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

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STATISTICAL ANALYSIS PLAN

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**

PROTOCOL NUMBER:	BO21223
STUDY DRUG:	RO5072759 (GAZYVA®, GAZYVARO™, GA101, obinutuzumab)
VERSION NUMBER:	2
IND NUMBER:	104405
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SPONSOR:	F. Hoffmann–La Roche Ltd
PLAN PREPARED BY:	[redacted]
DATE FINAL:	17 September 2012
DATE AMENDED:	See electronic date stamp below.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Name	Reason for Signing	Date and Time (UTC)
[redacted]	Company Signatory	12-Apr-2016 11:08 06

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The previous version of the statistical analysis plan (SAP) was submitted to the U.S. Food and Drug Administration (FDA) on 19 December 2012. The following changes are included in the amended SAP (version 2):

- The definition of “progression” was clarified and now contains symptomatic deterioration and disease transformation.
- Specified that histological information (follicular lymphoma [FL] or marginal zone lymphoma [MZL]) from the IXRS will be used for the determination of analysis populations in accordance with the protocol.
- The best overall response as an endpoint was removed in accordance with the protocol.
- The description of the minimal residual disease (MRD) analysis was removed as it will be provided in a separate report.
- The description of patient-reported outcomes (PRO) analysis was shortened. The pre-specified analysis in the Clinical Study Report will follow what has been outlined in the protocol.
- The section on medical resource utilization was shortened.
- The section on pharmacokinetic outcome measures was re-worded.
- Some of the sensitivity analyses were re-worded and two additional sensitivity analyses were added.
- Minor editorial changes were made to improve clarity and consistency.
- Appendix 1 (study protocol synopsis) and Appendix 2 (study flowchart) were updated to reflect the current version of the study protocol.
- Appendix 3 was updated to reflect the current version of the independent Data Monitoring Committee (iDMC) charter.

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1. BACKGROUND

This document expands upon the statistical section of Study Protocol BO21223 and provides additional detail of the planned statistical analyses. The analyses outlined in this document will supersede those specified in the protocol.

Study BO21223 was developed to examine the efficacy and safety of obinutuzumab (also known as RO5072759, GA101, GAZYVA®, or GAZYVARO™) compared with rituximab, in combination with chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone [CHOP]; cyclophosphamide, vincristine, and prednisone or prednisolone [CVP]; or bendamustine), and followed by obinutuzumab or rituximab maintenance therapy for responders in previously untreated patients with advanced, indolent non-Hodgkin's lymphoma (NHL).

2. STUDY DESIGN

Study BO21223 is an open-label, international, multicenter, randomized, Phase III study of patients with previously untreated, advanced, indolent NHL to investigate the efficacy and safety of obinutuzumab plus chemotherapy, followed by obinutuzumab maintenance therapy for responders (patients who demonstrate a complete response [CR] or a partial response [PR]), compared with rituximab plus chemotherapy followed by rituximab maintenance therapy for up to 2 years for responders. 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 responders (CR or PR) receiving maintenance therapy.

Prior to the initiation of the study, each site will choose one of the three chemotherapy regimens (CHOP, CVP, or bendamustine), and all patients with follicular lymphoma (FL) at that site will receive the chosen chemotherapy regimen for the duration of the study; however, a site may switch to another regimen if new scientific data become available and following Sponsor approval. For marginal zone lymphoma (MZL) patients, 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 receive either rituximab plus chemotherapy, followed by rituximab maintenance therapy in responders, or obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy in responders. Treatment phase is then defined as induction plus up to two years of maintenance.

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

2.1 PROTOCOL SYNOPSIS

The protocol synopsis is in Appendix 1. For additional details, see the Study Flowchart in Appendix 2.

2.2 OUTCOME MEASURES

Response and progression will be assessed according to the modified Revised Response Criteria for Malignant Lymphoma ([modified RRCML], Cheson et al. 2007; see Appendix C of the protocol). For patients with MZL with paraproteinemia, a criterion requiring the absence of paraprotein was added to the modified RRCML to meet the requirements of a CR. For patients with only splenic MZL, additional hematological parameters (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 reaching CR status. The assessment of response and progression by the investigator will be considered the primary analysis for all of the endpoints described in the study.

Response and progression will also be assessed by an Independent Review Committee (IRC). In the United States, IRC-assessed endpoints will be the basis of regulatory decisions. Both investigator and IRC assessments will be analyzed as primary and secondary outcomes as specified below.

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy endpoint for this study is progression-free survival (PFS) in follicular lymphoma patients as assessed by the investigator.

Although the primary efficacy endpoint is investigator-assessed PFS, PFS on the basis of IRC review will also be analyzed to support the primary analysis. In the United States, IRC-assessed PFS will be the basis of regulatory decisions.

An additional measure for confirming clinical response is taking positron emission tomography (PET) into consideration. Exploratory analyses suggest that response assessment including PET may be superior over clinical response assessment alone (Trotman et al. 2011). Therefore, assessment of response including PET will also be examined.

The primary efficacy endpoint, PFS, is defined in patients with follicular lymphoma (referred to as the *follicular lymphoma population* that is regarded as the primary analysis population) as the time from randomization to the first occurrence of progression, relapse, or death from any cause, where symptomatic deterioration and disease transformation are counted as a progression throughout. 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, on the date of randomization.

2.2.2 Secondary Efficacy Outcome Measures

A secondary outcome measure of PFS will be applied to all randomized patients (including follicular and marginal zone lymphoma patients, henceforth referred to as the *overall population*).

The following secondary outcome measures apply to the overall population and the follicular lymphoma population (in a first step, definitions of these secondary outcome measures will not consider PET assessments; as appropriate, further secondary endpoints will be defined to include PET assessments; see Section 4.4.2 for details):

- CR rate at the end of induction, defined as the percentage of patients with CR as the end-of-induction response. All other cases are designated CR non-responders.
- Overall survival (OS), defined as the time from the date of randomization to the date of death from any cause. OS for patients who are not reported to have died at the time of the analysis will be censored at the date at which the patient was last known to be alive, as documented by the investigator.
- Overall response rate (ORR) on the basis of the end-of-induction response. The ORR is defined as the percentage of patients with CR or PR as the end-of-induction response. All other cases are designated non-responders.
- Event-free survival (EFS), defined as the time from randomization to disease progression or relapse, death from any cause, or initiation of any non-protocol-specified anti-lymphoma treatment (NALT). If the specified event (disease progression or relapse, death, or initiation of a NALT) does not occur, EFS will be censored at the date of last tumor assessment. For patients without an event who have not had post-baseline tumor assessments, EFS will be censored on the date of randomization.
- Time to next anti-lymphoma treatment (TTNALT) 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. Patients without a TTNALT event will be censored at the date at which the patient was last known to be alive.
- Disease-free survival (DFS), defined as the time from the date of the first occurrence of a documented CR to the date of disease progression, relapse, or death from any cause (PFS event) for the subgroup of patients with a response of CR at any time prior to NALT. DFS for patients who have had no documented disease progression, relapse, or have not died after CR, will be censored at the last disease assessment date.
- Duration of response, defined as the time from the date of the first occurrence of a documented CR or PR to the date of disease progression, relapse, or death from any cause (PFS event) for the subgroup of patients with a response of CR or PR any time prior to NALT. For patients achieving a response who have not experienced disease progression, relapse, or died prior to the time of the analysis, the duration of response will be censored on the date of last disease assessment.
- Histologic transformation rate from an indolent to a more aggressive NHL at first progression, defined as the appearance of diffuse areas of large lymphoma cells

(e.g., FL grade 3b, diffuse large B-cell lymphoma [DLBCL], Burkitt-like lymphoma, acute lymphoblastic leukemia, prolymphocytic leukemia, and others) within a tumor site in patients with a repeated biopsy at the time of disease progression or relapse.

