of lenalidomide (20 mg) and the dose of bendamustine (90 mg/m^2) for arm **B** have been determined during the phase I part of the study.

The CBC should be checked at least weekly for the first cycle, and every two weeks during all subsequent cycles, or more frequently if clinically indicated.
During induction treatment, especially during the first two cycles, it is important to check serum chemistry frequently (especially tumor lysis parameters, as described in paragraph 10).
For dose delays and dose adjustments, see paragraph 9.2.2. If treatment is required to be held for toxicity for >28 days, the patient should go off protocol treatment.

Rituximab should be administered according to standard institutional practices, taking into account the special precautions given in paragraph 9.2.3. In patients in whom no adverse events are seen during the first rituximab administration, subsequent administrations can be done according to the rapid infusion schedule. The rituximab dose can be 'rounded' to the nearest 100 mg, as per local policy.
If a patient is able to receive the full dose of rituximab i.v. infusion during cycle 1, the next administrations (in cycle 2-6 and all maintenance doses) can also be given subcutaneously at a dose of 1400 mg (fixed dose). If the full dose of rituximab i.v. is not given during cycle 1, the subsequent administration will again be i.v. until a full dose of rituximab i.v. is administered successfully. Hereafter a switch to rituximab s.c. can take place. The choice of i.v. or s.c. use of rituximab is at the discretion of the local investigator.

Bendamustine should be dissolved in NaCl 0.9%, 500 ml, and can be administered as an intravenous infusion over one hour. Bendamustine should be administered preferrably as soon as possible after preparation, but always within 3.5 hours after preparation of the solution if kept at room temperature, or within 48 hours after preparation if kept refrigerated. Dose banding of bendamustine is allowed as per local guidelines.

In both arms, patients will receive induction therapy for 3 cycles, every 28 days, after which restaging using conventional CT scanning is performed. Patients who have progressive disease proven by CT-scan following 3 cycles of induction treatment will go off protocol. All other patients (patients with CR, PR or SD) will receive another 3 cycles of induction treatment, every 28 days.
Patients who are in PR or CR based on results of the PET-CT scan after 6 cycles of induction treatment, will receive rituximab maintenance treatment for a maximum of 2 years. Patients who for whatever reasons cannot continue with lenalidomide and/or lenalidomide/bendamustine after 4 or 5 induction cycles are allowed to continue with rituximab maintenance treatment if they are in PR or CR. Patients who are not in PR/CR after 4, 5 or 6 induction cycles, go off protocol treatment.
Further information about maintenance treatment is given in paragraph 9.3.

9.2.2 Dose adjustments

Lenalidomide dose reduction during a treatment cycle
The CBC should be checked at least weekly for the first cycle, and every two weeks during all subsequent cycles, or more frequently if clinically indicated.
During induction treatment, especially during the first two cycles, it is important to check serum chemistry frequently (especially tumor lysis parameters, as described in paragraph 10).

Lenalidomide intolerance and/or toxicity occurring during a treatment cycle should be managed as indicated in Table 1.
Subjects will be evaluated for adverse events (AEs) at each visit with the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 used as a guide for the grading of severity for non-hematologic toxicity (appendix H).

Table 1: Managing of lenalidomide dosing according to toxicity during a cycle

Hematologic Toxicity	
Neutropenia (ANC <1.0 × 10^9/l) associated with fever (temperature ≥ 38.5º C) or ANC ≤ 0.5 × 10^9/l	Hold (interrupt dose) until ANC ≥ 1.0 × 10^9/l in case of febrile neutropenia, or >0.5× 10^9/l in the absence of fever. Restart with one dose step reduction‡. Follow CBC weekly. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF (pegfilgrastim, filgrastim or lenograstim) is advised and the dose can be maintained for the next cycle at the investigators discretion.
Thrombocytopenia platelet count < 40 × 10^9/L	Hold (interrupt dose) and stop aspirin treatment. Follow CBC twice weekly. If thrombocytopenia resolves to ≥ 40 × 10^9/l restart at one step dose reduction and follow CBC weekly; restart aspirin.
Non-Hematologic Toxicity	
Non-blistering rash Grade 3 Grade 4	If Grade 3 hold (interrupt) dose, follow weekly. If the toxicity resolves to ≤ grade 1, restart with one step dose reduction. If grade 4 rash- discontinue lenalidomide permanently.
Desquamating (blistering) rash- any Grade	Discontinue lenalidomide permanently.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide permanently.
Sinus bradycardia/ other cardiac arrhythmia Grade 2 ≥ Grade 3	Hold (interrupt dose), if the toxicity resolves to ≤ grade 1 restart at one step dose reduction. If ≥ Grade 3 discontinue lenalidomide.
Allergic reaction or hypersensitivity Grade 2 Grade 3-4	Hold (interrupt dose). If the toxicity resolves to ≤ grade 1 restart at one step dose reduction. If Grade 3-4 discontinue lenalidomide.
Venous thrombosis/embolism ≥ Grade 3	Hold (interrupt) dose and start anticoagulation (management as clinically indicated). Once efficient anticoagulation is achieved, lenalidomide therapy can be resumed at the same dose level.

Other non-hematologic toxicity assessed as lenalidomide-related ≥ Grade 3	Hold (interrupt dose), follow at least weekly. If the toxicity resolves to ≤ grade 2 restart at one step dose reduction.
Clinical Tumor Lysis Syndrome (CTLS)	Scoring of CTLS and LTLS will be done according to CTC v3.0/Cairo and Bishop, see appendix I.[72]. Interrupt lenalidomide; hospitalise patient and administer IV hydration and rasburicase treatment as clinically indicated, until laboratory abnormalities have resolved. Do not use allopurinol because of the increased risk of Stevens-Johnson syndrome when used in combination with bendamustine/lenalidomide. Lenalidomide can then be restarted with a one step dose reduction. If the patient is considered to be no longer at risk for TLS, the patient can be treated at the original dose level in the next cycle, with additional protective measures (e.g. adequate hydration, rasburicase, unless the patient has G6PD deficiency, in which case the use of rasburicase is contraindicated) if indicated.
Laboratory Tumor Lysis Syndrome (LTLS)	If there is evidence of laboratory tumor lysis syndrome (LTLS) by Cairo-Bishop criteria[72]/CTC 3.0 (see appendix I) without clinical tumor lysis lenalidomide should be held and oral or IV hydration administered until laboratory abnormalities resolve, at which time lenalidomide can be restarted with continued monitoring every day for at least one week for LTLS. If LTLS occurs on rechallenge, after laboratory abnormalities return to baseline lenalidomide can be restarted with a one step dose reduction. Do not use allopurinol because of the increased risk of Stevens-Johnson syndrome when used in combination with bendamustine/lenalidomide; use rasburicase if indicated unless the patient has G6PD deficiency, in which case the use of rasburicase is contraindicated.
Hyperthyroidism or hypothyroidism	Hold lenalidomide (interrupt dose), evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose step reduction)

‡ Missed doses of lenalidomide are not caught up with later. Dose reduction of lenalidomide is to be done in three steps of 5 mg: if patients started with 20 mg first step; to 15 mg; next step to 10 mg, third step to 5 mg. If patients started at a lower dose, the dose must be reduced accordingly, using 5 mg steps. Patients who are not able to tolerate the lowest dose (5 mg) for any reason except for

hematologic toxicity will be discontinued from therapy. Patients who experience hematologic toxicity on lenalidomide 5 mg may be continued following recovery from toxicity if investigator feels that the subject is otherwise benefiting from therapy.

Instruction for starting the next cycle (lenalidomide-rituximab or lenalidomide-rituximab-bendamustine):

A new cycle of therapy may begin if the following criteria are met:

- The ANC is ≥ 1.0 × 10^9/l;
- The platelet count is ≥ 75× 10^9/l;
- Any lenalidomide- or bendamustine-related allergic reaction/hypersensitivity/rash or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other lenalidomide-related or bendamustine-related adverse event that may have occurred has resolved to ≤ grade 2 severity.
- Pregnancy test is confirmed negative for women of child bearing potential (within 24 hours before start of the cycle).
- Treatment is not held for more than 28 days. If treatment is required to be held for toxicity >28 days, the subject should go off protocol treatment.
- In patients gaining or losing more than 10% of the initial body weight while on study, the dose of bendamustine and rituximab should be recalculated.

If these conditions are not met, the subject will be evaluated weekly.

- If after one week the non-hematological toxicities have resolved as described above, and the hematologic toxicity has resolved (ANC ≥ 1.0 × 10^9/l and platelet count ≥ 75 × 10^9/l), the next cycle can be given at full dose.
- If after one week the non-hematological toxicities have resolved as described above, and the hematologic toxicity has not resolved, dose reduction of lenalidomide, or lenalidomide and bendamustine, will be applied according to table 2 (arm A, LR) or table 3 (phase I part of the study and arm B in the phase II part, LRB).

If dose delay and/or dose reduction is necessary because of granulocytopenia, the use of G-CSF, e.g. Neulasta, 6 mg s.c. single dose on day 3 of every subsequent cycle is strongly recommended. Alternatively lenograstim 150 microgram/m^2 daily or filgrastim 300 microgram/day can be used, starting on day 3 and continuing until day 14 and/or until the ANC has recovered to ≥ 1.0 × 10^9/l following the nadir of the cycle. Other G-CSF formulations/schedules according to local policy are also allowed. The use of primary G-CSF prophylaxis is also allowed.

If peripheral blood counts have recovered after a reduced cycle, full doses can be given for the next cycle. If dose reduction was necessary for two consecutive cycles, the dose reduction must be maintained.

There will be no dose modification for rituximab. If for any reason (toxicity/intolerance) rituximab administration has to be permanently discontinued, the reasons for discontinuation of rituximab should be noted in the CRF; the patient may continue in the protocol.

Table 2. Dose modifications for hematologic toxicity in arm A (LR) of the phase II part of the study, at the start of a new cycle

ANC x10^9/l		**Platelets x10^9/l**	**Lenalidomide**	**Rituximab**
≥ 1.0	and	≥ 75	20 mg o.d. d1-21	375 mg/m^2 (max. 800 mg) i.v. or 1400 mg flat dose s.c. o.d. d1
0.75-0.99	and/or	50-74	15 mg o.d. d1-21	375 mg/m^2 (max. 800 mg) i.v. or 1400 mg flat dose s.c. o.d. d1
< 0.75	and/or	< 50	Postpone treatment for another week	

o.d.: once daily

Table 3. Dose modifications for hematologic toxicity for patients in the phase I part of the study, at the start of a new cycle

ANC x10^9/l		**Platelets x10^9/l**	**Lenalidomide**	**Rituximab**	**Bendamustine**
≥ 1.0	and	≥ 75	RDL (10, 15 or 20 mg) o.d. d3-21	375 mg/m^2 (max. 800 mg) o.d. d1	RDL (70 mg/m^2, max. 150 mg or 90 mg/m^2, max. 200 mg) o.d. d1,2
0.75-0.99	and/or	50-74	RDL-1* o.d. d3-21	375 mg/m^2 (max. 800 mg) o.d. d1	RDL -1$^{\#}$ o.d. d1,2
< 0.75	and/or	< 50	Postpone treatment for another week		

o.d.: once daily

* If the assigned or administered dose is 10 mg, dose reduction to 5 mg; if the assigned or administered dose is 15 mg, dose reduction to 10 mg; if the assigned or administered dose is 20 mg, dose reduction to 15 mg

$^{\#}$ If the assigned or administered dose is 90 mg/m^2, dose reduction to 70 mg/m^2; if the assigned or administered dose is 70 mg/m^2, dose reduction to 50 mg/m^2

Table 4. Dose modifications for hematologic toxicity for patients in the phase II part of the study, at the start of a new cycle

ANC x10^9/l		Platelets x10^9/l	Lenalidomide	Rituximab	Bendamustine
≥ 1.0	and	≥ 75	20 mg o.d. d3-21	375 mg/m^2 (max. 800 mg) i.v. or 1400 mg flat dose s.c. o.d. d1	90 mg/m^2, max. 200 mg) o.d. d1,2
0.75-0.99	and/or	50-74	15 mg o.d. d3-21	375 mg/m^2 (max. 800 mg) i.v. or 1400 mg flat dose s.c. o.d. d1	70 mg/m^2, max. 150 mg o.d. d1,2
< 0.75	and/or	< 50	Postpone treatment for another week		

o.d.: once daily

Treatment is not held for more than 28 days. If treatment is required to be held for toxicity >28 days, the subject should go off protocol treatment.

