Official Title: A Multicenter, Phase III, Open-Label, Randomized Study in Previously Untreated Patients With Advanced, Indolent Non-Hodgkin's Lymphoma Evaluating The Benefit of Obinutuzumab (RO5072759) Plus Chemotherapy Compared With Rituximab Plus Chemotherapy Followed By Obinutuzumab or Rituximab Maintenance Therapy in Responders

NCT Number: NCT01332968

Document Date: Protocol Version A7: 15-February-2020

PROTOCOL

TITLE:	**A MULTICENTER, PHASE III, OPEN–LABEL, RANDOMIZED STUDY IN PREVIOUSLY UNTREATED PATIENTS WITH ADVANCED INDOLENT NON–HODGKIN'S LYMPHOMA EVALUATING THE BENEFIT OF GA101 (RO5072759) PLUS CHEMOTHERAPY COMPARED WITH RITUXIMAB PLUS CHEMOTHERAPY FOLLOWED BY GA101 OR RITUXIMAB MAINTENANCE THERAPY IN RESPONDERS**
PROTOCOL NUMBER:	BO21223
VERSION NUMBER:	*A7*
EUDRACT NUMBER:	2010–024132–41
IND NUMBER:	104405
TEST PRODUCT:	Obinutuzumab (GA101, RO5072759)
MEDICAL MONITOR:	[redacted], *Ph.D.*
SPONSOR:	F. Hoffmann–La Roche, Ltd
DATE FINAL:	Version 1: 14 January 2011
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IN COOPERATION WITH:	German Low Grade Lymphoma Study Group (GLSG) and East German Study Group for Hematology and Oncology (OSHO), Ludwig–Maximilians University Grosshadern Hospital, Marchioninistr. 15, 81377 Munich, Germany and National Cancer Research Institute (NCRI), 90 Tottenham Court Road, London W1T 4TJ, United Kingdom

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
15-Feb-2020 04:14:34	Company Signatory	[redacted]

CONFIDENTIAL STATEMENT

PROTOCOL AMENDMENT, VERSION A7:
RATIONALE

Study BO21223 has been amended in part to collect response after progression and administration of NALT (Sections 3.1.1, 4.5.7, and 4.6, and Appendices A1-A5). Additional changes are listed below:

- The Medical Monitor for the study has been changed to [redacted], Ph.D.
- Reference Safety Information has been added (Section 5.7).

Additional minor changes have been made to improve clarity and consistency. New information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTER, PHASE III, OPEN–LABEL, RANDOMIZED STUDY IN PREVIOUSLY UNTREATED PATIENTS WITH ADVANCED INDOLENT NON–HODGKIN'S LYMPHOMA EVALUATING THE BENEFIT OF GA101 (RO5072759) PLUS CHEMOTHERAPY COMPARED WITH RITUXIMAB PLUS CHEMOTHERAPY FOLLOWED BY GA101 OR RITUXIMAB MAINTENANCE THERAPY IN RESPONDERS**
PROTOCOL NUMBER:	BO21223
Eudract Number:	2010–024132–41
STUDY DRUG:	RO5072759 (GA101, obinutuzumab)
PHASE:	III
INDICATION:	Indolent non–Hodgkin's lymphoma
IND:	104,405
SPONSOR:	F. Hoffmann–La Roche, Ltd (ex–U.S.) Grenzacherstrasse 124 4070 Basel, Switzerland

Objectives

Primary Objective

The primary objective for this study is as follows:

- To evaluate the efficacy of obinutuzumab (GA101, RO5072759) plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in patients with previously untreated advanced follicular lymphoma, as measured by investigator–assessed progression–free survival (PFS)

Secondary Objectives

The following secondary objective applies to patients with previously untreated advanced indolent non–Hodgkin's lymphoma (NHL) (i.e., overall population):

- To evaluate and compare investigator–assessed PFS between the two arms

The following secondary objectives apply to patients with previously untreated advanced indolent NHL (i.e., overall population) and to the subset of patients with previously untreated advanced follicular lymphoma (i.e., follicular population):

- To evaluate and compare Independent Review Committee (IRC)–assessed PFS between the two arms
- To evaluate and compare overall response and complete response (CR) after the end of induction treatment, as assessed by the investigator, between the two arms, with and without fluorodeoxyglucose positron emission tomography (FDG–PET)
- To evaluate and compare overall response and CR after the end of induction treatment, as assessed by the IRC, between the two arms, with and without 18F–FDG–PET

- To evaluate and compare overall survival, event-free survival (EFS), disease–free survival (DFS), duration of response, and time to next anti–lymphoma treatment between the two arms

  EFS, DFS, and duration of response will be based on investigator assessment.
- To evaluate and compare the safety profiles between the two arms during induction and maintenance
- To assess patient–reported outcomes (PROs) in both arms

Study Design

This is an open–label, international, multicenter, randomized, Phase III study to investigate the efficacy and safety of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy for responders CR or partial response (PR) compared with rituximab plus chemotherapy followed by rituximab maintenance therapy for responders in patients with previously untreated advanced indolent NHL. Prior to the initiation of the study, each site will choose one of three chemotherapy regimens cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), cyclophosphamide, vincristine, and prednisone (CVP) or bendamustine) that is considered to be the standard of care for follicular lymphoma; all patients with follicular lymphoma at that site will receive the chosen chemotherapy regimen for the duration of the study (a site may switch to another regimen if new scientific data become available and after Sponsor approval). For non–follicular NHL, the investigator will have the option of choosing one of the three chemotherapy regimens (CHOP, CVP, or bendamustine) for each patient. All patients will then be randomized to either rituximab plus chemotherapy or obinutuzumab plus chemotherapy.

Approximately 1200 patients with follicular lymphoma will be recruited and randomly assigned in a 1:1 ratio to either obinutuzumab plus chemotherapy followed by obinutuzumab maintenance in responders or rituximab plus chemotherapy followed by rituximab maintenance in responders. In addition, approximately 200 patients with marginal zone lymphoma (MZL) will be recruited and randomly assigned in a 1:1 ratio to the two treatment arms.

The schedule for administration of rituximab or obinutuzumab will be dependent upon the accompanying chemotherapy regimen. In the control arm of the study (Arm A), six to eight doses of rituximab at 375 mg/m^2 will be administered by IV infusion with the accompanying chemotherapy regimen. In the experimental arm of the study (Arm B), eight to ten doses of obinutuzumab (including two additional doses of obinutuzumab on Days 8 and 15 of Cycle 1) at an absolute (flat) dose of 1000 mg will be administered by IV infusion with the accompanying chemotherapy regimen. Patients who demonstrate a CR or PR at the end of induction therapy will continue to receive rituximab at 375 mg/m^2 (Arm A) or obinutuzumab at a flat dose of 1000 mg (Arm B) every 2 months until disease progression for up to 2 years. Patients who demonstrate stable disease (SD) at the end of induction therapy will be followed for progression for up to 2 years according to the same follow–up schedule as responding patients (CR or PR) receiving maintenance (observation). If induction therapy was stopped for toxicity or any reason other than toxicity, then patients are discontinued from study treatment and go into follow–up directly.

All patients will be assessed for disease response by the investigator through use of regular clinical and laboratory examinations and computed tomography (CT) scans according to a modified version of the Revised Response Criteria for Malignant Lymphoma. Additional response criteria based on paraprotein assessment are in effect for the MZL population and based on hematological parameters and spleen size for the subset of splenic MZL patients. During induction treatment, tumor assessment is performed after three cycles for patients receiving bendamustine, after four cycles for patients receiving CVP or CHOP, and at the completion of induction therapy.

Following the completion of induction therapy, patients receiving maintenance therapy (CR or PR) or undergoing observation (SD) will be followed clinically every 2 months for 2 years (with CT scans every 4 months for the first year and then every 6 months for the second year). For patients who have not progressed at the maintenance or observation completion visit (25 months from Day 1 of Cycle 8 [CHOP/CVP arms] or Cycle 6 [bendamustine arm]), disease assessments will continue every 3 months for 3 years (with CT scans every 6 months) and then every 6 months for 2 years (with CT scans every year) (follow–up for disease progression).

After 5 years of follow–up or disease progression (whichever comes first), patients will still be followed every 6 months for overall survival and new anti–lymphoma treatment (NALT), or for disease progression if applicable, until the end of the study, which will be approximately 10.2 years after inclusion of the first patient. Patients who terminate induction early without progressive disease (PD) will be followed for PD, as per Appendix A–5, and in the extended follow–up for PD, NALT and overall survival. Patients who terminate induction early because of PD will go directly into the extended follow–up for NALT and overall survival. Patients who discontinue the protocol–defined treatment path and need to start an NALT in the absence of disease progression (e.g., if wrong diagnosis at screening and new diagnosis requires a change of treatment) will be followed for disease progression and overall survival. *For patients who progressed and received NALT, response after NALT will be collected.*

An independent radiologic and oncologic review of the responses of all patients by an IRC will also be conducted for the futility and efficacy analyses with and without PET.

Patients who discontinue all components of study therapy prior to disease progression (e.g., for toxicity) will enter the follow–up phase of the study and will continue to be followed for PD and overall survival (regardless of whether they subsequently receive NALT).

A retrospective quality assurance pathology review will be conducted on pathology samples to evaluate histology and CD20 status in addition to other prognostic features.

An IDMC will conduct periodic interim reviews of safety summaries, starting approximately 1 month after enrollment of the first patient and then approximately every 2 months until 100 patients have completed two cycles of study treatment. Afterward, the IDMC will conduct reviews of safety summaries approximately every 6 months. All summaries and analyses reviewed by the IDMC will be prepared by an Independent Data Coordinating Center (IDCC). Safety will be evaluated by monitoring dose delays and dose intensity, adverse events, serious adverse events, and deaths. These will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. Laboratory safety assessments will include regular monitoring of hematology, blood chemistry, and tests of immunologic parameters. In addition, tests for the presence of human anti–human antibodies (HAHAs) will be performed only in all patients receiving obinutuzumab.

Outcome Measures

Primary Efficacy Outcome Measure

The primary efficacy endpoint, PFS in patients with follicular lymphoma, is defined as the time from randomization to the first occurrence of progression or relapse as assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma, or death from any cause.

Secondary Efficacy Outcome Measures

For the endpoints below that specify disease response, response will be assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma and additional response criteria for MZL.

The following secondary outcome measure applies to patients with previously untreated advanced indolent NHL (i.e., overall population):

- Investigator–assessed PFS

The following secondary outcome measures apply to patients with previously untreated advanced indolent NHL (i.e., overall population) and to the subset of patients with previously untreated advanced follicular lymphoma (i.e., follicular population):

- IRC–assessed PFS
- CR and overall response (CR or PR) at the end of induction, as assessed by the investigator with and without FDG–PET
- CR and overall response (CR or PR) at the end of induction, as assessed by the IRC with and without FDG–PET
- Overall survival, defined as the time from randomization to death from any cause
- EFS, defined as the time from randomization to disease progression/relapse as assessed by the investigator, death from any cause, or start of an NALT

- DFS, defined for patients with a best overall response (BOR) of CR as the time from first occurrence of a documented CR to PD as assessed by the investigator or death from any cause. Patients who have had no documented disease progression or have not died after CR will be censored at the last disease assessment date.
- Duration of response, defined for patients with a BOR of CR or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse as assessed by the investigator or death from any cause. For patients achieving a response who have not progressed, relapsed, or died at the time of the analysis, duration of response will be censored on the date of last disease assessment.
- Time to next anti–lymphoma treatment, defined as the time from randomization to start of new non–protocol anti–lymphoma therapy or death from any cause
- Change from baseline to the end of study in PROs based on the FACT–Lym instrument, as outlined below.

  Change from baseline in all domains of the FACT–G

  Change from baseline in the total outcome index (TOI) (range, 0–116): sum of physical well–being (7 items), functional well–being (7 items), and Lym subscale (15 items) scores

  Change from baseline in the FACT–Lym subscale score (range, 0–60): 15 lymphoma–specific items

  Change from baseline in the FACT–Lym total score (range, 0–168): sum of physical well–being (7 items), social/family well–being (7 items), emotional well–being (6 items), functional well–being (7 items), and Lym subscale (15 items) scores
- EQ–5D summary scores at baseline, during treatment, after treatment, at the last assessment prior to progression, and at the first assessment after progression

Analysis of medical resource utilization data will be provided if required.

Safety Plan

This trial is designed to allow for early termination or a modification of the protocol (in particular, the dosing regimens) for safety concerns, based on the advice of an IDMC. The IDMC will be incorporated into the study to review safety data on a regular basis, including adverse events of special interest. The IDMC will meet 1 month after enrollment of the first patient and then approximately every 2 months until 100 patients have completed two cycles of study treatment. Afterward, the IDMC will meet approximately every 6 months. Both the Sponsor and the IDMC can request ad hoc IDMC meetings if potential safety concerns arise. Following each meeting, the IDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the IDMC may recommend stopping the study or closing a treatment arm as a result of safety reasons. The IDMC will also perform a safety review at the preplanned interim analyses for futility and efficacy.

Risks Associated with Obinutuzumab Therapy

The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, and fatigue, as well as other symptoms.

Respiratory infusion–related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI–CTCAE, Version 3.0, Grade 1 and 2 events), and $<$ 10% of the events were severe (Grade 3 events), occurring predominantly during the first hour of the infusion or shortly after the first infusion had finished; the events resolved with slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE–mediated allergic or anaphylactic reactions.

Cases of tumor lysis syndrome have been reported with obinutuzumab administration. To date, no patient has required hemodialysis for renal failure. Patients with a high tumor burden,

including patients with a lymphocyte count of $\geq 25 \times 10^9$/L (particularly, patients with B–cell CLL and MCL), are at increased risk for tumor lysis syndrome and severe IRRs.

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of granulocyte colony stimulating factors (G–CSF) has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G–CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G–CSF is recommended according to the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥60 years old and/or with comorbidities. The use of G–CSF is strongly recommended in Cycle 1 for all patients treated with obinutuzumab plus CHOP (G–CHOP).

Severe and life–threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. Based on the available evidence to date the greatest risk of hemorrhage in obinutuzumab–treated patients are observed in the first cycle. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia–related events, such as platelet inhibitors and anticoagulants, may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life–threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

On the basis of its anticipated mode of action, resulting in profound B–cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

Serious infections, including fatal, bacterial, fungal, and new or reactivated viral infections (e.g., cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C) have been reported with the B cell–depleting antibody rituximab, mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic stem–cell transplant. The risk of such infections with obinutuzumab is unknown. Physicians should be aware of symptoms suggestive of progressive multifocal leukoencephalopathy (PML) and consider the diagnosis of PML in any patient presenting with new–onset neurologic manifestations. Evaluation of PML includes but is not limited to consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture. To date, there have been no reports of patients experiencing PML while or after receiving obinutuzumab.

Cases (including fatal) of John Cunningham virus (JCV) infection resulting in PML (destructive infection of oligodendrocytes of the central nervous system white matter) have been reported in patients treated with anti–CD20 therapies, including rituximab and obinutuzumab.

The diagnosis of PML should be considered in any patient presenting with new–onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual–spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

Therapy with obinutuzumab and rituximab should be withheld during the investigation of potential PML and permanently discontinued in the case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the treatment of PML.

Risks Associated with Rituximab Therapy

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

Patients may be at risk for tumor lysis syndrome. A high number of circulating malignant cells ($\geq$ 25,000/mm^3) or high tumor burden confers a greater risk of tumor lysis syndrome. For patients with evidence of tumor lysis syndrome, rituximab should be discontinued and the patient treated as clinically indicated.

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately 1 month after the last dose.

Patients with chronic hepatitis B viral infection (i.e., hepatitis B surface antigen [HBsAg] positive) are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and hepatitis B core antibody [HBcAb] positive) are at a lower risk for reactivation. In a study of 51 HBV carriers with diffuse large B–cell lymphoma who received rituximab, 12% of patients developed evidence of reactivation (Niitsu et al. 2010). Patients who demonstrate evidence of reactivation while receiving an appropriate anti–viral therapy will discontinue study treatment.

Rare cases of PML have been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications. In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem–cell or solid–organ graft rejection. The diagnosis of PML in any patient treated with rituximab is extremely rare but should be suspected in any patient who develops new–onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem–cell transplant. Most cases of PML were diagnosed within 12 months after the patient's last infusion of rituximab.

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life threatening. Patients in the CHOP arm who have been treated with doxorubicin, an anthracycline–based chemotherapy, are at risk for cardiotoxicity and will be required to have assessments of left ventricular ejection fraction (LVEF) at baseline and at the end of induction treatment.

Serious infections, including fatal, bacterial, fungal, and new or reactivated viral infections (e.g., cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C), can occur during and up to 1 year following the completion of rituximab–based therapy.

Severe reactions, including fatal, mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens–Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.

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

Risks Associated with CHOP or CVP Chemotherapy

Please refer to prescribing information for doxorubicin, cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone for risks related to CHOP or CVP chemotherapy.

Risks Associated with Bendamustine Chemotherapy

Patients treated with bendamustine are likely to experience myelosuppression. Blood counts will be monitored weekly during the first cycle and then frequently throughout subsequent cycles of treatment. Patients who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The use of myeloid growth factors for the primary and secondary prevention of febrile neutropenia is permitted.

Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in postmarketing reports. Infection has been associated with hospitalization, septic shock, and death. Patients with myelosuppression following treatment with bendamustine are more susceptible to infections.

Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritis, and rash. In rare instances, severe anaphylaxis and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles of therapy. Patients should be monitored clinically and discontinue drug for every reaction.

Tumor lysis syndrome has been reported in association with bendamustine treatment in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of bendamustine and without intervention may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

A number of skin reactions have been reported in clinical trials and postmarketing safety reports. These events have included rash, toxic skin reactions, and bullous exanthema. Some events occurred when bendamustine was given in combination with other anti–cancer agents, so the precise relationship to bendamustine is uncertain.

In a study of bendamustine in combination with rituximab, one case of TEN occurred. TEN has been reported for rituximab. Cases of Stevens–Johnson syndrome and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. Allopurinol must not be given on days of bendamustine administration. Patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine should be withheld.

Premalignant and malignant diseases, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma, have developed in patients treated with bendamustine. The association with bendamustine has not been determined.

There are postmarketing reports of bendamustine extravasation resulting in hospitalization from erythema, marked swelling, and pain. Precautions should be taken to avoid extravasation, including monitoring of the IV infusion site for redness, swelling, pain, infections, and necrosis during and after administration of bendamustine.

Rare cases of transfusion–associated graft versus host disease have been reported following treatment of low–grade B–cell malignancies with the purine analogues fludarabine. The situation with newer purine antagonists such as bendamustine is unclear. Transfusions, if required, should be performed according to national guidelines.

Certain medications may interact with bendamustine. Caution should be used or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed. CYP1A2 inhibitors and inducers are not contraindicated. During treatment with bendamustine, patients will be provided with a card to keep with them that provides notification to other health care providers that the patient is taking bendamustine as a participant in a clinical study (see Appendix F).

Study Treatment

In the control arm (Arm A), six to eight doses of rituximab at 375 mg/m^2 will be administered by IV infusion with the accompanying chemotherapy regimen during induction, as outlined below:

- R–CHOP: Rituximab will be administered on Day 1 of Cycles 1–8 (21–day cycles). CHOP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2–5, of Cycles 1–6.

- R–CVP: Rituximab will be administered on Day 1 of Cycles 1–8 (21–day cycles). CVP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2–5, of Cycles 1–8.
- R–bendamustine: Rituximab will be administered on Day 1 of Cycles 1–6 (28–day cycles). Bendamustine will be administered on Days 1 and 2 of Cycles 1–6, with prednisone/prednisolone/methylprednisolone also administered on Day 1 of Cycle 1.

If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab on the day prior to CHOP or CVP or bendamustine with premedication is allowed. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R–Chemo and G–Chemo) in order to avoid any bias. Premedication before antibody administration in Cycle 1 is recommended and may include 100 mg prednisone/prednisolone or 80 mg methylprednisolone orally (within 12 hours but at least 60 minutes prior to start of antibody infusion) or IV (if less than 60 minutes prior to start of antibody infusion) in order to minimize cytokine release syndrome or allergic reactions. Premedication with prednisone/prednisolone/methylprednisolone is mandatory in patients who had an IRR until no IRRs occur anymore during antibody infusion. Withhold antihypertensive medication 12 hours prior to start of antibody infusion and during the infusion.

Patients randomized to receive rituximab plus chemotherapy who achieve a CR or PR at the end of induction therapy will continue to receive rituximab at 375 mg/m^2 every 2 months until disease progression for up to 2 years.

In the experimental arm (Arm B), eight to ten doses of obinutuzumab at 1000 mg will be administered by IV infusion with the accompanying chemotherapy regimen during induction, as outlined below.

- G–CHOP: Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (21–day cycles). CHOP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2–5, of Cycles 1–6
- G–CVP: Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (21–day cycles). CVP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2–5, of Cycles 1–8
- G–bendamustine: Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–6 (28 day cycles). Bendamustine will be administered on Days 1 and 2 of Cycles 1–6, with prednisone/prednisolone/methylprednisolone administered on Day 1 of Cycle 1

If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of obinutuzumab is allowed on the day prior to CHOP or CVP or bendamustine. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R–Chemo and G–Chemo) in order to avoid any bias. Premedication before antibody administration in Cycle 1 is recommended and may include 100 mg prednisone/prednisolone or 80 mg methylprednisolone orally (within 12 hours but at least 60 minutes prior to start of antibody infusion) or IV (if less than 60 minutes prior to start of antibody infusion) in order to minimize cytokine release syndrome or allergic reactions. Premedication with prednisone/prednisolone/methylprednisolone is mandatory in patients who had an IRR until no IRRs occur anymore during antibody infusion. Withhold antihypertensive medication 12 hours prior to start of antibody infusion and during the infusion.

Patients randomized to receive obinutuzumab plus chemotherapy who achieve a CR or PR at the end of induction therapy will continue to receive obinutuzumab at 1000 mg every 2 months until disease progression for up to 2 years.

Concomitant Therapy and Clinical Practice

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

Patients may receive prophylactic anti–viral medication to prevent hepatitis B reactivation in countries where they are administered as part of the standard of care or national guidelines.

The use of rasburicase for the treatment of tumor lysis syndrome and the prevention of hyperuricemia is allowed according to institutional guidelines.

The use of antibiotic and/or anti–viral prophylaxis according to institutional guidelines is also allowed.

Primary prophylaxis with granulocyte colony stimulating factors (G–CSF) is recommended as per the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO) guidelines—namely, in patients who are $\geq$60 years of age and/or with comorbidities. The use of G–CSF prophylaxis is strongly recommended in Cycle 1 for all patients treated with GA101 + CHOP.

Harvesting of stem cells by G–CSF alone (no additional chemotherapeutic agent) is allowed only if it is done between Cycle 5 Day 1 and Cycle 8 Day 1 (R/G–CHOP or R/G–CVP) or Cycle 4 Day 1 and Cycle 6 Day 1 (R/G–Bendamustine).

Patients who experience obinutuzumab infusion–related temperature elevations of $>$38.5°C or other minor infusion–related symptoms may be treated symptomatically with acetaminophen/paracetamol ($\geq$500 mg) and/or H_1– and H_2–receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion–related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β_2 agonists/epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice.

It is mandatory to follow the ASCO/EORTC/ESMO guidelines about the use of myeloid growth factors for the primary prevention of febrile neutropenia throughout the trial.

Mesna (2–mercaptoethane sulfonate sodium) may be administered as prophylaxis per institutional guidelines for patients treated with CHOP or CVP.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy (other than bendamustine, cyclophosphamide, doxorubicin, or vincristine)

  Although MTX is a chemotherapeutic agent, due to the low doses used in treating rheumatoid arthritis (typically 7.5 to a maximum of 20 mg/week) it is not considered chemotherapy for lymphoma. Therefore, patients treated before or during study conduct with MTX for rheumatoid arthritis are still eligible to participate in the study. It is recommended to stop MTX 2–3 weeks prior to starting immunochemotherapy since the combination of MTX and immunochemotherapy increases the risk of immunosuppression and the risk of infection, but MTX may be resumed during maintenance/observation/follow–up, if clinically indicated
- Radiotherapy
- Immunotherapy (other than rituximab and obinutuzumab)
- Hormone therapy (other than contraceptives, hormone–replacement therapy, or megestrol acetate)

  Hormonal therapy (e.g., GmRH–agonists) for egg cell harvest/fertility preservation prior to randomization is allowed in women of childbearing age
- Any therapies intended for the treatment of NHL whether U.S. Food and Drug Administration approved or experimental (outside of this study)

Statistical Methods

Primary Efficacy Analysis

The primary analysis population for efficacy is the intent–to–treat follicular population, defined as all randomized patients with follicular histology, according to local diagnosis provided in interactive voice or Web–based response system (IxRS). Patients will be analyzed according to the treatment arm to which they were randomized.

The primary efficacy endpoint, PFS in patients with follicular lymphoma, is defined as the time from randomization to the first occurrence of progression or relapse as assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma or death from any cause. PFS for patients without disease progression, relapse, or death will be censored at the time of the last tumor assessment or, if no tumor assessments were performed after the baseline visit, at the time of randomization.

Although the primary efficacy endpoint is the investigator–assessed PFS, PFS based on IRC assessments will also be analyzed to support the primary analysis. In the United States, IRC–assessed PFS will be the basis for regulatory decisions.

The primary analysis of the study will test the equality of PFS distributions in the obinutuzumab plus chemotherapy (G–Chemo) and rituximab plus chemotherapy (R–Chemo) arms, as follows:

H_0: $PFS_{G\text{-}Chemo} = PFS_{R\text{-}Chemo}$ versus H_1: $PFS_{G\text{-}Chemo} \neq PFS_{R\text{-}Chemo}$

Treatment comparison will be made using a two–sided stratified log–rank test (0.05 significance level) stratified by chemotherapy regimen (CHOP, CVP, or bendamustine) and FLIPI risk group (low, intermediate, or high). Kaplan–Meier methodology will be used to estimate PFS distribution for each treatment arm. The Kaplan–Meier curve will provide a visual description of the differences across treatment arms. Estimates of the treatment effect will be expressed as hazard ratios through use of a stratified Cox proportional–hazards analysis, including 95% confidence limits.

Median PFS is not expected to be reached in this study; hence, the 3–year and 4–year rates will be used to describe PFS in addition to the hazard ratio.

Missing Data

For PFS, patients who do not have documented disease progression or death will be treated as censored observations on the date of the last tumor assessment.

For overall survival, patients who do not have documented deaths will be censored on the last date they were known to be alive.

For response endpoints, patients with no response assessments (for whatever reason) will be considered non–responders.

Determination of Sample Size

Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Two–sided log–rank test at the 0.05 level of significance
- Powered for follicular lymphoma patient subset
- Eighty percent power to detect a hazard ratio for G–Chemo versus R–Chemo of 0.74, corresponding to an improvement in 3–year PFS from 70.7% to 77.4% or in median PFS from 6 years to 8.1 years (35%)

  Note that estimates of median PFS are not likely to be reached in either study arm.
- Exponential distribution of PFS
- An annual dropout rate of 2.5%
- Performance of interim analyses on PFS: one for futility when approximately 30% of the total (investigator–assessed) PFS events have occurred and one for efficacy when approximately 67% of the total PFS events have occurred. Efficacy and (nonbinding) futility boundaries will be computed using the Lan–DeMets approximation to the O'Brien–Fleming boundary shape.

  The futility boundary will be nonbinding.

In addition, a futility analysis based on CR rates at the end of induction determined by CT (or MRI, but not PET) will be performed on the first 170 follicular lymphoma patients randomized.

With these assumptions, 370 PFS events are required to achieve 80% power for the primary analysis. Recruitment will be staggered in order to recruit the first 170 patients in a smaller number of sites (approximately 125 sites), followed by the activation of all (approximately 200–250) sites after the IDMC meeting for futility based on CR rates. It is expected that during the first stage, after a 6-month ramp up, 18 patients per month will be recruited, and after the IDMC meeting and another 4–month ramp up, an accrual rate of

37 patients per month is expected. The 1200 follicular patients enrolled over 49 months and followed for an additional 29 months will be required to provide 370 PFS events, with a total duration for PFS follow-up of approximately 78 months (6.5 years).

Approximately 200 additional patients with non-follicular lymphoma will be enrolled. This number was based on a study of enrollment feasibility, which indicated that 200 patients would likely be enrolled in 49 months, in addition to the planned follicular enrollment. Although the study would not be powered to detect statistically significant differences in this 200-patient cohort, there would be a reasonable chance of detecting a trend.

The pharmacokinetic assessments will apply to a subpopulation of approximately 460 patients receiving obinutuzumab. This is the minimum number of patients needed to accurately construct a population pharmacokinetic model and will allow for the evaluation of the relationship between exposure and pharmacodynamic markers of response. Approximately 120 follicular patients will undergo pharmacokinetic sampling from each of the three chemotherapy groups (G-CHOP, G-CVP, and G-bendamustine), and 100 additional patients with non-follicular lymphoma will also undergo sampling. This sample size is believed to be sufficient to characterize with confidence the pharmacokinetics of obinutuzumab in the target population as well as the relationships between exposure to obinutuzumab and response. The pharmacokinetic sampling schedule in this study was determined using an optimal sampling strategy with the software PFIM and should result in a precision of parameter estimates lower than 20% for the main pharmacokinetic parameters.

Interim and Final Analyses

Although the study is open label, Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of study results. In order to monitor safety, Sponsor drug safety and medical monitoring staff will have access to the treatment assignments of particular patients. An IDMC will evaluate interim analysis results and determine whether the trial will be stopped early.

Three interim analyses are planned: two for futility and one for efficacy. The first interim analysis will be based on differences in end of induction CR rates in the first 170 enrolled follicular lymphoma patients. The analysis will be conducted once the 170 follicular lymphoma patients have reached their end-of-induction response assessment or have withdrawn prematurely. The IDMC may recommend to stop the study for futility if the observed difference in CR rate based on CT (or MRI, but not PET) is $< 3\%$ in favor of G-Chemo (i.e., CR rate needs to be $\geq 3\%$ higher on G-Chemo vs. R-Chemo).

The second interim analysis (futility on PFS) will be conducted when 30% of the required PFS events (i.e., approximately 111 events) will have occurred. The IDMC may recommend to stop the study for futility if the observed hazard ratio of obinutuzumab over rituximab is > 1 (futility boundary based on nonbinding O´Brien-Fleming beta-spending function).

At the time of the third interim analysis (efficacy on PFS) that will be conducted when 67% of the events have occurred (i.e., approximately 248 events), all patients will have been enrolled and followed for an estimated minimum of 11 months. PFS will be tested at the significance level determined using the O´Brien-Fleming alpha-spending function so the overall Type I error rate will be maintained at the 0.05 level. With 67% information, the alpha spending is 0.012.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADCC	antibody–dependent cellular cytotoxicity
ADLs	activities of daily living
AE	adverse event
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
B	bendamustine
BOR	best overall response
BSA	body surface area
CDC	complement–dependent cytotoxicity
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone (or prednisolone/methylprednisolone)
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMH	Cochran–Mantel–Haenszel
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, and prednisone (or prednisolone/methylprednisolone)
DFS	disease–free survival
DLBCL	diffuse large B–cell lymphoma
DLT	dose–limiting toxicity
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	eventfree survival
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
EuroQol	European Quality of Life
FACS	fluorescence–activated cell sorting
FACT–G	functional assessment instrument
FACT–Lym	Functional Assessment of Cancer Therapy for Lymphoma
FC	fludarabine and cyclophosphamide
FCM	fludarabine, cyclophosphamide, and mitoxantrone
FDA	Food and Drug Administration

Abbreviation	Definition
FDG	^{18}F–fluorodeoxyglucose
FLIPI	Follicular Lymphoma International Prognostic Index
FU	follow–up
G	GA101
G–CHOP	obinutuzumab plus CHOP
G–CSF	granulocyte colony stimulating factor
GClb	obinutuzumab plus chlorambucil
GCP	Good Clinical Practice
G–FC	obinutuzumab plus fludarabine and cyclophosphamide
GTD	greatest transverse diameter
HAHA	human anti–human antibody
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HRQoL	health–related quality of life
HTLV	human T–lymphotropic virus
IADLs	instrumental activities of daily living
ICH	International Conference on Harmonisation
IDCC	Independent Data Coordinating Center
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion–related reaction
IV	intravenous
IxRS	interactive voice or Web–based response system
JCV	John Cunningham Virus
LMWH	low molecular weight heparins
LVEF	left ventricular ejection fraction
MALT	mucosa–associated lymphoid tissue

Abbreviation	Definition
MCL	mantle cell lymphoma
MP	methylprednisolone
MRD	minimum residual disease
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTX	methotrexate
MUGA	multiple–gated acquisition
MZL	marginal zone lymphoma
NALT	new anti–lymphoma treatment
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non–Hodgkin's lymphoma
NK	natural killer [cell]
ORR	overall response rate
PCR	polymerase chain reaction
PD	progressive disease
PE	polyethylene
PET	positron emission tomography
PFS	progression–free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRIMA	Primary Rituximab and Maintenance (trial)
PRO	patient–reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
PVC	polyvinyl chloride
R	rituximab
RBC	red blood cell
RClb	rituximab plus chlorambucil
RCR	Roche Clinical Repository
R–CHOP	rituximab plus CHOP
R–CVP	rituximab plus CVP
SAE	serious adverse event
SD	stable disease
SDV	source data verification
SLL	small lymphocytic lymphoma
SPD	sum of the product of the diameters

Abbreviation	Definition
SUSAR	suspected unexpected serious adverse reaction
TEN	toxic epidermal necrolysis
TMA	tissue microarray
TOI	total outcome index
TTNLT	time to next anti–lymphoma treatment
ULN	upper limit of normal
US	United States
WM	Waldenström's macroglobulinemia

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

1.1.1 Non–Hodgkin's Lymphoma

Non–Hodgkin's lymphoma (NHL) is the most common hematologic malignancy in adults. It is estimated that in 2010 there were 93,172 new cases of NHL in Europe and 65,540 new cases of NHL in the United States (US; American Cancer Society 2010; GLOBOCAN 2010). The majority of NHLs (also known as malignant lymphoma) are of B–cell origin and are characterized by the expression of a membrane antigen, CD20, which is important in cell cycle initiation and differentiation (Anderson et al. 1984). NHL can be divided into aggressive and indolent NHL. Indolent NHLs are a heterogeneous group of malignant lymphomas and account for about one–third of all NHLs. Follicular lymphoma is the most common subtype of indolent NHL in the Western hemisphere and is associated with follicle center B–cells that typically contain the *BCL2* chromosome translocation t(14:18), which leads to overexpression of the intracellular anti–apoptotic protein Bcl–2. Although follicular lymphoma is the most common subtype of indolent NHL, there are also many histological non–follicular subtypes, including marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM; also known as lymphoplasmacytic lymphoma), mucosa–associated lymphoid tissue (MALT) lymphoma, and small lymphocytic lymphoma (SLL). Early–stage indolent NHL may be effectively treated with radiation therapy, but advanced stages remain incurable.

1.1.2 Natural History and Current Management of Indolent Non-Hodgkin's Lymphoma

The clinical course of indolent NHL is characterized by remission and relapse (Gallagher et al. 1986). The disease initially responds to radiation and/or immunochemotherapy with conventional agents, but patients eventually suffer multiple relapses distinguished by increasing refractoriness and decreasing duration of response in subsequent lines of therapy. Patients with advance–stage disease are not usually cured with conventional treatment and ultimately die from recurrent disease or treatment–related toxicity.

a. Immunochemotherapy in Follicular Lymphoma

There is no standard treatment for the management of advanced follicular lymphoma, and data from the National LymphoCare registry demonstrate that practice varies widely among physicians (Friedberg et al. 2009). For follicular lymphoma patients requiring treatment, immunochemotherapy with rituximab (MabThera®, Rituxan®), a monoclonal antibody directed against CD20, plus chemotherapy has demonstrated improvements in response rates, progression–free survival (PFS), and overall survival compared with chemotherapy alone in four studies (Hiddemann et al. 2005; Herold et al. 2007; Marcus et al. 2008; Salles et al. 2008) (see Table 1). Rituximab in combination with chemotherapy (e.g., CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CVP [cyclophosphamide, vincristine, and prednisone], or purine

analogue–based schemes such as those with fludarabine or bendamustine) for newly diagnosed patients with advanced Stage III and IV disease requiring treatment is strongly supported by both the 2009 European Society for Medical Oncology (ESMO) Guidelines Working Group recommendations (level of evidence: I; grade of recommendation: B) and the 2010 National Comprehensive Cancer Network (NCCN) guidelines (Category 1 recommendation based on high–level evidence, with a uniform NCCN consensus) (Dreyling 2009; Zelenetz et al. 2010).

Table 1 Phase III Trials of Rituximab plus Chemotherapy in Previously Untreated Patients with Follicular Lymphoma

Reference	Treatment	n	Median Follow–Up	Primary Endpoint	ORR and CR Rates	Overall Survival
Marcus et al. 2008	R–CVP vs. CVP for 8 cycles	321	53 months	Median TTF: 27 vs. 7 months	ORR = 81% vs. 57% CR = 41% vs. 10%	4–year OS: 83% vs. 77%
Hiddemann et al. 2005	R–CHOP vs. CHOP for 6–8 cycles	428	18 months	Treatment failure: 28/223 vs. 61/205	ORR = 96% vs. 90% CR = 20% vs. 17%	2–year OS: 95% vs. 90%
Herold et al. 2007	R–MCP vs. MCP for 6 cycles	201	47 months	PFS: not reached vs. 29 months	ORR = 92% vs. 75% CR = 50% vs. 25%	4–year OS: 87% vs. 74%
Salles et al. 2008	R–CHVP for 6 cycles vs. CHVP for 12 cycles; both with IFN	358	5 years	EFS: 53% vs. 37%	ORR = 94% vs. 85% CR = 63% vs. 34%	5–year OS: 84% vs. 79%

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone (or prednisolone/methylprednisolone); CHVP = cyclophosphamide, doxorubicin, etoposide, and prednisone; CR = complete response; CVP = cyclophosphamide, vincristine, and prednisone (or prednisolone/methylprednisolone); EFS = event–free survival; IFN = interferon; MCP = mitoxantrone, chlorambucil, and prednisolone; ORR = overall response rate (complete response plus partial response); OS = overall survival; PFS = progression–free survival; R = rituximab; TTF = time to treatment failure.

b. Immunochemotherapy in Non–Follicular Indolent Lymphoma

Rituximab has also demonstrated efficacy in patients with non–follicular indolent lymphoma, including MZL, WM, and SLL (Foran et al. 2000; Treon et al. 2001; Hainsworth et al. 2003). A Phase II trial conducted in 39 patients with MZL (Brown et al. 2009) showed high response rates (overall response rate [ORR] of 85%; complete response [CR] rate of 54%) with durable responses (79.5% PFS after 3.1 years) following treatment with rituximab and chemotherapy.

The uncommon nature of MZL with an incidence of about 2/100,000 has limited the number of dedicated studies on the optimal therapeutic approach. Historically,this subtype of indolent NHL has been studied in smaller non–randomized trials or in conjunction with other more prevalent types of indolent NHL, such as follicular lymphoma. As a result, treatment of MZL is approached in a fashion similar to treatment of follicular lymphoma, with similar results for rituximab monotherapy and rituximab plus chemotherapy. A randomized study comparing chemotherapy with chemotherapy plus rituximab in patients with extranodal MZL at a median follow–up time of 60 months showed an improvement in 5–year event–free survival (EFS) from 50% (95% confidence interval [CI], 40%, 9%) in those receiving chlorambucil to 68% (95% CI, 58%, 76%) in those receiving chlorambucil plus rituximab (Zucca and Dreyling 2010).

Rituximab is listed as an option for the treatment of advanced MZL in the recent ESMO and NCCN Clinical Practice Guidelines (Zelenetz et al. 2010; Zucca et al. 2010).

c. Maintenance Therapy after Induction Treatment

In addition to immunochemotherapy induction, two recent randomized clinical trials have demonstrated the benefit of maintenance rituximab in responding patients with both previously untreated and relapsed follicular lymphoma. In a clinical trial of patients with relapsed follicular lymphoma, responders to rituximab plus CHOP (R–CHOP) or CHOP underwent a second randomization to maintenance rituximab or observation. Patients who received maintenance rituximab demonstrated a superior median PFS (52 vs. 15 months) and 3 year overall survival (85% vs. 77%) compared with patients who underwent observation (van Oers et al. 2006). This benefit for maintenance rituximab was evident even for patients who received rituximab during induction therapy. Updated results from this study, with a median follow–up of 6 years, continued to demonstrate a significant improvement in PFS with rituximab maintenance versus observation (median PFS: 3.7 years vs. 1.3 years; $p < 0.001$; hazard ratio, 0.55) and in 5 year overall survival (74% vs. 64%) after either R–CHOP or CHOP induction (van Oers et al. 2010). Most recently, a study of patients with previously untreated follicular lymphoma that responded to rituximab in combination with CVP, CHOP, or FCM (fludarabine, cyclophosphamide, and mitoxantrone) who were later randomized to observation or 2 years of maintenance rituximab (the Primary Rituximab and Maintenance [PRIMA] trial) demonstrated an improvement in PFS with the addition of

maintenance rituximab. Patients who received 2 years of rituximab maintenance demonstrated a 2–year PFS of 82%, compared with 66% for the observation group ($p < 0.001$; hazard ratio, 0.50; overall survival data are still immature) (Salles et al. 2011). These studies have set a new standard for the treatment of patients with follicular lymphoma.

Despite these encouraging results, therapy for indolent NHL is not curative.
The majority of patients will ultimately die from progressive disease (PD). It is important to introduce new agents that may potentially alter the natural history of indolent NHL. One such candidate is obinutuzumab (RO5072759, GA101), a novel glyco–engineered anti–CD20 monoclonal antibody that has shown efficacy with an acceptable toxicity profile in Phase I and Phase II trials.

This trial will test whether obinutuzumab combined with chemotherapy followed by maintenance obinutuzumab can improve the outcome over rituximab combined with chemotherapy followed by maintenance rituximab in patients with previously untreated indolent NHL. The study aims to obtain an improvement of 25 months for obinutuzumab plus chemotherapy versus rituximab plus chemotherapy, corresponding to a hazard ratio of 0.74 for an improvement in median PFS from 6 to 8.1 years.

1.2 BACKGROUND ON THE MOLECULE

1.2.1 Obinutuzumab (RO5072759, GA101) Structure and Mechanism of Action

Obinutuzumab is a humanized and glyco–engineered monoclonal antibody, derived by humanization of the parental B–Ly1 mouse antibody and subsequent glyco–engineering leading to the following characteristics (Beers et al. 2010; Mössner et al. 2010):

- High–affinity binding to CD20
- Type II binding to the CD20 epitope, leading to low complement–dependent cytotoxicity (CDC) related to the recognition of the CD20 epitope and the lack of CD20 localization into lipid rafts after binding of the monoclonal antibody to CD20
- Compared with the chimeric Type I anti–CD20 antibody rituximab, increased antibody–dependent cellular cytotoxicity (ADCC) related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa expressed by natural killer (NK) cells and monocytes
- Compared with rituximab, increased direct cell–death induction related to an elbow hinge amino exchange of the Fab region and Type II binding of the CD20 epitope

Given the significantly greater ADCC and direct cell–death induction, it is possible that obinutuzumab may have greater efficacy than rituximab, particularly in the 80%–85% of patients who are carriers of the FcγRIIIa low–affinity receptor polymorphism (FF/FV genotype; see Section 3.2.2.b), since such patients may have decreased overall survival compared with patients with the high–affinity (V/V) polymorphism who demonstrate

improved survival following therapy with chemotherapy plus either rituximab or I−131 tositumomab (Persky et al. 2009).

1.2.2 Nonclinical Efficacy with Obinutuzumab

Obinutuzumab has demonstrated in vivo efficacy superior to that of rituximab in various human lymphoma xenograft models. Both antibodies have been compared in human SUDHL−4 cells (a diffuse large B−cell lymphoma [DLBCL] model) that were subcutaneously injected into severe combined immunodeficient beige mice. Therapy began when tumors were established and rapidly growing.

It was shown that rituximab at 10 mg/kg inhibited tumor growth more than rituximab at 1 mg/kg; however, increasing the dose to 30 mg/kg did not result in increased efficacy of rituximab. In contrast, obinutuzumab showed a dose−dependent increase in efficacy in the range of 1−30 mg/kg and resulted in complete tumor regression in all animals and in lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

Additional studies have also shown similar results, because obinutuzumab treatment was able to control tumor growth when vehicle− and rituximab−treated tumors were not controlled (Mössner et al. 2010).

For more detailed nonclinical information on obinutuzumab, please refer to the current version of the obinutuzumab Investigator's Brochure.

1.2.3 Clinical Experience with Obinutuzumab in Non−Hodgkin's Lymphoma

As of June 2010, clinical data on obinutuzumab are available from four Phase I or II studies (Studies BO20999, BO21003, BO21000, and JO21900) and two Phase III studies (Studies GAO4753g and BO21004/CLL−11). More than 350 patients with CD20−positive malignant disease have been treated with obinutuzumab.

Results from the aggressive and indolent NHL cohorts in ongoing studies are described below. For more detailed clinical information on obinutuzumab and for information regarding chronic lymphocytic leukemia (CLL) cohorts and all Phase I studies, please refer to the obinutuzumab Investigator's Brochure.

a) Study BO20999 (Phase I/II): Obinutuzumab Monotherapy

The results from the Phase II part of the study are presented below.

Patients with Indolent Non−Hodgkin's Lymphoma

Forty patients with relapsed or refractory indolent NHL were randomized to receive obinutuzumab in a low−dose cohort (n = 18) or a high−dose cohort (n = 22). Patients were pretreated with a median of four prior regimens (range, 1−13), and the majority (39 of 40) had received prior rituximab treatment. More than half of these patients (24 of

40) were considered to be rituximab refractory, and 25% (10 of 40) of all patients had previously received an autologous stem-cell transplant. The low–dose cohort received obinutuzumab 400 mg on Days 1 and 8 of Cycle 1 followed by obinutuzumab 400 mg on Day 1 of Cycles 2-8 (21–day cycles), and the high–dose cohort received obinutuzumab 1600 mg on Days 1 and 8 of Cycle 1 followed by obinutuzumab 800 mg on Day 1 of Cycles 2–8 (21–day cycles). The end-of-treatment response rate (response evaluation 4 weeks after the end of treatment) was 17% in the low–dose cohort (3 with partial response [PR], 6 with stable disease [SD], 7 with PD, and 2 unevaluable) and 55% in the high–dose cohort (2 with CR, 10 with PR, 6 with SD, and 4 with PD).