- Conversion rate, defined as the proportion of patients with a PR at the end of induction therapy who convert to a CR, and patients with SD at the end of induction therapy who convert to a CR or to a PR, at any time during maintenance therapy or post-induction observation.

As with PFS, the secondary endpoints of CR rate and ORR will also be evaluated on the basis of IRC assessment.

2.2.3 Clinical and Biomarker Exploratory Outcome Measures

Among the follicular lymphoma patient population receiving obinutuzumab, the portion of patients with anti-obinutuzumab antibodies (HAHA) will be assessed after the last dose and during the washout phase until month 48 follow-up.

Analysis of other biomarker and exploratory endpoints as defined in the protocol, but not mentioned here, will be provided in separate reports.

2.2.4 Patient-Reported Outcome Measures

The high-level patient-reported outcome (PRO) measures are as follows:

- Change from baseline to the end of study in PROs based on the Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) instrument.
- European Quality of Life EQ-5D summary scores at baseline, during treatment, after treatment, at the last assessment prior to progression, and at the first assessment after progression.

2.2.5 Pharmacoeconomic Outcomes – Medical Resource Utilization

Medical resource utilization data will be described if requested.

2.2.6 Pharmacokinetic Outcome Measures

The pharmacokinetic (PK) analysis from this study will be used as an external validation of the earlier developed population PK model, separately for FL and MZL.

The PK outcomes are as follows:

- Generate simulations from the final model to illustrate typical predictions and inter-individual variability of concentrations for FL and MZL patients, overall and by covariates identified by the model.
- Generate and summarize individual predictions of the total clearance of the drug (CL), the volume of distribution for the central compartment (V_C), the volume of distribution under steady-state conditions (V_{SS}), the maximum concentration observed (C_{max}), the steady-state concentration at the end of a dosing interval (C_{trough}), the terminal half-life ($t_{1/2,term}$), the effective half-life ($t_{1/2,eff}$), and the area

under the concentration–time curve from time zero to the end of the dosing period ($AUC_{0-\tau}$) by disease and by covariates.

- Generate individual exposure estimates for graphical exposure-response analysis.

2.2.7 Safety Outcome Measures

The safety outcome measures include:

- Incidence, nature, and severity of adverse events (including serious adverse events) compared between the two treatment arms.
- Deaths
- Changes in vital signs, physical findings, and clinical laboratory results.
- Incidence of hepatitis B reactivation. Hepatitis B reactivation will be defined as an elevation in serum hepatitis B virus (HBV) DNA to >29 IU/L.

2.3 DETERMINATION OF SAMPLE SIZE

The primary endpoint of investigator-assessed PFS was used for sample size estimation. Estimates of the number of events required to demonstrate efficacy with respect to PFS were made on the basis of the following assumptions:

- Two-sided log-rank test at the 0.05 level of significance.
- Powered for the follicular lymphoma population.
- Eighty percent power to detect a hazard ratio for obinutuzumab-combined chemotherapy versus rituximab-combined chemotherapy of 0.74, corresponding to an improvement in 3-year PFS from 70.7% to 77.4% or in median PFS from 6 to 8.1 years (35%). 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 futility analysis when approximately 30% of the total (investigator-assessed) PFS events have occurred (2nd Interim [futility]; see Table 1), and one efficacy analysis (3rd Interim [efficacy]; see Table 1) when approximately 67% of the total (investigator-assessed) PFS events have occurred. Efficacy and (non-binding) futility boundaries will be calculated using the Lan-DeMets approximation to the O'Brien-Fleming boundary shape.

In addition, a futility analysis on the basis of CR rates at the end of induction (1st Interim [futility]; see Table 1), as determined by CT (or magnetic resonance imaging [MRI], but not PET), will be performed on the first 170 randomized follicular lymphoma patients. For this CR futility analysis, we expect that approximately 15% of the total investigator-assessed PFS events have occurred.

With the above assumptions, 370 PFS events are required to achieve 80% power for the primary analysis (Final; according to Table 1). Recruitment will be staggered to recruit the first 170 patients at a smaller number of sites (first stage, approximately 125 sites),

followed by the activation of all sites (approximately 250 sites) after the independent Data Monitoring Committee (iDMC) meeting for the 1st Interim (futility). It is expected that during the first stage, after a 6-month ramp up, 18 patients per month will be recruited; after the iDMC meeting for the 1st Interim (futility) and another 4-month ramp up, an accrual rate of 37 patients per month is expected. Twelve hundred follicular patients, enrolled over 49 months and followed for an additional 29 months after randomization of the last patient, will be required to provide 370 PFS events, with a total duration of PFS follow-up of approximately 78 months (6.5 years). It is anticipated that in the worst case, the number of corresponding IRC events at clinical cut-off would be, at most, 10% lower than the number of investigator-assessed events. Such a worst case loss in number of events would result in a reduction in the power of approximately 5% to detect the assumed treatment difference. The primary analysis will incorporate all events up to the clinical cut-off date. This analysis will capture 370 investigator-assessed PFS events.

Approximately 200 additional patients with non-follicular lymphoma (i.e., with MZL) will be enrolled. This number was selected on the basis of estimation from the enrollment feasibility assessment prior to the start of the study. This estimation indicated that at least 200 MZL patients would likely be enrolled in 49 months, in addition to the planned follicular lymphoma patient enrollment. As such, data from the MZL patients can be interpreted in context of subgroup analyses. However, this subgroup is not powered to detect statistically significant differences.

Pharmacokinetic assessments will apply to a subpopulation of approximately 460 patients receiving obinutuzumab. This sample size will allow the accurate identification and quantification of the influence of covariates on PK parameters. In addition, this sample size is reasonable to indicate whether the variability in pharmacodynamic markers of response (e.g., tumor size shrinkage) could be attributed to exposure. Approximately 120 patients with follicular lymphoma will undergo pharmacokinetic sampling from each of the three chemotherapy groups (obinutuzumab-CHOP, obinutuzumab-CVP, and obinutuzumab-bendamustine), and 100 additional patients with non-follicular lymphoma will also undergo sampling. This sample size is believed to be sufficient to confidently characterize the pharmacokinetics of obinutuzumab in the target population, as well as the relationship between the exposure to obinutuzumab and response. The pharmacokinetic sampling schedule in this study was determined using an optimal sampling strategy and should result in a coefficient of variation of <20% for the main pharmacokinetic parameter estimates. In addition to the determination of T, B, and NK cells in all patients, absolute and relative B cell subsets will be determined by multicolor flow cytometry (FACS) on the basis of a combination of several CD antigens and surface immunoglobulins over time in approximately 60 patients of each therapeutic group (rituximab-CHOP, obinutuzumab-CHOP, rituximab-CVP, obinutuzumab-CVP, rituximab-bendamustine, and obinutuzumab-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 the generation of an initial hypothesis.

2.4 ANALYSIS TIMING

On the basis of the assumptions outlined in Section 2.3, the timing of the three interim and final analyses have been estimated as outlined below (Table 1).

Table 1 Timing of Analyses: Primary Efficacy and Futility

Analysis Type	Approximate Timing of Analysis on the Basis of Investigator-Assessed PFS Events in fITT (Percentage of Information)	Approximate Timing of Analysis under H1 (in Months after FPI in fITT)	Endpoint	Adjusted Two-Sided α-Level	Cumulative Two-Sided α-Level
1st interim (futility)	170 follicular lymphoma patients EOI response		EOI CR rate	NA	NA
2nd interim (futility)	111 PFS events (30%)	43	INV PFS	0.000085	0.000085
3rd interim (efficacy)	248 PFS events (67%)	60	INV PFS	0.012	0.012
Final	370 PFS events (100%)	79	INV PFS	0.046	0.05

CR = Complete Response; EOI = end-of-induction; FPI = first patient in; H1 = alternative hypothesis; INV = investigator-assessed; PFS = progression-free survival; fITT = intent-to-treat follicular lymphoma population

Further details of the interim analyses can be found in Section 4.7.