In case of major delays and/or dose reductions, please consult one of the study coordinators!

9.2.3 Special precautions and supportive care

- It is advised to start first with administration of bendamustine, because of the short sustainability (see paragraph 9.7.2)
- All patients should be well hydrated prior to the first 2 cycles. Advise patients to begin oral hydration approximately 30 ml/kg/day, approximately 2 l/day) 48 hours prior to the start of day 1 of the cycle, and to continue with this regimen until day 3. Compliance must be reviewed with the patient and documented by the site personnel prior to initiation of the cycle. Treatment is to be delayed if oral hydration is deemed to be unsatisfactory.
- For patients who are considered by the treating physician to be at high risk for tumor lysis syndrome, specific precautions should be maintained.
  Treatment with lenalidomide and bendamustine is associated with an increased risk of tumor lysis syndrome (TLS). Because the concomitant use of allopurinol has been associated with severe skin reactions including Stevens Johnson Syndrome/toxic epidermal necrolysis, the use of allopurinol should be avoided. In patients with high tumorload, the use of low-dose rasburicase (3 mg flat dose iv) before start of cycle 1 is strongly advised, unless the patient has G6PD deficiency, in which case the use of rasburicase is contraindicated. This may be repeated when necessary at the discretion of the treating physician. TLS lab should be checked twice daily during at least the first 48 hours as per the Cairo Bishop criteria.G-CSF as

secondary prophylaxis: if dose delay and/or dose reduction is necessary because of granulocytopenia, the use of G-CSF, Neulasta, 6 mg s.c. on day 3 of every subsequent cycle is strongly recommended to prevent further dose delays, dose reductions and occurrence of febrile neutropenia. Alternatively lenograstim 150 microgram/m^2 daily or filgrastim 300 microgram/day can be used. Other G-CSF formulations/schedules and the use of primary prophylaxis according to local policy are also allowed.

- Before the first rituximab dose the patient should receive clemastine 2 mg i.v. or p.o. (or any other equivalent antihistamine premedication), and paracetamol 1000 mg orally. During the first cycle of LR or LRB the patient should also receive prednisolone 25 mg i.v. (or a comparable corticosteroid dose such as hydrocortisone 100 mg) prior to the rituximab or bendamustine (whichever is given first) administration on day 1 and prior to bendamustine dosing on day 2. In subsequent cycles, prednisolone and clemastine are only given when clinically indicated (e.g. when the patient had an infusion reaction following infusion of rituximab and/or bendamustine).
- All subjects should receive thrombosis prophylaxis during induction treatment unless per the investigator discretion medical justification exists for why thrombosis prophylaxis should be held. Such reasons for holding thrombosis prophylaxis should be clearly documented. The recommended prophylaxis is aspirin [ASA] 75-100 mg daily or low-molecular-weight heparin (LMWH). Patients with additional risk factors (e.g. prior thrombotic event) should be treated with LWMH or oral vitamin K antagonists, as per local institutional practices.
- Antibiotic prophylaxis with cotrimoxazol and (val)aciclovir is mandatory for patients treated with bendamustine.The antibiotic prophylaxis should be continued until the CD4 count has recovered to >0.2x10^9/l (which can be up to 6-9 months following completion of bendamustine treatment).
- In patients with fever of unknown origin, check for CMV reactivation by CMV PCR and treat CMV reactivation according to local institutional practices.
- Antiemetic therapy is advised as per local institutional guidelines for moderately emetogenic chemotherapy, e.g. with 5HT3 antagonists and metoclopramide.
- According to the SPC of bendamustine, there is no need to irradiate blood products after bendamustine treatment. Local guidelines for irradiation of blood products should be followed.
- For patients who are treated with bendamustine yellow fever vaccination or any vaccination with other live viruses is prohibited at least until one year after the last administration of Bendamustine
- In order to prevent pregnancies during the use of lenalidomide, patient information, patient registration and patient counselling will occur as defined in the Lenalidomide Pregnancy

Prevention Risk Management Plan. For guidelines concerning the risk of pregnancy during use of bendamustine and rituximab see paragraph 12.5

Management of rash

For (dis)continuation of lenalidomide, see table 1 (page 30). For symptomatic treatment, the following guideline can be used. Reassess patients weekly.

- Grade 1 maculopapular rash (<10% of body surface area (BSA)): Study drug may be continued. Consult dermatologist and start application of topical treatment to affected areas (e.g. triamcinolon cream 0.1% or equivalent steroid cream class 2 for a facial rash; dermovate or equivalent steroid cream class 4 for other parts of the body).
- Grade 2 maculopapular rash (≥ 10% but ≤30% of BSA): study drug may be continued; consult dermatologist and start application of topical treatment to affected areas (see above) and start treatment with oral steroids (e.g. prednisolone 0.5 mg/kg day 1-7, day 7-10 15 mg, day 11-14 5 mg, then stop). Discontinue study drug if rash worsens.
- Grade 3 maculopapular rash (>30% of BSA): discontinue study drug; start application of topical treatment to affected areas (see above) and start treatment with oral steroids (e.g. prednisolone 0.5 mg/kg day 1-7, day, day 7-10 15 mg, day 11-14 5 mg, then stop).
  If the toxicity resolves to ≤ grade 1, restart with one step dose reduction.

Management of TFR (tumor flare reaction)

Investigators should be aware of the possibility of a TFR and should not assess swollen lymph nodes prematurely as progressive disease. Reassess lymph node size approximately 10 days after start of TFR treatment. A tumor flare reaction ≥ grade 2 should be treated symptomatically using steroids according to the following schedule: prednisolone day 1-3 25 mg, day 4-6 20 mg, day 7-10 10 mg, day 11-14 5 mg, then stop. Antilymphoma treatment as per treatment arm (LR or LRB) can be continued.

9.3 Rituximab maintenance treatment

9.3.1 Treatment schedule

Patients in PR or CR after induction treatment with LR or LRB will continue with rituximab maintenance treatment. Rituximab maintenance treatment should start 3 months after the start of the last induction cycle. A maximum of 8 administrations (2 years) are given. Rituximab can be given either i.v. or s.c.

Agent	**Dose/day**	**Route of administration**	**Days**
Rituximab if	375 mg/m^2 (max 800 mg) o.d.	i.v.	1 q 3 months

given i.v.			
Rituximab if given s.c.*	1400 mg fixed dose o.d.	s.c.	1 q 3 months

o.d.: once daily

Rituximab maintenance treatment is stopped earlier in case of relapse or progressive disease, or excessive toxicity

9.3.2 Dose adjustments

There are no dose adjustments for rituximab maintenance treatment.

9.3.3 Special precautions and supportive care

Standard premedication should include oral paracetamol 1000 mg and an oral or intravenous antihistamine, e.g. clemastine 2 mg; the use of steroids is usually not necessary in patients pretreated with rituximab during the induction phase. This should be managed at the discretion of the treating physician, according to local institutional policies.

9.4 Co-intervention

Patients with a history of idiopathic deep venous thrombosis and/or pulmonary embolism can be included in the study, but the use of LMWH or oral vitamin K antagonists is advised instead of aspirin. In order to prevent pregnancies during the use of lenalidomide, patient information, patient registration and patient counselling will occur as defined in the Lenalidomide Risk Management Program.

9.5 The Investigational Medicinal Product Lenalidomide

9.5.1 Summary of known and potential risks

The most common side effects of lenalidomide (seen in more than 1 patient in 10) are neutropenia, fatigue, asthenia, constipation, muscle cramp, thrombocytopenia, anemia, diarrhoea and rash. For the full list of all side effects reported with lenalidomide, see the Investigator Brochure (IB).
Lenalidomide is expected to be harmful to the unborn child. Therefore, lenalidomide must never be used in women who are pregnant. It must also not be used in women who could become pregnant, unless they take all of the necessary precautions to ensure that they are not pregnant before treatment and that they do not become pregnant during or soon after treatment. In patients with MM, treatment with lenalidomide (especially when used after autologous SCT and/or as long-term maintenance) has

been associated with a slightly increased risk of second neoplasms. Thusfar, this has not been observed in patients with lymphoma treated with lenalidomide.

9.5.2 Preparation and labeling

Lenalidomide will be shipped to trial sites in containers labeled as an Investigational Medicinal Product. Lenalidomide will be prepared and labeled in compliance with GMP and other applicable regulatory requirements.

9.5.3 Storage and handling

The investigational medicinal product should be stored in such a manner that accidental loss or destruction or access by an unauthorized person is prevented.

9.5.4 Study drug supply

The sponsor will arrange delivery of lenalidomide to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.
For The Netherlands and Germany Lenalidomide will be distributed by a central pharmacy (Hospital Pharmacy of the University Hospital Dresden). For United Kingdom local distribution will be arranged.

9.5.5 Drug accountability

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use/ return by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

9.5.6 Study drug return and destruction

Partially used investigational medicinal product should not be redispensed to either the same or another patient after it has been returned.

The trial site should destroy used or partially used study drug containers after drug accountability records have been completed. Destruction should be documented.

9.6 The Investigational Medicinal Product Rituximab

9.6.1 Summary of known and potential risks

When used to treat non-Hodgkin's lymphoma or CLL, the most common side effects seen with rituximab (seen in more than 1 patient in 10) are reactions related to the infusion (mainly fever, chills and shivering). The s.c. administration of rituximab can cause local skin reactions. Symptoms that were reported included pain, swelling, induration, hemorrhage, erythema, pruritus and rash. Some local skin reactions occurred more than 24 hours after the rituximab s.c. administration. The majority of the reactions seen following administration of rituximab s.c. were mild or moderate and resolved without any specific treatment.
For a complete list of side effects please see the current Summary of Product Characteristics for rituximab i.v. and the current Investigator Brochures for rituximab s.c.

9.6.2 Preparation and labeling

Rituximab with commercial labeling and packaging will be used. If applicable national laws and regulations do not allow this, the sponsor will arrange appropriate labeling and packaging.

9.6.3 Storage and handling

Rituximab should be stored and handled in accordance with the instructions in the summary of product characteristics or package insert.

9.6.4 Study drug supply

The investigator should use commercially available rituximab. If applicable national laws and regulations do not allow this, the sponsor will arrange delivery of rituximab to trial sites. No investigational medicinal product will be shipped until the sponsor has verified that all regulatory required documents and approvals for the site are available.

9.6.5 Drug accountability

As rituximab will be used from commercial stock, no drug accountability is required other than regular pharmacy procedures.

If national law requires detailed drug accountability please refer to paragraph 9.5.5 for more information.

9.7 The Investigational Medicinal Product Bendamustine

9.7.1 Summary of known and potential risks

The most common side effects of bendamustine (seen in more than 1 patient in 10) are neutropenia, thrombocytopenia, infections, fatigue, asthenia, rash, nausea, and fever during or following infusion. For the full list of all side effects reported with bendamustine, see the Investigator Brochure.
The use of allopurinol should be avoided in combination with bendamustine, because of the risk of Stevens Johnson Syndrome, which has been observed in patients using bendamustine in combination with allopurinol.

9.7.2 Preparation and labeling

Bendamustine will be shipped to trial sites in containers labeled as an Investigational Medicinal Product. Bendamustine will be prepared and labeled in compliance with GMP and other applicable regulatory requirements.

Bendamustine (Levact®, Ribomustin®) is available in two different vial sizes, bendamustine 25 mg or 100 mg vials (mannitol as excipient).

The dry substance of bendamustine has to be reconstituted under sterile conditions with water for injection, then diluted with sodium chloride 0.9% solution for injection, and then administered by intravenous infusion. Aseptic techniques should be used.

1. Reconstitution
   - Reconstitute each vial of bendamustine containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking
   - Reconstitute each vial of bendamustine containing 100 mg bendamustine hydrochloride in 40 ml water for injection by shaking.

   The reconstituted concentrate contains 2.5 mg bendamustine hydrochloride per ml, and appears as a clear colourless solution.

2. Dilution

   As soon as a clear solution is obtained (usually after 5-10 minutes), dilute the total recommended dose of bendamustine immediately with 0.9% NaCl solution, to produce a final volume of about 500 ml.

   Bendamustine must be diluted with 0.9% NaCl solution and not with any other injectable solution.

   The solution has to be thoroughly mixed.

3. Administration

   The solution is administered by intravenous infusion over 30-60 min.