Obinutuzumab was well tolerated in both cohorts. During the treatment period, 9 patients experienced a total of 12 serious adverse events, with 4 (all in the high–dose cohort) assessed by the investigator as related to obinutuzumab (herpes zoster, neutropenia, febrile neutropenia, and pancreatitis). During the additional follow–up period, 2 patients reported serious adverse events of pyrexia (low–dose cohort) and bacteremia (high–dose cohort). The most common adverse events (all grades), occurring with an incidence of $\geq$ 10%, were infusion–related reaction (IRR; 73%), asthenia (33%), nasopharyngitis (13%), peripheral edema (10%), pyrexia (10%), abdominal pain (10%), bronchitis (10%), and nausea (10%). Thirty–three percent of patients had Grade 3 or 4 adverse events; the three most common were lymphopenia (8%), neutropenia (8%), and infections (10%).

Patients with Aggressive Non–Hodgkin's Lymphoma

Forty patients with aggressive NHL were enrolled into the Phase II part of the study. Of these patients with aggressive NHL (25 with DLBCL and 15 with mantle–cell lymphoma [MCL]), 19 were treated in the high–dose cohort (15 with DLBCL and 4 with MCL) and 21 were treated in the low–dose cohort (10 with DLBCL and 11 with MCL). Preliminary safety and efficacy data are available (data on file). The primary endpoint was end–of–treatment response, assessed 4 weeks after the last infusion (25 weeks after treatment start). Patients were heavily pretreated (median of three prior therapies), with 63% of patients having not responded to or relapsed within 6 months after a previous rituximab-containing regimen (rituximab refractory); 45% of patients completed all nine infusions. The end–of–treatment response rate was 24% in the low–dose cohort (DLBCL: 2 with PR, 1 with CR unconfirmed); MCL: 2 with CR) and 32% in the high–dose cohort (DLBCL: 4 with PR; MCL: 2 with PR).

The five most common adverse events were IRR (75%), infection (25%), asthenia (18%), anemia (15%), and lymphopenia (15%). Fifty percent of patients had Grade 3 or 4 adverse events; the five most common were lymphopenia (15%), anemia (10%), thrombocytopenia (8%), IRR (8%), and tumor lysis syndrome (5%). Serious adverse events occurring in 2 or more patients included cardiac failure (n = 2), IRR (n = 3), tumor lysis syndrome (n = 2), and anemia (n = 2). There was one Grade 5 adverse event, cardiorespiratory arrest that was thought to be secondary to ventricular arrhythmia.

b) Study BO21003 (Phase II): Obinutuzumab Monotherapy plus Maintenance

Study BO21003 is an ongoing, open–label, multicenter, randomized, Phase I/II study to investigate the efficacy and safety of obinutuzumab monotherapy compared with that of rituximab monotherapy in patients with relapsed indolent NHL. The Phase II portion of the study began in July 2009, and approximately 176 patients have been enrolled. An interim analysis for safety and a futility analysis for efficacy were performed in July 2010 with use of data from 78 patients. Per the protocol, futility stopping rules recommended a halt to the trial if the rituximab arm had 2 more patients with a response at the end of treatment than did the obinutuzumab arm ($\Delta < -3.14\%$). The internal monitoring committee's recommendation was to continue the study as planned. No new safety issues were identified.

c) Study BO21000 (Phase Ib): Obinutuzumab in Combination with Chemotherapy

Study BO21000 is an ongoing, open–label, randomized Phase I/II trial investigating two doses of obinutuzumab (400 mg and 1600/800 mg) in combination with chemotherapy given every 4 weeks for a maximum of six cycles (obinutuzumab plus fludarabine and cyclophosphamide [G–FC]) or a maximum of eight cycles (obinutuzumab plus CHOP [G-CHOP]) in patients with relapsed or refractory follicular lymphoma. In the 1600/800 mg G–CHOP arm, patients receive a cumulative dose of 7200-8000 mg of obinutuzumab, depending on the standard number of cycles delivered. Patients with a PR or CR who complete a minimum of four cycles of G–FC or six cycles of G–CHOP have the option of receiving maintenance therapy with obinutuzumab alone every 3 months for up to 2 years. Currently, safety data from the induction period are available. Of 56 patients enrolled with relapsed/refractory disease, all 28 patients treated with G–CHOP have completed the induction treatment, whereas 6 of the 28 patients who started G–FC withdrew early from induction treatment. Reasons for withdrawal from study treatment for the 6 patients who withdrew from the G–FC arm were PD for 1 patient and adverse events reported in 5 patients: neutropenia (3 patients) and rash and infection (1 patient each).

Overall, between the low–dose and high–dose arms, the rate of adverse events by system organ class did not differ greatly, and given the small numbers of patients, definitive conclusions cannot be drawn about differences between low–dose and high-dose obinutuzumab adverse event rates. All 56 patients experienced at least one adverse event. The most commonly reported events were classified under the system organ class "general disorders and administration–site conditions," with the highest rate for IRR events, regardless of the chemotherapy backbone and dose level group considered.

The rate of IRRs was 68% of patients in the G–CHOP arm and 82% of patients in the G-FC arm; 7% of events were Grade 3 or 4 events in both chemotherapy arms. Events in the gastrointestinal disorders system organ class were the second most common

reported adverse events and were reported in 86% and 71% of patients in the G-CHOP and G–FC arms, respectively. Infection and infestation events were experienced by 79% (93% high dose; 64% low dose) of the patients in the G–CHOP arm and 57% (57% high dose; 57% low dose) of the patients in the G–FC arm. Grade 3 and 4 infection and infestation events were reported in 21% of patients in the G–CHOP arm and 29% of patients in the G-FC arm.

Blood and lymphatic system events, with neutropenia being the most common event, were observed for 57% and 64% of the patients in the G–CHOP and G–FC arms, respectively. Of these events, 46% and 61% were considered Grade 3 or 4 events. Neutropenic events (i.e., neutropenia, febrile neutropenia, neutropenic sepsis, and neutropenic infections) were reported in 14 patients (50%) and 17 patients (61%) in the G–CHOP and G–FC arms, respectively. Serious adverse events were reported in 8 patients (29%) and 7 patients (25%) receiving G-CHOP and G–FC induction, respectively. Infections were the most commonly reported events. No deaths have been reported during the induction treatment period (Davies et al. 2011).

The protocol was amended to include obinutuzumab at a flat dose of 1000 mg plus bendamustine (G-bendamustine) or CHOP in previously untreated patients with follicular lymphoma. Again, patients with a PR or CR who complete a minimum of six cycles of G-CHOP or four cycles of G-bendamustine have the option of receiving maintenance therapy with obinutuzumab alone every 3 months for up to 2 years. For the patient cohort with untreated follicular lymphoma, 80 treatment–naive patients will be enrolled, with 40 patients in each cohort. Enrollment has meanwhile been completed, with 40 patients recruited into the G-CHOP cohort and 41 patients in the G-bendamustine cohort. The Data and Safety Monitoring Board evaluated safety of the patients throughout the study without requesting modifications to the protocol.

d) Study GAO4753g (Phase III): Obinutuzumab in Combination with Chemotherapy

Study GAO4753g is an ongoing, open–label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with that for bendamustine plus obinutuzumab in patients with rituximab–refractory indolent NHL. Approximately 360 patients will be enrolled. The first patient was enrolled in April 2010, and approximately 60 patients have been enrolled through May 2011. No safety data are available yet. The Data and Safety Monitoring Board evaluated safety of the first 20 patients without requesting modifications to the protocol.

e) Summary of Safety and Efficacy Results

With consideration of all the available obinutuzumab Phase I and II data, the data strongly suggest that obinutuzumab could represent a more effective treatment than the well–established anti-CD20 antibody rituximab, offering improved outcomes for patients without significantly compromising safety.

For more information relating to safety and efficacy in the NHL indication, refer to the obinutuzumab Investigator's Brochure.

1.2.4 Pharmacokinetic and Pharmacodynamic Data for Obinutuzumab

A population pharmacokinetic model has been developed for Studies BO20999 and BO21003 to characterize the pharmacokinetics of obinutuzumab and its variability. A two-compartment model, comprising both a linear clearance pathway and a non–linear time–varying clearance pathway, was fitted to the data. Data are available for a total of 134 patients following intravenous (IV) administration of obinutuzumab in Studies BO20999 (n = 114) and BO21003 (n = 20).

Following infusion of obinutuzumab, the elimination appears to be characterized by a clearance that is dependent on time; that is, starting at a typical value of 594 mL/day and then gradually decreasing to an asymptote of 112 mL/day at steady state. Tumor burden potentially contributes significantly to the clearance of obinutuzumab, especially at the beginning of treatment when there is an excess of CD20 cells. As tumor burden decreases, the clearance reaches an asymptote, which is thought to be primarily a function of the proteolytic metabolic clearance. Consequently, some patients with a high tumor burden appear to clear the drug from the plasma faster than patients with a low tumor burden because obinutuzumab binds to the CD20–positive tumor cells and is effectively removed from the plasma. Therefore, the clearance of the drug will vary with time since repeated treatments with obinutuzumab will reduce the quantity of CD20–positive tumor cells.

Treatment with obinutuzumab resulted in extensive B–cell depletion, with all patients showing a reduction in cell count to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before or after infusion, but changes have been observed in the levels of interleukin–6 and interleukin–8 before and after infusion.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Indolent NHL is characterized by a pattern of remission and relapses and is incurable with standard treatment options. In spite of the progress made in the treatment of patients with indolent NHL based on the addition of rituximab to chemotherapy, a significant number of patients will relapse and ultimately die of PD or treatment–related toxicity. Therefore, obtaining better outcomes for previously untreated patients is of critical importance.

Phase II and III trials have confirmed the safety and efficacy of combining rituximab, an anti–CD20 monoclonal antibody, with various chemotherapy regimens such as CVP, CHOP, and bendamustine in previously untreated patients with indolent NHL. The addition of an anti–CD20 monoclonal antibody to conventional chemotherapy improves efficacy without adding significant toxicity (Czuczman et al. 2005; Rummel et al. 2005,

2009; Marcus et al. 2008; Salles et al. 2008). Several additional Phase III trials have demonstrated the benefit of adding anti-CD20 maintenance therapy following induction treatment with single–agent rituximab, chemotherapy, or immunochemotherapy (Ghielmini et al. 2004; van Oers et al. 2006; Hochster et al. 2009; Martinelli et al. 2010; Salles et al. 2011).

Nonclinical data have demonstrated that the novel humanized glyco-engineered, Type II monoclonal anti–CD20 antibody obinutuzumab may have activity against rituximab-resistant cell lines and that the combination of obinutuzumab and chemotherapy has, at a minimum, an additive effect in relation to efficacy (see the obinutuzumab Investigator's Brochure; Mössner et al. 2010). This is consistent with the hypothesis that rituximab therapy may potentially sensitize tumor cells to chemotherapy–induced cell death when combined with chemotherapy (Plosker and Figgitt 2003). Compared with the chimeric Type I anti–CD20 antibody rituximab, obinutuzumab demonstrates increased ADCC related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa expressed by NK cells and monocytes (Mössner et al. 2010). Improved ADCC with obinutuzumab may therefore be particularly important in the 80%–85% of patients who are carriers of the low–affinity FcγRIIIa allele, because such patients have a decreased overall survival compared with carriers of the high–affinity FcγRIIIa allele who demonstrate improved survival following therapy with chemotherapy plus either rituximab or I-131 tositumomab (Persky et al. 2009).

In clinical trials (see Section 1.2.3), obinutuzumab demonstrated activity in patients with relapsed or refractory indolent lymphoma with an acceptable toxicity profile (Morschhauser et al. 2009; Salles et al. 2009; Sehn et al. 2009). In these trials, the majority of patients had been previously treated with multiple lines of therapy and many were rituximab refractory. Phase I/II data indicate that obinutuzumab may offer an improved treatment option over the well–established anti–CD20 antibody rituximab. Moreover, preliminary data suggest that the safety profile of obinutuzumab is similar to that of rituximab.

In terms of safety, differences in the molecular structure and mode of action between obinutuzumab and rituximab may result in different safety profiles. In particular, adverse events relating to more rapid and extensive CD20–positive–cell depletion, both malignant and normal, may be more common with obinutuzumab. The safety data available to date, with more than 470 patients treated at doses of up to 2000 mg, show that obinutuzumab is well tolerated and has a safety profile similar to that of rituximab. So far, no maximum tolerated dose, no dose-limiting toxicities (DLTs), and no dose–related trends in the incidence of adverse events have been observed.

Given the nonclinical data demonstrating superior direct cell–death induction with obinutuzumab when compared with rituximab and clinical data showing efficacy and a favorable safety profile, it is hypothesized that the addition of obinutuzumab to

chemotherapy followed by maintenance obinutuzumab may provide additional clinical benefit over rituximab plus chemotherapy followed by maintenance rituximab in previously untreated patients with indolent NHL.

The head–to–head design of the study, precautionary safety measures, and regular monitoring of safety by an Independent Data Monitoring Committee (IDMC) and the Sponsor enables early identification of safety signals in the study and minimizes the risk to enrolled patients. In conclusion, it is considered that the benefit–risk ratio for this study is favorable.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective for this study is as follows:

- To evaluate the efficacy of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in patients with previously untreated advanced follicular lymphoma, as measured by investigator–assessed PFS

2.2 SECONDARY OBJECTIVES

The following secondary objective applies to patients with previously untreated advanced indolent NHL (i.e., overall population):

- To evaluate and compare investigator–assessed PFS between the two arms

The following secondary objectives apply to patients with previously untreated advanced indolent NHL (i.e., overall population) and to the subset of patients with previously untreated advanced follicular lymphoma (i.e., follicular population):

- To evaluate and compare Independent Review Committee (IRC)–assessed PFS between the two arms
- To evaluate and compare overall response and CR after the end of induction treatment, as assessed by the investigator, between the two arms, with and without ^{18}F–fluorodeoxyglucose positron emission tomography (FDG–PET)
- To evaluate and compare overall response and CR after the end of induction treatment, as assessed by the IRC, between the two arms, with and without FDG-PET
- To evaluate and compare overall survival, EFS, disease–free survival (DFS), duration of response, and time to next anti–lymphoma treatment between the two arms

  EFS, DFS, and duration of response will be based on investigator assessment.
- To evaluate and compare the safety profiles between the two arms during induction and maintenance
- To assess patient–reported outcomes (PROs) in both arms

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate and compare the proportion of patients who transform to aggressive histology at first relapse between the two arms
- To evaluate the proportion of patients with a PR or SD at the end of induction treatment who convert to CR or to PR/CR, respectively, during maintenance treatment or post–induction observation, as assessed by the investigator
- To characterize the pharmacokinetics and pharmacodynamics of obinutuzumab in combination with chemotherapy
- To compare the efficacy of obinutuzumab versus rituximab within each chemotherapy subset
- To assess the prognostic and predictive ability of baseline clinical factors, which may include activities of daily living (ADLs), instrumental activities of daily living (IADLs), Follicular Lymphoma International Prognostic Index 2 (FLIPI2) score, International Prognostic Index (IPI) score, and FDG–PET imaging
- To assess the prognostic and predictive ability of biomarkers (such as Fcγ Receptor polymorphisms) pertaining to the biology of follicular lymphoma and factors relating to the host immune system (may include immunohistochemistry [IHC] and gene expression assessment of specific targets or gene profiles)
- To assess the prognostic and predictive value of *BCL2/IgH* rearrangement and other markers of minimum residual disease (MRD) in patients with follicular lymphoma at baseline, during induction, at the completion of induction therapy, during maintenance therapy or observation, and during follow–up (IgH clonality may be used as a marker of MRD in patients without an identifiable *BCL2/IgH* translocation at baseline)
- To correlate FDG–PET results with efficacy parameters
- A dedicated analysis to adequately assess PFS in the MZL subcohort will be performed
- To identify and characterize changes in tumor gene expression and cell surface markers that occur in patients who have relapsed and/or transformed after initial treatment with a rituximab– or obinutuzumab–containing regimen

3. STUDY DESIGN

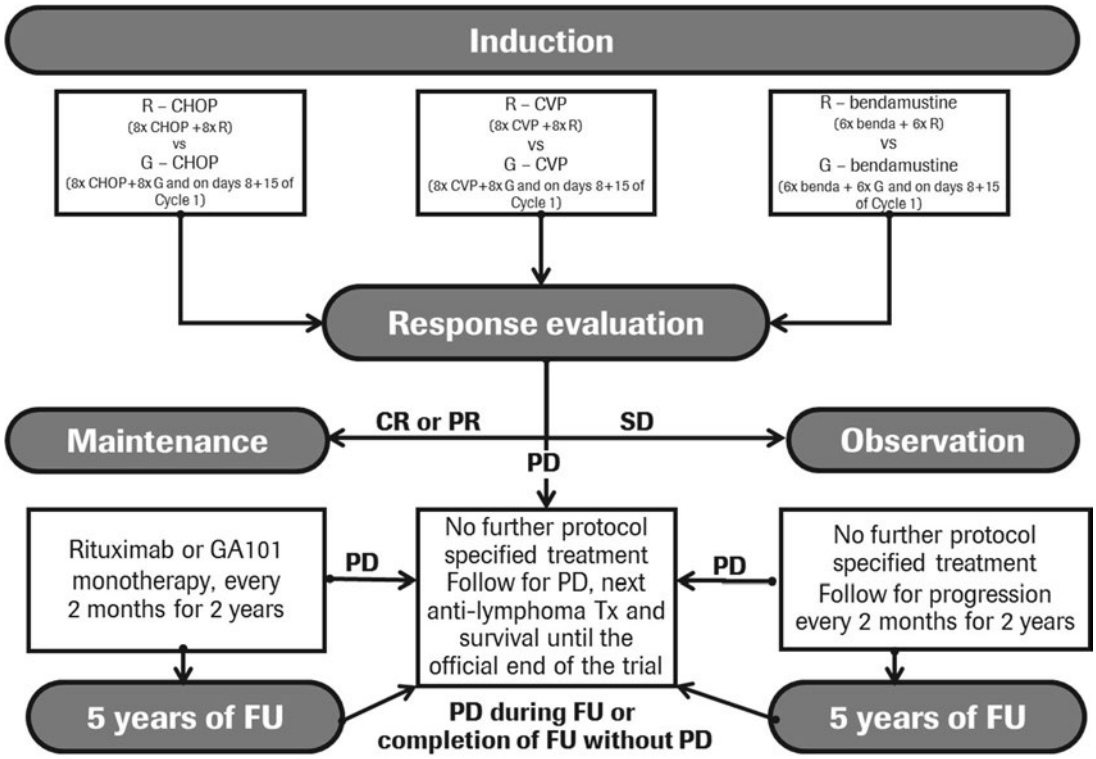
3.1 DESCRIPTION OF THE STUDY

3.1.1 Study Overview

This is an open–label, international, multicenter, randomized, Phase III study to investigate the efficacy and safety of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy for responders (CR or PR) compared with rituximab plus chemotherapy followed by rituximab maintenance therapy for responders in patients with previously untreated advanced indolent NHL. Prior to the initiation of the study, each site will choose one of three chemotherapy regimens (CHOP, CVP, or

bendamustine) that is considered to be the standard of care for follicular lymphoma; all patients with follicular lymphoma at that site will receive the chosen chemotherapy regimen for the duration of the study (a site may switch to another regimen if new scientific data become available and after Sponsor approval). For non–follicular NHL, the investigator will have the option of choosing one of the three chemotherapy regimens (CHOP, CVP, or bendamustine) for each patient. All patients will then be randomized to either rituximab plus chemotherapy or obinutuzumab plus chemotherapy. A study schema is provided in Figure 1.

Figure 1 Study Schema



Benda = bendamustine; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone; CR = complete response; CVP = cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone; FU = follow up; G = GA101; PD = progressive disease; PR = partial response; R = rituximab; SD = stable disease.

Approximately 1200 patients with follicular lymphoma will be recruited and randomly assigned in a 1:1 ratio to either obinutuzumab plus chemotherapy followed by obinutuzumab maintenance in responders or rituximab plus chemotherapy followed by rituximab maintenance in responders. In addition, approximately 200 patients with MZL will be recruited and randomly assigned in a 1:1 ratio to the two treatment arms.

Randomization will be performed separately for follicular and non–follicular patients. The randomization scheme will ensure approximately equal samples sizes in the two treatment arms for the following stratification factors:

- Chemotherapy regimen (CHOP, CVP, or bendamustine)
- Follicular Lymphoma International Prognostic Index (FLIPI) risk group (low, intermediate, or high according to FLIPI) in patients with follicular lymphoma or IPI risk group (low/low–intermediate vs. high–intermediate/high) in patients with non-follicular lymphoma
- Geographic region (Western Europe, Eastern Europe, South and Central America, North America, Asia, and "Other")

Randomization will be conducted with the aid of an interactive voice or Web-based response system (IxRS). Study treatment must begin within 7 days after randomization.

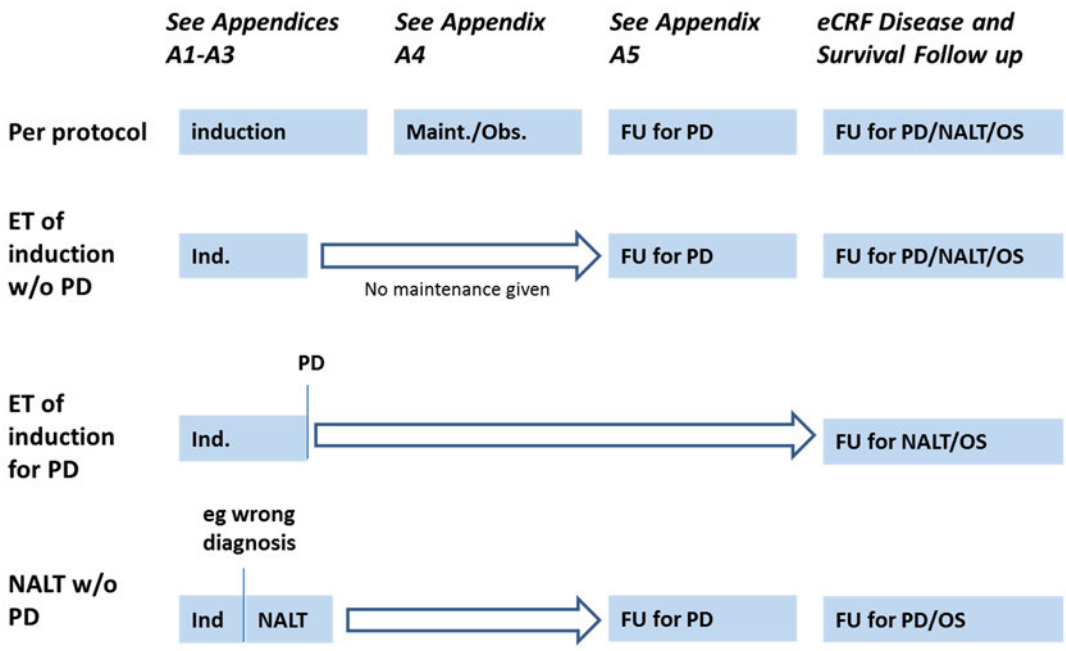
The schedule for administration of rituximab or obinutuzumab will be dependent upon the accompanying chemotherapy regimen. In the control arm of the study (Arm A), six to eight doses of rituximab at 375 mg/m^2 will be administered by IV infusion with the accompanying chemotherapy regimen. In the experimental arm of the study (Arm B), eight to ten doses of obinutuzumab (including two additional doses of obinutuzumab on Days 8 and 15 of Cycle 1) at an absolute (flat) dose of 1000 mg will be administered by IV infusion with the accompanying chemotherapy regimen. It is mandatory that the full number of cycles be given for each immunochemotherapy regimen during induction. Patients who demonstrate a CR or PR at the end of induction therapy will continue to receive rituximab at 375 mg/m^2 (Arm A) or obinutuzumab at a flat dose of 1000 mg (Arm B) every 2 months until disease progression for up to 2 years. Patients who demonstrate SD at the end of induction therapy will be followed for progression for up to 2 years according to the same follow–up schedule as responding patients (CR or PR) receiving maintenance (observation). If induction therapy was stopped for toxicity or any reason other than toxicity, then patients are discontinued from study treatment and go into follow–up directly.

All patients will be assessed for disease response by the investigator through use of regular clinical and laboratory examinations and computed tomography (CT) scans according to a modified version of the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix C). Additional response criteria based on paraprotein assessment are in effect for the MZL population and based on hematological parameters and spleen size for the subset of splenic MZL patients. During induction treatment, tumor assessment is performed after three cycles for patients receiving bendamustine, after four cycles for patients receiving CVP or CHOP, and at the completion of induction therapy.

Following the completion of induction therapy, patients receiving maintenance therapy (CR or PR) or undergoing observation (SD) will be followed clinically every 2 months for

2 years (with CT scans every 4 months for the first year and then every 6 months for the second year). For patients who have not progressed at the maintenance or observation completion visit (25 months from Day 1 of Cycle 8 [CHOP/CVP arms] or Cycle 6 [bendamustine arm]), disease assessments will continue every 3 months for 3 years (with CT scans every 6 months) and then every 6 months for 2 years (with CT scans every year) (follow–up for disease progression). After 5 years of follow–up or disease progression (whichever comes first), patients will still be followed every 6 months for overall survival and new anti–lymphoma treatment (NALT), or for disease progression if applicable, until the end of the study, which will be approximately 10.2 years after inclusion of the first patient. Patients who terminate induction early without PD will be followed for PD, as per Appendix A-5, and in the extended follow–up for PD, NALT, and overall survival. Patients who terminate induction early because of PD will go directly into the extended follow–up for NALT and overall survival. Patients who discontinue the protocol–defined treatment path and need to start an NALT in the absence of disease progression (e.g., if wrong diagnosis at screening and new diagnosis requires a change of treatment) will be followed for disease progression and overall survival (Figure 2). *For patients who progressed and received NALT, response after NALT will be collected.*

Figure 2 Sequence of Study Phases in Study BO21223 (GALLIUM)



CR = complete response; eCRF = electronic Case Report Form; ET = early termination; FU = follow up; Ind. = induction treatment; Maint = maintenance; NALT = new anti–lymphoma therapy, Obs. = observation; OS = overall survival, PD = progressive disease; PR = partial response; SD = stable disease; w/o = without.

Note: Following the completion of induction therapy, patients receiving maintenance therapy (CR or PR) or undergoing observation (SD) will be followed as per Appendix A-5. After 5 years of follow–up or disease progression (whichever comes first), patients will enter the extended follow–up for overall survival and NALT until the end of the study. Patients who terminate induction early without PD will be followed for PD as per Appendix A-5, and in the extended follow–up for PD, NALT, and overall survival. Patients who terminate induction early because of PD will go directly into the extended follow-up for NALT and overall survival. Patients who discontinue the protocol-defined treatment path and need to start an NALT in the absence of disease progression (e.g., if wrong diagnosis at screening and new diagnosis requires a change of treatment) will be followed for disease progression and overall survival. *For patients who progressed and received NALT, response after NALT will be collected.*

For the first futility analysis based on CR rates at the induction completion/end-of-treatment visit in 170 patients with follicular lymphoma, the response assessment by investigator and IRC based on CT (magnetic resonance imaging [MRI]) will be complemented in an exploratory analysis with data from two other methods of response assessment:

- Evaluation of response by FDG-PET is mandatory at induction completion/end–of–therapy visit (only if screening PET was positive) 6–8 weeks after Day 1 of the last cycle of induction for the first 170 patients with follicular lymphoma at those sites that have a PET scanner available. This may require specific approval in some countries. In such instances, PET becomes mandatory only after necessary approvals have been obtained.
- The depth of response will be assessed by determination of MRD via polymerase chain reaction (PCR)–based detection of *BCL2/IgH* rearrangements in the first 170 patients with follicular lymphoma at screening, mid–term induction (i.e., before Cycle 4 Day 1 for R/G–bendamustine, before Cycle 5 Day 1 for R/G–CHOP or -CVP), induction completion/end of therapy and during maintenance/observation at Month 4. MRD detection will be based on peripheral blood and bone marrow aspirate samples. MRD peripheral blood samples are mandatory and are required at all time points in all patients with follicular lymphoma. MRD bone marrow aspirate samples are mandatory at screening in all patients with follicular lymphoma. At induction completion/end of therapy, MRD bone marrow aspirate samples are mandatory in responders (CR+PR) in whom bone marrow involvement was diagnosed by morphology at screening and are optional but strongly recommended in responders (CR+PR) in whom no bone marrow involvement was diagnosed by morphology at screening. This recommendation is based on the observation that, at screening, bone marrow involvement is detectable on the level of minimal residual disease in the large majority of patients even if it appears to be negative by morphology.

After passing the first futility analysis, PET and MRD will be integrated into additional exploratory analyses in the following manner for the full study:

- Additional optional FDG–PET scans (e.g., in all other lymphoma patients beyond the first 170 patients with follicular lymphoma) are permitted if the investigator chooses to perform them.
- Assessment of MRD is mandatory via PCR–based detection of *BCL2/IgH* rearrangements in all patients with follicular lymphoma at screening; mid–term induction (i.e., before Cycle 4 Day 1 for R/G–bendamustine, before Cycle 5 Day 1 for R/G-CHOP or –CVP); induction completion/end of therapy; during maintenance/observation at Months 4, 8, 12, and 18 and at maintenance or observation completion/end of therapy; and during follow-up at Months 30, 36, 42, 48, 54, 60, 72, and 84. MRD detection will be based on peripheral blood and bone marrow aspirate samples. MRD peripheral blood samples are mandatory and are required at all time points in all patients with follicular lymphoma. MRD bone marrow aspirate samples are mandatory at screening in all patients with follicular lymphoma. At induction completion/end of therapy, MRD bone marrow aspirate samples are mandatory in responders (CR + PR) in whom bone marrow involvement was diagnosed by morphology at screening and are optional but strongly recommended in responders (CR + PR) in whom no bone marrow involvement was diagnosed by morphology at screening. This recommendation is based on the observation that, at screening, bone marrow involvement is detectable on the level of minimal residual disease in the large majority of patients even if it appears to be negative by morphology.

An independent radiologic and oncologic review of the responses of all patients by an IRC will also be conducted for the futiliy and efficacy analyses with and without PET.

Patients who discontinue all components of study therapy prior to disease progression (e.g., for toxicity) will enter the follow–up phase of the study and will continue to be followed for PD and overall survival (regardless of whether they subsequently receive NALT).

A retrospective quality assurance pathology review will be conducted on pathology samples to evaluate histology and CD20 status in addition to other prognostic features.

An IDMC will conduct periodic interim reviews of safety summaries, starting approximately 1 month after enrollment of the first patient and then approximately every 2 months until 100 patients have completed two cycles of study treatment. Afterward, the IDMC will conduct reviews of safety summaries approximately every 6 months. All summaries and analyses reviewed by the IDMC will be prepared by an Independent Data Coordinating Center (IDCC). Safety will be evaluated by monitoring dose delays and dose intensity, adverse events, serious adverse events, and deaths. These will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. Laboratory safety assessments will include regular monitoring of hematology, blood chemistry, and tests of immunologic

parameters. In addition, tests for the presence of human anti–human antibodies (HAHAs) will be performed only in all patients receiving obinutuzumab.

Study assessments are listed in the flowcharts provided in Appendix A.

3.1.2 Patient-Reported Outcomes

Patients will assess their health–related quality of life (HRQoL) using two validated questionnaires: the Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) (see Appendix D) and European Quality of Life (EuroQol) EQ–5D (see Appendix E). The FACT-Lym and EQ-5D will enable assessment of the differences between treatment arms with respect to overall HRQoL and changes in HRQoL brought about by symptom worsening/alleviation and treatment toxicity. The PRO questionnaires will be self–administered at the investigational site prior to administration of study drug and prior to any other study assessments, to ensure that the validity of the instruments is not compromised and to ensure that data quality meets regulatory requirements.

The FACT–Lym questionnaire (Webster et al. 2005) consists of the four domains (physical, social/family, emotional, and functional well–being) found in the general functional assessment instrument (FACT–G) plus a 15-item lymphoma-specific subscale that assesses B–symptoms and changes in HRQoL. Cella and colleagues developed and scientifically validated the instrument in a general lymphoma population, including patients with either aggressive or indolent disease (Cella et al. 2005). Items for inclusion in the lymphoma subscale were selected on the basis of symptom relevance, disease specificity, and clinical relevance.

The EQ–5D is a generic preference-based health utility measure that provides a single index value for health status. The EQ–5D consists of two parts. The first part, health-state classification, contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The second part, consisting of a visual analogue scale, will not be used.

3.1.3 Medical Resource Utilization

Analysis of medical resource utilization will be provided if required.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Study Drug Dosing

a. Rationale for Obinutuzumab Dose

A unit dose of 1000 mg of obinutuzumab was chosen after data from completed Phase I studies were reviewed by participating investigators and the Sponsor. This unit dose of obinutuzumab was based on the following findings:

- No DLTs were observed, and no maximum tolerated dose was reached in Phase I (doses of 50–2000 mg were tested).

- Clinical activity (responses) was observed at all dose levels tested.
- Pharmacokinetic analyses suggested that a decreased variability of drug exposure related to tumor burden was achieved at doses above 800 mg given on Days 1, 8, and 22 and then every 3 weeks thereafter, for a total of nine doses.
- Obinutuzumab was well tolerated, with a preliminary safety profile similar to that of rituximab in NHL patients (i.e., mainly Grade 1 or 2 toxicities, with more frequent IRRs around the time of the first infusion and a decreased frequency with subsequent infusions).

After a comprehensive review of all safety, efficacy, and pharmacokinetic data obtained in Phase I studies, an obinutuzumab dose of 1000 mg for all infusions was chosen for use in future Phase II and Phase III NHL studies, because this dose is most likely to be well tolerated and efficacious in a majority of NHL patients regardless of their initial tumor burden. To coordinate the dosing of study drugs during the first 6 months of treatment, obinutuzumab will be administered for six 28–day cycles or for eight 21–day cycles, depending on the accompanying chemotherapy regimen. Pharmacokinetic modeling suggests that giving additional doses of obinutuzumab on Days 8 and 15 of Cycle 1 will be needed to saturate target–mediated clearance and achieve and maintain a steady state of drug early and for as long as possible during treatment.

In Phase I studies, obinutuzumab given as monotherapy to patients with CD20–positive B–cell malignancies was well tolerated up to and including a single dose of 2000 mg and cumulative doses per treatment regimen of 17,200 mg. Responses were observed in all cohorts, with B–cell depletion observed even at the lowest dose. No DLTs were observed. A high intra–individual and inter–individual degree of antibody clearance was observed.

As for most modern monoclonal antibodies, a flat dose (not adapted to body weight or body surface area [BSA]) was chosen since antibody clearance is determined mostly by the target (i.e., for anti–CD20 antibodies accessibility to normal or malignant tumor cells in various compartments, such as blood, bone marrow, nodal or extranodal sites of disease, or lymphatic organs). This flat dose is in contrast to the first monoclonal antibody licensed for the treatment of B–cell malignancies, for which dosing was based on BSA. In the 1990s, when little was known about the toxicity of monoclonal antibodies, development of these agents followed an approach typical for cytotoxic drugs, which usually had DLTs. DLTs were usually a function of the capacity to eliminate the drug by organs such as the liver and spleen. This narrows the therapeutic window and necessitates the adaptation of the dose according to body weight or BSA. It is widely accepted that for most monoclonal antibodies, including anti–CD20 antibodies, there is a wide therapeutic window that does not need to rely on dosing by body weight or BSA. Because quantifying the target and individual dosing according to target has been notoriously difficult, the currently accepted approach for most monoclonal antibodies, including nearly all anti-CD20 antibodies in various stages of development, is flat dosing.

Pharmacokinetic analyses in the Phase I studies, together with published data on rituximab, showed that patients with higher disease burden have faster clearance of the antibody and thus may require higher doses to saturate this target population. In recent studies of rituximab, a similar concept is the basis for a dose–dense R–CHOP regimen, used for example by the German High Grade Non–Hodgkin's Lymphoma Study Group, where dose densification of rituximab resulted in higher serum levels and in higher CR and EFS rates in a study in elderly patients with poor–prognosis DLBCL (Reiser et al. 2006). This finding was further substantiated by a modeling and simulation experiment, suggesting an even higher degree of variability at lower obinutuzumab doses.

Thus, to further understand a potential dose effect, patients were randomized to two different doses of GA10 in the Phase II part of Study BO20999: a low–dose regimen consisting of obinutuzumab 400 mg on Days 1 and 8 of Cycle 1 followed by obinutuzumab 400 mg on Day 1 of Cycles 2–8 and a high–dose regimen consisting of obinutuzumab 1600 mg on Days 1 and 8 of Cycle 1 followed by obinutuzumab 800 mg on Day 1 of Cycles 2–8. The cumulative dose was 3600 mg for the low–dose cohort and 8800 mg for the high–dose cohort. A typical dose for the reference antibody, rituximab, is about 5000–6000 mg (375 mg/m^2 for eight doses), which would fall between the low and high doses tested for obinutuzumab. Pharmacokinetic simulations show that the 95% confidence limits for exposure are between the low and high doses and are not overlapping.

No DLTs were observed across the two doses. Although there was a slight increase in IRRs and neutropenia rates for the high–dose cohort, the regimen was generally well tolerated. As expected, a decreased pharmacokinetic variability was observed at the higher dose. Most importantly, improved efficacy was observed with the higher dose in the indolent cohort, with an ORR of 55% compared with an ORR of 13% in the low–dose cohort. Findings in the aggressive cohort did not show a marked difference in response rates between the high and low doses, yet this cohort was further subdivided by the inclusion of patients with relapsed DLBCL and relapsed MCL, and small numbers might have prevented a more compelling result.

Overall, it was concluded that a higher dose of obinutuzumab can be delivered and that the available evidence from nonclinical studies, pharmacokinetic studies, modeling and simulation, and clinical trials in patients with NHL (Phase I and Phase II) are suggestive of a higher dose being more appropriate to saturate the target in the majority of patients with NHL and, thus, being more efficacious than a lower dose.

In the high–dose cohort of Study BO20999, the first two doses of obinutuzumab were set at 1600 mg. This dose was well tolerated but resulted in application times for patients up to and exceeding 5 hours. To maintain the loading dose concept and provide a significant amount of antibody early during the treatment course, it was therefore decided to change the application time and dose during the first 2 weeks of future

studies from a 1600 mg dose on Days 1 and 8 to a 1000 mg dose on Days 1, 8, and 15, thus providing comparably fast rising pharmacokinetic exposure and early target saturation, while avoiding the practical challenges of delivering 1600 mg on 1 day together with chemotherapy. All other doses were also set at 1000 mg, and this schema (i.e., Days 1, 8, and 15 of Cycle 1 followed by subsequent doses given in 3– or 4-week intervals) has been selected as the obinutuzumab dosing regimen for use in all future obinutuzumab Phase III studies. This schema results in an exposure to obinutuzumab during the first 2 weeks of 3000 mg and a cumulative exposure of 10,000 mg and is therefore very close to the regimen that has delivered thus far the best results for obinutuzumab in both indolent and aggressive NHL.

b. Rationale for Chemotherapy in Combination with Rituximab or Obinutuzumab

Rituximab in combination with chemotherapy (e.g., CHOP, CVP, or purine analogue–based schemes such as those with fludarabine or bendamustine) for newly diagnosed patients with advanced Stage III and IV disease requiring treatment is strongly supported by several clinical trials and both the ESMO and NCCN guidelines. However, there is no universally accepted standard of care for the accompanying chemotherapy regimen administered for the first–line treatment of indolent NHL. Therefore, sites will be able to choose among three different chemotherapy regimens (i.e., CHOP, CVP, or bendamustine) that are widely accepted for the first–line treatment of follicular lymphoma. Allocation by site was chosen in order to possibly achieve a better understanding of the optimal first–line chemotherapy regimen for patients with follicular lymphoma. For non–follicular lymphoma, investigators will choose among three different chemotherapy regimens because patients with MZL may respond to less toxic chemotherapies. This will allow sites that choose CHOP for the treatment of follicular lymphoma to use CVP or bendamustine for the treatment of non-follicular lymphoma.

Combination Therapy with CHOP

R–CHOP is one of the standard induction regimens for previously untreated patients with indolent NHL (Czuczman et al. 1999; Zinzani et al. 2004; Hiddemann et al. 2005; Salles et al. 2011). The CHOP dosing regimen consists of IV cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (maximum dose, 2 mg) on Day 1 and oral prednisone 100 mg on Days 1–5 of each 21–day cycle. Six cycles were administered in most studies, but in some studies, the number of cycles was dependent on the response to the first four courses. Patients achieving a CR after four cycles are treated with a total of six cycles only, whereas all other patients are treated with eight cycles. Rituximab 375 mg/m^2 IV was administered on a variable schedule during earlier studies. In a trial by Czuczman et al. (1999), the first and second rituximab infusions were given on Days 1 and 6 of Cycle 1 (prior to the first CHOP cycle on Day 8), the third and fourth rituximab infusions were given 2 days prior to the third and fifth CHOP cycles, respectively, and the fifth and sixth rituximab infusions were given on Days 134 and 141, respectively, after the sixth CHOP cycle. In other trials, rituximab 375 mg/m^2 was

administered the day before each CHOP cycle (Hiddemann et al. 2005). Most recently, in the PRIMA study, rituximab 375 mg/m^2 was administered on Day 1 of each of six CHOP cycles. A seventh and eighth dose of rituximab were administered 21 and 42 days, respectively, after the sixth CHOP cycle.

In Study BO21000, two different obinutuzumab dosing regimens were administered with a standard CHOP regimen to relapsed or refractory patients. The low–dose cohort received obinutuzumab 400 mg on Days 1 and 8 of Cycle 1 followed by obinutuzumab 400 mg on Day 1 of Cycles 2–8 (21–day cycles), and the high–dose cohort received obinutuzumab 1600 mg on Days 1 and 8 of Cycle 1 followed by obinutuzumab 800 mg on Day 1 of Cycles 2–8 (21 day cycles). In addition, obinutuzumab at a flat dose of 1000 mg was administered with CHOP on Days 1 and 8 of Cycle 1 and on Day 1 of Cycles 2–8 to previously untreated patients.

Given this experience, the CHOP regimen in this study will consist of the following agents:

- Cyclophosphamide 750 mg/m^2 IV on Day 1 of each of six 21–day cycles
- Doxorubicin 50 mg/m^2 IV on Day 1 of each of six 21–day cycles
- Vincristine 1.4 mg/m^2 IV (maximum dose, 2 mg) on Day 1 of each of six 21-day cycles
- Prednisone 100 mg orally on Days 1–5 of each of six 21–day cycles (or 100 mg prednisolone in countries or sites without availability of prednisone or with strong preference for prednisolone or 80 mg methylprednisolone in countries or sites without availability of prednisone/prednisolone)

Rituximab will be administered at 375 mg/m^2 IV on Day 1 of each of eight 21–day cycles. Obinutuzumab will be administered at a flat dose of 1000 mg on Day 1 of each of eight 21–day cycles and on Days 8 and 15 of Cycle 1 to achieve appropriate levels of drug. If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab or obinutuzumab is allowed on the day prior to administration of CHOP with premedication. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count).

This dosing regimen provides a total dose of R–CHOP and G–CHOP that is consistent with that used in prior studies in previously untreated patients with indolent NHL.

Combination Therapy with CVP

CVP is a standard induction regimen for patients with indolent NHL. The addition of eight doses of rituximab to eight cycles of CVP (R–CVP) has been shown to significantly improve the clinical outcome of previously untreated patients with follicular lymphoma (Marcus et al. 2005, 2008; Salles et al. 2011). In these trials, patients treated with R-CVP received IV cyclophosphamide 750 mg/m^2 and vincristine 1.4 mg/m^2 on Day 1

(maximum dose, 2 mg) and oral prednisone 40 mg/m^2 on Days 1–5 of each of eight 21-day cycles. Patients treated with R-CVP also received IV rituximab 375 mg/m^2 on Day 1 of each cycle.

Given this experience, the CVP regimen in this study will consist of the following agents:

- Cyclophosphamide 750 mg/m^2 IV on Day 1 of each of eight 21–day cycles
- Vincristine 1.4 mg/m^2 IV (maximum dose, 2 mg) on Day 1 of each of eight 21–day cycles
- Prednisone 100 mg orally on Days 1–5 of each of eight 21–day cycles (or 100 mg prednisolone in countries or sites without availability of prednisone or with strong preference of prednisolone or 80 mg methylprednisolone in countries or sites without availability of prednisone/prednisolone)

Rituximab will be administered at 375 mg/m^2 IV on Day 1 of each of eight 21–day cycles. Obinutuzumab will be administered at a flat dose of 1000 mg on Day 1 of each of eight 21–day cycles and on Days 8 and 15 of Cycle 1 to achieve appropriate levels of drug. If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab or obinutuzumab is allowed on the day prior to administration of CVP with premedication. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count).

This dosing regimen provides a total dose of R–CVP and G–CVP that is consistent with that used in prior studies in previously untreated patients with indolent NHL.

Combination Therapy with Bendamustine

Bendamustine with and without rituximab has demonstrated efficacy in patients with relapsed or refractory indolent NHL (Rummel et al. 2005; Friedberg et al. 2008; Robinson et al. 2008; Kahl et al. 2010). A recent Phase III trial also demonstrated the efficacy of bendamustine plus rituximab in previously untreated patients with indolent NHL (Rummel et al. 2009). Bendamustine when administered as first–line therapy for patients with indolent NHL and MCL demonstrated an improvement in PFS from 34.8 months to 54.8 months and an improvement in the CR rate from 30.8% to 40.1% with less toxicity when compared with R–CHOP.

Clinical studies testing the combination of bendamustine plus rituximab have administered bendamustine 90 mg/m^2 on Days 2 and 3 of each 28-day cycle and rituximab on Day 1 of each 28-day cycle because of concerns of additive toxicity (Rummel et al. 2005, 2007; Robinson et al. 2008). Importantly,in the study of previously untreated patients with indolent NHL (Rummel et al. 2009), a dose of 90 mg/m^2 was given every 28 days in combination with rituximab. Ninety-six percent of patients received the full six cycles (average of 5.58 cycles administered). In addition, 90 mg/m^2 is the dose of bendamustine recommended for use in combination with

rituximab at a consensus conference of hematologists who had extensive experience with bendamustine (Cheson et al. 2010).

Given this experience, the bendamustine regimen in this study will consist of IV bendamustine 90 mg/m^2 given on Days 1 and 2 of each of six 28–day cycles, with oral prednisone (or prednisolone) 100 mg (or 80 mg of methylprednisolone) also administered on Day 1 of Cycle 1. Rituximab will be administered at 375 mg/m^2 IV on Day 1 of each of six 28–day cycles. Obinutuzumab will be administered at a flat dose of 1000 mg on Day 1 of each of six 28-day cycles and on Days 8 and 15 of Cycle 1 to achieve appropriate levels of drug. If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab or obinutuzumab is allowed on the day prior to administration of bendamustine with premedication. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an infusion–related reaction (high tumor burden, high peripheral lymphocyte count).