3. STUDY CONDUCT

3.1 RANDOMIZATION

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 an interactive voice or web-based response system (IXRS®). Randomization will be performed separately for patients with follicular and non-follicular lymphoma through the IXRS with the use of a hierarchical dynamic randomization scheme.

The randomization scheme will ensure approximately equal sample sizes in the two treatment arms for the following stratification factors:

- Chemotherapy regimen (CHOP, CVP, or bendamustine).
- FL International Prognostic Index (FLIPI; version 1 [Solal-Celigny et al. 2004]) risk group (low, intermediate, or high) in patients with follicular lymphoma or International Prognostic Index (IPI) risk group (low or low-intermediate vs. high-intermediate or high) in patients with non-follicular lymphoma.
- Geographic region (Western Europe, Eastern Europe, South and Central America, North America, Asia, or other).

The randomization 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 the FLIPI risk group (low, intermediate, high) in follicular lymphoma patients or the IPI risk group (low or low-intermediate risk vs. intermediate-high or high risk) in non-follicular lymphoma patients. If the first two levels are balanced, the third level ensures treatment balance within each geographic region (Western Europe, Eastern Europe, South and Central America, North America, Asia, or other).

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

Discordances between the IXRS and the electronic Case Report Form (eCRF) data will be summarized.

3.2 INDEPENDENT REVIEW FACILITY

An independent assessment of response and progression, on the basis of CT (or MRI) scans plus pertinent clinical data (with or without PET), will be provided by an IRC with appropriate expertise in interpreting 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 the procedures to be followed for the study can be found in the IRC charter (see Appendix 3).

For all investigator-assessed response analyses (interim end-of-treatment response, and PFS [futility and efficacy], and final PFS), there will be a corresponding analysis of the IRC-determined data.

3.3 DATA MONITORING

An iDMC will conduct periodic interim reviews of safety summaries, beginning approximately 1 month after the enrollment of the first patient, and then approximately every 2 months until at least 100 patients have completed two cycles of study treatment.

The iDMC will then 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.

Further details of the definition, the role, and the responsibility of the iDMC are provided in a separate document, the iDMC charter (see Appendix 3).

4. STATISTICAL METHODS

Except where specified, all continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum, and maximum). All categorical variables will be summarized by treatment group with frequency counts and percentages.

All statistical tests will be two-sided.

4.1 ANALYSIS POPULATIONS

For the determination of analysis populations, histological information (FL or MZL) from the IXRS will be used.

4.1.1 Intent-to-Treat Follicular Population

The primary efficacy analysis population is the intent-to-treat follicular lymphoma population (fITT), defined as all randomized patients with follicular histology. Patients will be analyzed according to the treatment arm to which they were randomized.

4.1.2 Intent-to-Treat Population

The primary and key secondary efficacy parameters will be determined in the intent-to-treat population, defined as all randomized patients (overall population, ITT).

4.1.3 Per-Protocol Population

A per-protocol analysis population is not defined for this study. The protocol violations will be documented.

4.1.4 Pharmacokinetic Evaluable Population

Pharmacokinetic analyses and the evaluable population will be defined in a separate analysis plan.

Patient data will be included in the PK analysis if they contain sufficient dosing information and at least one adequately documented and quantifiable concentration per patient.

4.1.5 Safety Population

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 (i.e., a patient who received obinutuzumab at least once for any reason will be analyzed under the obinutuzumab-chemotherapy treatment arm; if only chemotherapy and/or rituximab was received, the patient will be analyzed under the rituximab-chemotherapy treatment arm).

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, eligibility violations, study drug administration, and patient disposition will be summarized according to treatment arm in all randomized patients, as well as 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.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

All analyses will be performed for the follicular lymphoma population, as well as for the overall population, unless otherwise specified.

Demographic and baseline characteristics, including—but not limited to—sex, age, race, ethnicity, baseline weight, height, baseline body surface area (BSA), and Eastern Cooperative Oncology Group (ECOG) performance status (at baseline), as well as Ann Arbor stage (at baseline), will be summarized according to treatment arm in all randomized patients and by histology (follicular vs. non-follicular). A table will summarize the three stratification factors (chemotherapy, FLIPI/IPI score, and geographic region). Medical history, including diagnosis (e.g., follicular lymphoma, MZL) and time since diagnosis (categorical), will be summarized according to treatment group.

Should country policy prohibit the collection of race or age information, then patients will appear in the missing category of summary tables.

4.4 EFFICACY ANALYSIS

4.4.1 Primary Efficacy Endpoint

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: $PFS_{G\text{-}Chemo} = PFS_{R\text{-}Chemo}$ vs. H_1: $PFS_{G\text{-}Chemo} \neq PFS_{R\text{-}Chemo}$

The treatment comparison will be made in the fITT population using a two-sided, stratified log-rank test (overall level of significance of 0.05) that was stratified by chemotherapy regimen (CHOP, CVP, or bendamustine) and FLIPI risk group (low, intermediate, or high). For cases in which a patient is misrandomized with respect to a stratification factor (i.e., there is a discrepancy between the IXRS-recorded stratification

factor level and the eCRF-recorded stratification factor level for chemotherapy regimen or FLIPI), the eCRF data will be used in the primary analysis. Discordances between the IXRS and the eCRF data will be summarized. Because geographic region is not expected to be strongly prognostic, region will not be included as a factor in the stratified analyses, to avoid loss of efficiency.

Kaplan-Meier methodology will be used to estimate PFS distribution for each treatment arm. These curves will also provide a visual description of the differences among treatment arms. Estimates of treatment effect will be expressed as hazard ratios through the use of a stratified Cox proportional hazards analysis, including 95% confidence intervals.

The median PFS is not expected to be reached in this study; hence, the estimated 2-year and 3-year probabilities, including 95% confidence intervals, will be used to describe PFS in addition to the hazard ratio.

4.4.2 Secondary Efficacy Endpoints

All analyses of secondary efficacy endpoints will be performed for the follicular lymphoma population and the overall population, with the exception of PFS, which will be analyzed only in the overall population as a secondary efficacy endpoint (PFS for fITT is the primary efficacy endpoint).

To adjust for multiple testing of key secondary efficacy endpoints, thereby controlling the overall type I error at a two-sided level of significance of 0.05, a fixed sequence testing procedure will be used (Westfall and Krishen 2001). The following endpoints will be tested in the order given (see also Section 2.2.2 for secondary endpoints not included in the fixed sequence testing procedure):

- PFS in all randomized patients.
- CR rate without PET at the end of induction therapy in the follicular lymphoma population.
- CR rate without PET at the end of induction therapy in the overall population.
- OS in the follicular lymphoma population.
- OS in the overall population.
- ORR without PET at the end of induction therapy in the follicular lymphoma population.
- ORR without PET at the end of induction therapy in the overall population.

The remaining secondary endpoints (EFS; TTNALT; DFS; duration of response; CR rate and ORR taking into account PET [where applicable]) will not be adjusted for multiple testing.

A given hypothesis in the list above will only be rejected once all previous hypotheses have been rejected at a two-sided level of significance of 0.05. All analyses will be

performed on the basis of the investigator's assessment. For U.S. regulatory decision making, the key secondary analyses of PFS, CR rate, and ORR will be performed on the basis of IRC assessments. The same fixed testing sequence as for the investigator-assessed endpoints will be applied.