4. Storage/Stability of final infusion solution

   Infusion solutions prepared according to the instructions outlined here remain physically and chemical stable for 3.5 hours at 25˚C/60% relative humidity and for 2 days under refrigeration. It is however preferable that the prepared solution is administered as soon as possible after preparation.

The vials are for single use only.
Any unused product or waste material should be disposed of in accordance with local requirements.

When handling bendamustine, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes!). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbing disposable foil. Pregnant personnel should be excluded from handling cytostatics.

9.7.3 Storage and handling

Bendamustine should be stored and handled in accordance with the instructions in the summary of product characteristics or package insert.

9.7.4 Study drug supply

The study drug bendamustine will be provided by Mundipharma. No investigational medicinal product will be shipped until the sponsor has verified that all
regulatory required documents and approvals for the site are available.
For The Netherlands and Germany Lenalidomide will be distributed by a central pharmacy (Hospital Pharmacy of the University Hospital Dresden). For United Kingdom local distribution will be arranged.

9.7.5 Drug accountability

The investigator, or a pharmacist or other appropriate individual who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial patients (if applicable). Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.
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9.7.6 Study drug return and destruction

Partially used investigational medicinal product should not be redispensed to either the same or another patient after it has been returned.
The trial site should destroy used or partially used study drug containers after drug accountability records have been completed. Destruction should be documented.
Unused investigational medicinal product should be retained until the sponsor has instructed the investigator on the return or destruction of the product.

10 Study procedures

10.1 Time of clinical evaluations

- At entry: laboratory tests within *2* weeks before start of treatment, BM and PET-CT scan maximally 4 weeks old, lymph node biopsy or FNA obtained at any time after previous treatment. In case of clinical suspicion of transformation a recent biopsy/FNA is required (within 3 months prior to study entry)
- During cycle 1 and 2 as indicated in table 10.2 (during cycle 1 TLS lab twice daily during at least the first 48 hours in high risk patients and then twice weekly until day 14); in non-high risk patients twice weekly until day 14
- Prior to each cycle and on day 28 of cycle 6
- On day 14 of cycle 3-6
- 6-8 weeks after start of induction cycle 6
- Before each administration of rituximab maintenance treatment (month 3, 6, 9, 12, 15, 18, 21 and 24 of maintenance treatment)
- After 12 and 24 months of maintenance treatment
- End of protocol treatment

- During follow up every 3 months for 2 years and every 6 months thereafter, up to 8 years after registration
- At progressive disease

All patients will be followed until 8 years after registration.

10.2 Required investigations

	At entry[1]	During cycle 1 -2[2]	Prior to each cycle, day 28 cycle 6	Day 14 cycle 3-6	After cycle 3 and cycle 6[15]	Prior to each Main-tenance	After 1 year of Main-tenance	End of protocol treat-ment	Follow-up[13]	Suspicion of pro-gressive Disease
Informed consent	x									
Medical history	x									
Baseline concomitant diseases / Adverse events	x	x[2]	x	x	x	x		x	x	x
Co-medication	x	x[2]	x	x	x	x		x	x	x
Physical examination	x	x[2]	x	x	x	x		x	x	x
Ann Arbor stage	x									
FLIPI score	x									
Lab tests[2]										
• hematology	x	x[16]	x	x	x	x		x	X[20]	x
• blood chemistry	x	x[2]	x		x	x		x	X[20]	x
• TLS	x	x[2]	o.i.	o.i.						
• IgG,A,M	x				x[18]		x	x		
• coagulation	x									
HIV, hepatitis B and C serology	x[1]									
Urine analysis	x[1]									
Pregnancy test[3]	x		x[3]							
BM aspirate and biopsy	x				x[10]			x[10]		x[10]
Lymph node biopsy	x[4]									
Imaging										
• CT scan	x				x[11]		x	x	x[14]	x[14]
• PETscan [17]	x				x[11]			x[12]		
Central lab for side study all patients (phase II only):[5,17]										
• **PB FC/plasma**	x	x[8]	x[9]		x		x	x		
• **PB MRD**	x				x		x	x		
• **BM MRD**	x				x[10]			x[10]		

	At entry[1]	During cycle 1-2[2]	Prior to each cycle, day 28 cycle 6	Day 14 cycle 3-6	After cycle 3 and cycle 6[15]	Prior to each Main-tenance	After 1 year of Main-tenance	End of protocol treat-ment	Follow -up[13]	Suspicion of pro-gressive Disease
Central lab for biopsy side study (phase II only) • FNA LN • LN core biopsy • PB FC/plasma	x[6]	 x[7] x[7] x[7]								
Additional tests • ECG[19] • Chest X-ray[19]	 x x									

1. Laboratory tests should be performed within 2 weeks prior to start of treatment; BM and PET-CT can be maximally 4 weeks old.
2. During cycle 1: TLS lab twice daily in high risk patients for at least 48 hours and then twice weekly until day 14 and in non-high risk patients twice weekly until day 14, e.g. on day 4, 7, 10, 14. TLS parameters during subsequent cycles only on indication (i.e. in case of TLS during cycle 1).

   During cycle 1 and 2 : CBC, liverenzymes, adverse events, comedication and physical examination weekly e.g. day 7, 14 and 21.

   For dose modifications in case of abnormal lab values, see section 9.2.2.
3. In all premenopausal women: as defined in the Lenalidomide Pregnancy Prevention Risk Management Plan (also see below).
4. At entry, a lymph node biopsy is to be performed If a lymph node biopsy is not possible, FNA should at least be performed to demonstrate relapse and CD20 positivity and to exclude transformation. Local pathology for diagnosis of relapsed FL is sufficient for study entry.
5. For more details about the side study (central lab) see lab manual and below.
6. In patients who have given informed consent for FNA/core biopsy side study: within 1 week before start of treatment and at 2-4 days after start lenalidomide treatment (see lab manual for instructions)
7. In patients who have given informed consent for FNA/core biopsy side study: also on day 6-8 after start of cycle1 (see lab manual for instructions).
8. In all patients: on day 14 of cycle 1.
9. Before start of cycle 2 only.
10. BM only after cycle 6 (or end of induction if only 4 or 5 cycles of induction are given) and at the end of maintenance, and ***only if positive at entry and otherwise in CR***. It should be scheduled 2-4 weeks after the end of cycle 6 (i.e. 6-8 weeks after the start of cycle 6). At suspicion of progressive disease if clinically indicated.
11. After cycle 3 (before cycle 4) only a CT-scan, not a PET scan. After cycle 6 PET-CT scan, with diagnostic CT (with iv and oral contrast) to be scheduled 2-4 weeks after the end of cycle 6 (i.e. 6-8 weeks after the start of cycle 6).

12. A PET scan at the end of maintenance is optional.
13. Follow-up every 3 months for 2 years and every 6 months thereafter, until 8 years after registration.
14. Once yearly during follow up, or earlier when clinically suspected of relapse/progression. This is until diagnosis of relapse/progression. In the Netherlands, during follow up, instead of CT scans a chest X-ray and ultrasound of the abdomen are also allowed.
15. If only 4 or 5 cycles of induction treatment are given before continuing with maintenance treatment, the evaluations mentioned 'after cycle 6' should be performed.
16. Hematology during cycle 1 and 2 weekly.
17. The PET-CT scan and central lab for side studies will only be performed in the phase II part of the study.
18. IgG, IgA, IgM only after cycle 6.
19. Recommended
20. After relapse/progression in follow up, hematology and blood chemistry are not mandatory at the specified timelines.

Medical history

Only at entry

Standard medical history, with special attention for:

- WHO performance status (see appendix F)
- B symptoms
- prior and present other diseases/comorbidity
- antecedent hematological or oncological diseases
- previous chemotherapy or radiotherapy for FL, response to these previous treatments (CR, PR, SD or PD) and duration of response
- concomitant medications

Baseline concomitant diseases / Adverse events to be established:

- At entry
- Weekly during cycle 1 and 2
- At day 14 during cycles 3 until cycle 6
- Prior to each cycle and on day 28 of cycle 6
- Prior to (and within one week of) each administration of rituximab maintenance treatment (month 3, 6, 9, 12, 15, 18, 21 and 24 of maintenance treatment)
- Each Follow up visit
- At suspicion of progressive disease

Physical examination to be performed:

- At entry
- Weekly during cycle 1 and 2
- At day 14 during cycles 3 until cycle 6
- Prior to each cycle and on day 28 of cycle 6

- Prior to (and within one week of) each administration of rituximab maintenance treatment (month 3, 6, 9, 12, 15, 18, 21 and 24 of maintenance treatment)
- Each Follow up visit
- At suspicion of progressive disease

Standard physical examination including special attention for:

- Vital signs (pulse, blood pressure, temperature)
- WHO performance status (see appendix F)
- Tumor flare reaction
- Adverse Events
- Presence or absence of lymphadenopathy and hepatosplenomegaly
- Body weight (height only at entry)

Lab tests (standard hematology and chemistry) should be checked:

- At entry
- Weekly during cycle 1 and cycle 2 (during cycle 1 TLS lab twice daily during at least the first 48 hours in high risk patients and then twice weekly until day 14; in non-high risk patients twice weekly until day 14; CBC and liverenzymes weekly)
- At day 14 during cycle 3 until cycle 6 (only CBC; TLS lab only on indication)
- Prior to each cycle (max. day -4) and on day 28 of cycle 6
- Prior to (and within one week of) each administration of rituximab maintenance treatment (month 3, 6, 9, 12, 15, 18, 21 and 24 of maintenance treatment)
- Each Follow up visit
- End of protocol treatment
- At progressive disease

Hematology

Hemoglobin, Leukocyte count, differential count, Platelets

Blood chemistry

At entry:

Sodium; potassium; calcium; phosphate; creatinine; calculated creatinine clearance (see appendix D); uric acid; bilirubin (total and direct); ASAT; ALAT; alkaline phosphatase; gamma glutamyl transferase; LDH; glucose; albumin; β-2 microglobulin

Other timepoints:

creatinine; bilirubin (total and direct); ASAT; ALAT; alkaline phosphatase; gamma glutamyl transferase; LDH; calcium; albumin

TLS lab

- at entry
- twice daily during at least the first 48 hours in high risk patients and then twice weekly until day 14; in non-high risk patients twice weekly until day 14; during subsequent cycles on indication.

TLS lab should include:

creatinine; calcium; phosphate; sodium, potassium; uric acid; LDH

Additional chemistry: IgG, IgM, IgA levels and M protein screening (M protein monitoring to be repeated at subsequent timepoints only if positive at entry) must be done: at entry; after cycle 6; after 12 and 24 months of maintenance treatment; or at early withdrawal if applicable.

Coagulation should include:

aPTT, PT or APTR and INR (only at study entry, otherwise on indication)

Pregnancy test

In all premenopausal women a pregnancy test (serum or urine) should be performed as defined in the Lenalidomide Pregnancy Prevention Risk management plan:

- at entry
- in women with regular or no menstrual cycle : weekly for the first 28 days of study participation and then every 28 days while on lenalidomide treatment at lenalidomide discontinuation, and at day 28 following lenalidomide discontinuation.
- If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on lenalidomide treatment, at lenalidomide discontinuation, and at days 14 and 28 following lenalidomide discontinuation.

Lymph node biopsy

Before study entry (at any time prior to study entry, but in any case after previous treatment), a lymph node biopsy for confirmation of a diagnosis of relapsed FL and exclusion of transformation (both

according to the WHO classification 2008[3]) should be performed. CD20 positivity should be confirmed. In case of clinical suspicion of transformation a recent biopsy/FNA is required (within 3 months prior to study entry).
If a lymph node biopsy is not at all possible, at the very least core biopsies/FNA should be performed to demonstrate relapse and CD20 positivity, and to exclude transformation.
Local pathology assessment for diagnosis of relapsed FL is sufficient for study entry.
Representative formalin-fixed paraffin-embedded biopsy samples and if available cryopreserved tissue samples should be sent to the central pathology registry for central pathology review and ancillary biological side studies (see 10.4.1 and lab manual).

Bone marrow

Bone marrow aspirate for morphology, flow cytometry, and molecular studies (for details see lab manual) and bone marrow biopsy (at least 2 cm), for morphology and immunohistochemistry must be done:

- At entry
- At the end of induction (usually after cycle 6 (6-8 weeks after the start of cycle 6; 2-4 weeks after the end of cycle 6) and at the end of maintenance (only if positive at entry, and only to confirm CR)
- At progressive disease or relapse if clinically indicated

Central lab

Evaluations by the central lab only apply for patients in phase II part of the study.