This dosing regimen provides a total dose of bendamustine that is consistent with the recommendations of the consensus conference for patients with relapsed or refractory indolent NHL.

c. Rationale for Maintenance Treatment

Rituximab has been studied as a maintenance therapy in a variety of settings. A Phase II trial of rituximab monotherapy (once weekly for 4 weeks) followed by rituximab maintenance therapy, consisting of additional courses (once weekly for 4 weeks) every 6 months, for patients with previously untreated indolent NHL was the first to demonstrate the benefits of maintenance with an anti–CD20 monoclonal antibody (Hainsworth et al. 2002). The ORR at 6 weeks following induction was 47%. With continued rituximab, the final ORR increased to 73%, with 37% having a CR.

Among patients with previously untreated high–tumor–burden follicular lymphoma who have a response to prior immunochemotherapy (R–FC, R–CHOP, or R-CVP), treatment with 2 years of maintenance rituximab significantly improves PFS with little additional toxicity (Salles et al. 2011). In that trial, responding patients who received rituximab 375 mg/m^2 IV every 8 weeks for 2 years following induction immunochemotherapy demonstrated a 2-year PFS of 82%, compared with 66% in the observation group ($p < 0.001$; hazard ratio, 0.5; no difference in overall survival).

Additional supporting evidence for rituximab maintenance is provided by trials in the relapsed or refractory setting that randomized patients to rituximab maintenance or observation following induction with immunochemotherapy or immunotherapy alone (van Oers et al. 2006, 2010; Martinelli et al. 2010). Taken together, these trials support the administration of anti–CD20 maintenance therapy to responding patients in this trial.

3.2.2 Rationale for Required Biomarker Research Samples

a. Minimum Residual Disease Assessment

The t(14;18)(q32;q21) translocation found in 80%–90% of patients with follicular lymphoma results in the overexpression of BCL2 and may have prognostic value as a surrogate endpoint in clinical trials of follicular lymphoma. Randomized studies have demonstrated that molecular remission is the most predictive factor of outcome in terms of PFS, DFS, and duration of response (Ladetto et al. 2007; Hirt et al. 2008). A study by Rambaldi et al. (2004) demonstrated that lower baseline levels of *BCL2/IgH*–positive cells (i.e., those with the translocation) in the bone marrow prior to treatment correlated with the achievement of a complete clinical and molecular response following the sequential administration of CHOP and rituximab. Patients who achieve a CR or PR following induction chemotherapy and whose disease remains undetectable for the BCL2 translocation by PCR following treatment with rituximab or Yttrium-90 ibritumomab tiuxetan have significantly improved median PFS.

In this study, *BCL2/IgH* rearrangement will be measured at baseline, during induction, at the end of induction therapy, and at Month 4 of maintenance or observation to determine whether changes after one cycle of therapy or after completion of induction therapy are predictive of PFS. In patients without an identifiable *BCL2/IgH* rearrangement, clonal IgH rearrangements may be used as a marker of MRD. Additionally, *BCL2/IgH* rearrangement will be measured during maintenance therapy or observation to determine the ability of rituximab or obinutuzumab to convert patients from MRD positive to MRD negative with the addition of maintenance treatment. Reappearance of the *BCL2/IgH* rearrangement after achievement of MRD negativity may also be assessed as an early marker of relapse or progression during treatment or follow–up.

b. Fcγ Receptor Gene Polymorphism

The actual causes of rituximab treatment failure remain largely unknown. In vitro studies suggested that rituximab induces lymphoma cell lysis in vitro through ADCC, CDC, or direct signaling leading to apoptosis. ADCC requires leukocyte receptors for the Fc portion of IgG (FcγR). The implication of FcγR in the anti-tumor effects of anti-CD20 antibodies against human lymphoma cell lines has been demonstrated in murine models, and rituximab has significantly reduced anti–tumor effects in FcγR-deficient mice. There are three classes of FcγR (FcγRI, FcγRII, and FcγRIII), and their subclasses are encoded by eight genes in humans. Some of those genes display a functional allelic polymorphism generating allotypes with different receptor properties. One of those genetic factors is a gene dimorphism in *FCGR3A,* which encodes FcγRIIIa with either a phenylalanine (F) or a valine (V) at amino acid position 158. It has been clearly demonstrated that human IgG1 binds more strongly to homozygous FcγRIIIa-158V/V NK cells than to homozygous FcγRIIIa–158F/F or heterozygous FcγRIIIa–158F/V NK cells.

Cartron et al. (2002) and Weng and Levy (2003) have shown an association between the FCGR3A genotype and clinical and molecular responses to rituximab. The FCGR3A-158V/V genotype is associated with a higher response rate to rituximab treatment in follicular lymphoma (Weng et al. 2010). Kim et al. (2006) also evaluated the impact of FcγR polymorphism on the response to R-CHOP therapy for patients with DLBCL. In patients treated with R–CHOP, the FCGR3A-158V allele was significantly correlated with a higher CR rate compared with the FCGR3A–158F allele, whereas no difference was found between FCGR2A polymorphisms.

FCGRIIB/IIC is the only inhibitory low affinity Fcγ receptor and therefore is critical for maintaining the balance of activatory and inhibitory signaling. A polymorphism in FCGR2B that alters an isoleucine to a threonine in the transmembrane region in exon 5 (I232T) is associated with the presence and severity of autoimmune disease (Niederer et al. 2010a, 2010b).

The optimization of the interaction between antibodies and FcγR has emerged as a promising technology to enhance the activity of therapeutic antibodies for cancer treatment. Given the significantly greater ADCC and direct cell-death induction associated with obinutuzumab, it is possible that obinutuzumab may have greater efficacy than rituximab, particularly in the 80%–85% of patients who are carriers of the FcγRIIIa low-affinity receptor polymorphism. Given the enhanced ADCC, it is necessary to observe the outcome of patients on the basis of FcγR to select a therapy for patients who are most likely to derive maximum clinical benefit from it. Further studies may provide an increased understanding of the relationship between FcγR polymorphisms and response to monoclonal antibodies.

c. Gene Expression Profiling

Prognostic markers that predict the clinical behavior of follicular lymphomas with greater accuracy are needed to guide treatment management decisions. It has been shown that the length of survival among patients with follicular lymphoma correlates with the molecular features of the non–malignant immune cells present in the tumor at diagnosis (Dave et al. 2004). More recently, expression levels of 35 candidate genes have identified an immune signature associated with shorter survival intervals (Byers et al. 2007), and this information may be used in the future to optimize therapy.

d. Analysis of Biopsy at Relapse or Transformation

Treatment with rituximab has dramatically improved the outcome of patients with indolent and aggressive B–cell NHL (Cheson and Leonard 2008).
Typically, NHL patients respond to several lines of rituximab–based therapies. However, approximately 50% of patients with relapsed or refractory CD20–positive follicular lymphoma do not respond to initial therapy with rituximab (innate resistance) and are primary refractory (McLaughlin et al. 1998). Furthermore, NHL patients who do respond

to standard chemotherapy or rituximab–based treatment regimens eventually relapse and acquire rituximab resistance. Acquired resistance to rituximab may be explained only in part by the loss of CD20 expression (Kennedy et al. 2002). Because of the more widespread use of rituximab maintenance therapy for indolent NHL, increased selection for antibody resistance can be expected (Stolz et al. 2007). In addition, patients with CD20–positive B–cell NHL with adverse prognostic features still exhibit less favorable outcomes, despite rituximab-based first–line therapies.

The mechanisms responsible for primary and acquired resistance to rituximab therapy are not well understood. Nonclinical data derived primarily from culture cell lines and xenograft mouse models have not revealed any unifying mechanisms of resistance. However, the following are some of the possible mechanisms that may contribute to development of rituximab resistance:

- Upregulation of anti–apoptotic factors and downregulation of pro–apoptotic factors (Stolz et al. 2007)
- Down–regulation of CD20 on the cell surface (Davis et al. 1999; Czuczman et al. 2008)
- Decreased complement activation (Klepfish et al. 2009)
- Up–regulation of complement inhibitors CD55 and CD59 (Cruz et al. 2007)
- Membrane/lipid raft abnormality (Smith 2003)

The clinical significance of these mechanisms remains unclear. Identifying and characterizing changes in tumor gene expression that occur with disease progression or transformation in follicular lymphoma, which is one of the exploratory objectives of the current clinical study, may provide a better understanding of genetic mechanisms contributing to development of resistance to rituximab or obinutuzumab in these disorders.

3.2.3 Rationale for Optional Biomarker Samples (Stored in the Roche Clinical Repository)

The Sponsor is committed to the collection of biomarker samples in all clinical studies. The objective of biomarker profiling is to enable development of treatments specifically targeted for optimal patient benefit (personalized health care). If a patient consents, the following material will be collected and stored in the Roche Clinical Repository (RCR) for up to 15 years:

Sample Material	Time Point
Serum and plasma	• At screening only
Unstained sections, tissue microarrays, and tumor RNA and tumor DNA extracted from the residual tissue biopsy	• At baseline • At progression/transformation
DNA extracted from a sample of peripheral blood (leftover DNA after analysis for FcγReceptor gene single−nucleotide polymorphism) [a]	• At screening only
DNA extracted from samples of peripheral blood and bone marrow aspirates (leftover DNA after analysis of *BCL2/IgH* [minimum residual disease]) [a]	• At screening (peripheral blood and bone marrow aspirate) • Before Cycle 5 Day 1 (CHOP/CVP) or Cycle 4 Day 1 (bendamustine) (peripheral blood only) • At end of induction/early termination (peripheral blood and bone marrow aspirate) • During maintenance/observation at Months 4, 8, 12, and 18 and at maintenance/observation completion (peripheral blood only) • During follow−up at Months 30, 36, 42, 48, 54, 60, 72, and 84 (peripheral blood only)

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone (or prednisolone or methylprednisolone); CVP = cyclophosphamide, vincristine, and prednisone (or prednisolone or methylprednisolone).

[a] See additional DNA substudy protocol for further details.

The RCR is a centrally administered facility for the long−term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., RNA, DNA, proteins, peptides). Specimens will be used for research purposes related to NHL to identify biomarkers that are predictive of response to rituximab or obinutuzumab treatment in terms of dose, safety, and tolerability and will help to better understand the pathogenesis, course, and outcome of indolent NHL only. The tissue blocks will be

returned to the local pathology laboratories according to country-specific procedures after the requisite material is obtained.

For more details on DNA collection in the RCR, please see the Study BO21223 DNA substudy protocol.

Specimens will be collected for storage in the RCR and may be used to achieve the following exploratory objectives:

- To study the association of biomarkers with efficacy and/or adverse events associated with medicinal products
- To increase knowledge and understanding of disease biology
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

3.3 OUTCOME MEASURES

3.3.1 Primary Efficacy Outcome Measure

The primary efficacy endpoint, PFS in patients with follicular lymphoma, is defined as the time from randomization to the first occurrence of progression or relapse as assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix C) or death from any cause.

3.3.2 Secondary Efficacy Outcome Measures

For the endpoints below that specify disease response, response will be assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma and additional response criteria for MZL (see Appendix C).

The following secondary outcome measure applies to patients with previously untreated advanced indolent NHL (i.e., overall population):

- Investigator–assessed PFS

The following secondary outcome measures apply to patients with previously untreated advanced indolent NHL (i.e., overall population) and to the subset of patients with previously untreated advanced follicular lymphoma (i.e., follicular population):

- IRC–assessed PFS
- CR and overall response (CR or PR) at the end of induction, as assessed by the investigator with and without FDG–PET
- CR and overall response (CR or PR) at the end of induction, as assessed by the IRC with and without FDG–PET
- Overall survival, defined as the time from randomization to death from any cause
- EFS, defined as the time from randomization to disease progression/relapse as assessed by the investigator, death from any cause, or start of an NALT

- DFS, defined for patients with a best overall response (BOR) of CR as the time from first occurrence of a documented CR to PD as assessed by the investigator or death from any cause. Patients who have had no documented disease progression or have not died after CR will be censored at the last disease assessment date.
- Duration of response, defined for patients with a BOR of CR or PR as the time from first occurrence of a documented CR or PR to disease progression/relapse as assessed by the investigator or death from any cause. For patients achieving a response who have not progressed, relapsed, or died at the time of the analysis, duration of response will be censored on the date of last disease assessment.
- Time to next anti−lymphoma treatment, defined as the time from randomization to start of new non−protocol anti−lymphoma therapy or death from any cause
- Change from baseline to the end of study in PROs based on the FACT−Lym instrument, as outlined below

  Change from baseline in all domains of the FACT−G

  Change from baseline in the total outcome index (TOI) (range, 0−116): sum of physical well−being (7 items), functional well−being (7 items), and Lym subscale (15 items) scores

  Change from baseline in the FACT−Lym subscale score (range, 0−60): 15 lymphoma−specific items

  Change from baseline in the FACT−Lym total score (range, 0−168): sum of physical well−being (7 items), social/family well−being (7 items), emotional well-being (6 items), functional well−being (7 items), and Lym subscale (15 items) scores
- EQ−5D summary scores at baseline, during treatment, after treatment, at the last assessment prior to progression, and at the first assessment after progression

Analysis of medical resource utilization data will be provided if required.

3.3.3 Safety Outcome Measures

The safety outcome measures are as follows:

- Incidence, nature, and severity of adverse events with obinutuzumab plus chemotherapy followed by obinutuzumab versus rituximab plus chemotherapy followed by rituximab
- Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment administration
- Incidence of hepatitis B reactivation

  Hepatitis B reactivation will be defined as an elevation in serum hepatitis B virus (HBV) DNA to more than 29 IU/L.

3.3.4 Exploratory Outcome Measures

a. Pharmacokinetic/Pharmacodynamic Outcome Measures

The pharmacokinetic and pharmacodynamic outcome measures are as follows:

- Pharmacokinetic profile (i.e., plasma concentration–time profile, predose trough concentrations, and clearance rates) of obinutuzumab in induction and maintenance settings among a subset of patients receiving obinutuzumab.

b. Clinical and Biomarker Exploratory Outcome Measures

The following outcome measures apply only to patients with previously untreated advanced follicular lymphoma (i.e., follicular population), unless otherwise specified:

- Histologic transformation rate from an indolent to a more aggressive NHL at first progression, as assessed by the investigator, defined as the appearance of diffuse areas of large lymphoma cells within a tumor site in patients with a repeat biopsy at the time of disease progression/relapse (overall population, follicular population and MZL population)
- Conversion rate, defined as the proportion of patients with a PR or SD at the end of induction therapy who convert to a CR or to a PR/CR, respectively, at any time during maintenance therapy or post–induction observation, as assessed by the investigator (overall population, follicular population, and MZL population)
- MRD negativity, defined as the absence of *BCL2/IgH* rearrangement or IgH clonality in whole blood and/or bone marrow in follicular lymphoma patients with evidence of *BCL2/IgH* rearrangement or IgH clonality at baseline (follicular population only)
- Risk of progression as a function of baseline levels of *BCL2/IgH* rearrangement or other markers of MRD (follicular population only)
- Risk of progression as a function of the absence of *BCL2/IgH* rearrangement and other markers of MRD at the end of induction and maintenance therapy (follicular population only)
- Risk of progression as a function of a decrease in *BCL2/IgH* rearrangement and other markers of MRD during therapy (follicular population only)
- Relationship between FDG–PET values at baseline and changes at the end of induction treatment and clinical outcome (i.e., CR rate, DFS, PFS, etc.)
- Relationship between chemotherapy regimen and efficacy outcomes (overall population, follicular population, and MZL population)
- Incidence of HAHAs among patients receiving obinutuzumab
- Relationship between various clinical factors (e.g., FLIPI2 score, IPI score, ADLs/IADLs) or baseline markers (e.g., Fcγ receptor status, IHC, and tumor gene profiling) and clinical outcome parameters in patients from both arms of the study (overall population, follicular population, and MZL population)
- To assess the prognostic ability of a gene–expression profile of tumor biopsy specimens obtained from all patients at diagnosis to predict risk of progression

- Changes in tumor gene expression profiles and cell surface markers between the time of initial biopsy and the time when progressive and/or transformed disease is diagnosed
- Change in B cell populations defined by CD19/CD22/CD79b/CD5/CD10/kappa/lambda in 60 patients of each antibody-chemotherpy combination group (R–CHOP, G–CHOP, R–CVP, G–CVP, R-bendamustine, G–bendamustine) and in all patients with splenic MZL
- Change in B– ($CD19^+$), T– ($CD3^+$, $CD4^+$, $CD8^+$), and NK cell ($CD56^+$) counts over time in all patients

3.4 SAFETY PLAN

This trial is designed to allow for early termination or a modification of the protocol (in particular, the dosing regimens) for safety concerns, on the basis of the advice of an IDMC. The IDMC will be incorporated into the study to review safety data on a regular basis, including adverse events of special interest (see Section 5.1.3). The IDMC will meet 1 month after enrollment of the first patient and then approximately every 2 months until 100 patients have completed two cycles of study treatment. Afterward, the IDMC will meet approximately every 6 months. Both the Sponsor and the IDMC can request ad hoc IDMC meetings if potential safety concerns arise. Following each meeting, the IDMC will recommend to the Sponsor whether the study should continue according to the protocol or may suggest changes to the protocol based on the outcome of the data review. In exceptional cases, the IDMC may recommend stopping the study or closing a treatment arm as a result of safety reasons. The IDMC will also perform a safety review at the preplanned interim analyses for futility and efficacy (see Section 4.10.10 and the Statistical Analysis Plan for details).

For dose delay, dose modification, and treatment discontinuation instructions, see Section 4.3.

3.4.1 Risks Associated with Obinutuzumab Therapy

No evidence available at the time of the approval of this protocol indicates that special warnings or precautions are appropriate, other than those noted in the obinutuzumab Investigator's Brochure and as described in the following sections.

a. Infusion–Related Reactions and Hypersensitivity Reactions (Including Anaphylaxis)

The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, and fatigue, as well as other symptoms.

Respiratory infusion–related symptoms, such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema, have also been reported. These IRRs were mostly mild or moderate (NCI CTCAE, Version 3.0, Grade 1 and 2 events), and $<$10% of the events were severe (Grade 3 events), occurring predominantly during the

first hour of the infusion or shortly after the first infusion had finished; the events resolved with slowing or interruption of the infusion and supportive care. The incidence and severity of IRRs decreased with subsequent infusions. Extensive tumor burden predominantly localized in the blood circulation (e.g., high peripheral lymphocyte count in patients with CLL) may be a predisposing factor for the development of IRRs.

IRRs may be clinically indistinguishable from IgE–mediated allergic or anaphylactic reactions.

b. Tumor Lysis Syndrome

Cases of tumor lysis syndrome have been reported with obinutuzumab administration. To date, no patient has required hemodialysis for renal failure. Patients with a high tumor burden, including patients with a lymphocyte count of $\geq 25 \times 10^9$/L (particularly, patients with B-cell CLL and MCL), are at increased risk for tumor lysis syndrome and severe IRRs.

c. Neutropenia

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of granulocyte colony stimulating factors (G–CSF) has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G–CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G–CSF is recommended according to the American Society of Clinical Oncology (ASCO), European Organisation for Research and Treatment of Cancer (EORTC), and ESMO guidelines, namely for patients who are ≥60 years old and/or with comorbidities (Lyman et al. 2004). The use of G–CSF is strongly recommended in Cycle 1 for all patients treated with G–CHOP.

d. Thrombocytopenia

Severe and life threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. Based on the available evidence to date the greatest risk of hemorrhage in obinutuzumab-treated patients is observed in the first cycle. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia–related events, such as platelet inhibitors and anticoagulants, may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the

event resolves, and dose delays should be considered in case of severe or life–threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician.

e. Infection

On the basis of its anticipated mode of action, resulting in profound B–cell depletion, obinutuzumab may be associated with an increased risk of infections. Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered to patients with active severe infections.

Serious infections, including fatal, bacterial, fungal, and new or reactivated viral infections (e.g., cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C) have been reported with the B cell–depleting antibody rituximab, mainly in patients who had received the drug in combination with chemotherapy or as part of a hematopoietic stem-cell transplant. The risk of such infections with obinutuzumab is unknown. Physicians should be aware of symptoms suggestive of progressive multifocal leukoencephalopathy (PML) and consider the diagnosis of PML in any patient presenting with new–onset neurologic manifestations. Evaluation of PML includes but is not limited to consultation with a neurologist, brain MRI, and lumbar puncture. To date, there have been no reports of patients experiencing PML while or after receiving obinutuzumab.

Cases (including fatal) of John Cunningham virus (JCV) infection resulting in PML (destructive infection of oligodendrocytes of the central nervous system white matter) have been reported in patients treated with anti–CD20 therapies, including rituximab and obinutuzumab.

The diagnosis of PML should be considered in any patient presenting with new–onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual–spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

Therapy with obinutuzumab and rituximab should be withheld during the investigation of potential PML and permanently discontinued in the case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the treatment of PML.

There may be additional potential health risks, including hitherto unknown risks, derived from exposure to obinutuzumab.

3.4.2 Risks Associated with Rituximab Therapy

See the prescribing information for rituximab for full information.

a. Infusion–Related Reactions

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

b. Tumor Lysis Syndrome

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

c. Hepatitis B Virus Reactivation

HBV reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab. The median time to diagnosis of hepatitis was approximately 4 months after the initiation of rituximab and approximately 1 month after the last dose.

Patients with chronic hepatitis B viral infection (i.e., hepatitis B surface antigen [HBsAg] positive) are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and hepatitis B core antibody [HBcAb] positive) are at a lower risk for reactivation. In a study of 51 HBV carriers with DLBCL who received rituximab, 12% of patients developed evidence of reactivation (Niitsu et al. 2010). Patients who demonstrate evidence of reactivation while receiving an appropriate anti–viral therapy will discontinue study treatment.

d. Progressive Multifocal Leukoencephalopathy

Rare cases of PML have been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson et al. 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem-cell or solid–organ graft rejection. The diagnosis of PML in any patient treated with rituximab is extremely rare but should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem–cell transplant. Most cases of PML were diagnosed within 12 months after the patient's last infusion of rituximab (please also refer to Section 3.4.1.e).

e. Cardiac Toxicity

Angina and cardiac arrhythmias have occurred with rituximab treatment and can be life threatening. Patients in the CHOP arm who have been treated with doxorubicin, an anthracycline–based chemotherapy, are at risk for cardiotoxicity and will be required to have assessments of left ventricular ejection fraction (LVEF) at baseline and at the end of induction treatment.

f. Infection

Serious infections, including fatal, bacterial, fungal, and new or reactivated viral infections (e.g., cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C), can occur during and up to 1 year following the completion of rituximab–based therapy.

g. Severe Mucocutaneous Reactions

Severe reactions, including fatal, mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1 to 13 weeks following rituximab exposure.

h. Bowel Obstruction and Perforation

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

3.4.3 Risks Associated with CHOP Chemotherapy

Please refer to prescribing information for doxorubicin, cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone for risks related to CHOP chemotherapy.

Patients in the CHOP arm treated with doxorubicin, an anthracycline–based chemotherapy, are at risk for cardiotoxicity. Although the risk increases with cumulative dose, irreversible cardiotoxicity may occur at any dose level. Patients with preexisting heart disease, hypertension, concurrent administration of other antineoplastic agents, prior or concurrent chest irradiation, and advanced age are at increased risk. Baseline and periodic monitoring of ECGs and LVEF, as determined by echocardiogram or multiple–gated acquisition (MUGA) scan, will be required. The evaluation of LVEF is required at baseline and after 300 mg/m^2 of doxorubicin (Schwartz et al. 1987). Patients who receive doxorubicin and develop evidence of impaired cardiac function (LVEF of $\leq$ 50% in the presence of an absolute decrease in LVEF of $\geq$ 10%) will be given the option of switching to a non-cardiotoxic regimen (i.e., CVP) or discontinuing from trial participation.

3.4.4 Risks Associated with CVP Chemotherapy

Please refer to prescribing information for cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone for risks related to CVP chemotherapy.

3.4.5 Risks Associated with Bendamustine Chemotherapy

a. Myelosuppression

Patients treated with bendamustine are likely to experience myelosuppression. Blood counts will be monitored weekly during the first cycle and then frequently throughout subsequent cycles of treatment. Patients who experience Grade 3 or 4 neutropenia or thrombocytopenia should be monitored until neutrophil and platelet values return to at least Grade 2. The use of myeloid growth factors for the primary and secondary prevention of febrile neutropenia is permitted.

b. Infections

Infection, including pneumonia and sepsis, has been reported in patients in clinical trials and in postmarketing reports. Infection has been associated with hospitalization, septic shock, and death. Patients with myelosuppression following treatment with bendamustine are more susceptible to infections.

c. Infusion–Related Reactions and Anaphylaxis

Infusion reactions to bendamustine have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus, and rash. In rare instances, severe anaphylaxis and anaphylactoid reactions have occurred, particularly in the second and subsequent cycles

of therapy. Patients should be monitored clinically and discontinue drug for every reaction.

d. Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in association with bendamustine treatment in clinical trials and in postmarketing reports. The onset tends to be within the first treatment cycle of bendamustine and without intervention may lead to acute renal failure and death. Preventive measures include maintaining adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol has also been used during the beginning of bendamustine therapy. However, there may be an increased risk of severe skin toxicity when bendamustine and allopurinol are administered concomitantly.

e. Skin Reactions

A number of skin reactions have been reported in clinical trials and postmarketing safety reports. These events have included rash, toxic skin reactions, and bullous exanthema. Some events occurred when bendamustine was given in combination with other anti-cancer agents, so the precise relationship to bendamustine is uncertain.

In a study of bendamustine in combination with rituximab, one case of TEN occurred. TEN has been reported for rituximab. Cases of Stevens–Johnson syndrome and TEN, some fatal, have been reported when bendamustine was administered concomitantly with allopurinol and other medications known to cause these syndromes. Allopurinol must not be given on days of bendamustine administration. Patients with skin reactions should be monitored closely. If skin reactions are severe or progressive, bendamustine should be withheld.

f. Other Malignancies

Premalignant and malignant diseases, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia, and bronchial carcinoma, have developed in patients treated with bendamustine. The association with bendamustine has not been determined.

g. Extravasation

There are postmarketing reports of bendamustine extravasation resulting in hospitalization to treat erythema, marked swelling, and pain. Precautions should be taken to avoid extravasation, including monitoring of the IV infusion site for redness, swelling, pain, infections, and necrosis during and after administration of bendamustine.

h. Transfusion–Associated Graft versus Host Disease

Rare cases of transfusion–associated graft versus host disease have been reported following treatment of low–grade B cell malignancies with the purine analogues fludarabine (Hutchinson et al. 2002; Leitman et al. 2003) and cladribine (Zulian et al. 1995). The situation with newer purine antagonists such as bendamustine is unclear. Transfusions, if required, should be performed according to national guidelines.

i. Possible Interactions with CYP1A2 Inhibitors and Inducers

Certain medications may interact with bendamustine. Caution should be used or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed. CYP1A2 inhibitors and inducers are not contraindicated. During treatment with bendamustine, patients will be provided with a card to keep with them that provides notification to other health care providers that the patient is taking bendamustine as a participant in a clinical study (see Appendix F).

3.5 STUDY PATIENTS AND ANALYSIS GROUPS

Different etiologic, genetic, or environmental factors may influence the development of follicular lymphoma (Biagi and Seymour 2002). There is evidence to suggest a decreased incidence of follicular lymphoma in Asian countries relative to Western countries, which may be reflective of underlying differences in molecular pathways. Since this is an international study, the study population will allow the evaluation of obinutuzumab in populations with potentially heterogeneous disease pathways and treatment settings.

The primary endpoint analysis (PFS) will be performed for the follicular lymphoma patient population.

3.6 CONTROL GROUPS

Patients will be randomized in a 1:1 ratio to either rituximab plus chemotherapy followed by rituximab maintenance in responders (Arm A) or obinutuzumab plus chemotherapy followed by obinutuzumab maintenance in responders (Arm B), with chemotherapy consisting of CHOP, CVP, or bendamustine. The control (or comparator) arm of the study will be rituximab plus chemotherapy followed by rituximab maintenance in responders. No crossover between the obinutuzumab and rituximab arms will be allowed.

Immunotherapy with rituximab is a key component of the treatment of patients with follicular lymphoma. In the control arm, rituximab at 375 mg/m^2 will be administered by IV infusion on Day 1 of each 21–day or 28-day cycle for up to eight cycles. There is no standard chemotherapy in combination with rituximab. Prior to study initiation, each site will choose one of three chemotherapy regimens (CHOP, CVP, or bendamustine), and all patients with follicular lymphoma at that site will receive the chosen chemotherapy

regimen for the duration of the study (a site may switch to another regimen if new scientific data become available and after Sponsor approval). For non–follicular lymphoma, the investigator will have the option of choosing one of the three chemotherapy regimens (CHOP, CVP, or bendamustine) for each patient.

Rituximab, as the first monoclonal antibody, was developed with dosing that is based on BSA. The dose of 375 mg/m^2 results in an average dose of 650 mg for a patient with a BSA of 1.73 m^2, which is consistent with MabThera® and RITUXAN® prescribing information and with current medical practice.

In contrast, obinutuzumab is administered as a flat dose of 1000 mg on the basis of Phase I–II trials supporting this dose. Although this may result in an obvious discrepancy in dose between the two agents, obinutuzumab is being tested against the dose of rituximab that is approved by the European Medicines Agency, the U.S. Food and Drug Administration (FDA), and other global regulatory authorities.

See Section 3.2.1 for a rationale supporting the control arm treatment regimen.

3.7 MINIMIZATION OF BIAS

Because of the use of weight–based versus flat dosing and the use of different dosing schedules for obinutuzumab, rituximab, and chemotherapy, this will be an open-label study. To minimize the potential biases, the following procedures will be incorporated in the study.

Patients will be randomized to the two treatment arms through use of an IxRS. Drug assignment will be performed by the IxRS.

For study treatment decisions, response and progression will be assessed by the investigator on the basis of physical examinations, radiography, hematology, serum chemistry, and bone marrow examinations, through use of Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix C).

PET results should be treated as exploratory data and should not be used for study treatment decisions. The decision for maintenance or observation should rely solely on the results obtained by all other methods, but not PET.

PET should also not be used to diagnose relapse or disease progression. Every finding of relapse or progression by PET needs to be confirmed by CT (MRI).

An independent assessment of response and progression, based on CT (MRI) scans plus pertinent clinical data with or without PET, will be provided by an IRC with appropriate expertise in reading radiology and oncology examinations. The IRC assessment will be blinded with respect to treatment arm and investigator assessment. Instructions to sites for processing and submitting imaging scans will be provided by the

IRC. IRC membership and procedures to be followed for the study will be detailed in an IRC charter.

An IDMC will be incorporated to monitor patient safety and efficacy. All analyses for the IDMC's reviews will be prepared by an IDCC. Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of study results. A guidance document detailing the procedures to be followed for keeping blinding will be observed by the study operations team. Treating clinical staff at investigator sites and Sponsor drug safety and medical monitoring staff will have access to the treatment assignments of particular patients to allow for safety monitoring. IDMC membership and procedures to be followed for the study will be detailed in an IDMC charter.

3.8 END OF STUDY

The end of the study is defined as the date of the last follow-up visit (to occur 5 years after the last study treatment) of the last patient entered, or sooner, if all patients have progressed, died, or withdrawn from the study. With consideration of a recruitment period of approximately 2.5 years, the overall duration of the study is planned to be approximately 10.2 years (or shorter, if all patients have progressed, died, or withdrawn from the study). The Sponsor has the right to terminate the study at any time.

3.9 ETHICAL CONSIDERATIONS

Any information obtained from this research will be treated as confidential. The information collected will not be provided to any third parties, such as insurers or employers (other than those required by law), but will be provided to health authorities (e.g., European Medicines Agency or FDA), the Sponsor (Genentech, South San Francisco, U.S.A.; F. Hoffmann-La Roche Ltd, Basel, Switzerland), and the Sponsor's collaborators. The results of these analyses will be treated with the same level of confidentiality as the rest of the data arising from this study.

Patients will provide a blood sample for FcγRIIIa, FcγRIIa, and FcγRIIb/c polymorphism analysis. After completion of this analysis, any DNA material used to determine polymorphisms will be destroyed. The disposal of remaining DNA material will be documented according to standard operating procedures, and no other assessments or analyses of the DNA samples will be performed. Samples will not be identified with patients' names, pictures, or any government-issued identification numbers (e.g., Social Security number). A unique sample identification number will be used to identify samples (these are considered patient identifiers under the Heath Insurance Portability and Accountability Act). Samples will be linked with clinical data from the Sponsor's clinical database (including outcome data) with use of the study identification number.

3.10 ADMINISTRATIVE STRUCTURE

In the United States, this trial will be sponsored and managed by Genentech. F. Hoffmann–La Roche will sponsor this trial outside of the United States, with management responsibilities being shared by Genentech and Roche. Genentech and Roche have authorized Roche Registrations, a company formed under the laws of England, to act as their legally authorized representative for the purposes of Article 19 of Directive 2001/20/EC relating to the implementation of Good Clinical Practice (GCP) in the conduct of clinical trials on medicinal products for human use. Reference to "Sponsor" in this protocol will mean Genentech for the United States and F. Hoffmann–La Roche for all countries outside of the United States.

Approximately 250 sites from 30–40 countries, including the United States, Canada, Europe, and potentially South and Central America, Japan, China, Australia, and Southeast Asia, will enroll up to 1400 patients.

Randomization and drug assignment will be performed by an IxRS. The IxRS will also manage obinutuzumab, bendamustine, and rituximab inventory for all sites globally. Electronic data capture (EDC) will be utilized for this study.

A central laboratory will be used for a subset of laboratory assessments, as specified in Section 4.5.1.c; otherwise, local laboratories will be used.

An IRC will perform independent assessments of response and progression for all patients enrolled in the study.

An external IDMC will be mandated for the purpose of evaluating interim safety, tolerability, and efficacy, according to policies and procedures detailed in the IDMC charter.

An independent Science and Ethics Advisory Group, consisting of experts in the fields of biology, ethics, sociology, and law, will advise the Sponsor regarding the use of specimens stored in the RCR and on the scientific and ethical aspects of handling genetic information.

A Protocol Steering Committee consisting of a panel of hematologists/oncologists has been consulted for this study. The Protocol Steering Committee provided scientific input into the design of the study and the development of the study protocol. In addition, the committee will supervise the overall execution of the trial, generate and approve study policies, consider modifications of the protocol and operations, and plan and draft study-related publications. Additionally, the committee will provide scientific input for the analysis of samples collected for future scientific research.

3.11 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the principles of the Declaration of Helsinki, U.S. FDA regulations, the International Conference on Harmonisation (ICH) E6 Guideline for GCP, and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENT SELECTION

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically documented, CD20−positive, indolent B−cell NHL consisting of one of the following: follicular lymphoma (Grades 1−3a) splenic MZL, nodal MZL, or extranodal MZL

  Tissue diagnostic procedures must be performed within 12 months prior to randomization. Biopsy material from an excisional or core biopsy must be submitted for retrospective central confirmation. Tissue samples dated >12 months prior to randomization can be accepted only if tissue material is available for retrospective confirmation, if there is no clinical indication for transformation of disease, and if the request for additional biopsy would be unethical treatment of the patient. Bone marrow alone is not suited to make the diagnosis of follicular lymphoma.

  Approximately 200 patients with MZL (splenic, nodal, or extranodal) can be randomized. After reaching the cap of 200, recruitment of patients with MZL will be stopped.

  In patients with splenic MZL without splenic tissue available for histologic review, the diagnosis may be confirmed by the presence of splenomegaly and typical morphologic and immunophenotypic findings in the blood and bone marrow. Bone marrow must be submitted for retrospective central confirmation.

- Stage III or IV disease or Stage II bulky disease

  Bulky disease is defined as a tumor diameter of ≥ 7 cm.

- For patients with follicular lymphoma: requirement for treatment, defined as meeting at least one of the following criteria:

  Bulky disease, defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in the greatest diameter

  Local symptoms or compromise of normal organ function due to progressive nodal disease or extranodal tumor mass

  Presence of B symptoms (fever, drenching night sweats, or unintentional weight loss of $>10\%$ of normal body weight over a period of 6 months or less)

  Presence of symptomatic extranodal disease (e.g., pleural effusions, peritoneal ascites)

Cytopenias due to underlying lymphoma (i.e., absolute neutrophil count $< 1.0 \times 10^9$/L, hemoglobin < 10 g/dL, and/or platelet count $< 100 \times 10^9$/L)

Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm

Symptomatic splenic enlargement

- For patients with symptomatic splenic, nodal, or non–gastric extranodal MZL: disease that is de novo or has relapsed following local therapy (i.e., surgery or radiotherapy) and requires therapy, as assessed by the investigator
- For patients with symptomatic gastric extranodal MZL: *Helicobacter pylori*–negative disease that is de novo or has relapsed following local therapy (i.e., surgery or radiotherapy) and requires therapy, as assessed by the investigator, or *H. pylori*–positive disease that has remained stable, progressed, or relapsed following antibiotic therapy and requires therapy, as assessed by the investigator (see Appendix G for additional details regarding gastric extranodal MZL)
- At least one bi–dimensionally measurable lesion (> 2 cm in its largest dimension by CT scan or MRI)

  In patients with splenic MZL, an enlarged spleen on CT scan or extending at least 2 cm below the costal margin by physical examination will constitute measurable disease providing that no explanation other than lymphomatous involvement is likely. For an enlarged liver to constitute the only measurable disease parameter, a liver biopsy showing proof of NHL in the liver is required.
- Able and willing to provide written informed consent and to comply with the study protocol
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 (see Appendix H)
- Adequate hematologic function (unless abnormalities are related to NHL), defined as follows:

  Hemoglobin ≥ 9.0 g/dL

  Absolute neutrophil count $\geq 1.5 \times 10^9$/L

  Platelet count $\geq 75 \times 10^9$/L
- For men who are not surgically sterile: agreement to use a barrier method of contraception during the treatment phase and for at least 3 months after the last dose of obinutuzumab and rituximab or bendamustine or according to institutional guidelines for CHOP or CVP chemotherapy, whichever is longer. In addition, male patients must agree to request that their partners use an additional method of contraception, such as oral contraceptives, intrauterine device, barrier method of contraception, or spermicidal jelly.

- For women of reproductive potential who are not surgically sterile: agreement to use two adequate methods of contraception, such as oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly during the treatment period and for at least 12 months after the last dose of obinutuzumab or rituximab, for at least 3 months after the last dose of bendamustine or according to institutional guidelines for CHOP or CVP chemotherapy, whichever is longer.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of severe allergic or anaphylactic reactions to monoclonal antibody therapy (e.g., patients in whom dosing with rituximab would be contraindicated for safety reasons)
- Known hypersensitivity to any of the study drugs
- Known sensitivity to murine products
- History of sensitivity to mannitol
- Central nervous system lymphoma, leptomeningeal lymphoma, or histologic evidence of transformation to a high–grade or diffuse large B-cell lymphoma
- Grade 3b follicular lymphoma, SLL, or WM
- Ann Arbor Stage I disease (see Appendix H)
- For patients with follicular lymphoma: prior treatment for NHL by chemotherapy, immunotherapy, or radiotherapy

  Low–dose methotrexate (MTX) in rheumatoid arthritis (typically 7.5 to a maximum of 20 mg/week) is not considered chemotherapy for lymphoma. It is recommended to stop MTX 2-3 weeks prior to starting immunochemotherapy since the combination of MTX and immunochemotherapy increases the risk of immunosuppression and of infection
- For patients with non–follicular lymphoma: prior treatment with chemotherapy or immunotherapy
- Regular treatment with corticosteroids during the 4 weeks prior to the start of Cycle 1, unless administered for indications other than NHL at a dose equivalent to $\leq$ 30 mg/day prednisone

  Patients receiving corticosteroid treatment with $\leq$ 30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to randomization.

  If glucocorticoid treatment is urgently required for medical reasons (e.g., complications imminent if not treated at least with glucocorticoids; strong discomfort/pain of the patient due to lymphoma), prednisone 100 mg or equivalent can be given for a maximum of 5 sequential days, but all tumor assessments must be completed prior to the start of glucocorticoid treatment. Glucocorticoid treatment must be stopped prior to randomization.

In cases when a glucocorticoid pre–treatment/pre–phase was done externally prior to considering the patient for study inclusion, glucocorticoids must be stopped for at least 7 days before screening assessments can begin.

- Patients with a history of confirmed PML
- History of prior other malignancy with the exception of:

  Curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study

  Other cancers not specified above which have been curatively treated by surgery alone and from which subject is disease–free for ≥ 5 years without further treatment
- Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, severe arrhythmia, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- For patients who will be receiving CHOP: LVEF $< 50\%$ by MUGA scan or echocardiogram
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 4 weeks prior to the start of Cycle 1

  Patients with suspected active or latent tuberculosis (latent tuberculosis needs to be confirmed by positive Interferon–gamma release assay)
- Vaccination with a live vaccine within 28 days prior to randomization
- Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis
- Any of the following abnormal laboratory values (unless any of these abnormalities are due to underlying lymphoma):

  Creatinine > 1.5 times the upper limit of normal (ULN) (unless creatinine clearance normal) or calculated creatinine clearance < 40 mL/min (using Cockcroft–Gault formula; see Appendix I)

  AST or ALT $> 2.5 \times$ ULN

  Total bilirubin $> 1.5 \times$ ULN (or $> 3 \times$ ULN for patients with documented Gilbert syndrome)

  International normalized ratio (INR) or prothrombin time (PT) $> 1.5 \times$ ULN in the absence of therapeutic anticoagulation

  Partial thromboplastin time (PTT) or activated PTT (aPTT) $> 1.5 \times$ ULN in the absence of a lupus anticoagulant

- Positive test results for chronic HBV infection (defined as positive HBsAg serology)

  Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HB_SAb) after vaccination or prior but cured hepatitis B are eligible.

- Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)

  Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.

- Known history of HIV seropositive status.

  In countries where mandatory testing by health authorities is required, HIV testing will be performed.

- Positive test results for human T−lymphotropic 1 (HTLV 1) virus

  HTLV testing is required in patients from endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia).

- Pregnant or lactating

- Life expectancy < 12 months

- Participation in another clinical trial with drug intervention within 28 days prior to start of Cycle 1 and during the study

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained and eligibility has been established, the study site will obtain the patient's unique identification number and treatment assignment from the IxRS. Randomization will be performed separately for follicular and non−follicular patients through the IxRS with use of a hierarchical dynamic randomization scheme. The scheme is designed with three levels. The first level ensures approximately equal numbers of patients between the two treatment arms overall. If the first level is balanced, the second level ensures treatment balance within the strata defined by 1) chemotherapy regimen (CHOP, CVP, bendamustine) and 2) either FLIPI risk group (low, intermediate, high) in follicular lymphoma patients or IPI risk group (low/low-intermediate risk versus intermediate−high/high risk) in non−follicular lymphoma patients. If the first two levels are balanced, the third level ensures treatment balance within geographic region (Western Europe, Eastern Europe, South and Central America, North America, Asia, and Other). Since geographic region is not expected to be strongly prognostic, in order to avoid loss of efficiency, the region factor will be included in the randomization but not in the primary or secondary stratified analyses.

Because of the two different study arms with different administration schedules, it is very difficult to keep blinding for the investigators. Therefore, this study will be conducted in an open-label manner. However, the IRC will remain blinded to treatment assignment.

Approximately 200 patients with MZL (splenic, nodal, or extranodal) can be randomized. After reaching the cap of 200, recruitment of patients with MZL will be stopped. All patients who are randomized into IxRS on the day the cap is reached will be allowed to enter the trial provided they meet all other eligibility criteria.

4.3 STUDY TREATMENT

4.3.1 Formulation

a. Rituximab

Rituximab is packaged in 10 mL (100 mg) and 50 mL (500 mg) single-dose, pharmaceutical-grade glass vials at a concentration of 10 mg/mL of protein. The antibody is formulated for IV injection as a sterile product in a solution of sodium chloride (pH 6.5) containing polysorbate 80 and sodium citrate. The Sponsor will provide rituximab to investigational sites as an investigational medicinal product (IMP).

For further details, see the MabThera® or RITUXAN® prescribing information.

b. Obinutuzumab

Obinutuzumab is provided as a single-dose, sterile liquid formulation in 50 mL pharmaceutical-grade glass vials containing a nominal 1000 mg of obinutuzumab. The formulated drug product consists of 25 mg/mL drug substance (G3 material) formulated in histidine, trehalose, and poloxamer 188. The vials contain 41 mL (with 2.5% overfill). The Sponsor will provide obinutuzumab to investigational sites as an IMP.

For further details, see the obinutuzumab Investigator's Brochure.

c. CHOP Chemotherapy

For details on drug formulations, see the cyclophosphamide, vincristine, doxorubicin, or prednisone/prednisolone/methylprednisolone prescribing information.

d. CVP Chemotherapy

For details on drug formulations, see the cyclophosphamide, vincristine, or prednisone/prednisolone/methylprednisolone prescribing information.

e. Bendamustine

Bendamustine is provided as a single–use vial containing 220 mg of powder for the preparation of an infusion solution that contains 100 mg of bendamustine hydrochloride. The Sponsor will provide bendamustine to investigational sites as an IMP.

For further details, see the Levact® prescribing information.

4.3.2 Dosage, Administration, and Storage

a. Rituximab

In the control arm (Arm A), six to eight doses of rituximab at 375 mg/m^2 will be administered by IV infusion with the accompanying chemotherapy regimen during induction, as outlined below and described in more detail in Sections 4.3.2.c through 4.3.2.e.

- R–CHOP: Rituximab will be administered on Day 1 of Cycles 1–8 (21-day cycles). CHOP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2–5, of Cycles 1–6.
- R–CVP: Rituximab will be administered on Day 1 of Cycles 1–8 (21 –day cycles). CVP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2 – 5, of Cycles 1 – 8.
- R–bendamustine: Rituximab will be administered on Day 1 of Cycles 1 – 6 (28-day cycles). Bendamustine will be administered on Days 1 and 2 of Cycles 1 – 6, with prednisone/prednisolone/methylprednisolone also administered on Day 1 of Cycle 1.

If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab on the day prior to CHOP or CVP or bendamustine with premedication is allowed. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R–Chemo and G–Chemo) in order to avoid any bias. Premedication before antibody administration in Cycle 1 is recommended and may include 100 mg prednisone/prednisolone or 80 mg methylprednisolone orally (within 12 hours but at least 60 minutes prior to start of antibody infusion) or IV (if less than 60 minutes prior to start of antibody infusion) in order to minimize cytokine release syndrome or allergic reactions. Premedication with prednisone/prednisolone/methylprednisolone is mandatory in patients who had an IRR until no IRRs occur anymore during antibody infusion. Withhold antihypertensive medication 12 hours prior to start of antibody infusion and during the infusion. For the management of IRRs and anaphylaxis, see Section 4.3.5.a.

Patients randomized to receive rituximab plus chemotherapy who achieve a CR or PR at the end of induction therapy will continue to receive rituximab at 375 mg/m^2 every 2 months until disease progression for up to 2 years.