Time-to-event endpoints, such as OS, EFS, DFS, duration of response, and TTNALT, will be analyzed using the same statistical methods as described for the primary analysis of PFS (see Section 4.4.1). Indolent histology (follicular or non-follicular) will also be included as a stratification factor in the stratified analyses for the ITT population.

Response rates in the treatment groups will be compared using stratified Cochran-Mantel-Haenszel (CMH) tests. The stratification factors are the same as those specified for the PFS analysis. In addition, rates and 95% confidence intervals will be reported for each treatment group.

The histological transformation rate at first progression and the conversion rate will be compared using stratified CMH tests. Rates, including 95% confidence intervals, will be estimated for each treatment group.

4.4.3 Exploratory Efficacy Endpoints

The fITT population is the primary population for all efficacy measures and will be the only population examined for all exploratory analyses (or a subgroup of this population, as defined below).

The potential association between FcγR genotype, response category, minimal residual disease (MRD) qualitative status (negative or positive), and PFS will be assessed using Kaplan-Meier curves and log-rank tests. Response rates by FcγR genotype and MRD negativity status at the end of induction treatment 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 4.4.2 and 4.4.4.

4.4.4 Sensitivity Analyses

The fITT population is the primary population for all efficacy measures and will be the only population examined in all sensitivity analyses. The following sensitivity analyses for both IRC and investigator-assessed PFS will be performed:

- Unstratified log-rank test.
- Re-randomization test of the primary endpoint to assess the sensitivity of the stratified log-rank test to the dynamic randomization procedure. See Kaiser 2012 for details.
- The impact of loss to follow-up will be assessed by a worst-case analysis that assigns event outcomes to patients who withdrew 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.

- A missed assessment potential impact analysis will be performed to assess the robustness of the result of the analysis of PFS. In this analysis, if patients have missed an assessment prior to the date of the clinical data cut-off or prior to PD, they will be counted as having progressed of the day after their last complete response assessment.
- PFS analyses will be repeated with censoring at the initiation of NALT prior to disease progression, to assess potential confounding of the treatment effect estimates by subsequent therapy.
- Patients who discontinue the study treatment for other reasons than disease progression or death will be counted as having progressed at the time of discontinuation (event will be date of last dose for early treatment discontinuations).
- Patients who died more than 6 months after their last response assessment and showed no sign of progression will be censored at the last available response assessment.

For IRC and investigator-assessed CR rate and ORR, the effect of prognostic factors on the probability of a CR and an overall response will be assessed in an exploratory analysis with the use of logistic regression.

4.4.5 Subgroup Analyses

Subgroup analyses of investigator-assessed PFS, IRC-assessed PFS, CR rate and ORR (all without PET) will be performed for the fITT and ITT populations according to prognostic factors to assess internal consistency. The estimated probabilities in yearly intervals, as well as the hazard ratio and their 95% confidence intervals (for time-to-event endpoints) or response rates, as well as the odds ratio and their 95% confidence intervals (for binary endpoints), will be reported separately for each level of the following subgroups:

- Baseline characteristics (age at randomization, sex, race).
- Stratification factors (chemotherapy regimen, FLIPI or IPI risk group, geographic region).
- Potential prognostic factors (including, but not limited to, ECOG performance status, Ann Arbor stage, histology [follicular vs. non-follicular], Fcγ receptor status, activities of daily living [ADL], instrumental activities of daily living [IADL]).

All patient characteristics and prognostic factors are measured at or before randomization.

4.4.6 Patient-Reported Outcomes

Unless otherwise specified, PRO analyses will include all randomized patients who have a baseline and at least one post-baseline PRO assessment. Patients in this subset will be analyzed according to their randomized treatment assignment, irrespective of the treatment received. The analyses will be performed separately for fITT and ITT, and the

PRO sections in the clinical study report will be reported according to what was specified in the protocol.

4.4.7 Pharmacoeconomic Analyses

Analysis of pharmacoeconomic data and production of a final pharmacoeconomic report will be handled separately from the final clinical report of this study. Information obtained from the collection of medical care utilization data in this study may be combined with other data, such as cost data or other clinical parameters, in the production of a final pharmacoeconomic report.

4.4.8 Pharmacokinetic Analyses

Pharmacokinetic analyses will be defined in a separate final pharmacokinetic report.

4.4.9 Pharmacodynamic Analysis

For each visit at which $CD19^+$ B-cell measurements are made, 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
- B-cell depletion is defined as a CD19 measurement of $<0.07 \times 10^9$/L and can only occur after at least one dose of study drug has been administered. Time to depletion is defined as the number of days between the first intake of study drug and the date of first depletion.
- B-cell recovery is defined as a CD19 measurement of $\geq 0.07 \times 10^9$/L, for which the patient's previous CD19 measurement revealed B-cell depletion. B-cell recovery will only be considered possible after the patient has had his last dose of study treatment. Time to B-cell recovery will be defined as the time from B-cell depletion until B-cell recovery.

4.5 SAFETY ANALYSES

The population for analyzing safety will be the safety analysis population. Key treatment exposure and adverse event tables will also be generated by tumor histology.

4.5.1 Exposure to Study Medication

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

Withdrawals of patients from study treatment will be reported as listings and summary tables.

4.5.2 Adverse Events

Verbatim descriptions of adverse events will be mapped to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. For adverse events, the most extreme severity will be used for reporting. All adverse events occurring during or after the first treatment will be summarized by treatment arm and divided by body system, NCI CTCAE grade, and relationship to trial treatment. In tables of the overall incidence of adverse events, patients who experienced the same event on more than one occasion are counted only once in the calculation of event frequency, and the adverse event with the most extreme severity will be included.

For selected events of particular interest (e.g., infusion-related reaction [IRR], infections, tumor lysis syndrome [TLS], or neutropenia), more detailed analyses will be conducted. The analysis will depend on the specific question of interest for that particular adverse event.

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

In addition, all serious adverse events will be summarized.

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

4.5.3 Laboratory Data

Laboratory data with values outside of the normal ranges will be identified. Additionally, selected laboratory data will be summarized according to treatment arm and graded according to NCI CTCAE, Version 4.0. Of note, abnormal laboratory data that are clinically significant will be reported as adverse events and summarized in the adverse event tables. Shift from baseline tables will be assessed on the basis of the NCI CTCAE, Version 4.0 grading system.

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

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

4.5.4 Vital Signs

Vital signs (absolute values and changes from baseline) will be summarized according to treatment arm over time, without any replacement for missing data. Descriptive statistics will be tabulated for ECOG performance status. ECG, left ventricular ejection fraction (LVEF), and physical examination abnormalities will be listed.

4.6 MISSING DATA

For PFS, patients who do not have documented disease progression or death will have observations censored on the date of the last tumor assessment or, if no tumor assessments were performed after the baseline visit, at the time of randomization.

For OS, patients for whom death has not been documented will have observations censored on the last date at which they were known to be alive.

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

4.7 INTERIM 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. 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 provide a recommendation as to whether to stop the trial early. However, all interim analyses are non-binding and the Sponsor will make the final decision regarding early termination of the trial for reasons of either futility or efficacy.

All summaries and analyses according to treatment arm will be prepared by an iDCC for the iDMC review. 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 3.3. Three interim analyses are planned: two for futility (one on CR and one on PFS) and one for efficacy (on PFS).