Imaging

A CT scan or PET-CT (with diagnostic CT with iv and oral contrast) of the cervical region, chest, abdomen and pelvis with bidimensional measurements must be performed. For the measurement of the lymph nodes involved, a contrast-enhanced CT is required. Therefore, if a non-contrast enhanced PET-CT is performed, the patient also needs a contemporaneous contrast-enhanced CT (separate study to the PET-CT).
Description of nodal regions according to the FLIPI score (see appendix E) should be performed.
NB in the phase I part of the study, PET scans are not required (and not reimbursed).

The following imaging studies should be performed:

- PET-CT scan at entry and at the end of induction (usually after cycle 6, alternatively after cycle 4 or 5 if induction treatment is stopped earlier because of toxicity), with diagnostic CT (with iv and oral contrast). A PET scan at the end of maintenance is optional. (In the phase I part of the study, only a CT scan can be made. PET scans are not required in the phase I part.)

- CT scan 3-4 weeks after cycle 3 (before start of cycle 4), after 1 year of maintenance and at the end of maintenance or at the end of protocol treatment if maintenance is stopped early. Thereafter yearly imaging is to be performed. In the Netherlands, instead of CT scans, during follow-up patients can also be followed with a chest X-ray and ultrasound of the abdomen.
- CT scan at clinical suspicion of progressive disease to confirm relapse/progression

Additional tests at entry

- Chest X-Ray (recommended)
- ECG (recommended)
- HIV & hepatitis B and C screening
- Routine urine analysis (dipstick)

Side studies: Sampling of peripheral blood, BM, lymph node FNA and core needle biopsies (only for patients in phase II part of the study)

	PB MRD	BM MRD	PB FC	Plasma	FNA LN*	Core biopsies LN*
T1 = before start	X	X	X	X	X*	
T2 = +6-8 days*,&			X*,&	X*,&	X*,&	X*,&
T3 = before cycle 2			X	X		
T4 = before cycle 4	X		X	X		
T5 = after cycle 6	X	X#	X	X		
T6 = after 1 yr of maint	X		X	X		
T7 = end of maint	X	X#	X	X		

* only in patients who have given informed consent for the FNA/core biopsy side study, and only in cycle 1. This will be done at selected study sites only in the Netherlands and Germany. To be eligible for the FNA/biopsy side study, a pretreatment biopsy has to be available.

& 6-8 days after start of cycle 1

Only in patients with bone marrow involvement at study entry, and only if a bone marrow examination is repeated to confirm CR.

Sampling of peripheral blood and bone marrow for side studies is only done in patients participating in the phase II part of the study.

More details will be given in the laboratory manual.

10.3 Response evaluation

Response will be evaluated :

- after cycle 3 (just before cycle 4)
- after cycle 6 (at the end of induction; if for reasons of toxicity only 4 or 5 cycles of induction treatment are given, evaluation should be done after the last cycle of induction treatment)
- after 1 year of rituximab maintenance and at the end of maintenance
- at the end of protocol treatment
- at early withdrawal
- yearly during follow up
- at suspicion of progression

according to appendix C.

10.3.1 Definition of Response

Response will be determined according to the definitions of response (Cheson criteria, revised version 2007) and documented at visits outlined in the table with required investigations (par. 10.2). For a tabular summary of all criteria of response definition in NHL patients see Appendix C.
Because for the patients in phase I of the study a PET scan is not required or reimbursed, they should be evaluated as if the FDG-PET scan was negative (category 2b in the revised Cheson criteria).

10.4 Central review

10.4.1 Pathology review

Once a patient is registered in the study, HOVON Pathology Facility and Biobank will be notified by the HOVON Data Center and biopsy samples for review and planned side studies will be requested from the local pathology laboratory according to routine procedures. In this request it is mentioned that the patient has given informed consent for review and for the additional research on the (coded) material. A coded pathology report with the pathology number of the specimen, age and gender of the patient, the HOVON protocol number and the HOVON patient study number should be provided together with the specimens for review and research. According to the guidelines of HOVON, the name and all data that can lead to direct identification of the patient should be omitted from all correspondence.
Fifteen unstained slides from paraffin embedded specimens of a representative lymph node biopsy or biopsy of a representative extranodal site, together with a representative paraffin embedded tissue block as well as a copy of the report should be sent to the HOVON Pathology Facility and Biobank at the time of registration.

If only very limited material is available (e.g. endoscopic biopsy samples, large needle biopsy samples) 10 unstained sections may be sent for immunohistochemical confirmation only and/or the immunohistochemical stains from the original lab, that will be returned immediately after review.
Both diagnostic pre-treatment material and material of confirmation of relapse should be sent.
Confirmation of diagnosis (by the review panel) is not necessary for registration and start of treatment.
Central review is performed to confirm the detailed classifying diagnosis. Classification includes immunophenotypical characterization by a standard panel of markers depending on the specific lymphoma type. The review analysis will be done without knowledge of patient clinical outcome.
Central review is done for Dutch cases by Daphne de Jong, for German cases by Wolfram Klapper and for UK cases by Sarah Coupland. In case of diagnostic difficulties and/or major discrepancies with clinical consequences for treatment and/or follow-up, the review pathologists will discuss those cases together, and report to the principal investigator as soon as possible. The principal investigator will be responsible for communication with the local treating physician(s).
Additional molecular studies may be performed as part of the diagnostic review process if needed.
Within 3 months after the review process and integration in the TMA, the material will be returned to the original laboratory. In the UK it will be kept until the end off study. A copy of the results of the review will be sent to the HOVON Data Center.

All histological materials are to be sent to:
HOVON Pathology Facility and Biobank
Department of Pathologie Medical Administration
t.a.v. N. Hijmering
VU University Medical Center
Department of Pathology ZH 1 E 20
De Boelelaan 1117
1081 HV Amsterdam
The Netherlands
tel: 31-20-4444978
fax: 31-20-4444586
daphne.dejong@vumc.nl, n.hijmering@vumc.nl

Dr. W. Klapper (for GLSG patients)
Department of Pathology
Hematopathology Section and Lymph Node Registry
PO Box 7154
D-24171 Kiel, Germany
Tel: +49-431-597-3399

Fax: +49-431-597-4129

Dr. S. Coupland (for UK patients)
Dept of Molecular & Clinical Cancer Medicine
University of Liverpool
5th Floor Duncan Building
Daulby Street
Liverpool
L69 3GA, UK
Tel: +44-151-706-5885
Fax:+44-151-706-5859

Further details can be found in the laboratory manual.

10.4.2 PET review

For central PET review all FDG-PET scans, with and without attenuation correction, and CT-scans will be anonymized and either uploaded to a secure ftp-server or burnt on a CD-rom. The PET review will take place retrospectively.
Whole body scans will be displayed in both projection and volume views, the latter using coronal, sagittal and transaxial views. At least three experienced readers from the HOVON Imaging group, the GLSG and the UK will independently interpret the images on an image display and score each lymph node region according to visual assessment as positive or negative. The PET scans are scored with knowledge of the CT data. A residual mass > 2 cm in greatest transverse diameter on CT, regardless of their location, is considered positive on PET in case of clearly enhanced diffuse or focal uptake higher than that of mediastinal blood pool activity. A smaller residual mass or a normal sized lymph node (i.e., < 2cm in diameter) should be considered positive if its activity is above that of the surrounding background. PET is also considered positive in case of new sites with focally enhanced uptake considered to represent lymphoma involvement.
Further details (e.g. acquisition protocol, use of standard uptake values (SUV) can be found in the lab manual.

10.5 Side studies

Objectives of the side studies are:

- **To identify tissue-based predictive factors for response**. In the non-chemotherapy-based lenalidomide-rituximab regimen and in the chemotherapy-based lenalidomide-rituximab-

bendamustine regimen, various tissue-associated markers will be explored both on tumor cells and on non-malignant cells of the tumor microenvironment using tissue microarrays and immunohistochemistry on whole sections of the lymphoma biopsy samples. These studies will be supported by gene expression profiling (Affymetrix arrays) and/or mutation analysis in a selection of patients as well as by evaluation by FACS analysis of T cell and NK cell subsets in peripheral blood. Martin Dreyling, Christian Buske, Ton Hagenbeek, Marie José Kersten, and the central pathologists for HOVON, Daphne de Jong (VU University Medical Center) and the GLSLG, Wolfram Klapper (University of Kiel) are all involved in the LLBC (Lunenburg Lymphoma Biomarker Consortium). Our laboratories have a long-standing research interest in the biology of follicular lymphoma, using various techniques such as automated scoring of immunohistochemical stains on tissue microarray, mutation analysis by NGS and gene expression profiling. Both HOVON and GLSG have successfully completed several clinical trials mainly studying immunochemotherapy in patients with follicular lymphoma.

- **To study longitudinally the effect of lenalidomide versus lenalidomide-bendamustine on T cell subsets and NK cells in peripheral blood and at the tissue level.** Because lenalidomide has been shown to augment and activate T-cells and NK-cells[69], and bendamustine has been shown to have an immunosuppressive effect, it will be relevant to study the effect of lenalidomide alone versus the combination of lenalidomide and bendamustine on macrophages, T cell and NK cell subsets during treatment, both in the peripheral blood, and at the tissue level based on fine needle aspirates obtained after 6-8 days after start of treatment in cycle 1. Peripheral blood will be collected in all patients (HOVON/GLSG/UK). FNA/rebiopsy studies will be done only in a subset of patients (only HOVON and GLSG). UK peripheral blood samples will be stored centrally in the UK and analysed at the AMC. All the analyses will be done in the laboratory for experimental hematology and immunology at the AMC (for HOVON and UK patients), and at the laboratory for experimental hematology of the University of Kiel (for GLSG patients). In a subset of patients (15-20 patients in each arm, with easily accessible peripheral lymph nodes) fine needle aspiration (FNA) will be performed before start of lenalidomide in cycle 1, and fine needle aspiration and large core needle biopsies (3x 16G, two of which will be snap-frozen, one will be formalin-fixed) will be performed on day 6-8 after start of treatment in cycle 1. Flow cytometric analysis (FNA) and immunohistochemistry will be performed to study T cell populations/subsets, NK cells and macrophages, in order to study the effect of treatment on the tumor microenvironment (see above). FNA/rebiopsy studies will be done only in a subset of patients (only HOVON and GLSG) to study the effect of lenalidomide and bendamustine on T-, NK- and macrophage subsets at the tissue level as well. The tissue samples will be studied centrally via the HOVON Pathology Facility and Biobank at VUmc.
- **To study the biological mechanisms of tumor cell kill.** In the subset of patients in whom pre- and post-treatment FNA/biopsies will be performed. RNA will be isolated from a snap-frozen biopsy

for gene expression analysis and RT-MLPA (multiplex ligation-dependent amplification procedure) using an MLPA assay specifically designed to monitorat 33 apoptosis regulators[70]. Previously, this has been described by us to be feasible and highly informative about the mechanisms of the treatment effect of low-dose radiotherapy in follicular lymphoma[71]. These studies will be performed at the laboratory for experimental hematology and immunology at the Academic Medical Center (MLPA, flow cytometry for HOVON patients), at the laboratory for experimental hematology of the University of Kiel (flow cytometry for GLSG patients); and at the laboratory for experimental hematology of the University of Ulm (gene expression profiling).

- **To evaluate prospectively the quality of the response in both arms.** Recent data have shown that OS is significantly increased in FL patients reaching a CR when compared to patients reaching a PR[20], indicating that the quality of the response is important. We therefore propose to study the depth of the response by looking at the rate of molecular remission and the rate of FDG-negativity in the phase II part of the trial:
    - **clinical utility of PET-CT scanning in FL** (PET-CT scans to be performed before start and at the end of induction (before start of maintenance), and recommended at the end of maintenance treatment). There are only few prospective data on the utility of PET-CT scanning in FL, and therefore this study using a highly effective treatment modality may provide important information on this subject.
    - **To evaluate the rate of molecular remission in both arms** (in PB after 3 cycles, at the end of induction (after cycle 6, before start of maintenance), after one year of maintenance and at the end of maintenance treatment). Evaluation of molecular remission will be performed by BCL2/IgH quantitative real-time PCR centrally by Sanquin (prof. dr. E. van der Schoot) for HOVON/UK patients and at the laboratory for experimental hematology of the University of Kiel (dr. C. Pott) for GLSG patients.

Logistic details concerning the collection, sending and storage of materials for the side studies can be found in the lab manual.