See Appendix J for rituximab preparation instructions. For patients in Arm A, rituximab infusions will be administered per institutional guidelines or per the instructions outlined in Table 2.

Table 2 Administration of First and Subsequent Infusions of Rituximab

First Infusion (Day 1 of Cycle 1)	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hour. • If no infusion–related or hypersensitivity reaction occurs, increase the infusion rate in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication including 100 mg prednisone/prednisolone or 80 methylprednisolone or equivalent (until no further IRR occurs), begin infusion at an initial rate of 50 mg/hour and follow instructions for first infusion. • If the patient tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hour), begin infusion at a rate of 100 mg/hour. • If no reaction occurs, increase the infusion rate in 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

In all parts of the study, rituximab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 4.3.5.a.

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of rituximab. Do not administer as an IV push or bolus. Administration sets with polyvinyl chloride (PVC) or polyethylene (PE) as a product contact surface and IV bags with PVC or PE as a product contact surface are compatible and can be used. Do not use an additional in–line filter because of potential adsorption.

After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 2 hours to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be

de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed. During maintenance, for those patients who tolerate the antibody infusion well without IRR, the IV line may be removed or the central venous catheter may be de–accessed immediately after the end of antibody infusion.

For this study, rituximab produced by Roche (MabThera®) or Genentech (Rituxan®) is used. For specifications on stability and storage of rituximab, please refer to the instruction provided with the respective product information.

The prepared infusion solution of rituximab is physically and chemically stable for 24 hours at 2°C-8°C and subsequently 12 hours at room temperature. The product should be used immediately. If not used immediately, in–use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions. Rituximab should not be frozen or shaken. Mix gently. Do not use rituximab beyond the expiration date stamped on the carton.

b. Obinutuzumab

In the experimental arm (Arm B), eight to ten doses of obinutuzumab at 1000 mg will be administered by IV infusion with the accompanying chemotherapy regimen during induction, as outlined below and described in more detail in Sections 4.3.2.c through Section 4.3.2.e.

- G–CHOP: Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (21–day cycles). CHOP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2–5 of Cycles 1–6.
- G–CVP: Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–8 (21–day cycles). CVP will be administered on Day 1, with prednisone/prednisolone/methylprednisolone also administered on Days 2–5 of Cycles 1–8.
- G–bendamustine: Obinutuzumab will be administered on Days 1, 8, and 15 of Cycle 1 and on Day 1 of Cycles 2–6 (28-day cycles). Bendamustine will be administered on Days 1 and 2 of Cycles 1–6, with prednisone/prednisolone/methylprednisolone administered on Day 1 of Cycle 1.

If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of obinutuzumab is allowed on the day prior to CHOP or CVP or bendamustine. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R–Chemo and G-Chemo) in order to avoid any bias.

Premedication before antibody administration in Cycle 1 is recommended and may include 100 mg prednisone/prednisolone or 80 mg methylprednisolone orally (within 12 hours but at least 60 minutes prior to start of antibody infusion) or IV (if less than 60 minutes prior to start of antibody infusion) in order to minimize cytokine release syndrome or allergic reactions. Premedication with prednisone/prednisolone/methylprednisolone is mandatory in patients who had an IRR until no IRRs occur anymore during antibody infusion. Withhold antihypertensive medication 12 hours prior to start of antibody infusion and during the infusion. For the management of IRRs and anaphylaxis, see Section 4.3.5.a.

Patients randomized to receive obinutuzumab plus chemotherapy who achieve a CR or PR at the end of induction therapy will continue to receive obinutuzumab at 1000 mg every 2 months until disease progression for up to 2 years.

See Appendix K for obinutuzumab preparation instructions. For patients in Arm B, obinutuzumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion (Day 1 of Cycle 1)	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hour. • If no infusion–related or hypersensitivity reaction occurs, increase the infusion rate in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, use full premedication including 100 mg prednisone/prednisolone or 80 mg methylprednisolone (until no further IRR occurs), begin infusion at an initial rate of 50 mg/hour and follow instructions for first infusion. • If the patient tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hour), begin infusion at a rate of 100 mg/hour. • If no reaction occurs, increase the infusion rate in 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

In all parts of the study, obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately

available, and patients should be under close supervision of the investigator at all times. For the management of IRRs and anaphylaxis, see Section 4.3.5.a.

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Administration sets with PVC, polyurethane, or PE as a product contact surface and IV bags with polyolefin, polypropylene, PVC, or PE as a product contact surface are compatible and can be used. In addition, inline–filters with poly ethersulphone as product contact surface, stopcocks with polycarbonate, and catheters with polyether urethane can be used.

After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥2 hours to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed. During maintenance, for those patients, who tolerate the antibody infusion well without IRR, the IV line may be removed or the central venous catheter may be de-accessed immediately after the end of antibody infusion.

Obinutuzumab drug product should be stored at 2°C–8°C and protected from light. Chemical and physical in–use stability for obinutuzumab dilutions in 0.9% sodium chloride in the concentration range of 0.4 to 20 mg/mL have been demonstrated for up to 24 hours at 2°C–8°C followed by 24 hours at ambient temperature and ambient room lighting. The product should be used immediately. If not used immediately, in–use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than indicated above. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use obinutuzumab beyond the expiration date stamped on the carton.

c. CHOP plus Rituximab (R–CHOP) or Obinutuzumab (G–CHOP)

It is mandatory to administer a total of six 21–day cycles of CHOP. If CHOP is discontinued for any reason other than toxicity, patients will be discontinued from study treatment and proceed to follow–up directly without maintenance.

CHOP will be administered according to the standard preparation and infusion procedures of each investigational site. Prednisone can be replaced by prednisolone or an equivalent dose of methylprednisolone in countries or sites where prednisone is not available or where it is not the therapy of choice. When rituximab or obinutuzumab is administered on the same day as prednisone/prednisolone/methylprednisolone, it is recommended that prednisone/prednisolone/methylprednisolone be given within

12 hours but at least 60 minutes prior to the rituximab or obinutuzumab infusion. If there are < 60 minutes before start of antibody, IV application of prednisone/prednisolone/methylprednisolone is preferred. The order of administration of cyclophosphamide, doxorubicin, and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after rituximab or obinutuzumab.

If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab or obinutuzumab on the day prior to CHOP with premedication is allowed. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R-CHOP and G–CHOP) in order to avoid any bias.

Doses will be administered for R–CHOP recipients as shown in Table 4 and for G -CHOP recipients as shown in Table 5. For the purposes of this study, Day 1 is the day when the first cycle of R/G–CHOP is initiated. In patients who experience an adverse event during antibody infusion, administration of rituximab or obinutuzumab and application of chemotherapy may be continued on the following day if clinically required.

If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 21 days.

Empiric dose adjustment in obese patients (defined as a body mass index ≥ 30, as measured in kg/m^2) may be implemented per institutional guidelines. There will be no dose modification for changes in weight unless a patient's weight increases or decreases by > 10% from weight at screening. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. Capping the dose of cyclophosphamide and doxorubicin according to BSA is not recommended but may be done if required by institutional guidelines.

Table 4 Dosing with Rituximab plus CHOP

Treatment	Dose	Mode	Cycles 1–6 [a]		Cycles 7 and 8 [a]
			Day 1 [b]	Days 2–5	Day 1 [b]
Prednisone (or prednisolone/ methylprednisolone[c])	100 (80[c]) mg	Oral	x	x	
Rituximab	375 mg/m^2	IV	x		x
Cyclophosphamide	750 mg/m^2	IV	x		
Doxorubicin	50 mg/m^2	IV	x		
Vincristine	1.4 mg/m^2 (2 mg max)	IV	x		

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone; IV = intravenous; max = maximum; R = rituximab.

Note: Oral prednisone/prednisolone/methylprednisolone should be given at least 60 minutes prior to rituximab (when applicable). If there are < 60 minutes before start of rituximab, IV application of prednisone/prednisolone/methylprednisolone is preferred. The order of administration of cyclophosphamide, doxorubicin, and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after rituximab.

[a] Treatment administered in 21–day cycles.

[b] If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab on the day prior to CHOP with premedication is allowed. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R–CHOP and G-CHOP) in order to avoid any bias. In patients who experience an adverse event during rituximab infusion, administration of rituximab may be continued on the following day if clinically required. If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 21 days.

[c] Methylprednisolone can be used at sites/countries in which IV prednisone/prednisolone is not available. It should be administered at an equivalent dose of 80 mg to 100 mg prednisone/prednisolone.

Table 5 Dosing with Obinutuzumab plus CHOP

			Cycle 1 [a]				Cycles 2–6 [a]		Cycles 7 and 8 [a]
Treatment	Dose	Mode	Day 1 [b]	Days 2–5	Day 8	Day 15	Day 1 [b]	Days 2–5	Day 1
Prednisone (or prednisolone/ methylprednisolone[c])	100 (80[c]) mg	Oral	x	x			x	x	
Obinutuzumab	1000 mg	IV	x		x	x	x		x
Cyclophosphamide	750 mg/m^2	IV	x				x		
Doxorubicin	50 mg/m^2	IV	x				x		
Vincristine	1.4 mg/m^2 (2 mg max)	IV	x				x		

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone; IV = intravenous; max = maximum.

Note: Oral prednisone/prednisolone/methylprednisolone should be given within 12 hours but at least 60 minutes prior to obinutuzumab (when applicable). If there are < 60 minutes before start of obinutuzumab, IV application of prednisone/prednisolone/methylprednisolone is preferred. The order of administration of cyclophosphamide, doxorubicin, and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after obinutuzumab.

[a] Treatment administered in 21–day cycles.

[b] If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of obinutuzumab is allowed on the day prior to CHOP with premedication. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R–CHOP and G–CHOP) in order to avoid any bias. In patients who experience an adverse event during obinutuzumab infusion, administration of obinutuzumab may be continued on the following day if clinically required. If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 21 days.

c Methylprednisolone can be used at sites/countries in which IV prednisone/prednisolone is not available. It should be administered at an equivalent dose of 80 mg to 100 mg prednisone/prednisolone.

d. CVP plus Rituximab (R–CVP) or Obinutuzumab (G–CVP)

It is mandatory to administer a total of eight 21–day cycles of CVP. If CVP is discontinued for any reason other than toxicity, patients will be discontinued from study treatment and proceed to follow–up directly without maintenance.

CVP will be administered according to the standard preparation and infusion procedures of each investigational site. Prednisone can be replaced by prednisolone or an

equivalent dose of methylprednisolone in countries or sites where prednisone is not available or where it is not the therapy of choice. When rituximab or obinutuzumab is administered on the same day as prednisone/prednisolone/methylprednisolone, it is recommended that prednisone/prednisolone/methylprednisolone be given at least 60 minutes prior to the rituximab or obinutuzumab infusion. If there are <60 minutes before start of antibody, IV application of prednisone/prednisolone/methylprednisolone is preferred. The order of administration of cyclophosphamide and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after rituximab or obinutuzumab.

If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab or obinutuzumab on the day prior to CVP with premedication is allowed. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R-CVP and G–CVP) in order to avoid any bias.

Doses will be administered for R–CVP recipients as shown in Table 6 and for G-CVP recipients as shown in Table 7. For this study, Day 1 is the day when the first cycle of R/G–CVP is initiated. In patients who experience an adverse event during antibody infusion, administration of rituximab or obinutuzumab and application of chemotherapy may be continued on the following day if clinically required.

If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 21 days.

Empiric dose adjustment in obese patients (defined as a body mass index ≥ 30, as measured in kg/m^2) may be implemented per institutional guidelines. There will be no dose modification for changes in weight unless the patient's weight increases or decreases by $>10\%$ from weight at screening. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. Capping the dose of cyclophosphamide according to BSA is not recommended but may be done if required by institutional guidelines.

Table 6 Dosing with Rituximab plus CVP

Treatment	Dose	Mode	Cycles 1–8 [a]	
			Day 1 [b]	Days 2–5
Prednisone (or prednisolone /methylprednisolone[c])	100 (80[c]) mg	Oral	x	x
Rituximab	375 mg/m^2	IV	x	
Cyclophosphamide	750 mg/m^2	IV	x	
Vincristine	1.4 mg/m^2 (2 mg max)	IV	x	

CVP = cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone; IV = intravenous; max = maximum; R = rituximab.

Note: Oral prednisone/prednisolone/methylprednisolone should be given within 12 hours but at least 60 minutes prior to rituximab (when applicable). If there are < 60 minutes before start of rituximab, IV application of prednisone/prednisolone/methylprednisolone is preferred. The order of administration of cyclophosphamide and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after rituximab.

[a] Treatment administered in 21–day cycles.

[b] If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab is allowed on the day prior to CVP with premedication. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R-CVP and G–CVP) in order to avoid any bias. In patients who experience an adverse event during rituximab infusion, administration of rituximab may be continued on the following day if clinically required. If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 21 days.

[c] Methylprednisolone can be used at sites/countries in which IV prednisone/prednisolone is not available. It should be administered at an equivalent dose of 80 mg to 100 mg prednisone/prednisolone.

Table 7 Dosing with Obinutuzumab plus CVP

Treatment	Dose	Mode	Cycle 1 [a]				Cycles 2–8 [a]	
			Day 1 [b]	Days 2–5	Day 8	Day 15	Day 1 [b]	Days 2–5
Prednisone (or prednisolone/ methylprednisolone[c])	100 (80[c]) mg	Oral	x	x			x	x
Obinutuzumab	1000 mg	IV	x		x	x	x	
Cyclophosphamide	750 mg/m^2	IV	x				x	
Vincristine	1.4 mg/m^2 (2 mg max)	IV	x				x	

CVP = cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone; G = GA101; IV = intravenous; max = maximum.

Note: Oral prednisone/prednisolone/methylprednisolone should be given within 12 hours but at least 60 minutes prior to obinutuzumab (when applicable). If there are < 60 minutes before start of obinutuzumab, IV application of prednisone/prednisolone/methylprednisolone is preferred. The order of administration of cyclophosphamide and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after obinutuzumab.

[a] Treatment administered in 21–day cycles.

[b] If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of obinutuzumab is allowed on the day prior to CVP with premedication. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R–CVP and G–CVP) in order to avoid any bias. In patients who experience an adverse event during obinutuzumab infusion, administration of obinutuzumab may be continued on the following day if clinically required. If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 21 days.

[c] Methylprednisolone can be used at sites/countries in which IV prednisone/prednisolone is not available. It should be administered at an equivalent dose of 80 mg to 100 mg prednisone/prednisolone.

e. Bendamustine plus Rituximab (R–Bendamustine) or Obinutuzumab (G-Bendamustine)

It is mandatory to administer a total of six 28–day cycles of bendamustine. If bendamustine is discontinued for any reason other than toxicity, patients will be discontinued from study treatment and proceed to follow–up directly without maintenance.

On Day 1 of Cycle 1, it is recommended that oral prednisone/prednisolone/methylprednisolone be given within 12 hours but at least 60 minutes prior to the rituximab or obinutuzumab infusion as premedication. If there

are < 60 minutes before start of antibody, IV application of prednisone/prednisolone/methylprednisolone is preferred. Bendamustine at a dose of 90 mg/m2 will be administered by IV infusion over 60 minutes on Days 1 and 2 of each cycle. There must be a minimum of 12 hours between each bendamustine administration. Bendamustine should be administered at least 30 minutes after rituximab or obinutuzumab. Doses will be administered for R-bendamustine recipients as shown in Table 8 and for G-bendamustine recipients as shown in Table 9. For the purposes of this study, Day 1 is the day when the first cycle of R/G–bendamustine is initiated.

If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab on the day prior to bendamustine with premedication is allowed. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R-bendamustine and G–bendamustine) in order to avoid any bias.

In patients who experience an adverse event during antibody infusion, administration of rituximab or obinutuzumab and application of chemotherapy may be continued on the following day if clinically required. If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 28 days.

Empiric dose adjustment in obese patients (defined as a body mass index ≥ 30, as measured in kg/m^2) may be implemented per institutional guidelines. There will be no dose modification for changes in weight unless the patient's weight increases or decreases by > 10% from weight at screening. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments. Capping the dose of bendamustine according to BSA is not recommended but may be done if required by institutional guidelines.

Table 8 Dosing with Rituximab plus Bendamustine

Treatment	Dose	Mode	Cycle 1–6 [a]	
			Day 1 [b]	Day 2
Prednisone	100 (80[c]) mg	Oral	x[c]	
Rituximab	375 mg/m^2	IV	x	
Bendamustine	90 mg/m^2	IV	x	x

IV = intravenous; R = rituximab.

Note: Bendamustine is to be administered at least 30 minutes after rituximab.

[a] Treatment is administered in 28–day cycles.

[b] If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab on the day prior to bendamustine with premedication is allowed. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an infusion–related reaction (high tumor burden, high peripheral lymphocyte count). However, both optional changes to the administration schedule have to be done equally in both study arms (R-bendamustine and G-bendamustine) in order to avoid any bias. In patients who experience an adverse event during rituximab infusion, administration of rituximab and application of chemotherapy may be continued on the following day if clinically required. If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 28 days.

[c] Oral prednisone/prednisolone/methylprednisolone is given only on Cycle 1 Day 1 within 12 hours but at least 60 minutes prior to administration of rituximab. If there are < 60 minutes before start of rituximab, IV application of prednisone/prednisolone/methylprednisolone is preferred. Methylprednisolone can be used at sites/countries in which IV prednisone/prednisolone is not available. It should be administered at an equivalent dose of 80 mg to 100 mg prednisone/prednisolone.

Table 9 Dosing with Obinutuzumab plus Bendamustine

Treatment	Dose	Mode	Cycle 1 [a]				Cycles 2–6 [a]	
			Day 1 [b]	Day 2	Day 8	Day 15	Day 1 [b]	Day 2
Prednisone	100 (80[c]) mg	Oral	x[c]					
Obinutuzumab	1000 mg	IV	x		x	x	x	
Bendamustine	90 mg/m^2	IV	x	x			x	x

IV = intravenous.

Note: Bendamustine is to be administered at least 30 minutes after obinutuzumab.

[a] Treatment is administered in 28–day cycles.

[b] If it is the strong preference of the investigator or of the site (e.g., for logistical or safety reasons), the administration of rituximab is allowed on the day prior to bendamustine with premedication. It is also allowed to split the antibody infusion over 2 days if the patient is at increased risk for an infusion–related reaction (high tumor burden, high peripheral lymphocyte count). In patients who experience an adverse event during obinutuzumab infusion, administration of obinutuzumab and application of chemotherapy may be continued on the following day if clinically required. If the chemotherapy component is started later than Day 1 of the cycle, then planned Day 1 of the next cycle should be calculated from the day when chemotherapy was actually initiated, in order to maintain the regular chemotherapy interval of 28 days.

[c] Oral prednisone/prednisolone/methylprednisolone is given only on Cycle 1 Day 1 within 12 hours but at least 60 minutes prior to administration of obinutuzumab. If there are < 60 minutes before start of obinutuzumab, IV application of prednisone/prednisolone/methylprednisolone is preferred. Methylprednisolone can be used at sites/countries in which IV prednisone/prednisolone is not available. It should be administered at an equivalent dose of 80 mg to 100 mg prednisone/prednisolone.

See Appendix L for full bendamustine preparation instructions. Unreconstituted bendamustine should be stored at ambient temperature (up to 25°C [77°F] with deviations permitted up to 30°C [86°F]).

After reconstitution and dilution, the final preparation is stable for 3.5 hours at 25ºC and 2 days at 2°C to 8°C in polyethylene bags.

From a microbiological perspective, the ready–for–use preparation should be used immediately unless the dilution method precludes a risk of microbial infection. If the ready–for–use preparation is not used immediately, the user is responsible for the duration and conditions of storage.

4.3.3 Premedication

a. Rituximab and Obinutuzumab

General Guidelines

All rituximab or obinutuzumab infusions should be administered after premedication with oral acetaminophen/paracetamol (e.g., 650–1000 mg) and an antihistamine such as diphenhydramine (e.g., 50–100 mg) 30–60 minutes prior to starting each infusion (unless contraindicated). If the chemotherapy regimen contains oral prednisone/prednisolone/methylprednisolone or if premedication with glucocorticoids is done orally, these tablets should be taken within 12 hours but at least 60 minutes prior to start of antibody infusion. If there are < 60 minutes before start of antibody, IV application of prednisone/prednisolone/methylprednisolone is preferred. For patients who did not experience infusion-related symptoms with their previous infusion, premedication for subsequent infusions may be omitted at the investigator's discretion.

Premedication for Patients at High Risk for Tumor Lysis Syndrome

Patients who are considered to have a high tumor burden and who are considered to be at risk for tumor lysis by the investigator should additionally receive tumor lysis prophylaxis prior to the initiation of treatment. These patients should be well hydrated. Starting 1–2 days before the first dose of rituximab, it is desirable to maintain a fluid intake of approximately 3 L/day. In addition, it is recommended that all patients considered to have high tumor burden and who are considered to be at risk for tumor lysis be treated with allopurinol 300 mg/day orally or a suitable alternative treatment starting 2–3 days prior to treatment on Day 1 of Cycle 1. These patients may continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator. Allopurinol should be administered with caution in patients receiving bendamustine because of the potential for skin reactions. Allopurinol must not be given on days of bendamustine administration (see Section 4.3.4.c).

b. CHOP, CVP, and Bendamustine

Cyclophosphamide, doxorubicin, and bendamustine have a moderate risk of emesis. It is recommended that infusions be administered following premedication with a serotonin (5–HT3) antagonist (e.g., dolasetron, ondansetron) or per institutional practice.

4.3.4 Dosage Modification Guidelines

a. Dosage Modification during Induction Therapy with R–CHOP or G-CHOP

Dose modifications are based on all laboratory values obtained within 72 hours prior to a study treatment infusion. The recommended dose modifications are in effect only for toxicities that are present within 72 hours prior to Day 1 of the next cycle. Toxicities that occur during the cycle and that subside prior to the next cycle should not trigger the

suggested dose modifications. Dose delays apply to all adverse events; dose modifications are applied only for adverse events that are considered drug related.

Nonhematologic Toxicity

Cardiotoxicity. A cumulative dose of 300 mg/m^2 of doxorubicin in this study should not be exceeded. Doxorubicin should be discontinued if evidence of left ventricular dysfunction or congestive heart failure develops.

Hepatic Toxicity. If bilirubin level is abnormal, the doxorubicin dose should be reduced to avoid myelotoxicity as outlined below.

Serum bilirubin 1.5–3.0 mg/dL	• Decrease doxorubicin dose to 25 mg/m^2. • If improvement to $<$1.5 mg/dL, resume doxorubicin at 50 mg/m^2.
Serum bilirubin $>$3.0 mg/dL or severe hepatic impairment	• Delay doxorubicin for a maximum of 3 weeks. • If improvement to 1.5–3.0 mg/dL, resume doxorubicin at 25 mg/m^2. If improvement to $<$1.5 mg/dL, resume doxorubicin at 50 mg/m^2. • If no improvement, discontinue doxorubicin.

Neurotoxicity. Dosing should be modified for neurotoxicity as outlined below.

Grade 4 neurotoxicity	• Hold R–CHOP or G–CHOP for a maximum of 3 weeks. • If improvement to Grade $\leq$2 within 3 weeks, continue full dose of R–CHOP or G–CHOP, but without vincristine. • If improvement to Grade 3 only within 3 weeks, administer R or G without CHOP in the next cycle. If improvement to Grade $\leq$2 within 6 weeks, continue full dose of R–CHOP or G-CHOP, but without vincristin. If still Grade 3 after 6 weeks, continue therapy with R or G alone for all subsequent cycles.
Grade 1– 3 neurotoxicity	• Reduce vincristine for all subsequent cycles to 1 mg absolute; do not delay R–CHOP or G–CHOP. • If worsening despite dose reduction to 1 mg, eliminate vincristin for all subsequent cycles; do not delay R-CHOP or G–CHOP.

Tumor Lysis Syndrome. For patients with evidence of tumor lysis syndrome, treatment with R–CHOP or G–CHOP should be discontinued and the patient should be treated as clinically indicated. Following the complete resolution of tumor lysis syndrome complications, treatment with R–CHOP or G–CHOP may be resumed at the full dose at the next scheduled infusion in conjunction with prophylactic therapy.

Hepatitis B Virus Reactivation. For the subset of patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA levels at screening, HBV DNA

levels must be followed approximately every 3–4 weeks during induction and then approximately every 4 weeks (see Section 4.3.5.c). Treatment with R-chemo or G-chemo will be held for patients with a serum HBV DNA level of ≥29 IU/mL. Patients should begin treatment with anti–viral medication immediately after the first report showing HBV DNA ≥29 IU/mL. Retest HBV DNA level as soon as possible to rule out a false–positive report and to confirm HBV reactivation (≥29 IU/mL) (best prior to treatment; e.g., when prescribing the anti–viral treatment). If HBV reactivation is confirmed in a second test, continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and immediately refer the patient to a gastroenterologist or hepatologist for additional management. If a second test does not confirm HBV reactivation and was taken prior to start of anti–viral therapy, then anti–viral therapy may be stopped again, and R–chemo/G–chemo may be resumed. If a second test does not confirm HBV reactivation but was potentially confounded because it was taken only after the start of anti–viral therapy, then continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and refer the patient to a gastroenterologist or hepatologist for additional management. Patients may resume R-chemo or G-chemo once HBV DNA levels decrease to undetectable levels (<10 IU/mL) or if retest does not confirm HBV reactivation. If the HBV DNA level exceeds 100 IU/mL and are increasing while a patient is receiving anti–viral medication, treatment with R–chemo or G-chemo will be discontinued.

If HBV DNA level is detectable but <29 IU/mL, then continue with R–chemo/G–chemo, but retest at close intervals (e.g., every 3–4 weeks). If HBV DNA is still detectable but <29 IU/mL on retest, then continue to administer treatment and retest at close intervals (e.g., every 3–4 weeks). If HBV DNA is ≥29 IU/mL on retest, then follow the instructions for HBV DNA levels ≥29 IU/mL (see above).

HBV DNA level of ≥29 IU/mL	• Hold R–chemo/G–chemo. • Begin anti–viral medication immediately after the first report showing HBV DNA ≥29 IU/mL • Retest HBV DNA level as soon as possible to rule out a false–positive report and to confirm HBV–reactivation (≥29 IU/mL) (best prior to treatment; e.g., when prescribing the anti–viral treatment). • If HBV reactivation is confirmed in second test, continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and refer the patient to a gastroenterologist or hepatologist for additional management. • If a second test does not confirm HBV reactivation and was taken prior to start of anti-viral therapy, then anti–viral therapy may be stopped again, and R-chemo/G–chemo may be resumed. Retest the patient at close intervals (every 3–4 weeks). • If a second test does not confirm HBV reactivation but was potentially confounded because it was taken only after the start of ant-viral therapy, then continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and refer the patient to a gastroenterologist or hepatologist for additional management. • Resume R–chemo or G–chemo once HBV DNA levels decrease to undetectable levels (<10 IU/mL) or if retest does not confirm hepatitis B reactivation.
HBV DNA level of >100 IU/mL and increasing while on appropriate anti-viral medication	Discontinue R–chemo/G–chemo.
• HBV DNA level detectable but <29 IU/mL	• Continue with R–chemo/G–chemo, but retest at close intervals (e.g., every 3–4 weeks). If HBV DNA still detectable, but <29 IU/mL on retest • Continue to administer treatment and retest at close intervals (e.g., every 3–4 weeks). If HBV DNA ≥29 IU/mL on retest • Follow instructions for HBV DNA level of ≥29 IU/mL (see above).

Progressive Multifocal Leukoencephalopathy (PML). The diagnosis of PML should be considered in any patient presenting with new–onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as "cortical" (e.g., aphasia or visual–spatial disorientation) can occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

Therapy with obinutuzumab or rituximab should be withheld during the investigation of potential PML and permanently discontinued in the case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the treatment of PML.

Other Nonhematologic Toxicities. For nausea or vomiting of all grades, optimize anti-emetic therapy.

For Grade ≥ 2 nonhematologic toxicities (excluding alopecia, nausea, and vomiting), treatment with R–CHOP or G–CHOP will be delayed for a maximum of 3 weeks until resolution to Grade ≤ 1 (or baseline for all except hemorrhagic cystitis); for Grade 3 or 4 toxicities, dosing will be modified or discontinued as outlined in Table 10. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

If surgery is required as a result of a life–threatening condition unrelated to treatment, Day 1 of the next cycle may be delayed up to a total of 8 weeks.

There will be no dose reductions of rituximab (375 mg/m^2) or obinutuzumab (1000 mg). If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses will not be skipped but given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. For Grade 3 or 4 nonhematologic toxicities, doses of cyclophosphamide and doxorubicin should be decreased as outlined in Table 10.

Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

For Grade ≥ 3 hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with R–CHOP or G–CHOP will be delayed for a maximum of 3 weeks until resolution to Grade ≤ 2. In case of recurring Grade 3

hematological toxicity, dosing of cyclophosphamide, doxorubicin, rituximab, or obinutuzumab will be modified or discontinued as outlined in Table 10. For Grade 4 toxicities, dosing will be modified or discontinued as outlined in Table 10. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reduction of rituximab (375 mg/m^2) or obinutuzumab (1000 mg). If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses will not be skipped but given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. If cytopenia is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the cyclophosphamide and doxorubicin doses, for the first cycle only. Even in the absence of bone marrow infiltration, cytopenias occurring on Cycle 1 Day 8 and/or Cycle 1 Day 15 may be handled by delaying drug administration for a maximum of 3 weeks but do not necessarily trigger a dose reduction of cyclophosphamide and doxorubicin in Cycle 2.

Table 10 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or CHOP during Induction Therapy

Event	Dose Delay or Modification
Grade 3 or 4 nonhematologic toxicity [a, b]	• Delay doses of R–CHOP or G–CHOP for a maximum of 3 weeks. • First episode: If improvement to Grade ≤ 1 or baseline, decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin dose to 35 mg/m^2 for subsequent cycles. • Second episode: If improvement to Grade ≤ 1 or baseline, decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2 for subsequent cycles. • Third episode: Discontinue CHOP. [c] If improvement to Grade ≤ 1 or baseline, continue full dose of rituximab or obinutuzumab. • Fourth episode: Discontinue all study treatment. [c]
Grade 2 nonhematologic toxicity [a, b]	• Delay doses of R–CHOP or G–CHOP for a maximum of 3 weeks. • If improvement to Grade ≤ 1 or baseline, administer previous dose of CHOP with full dose of rituximab or obinutuzumab.
Grade 1 nonhematologic toxicity [a]	• No dose reduction or delay.
Grade 2–4 hemorrhagic cystitis	• Delay doses of R–CHOP or G–CHOP for a maximum of 3 weeks. • If improvement to Grade ≤ 1, decrease cyclophosphamide dose to 500 mg/m^2 for next cycle. Mesna and hydration during the next administration of cyclophosphamide is recommended. • If symptoms do not recur, cyclophosphamide dose may be again increased to 750 mg/m^2 for subsequent cycles.

Table 10 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or CHOP during Induction Therapy (cont.)

Event	Dose Delay or Modification
Grade 4 hematologic toxicity [b, c, d, e, f]	• Delay doses of R–CHOP or G–CHOP for a maximum of 3 weeks. • Administer myeloid growth factors for neutropenia as allowed per institutional guidelines. • Administer RBCs or platelets as required. • First episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin dose to 35 mg/m^2 for subsequent cycles. [c, f] • In patients who are not receiving concomitant anticoagulants or platelet inhibitors, hold obinutuzumab in cases of severe thrombocytopenia (platelet count <10,000/μL) or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip doses of obinutuzumab for the sake of maintaining the chemotherapy schedule. • In patients who are receiving concomitant anticoagulants or platelet inhibitors, hold obinutuzumab in cases of platelets <20,000/μL or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip any doses of obinutuzumab for the sake of maintaining the chemo schedule. For patients who are on LMWH, when thrombocytopenia with platelets <20,000/μL develops, reduce the dose of LMWH used. [d] For patients who are on platelet inhibitors when thrombocytopenia with platelet < 20,000/μL develops, consideration should be given to temporarily pause their use. [d, e] • Second episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2 for subsequent cycles. [c] • Third episode: Discontinue CHOP. [c] If improvement to Grade ≤2, continue full dose of rituximab or obinutuzumab. • Fourth episode: Discontinue all study treatment.[c]

Table 10 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or CHOP during Induction Therapy (cont.)

Event	Dose Delay or Modification
Grade 3 hematologic toxicity [b,c,f]	• Delay doses of R–CHOP or G–CHOP for a maximum of 3 weeks. • Administer myeloid growth factors for neutropenia as allowed per institutional guidelines. • Administer RBCs or platelets as required. • First episode: If improvement to Grade ≤2, administer previous dose of CHOP with full dose of rituximab or obinutuzumab. [c,f] • Second episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 500 mg/m^2 and doxorubicin dose to 35 mg/m^2 for subsequent cycles. [c] • Third episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 375 mg/m^2 and doxorubicin dose to 25 mg/m^2 for subsequent cycles. [c] • Fourth episode: Discontinue CHOP. [c] If improvement to Grade ≤2, continue full dose of rituximab or obinutuzumab. • Fifth episode: Discontinue all study treatment. [c]
Grade 1 or 2 hematologic toxicity	• No dose reduction or delay.

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone; G = GA101; LMWH = low molecular weight heparins; NHL = non-Hodgkin's lymphoma; R = rituximab; RBC = red blood cell .

[a] Alopecia, nausea, and vomiting excluded. In case of nausea or vomiting of all grades, optimize anti-emetic therapy; for cardiotoxicity, hepatic toxicity, neurotoxicity, tumor lysis syndrome, or hepatitis B virus reactivation, see guidelines above this table.

[b] Dose delays apply to all adverse events; dose modifications are applied for only adverse events that are considered drug related.

[c] Dose modifications are based on all laboratory values obtained within 72 hours prior to Day 1 of the next cycle. The recommended dose modifications are in effect only for toxicities that are present within 72 hours prior to Day 1 of the next cycle. Toxicities that occur during the cycle and that subside prior to the next cycle should not trigger the suggested dose modifications.

[d] If the clinical condition of patient requires the use of concomitant anticoagulants, the patients are at increased risk of bleeding when thrombocytopenia with platelets <20,000µL develops. When possible, replace prior therapy with vitamin K antagonists with LMWH before Cycle 1 Day 1.

[e] Clinical decision making may be adjusted depending on the patient–specific assessment of benefit and risk.

[f] If cytopenia is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the cyclophosphamide and doxorubicin doses, for the first cycle only. Even in the absence of bone marrow infiltration, cytopenias occurring on Cycle 1 Day 8 and/or Cycle 1 Day 15 may be handled by delaying drug administration for a maximum of 3 weeks but do not necessarily trigger a dose reduction of cyclophosphamide and doxorubicin in Cycle 2.

b. Dosage Modification during Induction Therapy with R–CVP or G-CVP

Dose modifications are based on all laboratory values obtained within 72 hours prior to a study treatment infusion. The recommended dose modifications are in effect for only toxicities that are present within 72 hours prior to Day 1 of the next cycle. Toxicities that occur during the cycle and that subside prior to the next cycle should not trigger the suggested dose modifications. Dose delays apply to all adverse events; dose modifications are applied only for adverse events that are considered drug related.

Nonhematologic Toxicity

Neurotoxicity. Dosing should be modified for neurotoxicity as outlined below.

Grade 4 neurotoxicity	• Hold R–CVPor G–CVP for a maximum of 3 weeks. • If improvement to Grade≤ 2 within 3 weeks, continue full dose of R–CVP or G–CVP but without vincristine. • If improvement to Grade 3 only within 3 weeks, administer R or G without CVP in the next cycle. If improvement to Grade ≤2 within 6 weeks, continue full dose of R–CVP or G-CVP but without vincristine. If still Grade 3 after 6 weeks, continue therapy with R or G alone for all subsequent cycles.
Grade 1–3 neurotoxicity	• Reduce vincristine for all subsequent cycles to 1 mg absolute; do not delay R–CVP or G–CVP. • If worsening despite dose reduction to 1 mg, eliminate vincristine for all subsequent cycles; do not delay R-CVP or G–CVP.

Tumor Lysis Syndrome. For patients with evidence of tumor lysis syndrome, treatment with R–CVP or G–CVP should be discontinued and the patient should be treated as clinically indicated. Following the complete resolution of tumor lysis syndrome complications, treatment with R–CVP or G–CVP may be resumed at the full dose at the next scheduled infusion in conjunction with prophylactic therapy.

Hepatitis B Virus Reactivation. Refer to Section 4.3.4.a.

Progressive Multifocal Leukoencephalopathy (PML). Refer to Section 4.3.4.a.

Other Nonhematologic Toxicities. For nausea or vomiting of all grades, optimize anti-emetic therapy.

For Grade ≥2 nonhematologic toxicities (excluding alopecia, nausea, and vomiting), treatment with R–CVP or G–CVP will be delayed for a maximum of 3 weeks until resolution to Grade ≤1 (or baseline for all except hemorrhagic cystitis); for Grade 3 or 4 toxicities, dosing will be modified or discontinued as outlined in Table 11. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator

and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reductions of rituximab (375 mg/m^2) or obinutuzumab (1000 mg). If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses will not be skipped but given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. For Grade 3 or 4 nonhematologic toxicities, the cyclophosphamide dose should be decreased as outlined in Table 11.

Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

For Grade $\geq$3 hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with R–CVP or G–CVP will be delayed for a maximum of 3 weeks until resolution to Grade $\leq$2. In case of recurring Grade 3 hematological toxicity, dosing of cyclophosphamide, rituximab, or obinutuzumab will be modified or discontinued as outlined in Table 11. For Grade 4 toxicities, dosing will be modified or discontinued as outlined in Table 11. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

If surgery is required as a result of a life–threatening condition unrelated to treatment, Day 1 of the next cycle may be delayed up to a total of 8 weeks.

There will be no dose reductions of rituximab (375 mg/m^2) or obinutuzumab (1000 mg). If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses will not be skipped but given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. If cytopenia is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the cyclophosphamide dose, for the first cycle only. Even in the absence of bone marrow infiltration, cytopenias occurring on Cycle 1 Day 8 and/or Cycle 1 Day 15 may be handled by delaying drug administration for a maximum of 3 weeks but do not necessarily trigger a dose reduction of cyclophosphamide in Cycle 2.

Table 11 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or CVP during Induction Therapy

Event	Dose Delay or Modification
Grade 3 or 4 nonhematologic toxicity [a, b]	• Delay doses of R–CVP or G–CVP for a maximum of 3 weeks. • First episode: If improvement to Grade ≤ 1 or baseline, decrease cyclophosphamide dose to 500 mg/m^2 for subsequent cycles. [c] • Second episode: If improvement to Grade ≤ 1 or baseline, decrease cyclophosphamide dose to 375 mg/m^2 for subsequent cycles. [c] • Third episode: Discontinue CVP. [c] If improvement to Grade ≤ 1 or baseline, continue full dose of rituximab or obinutuzumab. • Fourth episode: Discontinue all study treatment. [c]
Grade 2 nonhematologic toxicity [a, b]	• Delay doses of R–CVP or G–CVP for a maximum of 3 weeks. • If improvement to Grade ≤ 1 or baseline, administer previous dose of CVP with full dose of rituximab or obinutuzumab.
Grade 1 nonhematologic toxicity [a]	• No dose reduction or delay.
Grade 2–4 hemorrhagic cystitis	• Delay doses of R–CVP or G–CVP for a maximum of 3 weeks. • If improvement to Grade ≤ 1, decrease cyclophosphamide dose to 500 mg/m^2 for next cycle. Mesna and hydration during the next administrations of cyclophosphamide is recommended. • If symptoms do not recur, cyclophosphamide dose may be again increased to 750 mg/m^2 for subsequent cycles.

Table 11 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or CVP during Induction Therapy (cont.)

Event	Dose Delay or Modification
Grade 4 hematologic toxicity [b, c, d, e, f]	• Delay doses of R–CVP or G–CVP for a maximum of 3 weeks. • Administer myeloid growth factors for neutropenia as allowed per institutional guidelines. • Administer RBCs or platelets as required. • First episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 500 mg/m^2 for subsequent cycles. [c, f] • In patients who are not receiving concomitant anticoagulants or platelet inhibitors, hold obinutuzumab in case of severe thrombocytopenia (platelets <10,000/µL) or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip doses of obinutuzumab for the sake of maintaining the chemotherapy schedule. • In patients who are receiving concomitant anticoagulants or platelet inhibitors, hold obinutuzumab in case of platelets <20,000/µL or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip any doses of obinutuzumab for the sake of maintaining the chemotherapy schedule. For patients who are on LMWH, when thrombocytopenia with platelets <20,000/µL develops, reduce the dose of LMWH used. [d] For patients who are on platelet inhibitors when thrombocytopenia with platelets <20,000/µL develops, consideration should be given to temporarily pause their use. [d, e] • Second episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 375 mg/m^2 for subsequent cycles. [c] • Third episode: Discontinue CVP. [c] If improvement to Grade ≤2, continue full dose of rituximab or obinutuzumab. • Fourth episode: Discontinue all study treatment. [c]

Table 11 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or CVP during Induction Therapy (cont.)

Event	Dose Delay or Modification
Grade 3 hematologic toxicity [b,c,f]	• Delay doses of R–CVP or G–CVP for a maximum of 3 weeks. • Administer myeloid growth factors for neutropenia as allowed per institutional guidelines. • Administer RBCs or platelets as required. • First episode: If improvement to Grade ≤2, administer previous dose of CVP with full dose of rituximab or obinutuzumab. • Second episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 500 mg/m^2 for subsequent cycles. [c] • Third episode: If improvement to Grade ≤2, decrease cyclophosphamide dose to 375 mg/m^2 for subsequent cycles. [c] • Fourth episode: Discontinue CVP. [c] If improvement to Grade ≤2, continue full dose of rituximab or obinutuzumab. • Fifth episode: Discontinue all study treatment. [c]
Grade 1 or 2 hematologic toxicity	• No dose reduction or delay.

CVP = cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone; G = GA101; LMWH = low molecular weight heparins; NHL = non-Hodgkin's lymphoma; R = rituximab; RBC = red blood cell.

[a] Alopecia, nausea, and vomiting excluded; for nausea or vomiting of all grades, optimize anti-emetic therapy; for neurotoxicity, tumor lysis syndrome, or hepatitis B virus reactivation, see guidelines above this table.

[b] Dose delays apply to all adverse events; dose modifications are applied for only adverse events that are considered drug related.

[c] Dose modifications are based on all laboratory values obtained within 72 hours prior to Day 1 of the next cycle. The recommended dose modifications are in effect only for toxicities that are present within 72 hours prior to Day 1 of the next cycle. Toxicities that occur during the cycle and that subside prior to the next cycle should not trigger the suggested dose modifications.

[d] If the clinical condition of patient requires the use of concomitant anticoagulants, the patients are at increased risk of bleeding when thrombocytopenia with platelets <20,000/µL develops. When possible, replace prior therapy with vitamin K antagonists with LMWH before Cycle 1 Day 1.

[e] Clinical decision making may be adjusted depending on the patient–specific assessment of benefit and risk.

[f] If cytopenia is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the cyclophosphamide and doxorubicin doses for the first cycle only. Even in the absence of bone marrow infiltration, cytopenias occurring on Cycle 1 Day 8 and/or Cycle 1 Day 15 may be handled by delaying drug administration for a maximum of 3 weeks but do not necessarily trigger a dose reduction of cyclophosphamide and doxorubicin in Cycle 2.

c. Dosage Modification during Induction Therapy with R–Bendamustine or G-Bendamustine

Dose modifications are based on all laboratory values obtained within 72 hours prior to a study treatment infusion. The recommended dose modifications are in effect only for toxicities that are present within 72 hours prior to Day 1 of the next cycle. Toxicities that occur during the cycle and that subside prior to the next cycle should not trigger the suggested dose modifications. Dose delays apply to all adverse events; dose modifications are applied only for adverse events that are considered drug related.

Nonhematologic Toxicity

Tumor Lysis Syndrome. For patients with evidence of tumor lysis syndrome, treatment with R–bendamustine or G–bendamustine should be discontinued and the patient should be treated as clinically indicated. Following the complete resolution of tumor lysis syndrome complications, treatment with R–bendamustine or G–bendamustine may be resumed at the full dose at the next scheduled infusion in conjunction with prophylactic therapy.

Patients receiving prophylactic allopurinol should be monitored for skin reactions. Skin reactions reported in clinical trials and postmarketing experience have included rash, toxic skin reactions, and bullous exanthema. Cases of Stevens–Johnson syndrome and TEN have been reported when bendamustine was administered concomitantly with allopurinol and other agents known to cause these syndromes. Skin reactions should be monitored closely. In order to avoid such interaction, allopurinol must not be given on the days of bendamustine administration. Bendamustine therapy should be withheld or discontinued for conditions that are severe or progressive.

Hepatitis B Virus Reactivation. Please refer to Section 4.3.4.a.

Progressive Multifocal Leukoencephalopathy (PML). Please refer to Section 4.3.4.a.

Other Nonhematologic Toxicities. For nausea or vomiting of all grades, optimize anti-emetic therapy.

For Grade ≥ 2 nonhematologic toxicities (excluding alopecia, nausea, and vomiting), treatment with R–bendamustine or G-bendamustine will be delayed for a maximum of 3 weeks until resolution to Grade ≤ 1 (or baseline for all except hemorrhagic cystitis); for Grade 3 or 4 toxicities, dosing will be modified or discontinued as outlined in Table 12. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

There will be no dose reductions of rituximab (375 mg/m^2) or obinutuzumab (1000 mg). If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses will not be skipped but given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. For Grade 3 or 4 nonhematologic toxicities, the bendamustine dose should be decreased as outlined in Table 12.

Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

For Grade $\geq$3 hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with R–bendamustine or G–bendamustine will be delayed for a maximum of 3 weeks until resolution to Grade $\leq$2. In case of recurring Grade 3 hematological toxicity, dosing of bendamustine, rituximab, or obinutuzumab will be modified or discontinued as outlined in Table 12. For Grade 4 toxicities, dosing will be modified or discontinued as outlined in Table 12. Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 3 weeks, study treatment will be discontinued.

If surgery is required as a result of a life–threatening condition unrelated to treatment, Day 1 of the next cycle may be delayed up to a total of 8 weeks.

There will be no dose reductions of rituximab (375 mg/m^2) or obinutuzumab (1000 mg). If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, these doses will not be skipped but given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. If cytopenia is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the bendamustine dose, for the first cycle only. Even in the absence of bone marrow infiltration, cytopenias occurring on Cycle 1 Day 8 and/or Cycle 1 Day 15 may be handled by delaying drug administration for a maximum of 3 weeks but do not necessarily trigger a dose reduction of bendamustine in Cycle 2.