The first interim futility 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 halting the study for futility if the observed difference in CR rates on the basis of CT (or MRI, but not PET) is $<3\%$ in favor of obinutuzumab-chemotherapy (i.e., CR rate needs to be $\geq 3\%$ higher for obinutuzumab-chemotherapy relative to rituximab-chemotherapy). The iDMC will consider further supporting data (e.g., PET, MRD), as described in the futility analysis specifications, for their recommendation.

The second interim analysis (futility on PFS) will be conducted when 30% of the required investigator-assessed PFS events (i.e., approximately 111 events) will have occurred. The iDMC may recommend stopping the study for futility if the observed hazard ratio of obinutuzumab over rituximab is >1 (futility boundary assessed on the basis of the non-binding O'Brien-Fleming β-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 α-spending function such that the overall type I error rate will be maintained at the 0.05 level. With 67% information, the α spending is 0.012.

The (final) primary efficacy analysis will take place when 370 investigator-assessed PFS events have been observed among the follicular population.

A corresponding analysis will be performed on the basis of IRC-assessed PFS events observed in the same timeframe as the 370 investigator-assessed PFS events. It is anticipated that the number of IRC events will be slightly lower (by approximately 10%) than the investigator-determined events.

In the event that the trial is terminated early (at an interim analysis), an analysis would examine all IRC data up to—and no further than—the time of study termination.

The iDMC will also review safety summaries at each of the interim analyses, in addition to ongoing, periodic safety monitoring.

In the event that the follicular lymphoma population accrues the planned number of patients, 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 lymphoma subset irrespective of when the non-follicular lymphoma population has completed enrollment.

Further details of the interim analyses will be described in the iDMC charter.

5. REFERENCES

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Appendix 1
Protocol Synopsis

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:	104405
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 CR after the end of induction treatment, as assessed by the investigator, between the two arms, with and without FDG-PET

- 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 18F-fluorodeoxyglucose positron emission tomography (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

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 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.

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 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 (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 anNALT 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.

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 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.

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*.

Appendix 1
Protocol Synopsis (cont.)

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.

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Appendix 1
Protocol Synopsis (cont.)

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.

Appendix 1
Protocol Synopsis (cont.)

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

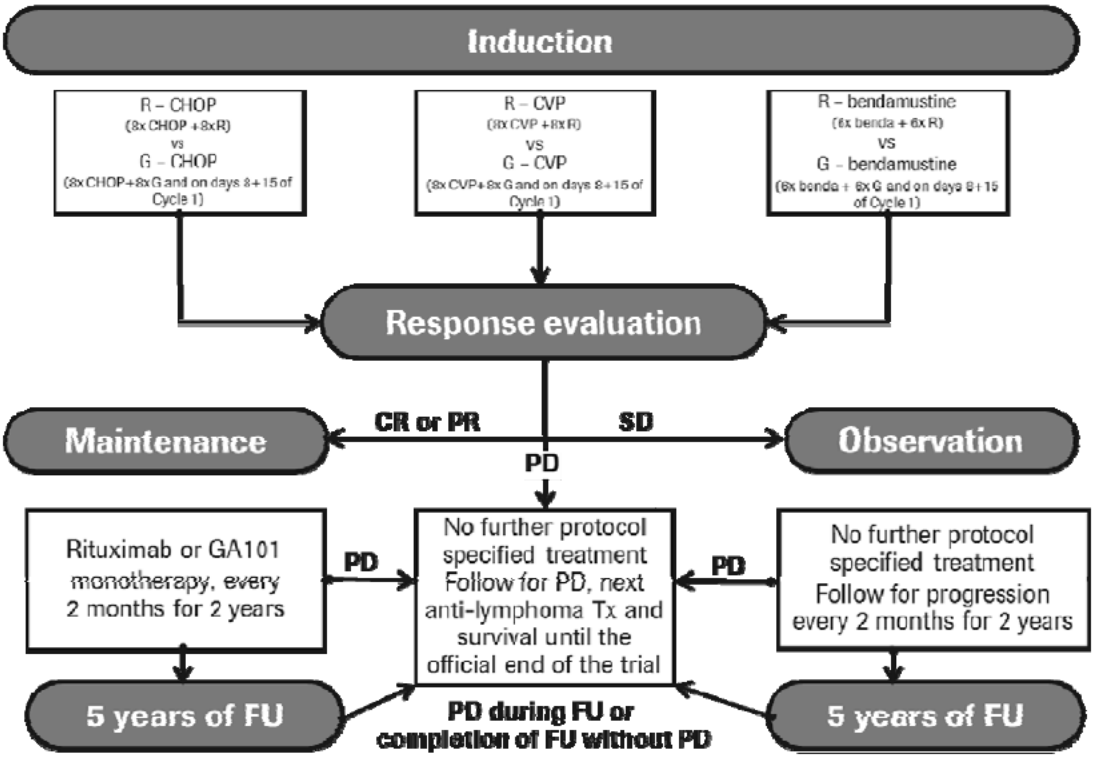
of particular patients. An IDMC will evaluate interim analysis results and determine whether the trial will be stopped early.

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.

Appendix 2
Study Flowchart



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.

Appendix 3
iDMC Charter

CHARTER FOR THE INDEPENDENT DATA MONITORING COMMITTEE

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:	BO21223
AUTHORS:	[redacted], Study Statistician [redacted], Clinical Science
EUDRACT NUMBER:	2010-024132-41
SPONSOR:	F. Hoffmann–La Roche, Ltd.
APPROVED BY:	[redacted], [redacted]
DATE FINAL:	*9 July 2013 (version 3)* *26 October 2011 (version 2)* *4 July 2011 (version 1)*

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STUDY Number BO21223

I have read this charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

[redacted] July 24, 2013
Date

[redacted], Ph.D.,
[redacted]
F. Hoffmann-La Roche, Ltd
1 DNA Way, MS [redacted]
South San Francisco,
CA 94080, USA

[redacted] Date

[redacted] Ph.D.,
Professor of [redacted]
[redacted]
Germany

INDEPENDENT DATA MONITORING COMMITTEE MEMBER SIGNATURES

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**

STUDY Number BO21223

I have read this charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

[redacted] _____ Date _____

[redacted] Ph.D.,
[redacted]
F. Hoffmann-La Roche, Ltd
1 DNA Way, MS [redacted]
South San Francisco,
CA 94080, USA

[redacted] Aug 13, 2013

[redacted] Date

[redacted] Ph.D.,
Professor of
[redacted]
[redacted] Germany

INDEPENDENT DATA MONITORING COMMITTEE MEMBER SIGNATURES

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**

STUDY Number BO21223

I have read this charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

[redacted], M.D. _____ 25/07/2013
Professor Date
[redacted] UK

[redacted], M.D., Ph.D. _____
Professor of Date
[redacted] US

INDEPENDENT DATA MONITORING COMMITTEE MEMBER SIGNATURES

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**

STUDY Number BO21223

I have read this charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

[redacted], M.D.
Professor
[redacted]
UK

Date

[redacted]
[redacted], M.D., Ph.D.
Professor of [redacted]
[redacted]
US

8/8/13
Date

INDEPENDENT DATA MONITORING COMMITTEE MEMBER SIGNATURES

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STUDY Number BO21223

I have read this charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

[redacted], M.D., Ph.D.
[redacted]
Professor of [redacted]
[redacted], USA

5 Aug 2013
Date

[redacted], M.D., Ph.D.
[redacted]
Spain

Date

INDEPENDENT DATA MONITORING COMMITTEE MEMBER SIGNATURES

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**

STUDY Number BO21223

I have read this charter and confirm that, to the best of my knowledge, it accurately describes the conduct of the independent Data Monitoring Committee.