11 Withdrawal of patients or premature termination of the study

11.1 Specific criteria for withdrawal of individual patients

Patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a patient from the study for urgent medical reasons. Specific criteria for withdrawal are:

- Death
- Excessive toxicity
- No compliance of the patient

- Refusal to continue protocol treatment
- Progression/relapse during protocol treatment
- Not at least PR after 6 cycles.

11.2 Follow up of patients withdrawn from treatment

Patients who are withdrawn from treatment for other reasons than death will be followed as described in 10.2 for follow up.
For patients who are withdrawn from treatment because in hindsight they did not fulfill the eligibility criteria (see 8.1) at time of enrollment, data will be collected until 30 days after the last protocol treatment given. SAE information will be collected as described in 12.3
No further information will be collected for patients who have withdrawn their consent. If a patient withdraws consent please consult HOVON Data Center.
Patients who are withdrawn from protocol treatment will receive medical care according to local practice.

11.3 Premature termination of the study

The sponsor may decide to terminate the study prematurely based on the following criteria:

- One of the stopping rules has been reached [paragraph 14.1];
- There is evidence of an unacceptable risk for study patients (i.e. safety issue);
- There is reason to conclude that it will not be possible to collect the data necessary to reach the study objectives and it is therefore not ethical to continue enrolment of more patients; for example insufficient enrolment that cannot be improved.
- The DSMB recommends to end the trial based on viable arguments other than described above

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s) and the regulatory authorities of the decision to terminate the study. The sponsor will provide information regarding the time lines of study termination and instructions regarding treatment and data collection of enrolled patients.

12 Safety

12.1 Definitions

Adverse event (AE)
An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject during protocol treatment. An AE does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious adverse event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose results in:

- Death
- A life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- Hospitalization or prolongation of hospitalization
- Significant / persistent disability
- A congenital anomaly / birth defect
- Any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above, including suspected transmission of infectious agents by a medicinal product).

Note that relapse/progression of the FL do not have to be reported as an SAE but that ANY death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

Suspected unexpected serious adverse reaction (SUSAR)

All **suspected** Adverse Reactions which occur in the trial and that are both **unexpected** and **serious**. Suspected adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected. Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

12.2 Adverse event

12.2.1 Reporting of adverse events

Adverse events will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.

Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.
Adverse Events have to be reported on the Adverse Events CRF. Adverse Events will be scored according to the NCI Common Terminology Criteria for Adverse Events, version 4 (see appendix H) ***except for TLS and TFR which should be graded according to appendix I and appendix J.***
Pre-existing conditions will be collected on the baseline concomitant diseases CRF, i.e. active (symptomatic) diseases of any grade diseases under treatment, chronic diseases and long term effects of past events as present at the time of baseline assessment.

All Adverse Events have to be reported, with the exception of:

- A pre-existing condition that does not increase in severity; the pre-existing condition should be reported on the baseline concomitant diseases CRF
- AEs of CTCAE grade 1. ***However TLS and TFR MUST be reported in case of CTCAE grade ≥ 1 according to appendix I and J respectively.***
- Abnormal laboratory values that have been recorded as being not clinically significant by the investigator in the source documents
- Progression of the disease under study; complaints and complications as a result of disease progression remain reportable adverse events
- Hematological adverse events (information on hematologic toxicity (nadir) is collected on the treatment CRF)

12.2.2 Follow up of adverse events

All adverse events will be followed clinically until they have been resolved, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
Any ongoing adverse event that increases in severity is to be reported as a new adverse event on the CRF. Other follow up information is not collected on the CRF.

12.3 Serious Adverse Events

12.3.1 Reporting of serious adverse events

Serious Adverse Events (SAEs) will be reported from the first study-related procedure until 30 days following the last dose of any drug from the protocol treatment schedule or until the start of subsequent systemic therapy for the disease under study, if earlier.
Serious Adverse events occurring after 30 days should also be reported if considered at least possibly related to the investigational medicinal product by the investigator.

SAEs must be reported to the HOVON Data Center **within 24 hours** after the event was known to the investigator, using the SAE report form provided. This initial report should contain a minimum amount of information regarding the event, associated treatment and patient identification, as described in the detail in the instructions for the SAE report form. Complete detailed information should be provided in a follow-up report within a further 2 business days, if necessary.

The following events are not considered to be a Serious Adverse Event:

- Relapse/progression of the FL; **death or complications as a result of disease progression remain reportable serious adverse events**
- Hospitalization for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- Hospitalization for diagnostic investigations (e.g., scans, endoscopy, sampling for laboratory tests, bone marrow sampling) that are not related to an adverse event. Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- Hospitalization for a procedure that was planned prior to study participation (i.e. prior to registration or randomization). This should be recorded in the source documents. Prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.

12.3.2 Causality assessment of Serious Adverse Events

The investigator will decide whether the serious adverse event is related to trial medication, i.e. any of the products from the protocol treatment schedule. The decision will be recorded on the serious adverse event report. The assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship.

12.3.3 Follow up of Serious Adverse Events

All serious adverse events will be followed clinically until they are resolved or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
Follow up information on SAEs should be reported monthly until recovery or until a stable situation has been reached. The final outcome of the SAE should be reported on a final SAE report.

12.3.4 Processing of serious adverse event reports

The HOVON Data Center will forward all SAE reports within 24 hours of receipt to the Principal Investigator, Celgene, Mundipharma Research GmbH & Co. KG and Roche.
The HDC safety desk will evaluate if the SAE qualifies as a suspected unexpected serious adverse reaction (SUSAR).
The current IB (for lenalidomide and rituximab s.c.) and the SmPC (for rituximab i.v. and bendamustine) will be used as a reference document for expectedness assessment.
The HOVON Data Center will ensure that a six-monthly line listing of all reported SAEs is provided to the Ethics Committee(s) if this is required by national laws or regulations or by the procedures of the Ethics Committee.

12.4 Reporting Suspected Unexpected Serious Adverse Reactions

The HDC Safety Desk, on behalf of the sponsor, will ensure the reporting of any SUSARs to the Ethics Committees (EC), the Competent Authorities (CA), Celgene, Mundipharma Research GmbH & Co. KG, Roche and the investigators in compliance with applicable laws and regulations, and in accordance with any trial specific agreements between the sponsor and a co-sponsor or Celgene and Mundipharma Research GmbH & Co. KG and Roche.
Expedited reporting of SUSARs will occur no later than 15 days after the HOVON Data Center had first knowledge of the serious adverse event. For fatal or life-threatening cases this will be no later than 7 days for a preliminary report, with another 8 days for a complete report.
The manner of SUSAR reporting will be in compliance with the procedures of the Ethics Committees and Health Authorities involved.

12.5 Pregnancies

Patients being treated with bendamustine are advised not to father a child during and for up to 6 months following end of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with bendamustine.

Rituximab is known to pass the placenta and may get into breast milk. As a result, it may possible cause a temporary lymphopenia in the unborn baby, up to now is has not been described that the risk of infections for the baby is increased.
Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.
Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception at the same time, from the time of signing the informed consent form through until 12 months after the last dose of rituximab
- OR agree to completely abstain from heterosexual intercourse (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Male patients, even if surgically sterilized (i.e., status post-vasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose rituximab,
- OR agree to completely abstain from heterosexual intercourse (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

In order to prevent pregnancies during the use of lenalidomide, patient information, patient registration and patient counseling will occur as defined in the Lenalidomide Pregnancy Prevention Risk Management Plan (www.hovon.nl, documentation HOVON 110 FL trial).

Pregnancies of a female subject or the female partner of a male subject, occurring while the subject is on protocol treatment or within 6 months following the last dose of bendamustine and within 30 days following the last dose of lenalidomide and within 12 months following the last dose of rituximab from the protocol treatment schedule, should be reported to the sponsor. Pregnancies must be reported to the HOVON Data Center within 24 hours after the event was known to the investigator, using the pregnancy report form provided.

The investigator will follow the female subject until completion of the pregnancy, and must notify the sponsor of the outcome of the pregnancy within 5 days or as specified below. The investigator will provide this information as a follow-up to the initial pregnancy report. If the outcome of the pregnancy meets the criteria for classification as a SAE (i.e., spontaneous or therapeutic abortion, stillbirth, neonatal death, or congenital anomaly - including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs. In the case of a live “normal” birth, the sponsor should be informed as soon as the information is available. All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the investigator suspects is related to the in utero exposure to the investigational medicinal product(s) should also be reported.
The investigator is encouraged to provide outcome information of the pregnancy of the female partner of a male subject, if this information is available to the investigator and the female partner gives her permission.
HOVON Data Center will forward any information regarding (suspected) pregnancies to Celgene and Mundipharma Research GmbH & Co. KG immediately by fax or by phone or email.

12.6 Second Primary Malignancies

Second primary malignancies (SPM) will be monitored as events of interest and must be reported as serious adverse events within 24 hours on an SAE report form. This includes any second primary

malignancy, regardless of causal relationship to any study drug, occurring at any time for the duration of the study, from the time of signing informed consent until 8 years after registration in the trial.
Events of second primary malignancy are to be reported using the SAE report form and must be considered an “Important Medical Event” even if no other serious criteria apply. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (e.g., pathology report.).
The incidence of second primary malignancies is also monitored via a separate form (Second Primary Malignancy Report Form). This form should be filled out, dated and signed by the responsible investigator and returned to the HOVON Data Center within 24 hours after establishment of a second primary malignancy.
SPM must also be documented in the other appropriate page(s) of the CRF (e.g. Adverse Event Form and Follow up Form)

For each case of SPM occurring during treatment, contact the Principal Investigator to discuss if treatment needs to be discontinued

12.7 Reporting of safety issues

The sponsor will promptly notify all concerned investigators, the Ethics Committee(s), the regulatory authorities and Celgene and/or Mundipharma Research GmbH & Co. KG of findings that could affect adversely the safety of patients, impact the conduct of the trial, increase the risk of participation or otherwise alter the EC's approval to continue the trial.
In the occurrence of such an event the sponsor and the investigators will take appropriate urgent safety measures to protect the patients against any immediate hazard. The accredited Ethics Committee may suspend the study pending further review, except insofar as suspension would jeopardize the patient’s health. The local investigator will inform the patients.

12.8 Annual safety report

The sponsor will submit, once a year throughout the clinical trial, a safety report to the Ethics Committees and Competent Authorities of the concerned Member States. The content and format of the annual safety report will be according to the ICH E2F guideline ‘*Note for guidance on development safety update reports*’.

12.9 Data Safety and Monitoring Board

The Data and Safety Monitoring Board will advise the chair of the HOVON working group, the Principal Investigator and the Co-investigator(s) about the continuation of the study. The DSMB will evaluate the

general progress and the feasibility of the study, the quality and completeness of the data, side effects and safety, and differences between the arms.

The DSMB consists of at least 3 members, among whom (at least) one statistician and minimally two physicians. The members of the DSMB are invited on personal title on the basis of their expert knowledge of the disease involved or the research methodology. Members of the DSMB will have ample experience with randomized clinical trials.
The members of the DSMB will not be involved in the study, work at the HOVON Data Center, be a member of the HOVON board, or work in a hospital department participating in the study. The members will not have a conflict of interest due to ties with a company involved in the study.
The DSMB reports their written recommendations to the trial statistician. The report may consist of a confidential and a public part, where the confidential part contains references to unblinded data. The trial statistician forwards the public part of the DSMB recommendation to the Principal Investigator, the Co-investigator(s) and the chair of the HOVON working group involved. The DSMB recommendations are not binding.