Table 12 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or Bendamustine during Induction Therapy

Event	Dose Delay or Modification
Grade 3 or 4 nonhematologic toxicity [a,b]	• Delay doses of R–bendamustine or G–bendamustine for a maximum of 3 weeks. • First episode: If improvement to Grade ≤1 or baseline, decrease bendamustine dose to 60 mg/m^2 for subsequent cycles.[c] • Second episode: Discontinue bendamustine. If improvement to Grade ≤1 or baseline, continue full dose of rituximab or obinutuzumab. [c] • Third episode: Discontinue all study treatment. [c]
Grade 2 nonhematologic toxicity [a,b]	• Delay doses of R–bendamustine or G–bendamustine for a maximum of 3 weeks • If improvement to Grade ≤1 or baseline, administer previous dose of bendamustine with full dose of rituximab or obinutuzumab.
Grade 1 nonhematologic toxicity [a]	• No dose reduction or delay.
Grade 4 hematologic toxicity [b, c, d, e, f]	• Delay doses of R–bendamustine or G–bendamustine for a maximum of 3 weeks. • Administer myeloid growth factors for neutropenia as allowed per institutional guidelines. • Administer RBCs or platelets as required. • First episode: If improvement to Grade ≤2, decrease bendamustine dose to 60 mg/m^2 for subsequent cycles. [c, f] • In patients who are not receiving concomitant anticoagulants or platelet inhibitors, hold obinutuzumab in case of severe thrombocytopenia (platelets <10,000/µL) or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip doses of obinutuzumab for the sake of maintaining the chemotherapy schedule. • In patients who are receving concomitant anticoagulants or platelet inhibitors, hold obinutuzumab in case of platelets <20,000/µL or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip any doses of obinutuzumab for the sake of maintaining the chemotherapy schedule. For patients who are on LMWH, when thrombocytopenia with platelets <20,000/µL develop, reduce the dose of LMWH used. [d] For patients who are on platelet inhibitors when thrombocytopenia with platelet <20,000/µL develops, consideration should be given to temporarily pause their use. [d, e] • Second episode: If improvement to Grade ≤2, decrease dose of bendamustine to 50 mg/m^2 for subsequent cycles. [c] • Third episode: Discontinue bendamustine. If improvement to Grade ≤2, continue full dose of rituximab or obinutuzumab. • Fourth episode: Discontinue all study treatment. [c]

Table 12 Guidelines for Dose Delay or Modification of Obinutuzumab, Rituximab, or Bendamustine during Induction Therapy (cont.)

Event	Dose Delay or Modification
Grade 3 hematologic toxicity [b,c,f]	• Delay doses of R–bendamustine or G–bendamustine for a maximum of 3 weeks. • Administer myeloid growth factors for neutropenia as allowed per institutional guidelines. • Administer RBCs or platelets as required. • First episode: If improvement to Grade ≤2, decrease dose of bendamustine to 70 mg/m^2 with full dose of rituximab or obinutuzumab for subsequent cycles. [b,c] • Second episode: If improvement to Grade ≤2, decrease dose of bendamustine to 60 mg/m^2 with full dose of rituximab or obinutuzumab for subsequent cycles. [c] • Third episode: If improvement Grade ≤2, decrease dose of bendamustine to 50 mg/m^2 with full dose of rituximab or obinutuzumab for subsequent cycles. [c] • Fourth episode: Discontinue bendamustine. [c] If improvement to Grade ≤2, continue full dose of rituximab or obinutuzumab. • Fifth episode: Discontinue all study treatment. [c]
Grade 1 or 2 hematologic toxicity	• No dose reduction or delay.

G = GA101; LMWH = low molecular weight heparins; NHL = non-Hodgkin's lymphoma; R = rituximab; RBC = red blood cell.

[a] For tumor lysis syndrome or hepatitis B virus reactivation, see guidelines above this table.

[b] Dose delays apply to all adverse events; dose modifications are applied for only adverse events that are considered drug related.

[c] Dose modifications are based on all laboratory values obtained within 72 hours prior to Day 1 of the next cycle. The recommended dose modifications are in effect only for toxicities that are present within 72 hours prior to Day 1 of the next cycle. Toxicities that occur during the cycle and that subside prior to the next cycle should not trigger the suggested dose modifications.

[d] If the clinical condition of patient requires the use of concomitant anticoagulants, the patients are at increased risk of bleeding when thrombocytopenia with platelets <20,000/µL develops. When possible, replace prior therapy with vitamin K antagonists with LMWH before Cycle 1 Day 1.

[e] Clinical decision making may be adjusted depending on the patient–specific assessment of benefit and risk.

[f] If cytopenia is thought to be caused mainly by NHL infiltration of the bone marrow, the investigator may decide not to reduce the cyclophosphamide and doxorubicin doses for the first cycle only. Even in the absence of bone marrow infiltration, cytopenias occurring on Cycle 1 Day 8 and/or Cycle 1 Day 15 may be handled by delaying drug administration for a maximum of 3 weeks but do not necessarily trigger a dose reduction of cyclophosphamide and doxorubicin in Cycle 2.

d. Dosage Modification during Maintenance Therapy with Rituximab or Obinutuzumab

Nonhematologic Toxicity

Hepatitis B Virus Reactivation. For the subset of patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA levels at screening, HBV DNA levels must be followed approximately every 4 weeks during maintenance (see Section 4.3.5.c). Treatment with rituximab or obinutuzumab will be held for patients with a serum HBV DNA level of ≥29 IU/mL. Patients should begin treatment with anti-viral medication immediately after the first report showing HBV DNA ≥29 IU/mL. Retest HBV DNA level as soon as possible to rule out a false–positive report and to confirm HBV reactivation (≥29 IU/mL) (best prior to treatment; e.g., when prescribing the anti–viral treatment). If HBV reactivation is confirmed in a second test, continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and immediately refer the patient to a gastroenterologist or hepatologist for additional management. If a second test does not confirm HBV reactivation and was taken prior to start of anti–viral therapy, then anti–viral therapy may be stopped again, and rituximab or obinutuzumab may be resumed. If a second test does not confirm HBV reactivation but was potentially confounded because it was taken only after the start of anti–viral therapy, then continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and refer the patient to a gastroenterologist or hepatologist for additional management. Patients may resume rituximab or obinutuzumab once HBV DNA levels decrease to undetectable levels (<10 IU/mL) or if retest does not confirm HBV reactivation. If the HBV DNA level exceeds 100 IU/mL and are increasing while a patient is receiving anti–viral medication, treatment with rituximab or obinutuzumab will be discontinued.

If HBV DNA level is detectable but <29 IU/mL, then continue with rituximab or obinutuzumab, but retest at close intervals (e.g., every 3–4 weeks). If HBV DNA is still detectable but <29 IU/mL on retest, then continue to administer treatment and retest at close intervals (e.g., every 3–4 weeks). If HBV DNA is ≥29 IU/mL on retest, then follow the instructions for HBV DNA levels ≥29 IU/mL (see above).

HBV DNA level of ≥29 IU/mL	• Hold rituximab or obinutuzumab • Begin anti–viral medication immediately after the first report showing HBV DNA ≥29 IU/mL. • Retest HBV DNA level as soon as possible to rule out a false-positive report and to confirm HBV reactivation (≥29 IU/mL) (best prior to treatment; e.g., when prescribing the anti-viral treatment). • If HBV reactivation is confirmed in a second test, continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and immediately refer the patient to a gastroenterologist or hepatologist for additional management. • If a second test does not confirm HBV reactivation and was taken prior to start of anti–viral therapy, then anti–viral therapy may be stopped again, and rituximab or obinutuzumab may be resumed. Retest the patient at close intervals (every 3–4 weeks). • If a second test does not confirm HBV reactivation but was potentially confounded because it was taken only the after start of anti-viral therapy, then continue to treat for at least 1 year after the last dose of rituximab or obinutuzumab and refer the patient to a gastroenterologist or hepatologist for additional management. • Resume rituximab or obinutuzumab once HBV DNA levels decrease to undetectable levels (<10 IU/mL) or if retest does not confirm hepatitis B reactivation.
HBV DNA level of >100 IU/mL and increasing while on appropriate anti–viral medication	Discontinue rituximab or obinutuzumab.
HBV DNA level detectable but <29 IU/mL	Continue with rituximab or obinutuzumab, but retest at close intervals (e.g., every 3–4 weeks). If HBV DNA still detectable but <29 IU/mL on retest • Continue to administer treatment and retest at close intervals (e.g., every 3–4 weeks). If HBV DNA ≥29 IU/mL on retest • Follow instructions for HBV DNA level of ≥29 IU/mL (see above).

For the subset of patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA levels at screening, HBV DNA levels must be followed approximately every 4 weeks (see Section 4.3.5.c). Treatment with rituximab or obinutuzumab will be held for patients with a serum HBV DNA level of $>$ 100 IU/mL. Patients will begin treatment with anti–viral medication (treatment will continue for at least 1 year after the last dose of rituximab or obinutuzumab) and will be immediately referred to a gastroenterologist or hepatologist for management. Patients may resume rituximab or obinutuzumab once HBV DNA levels decrease to undetectable levels. If the HBV DNA level exceeds 100 IU/mL while a patient is receiving anti–viral medication, treatment with rituximab or obinutuzumab will be discontinued.

If the HBV DNA assay becomes positive and is within the range of 29–100 IU/mL, the patient should be retested within 2 weeks. If the HBV DNA assay is still positive, treatment with Rituximab or obinutuzumab will be held and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of rituximab or obinutuzumab) and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume treatment once the HBV DNA levels decrease to undetectable levels.

Progressive Multifocal Leukoencephalopathy (PML). The diagnosis of PML should be considered in any patient presenting with new–onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual–spatial disorientation) can occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

Therapy with obinutuzumab or rituximab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the treatment of PML.

Other Nonhematologic Toxicities. For Grade $\geq$ 2 nonhematologic toxicities, treatment with rituximab or obinutuzumab will be delayed for a maximum of 42 days until resolution to Grade $\leq$ 1 or baseline (see Table 13). Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 42 days, study treatment will be discontinued. Any delay should be caught up within the next few subsequent visits to keep the treatment period of the maintenance phase within 2 years.

There will be no dose reductions or skipping of rituximab (375 mg/m^2) or obinutuzumab (1000 mg).

Hematologic Toxicity

Note that lymphopenia is not considered to be a hematologic toxicity, because it is an expected outcome of therapy.

For Grade ≥3 hematologic toxicities (defined as neutropenia, anemia, or thrombocytopenia), treatment with rituximab or obinutuzumab will be delayed for a maximum of 42 days until resolution to Grade ≤ 2 (see Table 13). Resumption of dosing without complete resolution of toxicity may be considered only upon careful weighing of the risks and benefits to the patient and agreement between the investigator and the Sponsor. It is recommended that cycles be delayed in 1-week increments. If treatment is delayed for more than 42 days, study treatment will be discontinued. Any delay should be caught up within the next few subsequent visits to keep the treatment period of the maintenance phase within 2 years.

There will be no dose reductions of rituximab (375 mg/m^2) or obinutuzumab (1000 mg).

Table 13 Guidelines for Dose Delay or Modification of Obinutuzumab or Rituximab during Maintenance Therapy

Event	Dose Delay or Modification
Grade 2, 3, or 4 nonhematologic toxicity [a]	• Delay doses of rituximab or obinutuzumab for a maximum of 42 days.[b] • If improvement to Grade ≤1 or baseline, administer full dose of rituximab or obinutuzumab.
Grade 1 nonhematologic toxicity [a]	• No dose reduction or delay.
Grade 3 or 4 hematologic toxicity	• Delay doses of rituximab or obinutuzumab for a maximum of 42 days.[b] • Administer myeloid growth factors for neutropenia as allowed per institutional guidelines. • Administer RBCs or platelets as required. • If improvement to Grade ≤2, administer full dose of rituximab or obinutuzumab.
Grade 1 or 2 hematologic toxicity	• No dose reduction or delay.

RBC = red blood cell.

[a] For tumor lysis syndrome or hepatitis B virus reactivation, see guidelines above this table.

[b] Any delay should be caught up within the next few subsequent visits to keep the treatment period of the maintenance phase within 2 years.

4.3.5 Management of Toxicities

a. Infusion-Related Reactions and Anaphylaxis

Please refer to Section 4.4 for information relating to concomitant medications. Medications (including epinephrine for subcutaneous injections and corticosteroids and diphenhydramine for IV injection) and resuscitation equipment should be available for immediate use. Patients will receive premedication prior to infusion to decrease the risk of IRRs and will have regular monitoring of their vital signs during and after infusions.

Life–Threatening Infusion-Related Reactions and IgE–Mediated Anaphylaxis

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE–mediated anaphylactic reaction, rituximab or obinutuzumab should be discontinued and no additional rituximab or obinutuzumab should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from R/G chemotherapy and R/G maintenance.

Management of Symptoms Related to Rituximab or Obinutuzumab Infusion

Symptoms related to rituximab or obinutuzumab infusion should be managed as outlined in Table 14.

Table 14 Guidelines for Management of Symptoms Related to Rituximab or Obinutuzumab Infusion

Infusion-Related Symptoms [a]	Guidance
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and do not resume treatment.
Grade 3	• Hold infusion. • Give supportive treatment. [b] • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion. [c] • If the same adverse event recurs with the same severity, treatment must be permanently discontinued.
Grade 1–2	• Slow or hold infusion. • Give supportive treatment. [b] • Upon symptom resolution, may resume infusion rate escalation at the investigator's discretion. [c]

Note: This table is for infusion–related reactions (IRRs) according to investigator's judgment, not for IRRs according to the IRR definition for reporting purposes. Also, this table does not refer to management of IgE–mediated anaphylactic reactions, which should be managed as directed above (see Section 4.3.5.a, "Life–Threatening Infusion-Related Reactions and IgE–Mediated Anaphylaxis").

[a] Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0, for the grading of symptoms.

[b] Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine if they have not received such treatment in the previous 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg of IV prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors.

[c] Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour.

b. Cardiotoxicity

Infusions should be discontinued in the event of serious or life–threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusion of rituximab or obinutuzumab. Patients with preexisting cardiac conditions, including arrhythmias and angina, who have had recurrences of these events during rituximab or obinutuzumab therapy should be monitored throughout the infusion and immediate post–infusion period.

c. Hepatitis B Virus Reactivation

For the subset of patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA levels at screening, HBV DNA levels must be followed approximately every 3–4 weeks (depending on chemotherapy regimen) by real-time PCR through use of an assay with a limit of quantification of at least 10 IU/mL for at least 1 year after the last cycle of therapy.

Patients with a serum HBV DNA level of $>$ 100 IU/mL should immediately be started on treatment with an appropriate anti–viral medication and should be referred to a hepatologist/gastroenterologist for further management. Patients with a serum HBV DNA level in the range of 29–100 IU/mL should have their HBV DNA test repeated within 2 weeks. If the level is rising, patients should immediately be started on treatment with an appropriate anti–viral medication. Anti–viral treatment should continue for at least 1 year after the last cycle of therapy.

For the subset of patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA levels at screening, HBV DNA levels must be followed approximately every 3 – 4 weeks (depending on chemotherapy regimen and study phase) by real–time PCR through use of an assay with a limit of quantification of at least 29 IU/mL for at least 1 year after the last cycle of therapy.

Study treatment will be held for patients with a serum HBV DNA level of $\geq$ 29 IU/mL. Patients should begin treatment with anti-viral medication immediately after the first report showing HBV DNA $\geq$ 29 IU/mL. HBV DNA level is re–tested as soon as possible to rule out a false-positive report and to confirm HBV reactivation ($\geq$ 29 IU/mL) (best prior to (treatment; e.g., when prescribing the anti–viral treatment). If HBV reactivation is confirmed in a second test, antiviral treatment will continue for at least 1 year after the last dose of rituximab or obinutuzumab) and patient will be immediately referred to a gastroenterologist or hepatologist for additional management. If a second test does not confirm HBV reactivation and was taken prior to start of anti–viral therapy, then anti–viral therapy may be stopped again, and study treatment may be resumed. If a second test does not confirm HBV reactivation but was potentially confounded because it was taken only after the start of anti–viral therapy, then anti–viral treatment should continue for at least 1 year after the last dose of rituximab or obinutuzumab and the patient should be referred to a gastroenterologist or hepatologist for additional management. Patients may resume study treatment once HBV DNA levels decrease to undetectable levels ($<$ 10 IU/mL) or if retest does not confirm HBV reactivation. If the HBV DNA level exceeds 100 IU/mL and are increasing while a patient is receiving anti–viral medication, study treatment will be discontinued.

If HBV DNA level is detectable but $<$ 29 IU/mL, then study treatment may continue, but patient should be retested at close intervals (e.g., every 3–4 weeks). If HBV DNA is still detectable but $<$ 29 IU/mL on retest, then study treatment should be continued and

patient should be retested at close intervals (e.g., every 3–4 weeks). If HBV DNA is ≥29 IU/mL on retest, the instructions for HBV DNA levels ≥29 IU/m should be followed.

d. Progressive Multifocal Leukoencephalopathy (PML)

The diagnosis of PML should be considered in any patient presenting with new–onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual–spatial disorientation) can occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

Therapy with obinutuzumab or rituximab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the treatment of PML.

e. Febrile Neutropenia

It is mandatory to follow the ASCO/EORTC/ESMO guidelines about the use of myeloid growth factors for the primary prevention and treatment of febrile neutropenia throughout the trial (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011).

f. Hemorrhagic Cystitis

Patients should be adequately hydrated prior to and after cyclophosphamide administration and should be instructed to void frequently. Mesna (2-mercaptoethane sulfonate sodium) may be administered as prophylaxis per institutional guidelines. If gross hematuria develops, the cyclophosphamide dose should be decreased (see Table 10 and Table 11).

g. Gastrointestinal Toxicity

CHOP and CVP are associated with chemotherapy–induced nausea and vomiting. Anti-emetics should be administered per institutional guidelines.

4.3.6 Treatment Discontinuation Criteria

A patient should discontinue rituximab, obinutuzumab, or chemotherapy if any of the following occurs. If it is unclear as to which drug caused the toxicity, all agents should be discontinued.

- Grade 4 infusion–related symptom or anaphylaxis as per investigator's judgment; the patient should be withdrawn from study treatment (R/G chemotherapy and R/G maintenance) immediately.
- Recurrence of Grade 3 infusion–related symptom at re–challenge as per investigator's judgment despite adequate preventive measures (i.e., acetaminophen/paracetamol plus antihistamine plus corticosteroid), regardless of timing (e.g., within the same session or at a subsequent session)
- Fourth recurrence of Grade 4 hematologic toxicity (each episode of which delayed the start of the next treatment cycle) despite adequate dose reductions
- Fifth recurrence of Grade 3 hematological toxicity (each episode of which delayed the start of the next treatment cycle) despite adequate dose reductions
- Diagnosis of confirmed PML
- Grade ≥ 2 nonhematologic toxicity that does not resolve to Grade ≤ 1 or baseline despite delaying treatment for at least 3 weeks during induction treatment
- Grade ≥2 nonhematologic toxicity that does not resolve to Grade ≤1 or baseline despite delaying treatment for at least 6 weeks during the maintenance phase
- For R/G–CHOP/CVP: Fourth episode of Grade ≥ 2 nonhematologic toxicity (each episode of which delayed the start of the next treatment cycle) despite adequate dose reductions in R/G–CHOP/CVP
- For R/G–bendamustine: Third episode of Grade ≥ 2 nonhematologic toxicity (each episode of which delayed the start of the next treatment cycle) despite adequate dose reductions in R/G–bendamustine
- Grade 1–4 heart failure or Grade 3–4 left ventricular systolic dysfunction
- Hepatitis B exacerbation despite the initiation of the appropriate anti–viral therapy
- Disease progression

A patient should discontinue rituximab or obinutuzumab if any of the following occurs:

- Recurrent Grade 4 hematologic toxicity or Grade 3 or 4 nonhematologic toxicity despite discontinuation of CHOP, CVP, or bendamustine (as described in Table 10–Table 12).

Patients who discontinue rituximab or obinutuzumab treatment because of infusion–related symptoms may continue to receive chemotherapy alone and should continue to have disease assessments per the protocol. Patients who discontinue rituximab may not cross over to obinutuzumab.

Patients who discontinue chemotherapy prior to the completion of induction treatment because they have experienced a chemotherapy-specific toxicity should continue to receive rituximab or obinutuzumab alone as previously scheduled until disease progression.

Patients who discontinue chemotherapy prior to the completion of the full number of induction cycles for any reason other than toxicity should discontinue study treatment and go into follow–up directly without maintenance (see Appendix A-5).

It is mandatory that the full number of cycles will be given for each immunochemotherapy regimen during induction. If induction therapy was stopped for toxicity or any reason other than toxicity, then patients are discontinued from study treatment and go into follow–up directly without maintenance (see Appendix A-5).

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the study entry evaluation and the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF).

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

Patients may receive prophylactic anti–viral medication to prevent hepatitis B reactivation in countries where they are administered as part of the standard of care or national guidelines.

The use of rasburicase for the treatment of tumor lysis syndrome and the prevention of hyperuricemia is allowed according to institutional guidelines.

The use of antibiotic and/or anti–viral prophylaxis according to institutional guidelines is also allowed.

Primary prophylaxis with granulocyte colony stimulating factors (G–CSFs) is recommended as per the ASCO, EORTC, and ESMO guidelines–namely, in patients who are ≥ 60 years of age and/or with comorbidities (Lyman et al.2004). The use of G-CSF prophylaxis is strongly recommended in Cycle 1 for all patients treated with GA101 + CHOP.

Harvesting of stem cells by G–CSF alone (no additional chemotherapeutic agent) is allowed only if it is done between Cycle 5 Day 1 and Cycle 8 Day 1 (R/G–CHOP or R/G–CVP) or Cycle 4 Day 1 and Cycle 6 Day 1 (R/G–Bendamustine).

Patients who experience obinutuzumab infusion–related temperature elevations of $>38.5°C$ or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol (≥ 500 mg) and/or H_1– and H_2–receptor antagonists (e.g., diphenhydramine, ranitidine). Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with additional supportive therapies (e.g., supplemental oxygen, β_2 agonists/epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice.

a. Therapy for Febrile Neutropenia

It is mandatory to follow the ASCO/EORTC/ESMO guidelines about the use of myeloid growth factors for the primary prevention and treatment of febrile neutropenia throughout the trial (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011).

b. Hemorrhagic Cystitis

Mesna may be administered as prophylaxis per institutional guidelines for patients treated with CHOP or CVP.

4.4.2 Excluded Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy (other than bendamustine, cyclophosphamide, doxorubicin, or vincristine)

  Although MTX is a chemotherapeutic agent, due to the low doses used in treating rheumatoid arthritis (typically 7.5 to a maximum of 20 mg/week) it is not considered chemotherapy for lymphoma. Therefore, patients treated before or during study conduct with MTX for rheumatoid arthritis are still eligible to participate in the study. It is recommended to stop MTX 2-3 weeks prior to starting immunochemotherapy since the combination of MTX and immunochemotherapy increases the risk of immunosuppression and the risk of infection, but MTX may be resumed during maintenance/observation/follow–up, if clinically indicated
- Radiotherapy
- Immunotherapy (other than rituximab and obinutuzumab)
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)

  Hormonal therapy (e.g., GnRH–agonists) for egg cell harvest/fertility preservation prior to randomization is allowed in women of childbearing age
- Any therapies intended for the treatment of NHL, whether FDA approved or experimental (outside of this study)

Patients who require the use of any of these agents will be discontinued from study treatment but followed for PD and overall survival.

4.5 STUDY ASSESSMENTS

Signed informed consent will be obtained from the patient or patient's legally acceptable representative before any study–specific procedures are performed or any prohibited medications are withheld for purposes of study participation.

Test results or examinations that are performed as standard of care prior to obtaining informed consent and appropriately within 35 days prior to randomization may be used to satisfy screening requirements rather than repeating required tests. A separate optional informed consent is required for collection of optional research samples (see Section 4.5.1.h).

See Appendix A for the Study Flowcharts.

4.5.1 Definitions of Study Assessments

a. Physical Examination

A complete physical examination should include an evaluation of head, eye, ear, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

A targeted physical examination should be limited to systems of primary relevance—that is, cardiovascular, respiratory, those associated with symptoms, and those associated with tumor assessment (lymph nodes, liver, and spleen).

b. Tumor and Response Evaluation

All measurable disease must be documented at baseline and re-assessed within 14 days prior to each subsequent study visit. Response assessments will be performed by the investigator, based on physical examinations, CT/MRI scans, hematology, laboratory results, and bone marrow examinations, through use of Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix C). Response evaluation by the investigator shall be done with and without FDG–PET results or the PET portion of a combined PET–CT in the eCRF.

CT scans (with contrast) should include chest, abdomen, and pelvis scans; CT scans of the neck should be included if clinically indicated (i.e., if evidence of disease on physical

examination) and must be followed throughout the trial if there is disease involvement at baseline. MRIs of the chest, abdomen, and pelvis with a non–contrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). If MRI is used at screening, then MRI should be used throughout the study (same method during the entire study). In addition, the CT portion of a combined FDG–PET/CT scan may be used only if performed with contrast and collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. Any time the investigator suspects disease progression, a full tumor assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities).

- In the first 170 patients with follicular lymphoma, an FDG–PET is mandatory where a PET scanner is available. This may require specific approval in some countries. In such instances, FDG–PET becomes manadatory only after necessary approvals have been obtained.

PET scans are to be performed at screening and at induction completion/end of treatment visit (only if screening PET was positive) within 6–8 weeks after Day 1 of the last cycle, within 4–8 weeks (in case of early termination due to adverse event), or within 2–8 weeks after last dose (in case of early termination due to clinical disease progression).

In the overall study population, FDG–PET remains optional upon investigator's discretion.

If the screening PET scan is negative, subsequent FDG–PET scans need not be performed. Any time the investigator suspects disease progression on the basis of PET scan results, a full tumor assessment must be performed, including a CT scan (or MRI scan if CT scan is contraindicated), limited to areas of prior involvement (if required by local authorities to limit scans). FDG–PET standardized uptake values will be collected.

FDG–PET scan results will be incorporated in an exploratory analysis in a separate response assessment based on physical examinations, relevant clinical information, CT or MRI scans, and bone marrow examinations by the investigator and the IRC.

Bone marrow examinations should include a biopsy for morphology, an aspirate for local hematology (optional, if part of standard of care at site), and an aspirate for *BCL2/IgH* (=MRD) determination. Bone marrow examinations are required at screening for staging purposes in all patients (CR definition requires clearing of a previously infiltrated bone marrow) and in all patients with follicular lymphoma also for determination of *BCL2/IgH* (MRD) baseline levels. *BCL2/IgH* –based MRD determination will not be performed in patients with MZL.

If there was bone marrow infiltration at screening, then a subsequent bone marrow biopsy (trephine) at the induction completion visit is required for clinical response

evaluation for all patients who may have achieved a CR. In patients with a PR and continued bone marrow involvement, a subsequent bone marrow examination may be required to confirm a CR at a later time point. An additional bone marrow aspirate may be done if that is standard of care at the site.

If bone marrow involvement was diagnosed by morphology at screening, a subsequent bone marrow aspirate for *BCL2/IgH* (MRD) is required at the induction completion/end-of-treatment visit for all patients with follicular lymphoma who achieve a CR or PR (all responders). If bone marrow was free of lymphoma by morphology at screening, a subsequent bone marrow aspirate for *BCL2/IgH* (MRD) at the induction completion/end-of-treatment visit is optional but strongly recommended in responders (CR + PR). This recommendation is based on the observation that, at screening, bone marrow involvement is detectable on the level of minimal residual disease in the large majority of patients even if it appears to be negative by morphology.

Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

In patients with gastric extranodal MZL, the initial staging should include a gastroduodenal endoscopy with multiple biopsies from the stomach, duodenum, gastroesophageal junction, and any site that seems abnormal. If any disease sites are identified in this manner at screening, a subsequent gastroduodenal endoscopy and biopsy are required to confirm a CR. In addition, if other sites are involved at baseline, they should be appropriately staged at baseline and re-evaluated during follow–up. The diagnosis of CR in splenic MZL also requires the normalization of the blood counts (hemoglobin > 12g/dL; platelets $> 100 \times 10^9$/L; neutrophils $> 1.5 \times 10^9$/L) and no evidence of circulating clonal B cells.

In patients with splenic MZL, the spleen is considered a target lesion, and its size should be determined by ultrasound, CT/MRI, or by physical examination. Local guidelines for determining normal organ size are acceptable.

c. Laboratory Assessments

Samples for the following laboratory assessments will be analyzed at the study site's local laboratory: hematology, serum chemistry, urinalysis, serum electrophoresis and M protein, serum immunofixation, pregnancy test, HTLV testing, hepatitis B serology, hepatitis C serology and RNA, coagulation, and quantitative immunoglobulins. Samples for the following laboratory assessments will be sent to the Sponsor or designees for analysis: HBV DNA, flow cytometry (leukocyte immunophenotyping), biologic markers, pharmacokinetics, *BCL2/IgH* rearrangement, and HAHAs. Instruction manuals and supply kits will be provided for all central laboratory assessments. Flow cytometric determination of T, B, and NK cells (TBNK–Panel) will be performed in all patients of the trial (both rituximab– and obinutuzumab–treated patients). Flow cytometric

determination of B cell subsets (B cell panel) will be performed in 60 patients of each treatment group (R-CHOP, G–CHOP, R–CVP. G–CVP, R–bendamustine, G–bendamustine) and in all patients with splenic MZL. Pharmacokinetic assessments will be performed in a subset of approximately 460 patients receiving obinutuzumab. HAHA will be performed in all patients receiving obinutuzumab.

On days of study drug administration, pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion, and post-infusion laboratory samples should be drawn 0–30 minutes after the end of infusion, unless otherwise specified.

Protection of patient confidentiality will extend to any data generated from the assaying of these samples.

Laboratory assessments will include the following:

- Hematology includes hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell count, and absolute neutrophil count as routine components. Percent or absolute differential count [segmented neutrophils, banded neutrophils, eosinophils, lymphocytes, monocytes, basophils, malignant lymphocytes are done if clinically indicated {e.g., for differential diagnosis of any kind of clinically relevant cytopenia/cytophilia, or, e.g., if other undefined cells are present in the peripheral blood}]). In case of splenic MZL, the percent or absolute number of malignant lymphocytes ("villous lymphocytes") in peripheral blood should be assessed.
- Serum chemistries (sodium, potassium, chloride, bicarbonate [if clinically indicated], BUN, creatinine, calcium, phosphorus, total bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, uric acid, and β_2 microglobulin [β_2 microglobulin required only at screening]). Urinalysis: In a fresh sample of midstream urine, a dipstick testing for proteinuria is required.
- Creatinine clearance (glomerular filtration rate) according to Cockroft Gault during screening and approximately 1 year after last treatment.
- For MZL patients, serum electrophoresis (% albumin, alpha 1, alpha 2, beta, gamma), relative and absolute determination of M protein if present. If M protein is present, immunofixation for detection of Ig subtype (IgG, IgA, IgM, IgD, light–chain kappa or lambda) should be performed.
- Coagulation (PTT or aPTT, prothrombin time or INR)
- Pregnancy test: All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits and may be performed more frequently if required by local legislation. If a urine pregnancy test result is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

- Viral serology and detection

  Hepatitis B (HBsAg and total HBcAb and hepatitis B surface antibody [HBsAb])

  HBV DNA should be monitored centrally every 3 to 4 weeks (depending on chemotherapy regimen) by real-time PCR with a limit of quantification of at least 29 IU/mL until at least 1 year after the last treatment cycle in patients who are HBsAg negative and HBcAb positive.

  If a patient is HBsAg negative and HBcAb positive during screening, additional serology for HBsAb is required prior to Day 1 of Cycle 1.

  HCV antibody (also HCV RNA by PCR in a local laboratory if the patient is HCV antibody positive)

  HTLV−1 serology (for patients from endemic countries only; endemic countries include Japan, the Caribbean basin, South America, sub-Saharan Africa, and Melanesia)

- Quantitative immunoglobulins (IgG, IgA, and IgM)
- Flow cytometry (fluorescence-activated cell sorting [FACS] subsets)

  Whole-blood samples will be collected to determine

  In all patients: TBNK−Panel. The duration of B-cell depletion and recovery (CD19+), T−cell counts (CD3+, CD4+, CD8+), and NK−cell counts (CD56+)

  B cell panel: In 60 patients of each therapeutic group (R−CHOP, G−CHOP, R-CVP, G-CVP, R−bendamustine, G−bendamustine) and in all splenic MZL patients: B−cell subsets defined by a combination of B−cell markers.

- HAHAs (patients receiving obinutuzumab only)

  Although obinutuzumab is a humanized antibody, there is a risk that HAHAs could develop, thus reducing efficacy and/or resulting in symptomatic hypersensitivity reactions. Experience with similar humanized antibodies (e.g., trastuzumab) suggests that the incidence and titer of such antibodies will be low and that they will be unlikely to affect efficacy or cause unwanted immunological reactions (Genentech data on file). Nevertheless, samples will be collected to assess the possible induction of HAHAs in patients receiving obinutuzumab.

- Pharmacokinetic measurements (subset of patients receiving obinutuzumab only) (see Appendix B)
- Tumor tissue samples at screening and at time of progression/transformation will be collected from patients for central pathologic review and confirmation of CD20 positivity. Tissue should be collected within 12 months prior to randomization. Tissue samples dated $>$12 months prior to randomization can be accepted only if tissue material is available for retrospective confirmation, if there is no clinical indication for transformation of disease, and if the request for additional biopsy would be unethical treatment of the patient. Bone marrow alone is not suited to make the diagnosis of follicular lymphoma. In patients with splenic MZL without splenic tissue available for histologic review, the bone marrow must be submitted

for retrospective central confirmation. All tissue samples should be sent for quality assurance pathology review within 4 months after randomization. A formalin–fixed, paraffin–embedded tissue sample is preferred over 15–20 sections on coated slides. If the tissue sample is small, fewer sections (minimum, within range of 6–12) can be accepted. Remainders of the tissue blocks will be returned to local pathology according to country–specific procedures.

d. Electrocardiograms

A 12–lead ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine whenever possible.

e. Cardiac Function Evaluation

Patients randomized to R–CHOP or G–CHOP are required to have an evaluation of their cardiac function by MUGA scan or echocardiogram within 6 months prior to screening and after receipt of 300 mg/m^2 of doxorubicin (end of induction therapy).

f. Patient–Reported Outcomes

The PRO questionnaires (FACT–Lym and EQ–5D) should be self–administered at the investigational site. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. It is important that the questionnaires be administered before any other study procedure is performed during that study visit.

g. ECOG Performance Status, Ann Arbor Staging, IPI and FLIPI Index, ADLs/IADLs

The ECOG Performance Status scale and Ann Arbor staging classifications are provided in Appendix H. Appendix M provides a description of the IPI, FLIPI, and FLIPI2 indices and FLIPI nodal areas. Appendix N provides a description of ADLs/IADLs scoring scale.

h. Exploratory Biomarker Research (Required and Optional Components)

Samples will be collected from all patients to enable differentiation of predictive factors from prognostic factors. Samples will be collected to identify biomarkers that are predictive of response to obinutuzumab treatment (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of advanced follicular lymphoma and related diseases. In countries where DNA collection is restricted, local laws and regulations will apply and a separate consent may be issued to comply with local legislation.

All specimens for exploratory biomarker analyses (both required and optional) will be single coded like any other clinical sample (labeled and tracked using the patient's study identification number).

Required Exploratory Biomarkers

Required samples for exploratory biomarker research are as follows:

- Fcγ receptor polymorphisms (only in fully eligible patients)
- Tumor tissue sample at time of progression/transformation

  A tumor sample will be collected at time of progression from patients who undergo such a biopsy as part of the standard of care at their institution for central pathology review. A biopsy at the time of progression is not mandatory.
- Bone marrow aspirate for *BCL2/IgH* (MRD) analysis at screening (follicular lymphoma patients only) and at induction completion/early termination (only responders [CR and PR] in whom bone marrow involvement was diagnosed by morphology at screening)

  For each required bone marrow examination, a bone marrow aspirate is required for the analysis of clonal *BCL2/IgH* rearrangement (as a potential marker of tumor burden).

  Peripheral blood sample for *BCL2/IgH* (MRD) analysis in all patients with follicular lymphoma at screening, before Cycle 4 Day 1 bendamustine) or Cycle 5 Day 1 (CHOP/CVP), at induction completion/end of treatment, maintenance or observation Month 4, 8, 12, 18, at maintenance or observation completion/end-of-treatment visit, and during follow–up at Months 30, 36, 42, 48, 60, and 72.

Required exploratory biomarker samples will be stored for up to 5 years after completion of the study.

Optional Exploratory Biomarkers

Optional samples for exploratory biomarker research are as follows:

- Baseline serum and plasma samples to enable future analyses of protein expression (e.g., cytokine profiles)
- Leftover DNA from Fcγ receptor polymorphism samples (see DNA Substudy protocol)
- Leftover DNA from peripheral blood samples for for *BCL2/IgH* (MRD) analysis in all patients with follicular lymphoma at screening, before Cycle 4 Day 1 bendamustine) or Cycle 5 Day 1 (CHOP/CVP), at induction completion/end of treatment, maintenance or observation Month 4, 8, 12, 18, at maintenance or observation completion/end–of–treatment visit, and during follow–up at Months 30, 36, 42, 48, 60, and 72 (see DNA Substudy protocol)
- Bone marrow aspirate samples for MRD analysis at the induction completion/end–of–treatment visit from responding (CR + PR) patients with follicular lymphoma in whom no bone marrow involvement was diagnosed by morphology at screening

- Leftover DNA from bone marrow aspirate samples for MRD analysis at the induction completion/end–of–treatment visit from responding (CR + PR) patients with follicular lymphoma in whom no bone marrow involvement was diagnosed by morphology at screening (see DNA Substudy protocol).
- Residual tumor tissue sample from baseline biopsy sample

  In addition to central pathology review (see the Required Exploratory Biomarkers section), representative tumor sections from the original biopsy sample will be cut for generation of tissue microarrays (TMAs), extraction of tumor messenger ribonucleic acid (mRNA), microRNA, and DNA. If possible, two tissue cores will be punched for construction of a TMA. These samples may be used for the assessment of specific tumor biologic markers, including proteins, mRNA, microRNA, and DNA, in order to better understand the biology of NHL and disease prognosis to predict response to treatment with obinutuzumab (see DNA Substudy protocol).

  Assays on stored tissue samples may be performed by the Sponsor or at a central specialty laboratory.

  Any remaining tissue in the tissue block will be returned to the site according to country–specific procedures. Unused slides will not be returned.
- Residual tumor tissue from sample at time of progression/transformation

  In addition to central pathology review (see the Required Exploratory Biomarkers section), representative tumor sections from the sample at time of progression/transformation will be used for the assessment of specific tumor biologic markers, including proteins, mRNA, microRNA, and DNA, in order to better understand possible changes in tumor biology (e.g., histological transformation, gene expression, expression of surface markers) that may have occurred (see DNA Substudy protocol).

If patients consent to participate in the optional exploratory biomarker research, serum, plasma, leftover DNA from Fcγ Receptor polymorphism, peripheral blood and bone marrow *BCL2/IgH* (MRD) samples, and unstained sections, TMAs, as well as mRNA, microRNA, and DNA extracted from the residual tumor tissue specimens from the biopsy sample at baseline and at progression/transformation will be stored in the RCR for up to 15 years after database freeze to enable future research.

The RCR specimens will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The implementation and use of the RCR specimens is governed by the RCR policy to ensure the appropriate use of the RCR specimens.

Specimens in the RCR will be used for research purposes to identify biomarkers that are predictive of response to obinutuzumab treatment (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course, and outcome of advanced follicular lymphoma and related diseases.

i. Medical Resource Utilization

Where possible, medical resource utilization data will be collected from the clinical eCRFs completed by site staff (e.g., adverse events associated with hospitalization, concomitant therapy). Where necessary, patients will be asked whether they have received additional medical care and will be asked to identify the type of resource (e.g., primary care physician).

4.5.2 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study–specific screening tests or evaluations. Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site. A separate, optional informed consent is required for the optional research described in Section 4.5.1.h.

Screening tests and evaluations will be performed within 35 days prior to randomization. Results of standard–of–care tests or examinations performed prior to obtaining informed consent and within 14 days prior to study entry may be used; such tests do not need to be repeated for screening. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before initiation of study treatment.

Please see the Study Flowcharts provided in Appendix A for schedules of screening and pretreatment assessments.

4.5.3 Assessments during Induction Treatment

Local laboratory assessments may be performed within 72 hours prior to study drug administration on Day 1 of each cycle. Results must be reviewed and the review documented prior to study drug administration.

During induction treatment, all visits must occur within ±4 days from the scheduled date, unless otherwise noted. Assessments scheduled on the day of study drug administration should be performed prior to study drug infusion, unless otherwise noted.

Please see the Study Flowcharts provided in Appendix A for schedules of assessments to be performed during induction treatment.

4.5.4 Induction Completion/Early Termination Visit

Patients who complete the induction treatment period or discontinue early will be asked to return to the clinic within 6–8 weeks after Cycle 8 Day 1 (CHOP or CVP) or Cycle 6 Day 1 (bendamustine) for a follow–up visit. The visit at which a response assessment showed disease progression may be used as the early termination visit. An early termination visit should occur within 4–8 weeks after last dose (in case of early termination due to adverse event) or within 2–8 weeks after last dose (in case of early termination due to clinical disease progression).

See the Study Flowcharts provided in Appendix A for schedules of assessments to be performed at the induction completion/early termination visit.

4.5.5 Assessments during Maintenance Treatment or Observation

Patients who demonstrate a CR or PR at the end of induction therapy will be eligible to receive maintenance therapy with rituximab or obinutuzumab based upon the initial randomization. Patients should start treatment with rituximab or obinutuzumab 2 months ± 14 days after the last dose of immunochemotherapy and will continue to receive treatment every 2 months ± 14 days until disease progression for up to 2 years. If the end of induction/early termination visit was done 8 weeks after the last dose of immunochemotherapy, the first maintenance visit should be scheduled 7–14 days later in order to keep an interval between end of induction/early termination and maintenance Month 2.

Patients who demonstrate SD at the end of induction therapy will undergo observation for up to 2 years.

The schedule of 2–month visits should be maintained. During maintenance a month will be calculated as 28 days.

Patients receiving maintenance therapy or undergoing observation will be followed clinically every 2 months ± 14 days for 2 years (with CT scans every 4 months for the first year and then every 6 months for the second year) or until disease progression or patient discontinuation from the study, whichever comes first.

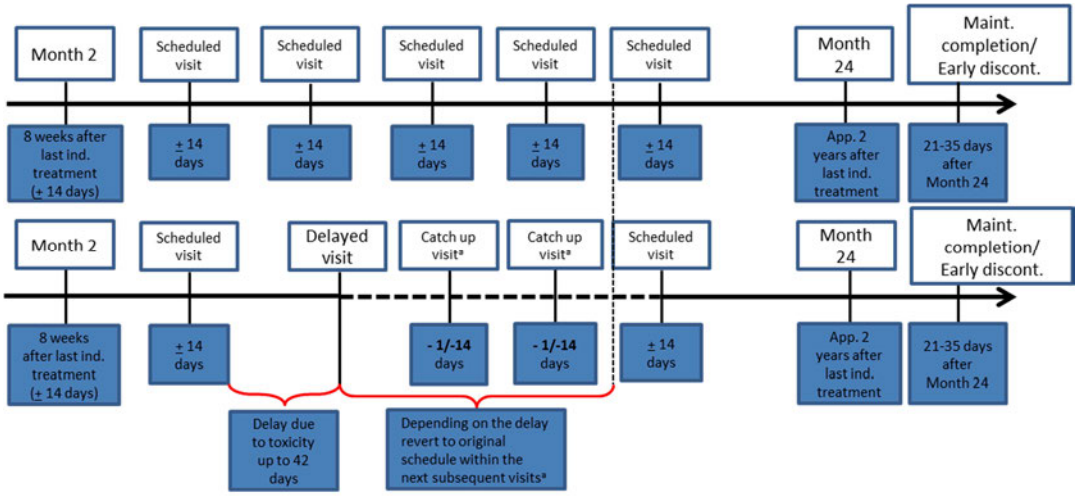
Tumor assessment (CT scan or MRI) may be performed within 14 days prior to study drug administration. If a dose of study drug is delayed, tumor assessment should be performed 14 days prior to the new planned visit (for Months 4, 8, 12, and 18).

Local laboratory assessments may be performed within 72 hours prior to study drug administration on Day 1 of each cycle. Results must be reviewed and the review documented prior to study drug administration.

See the Study Flowcharts provided in Appendix A-4 for schedules of assessments to be performed during maintenance treatment or observation.

Any delay in maintenance or observation visits should be reverted to the original schedule within the next few subsequent visits. No study drug infusion should be skipped due to a visit delay (see Figure 3).

Figure 3 Schema of Returning to Original Schedule after a Visit Delay in Maintenance



Note: This schema shows only two catch–up visits. More visits could be necessary in order to return to the original schedule.
Maint. = maintenance; Discont. = discontinuation

4.5.6 Maintenance or Observation Completion/Early Termination Visit

Patients who complete the maintenance treatment or observation period or who discontinue early will be asked to return to the clinic within 21–35 days after the last immunotherapy dose or the date of the decision to discontinuation for a maintenance or observation completion/ET visit.

The visit at which a response assessment showed disease progression may be used as the early termination visit.

Please see the Study Flowcharts provided in Appendix A for schedules of assessments to be performed at the maintenance or observation completion/early termination visit.

4.5.7 Follow–Up Assessments

a. Patients with a Response or Stable Disease

For patients who have a CR, a PR, or SD at the maintenance or observation completion visit, disease assessments will continue every 3 months ± 14 days for 3 years (with CT scans every 6 months) and then every 6 months ± 14 days for 2 years (with CT scans every year) until the end of the study (at approximately 10.2 years) or until disease progression, whichever occurs first. This assessment is consistent with both NCCN and ESMO guidelines. Patients will then be followed twice per year, starting 6 months after the last clinical visit, until the end of the study for the following:

- Disease progression
- NALT
- Survival

Patients who start an NALT or discontinue study drug in the absence of disease progression should be followed according to the above schedule.

b. Patients with Disease Progression

Patients with disease progression will be followed twice per year, starting 6 months after the last clinical visit, until the end of the study (at approximately 10.2 years) for the following:

- NALT
- Survival
- *Response after NALT*

c. Ongoing Adverse Events

Ongoing adverse events thought to be related to study drug treatment will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, NALT is initiated, the patient is lost to follow–up, the patient withdraws consent, or it has been determined that the study treatment or participation is not the cause of the adverse event.

See the Study Flowcharts provided in Appendix A for schedules of follow–up assessments.