[redacted] M.D., Ph.D.
[redacted]
Professor of
[redacted] Professor of
[redacted]

Date

[redacted] M.D., Ph.D.
[redacted]
Spain

July 23rd, 2013
Date

1. INTRODUCTION

Study BO21223 is an open-label, international, multicenter, randomized, Phase III study to investigate the efficacy and safety of obinutuzumab (GA101) plus chemotherapy followed by obinutuzumab maintenance therapy for responders (complete response [CR] or partial response [PR]) compared with rituximab plus chemotherapy followed by rituximab maintenance therapy for responders in patients with previously untreated advanced indolent non-Hodgkin's lymphoma (NHL).

For follicular lymphoma, prior to the initiation of the study, each site will choose one of three chemotherapy regimens considered to be the standard of care for follicular lymphoma:

- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone [or prednisolone])
- CVP (cyclophosphamide, vincristine, and prednisone [or prednisolone])
- Bendamustine

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.

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 lymphomas will be recruited and randomly assigned in a 1:1 ratio to the two treatment arms.

The primary objective of this study is to demonstrate superiority in progression-free survival (PFS) with obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy in patients with follicular lymphoma, based on investigator-assessed PFS.

Secondary objectives include comparison of PFS, event–free survival (EFS), disease–free survival (DFS), duration of response, time to next anti–lymphoma treatment on overall population, comparison of overall and complete response (OR and CR) rates and overall survival (OS), in follicular lymphoma and overall population, and safety between treatment arms.

PFS, overall response rate (ORR) and CR will also be assessed by an independent review committee (IRC) and will form secondary objectives. In the United States, IRC assessments will be the basis for regulatory decisions.

Terms and abbreviations used in this charter are defined in Table 1.

Table 1 Terms and Abbreviations

Abbreviation	Definition
audited data	data compared with their original source (physician's records, laboratory results, etc.) to ensure integrity and reliability
blinded data	data for which treatment assignment is not identified at the group level (treatment groups pooled)
Study Management Team (SMT)	team composed of Sponsor representatives directly involved with the trial; includes Medical Monitor, biostatistician, and Global Study Manager
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone [or prednisolone])
CRF	case report form
CR	complete response
CRO	contract research organization
CVP	cyclophosphamide, vincristine, and prednisone [or prednisolone])
DFS	disease–free survival
DRB	Data Review Board, consisting of employees of the Sponsor empowered to make critical decisions, such as whether to accept a recommendation from the iDMC to stop the clinical trial(s). For this study, the DRB is composed of the Chief Medical Officer (decision-maker), the Oncology Therapeutic Area Head, the Drug Safety Head, the Global Regulatory Head, and the Global Biometrics Head (Data Review Board Chair). The DRB Chair is Roche's point of contact for the iDMC members after the iDMC has reviewed unblinded data.
EFS	event–free survival
FDG	fluorodeoxyglucose
frozen database	Database that has been checked for consistency, completeness, and accuracy and to which no changes have been made after a specified date
HR	hazard ratio
iDCC	independent Data Coordinating Center wherein external data analysts provide current, accurate, and unblinded interim data summaries to the iDMC For this study: IST GmbH Soldnerstrasse 1, 68219 Mannheim, Germany
iDMC	independent Data Monitoring Committee
IRC	Independent review committee
SAP	statistical analysis plan

Abbreviation	Definition
IxRS	Interactive voice/web response system
Medical Monitor	Sponsor employee who is responsible for the overall conduct of a trial; also known as the clinical scientist
NHL	non-Hodgkin's lymphoma (NHL).
ORR	overall response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
pooled data	data for which treatment arms are combined
Roche Group	The Roche Group includes, among others, the following entities: F. Hoffmann–La Roche (Basel, Switzerland), Hoffmann–La Roche, Inc. (Nutley, USA), Roche Products, Ltd. (Welwyn, United Kingdom), Genentech, Inc. (South San Francisco, USA), Shanghai Roche Pharmaceuticals, Ltd. (Shanghai, China), Roche Palo Alto, LLC (Palo Alto, USA)
Sponsor	F. Hoffmann–La Roche, Ltd.
unblinded data	Data for which treatment assignment is identified as G-chemo or R-chemo at the group level

2. ROLE OF THE COMMITTEE

2.1 SAFETY

The independent Data Monitoring Committee (iDMC) shares with the Sponsor the responsibility for regularly monitoring the overall safety of the patients in the trial. By carefully reviewing overall rates of deaths, serious adverse events, and other specified safety events, the iDMC will help the Sponsor minimize patient exposure to unnecessary risk. The iDMC will also evaluate benefit and risk by reviewing efficacy and safety data during the scheduled interim analyses.

At the beginning of the study, intensive monitoring and analysis of all significant safety events will be performed. The first safety analysis by the iDMC will take place 1 month after randomization of the first patient and then approximately every 2 months until 100 patients (50 per arm) have completed two cycles of study treatment. Afterwards, 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.

For details of what will be presented to iDMC at each safety review, please see Appendix 1.

2.2 EFFICACY

The iDMC will be used to evaluate efficacy at three formal interim analyses, as well as periodic safety reviews as described in Section 2.1, and to recommend if the trial should be stopped early. Interim analyses of efficacy data will be conducted according to the methods specified in the study protocol and Statistical Analysis Plan (SAP). Recommendations to stop the trial because of substantial evidence of efficacy or lack of efficacy (futility) of the study drug must be based on the specified interim analysis methodology.

Three interim analyses are planned; two for futility and one for efficacy. The first interim analysis will be based on differences between the two treatment groups 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 rates is $<3\%$ in favor of obinutuzumab plus chemotherapy (i.e., CR rate should be $\geq 3\%$ higher on obinutuzumab plus chemotherapy vs. rituximab plus chemotherapy to continue the study).

The second interim analysis (futility on PFS) will be conducted when 30% of the required PFS events (i.e., approximately 111 events) have occurred among follicular lymphoma patients only. The iDMC may recommend to stop the study for futility if the observed hazard ratio (HR) of obinutuzumab over rituximab is >1 (futility boundary based on non–binding 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) among follicular lymphoma patients only, it is expected that 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 spent is 0.012.

Details of the efficacy analyses, and boundaries for interim analyses for the expected number of events, are specified in the interim SAP. An overview of the outputs is provided in Appendix 1 .

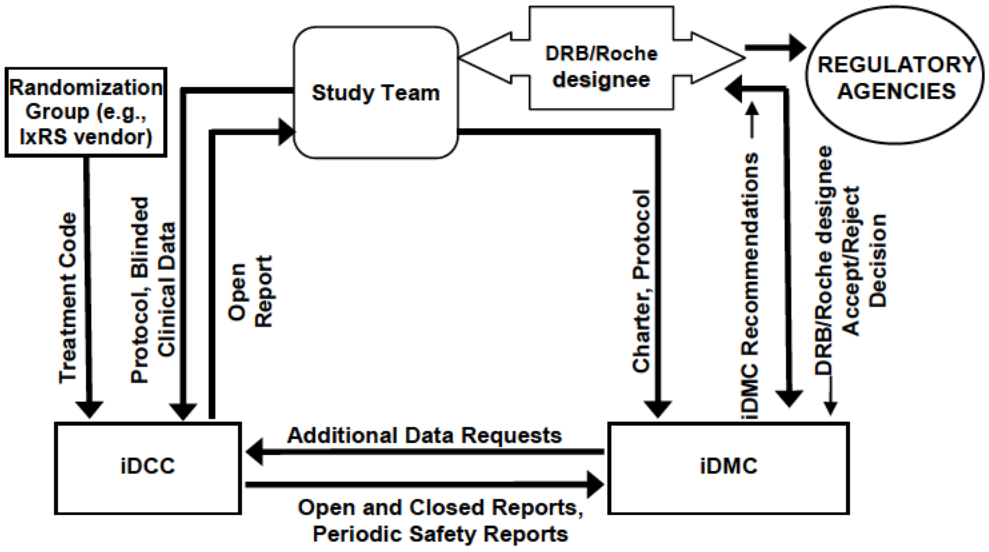
2.3 STUDY CONDUCT

The iDMC may alert the Sponsor to possible concerns related to the conduct of the trial. These include, but are not limited to, concerns about the appropriateness of the study population on the basis of characteristics of enrolled patients, adequacy of the randomization process, protocol violations, problems with protocol compliance, and problems with data completeness and cleanliness.