The DSMB will receive at least the following reports from the trial statistician for review:

- Interim analysis report (as described in 14.3)
- Annual safety data listing the incidence of (serious) adverse events, (serious) adverse reactions and SUSARs
- Annual progress data listing the number of enrolled patients and the status of data collection

13 Endpoints

13.1 Definitions

13.1.1 DLT and RDL (phase I)

Term	Abbreviation	Definition
Dose-limiting toxicity	DLT	Adverse event of severity or consequence that may limit dose escalation. In this trial, DLT is defined as: - grade ≥ 3 non-hematologic toxicity[#] - grade 4 neutropenia lasting ≥ 7 days* - grade 4 febrile neutropenia - grade 4 thrombocytopenia[‡] - death whatever the cause, except death due to lymphoma

		any of which must occur before day 29 of cycle I (for deciding on expansion or escalation) and cycle II (for establishing RDL)
Recommended phase II dose level	RDL	Dose (level) recommended for further study in phase II part of the study i.e. the maximum dose at which only 0/1 of 6 patients exhibit DLT after cycles I and II

 # Exceptions:

1. Non-hematologic toxicity clearly attributed to rituximab is not counted as DLT
2. For skin toxicity, grade 3 toxicity is only considered to be DLT if all criteria for grade 3 are met (CTC 4.0, Skin and subcutaneous tissue disorders – others, specify. Grade 3: Disabling; severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL) and/or if >90% of the body surface area is affected.
3. Laboratory abnormalities grade 3 are only considered to be DLT if they persist for > 2 weeks or if they do not return to ≤ grade 1
4. For nausea, vomiting, or diarrhea, subjects must have a grade 3 or 4 event that persists at this level despite the use of optimal symptomatic treatment, in order for these events to be considered a DLT
5. Any infection/fever requiring iv antibiotics is not considered to be a DLT, only grade 4 infection is considered to be a DLT
6. Grade 3 or 4 thromboembolic events and grade 3 hypertension are not considered to be DLT
7. If a DLT is attributed to progressive disease, it will not be counted as DLT.

* unless due to bone marrow infiltration of the lymphoma, and despite the use of G-CSF

‡ unless due to bone marrow infiltration of the lymphoma

13.1.2 Severe toxicity (phase II)

- all toxicities qualifying as DLT in paragraph 13.1.1 also qualify as severe toxicity in phase II of the study.

13.2 Phase I

Primary endpoints

- dose limiting toxicity
- recommended dose level of lenalidomide and of bendamustine in combination with rituximab (for arm B of the phase II of the study)

13.3 Phase II

Primary endpoints

- complete remission rate (based on the revised Cheson criteria[60])
- rate of severe toxicity.

Secondary endpoints

- Overall response rate following induction treatment and at the end of maintenance rituximab
- Molecular response rate.
- Event free survival (EFS; i.e. time from registration to induction failure, progression, relapse or death, whichever occurs first). A patient counts as induction failure if no PR or CR was achieved after induciton.
- progression free survival (PFS; i.e. time from registration to disease progression, relapse or death, whichever occurs first);
- disease free survival (DFS; i.e. time from CR to relapse or death, whichever comes first)
- time to next antilymphoma treatment
- overall survival (O.S.; i.e. time from registration until death)
- relative dose intensity of lenalidomide and, if applicable, bendamustine

14 Statistical considerations

14.1 Patient numbers and power considerations

14.1.1 Phase I

Due to the '3+3' dose-escalation scheme, a minimum of 15 and a maximum of 24 evaluable patients will be entered in the phase I part.
Patients who die of lymphoma within 28 days after start of cycle II without having obtained a DLT and patients who stop protocol treatment with 28 days after start of cycle II without having obtained a DLT, will be considered to be non-evaluable for DLT, and will be replaced.

14.1.2 Phase II

This is a 2-arm randomized phase II study, in which the response to and feasibility of both treatment arms will be analyzed separately. A formal comparison between the two treatment arms will not be performed. For each treatment arm, the optimal Bryant-Day[73] 2-stage design will be applied. This design shields patients from an ineffective or toxic treatment by requiring early termination of the trial if the CR rate during/after induction treatment is poor or the severe toxicity rate is high. The independent

DSMB will advise the principal investigators on the decision to continue one or two arms of the study after the interim analysis.
In this trial, patients count as having a CR if a CR is obtained during, or within 8 weeks after the last induction cycles. Since the PET-CT is considered to be experimental in this setting, assessment of CR is based on the conventional CT scan using the Cheson criteria.
For severe toxicity the same criteria are used that are used to define dose limiting toxicity (DLT): see paragraph 13.1.2.

The following parameters and decision rules are used:

- P_{CR0} is the largest CR probability which, if true, implies that the therapeutic activity is too low and does not warrant further investigation of the regimen. In the present trial, P_{CR0} has been taken as 20%.
- P_{CR1} is the lowest CR probability which, if true, implies that the therapeutic activity is sufficiently high and does warrant further investigation of the regimen. In the present trial, P_{CR1} has been taken as 35%.
- P_{tox0} is the smallest severe toxicity probability which, if true, implies that the severe toxicity is unacceptable and does not warrant further investigation of the regimen. In the present trial, P_{tox0} has been taken as 40%.
- P_{tox1} is the largest severe toxicity probability which, if true, implies that the severe toxicity is acceptable and does warrant further investigation of the regimen. In the present trial, P_{tox1} has been taken as 20%.

Statistical errors will be:

- α_{CR} is the accepted probability of recommending for further investigation a regimen with a true CR rate equal to or lower than P_{CR0}. In the present trial, α_{CR} has been taken as 0.10.
- α_{tox} is the accepted probability of recommending for further investigation a regimen with a true severe toxicity rate equal to or higher than $P_{tox0.}$ In the present trial, α_{tox} has been taken as 0.10.
- β is the accepted probability of rejecting from further trials a regimen with a true CR rate at least equal to P_{CR1} and a true toxicity rate equal to or lower than P_{tox1}. In the present trial, β has been taken as 0.10.

These design parameters imply that in each treatment arm a maximum of 68 registered patients will be assessable after induction treatment for CR rate and severe toxicity, with an interim analysis after the first 37 registered patients, or as soon as 14 severe toxicities have been reported in the first 37 registered patients, whichever comes first:

- if after the first 37 patients in a treatment arm ≤ 8 CRs (21.6%) are observed, or if ≥ 14 severe toxicities (37.8%) are observed, that arm will be closed to further patient entry with the conclusion

that the arm is not enough active or is too toxic, and should not be further investigated. Otherwise patient entry will be extended to 68 patients.
- if after 68 patients in a treatment arm ≤ 17 CRs (25.0%, 90% CI = 16.6-35.1%) are observed, or if ≥ 23 severe toxicities (33.8%, 90% CI = 24.3-44.4%) are observed, the conclusion will be that the arm is not enough active or is too toxic, and should not be further investigated.
- otherwise, the trial will conclude that the arm is active and feasible, and warrants further investigation in this patient population.

In order to overcome dropouts due to ineligibility, 75 patients will be included in each arm.
Additionally, decisions on feasibility of either of the 2 arms will be based on the median number of cycles that can be delivered, and the relative dose intensity which has been reached.

14.2 Statistical analysis

All main analyses will be according the intention to treat principle, restricted to eligible patients.
Since this is a randomized phase II study, no direct comparison between the arms will be performed. Both arms will be evaluated separately, based on efficacy and toxicity.
The main endpoints of the phase 2 are the proportion of patients who obtain a CR during induction chemotherapy and the proportion of patients with severe toxicity. This will be evaluated as soon as all data regarding induction treatment for all patients are available and have been validated. Additional analyses will be performed when for all patients the data on maintenance treatment have been evaluated, and also when complete follow up until 8 years from registration is available for all patients.

14.2.1 Efficacy analysis

- Per treatment arm, the response rate (especially CR) will be calculated along with the 95% confidence interval (CI). This will be done for response after induction and response on protocol treatment.

- Per treatment arm, the actuarial curves for EFS, PFS, DFS and OS, will be computed using the Kaplan-Meier method and 95% CIs will be constructed.

- Per treatment arm actuarial probabilities of progression and death without progression (= events for PFS) with corresponding standard errors will be calculated using the competing risk method. Similar analyses will also be performed for EFS and DFS.

14.2.2 Toxicity analysis

- Per treatment arm (or in the phase I part of the study, per dose level), the analysis of treatment toxicity will be done primarily by tabulation of the incidence of adverse events and infections by treatment cycle.

- Per treatment arm (or in the phase I part of the study, per dose level), the incidence of the adverse events defined as DLT or severe toxicity will be reported by cycle as well as by patient.

14.2.3 Additional analyses

Additional analyses may involve the analysis of prognostic factors, eg. age, Ann Arbor stage and FLIPI and prior therapy, with respect to response rate and survival endpoints. Logistic and Cox regression could be used for this purpose. Before any additional analysis will be performed, a separate analysis plan will be discussed with the PI. Any such analysis should, however, be considered as exploratory, i.e. hypothesis generating, and not confirmatory.

14.2.4 Statistical analysis plan (optional)

A detailed statistical analysis plan (SAP) will be made for the final analysis. It will be discussed with the study coordinators and can only affect the exploratory analyses, but not the primary analysis on which the sample size is based.

14.3 Interim analysis

Several safety analyses and one formal interim analyses are planned.
Phase I, establishing RDL: after every 3 patients have completed cycle 1 in each dose level of phase I of the study, a safety analysis is performed to determine whether patients can be included in the next dose level.
Phase II: an interim analysis will be performed after the first 37 patients have been registered and received induction treatment in each arm, or as soon as severe toxicities have been reported in 14 patients among the first 37 registered patients in each treatment arm, whichever comes first.
A DSMB will be installed which will advise the investigators at the end of the phase I part of the study on the determination of the recommended dose level, and will advise about (dis)continuation of each treatment arm at the interim analysis in the phase II part of the study.

15 Registration and Randomization

15.1 Regulatory Documentation

Required regulatory and administrative documents must be provided to the HOVON Data Center before shipment of study drug and before enrolment of the first patient. This will always include an Ethics Committee approval for the investigational site. The HOVON Data Center will provide each investigator with an overview of the required documents. Each investigational site will be notified when all requirements are met and enrolment can start.

15.2 Registration and Randomization

Eligible patients should be registered before start of treatment. Patients need to be registered at the HOVON Data Center by one of the following options:

- Trial Online Process (TOP, https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.
- By faxing the completed registration/randomization CRF +31.10.7041028 Monday through Friday, from 09:00 to 17:00 CET
- By phone +31.10.7041560 Monday through Friday, from 09:00 to 17:00 CET

Patients for the phase I part of the trial can only be registered by phone or by fax.

The following information will be requested at registration:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Local patient code (optional)
- Sex
- Date of birth
- Date written informed consent
- Pathology number (relapse)
- Original pathology laboratory (relapse)
- Specific items patient gives consent for (see ICF)
- Planned date start cycle 1
- Eligibility criteria, please make sure that you have detailed information available on disease status and prior treatment
- Stratification factors

All eligibility criteria will be checked with a checklist.

Patients will be randomized, stratified by FLIPI score (0-2 versus 3-5), number of prior treatments (1 versus 2-5), bendamustine pretreatment (no versus yes), relapse during rituximab maintenance (no versus yes) and by country with a minimization procedure, ensuring balance within each stratum and overall balance.
Each patient will be given a unique patient study number (a sequence number by order of enrolment in the trial). Patient study number and result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

Local Patient Code is a code assigned to the patient by the investigational site for local administrative purposes. The code may be up to 8 characters long (letters and numbers allowed). The code should be in compliance with privacy regulations. It should not contain identifying data, such as patient initials or the complete hospital record number. The local code will be visible in the confirmation messages sent by TOP to local participants after registration of the patient. The key to this local patient code should only be accessible by the local investigator and the local trial staff. Using or entering a local patient code is not obligatory.

16 Data collection and quality assurance

16.1 Case Report Forms

Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- Inclusion and exclusion criteria;
- Baseline status of patient including medical history and stage of disease;
- Timing and dosage of protocol treatment;
- Baseline concomitant diseases and adverse events;
- Parameters for response evaluation;
- Any other parameters necessary to evaluate the study endpoints;
- Survival status of patient;
- Reason for end of protocol treatment.

Each CRF page will be identified by a trial number, and a combination of patient study number (assigned at registration) and hospital identification.

The CRF will be completed on site by the local investigator or an authorized staff member. All CRF entries must be based on source documents. The CRF and instructions for completing the CRF will be provided by the HOVON Data Center.
The CRF pages must be made available to the HOVON Data Center at the requested time points as specified in the CRF instructions.
All data will be collected in the study database by the HOVON Data Center.

16.1.1 DLT data collection

To monitor the incidence of dose limiting toxicity (DLT) and the duration of myelosuppression a separate CRF (DLT-form) will be used. This DLT-form must be filled out by the responsible investigator for every patient, during cycle 1 and 2. The form should be dated, signed by the responsible investigator and returned to the HOVON Data Center by fax within 24 hours after DLT-occurrence, or weekly after start of cycle I and II if no DLT occurred. DLTs should be reported between start induction cycle 1 and day 29 after start induction cycle 2 or until start next treatment. Duration of myelosuppression must be reported on the DLT form until ANC recovery or until start next treatment (if not yet recovered). Investigators will weekly receive a reminder for sending in a new DLT form.