4.6 PATIENT DISCONTINUATION

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; for reasons of noncompliance (e.g., missed doses, visits); if the patient becomes pregnant; or if the investigator determines it is in the best interest of the patient. Patients who are discontinued because of investigators decision will be followed up for disease progession, NALT, *response after NALT, and survival.*

See Sections 4.5.4 and 4.5.6 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period.

4.6.1 Discontinuation from Study Treatment

Patients may discontinue chemotherapy treatment (i.e., CHOP, CVP, or bendamustine) early if they experience unacceptable toxicity as described in Section 4.3.4. Patients may also discontinue obinutuzumab or rituximab treatment early because of unacceptable toxicity as described in Section 4.3.6. The reasons for early discontinuation of treatment must be documented on the appropriate eCRF.

Patients who discontinue study treatment early because of an unacceptable toxicity should continue to be followed for both resolution of toxicity and disease progression as scheduled in Appendix A-5.

Patients must discontinue study treatment if they experience disease progression. After disease progression, patients will be followed until the next treatment and then for survival until study completion, starting 6 months after the last clinical visit (see Section 4.5.7 a).

The investigator has the right to discontinue a patient from study treatment for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study, for reasons of non–compliance (e.g., missed doses, visits), if the patient becomes pregnant, or if the investigator determines it is in the best interest of the patient.

See Sections 4.5.4 and 4.5.6 for assessments that are to be performed for patients who prematurely discontinue treatment during the primary study treatment period.

4.6.2 Discontinuation from Study

Patients have the right to voluntarily withdraw or discontinue from the study at any time for any reason. The investigator also has the right to withdraw a patient from the study at any time for any reason. Those patients who are withdrawn or withdraw from study participation (and not just study treatment) will not be followed up for any reason after consent has been withdrawn.

4.6.3 Withdrawal of Patients from the Roche Clinical Repository

Patients who give consent to allow collection of exploratory biomarker specimens for storage in the RCR have the right to withdraw their specimens at any time for any reason. If a patient wishes to withdraw his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Patient Withdrawal Form and enter the date of withdrawal in the patient's eCRF. A patient withdrawal from the study does not, by itself, constitute withdrawal of the specimen from the RCR; likewise, withdrawal of a patient's specimens from the RCR does not constitute a withdrawal from the study.

4.7 STUDY OR SITE DISCONTINUATION

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence

4.8 POST–TRIAL ACCESS

Currently, the Sponsor does not have any plans to provide obinutuzumab or other study interventions to patients after the conclusion of the study or any earlier withdrawal. Patients in the control arm are not allowed to cross over to receive obinutuzumab. The Sponsor will evaluate the appropriateness of continuing to provide obinutuzumab to study patients after evaluating the primary efficacy outcome measure and safety data gathered in the study.

4.9 ASSAY METHODS

Obinutuzumab concentration will be determined in serum through use of a sandwich ELISA method. Assay sensitivity was determined to be 4.05 ng/mL obinutuzumab in human serum.

A sandwich bridging ELISA was developed using conjugated obinutuzumab as a capture agent to detect anti–obinutuzumab antibodies in human serum.

4.10 STATISTICAL METHODS

All analyses will be performed for the follicular population and for the overall population unless otherwise specified.

4.10.1 Analysis of the Conduct of the Study

Enrollment, eligibility violations, study drug administration, and patient disposition will be summarized by treatment arm in all randomized patients and by histology (follicular and non–follicular). A summary of patient disposition will include whether treatment was completed or discontinued early and the reason for early treatment discontinuation.

4.10.2 Analysis of Treatment Group Comparability

Demographic and baseline characteristics, such as age, sex, race/ethnicity, and baseline ECOG Performance Status, will be summarized by treatment arm in all

randomized patients and by histology (follicular vs. non–follicular). Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data will include frequencies and percentages.

4.10.3 Efficacy Analyses

The primary analysis population for efficacy is the intent–to–treat follicular population, defined as all randomized patients with follicular histology, according to local diagnosis provided in IxRS. Patients will be analyzed according to the treatment arm to which they were randomized.

a. Primary Efficacy Endpoint

The primary efficacy endpoint, PFS in patients with follicular lymphoma, is defined as the time from randomization to the first occurrence of progression or relapse as assessed by the investigator according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix C) or death from any cause. PFS for patients without disease progression, relapse, or death will be censored at the time of the last tumor assessment or, if no tumor assessments were performed after the baseline visit, at the time of randomization.

Although the primary efficacy endpoint is the investigator–assessed PFS, PFS based on IRC assessments will also be analyzed to support the primary analysis. In the United States, IRC–assessed PFS will be the basis for regulatory decisions.

The primary analysis of the study will test the equality of PFS distributions in the obinutuzumab plus chemotherapy (G–Chemo) and rituximab plus chemotherapy (R-Chemo) arms, as follows:

H_0: $PFS_{G\text{-}Chemo} = PFS_{R\text{-}Chemo}$ versus H_1: $PFS_{G\text{-}Chemo} \neq PFS_{R\text{-}Chemo}$

Treatment comparison will be made using a two–sided stratified log–rank test (0.05 significance level) stratified by chemotherapy regimen (CHOP, CVP, or bendamustine) and FLIPI risk group (low, intermediate, or high). Kaplan–Meier methodology will be used to estimate PFS distribution for each treatment arm. The Kaplan–Meier curve will provide a visual description of the differences across treatment arms. Estimates of the treatment effect will be expressed as hazard ratios through use of a stratified Cox proportional–hazards analysis, including 95% confidence limits.

Median PFS is not expected to be reached in this study; hence, the 3–year and 4–year rates will be used to describe PFS in addition to the hazard ratio.

The following sensitivity analyses for PFS will also be performed:

- An unstratified log–rank test will be performed.

- A re–randomization test of the primary endpoint will be performed to assess the sensitivity of the stratified log–rank test to the dynamic randomization procedure.
- The impact of loss to follow–up will be assessed by a worst–case analysis that assigns event outcomes to patients who were lost prior to disease progression in the obinutuzumab arm at the next scheduled disease assessment date and censored outcomes to patients in the rituximab arm at the last disease assessment date.
- PFS analyses will be performed with censoring at the initiation of non–protocol–specified anti–lymphoma therapy to assess potential confounding of the treatment effect estimates by subsequent therapy.
- PFS analyses will be performed with censoring of patients who died more than 6 months after their last tumor assessment and showed no sign of progression (i.e., at the last available tumor assessment).
- A multivariate sensitivity analysis of PFS will be performed using Cox proportional–hazards regression to assess the treatment effect after adjustment for potential prognostic factors.

b. Secondary Efficacy Endpoints

All analyses of secondary efficacy endpoints will be performed for all randomized patients (i.e., overall population) and for the follicular subset of randomized patients (i.e., follicular population), with the exception of PFS, which will be performed for the overall population as a secondary efficacy endpoint (PFS for the follicular population is the primary efficacy endpoint). Patients will be analyzed according to the treatment arm to which they were randomized.

To adjust for multiple statistical testing of the primary and key secondary efficacy endpoints, thereby controlling the overall Type I error rate at a two–sided 0.05 level of significance, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used. These endpoints will be tested in the following order:

- PFS in all randomized patients (i.e., the overall population)
- CR rate at the end of induction therapy in the follicular population of randomized patients (i.e., the follicular population) based on tumor assessment without PET
- CR rate at the end of induction therapy in the overall population based on tumor assessment without PET
- Overall survival in the follicular population
- Overall survival in the overall population
- ORR at the end of induction therapy in the follicular subset of randomized patients (i.e., the follicular population) based on tumor assessment without PET
- ORR at the end of induction therapy in the overall population based on tumor assessment without PET

All analyses will be based on the investigator's assessment. For U.S. registration purposes, the key secondary analyses of PFS, CR rate, and ORR will be based on IRC assessments.

CR rate and ORR (CR or PR) at the end of induction are defined according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007; see Appendix C).

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients who were not reported as having died at the time of the analysis will be censored at the date when they were last known to be alive as documented by the investigator.

EFS is defined as the time from the date of randomization to the date to disease progression/relapse, death from any cause, or start of a NALT. If the specified event (disease progression/relapse, death, start of an NALT) does not occur, patients will be censored at the date of last tumor assessment. For patients who do not have post–baseline tumor assessments or documentation of NALT, EFS will be censored at the time of randomization.

DFS is defined for all patients with a CR as the time from the date the CR was first recorded to the date on which PD was first noted or the date of death from any cause. Patients with no documented disease progression or death after CR will be censored at the last disease assessment date.

BOR is defined as the best response assigned to a patient at any time point during the treatment or follow–up, prior to NALT.

Duration of response is defined for patients with a CR or PR as the time from the date of the initial response (CR or PR) to the date of progression/relapse or death from any cause. For patients achieving a response who have not progressed, relapsed, or died at the time of analysis, duration of response will be censored on the date of last disease assessment.

Time to next anti–lymphoma treatment (TTNLT) is defined as the time from the date of randomization to the start date of the next anti–lymphoma treatment or death from any cause. For patients who have not received the next anti-lymphoma treatment or died at the time of analysis, TTNLT will be censored at the date when the patient was last known to be alive without having received additional anti–lymphoma treatment.

Time–to–event endpoints such as overall survival, EFS, DFS, duration of response, and TTNLT will be analyzed using the same statistical methods described for the primary analysis of PFS (see Section 4.10.3.a). Indolent histology (follicular or non–follicular) will also be included as a stratification factor in the stratified analyses of the overall

population. Formal statistical comparison will not be performed for DFS and duration of response.

Response rates in the treatment groups will be compared using stratified Cochran-Mantel–Haenszel (CMH) tests. Stratification factors are chemotherapy regimen (CHOP, CVP, or bendamustine) and FLIPI risk group (low, intermediate, or high) in follicular lymphoma patients or IPI risk group (low/low–intermediate risk vs. intermediate-high/high risk) in non–follicular lymphoma patients. Indolent histology (follicular or non–follicular) will be included as a stratification factor in the stratified analyses of the overall population. In addition, rates and 95% confidence limits will be reported for each treatment group. The effect of prognostic factors will be assessed in an exploratory analysis with use of logistic regression. Patients with no response assessments (for whatever reason) will be considered non–responders.

Analysis of medical resource utilization data will be provided if required.

4.10.4 Safety Analysis

The safety analysis population will include all patients who receive any amount of study drug (obinutuzumab, rituximab, or chemotherapy [CHOP, CVP, or bendamustine]), and patients will be analyzed according to the treatment received. Key treatment exposure and adverse event tables will also be generated for follicular patients.

Treatment exposure will be summarized, including the number of cycles received by each patient, and the cumulative dose will be summarized by treatment arm.

Verbatim descriptions of adverse events will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms and graded according to NCI CTCAE, Version 4.0. All adverse events occurring during or after the first treatment will be summarized by treatment arm and NCI CTCAE grade. In addition, all serious adverse events will be summarized.

Deaths reported during the study treatment period and those reported after treatment completion/discontinuation will be summarized by treatment arm.

Adverse events leading to early treatment discontinuation and early study withdrawal will be summarized by arm and reason.

Laboratory data with values outside of the normal ranges will be identified. Additionally select laboratory data will be summarized by treatment arm and grade with use of NCI CTCAE. Of note, abnormal laboratory data that are clinically significant will be reported as adverse events and summarized in the adverse event tables.

Vital signs and other physical findings will be summarized by treatment arm.

The incidence of HAHAs will be summarized in patients receiving obinutuzumab.

The incidence of hepatitis B reactivation will be summarized in each arm of the substudy.

4.10.5 Patient–Report Outcomes

Unless otherwise specified, the PRO analyses will include all randomized patients who have a non–missing baseline and at least one post–baseline PRO assessment. Patients in this subset will be analyzed according to their randomized treatment assignment, regardless of treatment received. The analyses will be performed separately in the overall population and in the follicular population.

The percentage of participants randomized to each treatment group who complete the FACT–Lym questionnaire at each specified assessment point after baseline (i.e., PRO completion rates) will be calculated and compared. If significant differences in PRO completion rates are observed, additional analyses may be performed to examine the potential for reporting biases.

For each PRO endpoint, descriptive statistics for recorded values at each visit and changes from baseline will be presented using the PRO analysis set.

The proportion of patients who meet the following criteria (minimum important difference) for response (Carter et al. 2008) will be summarized by visit with use of available data:

- $\geq$6 point improvement in the FACT–Lym TOI
- $\geq$3 point improvement in the FACT–Lym subscale score
- $\geq$7 point improvement in the FACT–Lym total score

Analysis of certain time points will be selected as secondary in nature.

The EQ–5D is a questionnaire with five questions, each with three categories (no problem, moderate problem, severe problems) and a visual analogue scale from 0 (worst possible health state) to 100 (best possible health state). The number and percentage of patients in each of the three categories for each question will be tabulated.

4.10.6 Pharmacokinetic and Pharmacodynamic Analyses

a. Pharmacokinetic Analysis

Individual and mean serum obinutuzumab concentration versus time data will be tabulated and plotted. The serum pharmacokinetics of obinutuzumab will be analyzed as detailed below.

Nonlinear mixed effects modeling (with software NONMEM; Beal et al. 2009) will be used to analyze the obinutuzumab pharmacokinetic data in a subset of patients receiving obinutuzumab. The available pharmacokinetic profile data in patients with indolent NHL will be combined and used to develop a pharmacokinetic model including the effect of major covariates (e.g., sex, race/ethnicity, weight, biochemical and

hematologic parameters at baseline, degree of underlying disease) on the main pharmacokinetic parameters (e.g., total clearance of drug).

Exploratory graphical analyses will be performed to assess whether the occurrence of serious adverse events and abnormalities in the safety laboratory parameters in patients treated with obinutuzumab could be attributed to exposure. Exploratory graphical analysis will as well be performed to assess whether the variability in response could be attributed to the variability in obinutuzumab exposure. Relevant observed relationships between exposure and safety or efficacy parameters may be further characterized using different approaches such as logistic regression analysis and indirect response modeling.

b. Pharmacodynamic Analysis

For each visit at which $CD19^+$ B–cell measurements are taken, the following B-cell data will be listed for individual patients by treatment arm:

- Absolute counts
- Percentage relative to baseline count for the individual
- Extent of $CD19^+$ B–cell depletion (nadir)
- Duration of depletion
- Time to recovery

$CD19^+$ B–cell measurements will be summarized for each visit by the two treatment arms. The parameters summarized will be $CD19^+$ B–cell counts and percentage relative to baseline count, nadir, time to nadir, duration of depletion, and time to recovery.

Exploratory analyses will be performed to assess the possible relationship between the pharmacokinetics of obinutuzumab and B–cell depletion.

Further details of the analysis will be given in the Statistical Analysis Plan.

4.10.7 Exploratory Analyses

Histological transformation rate at first progression is defined as the appearance of diffuse areas of large lymphoma cells within a nodal or extranodal site. For this purpose, a biopsy or a cytological examination should be obtained at progression, if possible. This material should be available for central pathological review. This analysis will be restricted to patients with a biopsy at first progression. The transformation rate at first progression in the treatment groups will be compared using stratified CMH tests. Rates and 95% confidence limits will be estimated for each treatment group.

Conversion rate is defined as the proportion of patients with a PR or SD at the end of induction therapy who convert to a CR or to a PR/CR, respectively, at any time during maintenance therapy or post–induction observation. The conversion rate in

the treatment groups will be compared using stratified CMH tests. Rates and 95% confidence limits will be estimated for each treatment group.

Selected exploratory analysis for the MZL cohort will be performed.

The potential association between FcγR genotype, response category, MRD qualitative status (negative or positive), and PFS will be assessed using Kaplan-Meier curves and stratified log–rank tests. Response rates by FcγR genotype and MRD negativity status will be compared using χ^2 tests and logistic regression. In addition, FcγR genotype and MRD negative status will be included in multivariate analyses of PFS and response rates as described in Sections 4.10.3.a and 4.10.3.b. Additional details of the exploratory analyses will be provided in the Statistical Analysis Plan.

Biomarker data such as gene expression analysis will not be fully available at the time of the final analyses, and the analyses may not be included in the clinical study report.

4.10.8 Handling of Missing Data

For PFS, patients who do not have documented disease progression or death will be treated as censored observations on the date of the last tumor assessment.

For overall survival, patients who do not have documented deaths will be censored on the last date they were known to be alive.

For response endpoints, patients with no response assessments (for whatever reason) will be considered non-responders.

4.10.9 Determination of Sample Size

Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Two–sided log–rank test at the 0.05 level of significance
- Powered for follicular lymphoma patient subset
- Eighty percent power to detect a hazard ratio for G–Chemo versus R–Chemo of 0.74, corresponding to an improvement in 3–year PFS from 70.7% to 77.4% or in median PFS from 6 years to 8.1 years (35%)

  Note that estimates of median PFS are not likely to be reached in either study arm.
- Exponential distribution of PFS
- An annual dropout rate of 2.5%

- Performance of interim analyses on PFS: one for futility when approximately 30% of the total (investigator–assessed) PFS events have occurred and one for efficacy when approximately 67% of the total PFS events have occurred. Efficacy and (nonbinding) futility boundaries will be computed using the Lan–DeMets approximation to the O'Brien-Fleming boundary shape.

  The futility boundary will be nonbinding.

In addition, a futility analysis based on CR rates at the end of induction determined by CT (or MRI, but not PET) will be performed on the first 170 follicular lymphoma patients randomized. With these assumptions, 370 PFS events are required to achieve 80% power for the primary analysis. Recruitment will be staggered in order to recruit the first 170 patients in a smaller number of sites (approximately 125 sites), followed by the activation of all (approximately 200–250) sites after the IDMC meeting for futility based on CR rates. It is expected that during the first stage, after a 6–month ramp up, 18 patients per month will be recruited, and after the IDMC meeting and another 4-month ramp up, an accrual rate of 37 patients per month is expected. The 1200 follicular patients enrolled over 49 months and followed for an additional 29 months will be required to provide 370 PFS events, with a total duration for PFS follow–up of approximately 78 months (6.5 years).

Approximately 200 additional patients with non–follicular lymphoma will be enrolled. This number was based on a study of enrollment feasibility, which indicated that 200 patients would likely be enrolled in 49 months, in addition to the planned follicular enrollment. Although the study would not be powered to detect statistically significant differences in this 200–patient cohort, there would be a reasonable chance of detecting a trend.

The pharmacokinetic assessments will apply to a subpopulation of approximately 460 patients receiving obinutuzumab. This is the minimum number of patients needed to accurately construct a population pharmacokinetic model and will allow for the evaluation of the relationship between exposure and pharmacodynamic markers of response. Approximately 120 follicular patients will undergo pharmacokinetic sampling from each of the three chemotherapy groups (G–CHOP, G–CVP, and G-bendamustine), and 100 additional patients with non–follicular lymphoma will also undergo sampling. This sample size is believed to be sufficient to characterize with confidence the pharmacokinetics of obinutuzumab in the target population as well as the relationships between exposure to obinutuzumab and response. The pharmacokinetic sampling schedule in this study was determined using an optimal sampling strategy with the software PFIM (Bazzoli et al. 2010) and should result in a precision of parameter estimates lower than 20% for the main pharmacokinetic parameters.

In addition to the determination of T, B, and NK cells that are determined in all patients, absolute and relative B cell subsets determined by multicolor flow cytometry (FACS) based on a combination of several CD antigens and immunoglobulins over time will also

be analyzed in approximately 60 patients of each therapeutic group (R–CHOP, G–CHOP, R-CVP, G–CVP, R–bendamustine, G–bendamustine) as well as in all patients with splenic MZL. Because of the exploratory nature of this assessment and its complementary information to the determination of T, B, and NK cells, this sample size is arbitrary, but it is estimated to provide sufficient data for generation of a first hypothesis.

BCL2/IgH (MRD) analysis is exploratory in nature and currently it is not known what difference in MRD negativity between R– and G–chemotherapy is to be expected. In order to generate a first comprehensive data set and since the difference between R- and G–chemotherapy may be small, MRD assessment will be done in all patients with follicular lymphoma.

4.10.10 Interim and Final Analyses

Although the study is open label, Sponsor personnel will not have access to by-arm efficacy and safety summaries prior to the formal reporting of study results. In order to monitor safety, Sponsor drug safety and medical monitoring staff will have access to the treatment assignments of particular patients.

An IDMC will evaluate interim analysis results and determine whether the trial will be stopped early. All summaries and analyses by treatment arm for the IDMC review will be prepared by an IDCC. Members of the IDMC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities.

The interim safety monitoring plan is described in Section 3.4. Three interim analyses are planned: two for futility and one for efficacy. The first interim analysis will be based on differences in end of induction CR rates in the first 170 enrolled follicular lymphoma patients. The analysis will be conducted once the 170 follicular lymphoma patients have reached their end–of–induction response assessment or have withdrawn prematurely. The IDMC may recommend to stop the study for futility if the observed difference in CR rate based on CT (or MRI, but not PET) is $<3\%$ in favor of G-Chemo (i.e., CR rate needs to be $\geq 3\%$ higher on G–Chemo vs. R-Chemo).

The second interim analysis (futility on PFS) will be conducted when 30% of the required PFS events (i.e., approximately 111 events) will have occurred. The IDMC may recommend to stop the study for futility if the observed hazard ratio of obinutuzumab over rituximab is >1 (futility boundary based on nonbinding O´Brien–Fleming beta–spending function).

At the time of the third interim analysis (efficacy on PFS) that will be conducted when 67% of the events have occurred (i.e., approximately 248 events), all patients will have been enrolled and followed for an estimated minimum of 11 months. PFS will be tested at the significance level determined using the O´Brien–Fleming alpha–spending function so the overall Type I error rate will be maintained at the 0.05 level. With 67% information, the alpha spending is 0.012.

The IDMC will also review safety summaries at each of the interim analyses, in addition to the ongoing periodic safety monitoring.

In the event that the follicular lymphoma population accrues but the non–follicular lymphoma population fails to accrue the planned number of patients, the analyses will be triggered by the PFS events in the follicular subset regardless of when the non–follicular lymphoma population has completed enrollment.

Further details of the interim analyses will be described in the IDMC charter and Statistical Analysis Plan.

4.11 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this trial, including quality checking of the data. The data will be collected via EDC through use of eCRFs. The site will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system. The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Data from the central laboratory or IRC will be sent directly to the Sponsor, with use of the Sponsor's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored with the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol–defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology and clinical chemistry variables; measurement of protocol–specified vital signs; and other protocol–specified tests that are deemed critical to the safety evaluation of the study drug(s).

The Sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central Institutional Review Boards

(IRBs) or Ethics Committees (ECs) (except in countries where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of obinutuzumab. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events and no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events. The PRO data will be presented in separate tables, figures, and data listings from the adverse event data and will be included in the appropriate section of the final study report, as indicated in the statistical analysis plan.

5.1.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an IMP or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with NHL progression that were not present prior to the AE reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol–mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., invasive procedures such as biopsies, medication washout, or no treatment run–in).
- Preexisting medical conditions (other than NHL), judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 Serious Adverse Event

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)

- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

5.1.3 Protocol–Defined Events of Special Interest/Non-Serious Expedited Adverse Events

The following adverse events of special interest will need to be reported to the Sponsor expeditiously (see Section 5.4 for reporting instructions):

- Tumor lysis syndrome (irrespective of regulatory seriousness criteria)
- Serious IRR
- Serious neutropenia
- Serious infections
- Second malignancies

Hepatitis B reactivation will be followed as an AE of particular interest.

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol–mandated intervention will be recorded (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run–in).

After the initiation of study medications (Sponsor product or other IMP/Non–IMP), AEs and SAEs should be recorded as follows (unless patient begins NALT):

- All AEs (related and unrelated) will be recorded up to 28 days after the last dose of study drug.
- Grade ≥3 AEs (related and unrelated) will be recorded up to 6 months after the last dose of study drug.
- Grade 3 or 4 infections (related and unrelated) will be recorded up to 24 months after the last dose of study drug.
- Unrelated SAEs will be recorded up to 12 months after the last dose of study drug.

After the initiation of study medications (Sponsor product or other IMP/Non–IMP), AEs and SAEs should be recorded indefinitely:

- Study drug-related SAEs (even if the study has been closed).
- Second malignancies (even if study has been closed)

5.2.2 Eliciting Adverse Events

A consistent methodology of non–directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non–directive questions include:

> "How have you felt since your last clinic visit?"
>
> "Have you had any new or changed health problems since you were last here?"

5.2.3 Assessment of Severity and Causality of Adverse Events

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity, and causality.

Table 15 provides guidance for grading AE severity and Table 16 provides guidance for assessing the causal relationship to the investigational products.

The AE grading (severity) scale found in the NCI CTCAE (Version 4.0) will be used for AE reporting.

Table 15 Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event–specific NCI CTCAE grading criteria)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate (apply event-specific NCI CTCAE grading criteria)	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate IADLs [b]
3	Severe (apply event–specific NCI CTCAE grading criteria)	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs [c]
4	Life threatening	Life–threatening consequences; urgent intervention indicated
5	Death related to AE	

ADLs = activities of daily living; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IADLs = instrumental activities of daily living; NCI = National Cancer Institute.

The NCI CTCAE (Version 4.0) is available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 5.1.2).

[a] Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI CTCAE listing.

[b] ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[c] Self–care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Table 16 Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product on the basis of facts, evidence, science–based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions, or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the AE/SAE.

Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

a. Diagnosis/Causative Event versus Signs and Symptoms

All AEs and SAEs should be reported.

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single syndrome at the time of reporting, each individual sign and/or symptom should be recorded as an AE or SAE on the eCRF. If a constellation of signs and/or symptoms can be medically characterized as a single syndrome (e.g., nausea and vomiting), the most medically significant sign and/or symptom should be reported as the adverse event and the additional signs and/or symptoms captured in the additional case details section of the eCRF. If a diagnosis is subsequently established, the reported event term should be updated to reflect the medical diagnosis.

In general, AEs occurring secondary to other events (e.g., cascade of events or clinical sequelae) should be identified by their primary cause (causative event) and the additional sequelae captured in the additional case details section of the eCRF. However, AEs occurring secondary to an initiating event that are separated in time or medically significant should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to a renal failure, both events should be recorded separately on the eCRF.

Reporting of Infusion–Related Reactions:

Within this protocol, the Sponsor is using the following definition to identify adverse events which qualify as potential IRR:

> A potential IRR = all adverse events occurring during or within 24 hours from the end of antibody infusion that are judged as related to the antibody by the investigator.

The only exception to the rule that the diagnosis is the preferred term for AE reporting is the reporting of IRRs. For reporting purposes only (but not for clinical decision making), the adverse event containing the diagnosis IRR and all signs and symptoms that fall under the sponsor definition of a potential IRR (e.g., fever, hypotension) have to be reported as separate adverse events.

Each single infusion of antibody could lead to an IRR, therefore a separate IRR and signs and symptoms should be reported for each administration.

b. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should be recorded only once in the eCRF, and their initial grade and their most severe grade should be given on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded as separate AEs on Adverse Event eCRF.

c. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF. Criteria for clinical significance are the following:

- Laboratory abnormality is accompanied by clinical symptoms.
- Laboratory abnormality requires study drug dose modification or interruption or permanent discontinuation of study treatment.
- Laboratory abnormality requires more frequent follow–up assessments, further diagnostic investigation, etc.
- Laboratory abnormality requires a change in concomitant medication, therapy, or treatment.

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

d. Deaths

For this protocol, PFS is the primary efficacy endpoint. Deaths that occur during the protocol–specified AE reporting period (see Section 5.2.1) that are attributed by the investigator solely to progression of NHL will be recorded only on the Study Discontinuation eCRF. All other on-study deaths, regardless of attribution, will be recorded on an eCRF and expeditiously reported to the Sponsor. An IDMC will monitor the frequency of death from all causes.

When recording a death on an eCRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the eCRF.

During post–study survival follow–up, deaths attributed to progression of NHL will be recorded only on the Survival eCRF (i.e., not on the Adverse Event eCRF).

e. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical and Surgical History eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

f. Progression of Non–Hodgkin's Lymphoma

Progression of NHL should not be recorded as an AE or SAE if it is clearly consistent with the suspected progression of the underlying cancer as defined by the criteria as determined by protocol. These data will be captured as efficacy assessment data only.

Hospitalization due solely to the progression of underlying NHL should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively because of the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient’s clinical symptoms but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a

rare exception because every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

g. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. All hospitalizations (any overnight stay in an acute care hospital) should also be documented in the Medical Resource Use Form along with the admission and discharge dates.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

h. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 1 year after the last dose of investigational product or if the partner of a male patient becomes pregnant while receiving investigational therapy or within 3 months after the last dose of investigational product and paternity can be assured, a Pregnancy Report eCRF should be completed within 24 hours of learning of the pregnancy. The EDC system will generate an automatic PDF report that is delivered to the Sponsor. If the EDC is not accessible, the paper forms will have to be filled out, printed and faxed to the Sponsor, with use of the fax numbers listed in Section 5.4.2. When the EDC is available again, the investigator will have to enter the data again in the eCRF.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (because the Sponsor considers these medically significant), recorded on an eCRF, and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND PROTOCOL–DEFINED EVENTS OF SPECIAL INTEREST

5.4.1 Reporting Requirements for Fatal/Life–Threatening SAEs Related to Investigational Product

Any life–threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an eCRF within 24 hours as described herein.

Medical Monitor contact information will be distributed to sites.

An emergency medical call center help desk will access the Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with the Roche/Genentech medical contact for this study, and track all calls. The emergency medical call center help desk will be manned 24 hours a day, 7 days a week. Toll–free numbers will be distributed to all investigators running Roche Product Development clinical trials. The help desk will be used for medical emergencies that occur outside regular business hours or when the Medical Monitor cannot be reached.

5.4.2 Reporting Requirements for All SAEs and Protocol–Defined Events of Special Interest

Investigators will submit reports of all SAEs, regardless of attribution, and all protocol-defined events of special interest and pregnancies to the Sponsor within 24 hours after learning of the events. For initial SAE and protocol–defined events of special interest reports, investigators should record all case details that can be gathered within 24 hours on an eCRF and submit the report via the EDC system. A report will be generated and sent to the Sponsor's Drug Safety Department by the EDC system. In the event the EDC system is unavailable, a completed SAE or Serious/Non–Serious Expedited Adverse Event paper reporting form and fax coversheet should be faxed immediately upon completion to the Sponsor's Drug Safety Department or its designee at the fax numbers indicated below. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Sites in the United States:

Fax No.:	(650) 225-4682
Alternate Fax No.:	(650) 225-5288

For ex–U.S. sites: Country–specific contact information will be supplied to sites.

Relevant follow–up information should be submitted to the Sponsor's Drug Safety Department or its designee as soon as it becomes available and/or upon request.

Related SAEs **must** be collected and reported regardless of the time that has elapsed from the last study drug administration, even if the study has been closed. Suspected unexpected serious adverse reactions (SUSARs) are reported to investigators at each site and associated IRB/EC when the following conditions occur:

- The event must be an SAE.
- There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
- The adverse reaction must be unexpected, that is to say not foreseen in the Summary of Product Characteristics (for an authorized medicinal product) or the Investigator's Brochure (for an unauthorized medicinal product).

When all patients at a particular site are off treatment as defined by the protocol:

- Only individual SUSAR (suspected unexpected serious adverse reaction) reports originating in that particular trial will be forwarded to the site and associated IRB/EC on an expedited basis.
- Individual SUSARs considered to be a significant safety issue and/or which result in the Sponsor recommending a change to the Informed Consent Form will be reported in an expedited manner to all investigators and IRBs/ECs.
- SUSAR reports originating from other trials using the same IMP will be provided every 6 months to investigators and IRBs/ECs conducting long-term follow–up studies (with the exception of significant SUSARs, which will be reported in an expedited manner).

5.5 TYPE AND DURATION OF FOLLOW–UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST–STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if believed to

be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to the Sponsor's Drug Safety Department on the study eCRF. If the study eCRF is no longer available, the investigator should report the event directly to the Sponsor's Drug Safety Department via phone at (888) 835–2555.

5.7 *EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES*

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	*Document*
Obinutuzumab	*Obinutuzumab Oncology Investigator's Brochure*
Rituximab	*Mabthera Summary of Product Characteristics*
Bendamustine	*Levact Summary of Product Characteristics*

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study–related procedures at a specific site, the following documents must be on file with the Sponsor:

- Statement of investigator signed by the Principal Investigator

  The names of any subinvestigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae and evidence of licensure of the Principal Investigator and all subinvestigators
- Complete financial disclosure forms for the Principal Investigator and all subinvestigators

- Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

  The Sponsor or its designee must review any proposed deviations from the sample Informed Consent Form.
- Current laboratory certification of the laboratory performing the analysis (if other than a Sponsor-approved central laboratory), as well as current reference ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator's Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB/EC approval letters, and pertinent correspondence
- PD01 Form signed and dated by the Principal Investigator
- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study
- For global studies, a list of required documents will be provided to you by your local site monitor.

6.2 STUDY COMPLETION

The following data and materials are required by the Sponsor before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (if other than Sponsor–approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and subinvestigator, statement of compliance with local laws and regulations)
- A signed and dated Protocol Amendment Acceptance Form(s) (PD01) [if applicable]

- Updated financial disclosure forms for the Principal Investigator and all subinvestigators (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORMS

The Sponsor's Sample Informed Consent Form will be provided to each site. The Sponsor or its designee must review and approve any proposed deviations from the Sample Informed Consent Form or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for regulatory purposes.

The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC–approved Informed Consent Form must be provided to the Sponsor for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act regulations, the review, approval, and other processes outlined above apply except that IRB/EC review and approval may not be required per study site policies.

6.3.1 Pregnant Partner Consent

Partner consent will be requested if applicable.

6.3.2 Roche Clinical Repository Informed Consent

It is the responsibility of the investigator or a person designated by the investigator (if acceptable under local regulations) to obtain written informed consent from each individual who has consented to have his or her samples stored for future research in the RCR after adequate explanation of the aims, methods, objectives, and potential hazards. Patients must receive an explanation that they are completely free to refuse collection of their samples for future research and may withdraw their samples at any time and for any reason during the 15–year storage period of the specimens. The informed consent for an optional specimen donation will be incorporated as a specific section into the main Informed Consent Form. A second, separate, specific signature consenting to specimen donation will be required to document the study participant's agreement to collection of his or her samples for future research; if the participant declines, he or she will check a "no" box in the appropriate section and not provide a second signature.

The eCRF for the associated clinical study contains a page for documenting patient informed consent to the RCR, and this must be completed appropriately.

6.4 DEATH OR LOSS OF COMPETENCE OF PARTICIPANT WHO HAS DONATED A SPECIMEN THAT IS STORED IN THE ROCHE CLINICAL REPOSITORY

In case the Informed Consent Form and/or the study protocol do not provide any specific provisions for death or loss of competence, specimen and data will continue to be used as part of RCR research.

6.5 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator (or by the Sponsor on behalf of the Principal Investigator, if specified by local legislation) for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol–defined AEs to the Sponsor, investigators are required to **promptly** report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written Investigational New Drug (IND) safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's study file.

Sampling for the RCR is contingent on review and approval for the optional exploratory biomarker assessments and written informed consent by an appropriate regulatory body (depending on the country where the study is performed) and a site's IRB/EC. If a regulatory authority or site's IRB/EC does not approve the sampling for the optional exploratory assessments, the section on optional biomarker sampling will not be applicable.

6.6 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized representative to inspect study data, patients' medical records, and eCRFs. The Principal Investigator will permit the Sponsor's monitors/representatives and collaborators, the U.S. FDA, other regulatory agencies, IRBs, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.7 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Medidata (RAVE) EDC system. Sites will receive training and a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

6.8 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, patient–completed PRO questionnaires, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

6.9 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that 1) allows data entry only by authorized individuals; 2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); 3) protects the database from tampering; and 4) ensures data preservation.

In collaboration with the study monitor, the Sponsor's Quality Assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.10 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by the Sponsor. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

The Sponsor must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

6.11 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, the Sponsor's monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.12 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor for transfer of any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

6.13 FINANCIAL DISCLOSURE

The investigator will provide the Sponsor with sufficient accurate financial information (e.g., PD35 in the United States) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

7. CLINICAL STUDY REPORT

A clinical study report will be written and distributed to health authorities as required by applicable regulatory requirements.

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APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles)

	Screening		Treatment Period										Induction Completion /ET Visit [a]
	SD −35	SD −14	C1, D1 (SD1)	C1, D8 (SD8)	C1, D15 (SD15)	C2, D1 (SD22)	C3, D1 (SD43)	C4, D1 (SD64)	C5, D1 (SD85)	C6, D1 (SD106)	C7, D1 (SD127)	C8, D1 (SD148)	
Informed consent	x												
Optional RCR informed consent	x												
Discussion of fertility issues and sperm banking (in patients of childbearing age)	x												
Inclusion/exclusion criteria	x												
Tumor tissue sample for quality assurance pathology review [b]	x												
Demographics and medical history [c]	x		x										
FLIPI prognostic risk: follicular patients	x												
FLIPI2 prognostic risk: follicular patients	x												
IPI score: non–follicular patients	x												
Complete physical examination [d]	x												
Targeted physical examination [d]			x			x	x	x	x	x	x	x	x

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

	Screening		Treatment Period										Induction Completion /ET Visit [a]
	SD –35	SD –14	C1, D1 (SD1)	C1, D8 (SD8)	C1, D15 (SD15)	C2, D1 (SD22)	C3, D1 (SD43)	C4, D1 (SD64)	C5, D1 (SD85)	C6, D1 (SD106)	C7, D1 (SD127)	C8, D1 (SD148)	
Height, weight, BSA [e]	x		x			x	x	x	x	x	x	x	x
Vital signs [f]	x		x	x	x	x	x	x	x	x	x	x	x
IADLs/ADLs		x											
ECOG Performance Status	x					x	x	x	x	x	x	x	x
B symptoms	x								x				x
12–lead ECG	x												x
Left heart ejection fraction (2D–ECHO or MUGA scan)	x [g]												x
Hematology [h]		x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry [h]		x	x			x	x	x	x	x	x	x	x
Urine dipstick for protein [i]		x											x
Serum electrophoresis, M protein, and immunofixation (only in patients with MZL) [j]		x							x				x
Coagulation (PTT or aPTT, PT or INR)		x											
Pregnancy test [k]		x											x
HBV, HCV, and HTLV–1 serology [l]	x												
HBV DNA PCR [m]		(x)				(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
CHOP chemotherapy [n]			x			x	x	x	x	x			
Arm A: rituximab infusion [o]			x			x	x	x	x	x	x	x	

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

	Screening		Treatment Period										Induction Completion /ET Visit [a]
	SD −35	SD −14	C1, D1 (SD1)	C1, D8 (SD8)	C1, D15 (SD15)	C2, D1 (SD22)	C3, D1 (SD43)	C4, D1 (SD64)	C5, D1 (SD85)	C6, D1 (SD106)	C7, D1 (SD127)	C8, D1 (SD148)	
Arm B: obinutuzumab infusion [p]			x	x [q]	x [q]	x	x	x	x	x	x	x	
New anti–lymphoma treatment [ff]													x
Imaging–based tumor assessment [r]	x								x				x
FDG–PET [s]	x								(x)				x
Bone marrow biopsy [t]		x											x
Bone marrow aspirate for *BCL2/IgH* analysis: follicular patients [u]		x											x
FcγR typing [v]			x										
Blood for *BCL2/IgH* analysis: follicular patients [w]		x							x				x
HAHA samples: obinutuzumab arm only [x,q]		x											x
PK sampling: subset in obinutuzumab arm [q,y]			x	x	x	x		x		x			x
Leukocyte immunophenotyping (FACS) [z]		x				x			x				x
Quantitative immunoglobulins (IgA, IgG, IgM)		x											x
Optional serum and plasma samples for RCR [aa]		(x)											

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

	Screening		Treatment Period										Induction Completion /ET Visit [a]
	SD −35	SD −14	C1, D1 (SD1)	C1, D8 (SD8)	C1, D15 (SD15)	C2, D1 (SD22)	C3, D1 (SD43)	C4, D1 (SD64)	C5, D1 (SD85)	C6, D1 (SD106)	C7, D1 (SD127)	C8, D1 (SD148)	
Tumor tissue sample at time of relapse or transformation				(x) [bb]									
Adverse events [cc]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [dd]	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires [ee]			x				x						x

ADLs = Activities of Daily Living; AE = adverse event; aPTT = activated partial thromboplastin time; BSA = body surface area; BUN = blood urea nitrogen; C = Cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone (prednisolone or methylprednisolone [MP]); CR = complete response; CT = computed tomography; CVP = cyclophosphamide, vincristine, and prednisone (prednisolone, MP); D = Day; 2D-ECHO = two–dimensional echocardiogram; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EDTA = ethylenediaminetetraacetic acid; EOI = end of infusion; EQ–5D = European Quality of Life (EuroQol) Questionnaire; ET = early termination; FACS = fluorescence–activated cell sorter; FACT-Lym = Functional Assessment of Cancer Therapy for Lymphoma; FDG = ^{18}F-fluorodeoxyglucose; FLIPI = Follicular Lymphoma International Prognostic Index; G = GA101; HAHA = human anti–human antibody; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV = human T-lymphotropic virus; IADLs = Instrumental Activities of Daily Living; INR = international normalized ratio; IPI = International Prognostic Index; IV = intravenous; LDH = lactate dehydrogenase; MRD = minimum residual disease; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; MZL = marginal zone lymphoma; NK = natural killer cells; PCR = polymerase chain reaction; PET = positron emission tomography; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; R = rituximab; RBC = red blood cell; RCR = Roche Clinical Repository; SAE = serious adverse event; SD = Study Day; WBC = white blood cell.

Notes: **On treatment days, all assessments should be performed prior to dosing unless otherwise noted.**

The Cycle 1 Day 1 visit should be scheduled to allow subsequent visits to occur without delay. Study visits during induction treatment should occur on the scheduled day ± 4 days), with the exception of delays resulting from toxicities. Visits on Days 8 and 15 of C1 are optional for patients in the rituximab arm and are done if standard of care at the site. Visits on D15 of C2–8 are optional for all patients and are done if standard of care at the site.

(x) = conditional/optional; refer to footnote for details.

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[a] Induction completion should occur within 6–8 weeks after C8D1 (i.e., SD190–SD204). An early termination visit should occur within 4–8 weeks after last dose (in case of early termination due to adverse event) or within 2–8 weeks after last dose (in case of early termination due to clinical disease progression). In case of withdrawal from treatment due to toxicity, the first follow–up visit is scheduled 3 months (± 14 days) after last dose ("Month 27"; see Appendix A-5).

[b] A tissue sample is required for retrospective central confirmation of diagnosis and CD20 positivity of lymphoma and should be dated from within 12 months prior to study entry. Tissue samples dated > 12 months prior to study entry can be accepted only if tissue material is available for retrospective confirmation, if there is no clinical indication for transformation of disease, and if the request for additional biopsy would be unethical treatment of the patient. Bone marrow alone is not suited to make the diagnosis of follicular lymphoma. In patients with splenic MZL without splenic tissue available for histologic review, the bone marrow must be submitted for retrospective central confirmation. All tissue samples should be sent for quality assurance pathology review within 4 months after randomization. A formalin–fixed paraffin–embedded tissue sample is preferred over 15–20 sections (3–5–μm thickness) on coated slides. If the tissue sample is small, fewer sections (minimum within range of 6–12) can be accepted. Remainders of the tissue blocks will be returned to local pathology in accordance with local regulations.

[c] At screening, obtain demographic data and complete medical history. On Cycle 1 Day 1, obtain medical history since the screening visit.

[d] Complete physical examination includes all systems described in Section 4.5.1.a, including assessment of lymph nodes, hepatomegaly, and splenomegaly. The targeted physical examination should include only systems of most clinical relevance (i.e., cardiovascular, respiratory, those associated with clinical signs/symptoms, and lymph nodes, liver, and spleen).

[e] Height is measured at screening only. It is recommended that the DuBois BSA formula be used; however, BSA may be calculated using the investigator's preferred formula.

[f] Includes blood pressure, pulse rate, and temperature. On rituximab or obinutuzumab treatment days, vital signs should be measured prior to the infusion, then approximately every 15 minutes for 90 minutes, approximately every 30 minutes until the end of the infusion, and approximately every 60 minutes until the infusion line is removed.

[g] Performed at screening if not performed within 6 months prior to screening.

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[h] Samples should be drawn within 72 hours prior to the study drug infusion on treatment days. Hematology includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and absolute neutrophil count as routine components. Percent or absolute differential count (segmented neutrophils, banded neutrophils, eosinophils, lymphocytes, monocytes, basophils, malignant lymphocytes) are done if clinically indicated (e.g., for differential diagnosis of any kind of clinically relevant cytopenia/cytophilia or, e.g., if other undefined cells are present in the peripheral blood). In case of splenic MZL, the percent or absolute number of malignant lymphocytes ("villous lymphocytes") in peripheral blood should be assessed. Additional samples for hematology can be drawn according to the standard of care at the site. Serum chemistry includes sodium, potassium, chloride, bicarbonate (if clinically indicated), BUN, uric acid, serum creatinine, calcium, total bilirubin, total protein, albumin, phosphorus, ALT and AST, alkaline phosphatase, creatinine clearance, LDH, and β_2 microglobulin (creatinine clearance and β_2 microglobulin required only at screening). Visits on D8 and D15 of C1 are optional for hematology and serum chemistry for patients in the rituximab arm and for chemistry for patients in the obinutuzumab arm and are done if standard of care at the site. Visits on D15 of C2–8 are optional for all patients and are done if standard of care at the site. Values of serum chemistry/hematology from these optional visits may be obtained from local laboratories and should be entered into the eCRF if these visits took place.

[i] In a fresh sample of midstream urine, a dipstick testing for proteinuria is required.

[j] Serum electrophoresis is required in all patients with MZL and should report percentage of albumin, alpha 1, alpha 2, beta, and gamma fraction, as well absence/presence of an M protein. If an M protein is present, it should be quantified in g/L and the Ig subtype (IgG, IgA, IgM, IgD, light–chain kappa, or light–chain lambda) determined by immunofixation. If no M protein is found at baseline, serum electrophoresis and immunofixation do not need to be repeated at later time points.

[k] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits and may be performed more frequently if required by local legislation. If a urine pregnancy test result is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

[l] HBsAg, HBcAb, and HCV antibody serology required for all patients. HCV RNA required for patients who are HCV antibody positive. HTLV required for patients from endemic countries (Japan, the Caribbean basin, South America, sub–Saharan Africa, and Melanesia). Additional serology for HBsAb required prior to Cycle 1 Day 1 for patients who are HBsAg negative and HBcAb positive at screening.

[m] For patients who are HBsAg negative and HBcAb positive at screening only. HBV DNA levels will be measured centrally by real–time PCR with use of an assay with a limit of quanitification of at least 29 IU/mL.