3. ORGANIZATIONAL FLOW

Figure 1 illustrates the relationships between the Study team, the iDMC, the independent Data Coordinating Center (iDCC), the interactive voice/web response system (IxRS) vendor, the Data Review Board (DRB), and regulatory agencies.

Figure 1 Organizational Flow



DRB = Data Review Board; iDCC = independent Data Coordinating Center;
iDMC = independent Data Monitoring Committee; IxRS = interactive voice/web response system.

4. COMMITTEE MEMBERSHIP

4.1 MEMBERS

Chair: [redacted], Ph.D.
Professor of
[redacted]
Germany

Members: [redacted], M.D.
Professor
[redacted]
UK

[redacted], M.D., Ph.D.
Professor of
[redacted]
, US

Address details of administrative [redacted] of Prof. [redacted]:
[redacted]
Telephone
e-mail: [redacted]

[redacted], M.D., Ph.D.
[redacted]
Professor of
Professor of
[redacted]
US

[redacted], M.D., Ph.D.
[redacted]
, Spain

Each member's curriculum vitae is available in the Sponsor's files and will be provided to any regulatory agency upon request.

4.2 FINANCIAL DISCLOSURE AND CONFLICT OF INTEREST

No iDMC member may participate in the study as an investigator, co-investigator, subinvestigator, or patient, or in any other capacity that might compromise his or her privileged activities on the iDMC.

iDMC members are strongly discouraged from owning any stock in Roche (such as bearer shares, non-voting equity security [NES or Genussscheine], or American Depository Receipts [ADR]) or owning any stock in any other Sponsor of the study. In no event may iDMC members own stock in Roche or any other Sponsor of the study in excess of U.S. $50,000. iDMC members must disclose any payments they or their immediate family members may have received from the Roche Group in excess of U.S.$10,000 or its equivalent in the 12 months prior to the ratification of the charter. Such payments may include any combination of consulting fees, honoraria, donations of equipment, grants to fund ongoing research, or other payments exclusive of reimbursements to support the costs of conducting clinical trials.

iDMC members must disclose whether they serve on other iDMCs and whether any of these committees is involved with study drugs within the same therapeutic class as obinutuzumab. Members will attest that membership in other committees will not interfere with their objective judgment while serving on the trial, and the final decision will be made by the Chair of the iDMC.

The iDMC will be responsible for deciding whether consultancies or financial interests of the members may materially affect objectivity. This decision will be based on whether there is a reasonable belief that a member's objectivity is in doubt. Members of the iDMC will be responsible for advising the Sponsor of any changes in their financial interests in pharmaceutical companies, biotechnology companies, or contract research organizations (CROs) and any changes in consultancies that might lead to potential conflicts of interest. Members of the iDMC who develop potential or significant perceived conflicts of interest that may materially affect objectivity will be asked to resign from the iDMC and will be replaced.

4.3 DURATION OF IDMC MEMBERSHIP

iDMC membership will extend for the duration of the trial, up to the time the database is locked and the study is unblinded. If a member leaves the iDMC, the Sponsor will select a replacement.

5. COMMITTEE MEETINGS

5.1 ORGANIZATIONAL MEETING

The first meeting of the iDMC will be an organizational meeting. This meeting will formally establish the iDMC and thoroughly acquaint the iDMC with the protocol and interim analysis plan. It also affords the iDMC an opportunity to recommend final

revisions to the charter and to the communication plan between the iDMC and the Sponsor.

In addition to the iDMC members, the organizational meeting will be attended by members of the Study Management Team (SMT), one or more representatives of the DRB and the iDCC Statistician.

The following documents will be provided:

- Final protocol
- eCRF
- Draft iDMC charter
- Investigator brochure
- Interim analysis plan if available (to be sent to iDMC latest prior to the first interim efficacy analysis as outlined in Section 2.2).

5.2 SCHEDULED INTERIM ANALYSIS MEETINGS

According to the study protocol, three interim analyses and regular safety review are scheduled for the review of the accrued efficacy and safety data. Additional interim analyses may be conducted at the request of the iDMC or the SMT.

The iDMC meetings will be separated into two sessions. There will be an open session followed by a closed session, for which open and closed reports will be presented and discussed respectively.

5.2.1 Open Session

The open session will serve as a general study update and will provide a forum for iDMC members to question the Sponsor about the trial and to seek additional information deemed relevant to the interim analysis. Attendees will be the iDMC members, the iDCC Statistician, the Sponsor's Medical Monitor and biostatistician, others as appointed by the Sponsor and representatives from the German Low Grade Lymphoma Study, the Ostdeutsche Studiengruppe für Hämatologie und Onkologie, and the National Cancer Research Institute. This will be the only portion of the meeting during which the Sponsor representatives discuss the trial with the iDMC.

5.2.2 Closed Session

At the closed session, the iDMC will discuss the unblinded data and make recommendations regarding the study. Only iDMC members and the iDCC Statistician will attend the closed session. The Sponsor will not have access to the closed reports until study completion. However, if the iDMC recommends the study to be stopped then the DRB may request unblinded data as outlined in Section 6.5.

5.3 UNSCHEDULED MEETINGS

In addition to the regularly scheduled safety reviews, an unscheduled review of the data may be performed at the request of the iDMC or SMT, on the basis of a perceived concern for patient safety. The iDCC will prepare the necessary reports to which the Sponsor will remain blinded.

6. COMMUNICATION

The DRB Chair is the Sponsor's single point of contact for the iDMC members after the iDMC members have reviewed the unblinded data. iDMC members are to treat all communications regarding this clinical study, including reports, data, review meeting discussions, teleconferences, and meeting minutes, as confidential material.

6.1 OPEN REPORTS

The open reports will be prepared by the iDCC and distributed to the open-session attendees and the DRB Chair within 5 business days prior to each bimonthly safety review meeting and within 10 business days prior to the 6-monthly safety review meetings and interim analysis meetings. The open reports, which will be based on pooled blinded data, will not include safety or efficacy data, as described in Appendix 2.

6.2 CLOSED REPORTS

The closed reports will be prepared by the iDCC and provided to the iDMC within 5 business days prior to each bimonthly safety review meeting and within 10 business days prior to the latter safety review meetings and interim analysis meetings. Closed reports will be reviewed at closed sessions and will include unblinded efficacy and safety data, as well as unblinded baseline characteristics and protocol deviation data, as described in Appendix 1.

6.3 IDMC MINUTES

The iDMC Chair or a designated member of the iDMC, with the assistance of the iDCC Statistician, will prepare minutes of the open and closed sessions within 1 week following each iDMC meeting. Minutes of the open session will be distributed to the iDMC, the iDCC Statistician, the Sponsor's Medical Monitor and Biostatistician and the DRB Chair. Minutes of the closed session will be distributed to the iDMC and the iDCC Statistician only.

At the conclusion of the study, a complete set of the minutes of the closed sessions and the closed reports will be sent to the Sponsor study biostatistician.