16.1.2 Rapid reporting

In this trial the occurrence of TLS of grade ≥ 3 (graded according to appendix I) and prolonged cytopenias (necessitating >2 weeks dose delay) during induction treatment are considered of special interest. During cycle 1 and 2 of part I these events will be reported on the DLT form as described above.
To monitor the incidence of these events during cycles 3-6 of part I and among the patients in part II a separate CRF (Rapid Reporting Form) will be used. The form should be filled out, dated and signed by the responsible investigator and returned to the HOVON Data Center by fax within 24 hours after TLS of grade ≥ 3 or prolonged cytopenia (necessitating > 2 weeks delay) occurrence during induction treatment, or, if these events did not occur, a filled out, dated and signed Rapid Reporting Form must be faxed at day 28 of each cycle . Investigators will receive a reminder to fill out a rapid reporting form after each cycle.

16.2 Data quality assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator before the study, and site visits by the sponsor.

Data collected on the CRF will be verified for accuracy. If necessary, queries will be sent to the investigational site to clarify the data on the CRF. The investigator should answer data queries within the specified time line.

16.3 Monitoring

This trial is part of the HOVON Site Evaluation Visit program. Site evaluation visits are performed for HOVON studies to review the quality of overall trial conduct on a participating site and not the quality of one specific trial. The purpose is to collect quality data and facilitate improvement of the participating site. Data cleaning is not the goal of the site evaluation visits. Site evaluation visits will be performed according to the site evaluation visit plan.
A fundamental ingredient of the site evaluation visit is the interview with an investigator regarding the site's organization and trial procedures. The site documents from a randomly selected HOVON trial will serve as a guide to review the results of these procedures: the rights and well-being of patients are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).
The HOVON site evaluation visit plan applies to sites in the Netherlands and Belgium only. Monitoring of the quality of trial conduct in participating sites from other countries will be organized by the coordinating investigator or co-sponsor. The frequency and content of site visits will be equal to the specifications of the site evaluation visit plan.
Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects that during site evaluation visits the relevant investigational staff will be available, the source documentation will be available and a suitable environment will be provided for review of study-related documents.

16.4 Audits and inspections

The investigator will permit site-visits to carry out an audit of the study in compliance with regulatory guidelines. These audits will require access to all study records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected.
Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

17 Ethics

17.1 Accredited ethics committee or Institutional Review Board

An accredited Ethics Committee or Institutional Review Board will approve the study protocol and any substantial amendment.

17.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, the ICH-GCP Guidelines, the EU Clinical Trial Directive (2001/20/EG), and applicable regulatory requirements. The local investigator is responsible for the proper conduct of the study at the study site.

17.3 Patient information and consent

Written informed consent of patients is required before enrolment in the trial and before any study related procedure takes place.
The investigator will follow ICH-GCP and other applicable regulations in informing the patient and obtaining consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient. There is no set time limit for the patient to make a decision. The investigator should inform each patient if there is a specific reason why he/she must decide within a limited time frame, for example if patients condition necessitates start of treatment or if the trial is scheduled to close for enrolment.

The content of the patient information letter, informed consent form and any other written information to be provided to patients will be in compliance with ICH-GCP and other applicable regulations and should be approved by the Ethics Committee in advance of use.
The patient information letter, informed consent form and any other written information to be provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent. Any revised informed consent form and written information should be approved by the Ethics Committee in advance of use. The patient should be informed in a timely manner if new information becomes available that might be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

17.4 Benefits and risks assessment.

Currently, there is no standard treatment for patients with relapsed FL. Both lenalidomide and bendamustine have shown promising activity in FL, both in first line and in relapse. Since the toxicity of both drugs is relatively minor and in part non-overlapping, combination of these drugs is an attractive option.
The hypothesis is that combination treatment will induce better responses resulting in prolonged disease free survival. Risks for the patient relate to drug specific side-effects, in particular tumor lysis syndrome and clinically relevant neutropenia.

17.5 Trial insurance

Prior to the start of the trial, the sponsor will ensure that adequate insurance for patients is in place covering losses due to death or injury resulting from the trial, in accordance with applicable laws and regulations in each country where the trial is conducted. The sponsor will take out an insurance policy or delegate this responsibility to a national co-sponsor. Proof of insurance will be submitted to the Ethics Committee.
In addition, the sponsor will ensure that adequate insurance is in place for both investigator(s) and sponsor to cover liability pertaining to death or injury resulting from the trial.

18 Administrative aspects and publication

18.1 Handling and storage of data and documents

18.1.1 Patient confidentiality

Each patient is assigned a unique patient study number at enrolment. In trial documents the patient's identity is coded by patient study number as assigned at enrolment. In some cases date of birth is also listed.
The local investigator will keep a subject enrolment and identification log that contains the key to the code, i.e. a record of the personal identification data linked to each patient study number. This record is filed at the investigational site and should only be accessed by the investigator and the supporting site staff, and by representatives of the sponsor or a regulatory agency for the purpose of monitoring visits or audits and inspections.

18.1.2 Filing of essential documents

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies)
The investigator should file all essential documents relevant to the conduct of the trial on site. The sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and can be easily retrieved for review.

18.1.3 Record retention

Essential documents should be retained for 15 years after the end of the trial. They should be destroyed after this time.
Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the trial. Record retention and destruction after this time is subject to the site's guidelines regarding medical records.

18.1.4 Storage of samples

Biological samples should only be stored for the purpose of additional research if the patient has given consent. If no informed consent was obtained, samples should be destroyed after the patient has completed all protocol treatment and procedures.
Storage of biological samples on site is subject to the site's guidelines; samples may be labeled with the patients identifying information (e.g. name, hospital record number)
Samples that are shipped to another facility (e.g. a central laboratory) for a purpose as described in this protocol or for additional scientific research, should be stripped from any identifying information and labeled with a code (trial name or number and patient study number as assigned at enrolment).

18.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the Ethics Committee application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the patients of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be submitted to the Ethics Committee and to the Competent Authority.

Non-substantial amendments will not be submitted, but will be recorded and filed by the sponsor.

18.3 Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited Ethics Committee once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

18.4 End of study report

The sponsor will notify the accredited Ethics Committee and the Competent Authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.
In case the study is ended prematurely, the sponsor will notify the accredited Ethics Committee and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited Ethics Committee and the Competent Authority.

18.5 Publication policy

Final publication of trial results

Trial results will always be submitted for publication in a peer reviewed scientific journal regardless of the outcome of the trial – unless the trial was terminated prematurely and did not yield sufficient data for a publication.

The final publication of the trial results will be written by the Principal Investigator, the Co-investigators and the trial statistician on the basis of the statistical analysis performed by the trial statistician. A draft manuscript will be submitted for review to:

- All co-authors
- The chair of the relevant HOVON working group, who is entitled to share and discuss the manuscript with working group members
- An industry partner if so agreed in the contract between HOVON and company

After revision the final manuscript is submitted to the HOVON secretary for review of compliance with this policy. After approval by the HOVON board the manuscript will be sent to a peer reviewed scientific journal.

Authorship

Authors of the main manuscript will include the Principal Investigator, the Co-investigators, investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion rate), the trial statistician and the trial manager. If a substantial part of the publication is based on centrally reviewed data (e.g. cytogenetics or pathology), the central reviewer will be included as author. Others who have made a significant contribution to the trial may also be included as author, or otherwise will be included in the acknowledgement.

Authors of correlative manuscripts (e.g. results of side studies) will include the Principal Investigator, the Co-investigators, and those persons who have made a significant contribution to the published results.

The Principal Investigator should discuss and decide on the matter of authorship of the main manuscript prior to the start of the trial – with the exception of authors included on account of inclusion rate. The Principal Investigator is urged to use the maximum number of authors allowed by the journal to the full extent.

Interim and partial publications

Interim publications, abstracts or presentations of the study may include demographic data, overall results and prognostic factor analyses, results for secondary endpoints, but no comparisons between randomized treatment arms for the primary endpoint may be made publicly available before the recruitment is discontinued.

Investigators participating in the trial have a right to publish results from data they collected for the study. The Principal Investigator, the Co-investigator(s) and the trial statistician must approve any such publication, abstract or presentation based on patients included in this study. This is applicable to any individual patient or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study endpoints unless the final results of the trial have already been published.

Abstracts and presentations

Abstracts and presentations at public meetings will represent the trial as a project under HOVON affiliation. The abstract or presentation should not be represented under affiliation of the working group or a specific hospital.

Slides will be designed using the HOVON style template and any other presentation materials will show the HOVON logo.

If the trial is conducted in partnership with a co-sponsor (e.g. intergroup trial), the abstract and presentation should represent the co-sponsor contribution and slides may show the co-sponsor logo in addition to the HOVON logo.

Prior to its public use, the abstract or presentation is submitted to the HOVON secretary for review of compliance with this policy.

Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
AL	Amyloid Light-chain
ANC	Absolute Neutrophil Count
BJ	Bence Jones
BM	Bone Marrow
Ca	Calcium
CA	Competent Authority
CBC	Complete Blood Count
CKTO	Commissie voor Klinisch Toegepast Onderzoek
CLL	Chronic Lymphocytic Leukemia
CR	Complete Remission
CRi	Complete Remission with incomplete blood count recovery
CRF	Case Report Form
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic Cell
DFS	Disease Free Survival
DLBCL	Diffuse Large B Cell Lymphoma
DLT	Dose Limiting Toxicity
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
EBMT	European Group for Blood and Marrow Transplantation
EFS	Event Free Survival
FACS	Fluorescence-activated cell sorting
FC	Flow cytometry
FDC	Follicular Dendritic Cells
FDG	Fluorodeoxyglucose
FFS	Failure Free Survival
FISH	Fluorescence In Situ Hybridisation
FL	Follicular Lymphoma
FLC	Free Light Chain
FNA	Fine needle aspirate
FU	Follow up

GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastro-intestinal
GLSG	German Low-Grade Lymphoma Study Group
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma
HLA	Human Leukocyte histocompatibility Antigen
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
HRC	Hematocytology Review Committee
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IFM	Intergroup Français de Myelome
IMP	Investigational Medicinal Product
ISS	International Staging System
ITT	Intention To Treat
IU	International Units
IV	Intravenous
KCl	Potassium chloride
LDH	Lactate Dehydrogenase
LMWH	Low-Molecular-Weight Heparin
MCL	Mantle Cell Lymphoma
METC	Medical Ethical Review Committee
MLPA	Multiplex Ligation-dependent Probe Amplification
MM	Multiple Myeloma
MRD	Minimal residual disease
MZL	Marginal Zone Lymphoma
NaCl	Sodium Chloride
NCI	National Cancer Institute
NCRI	National Cancer Research Institute
NK cell	Natural killer cell
NR	Number
NYHA	New York Heart Association
OD	Once daily
ORR	Overall Response Rate
OS	Overall Survival

PB	Peripheral Blood
PD	Progressive Disease
PET	Positron Emission Tomografy
PFS	Progression Free Survival
PO	Per Os
PR	Partial Response
QoL	Quality of Life
RDL	Recommended Dose Level
RNA	Ribo Nucleic Acid
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
SPM	Second Primary Malignancy
SPEP	Serum protein electro-phoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction
(C)(L)TLS	(Clinical) (Laboratory) Tumor Lysis Syndrom
TFR	Tumor Flare Reaction
TMA	Tissue Micro Array
ULN	Upper Limit of Normal
UPEP	Urine protein electro-phoresis
VAD	Vincristine, Doxorubicin (Adriamycin), Dexamethasone
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen

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A. FOLLICULAR LYMPHOMA (WHO CLASSIFICATION)

Follicular Lymphoma: Grading

Grade 1: 0-5 centroblasts/hpf*

Grade 2: 6-15 centroblasts/hpf

Grade 3: >15 centroblasts/hpf

- Grade 3A: >15 centroblasts/hpf, but centrocytes are still present
- Grade 3B: centroblasts form solid sheets of blasts with no residual centrocytes

*hpf, high-power field

If diffuse areas of any size comprised predominantly or entirely of blastic cells are present in any case of follicular lymphoma, a diagnosis of diffuse large B-cell lymphoma is also made (e.g. diffuse large B-cell lymphoma with follicular lymphoma grade 1-2, grade 3A or grade 3B).

Patients with grade 3B follicular lymphoma, patients with areas of diffuse large B-cell, and patients with primary cutaneous follicular lymphoma are not eligible for the trial.