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[n] CHOP consists of cyclophosphamide 750 mg/m^2 IV on Day 1 of each cycle, doxorubicin 50 mg/m^2 IV on Day 1 of each cycle, vincristine 1.4 mg/m^2 IV (maximum 2 mg) on Day 1 of each cycle, and prednisone (prednisolone) 100 mg (or methylprednisolone [MP] 80 mg in countries/sites without availability of prednisone or prednisolone) orally on Days 1–5 of each cycle. When rituximab or obinutuzumab is administered on the same day as prednisone (prednisolone, MP), it is recommended that prednisone (prednisolone, MP) be given prior to the rituximab or obinutuzumab infusion. The order of administration of cyclophosphamide, doxorubicin, and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after rituximab or obinutuzumab. Dosage calculations for chemotherapy should be based on the patient's BSA. Empiric dose adjustment in obese patients (defined as a body mass index $\geq$ 30, as measured in kg/m^2) is not recommended, but may be implemented if required by institutional guidelines. There will be no dose modification for changes in patients' weight unless the weight increases or decreases by $>$ 10% from weight at screening. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments.

[o] Rituximab 375 mg/m^2 will be administered by IV infusion. Rituximab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride (unless contraindicated) and allopurinol (for patients with high tumor burden, if pretreatment with allopurinol is deemed appropriate). When given on the same day as CHOP chemotherapy, rituximab should be administered after prednisone (prednisolone, MP) but at least 30 minutes prior to cyclophosphamide, doxorubicin, and vincristine.

[p] Obinutuzumab 1000 mg will be administered by IV infusion. Obinutuzumab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride (unless contraindicated), and allopurinol (for patients with high tumor burden, if pretreatment with allopurinol is deemed appropriate). When given on the same day as CHOP chemotherapy, obinutuzumab should be administered after prednisone (prednisolone, MP) but at least 30 minutes prior to cyclophosphamide, doxorubicin, and vincristine.

[q] Patients receiving obinutuzumab only.

[r] Imaging–based tumor assessment: At screening, CT scan (with contrast) of the chest, abdomen, pelvis (and neck, if clinically indicated) should be done within 35 days prior to randomization. CT scans for response assessment should be done within 14 days prior to C5D1 and at the induction completion/early termination visit and may be limited to areas of prior involvement if required by local regulatory authorities. Any time the investigator suspects disease progression, a full tumor assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities). MRIs with a non-contrast CT scan of the chest may be used for patients for whom CT scans with contrast are contraindicated. If MRI is used at screening, then MRI should be used throughout the study (same method during the entire study). Combined FDG–PET/CT scans may be used only if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. Measurement of lymphoma lesions by ultrasound is not the preferred option because of the inherent interexaminer variability. However, in patients with splenic MZL, the spleen is considered a target lesion, and its size should be determined by ultrasound (length and thickness), CT/MRI, or by physical examination. For ultrasound/CT/MRI or physical examination measurements, local guidelines for determining normal organ size are acceptable.

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[s] FDG–PET is mandatory in the first 170 patients with follicular lymphoma at screening and at induction completion/ET (only if the result of the screening PET was positive) at all sites where a scanner is available. This may require specific approval in some countries. In such instances, PET becomes mandatory only after necessary approvals have been obtained. In the overall population, PET remains optional and at the investigator's discretion. If done, screening PET should be performed within 35 days prior to randomization. Within 14 days prior to C5D1, PET is optional and may be done at the investigator's discretion. At induction completion/ET, PET should be obtained within 6–8 weeks after C8D1 (i.e., SD190–SD204). An ET visit PET should occur within 4–8 weeks after last dose (in case of ET due to adverse event) or within 2–8 weeks after last dose (in case of ET due to clinical disease progression). The diagnosis of disease progression should not be based on PET alone but should always be confirmed by CT (MRI) imaging. PET results should not be used to make treatment decisions.

[t] A bone marrow biopsy (trephine) biopsy examination for local pathology must be performed at screening unless it was performed within 3 months prior to Cycle 1 Day 1. If positive at screening (i.e., showing infiltration by lymphoma), a subsequent bone marrow biopsy is required at the induction completion visit for patients who achieve a CR. In patients with continued bone marrow involvement or in patients with PR due to other reasons at EOI, a subsequent bone marrow biopsy may be required to confirm a CR at a later time point (e.g., during maintenance/observation). Any additional (unscheduled) bone marrow biopsies performed during the study will be at the discretion of the investigator.

[u] A bone marrow aspirate for central minimum residual disease assessment by PCR detection of *BCL2/IgH* rearrangement is performed in all patients with follicular lymphoma at screening. If the patient already had a diagnostic bone marrow biopsy without an aspirate within 3 months prior to Cycle 1 Day 1 before screening, it is still mandatory to perform the bone marrow aspirate for MRD assessment at screening, but the biopsy for pathology itself does not have to be repeated (see footnote t). At the induction completion/ET visit, a bone marrow aspirate sample is mandatory in responders (CR + PR) in whom bone marrow involvement was diagnosed by morphology at screening and is optional but strongly recommended in responders (CR + PR) in whom no bone marrow involvement was diagnosed by morphology at screening.
The recommendation is based on the observation that, at screening, bone marrow involvement is detectable on the level of minimal residual disease in the large majority of patients even if it appears to be negative by morphology. For each bone marrow aspirate performed on a patient, 4 mL of an EDTA-anticoagulated bone marrow aspirate is requested.

[v] A 3 mL blood sample will be taken for determination of FcγRIIIa, FcγRIIa, and FcγRIIb/IIc polymorphisms. Only patients who have successfully passed screening and are fully eligible for the study should have this sample taken.

[w] For follicular lymphoma patients only, a 9.5 mL EDTA blood sample will be taken for the analysis of clonal *BCL2/IgH* rearrangement (as a potential marker of tumor burden) at screening, before C5D1, and at induction completion/ET in all patients.

[x] A 5 mL blood sample will be taken for HAHA analysis in all patients receiving obinutuzumab (Arm B) before first administration of G–CHOP (baseline sample) and at induction completion/ET visit.

[y] Peak and trough PK samples for obinutuzumab levels should be drawn in a subset of approximately 460 patients receiving obinutuzumab (Arm B), per the schedule in Appendix B. All PK samples will be collected from the arm opposite to that receiving the infusion.

APPENDIX A–1
Study Flowchart: Induction Treatment with CHOP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[z] A 5 mL blood sample will be taken for the assessment of B cells, T cells, neutrophils, and NK cells in all patients (TBNK panel). This will include determination of relative and absolute numbers of $CD3^+$, $CD4^+$ $CD8^+$, $CD19^+$, and $CD56^+$ subsets. In addition, a more detailed analysis of B cell counts will be performed in approximately 60 patients of each therapeutic group (R–CHOP, G–CHOP, R–CVP, G–CVP, R-bendamustine, G-bendamustine) and in all patients with splenic MZL based on the markers CD45/CD19/CD22/CD79b/CD5/CD10/lambda/kappa (B cell panel).

[aa] If the patient consents to additional research, a 6 mL serum and a 6 mL plasma sample should be drawn prior to study drug administration for storage in the RCR. With consent to optional research, the residual tumor tissue specimens from the baseline biopsy sample will also be stored in the RCR.

[bb] If an additional biopsy is done as part of the standard of care at the time of relapse or transformation, a tissue sample will be collected at that time. A formalin-fixed paraffin embedded tissue block is preferred over 15–20 sections on coated slides.

[cc] Prior to initiation of study medications, only SAEs caused by a protocol–mandated intervention will be recorded. After initiation of study medications, AEs will be recorded as follows: all AEs will be recorded up to 28 days after the last dose of study drug, Grade 3 or 4 AEs will be recorded up to 6 months after the last dose of study drug, Grade $\geq$ 3 infections will be recorded up to 24 months after the last dose of study drug, unrelated SAEs will be recorded up to 12 months after the last dose of study drug, and study drug–related SAEs and secondary malignancies will be recorded indefinitely (even if the study has been closed).

[dd] Observation and collection of concomitant medication information will be continued throughout the study.

[ee] PRO questionnaires (FACT–Lym, EQ–5D) should be administered prior to any treatment assessments. PRO questionnaires should also be administered at first assessment after report of disease progression.

[ff] *Any response assessments performed after a patient progressed and received NALT should be reported.*

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles)

	Screening		Treatment Period										Induction Completion/ ET Visit [a]
	SD –35	SD –14	C1, D1 (SD1)	C1, D8 (SD8)	C1, D15 (SD15)	C2, D1 (SD22)	C3, D1 (SD43)	C4, D1 (SD64)	C5, D1 (SD85)	C6, D1 (SD106)	C7, D1 (SD127)	C8, D1 (SD148)	
Informed consent	x												
Optional RCR informed consent	x												
Discussion of fertility issues and sperm banking (in patients of childbearing age)	x												
Inclusion/exclusion criteria	x												
Tumor tissue sample for quality assurance pathology review [b]	x												
Demographics and medical history [c]	x		x										
FLIPI prognostic risk: follicular patients	x												
FLIPI2 prognostic risk: follicular patients	x												
IPI score: non–follicular patients	x												
Complete physical examination [d]	x												
Targeted physical examination [d]			x			x	x	x	x	x	x	x	x

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

Height, weight, BSA [e]	x		x			x	x	x	x	x	x	x	x
Vital signs [f]	x		x	x	x	x	x	x	x	x	x	x	x
IADLs/ADLs		x											
ECOG Performance Status	x					x	x	x	x	x	x	x	x
B symptoms	x								x				x
12–lead ECG	x												x
Hematology [g]		x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry [g]		x	x			x	x	x	x	x	x	x	x
Urine dipstick for protein [h]		x											x
Serum electrophoresis, M protein, and immunofixation (only in patients with MZL) [i]		x							x				x
Coagulation (PTT or aPTT, PT or INR)		x											
Pregnancy test [j]		x											x
HBV, HCV, and HTLV–1 serology [k]	x												
HBV DNA PCR [l]		(x)				(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
CVP chemotherapy [m]			x			x	x	x	x	x	x	x	
Arm A: rituximab infusion [n]			x			x	x	x	x	x	x	x	
Arm B: obinutuzumab infusion [o, p]			x	x	x	x	x	x	x	x	x	x	
New anti–lymphoma treatment [ee]													x

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

Imaging–based tumor assessment [q]	x								x				x
FDG–PET [r]	x								(x)				x
Bone marrow biopsy [s]		x											x
Bone marrow aspirate for *BCL2/IgH* analysis: follicular patients [t]		x											x
FcγR typing [u]			x										
Blood for *BCL2/IgH* analysis: follicular patients [v]		x							x				x
HAHA samples: obinutuzumab arm only [p, w]		x											x
PK sampling: subset in obinutuzumab arm [p, x]			x [a]	x	x	x		x		x			x
Leukocyte immunophenotyping (FACS) [y]		x				x			x				x
Quantitative immunoglobulins (IgA, IgG, IgM)		x											x
Optional serum and plasma samples for RCR [z]		(x)											
Tumor tissue sample at time of relapse or transformation				(x) [aa]									
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

Concomitant medications [cc]	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires [dd]			x				x						x

ADLs = Activities of Daily Living; AE = adverse event; aPTT = activated partial thromboplastin time; BSA = body surface area; BUN = blood urea nitrogen; C = Cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone (prednisolone or methylprednisolone [MP]); CR = complete response; CT = computed tomography; CVP = cyclophosphamide, vincristine, and prednisone (prednisolone, MP); D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EDTA = ethylenediaminetetraacetic acid; EOI = end of infusion; EQ–5D = European Quality of Life (EuroQol) Questionnaire; ET = early termination; FACS = fluorescence–activated cell sorter; FACT-Lym = Functional Assessment of Cancer Therapy for Lymphoma; FDG = ^{18}F-fluorodeoxyglucose; FLIPI = Follicular Lymphoma International Prognostic Index; G = GA101; HAHA = human anti–human antibody; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV = human T-lymphotropic virus; IADLs = Instrumental Activities of Daily Living; INR = international normalized ratio; IPI = International Prognostic Index; IV = intravenous; LDH = lactate dehydrogenase; MRD = minimum residual disease; MRI = magnetic resonance imaging; MZL = marginal zone lymphoma; NK = natural killer cells; PCR = polymerase chain reaction; PET = positron emission tomography; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; R = rituximab; RBC = red blood cell; RCR = Roche Clinical Repository; SAE = serious adverse event; SD = Study Day; WBC = white blood cell.

Notes: **On treatment days, all assessments should be performed prior to dosing unless otherwise noted.**

The Cycle 1 Day 1 visit should be scheduled to allow subsequent visits to occur without delay. Study visits during induction treatment should occur on the scheduled day (± 4 days), with the exception of delays resulting from toxicities. Visits on Days 8 and 15 of Cycle 1 are optional for patients in the rituximab arm and are done if standard of care at the site. Visits on Day 15 of Cycles 2–8 are optional for all patients and are done if standard of care at the site.

(x) = conditional/optional; refer to footnote for details.

[a] Induction completion should occur within 6–8 weeks after C8D1 (i.e., SD190–SD204). An early termination visit should occur within 4–8 weeks after last dose (in case of early termination due to adverse event) or within 2–8 weeks after last dose in case of early termination due to clinical disease progression). In case of withdrawal from treatment due to toxicity, the first follow–up visit is scheduled 3 months (± 14 days) after last dose (“Month 27”; see Appendix A-5).

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[b] A tissue sample is required for retrospective central confirmation of diagnosis and CD20 positivity of lymphoma and should be dated from within 12 months prior to study entryi. Tissue samples dated > 12 months prior to study entry can be accepted only if tissue material is available for retrospective confirmation, if there is no clinical indication for transformation of disease, and if the request for additional biopsy would be unethical treatment of the patient. Bone marrow alone is not suited to make the diagnosis of follicular lymphoma. In patients with splenic MZL without splenic tissue available for histologic review, the bone marrow must be submitted for retrospective central confirmation. All tissue samples should be sent for quality assurance pathology review within 4 months after randomization. A formalin–fixed paraffin–embedded tissue sample is preferred over 15–20 sections (3–5–µm thickness) on coated slides. If the tissue sample is small, fewer sections (minimum within range of 6–12) can be accepted. Remainders of the tissue blocks will be returned to local pathology in accordance with local regulations.

[c] At screening, obtain demographic data and complete medical history. On Cycle 1 Day 1 obtain medical history since the screening visit.

[d] Complete physical examination includes all systems described in Section 4.5.1.a, including assessment of lymph nodes, hepatomegaly, and splenomegaly. The targeted physical examination should include only systems of most clinical relevance (i.e., cardiovascular, respiratory, those associated with clinical signs/symptoms, and lymph nodes, liver, and spleen).

[e] Height is measured at screening only. It is recommended that the DuBois BSA formula be used; however, BSA may be calculated using the investigator's preferred formula.

[f] Includes blood pressure, pulse rate, and temperature. On rituximab or obinutuzumab treatment days, vital signs should be measured prior to the infusion, then approximately every 15 minutes for 90 minutes, approximately every 30 minutes until the end of the infusion, and approximately every 60 minutes until the infusion line is removed.

[g] Samples should be drawn within 72 hours prior to the study drug infusion on treatment days. Hematology includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and absolute neutrophil count as routine components. Percent or absolute differential count (segmented neutrophils, banded neutrophils, eosinophils, lymphocytes, monocytes, basophils, malignant lymphocytes) are done if clinically indicated (e.g., for differential diagnosis of any kind of clinically relevant cytopenia/cytophilia or, e.g., if other undefined cells are present in the peripheral blood). In case of splenic MZL, the percent or absolute number of malignant lymphocytes ("villous lymphocytes") in peripheral blood should be assessed. Additional samples for hematology can be drawn according to the standard of care at the site. Serum chemistry includes sodium, potassium, chloride, bicarbonate (if clinically indicated), BUN, uric acid, serum creatinine, calcium, total bilirubin, total protein, albumin, phosphorus, ALT and AST, alkaline phosphatase, creatinine clearance, LDH, and β_2 microglobulin (creatinine clearance and β_2 microglobulin required only at screening). Visits on Days 8 and 15 of Cycle 1 are optional for hematology and chemistry for patients in the rituximab arm and for chemistry for patients in the obinutuzumab arm and are done if standard of care at the site. Visits on Day 15 of Cycles 2–8 are optional for all patients and are done if standard of care at the site. Values of serum chemistry/hematology from these optional visits may be obtained from local laboratories and should be entered into the eCRF if these visits took place.

[h] In a fresh sample of midstream urine, a dipstick testing for proteinuria is required.

[i] Serum electrophoresis is required in all patients with MZL and should report percentage of albumin, alpha 1, alpha 2, beta, and gamma fraction, as well absence/presence of an M protein. If an M protein is present, it should be quantified in g/L and the Ig subtype (IgG, IgA, IgM, IgD, light–chain kappa, or light–chain lambda) determined by immunofixation. If no M protein is found at baseline, serum electrophoresis and immunofixation do not need to be repeated at later time points.

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[j] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits and may be performed more frequently if required by local legislation. If a urine pregnancy test result is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

[k] HBsAg, HBcAb, and HCV antibody serology required for all patients. HCV RNA required for patients who are HCV antibody positive. HTLV required for patients from endemic countries (Japan, the Caribbean basin, South America, sub–Saharan Africa, and Melanesia). Additional serology for HBsAb required prior to Cycle 1 Day 1 for patients who are HBsAg negative and HBcAb positive at screening.

[l] For patients who are HBsAg negative and HBcAb positive at screening only. HBV DNA levels will be measured centrally by real–time PCR with use of an assay with a limit of quanitification of at least 29 IU/mL.

[m] CVP consists of cyclophosphamide 750 mg/m^2 IV on Day 1 of each cycle, vincristine 1.4 mg/m^2 IV (maximum 2 mg) on Day 1 of each cycle, and prednisone (prednisolone) 100 mg (or MP 80 mg in countries/sites without availability of prednisone/prednisolone) orally on Days 1–5 of each cycle. When rituximab or obinutuzumab is administered on the same day as prednisone (prednisolone, MP), it is recommended that prednisone (prednisolone, MP) be given prior to the rituximab or obinutuzumab infusion. The order of administration of cyclophosphamide and vincristine will be determined by local institutional practice, but these agents should be administered at least 30 minutes after rituximab or obinutuzumab. Dosage calculations for chemotherapy should be based on the patient's BSA. Empiric dose adjustment in obese patients (defined as a body mass index ≥ 30, as measured in kg/m^2) is not recommended, but may be implemented if required by institutional guidelines. There will be no dose modification for changes in patients' weight unless the weight increases or decreases by $> 10\%$ from weight at screening. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments.

[n] Rituximab 375 mg/m^2 will be administered by IV infusion. Rituximab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride (unless contraindicated) and allopurinol (for patients with high tumor burden, if pretreatment with allopurinol is deemed appropriate). When given on the same day as CVP chemotherapy, rituximab should be administered after prednisone (prednisolone, MP) but at least 30 minutes prior to cyclophosphamide and vincristine.

[o] Patients receiving obinutuzumab only.

[p] Obinutuzumab 1000 mg will be administered by IV infusion. Obinutuzumab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride (unless contraindicated) and allopurinol (for patients with high tumor burden, if pretreatment with allopurinol is deemed appropriate). When given on the same day as CVP chemotherapy, obinutuzumab should be administered after prednisone (prednisolone, MP) but at least 30 minutes prior to cyclophosphamide and vincristine.

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[q] Imaging–based tumor assessment: At screening, CT scan (with contrast) of the chest, abdomen, pelvis (and neck, if clinically indicated) should be done within 35 days prior to randomization. CT scans for response assessment should be done within 14 days prior to C5D1 and at the induction completion/early termination visit, and may be limited to areas of prior involvement if required by local regulatory authorities. Any time the investigator suspects disease progression, a full tumor assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities). MRIs with a non–contrast CT scan of the chest may be used for patients for whom CT scans with contrast are contraindicated. If MRI is used at screening, then MRI should be used throughout the study (same method during the entire study). Combined FDG–PET/CT scans may be used only if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. Measurement of lymphoma lesions by ultrasound is not the preferred option because of the inherent interexaminer variability. However, in patients with splenic MZL, the spleen is considered a target lesion, and its size should be determined by ultrasound (length and thickness), CT/MRI, or by physical examination. For ultrasound/CT/MRI or physical examination measurements, local guidelines for determining normal organ size are acceptable.

[r] FDG–PET is mandatory in the first 170 patients with follicular lymphoma at screening and at induction completion/ET (only if screening PET was positive) at all sites where a scanner is available. This may require specific approval in some countries. In such instances, PET becomes mandatory only after necessary approvals have been obtained. In the overall population, PET remains optional and at the investigator's discretion. If done, screening PET should be performed within 35 days prior to randomization. Within 14 days prior to C5D1, PET is optional and may be done at the investigator's discretion. At induction completion/ET, PET should be obtained within 6–8 weeks after C8D1 (i.e., SD190–SD204). An ET visit PET should occur within 4–8 weeks after last dose (in case of ET due to adverse event) or within 2–8 weeks after last dose (in case of ET due to clinical disease progression). The diagnosis of disease progression should not be based on PET alone but should always be confirmed by CT (MRI) imaging. PET results should not be used to make treatment decisions.

[s] A bone marrow biopsy (trephine) for local pathology must be performed at screening unless it was performed within 3 months prior to Cycle 1 Day 1. If positive at screening (i.e., showing infiltration by lymphoma), a subsequent bone marrow examination is required at the induction completion visit for patients who achieve a CR. In patients with continued bone marrow involvement or in patients with PR due to other reasons at EOI, a subsequent bone marrow biopsy may be required to confirm a CR at a later time point (e.g., during maintenance/observation). Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

[t] A bone marrow aspirate for central MRD assessment by PCR detection of *BCL2/IgH* rearrangement is performed in all patients with follicular lymphoma at screening. If the patient already had a diagnostic bone marrow biopsy without an aspirate within 3 months prior to Cycle 1 Day 1, it is still mandatory to perform the bone marrow aspirate for MRD assessment at screening, but then the biopsy for pathology does not have to be repeated. At the induction completion/ET visit, a bone marrow aspirate sample is mandatory in responders (CR + PR) in whom bone marrow involvement was diagnosed by morphology at screening and is optional but strongly recommended in responders (CR + PR) in whom no bone marrow involvement was diagnosed by morphology at screening. The recommendation is based on the observation that, at screening, bone marrow involvement is detectable on the level of minimal residual disease in the large majority of patients even if it appears to be negative by morphology. For each bone marrow examination performed on a patient, 4 mL of an EDTA-anticoagulated bone marrow aspirate is requested.

[u] A 3 mL blood sample will be taken for determination of FcγRIIIa, FcγRIIa, and FcγRIIb/IIc polymorphisms. Only patients who have successfully passed screening and are fully eligible for the study should have this sample taken.

APPENDIX A–2
Study Flowchart: Induction Treatment with CVP plus Rituximab/Obinutuzumab (21–Day Cycles) (Cont.)

[v] For follicular lymphoma patients only, a 9.5 mL EDTA blood sample will be taken for the analysis of clonal *BCL2/IgH* rearrangement (as a potential marker of tumor burden) at screening, before C5D1, and at the induction completion/ET in all patients.

[w] A 5 mL blood sample will be taken for HAHA analysis in all patients receiving obinutuzumab (Arm B) before first administration of G–CVP (baseline sample) and at induction completion/ET visit.

[x] Peak and trough PK samples for obinutuzumab levels should be drawn in a subset of patients receiving obinutuzumab (Arm B), per the schedule in Appendix B. All PK samples will be collected from the arm opposite to that receiving the infusion.

[y] A 5 mL blood sample will be taken for the assessment of B–cells, T cells, and NK–cells in all patients (TBNK panel). This will include determination of relative and absolute numbers of $CD3^+$, $CD4^+$ $CD8^+$, $CD19^+$, and $CD56^+$ subsets. In addition, a more detailed analysis of B cell counts will be performed in approximately 60 patients of each therapeutic group (R–CHOP, G–CHOP, R–CVP, G–CVP, R-bendamustine, G–bendamustine) and in all patients with splenic MZL based on the markers CD45/CD19/CD22/CD79b/CD5/CD10/lambda/kappa (B cell panel).

[zz] If the patient consents to additional research, 6 mL serum and 6 mL plasma samples should be drawn prior to study drug administration for storage in the RCR. With consent to optional research, the residual tumor tissue specimens from the baseline biopsy sample will also be stored in the RCR.

[aa] If an additional biopsy is done as part of the standard of care at the time of relapse or transformation, a tissue sample will be collected at that time. A formalin–fixed paraffin–embedded tissue block is preferred over 15–20 sections on coated slides).

[bb] Prior to initiation of study medications, only SAEs caused by a protocol–mandated intervention will be recorded. After initiation of study medications, AEs will be recorded as follows: all AEs will be recorded up to 28 days after the last dose of study drug, Grade 3 or 4 AEs will be recorded up to 6 months after the last dose of study drug, Grade ≥ 3 infections will be recorded up to 24 months after the last dose of study drug, unrelated SAEs will be recorded up to 12 months after the last dose of study drug, and study drug–related SAEs *and secondary malignancies* will be recorded indefinitely (even if the study has been closed).

[cc] Observation and collection of concomitant medication information will be continued throughout the study.

[dd] PRO questionnaires (FACT–Lym, EQ–5D) should be administered prior to any treatment assessments. PRO questionnaires should also be administered at first assessment after report of disease progression.

[ee] *Any response assessments performed after a patient progressed and received NALT should be reported.*

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles)

	Screening		Treatment Period										Induction Completion/ ET Visit [a]
	SD −35	SD −14	C1, D1 (SD1)	C1, D2 (SD2)	C1, D8 (SD8)	C1, D15 (SD15)	C1, D22 (SD22)	C2, D1 (SD29)	C3, D1 (SD57)	C4, D1 (SD85)	C5, D1 (SD113)	C6, D1 (SD141)	
Informed consent	x												
Optional RCR informed consent	x												
Discussion of fertility issues and sperm banking (in patients of childbearing age)	x												
Inclusion/exclusion criteria	x												
Tumor tissue sample for quality assurance pathology review [b]	x												
Demographics and medical history [c]	x		x										
FLIPI prognostic risk: follicular patients	x												
FLIPI2 prognostic risk: follicular patients	x												
IPI score: non–follicular patients	x												
Complete physical examination [d]	x												
Targeted physical			x					x	x	x	x	x	x

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles) (Cont.)

	Screening		Treatment Period										Induction Completion/ ET Visit [a]
	SD –35	SD –14	C1, D1 (SD1)	C1, D2 (SD2)	C1, D8 (SD8)	C1, D15 (SD15)	C1, D22 (SD22)	C2, D1 (SD29)	C3, D1 (SD57)	C4, D1 (SD85)	C5, D1 (SD113)	C6, D1 (SD141)	
examination [d]													
Height, weight, BSA [e]	x		x					x	x	x	x	x	x
Vital signs [f]	x		x		x	x		x	x	x	x	x	x
IADLs/ADLs		x											
ECOG Performance Status	x							x	x	x	x	x	x
B symptoms	x									x			x
12–lead ECG	x												x
Hematology [g]		x	x		x	x	x	x	x	x	x	x	x
Serum chemistry [g]		x	x					x	x	x	x	x	x
Urine dipstick for protein [h]		x											x
Serum electrophoresis, M protein, and immunofixation (only in patients with MZL) [i]		x								x			x
Coagulation (PTT or aPTT, PT or INR)		x											
Pregnancy test [j]		x											x
HBV, HCV, and HTLV–1 serology [k]	x												
HBV DNA PCR [l]		(x)						(x)	(x)	(x)	(x)	(x)	(x)
Bendamustine [m]			x	x				x	x	x	x	x	
Arm A: rituximab infusion [n]			x					x	x	x	x	x	

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles) (Cont.)

	Screening		Treatment Period										Induction Completion/ ET Visit [a]
	SD –35	SD –14	C1, D1 (SD1)	C1, D2 (SD2)	C1, D8 (SD8)	C1, D15 (SD15)	C1, D22 (SD22)	C2, D1 (SD29)	C3, D1 (SD57)	C4, D1 (SD85)	C5, D1 (SD113)	C6, D1 (SD141)	
Arm B: obinutuzumab infusion [o]			x		x [p]	x [p]		x	x	x	x	x	
New anti–lymphoma treatment [ee]													x
Imaging–based tumor assessment [q]	x									x			x
FDG–PET [r]	x									(x)			x
Bone marrow biopsy [s]		x											x
Bone marrow aspirate for *BCL2/IgH* analysis: follicular patients [t]		x											x
FcγR typing [u]			x										
Blood for *BCL2/IgH* analysis: follicular patients [v]		x								x			x
HAHA samples: obinutuzumab arm only [p, w]		x											x
PK sampling: subset in obinutuzumab arm [p, x]			x [a]		x [a]	x [a]	x [a]	x [a]		x [a]		x [a]	x [a]
Leukocyte immunophenotyping (FACS): subset [y]		x						x		x			x
Quantitative immuno–globulins (IgA, IgG, IgM)		x											x

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles) (Cont.)

	Screening		Treatment Period										Induction Completion/ ET Visit [a]
	SD –35	SD –14	C1, D1 (SD1)	C1, D2 (SD2)	C1, D8 (SD8)	C1, D15 (SD15)	C1, D22 (SD22)	C2, D1 (SD29)	C3, D1 (SD57)	C4, D1 (SD85)	C5, D1 (SD113)	C6, D1 (SD141)	
Optional serum and plasma samples for RCR [z]		(x)											
Tumor tissue sample at time of relapse or transformation				(x) [aa]									
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [cc]	x	x	x	x	x	x	x	x	x	x		x	x
PRO questionnaires [dd]			x						x				x

ADLs = Activities of Daily Living; AE = adverse event; aPTT = activated partial thromboplastin time; BSA = body surface area; BUN = blood urea nitrogen; C = Cycle; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone (prednisolone or methylprednisolone [MP]); CR = complete response; CT = computed tomography; CVP = cyclophosphamide, vincristine, and prednisone (prednisolone, MP); D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EDTA = ethylenediaminetetraacetic acid; EOI = end of infusion; EQ–5D = European Quality of Life (EuroQol) Questionnaire; ET = early termination; FACS = fluorescence–activated cell sorter; FACT-Lym = Functional Assessment of Cancer Therapy for Lymphoma; FDG = ^{18}F–fluorodeoxyglucose; FLIPI = Follicular Lymphoma International Prognostic Index; G = GA101; HAHA = human anti–human antibody; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV = human T–lymphotropic virus; IADLs = Instrumental Activities of Daily Living; INR = international normalized ratio; IPI = International Prognostic Index; IV = intravenous; LDH = lactate dehydrogenase; MRD = minimum residual disease; MRI = magnetic resonance imaging; MZL = marginal zone lymphoma; NK = natural killer; PCR = polymerase chain reaction; PET = positron emission tomography; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; R = rituximab; RBC = red blood cell; RCR = Roche Clinical Repository; SAE = serious adverse event; SD = Study Day; WBC = white blood cell.

Notes: **On treatment days, all assessments should be performed prior to dosing unless otherwise noted.**

The Cycle 1 Day 1 visit should be scheduled to allow subsequent visits to occur without delay. Study visits during induction treatment should occur on the scheduled day (± 4 days), with the exception of delays resulting from toxicities. Visits on Days 8 and 15 of Cycle 1 are optional for patients in the rituximab arm and are done if standard of care at the site. Visits on Day 15 of Cycles 2–6 are optional for all patients and are done if standard of care at the site. Values of serum chemistry/hematology from these optional visits may be obtained from local laboratories and should be entered into the eCRF if these visits took place.

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles) (Cont.)

(x) = conditional/optional; refer to footnote for details.

[a] Induction completion should occur within 6–8 weeks after C6, D1 (i.e., SD190–SD204). An early termination visit should occur within 4–8 weeks after last dose (in case of early termination due to adverse event) or within 2–8 weeks after last dose (in case of early termination due to clinical disease progression). In case of withdrawal from treatment due to toxicity, the first follow–up visit is scheduled 3 months (± 14 days) after last dose ("Month 27"; see Appendix A-5).

[b] A tissue sample is required for retrospective central confirmation of diagnosis and CD20 positivity of lymphoma and should be dated from within 12 months prior to study entry. Tissue samples dated > 12 months prior to study entry can be accepted only if tissue material is available for retrospective confirmation, if there is no clinical indication for transformation of disease, and if the request for additional biopsy would be unethical treatment of the patient. Bone marrow alone is not suited to make the diagnosis of follicular lymphoma. In patients with splenic MZL without splenic tissue available for histologic review, the bone marrow must be submitted for retrospective central confirmation. All tissue samples should be sent forquality assurance pathology review within 4 months after randomization. A formalin–fixed paraffin-embedded tissue sample is preferred over 15–20 sections (3–5-µm thickness) on coated slides. If the tissue sample is small, fewer sections (minimum within range of 6–12) can be accepted. Remainders of the tissue blocks will be returned to local pathology in accordance with local regulations.

[c] At screening, obtain demographic data and complete medical history. On Cycle 1 Day 1, obtain medical history since the screening visit.

[d] Complete physical examination includes all systems described in Section 4.5.1.a, including assessment of lymph nodes, hepatomegaly, and splenomegaly. The targeted physical examination should include only systems of most clinical relevance (i.e., cardiovascular, respiratory, those associated with clinical signs/symptoms, and lymph nodes, liver, and spleen).

[e] Height is measured at screening only. It is recommended that the DuBois BSA formula be used; however, BSA may be calculated using the investigator's preferred formula.

[f] Includes blood pressure, pulse rate, and temperature. On rituximab or obinutuzumab treatment days, vital signs should be measured prior to the infusion, then approximately every 15 minutes for 90 minutes, approximately every 30 minutes until the end of the infusion, and approximately every 60 minutes until the infusion line is removed.

[g] Samples should be drawn within 72 hours prior to the study drug infusion on treatment days. Hematology includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and absolute neutrophil count as routine components. Percent or absolute differential count (segmented neutrophils, banded neutrophils, eosinophils, lymphocytes, monocytes, basophils, malignant lymphocytes) are done if clinically indicated (e.g., for differential diagnosis of any kind of clinically relevant cytopenia/cytophilia or, e.g., if other undefined cells are present in the peripheral blood). In case of splenic MZL, the percent or absolute number of malignant lymphocytes ("villous lymphocytes") in peripheral blood should be assessed. Additional samples for hematology can be drawn according to the standard of care at the site. Serum chemistry includes sodium, potassium, chloride, bicarbonate (if clinically indicated), BUN, uric acid, serum creatinine, calcium, total bilirubin, total protein, albumin, phosphorus, ALT and AST, alkaline phosphatase, creatinine clearance, LDH, and β_2 microglobulin (creatinine clearance and β_2 microglobulin required only at screening). Visits on Days 8 and 15 of Cycle 1 are optional for hematology and chemistry for patients in the rituximab arm and for chemistry in patients in the obinutuzumab arm and are done if standard of care at the site. Visits on Day 15 of Cycles 2–8 are optional for all patients and are done if standard of care at the site. Values of serum chemistry/hematology from these optional visits may be obtained from local laboratories and should be entered into the eCRF if these visits took place.

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles) (Cont.)

[h] In a fresh sample of midstream urine, a dipstick testing for proteinuria is required.

[i] Serum electrophoresis is required in all patients with MZL and should report percent of albumin, alpha 1, alpha 2, beta, and gamma fraction, as well absence/presence of an M protein. If an M protein is present, it should be quantified in g/L and the Ig subtype (IgG, IgA, IgM, IgD, light–chain kappa, or light-chain lambda) determined by immunofixation. If no M protein is found at baseline, serum electrophoresis and immunofixation do not need to be repeated at later time points.

[j] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits and may be performed more frequently if required by local legislation. If a urine pregnancy test result is positive, dosing will be delayed until the patient's status is determined by a serum pregnancy test.

[k] HBsAg, HBcAb, and HCV antibody serology required for all patients. HCV RNA required for patients who are HCV antibody positive. HTLV required for patients from endemic countries (Japan, the Caribbean basin, South America, sub–Saharan Africa, and Melanesia). Additional serology for HBsAb required prior to Cycle 1 Day 1 for patients who are HBsAg negative and HBcAb positive at screening.

[l] For patients who are HBsAg negative and HBcAb positive at screening only. HBV DNA levels will be measured centrally by real–time PCR with use of an assay with a limit of quantification of at least 29 IU/mL.

[m] Bendamustine will be administered at 90 mg/m^2 IV on Days 1 and 2 of each cycle, with 100 mg oral prednisone/prednisolone or 80 mg methylprednisolone also administered prior to the first dose of rituximab or obinutuzumab on Day 1 of Cycle 1. Bendamustine should be administered at least 30 minutes after rituximab or obinutuzumab when administered on the same day. Dosage calculations should be based on the patient's BSA. Empiric dose adjustment in obese patients (defined as a body mass index $\geq$ 30, as measured in kg/m^2) is not recommended but may be implemented if required by institutional guidelines. There will be no dose modification for changes in patients' weight unless the weight increases or decreases by $>$ 10% from weight at screening. The weight that triggered a dose adjustment will be taken as the new reference weight for future dose adjustments.

[n] Rituximab 375 mg/m^2 will be administered by IV infusion. Rituximab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride (unless contraindicated). When given on the same day, rituximab should be administered prior to bendamustine. It is recommended to treat with allopurinol 2–3 days prior to start of the cycle in patients with high tumor burden, if pretreatment with allopurinol is deemed appropriate. However, allopurinol must not be given on days of bendamustine administration.

[o] Obinutuzumab 1000 mg will be administered by IV infusion. Obinutuzumab should be administered after premedication with oral acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride (unless contraindicated) and allopurinol (for patients with high tumor burden, if pretreatment with allopurinol is deemed appropriate). When given on the same day, obinutuzumab should be administered prior to bendamustine. Allopurinol must not be given on days of bendamustine administration.

[p] Patients receiving obinutuzumab only.

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles) (Cont.)

[q] Imaging–based tumor assessment: At screening, CT scan (with contrast) of the chest, abdomen, pelvis (and neck, if clinically indicated) should be done within 35 days prior to randomization. CT scans for response assessment should be done within 14 days prior to C4 D1 and at the induction completion/early termination visit, and may be limited to areas of prior involvement if required by local regulatory authorities. Any time the investigator suspects disease progression, a full tumor assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities). MRIs with a non–contrast CT scan of the chest may be used for patients for whom CT scans with contrast are contraindicated. If MRI is used at screening, then MRI should be used throughout the study (same method during the entire study). Combined FDG–PET/CT scans may be used only if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. Measurement of lymphoma lesions by ultrasound is not the preferred option because of the inherent interexaminer variability. However, in patients with splenic MZL, the spleen is considered a target lesion, and its size should be determined by ultrasound (length and thickness), CT/MRI, or by physical examination. For ultrasound/CT/MRI or physical examination measurements, local guidelines for determining normal organ size are acceptable.

[r] FDG–PET is mandatory in the first 170 patients with follicular lymphoma at screening and at induction completion/ET (only if the result of the screening PET was positive) at all sites where a scanner is available. This may require specific approval in some countries. In such instances, PET becomes mandatory only after necessary approvals have been obtained. In the overall population, PET remains optional and at the investigator's discretion. If done, screening PET should be performed within 35 days prior to randomization. Within 14 days prior to C4, D1, PET is optional and may be done at the investigator's discretion. At induction completion/ET, PET should be obtained within 6–8 weeks after C6D1 (i.e., SD182–SD197). An ET visit PET should occur within 4–8 weeks after last dose (in case of ET due to adverse event) or within 2–8 weeks after last dose (in case of ET due to clinical disease progression). The diagnosis of disease progression should not be based on PET alone but should always be confirmed by CT (MRI) imaging. PET results should not be used to make treatment decisions.

[s] A bone marrow biopsy (trephine) for local pathology must be performed at screening unless it was performed within 3 months prior to Cycle 1 Day 1. If positive at screening (i.e., showing infiltration by lymphoma), a subsequent bone marrow examination is required at the induction completion visit for patients who achieve a CR. In patients with continued bone marrow involvement or in patients with PR due to other reasons at EOI, a subsequent bone marrow biopsy may be required to confirm a CR at a later time point (e.g., during maintenance/observation) Any additional (unscheduled) bone marrow examinations performed during the study will be at the discretion of the investigator.

[t] A bone marrow aspirate for central by PCR detection of *BCL2/IgH* rearrangement is performed in all patients with follicular lymphoma at screening. If the patient already had a diagnostic bone marrow biopsy without an aspirate within 3 months prior to Cycle 1 Day 1 before screening, it is still mandatory to perform the bone marrow aspirate for MRD assessment at screening, but the biopsy for pathology itself does not have to be repeated. At the induction completion/ET visit, a bone marrow aspirate sample is mandatory in responders (CR + PR) in whom bone marrow involvement was diagnosed by morphology at screening and is optional but strongly recommended in responders (CR + PR) in whom no bone marrow involvement was diagnosed by morphology at screening. The recommendation is based on the observation that, at screening, bone marrow involvement is detectable on the level of minimal residual disease in the large majority of patients even if it appears to be negative by morphology. For each bone marrow examination performed on a patient, 4 mL of an EDTA-anticoagulated bone marrow aspirate is requested.

[u] A 3 mL blood sample will be taken for determination of FcγRIIIa, FcγRIIa, and FcγRIIb/IIc polymorphisms. Only patients who have successfully passed screening and are fully eligible for the study should have this sample taken.

APPENDIX A–3
Study Flowchart: Induction Treatment with Bendamustine plus Rituximab/Obinutuzumab (28–Day Cycles) (Cont.)

[v] For follicular lymphoma patients only, a 9.5 mL EDTA blood sample will be taken for the analysis of clonal *BCL2/IgH* rearrangement (as a potential marker of tumor burden) at screening, before C4, D1, and at induction completion/ET in all patients.

[w] A 5 mL blood sample will be taken for HAHA analysis in all patients receiving obinutuzumab (Arm B) before first administration of G–bendamustine (baseline sample) and at induction completion/ET visit.

[x] Peak and trough PK samples for obinutuzumab levels should be drawn in a subset of patients receiving obinutuzumab (Arm B), per the schedule in Appendix B. All PK samples will be collected from the arm opposite to that receiving the infusion.

[y] A 5 mL blood sample will be taken for the assessment of B cells, T cells, and NK cells in all patients (TBNK panel). This will include determination of relative and absolute numbers of $CD3^+$, $CD4^+$ $CD8^+$, $CD19^+$, and $CD56^+$ subsets. In addition, a more detailed analysis of B cells counts will be performed in approximately 60 patients of each therapeutic group (R–CHOP, G–CHOP, R–CVP, G–CVP, R–bendamustine, G-bendamustine) and in all patients with splenic MZL based on the markers CD45/CD19/CD22/CD79b/CD5/CD10/lambda/kappa (B–cell panel).

[z] If the patient consents to additional research, serum and plasma samples should be drawn prior to study drug administration for storage in the RCR. With consent to optional research, the residual tumor tissue specimens from the baseline biopsy sample will also be stored in the RCR.

[aa] If an additional biopsy is done as part of the standard of care at the time of relapse or transformation, a tissue sample will be collected at that time. A formalin–fixed paraffin embedded tissue block is preferred over 15–20 sections on coated slides.

[bb] Prior to initiation of study medications, only SAEs caused by a protocol–mandated intervention will be recorded. After initiation of study medications, AEs will be recorded as follows: all AEs will be recorded up to 28 days after the last dose of study drug, Grade 3 or 4 AEs will be recorded up to 6 months after the last dose of study drug, Grade $\geq$ 3 infections will be recorded up to 24 months after the last dose of study drug, unrelated SAEs will be recorded up to 12 months after the last dose of study drug, and study drug–related SAEs and secondary malignancies will be recorded indefinitely (even if the study has been closed).

[cc] Observation and collection of concomitant medication information will be continued throughout the study.

[dd] PRO questionnaires (FACT–Lym, EQ–5D) should be administered prior to any treatment assessments. PRO questionnaires should also be administered at first assessment after report of disease progression.

[ee] *Any response assessments performed after a patient progressed and received NALT should be reported.*

APPENDIX A–4
Study Flowchart: Maintenance Treatment and Observation

Months from Cycle 8, Day 1 (CHOP/CVP), Cycle 6, Day 1 (bendamustine) (± 14 days)	Maintenance Treatment and Observation Period												Maintenance or Observation Completion/ ET Visit [a]
	2	4	6	8	10	12	14	16	18	20	22	24	
Targeted physical examination [b]	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight and BSA	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs [c]	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG Performance Status	x	x	x	x	x	x	x	x	x	x	x	x	x
B symptoms	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [d]	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry [e]	x	x	x	x	x	x[e]	x	x	x	x	x	x	x
Urine dipstick for protein [f]			x			x			x				x
Serum electrophoresis, M protein, and immunofixation (only in patients with MZL) [g]		x		x		x			x				x
Pregnancy test [h]													x
HBV DNA PCR [i]	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)
Arm A: rituximab infusion [j]	x	x	x	x	x	x	x	x	x	x	x	x	
Arm B: obinutuzumab infusion [k]	x	x	x	x	x	x	x	x	x	x	x	x	
New anti–lymphoma treatment [x]	x	x	x	x	x	x	x	x	x	x	x	x	x
Imaging–based tumor assessment [l]		x		x		x			x				x
FDG–PET [m]		(x)		(x)		(x)			(x)				(x)
Blood for *BCL2/IgH* analysis: follicular patients [n]		x		x		x			x				x
HAHA samples: obinutuzumab arm maintenance only [o]									x			x	x

APPENDIX A–4 (cont'd)
Study Flowchart: Maintenance Treatment and Observation

HAHA samples: obinutuzumab arm observation only o									x			x	x
PK sampling: subset in obinutuzumab arm, maintenance only [p]			x			x			x			x	x
PK sampling: subset in obinutuzumab arm, observation only [q]		x		x					x			x	x
Leukocyte immunophenotyping (FACS) [r]						x							x
Quantitative immunoglobulins (IgA, IgG, IgM)													x
Tumor tissue sample at time of relapse	(x) [s]												
Bone marrow biopsy	(x) [t]												
Adverse events [u]	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [v]	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires [w]	x					x							x

AE = adverse event; BSA = body surface area; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone (prednisolone/methylprednisolone); CT = computed tomography; CVP = cyclophosphamide, vincristine, and prednisone (prednisolone/methylprednisolone); ECOG = Eastern Cooperative Oncology Group; EDTA = ethylenediaminetetraacetic acid; EOI = end of infusion; EQ–5D = European Quality of Life (EuroQol) Questionnaire; ET = early termination; FACS = fluorescence–activated cell sorter; FACT-Lym = Functional Assessment of Cancer Therapy for Lymphoma; FDG = ^{18}F–fluorodeoxyglucose; G = GA101; HAHA = human anti–human antibody; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IV = intravenous; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; MZL = marginal zone lymphoma; NK = natural killer; PCR = polymerase chain reaction; PET = positron emission tomography; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; R = rituximab; RBC = red blood cell; SAE = serious adverse event; SD = stable disease; WBC = white blood cell.

Notes: **On treatment days, all assessments should be performed prior to dosing unless otherwise noted**.

Study visits should occur on the scheduled day (±14 days), with the exception of delays resulting from toxicities. In case of toxicity, the study visit should be shifted by +14 days if the window allows. If toxicity is still present, next treatment can be delayed up to 42 days. The delay should be caught up within the next few subsequent visits to keep the duration of maintenance to a maximum of 24 months. If the end of induction visit was done 8 weeks after the last dose of immunochemotherapy, the first maintenance visit should be scheduled 7–14 days later in order to keep an interval between end of induction and maintenance month 2.

(x) = conditional/optional; refer to footnote for details.

APPENDIX A–4 (cont'd)
Study Flowchart: Maintenance Treatment and Observation

[a] Patients who complete the maintenance treatment or observation period or who discontinue early will be asked to return to the clinic within 21–35 days after the last immunotherapy dose or date of the decision to discontinuation for a maintenance or observation completion/ET visit. The completion/ET visit will be approximately 25 months after Cycle 8, Day 1 (CHOP/CVP), or Cycle 6, Day 1 (bendamustine). At any time that the investigator suspects disease progression, a full tumor assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities). Patients who continue to demonstrate a response to treatment at the completion/ET and those who have stable disease will continue to be assessed every 3 months (±14 days) (CT every 6 months ±14 days) for an additional 3 years and then every 6 months ±14 days (CT yearly ±14 days) for 2 years or until disease progression, study withdrawal, or relapse (whichever occurs first). In case of withdrawal from treatment due to toxicity, the first follow–up visit is scheduled 3 months (±14 days) after last dose ("Month 27"; see Appendix A-5).

[b] The targeted physical examination should include only systems of most clinical relevance (i.e., cardiovascular, respiratory, those associated with clinical signs/symptoms, and lymph nodes, liver, and spleen).

[c] Includes blood pressure, pulse rate, and temperature. On rituximab or obinutuzumab treatment days, vital signs should be measured prior to the infusion, then approximately every 30 minutes until the end of the infusion and approximately every 60 minutes until the infusion line is removed.

[d] Samples should be drawn within 72 hours prior to the study drug infusion on treatment days. Hematology includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and absolute neutrophil count as routine components. Percent or absolute differential count (segmented neutrophils, banded neutrophils, eosinophils, lymphocytes, monocytes, basophils, malignant lymphocytes) are done if clinically indicated (e.g., for differential diagnosis of any kind of clinically relevant cytopenia/cytophilia or, e.g., if other undefined cells are present in the peripheral blood). In case of splenic MZL, the percent or absolute number of malignant lymphocytes ("villous lymphocytes") in peripheral blood should be assessed. Additional samples for hematology can be drawn according to the standard of care at the site.

[e] Samples should be drawn within 72 hours prior to the study drug infusion on treatment days. Serum chemistry includes sodium, potassium, calcium, ALT, AST, total bilirubin, serum creatinine, alkaline phosphatase, phosphorus, total protein, albumin, and LDH. Creatinine clearance according to Cockcroft–Gault formula must be assessed 1 year after the last treatment in all patients in the observation arm.

[f] In a fresh sample of midstream urine, a dipstick testing for proteinuria is required.

[g] Serum electrophoresis is required in all patients with MZL and should report percent of albumin, alpha 1, alpha 2, beta, and gamma fraction, as well absence/presence of an M protein. If an M protein is present, it should be quantified in g/L and the Ig subtype (IgG, IgA, IgM, IgD, light–chain kappa, or light–chain lambda) determined by immunofixation. If no M protein is found at baseline, serum electrophoresis and immunofixation do not need to be repeated at later time points.

[h] A urine pregnancy test should be performed for all women of childbearing potential (including those who have had a tubal ligation) at the completion of maintenance therapy. If a urine pregnancy test result is positive, the patient's status is determined by a serum pregnancy test.

[i] Performed monthly, for patients who are HBsAg negative and HBcAb positive at screening only. HBV DNA levels will be measured centrally by real-time PCR with use of an assay with a limit of quantification of at least 29 IU/mL.

[j] Patients in Arm A may continue to receive rituximab 375 mg/m^2 IV every 2 months (±14 days) for up to 2 additional years or until evidence of clinical progression (whichever occurs first).

[k] Patients in Arm B may continue to receive obinutuzumab 1000 mg IV every 2 months (±14 days) for up to 2 additional years until evidence of clinical progression (whichever occurs first).

APPENDIX A–4 (cont'd)
Study Flowchart: Maintenance Treatment and Observation

[l] Imaging–based tumor assessment: CT scan (with contrast) of the chest, abdomen, pelvis (and neck, if clinically indicated). CT scans for response assessment should be done within 14 days prior to the follow–up study visit and may be limited to areas of prior involvement if required by local regulatory authorities. Any time the investigator suspects disease progression, a full tumor assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities). MRIs with a non–contrast CT scan of the chest may be used for patients for whom CT scans with contrast are contraindicated. If MRI is used at screening, then MRI should be used throughout the study (same method during the entire study). Combined FDG–PET/CT scans may be used only if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. Measurement of lymphoma lesions by ultrasound is not the preferred option because of the inherent interexaminer variability. However, in patients with splenic MZL, the spleen is considered a target lesion, and its size should be determined by ultrasound (length and thickness), CT/MRI, or by physical examination. For ultrasound/CT/MRI or physical examination measurements, local guidelines for determining normal organ size are acceptable. PET is optional and may be done at the investigator's discretion.

[m] FDG–PET is optional and may be done at investigator's discretion.

[n] For follicular lymphoma patients only, a 9.5 mL EDTA blood sample will be taken for the analysis of clonal *BCL2/IgH* rearrangement (as a potential marker of tumor burden) in all patients.

[o] A 5 mL blood sample will be taken for HAHA analysis in all patients receiving obinutuzumab (Arm B).

[p] A blood sample for obinutuzumab levels should be drawn in a subset of patients from the obinutuzumab arm (Arm B) during maintenance at Months 6, 12, 18, and 24, and at the maintenance or observation completion visit/ET. For patients receiving obinutuzumab maintenance, a trough sample (0–4 hours before the start of infusion) and a peak sample (0–30 minutes after the end of infusion) should be drawn at each time point. All PK samples will be collected from the arm opposite to that receiving the infusion.

[q] A blood sample for obinutuzumab levels should be drawn in a subset of patients from the obinutuzumab arm (Arm B) during observation at Months 4 and 8, 18 and 24 and at the observation completion visit/ET. For patients in observation, only one sample should be drawn at each time point. All PK samples will be collected from the arm opposite to that receiving the infusion.

[r] A 5 mL blood sample will be taken for the assessment of B cells, T cells, and NK cells in all patients (TBNK panel). This will include determination of relative and absolute numbers of $CD3^+$, $CD4^+$ $CD8^+$, $CD19^+$, and $CD56^+$ subsets. In addition, a more detailed analysis of B cells counts will be performed in approximately 60 patients of each therapeutic group (R–CHOP, G–CHOP, R-CVP, G–CVP, R-bendamustine, G-bendamustine) and in all patients with splenic MZL based on the markers CD45/CD19/CD22/CD79b/CD5/CD10/lambda/kappa (B cell panel).

[s] If an additional biopsy is done as part of the standard of care at the time of relapse or transformation, a tissue sample will be collected at that time. A formalin–fixed paraffin embedded tissue block is preferred over 15–20 sections (3–5–μm thickness) on coated slides.

[t] In patients with continued bone marrow involvement or in patients without additional bone marrow biopsy at end of induction or PR/SD due to other reasons at EOI, a subsequent bone marrow biopsy may be required to confirm a CR at a later time point (e.g., during maintenance/observation).

[u] All AEs will be recorded up to 28 days after the last dose of study drug, Grade 3 or 4 AEs will be recorded up to 6 months after the last dose of study drug, Grade ≥3 infections will be recorded up to 24 months after the last dose of study drug, unrelated SAEs will be recorded up to 12 months after the last dose of study drug, and study drug–related SAEs and secondary malignancies will be recorded indefinitely (even if the study has been closed).

APPENDIX A–4 (cont'd)
Study Flowchart: Maintenance Treatment and Observation

[v] Observation and collection of concomitant medication information will be continued throughout the study.

[w] PRO questionnaires (FACT–Lym, EQ–5D) should be administered prior to any treatment assessments. PRO questionnaires should also be administered at first assessment after report of disease progression.

[x] *Any response assessments performed after a patient progressed and received NALT should be reported.*

APPENDIX A–5
Study Flowchart: Follow–Up

Months from Cycle 8, Day 1 (CHOP/CVP), Cycle 6, Day 1 (Bendamustine), or Last Treatment Cycle (Early Termination)	Year 1				Year 2				Year 3				Year 4		Year 5	
(± 14 days)	27	30	33	36	39	42	45	48	51	54	57	60	66	72	78	84
Targeted physical examination [a]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG Performance Status		x		x		x		x		x		x		x		x
B symptoms	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum electrophoresis, M protein, and immunofixation (only in patients with MZL) [c]		x		x		x		x		x		x		x		x
Lactate dehydrogenase	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
HBV DNA PCR and AST/ALT [d]	(x)	(x)	(x)	(x)												
New anti–lymphoma treatment [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Survival follow–up [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Imaging–based tumor assessment [f]		x		x		x		x		x		x		x		x
FDG–PET [g]		(x)		(x)		(x)		(x)		(x)		(x)		(x)		(x)
Blood for *BCL2/IgH* analysis: follicular patients [h]		x		x		x		x		x		x		x		x
HAHA samples (GA 101 arm only) [i]		x		x		x		x								
PK sampling (only in subset of obinutuzumab maintenance patients) [j]	x	x		x		x		x								
Leukocyte immunophenotyping (FACS) [k]		x		x		x		x				x				
Quantitative immunoglobulins (IgA, IgG, IgM)		x		x		x		x				x				
Tumor tissue sample at time of relapse	(x) [l]															

APPENDIX A–5 (cont'd)
Study Flowchart: Follow–Up

Months from Cycle 8, Day 1 (CHOP/CVP), Cycle 6, Day 1 (Bendamustine), or Last Treatment Cycle (Early Termination)	Year 1				Year 2				Year 3				Year 4		Year 5	
(± 14 days)	27	30	33	36	39	42	45	48	51	54	57	60	66	72	78	84
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires (FACT–Lym, EQ–5D) [o]				x				x				x		x		x
Urine dipstick for protein [p]		x		x		x		x								
Creatinine clearance [q]				x												

AE = adverse event; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone (prednisolone/methylprednisolone); CT = computed tomography; CVP = cyclophosphamide, vincristine, and prednisone (prednisolone/methylprednisolone); ECOG = Eastern Cooperative Oncology Group; EDTA = ethylenediaminetetraacetic acid; EQ–5D = European Quality of Life (EuroQol) Questionnaire; FACS = fluorescence–activated cell sorter; FACT-Lym = Functional Assessment of Cancer Therapy for Lymphoma; FDG = ^{18}F–fluorodeoxyglucose; HAHA = human anti–human antibody; G = GA101; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; MRI = magnetic resonance imaging; MZL = marginal zone lymphoma; NK = natural killer; PCR = polymerase chain reaction; PD = progressive disease; PET = positron emission tomography; PK = pharmacokinetic; PRO = patient-reported outcome; R = rituximab; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

(x) = conditional/optional; refer to footnote for details.

Study visits should occur on the scheduled days (± 14 days).

[a] The targeted physical examination should include only systems of most clinical relevance (i.e., cardiovascular, respiratory, those associated with clinical signs/symptoms, and lymph nodes, liver, and spleen).

[b] Hematology includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, and absolute neutrophil count as routine components. Percent or absolute differential count (segmented neutrophils, banded neutrophils, eosinophils, lymphocytes, monocytes, basophils, malignant lymphocytes) are done if clinically indicated (e.g., for differential diagnosis of any kind of clinically relevant cytopenia/cytophilia or, e.g., if other undefined cells are present in the peripheral blood). In case of splenic MZL, the percent or absolute number of malignant lymphocytes ("villous lymphocytes") in peripheral blood should be assessed. Additional samples for hematology can be drawn according to the standard of care at the site.

[c] Serum electrophoresis is required in all patients with MZL and should report percent of albumin, alpha 1, alpha 2, beta, and gamma fraction, as well absence/presence of an M protein. If an M protein is present, it should be quantified in g/L and the Ig subtype (IgG, IgA, IgM, IgD, light–chain kappa, or light–chain lambda) determined by immunofixation. If no M protein is found at baseline, serum electrophoresis and immunofixation do not need to be repeated at later time points.

APPENDIX A–5 (cont'd)
Study Flowchart: Follow–Up

[d] Performed every 4 weeks, for patients who are HBsAg negative and HBcAb positive at screening only. HBV DNA levels will be measured centrally by real–time PCR with use of an assay with a limit of quantification of at least 29 IU/mL.

[e] Patients with disease progression will be followed for new anti–lymphoma treatment and survival twice per year until the end of the study (approximately 10.2 years). *For patients who progressed and received NALT, any response after NALT should be reported.* Patients who complete the 5 years of follow–up without disease progression will be followed for PD, new anti–lymphoma treatment, and survival. The first visit in survival follow–up should be performed 6 months after the last clinical visit.

[f] Imaging–based tumor assessment: CT scan (with contrast) of the chest, abdomen, pelvis (and neck, if clinically indicated). CT scans for response assessment should be done within 14 days prior to the follow–up study visit and may be limited to areas of prior involvement if required by local regulatory authorities. Any time the investigator suspects disease progression, a full tumor assessment must be performed, including a CT scan (limited to areas of prior involvement if required by local authorities). MRIs with a non-contrast CT scan of the chest may be used for patients for whom CT scans with contrast are contraindicated. If MRI is used at screening, then MRI should be used throughout the study (same method during the entire study). Combined FDG–PET/CT scans may be used only if performed with contrast and if collected with resolution sufficient to allow accurate and consistent comparison of target lesion measurements with subsequent CT scans. Measurement of lymphoma lesions by ultrasound is not the preferred option because of the inherent interexaminer variability. However, in patients with splenic MZL, the spleen is considered a target lesion, and its size should be determined by ultrasound (length and thickness), CT/MRI, or by physical examination. For ultrasound/CT/MRI or physical examination measurements, local guidelines for determining normal organ size are acceptable.

[g] FDG–PET is optional and may be done at the investigator's discretion.

[h] For follicular lymphoma patients only, a 9.5 mL EDTA blood sample will be taken for the analysis of clonal *BCL2/IgH* rearrangement (as a potential marker of tumor burden) in all patients.

[l] A blood sample will be taken for HAHA analysis in all patients receiving obinutuzumab (Arm B).

[j] A blood sample will be taken for PK analysis in a subset of patients who received obinutuzumab as maintenance. All PK samples will be collected from the arm opposite to that receiving the infusion.

[k] A 5 mL blood sample will be taken for the assessment of B cells, T–cells, neutrophils, and NK cells in all patients (TBNK panel). This will include determination of relative and absolute numbers of $CD3^+$, $CD4^+$ $CD8^+$,$CD19^+$, and $CD56^+$ subsets. In addition, a more detailed analysis of B cell counts will be performed in approimately. 60 patients of each therapeutic group (R–CHOP, G–CHOP, R–CVP, G–CVP, R-bendamustine, G–bendamustine) and in all patients with splenic MZL based on the markers CD45/CD19/CD22/CD79b/CD5/CD10/lambda/kappa (B cell panel).

[l] If an additional biopsy is done as part of the standard of care at the time of relapse or transformation, a tissue sample will be collected at that time. A formalin–fixed paraffin embedded tissue block is preferred over 15–20 sections (3–5 µm thickness) on coated slides.

[m] All AEs will be recorded up to 28 days after the last dose of study drug, Grade 3 or 4 AEs will be recorded up to 6 months after the last dose of study drug, Grade $\geq$ 3 infections will be recorded up to 24 months after the last dose of study drug, unrelated SAEs will be recorded up to 12 months after the last dose of study drug, and study drug–related SAEs and secondary malignancies will be recorded indefinitely (even if the study has been closed).

[n] Observation and collection of concomitant medication information will be continued throughout the study.

APPENDIX A–5 (cont'd)
Study Flowchart: Follow–Up

[o] PRO questionnaires (FACT–Lym, EQ–5D) should be administered prior to any treatment assessments. PRO questionnaires should also be administered at first assessment after report of disease progression.

[p] In a fresh sample of midstream urine, a dipstick testing for proteinuria is required.

[q] Glomerular filtration rate should be measured according to Cockroft Gault 1 year after last treatment.

APPENDIX B
Pharmacokinetic Assessments

Ideally, all pharmacokinetic (PK) samples will be drawn from the arm opposite from the infusion arm. In patients with indwelling catheters, a PK sample may be drawn from the catheter after ample flushing.

Pharmacokinetic Sampling Schedule:

The PK sampling schedule below is applicable to a subset of patients receiving obinutuzumab. Approximately 23 samples per obinutuzumab-treated patient will be collected during the study.

Study Visit	Time Point	Type of Sample
Cycle 1, Day 1	Pre–infusion	Obinutuzumab Serum
	Post–infusion	Obinutuzumab Serum
Cycle 1, Day 8	Pre–infusion	Obinutuzumab Serum
	Post–infusion	Obinutuzumab Serum
Cycle 1, Day 15	Pre–infusion	Obinutuzumab Serum
	Post–infusion	Obinutuzumab Serum
Cycle 1, Day 22 (Benda)	No dose given	Obinutuzumab Serum
Cycle 2, Day 1 (CVP/CHOP/Benda)	Pre–infusion	Obinutuzumab Serum
	Post–infusion	Obinutuzumab Serum
Cycle 4, Day 1	Pre–infusion	Obinutuzumab Serum
	Post–infusion	Obinutuzumab Serum
Cycle 6, Day 1	Pre–infusion	Obinutuzumab Serum
	Post–infusion	Obinutuzumab Serum
Induction Completion/Early Termination Visit	No dose given	Obinutuzumab Serum
Maintenance Months 6, 12, 18, and 24	Pre–infusion	Obinutuzumab Serum
	Post–infusion	Obinutuzumab Serum
Maintenance or Observation completion/ET	No dose given	Obinutuzumab Serum
Observation Months 4, 8, 18, 24, and observation completion/ET	No dose given	Obinutuzumab Serum
Follow–up (only in patients who received maintenance treatment with obinutuzumab) Months 27, 30, 36, 42, and 48	No dose given	Obinutuzumab Serum

APPENDIX B (cont'd)
Pharmacokinetic Assessments

Note: Pre–infusion samples should be drawn 0–4 hours before the start of infusion. Post-infusion samples should be drawn 0–30 minutes after the end of the infusion. All PK samples will be collected from the arm opposite to that receiving the infusion.
Benda = bendamustine.

APPENDIX C
Modified Version of the Revised Response Criteria for Malignant Lymphoma

Selection of Target Lesions

Up to six of the largest dominant nodes or tumor masses selected according to all of the following:

- Clearly measurable in at least two perpendicular dimensions at baseline

  All nodal lesions must measure:

  $>$ 1.5 cm in greatest transverse diameter (GTD) regardless of short axis measurement, or

  If the GTD measures between 1.1−1.5 cm, the short axis must measure $>$ 1.0 cm.

- All extranodal lesions must measure $\geq$ 1.0 cm in the GTD.
- If possible, the lesions should be from disparate regions of the body
- Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved
- Extranodal lesions within the liver or spleen must be at least 1.0 cm in two perpendicular dimensions.

In splenic marginal zone lymphoma (MZL) only: The spleen should be selected as target lesion if splenomegaly is present. Spleen size should be determined for splenic MZL by ultrasound if possible or by CT/MRI or by physical examination.

Selection of Nontarget Lesions

Nontarget lesions will be qualitatively assessed at each subsequent time point. All of the sites of disease present at baseline and not classified as target lesions will be classified as nontarget lesions, including any measurable lesions that were not chosen as target lesions. Examples of nontarget lesions include:

- All bone lesions, irrespective of the modality used to assess them
- Lymphangitis of the skin or lung
- Cystic lesions
- Splenomegaly (except splenic MZL) and hepatomegaly (all lymphomas)
- Irradiated lesions
- Measurable lesions beyond the maximum number of six
- Groups of lesions that are small and numerous

  Pleural/pericardial effusions and/or ascites

- For this study, a significant increase in existing pleural effusions, ascites, or other fluid collections will be considered sufficient evidence of progression and will not require cytological proof of malignancy. Effusions, ascites or other fluid collections will be followed as non–target lesions.

  Existing effusions/ascites: Effusions, ascites, or other fluid collections will be followed as nontarget lesions. At each time point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed.

  New effusions/ascites: Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions.

Reporting Conventions

Unable to Assess (UA) Lesion Category

This category is reserved for target and non–target lesions that are deemed UA because:

- One or more target/nontarget cannot be assessed (e.g., inadequate scan coverage, contrast, artifacts, or other factors).
- Assessment methods used were inconsistent with those used (e.g., modality change, change in contrast administration).
- One or more target/non–target lesions were excised or irradiated and have not reappeared or increased.

Examples of UA lesions are a lung lesion in the hilum obstructing the bronchus and causing atelectasis of the lobe or a hypodense liver lesion that becomes surrounded by fatty infiltration. In both examples, the boundaries of the lesion can be difficult to distinguish. Every effort should be made to assign measurements to lesions that develop less distinct margins because they become much smaller.

Not Done (ND) Lesion Category

This category is reserved for target and nontarget lesions identified at baseline that were not imaged at a subsequent time point. Such incidents should be avoided with utmost diligence since they are likely to make response assessment impossible for the affected time point.

APPENDIX C (cont'd)
Modified Version of the Revised Response Criteria for Malignant Lymphoma

For the following cases, the ND lesion category should **not** be used:

- Lesions which were imaged but which were not measured by the radiologist/reviewer. In such cases, the radiologist has to provide a measurement unless the lesion is assessed as UA.
- Lesions which were imaged but resolved completely.

Effects of UA and ND Lesions on Response Assessment

If a target lesion is classified as UA or ND after baseline, the sum of the product of the diameters (SPD)/area (whichever applies) of the target lesions cannot accurately be determined for that time point. Therefore, a response of CR, PR, or SD cannot be assigned for that time point and the response assessment will be UA for this time point unless unequivocal progression is determined on the basis of nontarget or new lesions, or the evaluable target lesions.

PD can be determined without evaluation of all sites of disease on the basis of the GTD, area or SPD for target lesions, evaluation of unequivocal progression in nontarget lesions, or observation of a new lesion within the available radiographic or clinical assessments.

Too Small To Measure (TSTM)/Below Measurable Limit (BML) Lesion Category

Any target lesion findings identified on baseline images, which at a subsequent time point decreases in size to < 5 mm in both dimensions, should be categorized as TSTM or BML. The lesion, node, or mass should be assigned measurements of 5 mm $\times$ 5 mm (for the GTD and the short axis) on the Source Document for the purpose of calculating the area. If that lesion increases in size to ≥ 5 mm in any dimension afterward, its true size (GTD and short axis) should be recorded. If lesions have completely disappeared, a value of "0" should be assigned for the long and short axis dimensions. The purpose of the assigned value for the measurement is the acknowledgment that small findings are not accurately measured.

APPENDIX C (cont'd)
Modified Version of the Revised Response Criteria for Malignant Lymphoma

Time Point Response

Target Lesions	Non–Target Lesions	New Lesions[1]	Time Point Response
CR	CR	No	CR
CR	SD	No	PR
CR	UA/ND	No	UA
PR	UA/ND	No	UA
PR	CR	No	PR
PR	SD	No	PR
SD	UA/ND	No	UA
SD	CR	No	SD
SD	SD	No	SD
PD	ANY	Yes/No	PD
ANY	PD	Yes/No	PD
ANY	ANY	Yes	PD
UA/ND	Non–PD	No	UA
UA/ND	UA/ND	No	UA
CR	NA[3]	No	CR
PR	NA[3]	No	PR
SD	NA[3]	No	SD
NA[2]	SD	No	SD
NA[2]	CR	No	CR
NA[2]	UA/ND	No	UA
NA[2]	NA[3]	No	UA

Modified from Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579–86.

[1] Identification of new lesions at a post–baseline time point will result in a response assessment of PD. If an identified new lesion subsequently becomes UA, the time point response will be recorded as PD unless the new lesion has proven to have resolved.

[2] No target lesions identified at baseline.

[3] No non–target lesions identified at baseline.

Response should be determined on the basis of radiographic and clinical evidence of disease with use of the modified 2007 Cheson criteria below.

APPENDIX C (cont'd)
Modified Version of the Revised Response Criteria for Malignant Lymphoma

FDG–PET scans are mandatory in the first 170 patients with follicular lymphoma at sites where a PET scanner is available and where an approval has been obtained at screening and at completion of induction/end of treatment (only if the result of screening PET was positive) to assess response at the completion of induction (6–8 weeks after Day 1 of the last cycle). An early termination visit PET should occur within 4–8 weeks after the last dose (in case of early termination due to adverse event) or within 2–8 weeks after last dose (in case of early termination due to clinical disease progression).

An analysis of response rates including the assessment by FDG–PET scans will be performed as exploratory analyses for scientific purposes.

The use of FDG–PET for assessment of response has been clarified following the recommendations as published by Cheson et al. (2007) and Juweid et al. (2007). However, FDG–PET scans alone without confirmatory computed tomography (CT) progression should not be used for assessment of relapsed or progressive disease. For the determination of complete response or partial remission for patients with no pretreatment PET scan or when their PET scan is positive before treatment, a post-treatment residual mass of any size is permitted as long as it is PET negative. In addition, assessment of PET results should be made according to the criteria of Juweid et al. (2007).

Complete Remission (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present prior to therapy
2. 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, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

3. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy. 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 until data become available demonstrating a clear difference in patient outcome.
4. In patients with splenic MZL, normalization of the blood counts (hemoglobin $>$ 12 g/dL; platelets $> 100 \times 10^9$/L; neutrophils $> 1.5 \times 10^9$/L and no evidence of circulating clonal B cells) will be required. For determination of splenic response by ultrasound/CT/MRI/physical examination, local guidelines for determining normal organ size are acceptable, but the spleen must be of normal size with no intrasplenic lesion present.
5. In patients with extranodal (MALT) MZL with gastrointestinal involvement at screening the response should be assessed with both endoscopy and histology. Definition of complete histologic regression is obtained when the post–treatment biopsies show no sign of remaining lymphoma but instead an empty tunica propria with small basal clusters of lymphocytes and scattered plasma cells.
6. In patients with MZL and paraprotein at screening, paraprotein must be absent by serum electrophoresis and immunofixation.

In patients for whom PET imaging is available, a second response assessment should be made with incorporation of PET imaging results:

- The designation of CR requires the following: all CR requirements as described above for a CT–only CR. However, if there is a PET scan positive before therapy, a post–treatment residual mass of any size is permitted as long as it is PET negative.

Partial Remission (PR)

1. $\geq$50% decrease in SPD of up to 6 of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following: a) they should be clearly measurable in at least 2 perpendicular dimensions; b) if possible, they should be from disparate regions of the body; c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen
3. Splenic and hepatic nodules must regress by $\geq$50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified (e.g., large–cell lymphoma or small neoplastic B cells). Patients who achieve a complete remission by the above criteria but who have persistent morphologic bone marrow involvement will be considered partial responders.
6. No new sites of disease should be observed (e.g., nodes > 1.5 cm in any axis).

In patients for whom PET imaging is available, a second response assessment should be made:

- For patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post–treatment PET should be positive in at least one previously involved site. Assessment of PET should follow the criteria described by Juweid et al. 2007.

In splenic MZL, partial response in the spleen is defined as a reduction of splenomegaly from baseline by ≥50%, but the spleen is still of abnormal size.

In extranodal (MALT) MZL, partial histologic regression is defined as post–treatment biopsy samples revealing either focal atypical lymphoid cells or lymphoepithelial destruction and an empty tunica propria as signs of lymphoma regression.

Stable Disease (SD)

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

In patients for whom PET imaging is available, a second response assessment should be made:

- PET should be positive at prior sites of disease with no new areas of involvement on the post–treatment CT or PET scan. Assessment of PET should follow the criteria described by Juweid et al. (2007).

APPENDIX C (cont'd)
Modified Version of the Revised Response Criteria for Malignant Lymphoma

Relapsed Disease (RD; after CR) or Progressive Disease (PD; for Patients with PR or SD)

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 be considered abnormal only 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.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, 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 $\geq 50\%$ and to a size of 1.5×1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. In patents with gastric MALT, relapse of the underlying gastric MALT lymphoma will be diagnosed whenever lymphoepithelial lesions are again present after the patient had entered CR.
5. If FDG–PET has been obtained, PD should be designated only if there are CT criteria for progression and the lesions are PET positive if the patient had PET-positive disease prior to therapy. FDG–PET is not mandatory for surveillance of progression.
6. In splenic MZL, in addition to criteria 1–5, PD should be designated if spleen size increases due to lymphoma by ≥50% from nadir or becomes of unequivocally abnormal size again after having reached normal size before.

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease.

Clarification 1: The investigators should be aware that, in small lymph nodes, a difference of only a few millimeters can result in an increase of more than 50% in the calculation of the SPD. Since the precision in comparing small differences in the diameters with former CT scans may be limited, in this situation, the investigator should check very carefully whether the observed differences can be a result of these limitations. This is especially important if a small increase is seen in only one site. Progression should be assessed only if it is considered unequivocal progression. A new evaluation after some weeks may be necessary to determine whether there was true progression in that lesion.

APPENDIX C (cont'd)
Modified Version of the Revised Response Criteria for Malignant Lymphoma

Clarification 2: In cases where only one target lesion was documented at baseline and it has subsequently been surgically removed after the baseline scan was obtained and after the first day of treatment, the response assignment will be considered UA unless there is progression elsewhere, qualifying the time point as PD.

References:

Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J Clin Oncol 2007;25:571–8.

Matutes E, Oscier D, Montalban C, et al. Splenic marginal zone lymphoma proposals for a revision of diagnostic, staging and therapeutic criteria. *Leukemia 2008;* **22:**487–95.

APPENDIX D
Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

	PHYSICAL WELL–BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL–BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.					
GS7	I am satisfied with my sex life	0	1	2	3	4

APPENDIX D (cont'd)
Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	EMOTIONAL WELL–BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL–BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

APPENDIX D (cont'd)
Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) (Version 4)

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

APPENDIX E
EuroQol's EQ–5D Questionnaire

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self–Care

I have no problems with self–care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g., work, study, housework, family, or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

APPENDIX F
Commonly Used CYP1A2 Inhibitors and Inducers

Based on the product information for bendamustine, no formal clinical assessments of pharmacokinetic drug-drug interactions between bendamustine and other drugs have been conducted. Bendamustine's active metabolites, gamma-hydroxy bendamustine (M3) and N-desmethyl–bendamustine (M4), are formed via cytochrome P450 CYP1A2. Inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites.

The medications listed below are not contraindicated; however, caution should be used, or alternative treatments with medications that are not CYP1A2 inhibitors or inducers should be considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed for your patient's medical condition. This list is not exhaustive.

CYP1A2 Inhibitors
Amiodarone
Amitriptyline
Amlodipine
Anastrozole
Caffeine
Cimetidine (Tagamet)
Ciprofloxacin (Cipro)
Citalopram
Clarithromycin
Clotrimazole
Clozapine
Diclofenac
Diltiazem
Echinacea
Ethinyl Estradiol
Fluoroquinolones
Fluconazole
Fluvoxamine
Gemfibrozil
Ginseng
Imipramine
Isoniazid

CYP1A2 Inhibitors (continued)
Ketoconazole
Lidocaine
Losartan
Erythromycin
Estrogens
Mexiletine
Modafenil
Nifedipine
Olanzapine
Omeprazole
Ondansetron
Paroxetinee
Propafenone
Propanolol
Ranitidine
Sertraline

APPENDIX F (cont'd)
Commonly Used CYP1A2 Inhibitors and Inducers

CYP1A2 Inducers
Barbiturates (e.g., Phenobarbital)
Cruciferous vegetables (broccoli, cauliflower, arugula, brussel sprouts, cabbage, kale, chard, turnips, radishes, wasabi, bok choy, watercress, collard greens)
Char–grilled meat
Carbamazepine (e.g., Tegretol)
Primidone
Rifampin (e.g., Rifadin)
Smoking
Triamterene (Dyrenium)
Zolmitriptan (Zomig)
Adapted from ***ctep****.cancer.gov/protocolDevelopment/docs/****cyp1a2****.doc*

Sample Card to be handed to patients on the BO21223 study. This card may be adapted to comply with local guidelines:

During this clinical study, I am receiving a drug called bendamustine. This drug is approved for the treatment of lymphoma in the United States of America and a number of the European Union member states. The following medications and substances are examples of drugs and substances that may alter blood levels of bendamustine:

Fluvoxamine
Ciprofloxacin
Omeprazole
Smoking

Caution must be used or alternative treatments be considered if treatment with one of these listed drugs or substances or another CYP1A2 inhibitor or inducer is needed.
If you have further questions, please contact the study doctor whose name and contact number are indicated on the other side of this card.

APPENDIX G
Inclusion Criteria for Patients with Gastric Extranodal Marginal Zone Lymphoma

The following patients with gastric extranodal marginal zone lymphoma are eligible for enrollment:

- Patients with *Helicobacter pylori*–negative disease that is de novo or has relapsed following local therapy (i.e., surgery or radiotherapy)
- Patients *originally* diagnosed with *H. pylori*–positive disease that remained stable, progressed, or relapsed following antibiotic therapy, including the following:

  Patients with clinical (endoscopic) and histological evidence of disease progression at any time after *H. pylori* eradication

  Patients with stable disease with persistent lymphoma at least 1 year after *H. pylori* eradication

  Patients with disease that relapsed (without *H. pylori* re–infection) after a remission

  Patients who failed either first–line antibiotics or further local treatment (surgery or radiotherapy)

APPENDIX H
ECOG Performance Status Scale and Ann Arbor Staging

ECOG Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about $>$50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair $>$50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to a bed or chair
5	Dead

Ann Arbor Staging

Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) [a]
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site[b] (IIIE), or both (IIIES)
Stage IV[b]	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

[a] The designation "E" generally refers to **extranodal contiguous extension** (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the **only site of disease** should be classified as IE, rather than Stage IV.

[b] Involvement of bone marrow at screening will always qualify for Ann Arbor Stage IV and should be recorded as extranodal involvement.

All cases are subclassified to indicate the absence (A) or presence (B) of the systemic ("B") symptoms of significant unexplained fever ($>$38°C), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

APPENDIX H (cont'd)
ECOG Performance Status Scale and Ann Arbor Staging

Adapted from:

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971;31:1860-1.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J Clin Oncol 1989;7:1630-6.

APPENDIX I
Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140 - \text{Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = 0.85 \times \frac{(140 - \text{Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference:

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

APPENDIX J
Rituximab Preparation Instructions

All transfer procedures require strict adherence to aseptic techniques, preferably in a laminar flow hood. Prepare rituximab solution as follows:

- Refrigerate (2°C–8°C) all materials and solutions prior to use. Do not freeze or store at room temperature.
- Use sterile, non–pyrogenic disposable containers, syringes, needles, stopcocks, and transfer tubing, etc.
- Transfer of rituximab from the glass vial should be made by using a suitable sterile graduated syringe and large gauge needle.
- Transfer the appropriate amount of rituximab from the graduated syringe into a partially filled IV pack containing sterile pyrogen–free 0.9% sodium chloride solution (saline solution). Discard any unused portion left in the vial.
- Mix by inverting the bag gently. DO NOT USE A VACUUM APPARATUS to transfer the product from syringe to the plastic bag. HANDLE GENTLY AND AVOID FOAMING, because this may lead to the denaturing of the product proteins.
- Place an IV administration into the outflow port of the bag containing the infusion solution.
- NOTE: DO NOT USE evacuated glass containers that require vented administration sets because this causes foaming as air bubbles pass through the solution.
- The administration of rituximab will be accomplished by slow IV infusion. CAUTION: DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.
- Do not infuse concomitantly with another IV solution or IV medications.

It is recommended that rituximab be given at a dilution of 2 mg/mL for ease in calculating dose administration.

APPENDIX K
Obinutuzumab Preparation Instructions

Reconstituted obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to the final drug concentration of 4 mg/mL. Using a 250 mL infusion bag containing 0.9% sodium chloride, withdraw and discard 40 mL of the sodium chloride. Withdraw 40 mL of obinutuzumab from a single glass vial and inject into an infusion bag (discard any unused portion of obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution; do not shake.

APPENDIX L
Bendamustine Preparation Instructions

Bendamustine Preparation Instructions

For preparation of the ready–for–use solution, the contents of one bendamustine vial are dissolved in water for injection as follows:

First dissolve contents of the bendamustine vial containing 25 mg bendamustine hydrochloride in 10 mL water for injection or contents of bendamustine vial containing 100 mg bendamustine hydrochloride in 40 mL water for injection, while shaking the vial.

Once a clear solution has been obtained (generally after 5–10 minutes), the total bendamustine dose is diluted immediately with 0.9% NaCl solution to a final volume of 500 mL. Bendamustine must not be diluted with other basic infusion or injection solutions apart from isotonic saline solution.

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 ºC/ 60% RH and 2 days at 2°C to 8°C in polyethylene bags.

From a microbiological point of view, the ready–to–use preparation should be used immediately unless the dilution method precludes the risk of microbial contamination.

If the ready–to–use preparation is not used immediately, the user is responsible for the duration and conditions of storage.

Incompatibilities

Bendamustine must not be mixed with other substances in an infusion. The powder must be dissolved only in water for injection and further diluted with isotonic saline.

APPENDIX M
Follicular Lymphoma International Prognostic Index and International Prognostic Index

Follicular Lymphoma International Prognostic Index (FLIPI)

Risk Factors	
Ann–Arbor Stage III or IV	
Age > 60 years	
Serum LDH > 1 × ULN	
Anemia (hemoglobin < 120 g/L)	
Involved nodal areas > 4	
FLIPI Risk Group	Number of FLIPI Risk Factors
Low	0 or 1
Intermediate	2
High	3–5

FLIPI = Follicular Lymphoma International Prognostic Index; LDH = lactate dehydrogenase; ULN = upper limit of normal.

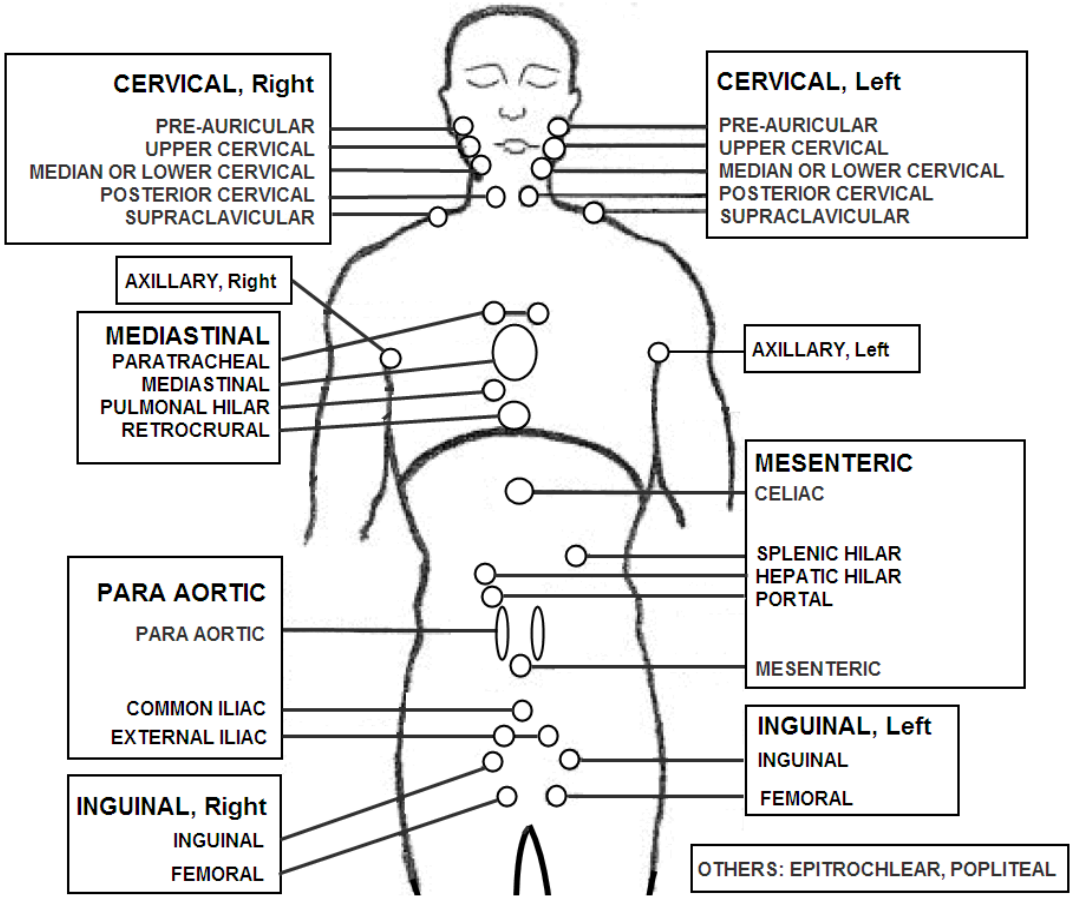
The results of FDG–PET should not be taken into account for calculation of FLIPI since this prognostic score was established without FDG–PET.

Adapted from:

Solal–Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–64.

APPENDIX M (cont'd)
Follicular Lymphoma International Prognostic Index and International Prognostic Index

Follicular Lymphoma International Prognostic Index (FLIPI) Nodal Areas



Reference modified from:

Solal–Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–64.

APPENDIX M (cont'd)
Follicular Lymphoma International Prognostic Index and International Prognostic Index

Follicular Lymphoma International Prognostic Index (FLIPI) 2

Risk Factors	
Bone marrow involvement	
Age >60 years	
β_2 microglobulin $>1\times$ ULN	
Anemia (hemoglobin <120 g/L)	
Longest diameter of largest involved node >6 cm	
FLIPI2 Risk Group	Number of FLIPI2 Risk Factors
Low	0
Intermediate	1 or 2
High	3–5

FLIPI2 = Follicular Lymphoma International Prognostic Index 2; LDH = lactate dehydrogenase; ULN = upper limit of normal.

The results of FDG–PET should not be taken into account for calculation of FLIPI2 since this prognostic score was established without FDG–PET.

Adapted from:

The results of FDG–PET should not be taken into account for calculation of FLIPI2 since this prognostic score was established without FDG–PET.:

Federico M, Bellei M, Marcheselli L, et al. Follicular Lymphoma International Prognostic Index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009;27:4555–62.

APPENDIX M (cont'd)
Follicular Lymphoma International Prognostic Index and International Prognostic Index

International Prognostic Index (IPI)

Risk Factors	
Ann–Arbor Stage III or IV	
Age > 60 years	
Serum LDH > 1 × ULN	
ECOG Performance Status ≥ 2	
Extranodal involvement ≥ 2	
IPI Risk Group	Number of IPI Risk Factors
Low	0 or 1
Low–intermediate	2
High–intermediate	3
High	4 or 5

ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; ULN = upper limit of normal.

The results of FDG–PET should not be taken into account for calculation of IPI since this prognostic score was established without FDG–PET.

Adapted from:

The International Non–Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non–Hodgkin's lymphoma. N Engl J Med 1993;329:987–99.

APPENDIX N
Activities of Daily Living Scale and Instrumental Activities of Daily Living Scale

Katz Basic Activities of Daily Living (ADLs) Scale

Independence	Dependence	Activities
Points (1) *NO* supervision, direction, or personal assistance	Points (0) *WITH* supervision, direction, personal assistance, or total care	Points (1 or 0)
Bathing (sponge bath, tub bath, or shower): Receives either no assistance or assistance in bathing only one part of body	Bathing: Needs help with bathing more than one part of the body, getting in or out of the tub or shower; requires total bathing	Bathing Points:_____
Dressing: Gets clothes and dresses without any assistance except for tying shoes	Dressing: Needs help with dressing self or needs to be completely dressed	Dressing Points:_____
Toileting: Goes to toilet room, uses toilet, arranges clothes, and returns without any assistance (may use cane or walker for support and may use bedpan/urinal at night)	Toileting: Needs help transferring to the toilet or cleaning self, or uses bedpan or commode	Toileting Points:_____
Transferring: Moves in and out of bed and chair without assistance (may use cane or walker)	Transferring: Needs help in moving from bed to chair or requires a complete transfer	Transferring Points:_____
Continence: Controls bowel and bladder completely by self (without occasional "accidents")	Continence: Is partially or totally incontinent of bowel or bladder	Continence Points:_____
Feeding: Feeds self without assistance (except for help with cutting meat or buttering bread)	Feeding: Needs partial or total help with feeding or requires parenteral feeding	Feeding Points:_____
		Total Points:_____

Scoring:

6 points = high (patient independent)

0 points = low (patient very dependent)

Reference:

Katz S, Down TD, Cash HR, et al. Progress in the development of the index of ADL. Gerontologist 1970;10:20.

APPENDIX N
Activities of Daily Living Scale and Instrumental Activities of Daily Living Scale (cont.)

Lawton–Brody Instrumental Activities of Daily Living (IADLs) Scale

A. Ability to Use Telephone 1. Operates telephone on own initiative—looks up and dials numbers, etc. 2. Dials a few well–known numbers 3. Answers telephone but does not dial 4. Does not use telephone at all	 1 1 1 0	**E. Laundry** 1. Does personal laundry completely 2. Launders small items—rinses stockings, etc. 3. All laundry must be done by others	 1 1 0
B. Shopping 1. Takes care of all shopping needs independently 2. Shops independently for small purchases 3. Needs to be accompanied on any shopping trip 4. Completely unable to shop	 1 0 0 0	**F. Mode of Transportation** 1. Travels independently on public transportation or drives own car 2. Arranges own travel via taxi, but does not otherwise use public transportation 3. Travels on public transportation when accompanied by another 4. Travel limited to taxi or automobile with assistance of another 5. Does not travel at all	 1 1 1 0 0
C. Food Preparation 1. Plans, prepares, and serves adequate meals independently 2. Prepares adequate meals if supplied with ingredients 3. Heats, serves, and prepares meals or prepares meals but does not maintain adequate diet 4. Needs to have meals prepared and served	 1 0 0 0	**G. Responsibility for Own Medications** 1. Is responsible for taking medication in correct dosages at correct time 2. Takes responsibility if medication is prepared in advance in separate dosage 3. Is not capable of dispensing own medication	 1 0 0
D. Housekeeping 1. Maintains house alone or with occasional assistance (e.g., "heavy work domestic help") 2. Performs light daily tasks such as dish washing, bed making 3. Performs light daily tasks but cannot maintain acceptable level of cleanliness 4. Needs help with all home maintenance tasks 5. Does not participate in any housekeeping tasks	 1 1 1 1 0	**H. Ability to Handle Finances** 1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income 2. Manages day–to–day purchases, but needs help with banking, major purchases, etc. 3. Incapable of handling money	 1 1 0
		Total Points:	