Excerpted from N. Harris, et al. Follicular lymphoma. WHO classification of neoplastic diseases of the hematopoietic and lymphoid tissues 2008

B. ANN ARBOR STAGE

Stage I:

-I: Involvement of a single lymph node region.

-IE: Localized involvement of a single extralymphatic organ or site.

Stage II:

-II: Involvement of 2 or lymph node regions on the same side of the diaphragm.

-IIE: Localized involvement of a single associated extralymphatic organ or site and it 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.

B symptoms:

The absence or presence of fever and/or night sweats and/or unexplained loss of 10% of body weight or more in the 6 months preceding diagnosis is denoted as suffix letter A or B, respectively.

C. MEASURABLE DISEASE, RESPONSE AND ENDPOINTS

Definition of measurable disease and size of disease
Response evaluation is primarily based on bi-dimensionally measurable nodes, nodal masses or nodules in liver or spleen.

On a CT scan at least 2 or more clearly demarcated lesions/nodes with a long axis of >1.5 cm and a short axis of ≥1.0 cm, or one clearly demarcated lesion/node with a long axis of >2.0 cm and a short axis of ≥1.0 cm should be present, in an area not previously irradiated.
Nodes with a largest diameter of ≤ 1 cm are considered normal and not pathologic. The size of a single node, nodal mass or nodule is defined as the product of the two largest perpendicular diameters (PPD). Nodes of which only one dimension is specified are considered as circular for the calculation of PPD size. If after treatment a nodal mass consisting of individual confluent nodes breaks up in separate nodes the sum of the PPD of the separate nodes must be compared with the size of the pretreatment nodal mass.
All nodules in liver and spleen are considered pathologic, irrespective of size.
The sum of the PPD (SPD) of a set of indicator lesions is used as a quantitative measure for response evaluation. The indicator lesions have to be chosen from the nodes and nodal masses in the following way.
If the number of nodes or nodal masses before treatment is 6 or less, all these are considered as indicator lesions. If the number of nodes or nodal masses is more than 6, a minimum number of at least 6 indicator lesions have to be chosen. These nodes or nodal masses should be selected according to the following features:

a) they should be among the largest dominant sites
b) they should be clearly measurable in at least two perpendicular dimensions
c) they should be from as disparate regions of the body as possible
d) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

The choice of the indicator lesions should be made before start of treatment. All indicator lesions must be numbered and measured bi-dimensionally before start of treatment and at the evaluation times specified in the protocol. The location and size must be documented and reported in the CRF.

Assessable disease
Assessable disease is considered all abnormalities that are not bi-dimensionally measurable, e.g. positive bone marrow or peripheral blood.

Revised Response and Progression Criteria

Excerpted from Cheson BD, et al. Revised response criteria for malignant lymphoma.
J Clin Oncol 2007;25 579-586.

Complete Remission (CR)
The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy.

2.a. Typically FDG-avid lymphoma: when the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

2.b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET san, or if a pretreatment PET scan was negative: all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy). Previously involved nodes that were 1.1–1.5 cm in their long axis and > 1.0 cm in their short axis prior to treatment must have decreased to ≤ 1 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal in size may contain lymphoma, whereas an enlarged spleen may reflect

variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes rather than lymphoma.

4. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on bone marrow aspirate or biopsy at restaging. The biopsy sample on which this determination is made must be adequate (≥ 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but demonstrating a small population of clonal lymphocytes by flow cytometry will be considered a CR.

Complete remission (unconfirmed) (CRu)
The category of CRu is eliminated in the updated Cheson response criteria.

Partial Remission (PR)
In general mediastinal blood pool activity is recommended as the reference background activity to define PET-positivity for a residual mass > 2 cm in greatest transverse diameter, regardless of its location. A smaller residual mass or a normal-sized lymph node (i.e. < 1 cm in short axis) should be considered positive if its activity is above that of the surrounding background.

The designation of PR requires the following:

1. ≥ 50% decrease in the sum of the product of the diameters (SPD) of the indicator lesions.

2. No increase in the size of other nodes, liver, or spleen compatible with progression disease.

3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules in their PPD.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and not measurable disease.

5. Bone marrow assessment is irrelevant for determination of a PR if at other (nodal) location PR is established.

6. No new sites of disease.

7.a. Typically FDG-avid lymphoma: If the PET scan was positive prior to therapy, the post-treatment PET should be positive in at least one previously involved site.
7.b. Variably FDG-avid lymphomas/FDG-avidity unknown; If a pretreatment PET scan was negative, or in patients without a pretreatment PET scan, standard CT criteria should be used.

All patients who meet the criteria for CR except for involvement of other organs or persistent morphologic bone marrow involvement will be considered partial responders.

Stable Disease (SD)
The designation of SD requires the following:

1. Failing to attain the criteria needed for a CR or PR, but not fulfilling those for progressive disease (see below).

2.a. Typically FDG-avid lymphomas: the PET scan should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET scan
2.b. Variably FDG-avid lymphomas/FDG avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for patients with PR or SD)
The designation of RD/PD requires the following:
Lymph nodes should be considered abnormal if the long axis is > 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1–1.5 cm it should only be considered abnormal if its short axis is > 1.0 cm. Lymph nodes ≤ 1.0 cm by ≤ 1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities (preferably histology) or increase by ≥ 50% in the SPD of previously involved sites

2. ≥ 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node ≥ 50% increase in the PPD, or the size of other lesions (e.g. splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

3. Lesions should be PET-positive if observed in a typical FDG-avid lymphoma or one that was PET-positive prior to therapy, unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative or no pretreatment PET; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology,Immuno-histochemistry should be negative
PR	Regression of measuable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative or no pretreatment PET; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in their PPD) no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified (large cell or small cell)
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative or no pretreatment PET; <50% change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy or no pretreatment PET.	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Endpoints

End Point	Patients	Definition	Measured From
Overall survival	All	Death as a result of any cause	Entry onto study
Progression-free survival	All	Disease progression or death as a result of any cause	Entry onto study
Event-free survival	All	Failure of treatment* or death as a result of any cause	Entry onto study
Time to progression	All	Time to progression or death as a result of lymphoma	Entry onto study
Disease-free survival	in CR	Time to relapse or death as a result of lymphoma or acute toxicity of treatment	Documentation of response
Response duration	In CR or PR	Time to relapse or progression	Documentation of response
Lymphoma-specific survival	All	Time to death as a result of lymphoma	Entry onto study
Time to next treatment	All	Time to new treatment	End of primary treatment

* failure is defined as either no CR or PR on treatment, or relapse.

D. Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance

For Serum creatinine concentration in mg/dl:

$$\text{CrCl} = \frac{(140-\text{age}+) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{72 \times \text{serum creatinine (mg/dL)}} = \text{(ml/min)}$$

For Serum creatinine concentration in µmol/L:

$$\text{CrCl} = \frac{(140-\text{age}+) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{0.81 \times \text{serum creatinine (µmol/l)}} = \text{(ml/min)}$$

+ age in years, weight (wt) in kilograms

Reference: Cockcroft and Gault 1976

E. FLIPI parameters:

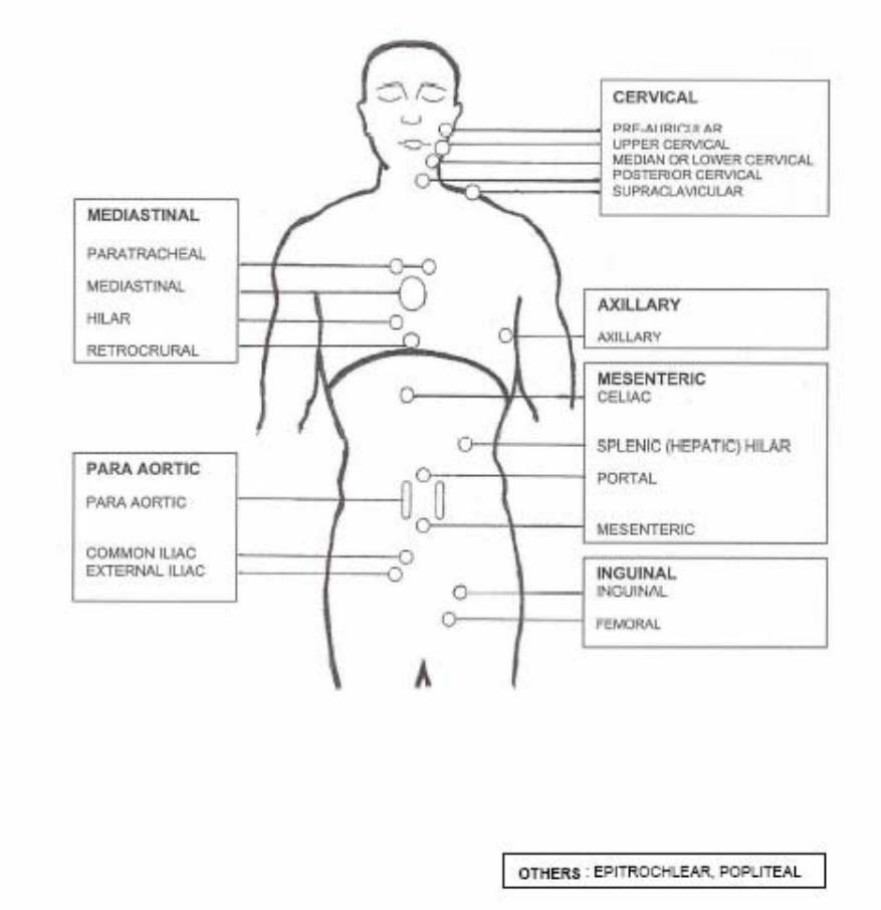
Five adverse prognostic factors were selected:

1. Age (> 60 vs. ≤ 60)
2. Ann Arbor Stage (III-IV vs. I-II)
3. Hemoglobin level (< 12g/dl vs. ≥ 12 g/dl)
4. Number of nodal areas (> 4 vs. ≤ 4)
5. Serum LDH level (> normal vs. ≤ normal)

Three risk groups were defined:

1. LOW RISK (0-1 adverse factor)
2. INTERMEDIATE RISK (2 adverse factors)
3. HIGH RISK (≥ 3 adverse factors)

FLIPI nodal areas[8]



F. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

5 Death

G. NYHA scoring list

The New York Heart Association functional and therapeutic classification applied to dyspnoea

Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest

H. Common Terminology Criteria for Adverse Events

The grading of adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 4. A complete document may be downloaded from the HOVON website:

http://www.hovon.nl (under Trials > General information about studies)

I. Cairo-Bishop grading classification of tumor lysis syndrome

Table III. Cairo–Bishop grading classification of tumour lysis syndrome.

	Grade 0*	Grade I	Grade II	Grade III	Grade IV	Grade V
LTLS#	–	+	+	+	+	+
Creatinine†/‡	≤1·5 × ULN	1·5 × ULN	>1·5–3·0 × ULN	>3·0–6·0 × ULN	>6·0 ULN	Death§
Cardiac arrhythmia‡	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator)	Life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)	Death§
Seizure‡	None	–	One brief generalised seizure; seizure(s) well controlled by anti-convulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death§

Clinical tumour lysis syndrome (CTLS) requires one or more clinical manifestations along with criteria for laboratory tumour lysis syndrome (LTLS). Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade.

*No laboratory tumour lysis syndrome (LTLS).

†Creatinine levels: patients will be considered to have elevated creatinine if their serum creatinine is 1·5 times greater than the institutional upper limit of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: > 1 < 12 years, both male and female, 61·6 μmol/l; ≥ 12 < 16 years, both male and female, 88 μmol/l; ≥16 years, female, 105·6 μmol/l; ≥16 years, male 114·4 μmol/l.

‡Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration).

§Attributive probably or definitely to CTLS.

Laboratory tumour lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 d before or 7 d after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricaemic agent(s).

From: Cairo MS, Bishop M. Tumor lysis syndrome: new therapeutic strategies and classification[72]

J. Grading of tumor flare syndrome

According to CTCAE version 3.0

Grade	1	2	3	4	5
Tumor flare	Mild pain not interfering with function	Moderate pain; pain or analgesics interfering with function, but not interfering with ADL	Severe pain; pain or analgesics interfering with function and interfering with ADL	Disabling	Death

REMARK: Tumor flare is characterized by a constellation of signs and symptoms in direct relation to initiation of therapy (e.g., anti-estrogens/androgens, additional hormones, immunomodulatory drugs). The symptoms/signs can include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.