6.4 IDMC RECOMMENDATIONS

At each interim analysis and safety review, the iDMC will recommend that the trial either continues or stops. The iDMC may also recommend a protocol amendment. The recommendations will be based on the guidelines outlined in Section 2 with further details given below for Safety (Section 6.4.1) and Efficacy (Section 6.4.2).

Recommendations will be made by a majority vote of the iDMC members in attendance. The Chair, the iDCC Statistician, and two additional medical members of the iDMC must be present for the meeting to be quorate. The iDCC Statistician does not have a vote but needs to be present at the meeting to help the iDMC interpret the data. If the vote is a tie, the Chair has the casting vote.

The iDMC Chair will notify the DRB Chair of the iDMC's recommendations, in a meeting or by telephone (e-mail may also be used if time zones make either a meeting or a telephone call unfeasible), immediately after the closed session and will follow up with a written communication within 24 hours.

6.4.1 Safety Recommendations

Following each review of the safety data, the iDMC should make one of the following recommendations to the DRB:

1. Continuation of the study without modification
2. Continuation of the study with modification
3. Suspension of recruitment pending further evaluation of a safety issue
4. Discontinuation of the entire study (unacceptable safety profile in all arms)

Should the iDMC recommendation be (3) or (4) and the Sponsor accepts the recommendation then one of the following actions will be taken.

6.4.1.1 Consequences Following Hold due to an Event

If the accepted recommendation after safety review is that recruitment be placed on hold, then all further randomization will stop. The event causing concern will be thoroughly investigated by the Sponsor. The Sponsor will report the outcome of this investigation to the iDMC. Depending on these findings the iDMC will recommend continuing recruitment or discontinuing the study.

6.4.1.2 Consequences Following Discontinuation of the Entire Study

If the accepted recommendation is that the entire study be discontinued during the recruitment period then further randomization will stop immediately.

In case of a safety concern, patients already randomized who have not completed the treatment schedule will be withdrawn from treatment. The timing of this action will depend on the nature and severity of the events causing discontinuation and will be determined by the Sponsor in consultation with the iDMC. However, if efficacy without toxicity was observed for any patient, this patient may continue treatment as scheduled at the investigator's discretion and if the patient wishes to continue.

6.4.2 Efficacy Recommendations

The following guidelines may be used by the iDMC for making stopping recommendations based on the interim efficacy analyses.

Although these guidelines are in place, the iDMC has authority to deviate from these guidelines if safety or additional efficacy analyses (e.g. robustness assessments) indicate that a different recommendation is more appropriate.

6.4.2.1 CR Futility Analysis

The iDMC may recommend stopping the study for futility if the observed difference in IRC-assessed end of induction CR rates is < 3% in favor of G-chemo (see Section 2.2). In addition the following should be considered before recommending stopping the study:

- Difference in investigator-assessed CR rates
- Consistency of the observed difference in IRC–assessed CR rates with that of investigator-assessed CR rate difference
- Differences in CR rate when positron emission tomography (PET) results are incorporated into the response assessments (for both investigator and IRC assessments) at end of induction
- Differences in minimal residual disease (MRD) results
- Differences in overall response (OR) rates at end of induction

IRC–assessed CR rates are chosen for the primary decision making for this futility analysis because response rate assessed by IRC is considered to provide more uniform data (Osby et al. 2001).

An additional measure for confirming clinical response is taking fluorodeoxyglucose (FDG)–PET into consideration, but this remains experimental due to ongoing technical validation and standardization issues. However, CR assessment including PET has been suggested as being superior to clinical CR alone in predicting time-based outcomes (PFS). Therefore assessment of response including FDG-PET should also be examined.

For a detailed outline of the recommendation to the iDMC how to reach a futility recommendation we refer to the CR futility interim analysis specification document.

6.4.2.2 PFS Futility Analysis (at 30% PFS information)

The iDMC may recommend stopping the study for futility if the investigator-assessed PFS crosses the pre-defined boundary (HR >1, see Section 2.2). In addition the following should be considered before recommending stopping the study:

- Consistency of the HR estimate with that of IRC-assessed PFS
- Consistency when using an unstratified analysis instead of the primary stratified analysis
- Differences in response rates (CR and OR)

6.4.2.3 PFS Efficacy Analysis (at 67% PFS information)

1. The iDMC may recommend stopping the study at 67% PFS information (i.e., the primary analysis of the study will be conducted) when the primary endpoint, based on investigator-assessed PFS, crosses the pre-defined boundary (see above Section 2.2). In addition the following should be considered before recommending stopping the study:

   To evaluate the robustness of the treatment effect as measured by investigator-assessed PFS, the iDMC should consider the consistency of the HR estimate with that of IRC-assessed PFS.

   Consistency in results should be fulfilled when using an unstratified analysis instead of the primary stratified analysis for PFS.

2. The iDMC is guided to recommend study continuation as planned if the result of the primary analysis does not cross the pre-specified boundary and/or is not persuasive and/or is not consistent with the secondary analyses described above under 1.

Although these guidelines are in place, the iDMC has authority to deviate from these guidelines if safety or additional efficacy analyses (e.g., robustness assessments) indicate that a different recommendation is more appropriate.

6.5 SPONSOR DECISIONS

Upon receipt of the iDMC's recommendations, the DRB will review the recommendations, obtain input or additional data as deemed necessary from the iDMC, SMT, regulatory agencies, or other bodies such as the Ethics Committee/Internal Review Board, and, on behalf of the Sponsor, accept or reject the recommendations.

If the iDMC and the DRB agree to amend the protocol or to stop the trial, the Sponsor will inform regulatory agencies of the decision prior to notifying the investigational centers and Ethics Committees. In case of urgent safety restrictions the investigators may be notified prior to informing regulatory agencies. Public disclosure of the decision, as appropriate, will be made by the Sponsor.

If the iDMC recommends that the trial be stopped prematurely for efficacy reasons, the DRB may request unblinded data from the iDCC upon which to base its decision (proper Health Authority feedback will be sought prior to making this request). If the DRB decides to continue the trial, the DRB Chair will first discuss with the iDMC Chair the rationale for the decision and, thereafter, will provide a written explanation of the decision to the iDMC within 3 business days. At no point in the trial will the clinical team have access to the unblinded interim data.

The DRB Chair will communicate all decisions to the iDMC Chair and the Sponsor's Statistician. The Sponsor's DRB regulatory representative or designee will communicate the Sponsor's decisions to regulatory agencies as appropriate. The iDMC Chair will communicate the Sponsor's decision to the rest of the iDMC.

7. REFERENCES

1. Osby E, Taube A, Cavallin-Ståhl E, et al. Reproducibility of tumor response evaluation in patients with high-grade malignant non-Hodgkin's lymphoma. Med Oncol. 2001;18(2):137–40.

Appendix 1
Closed Reports

Closed reports will contain listings and summaries by treatment arm.

Safety monitoring every 2 months

- Demographics and disease characteristics
- All AEs
- Grade 3 and 4 AEs
- SAEs
- AEs of special interest:
  - Tumor lysis syndrome
  - Serious infections
  - Serious neutropenia
  - Serious infusion-related reactions (IRRs)
- Event of particular interest
  - Hepatitis B reactivation
- Laboratory data (hematology and biochemistry)
- Treatment discontinuations
- Treatment exposure
- Deaths

Safety monitoring every 6 months

The same outputs as given above for bimonthly safety will be provided. In addition the following will be provided:

- Detailed information regarding study treatment and chemotherapy (e.g., dosing, cycle length) for evaluation of dose density and dose intensity
- Concomitant medications
- Narratives on tumor lysis syndrome (TLS)

Efficacy Interim Analysis for CR futility

The following list outlines the outputs that will be provided at the interim futility analysis based on CR rate. Details will be given in the interim SAP.

- Summary of IRC-assessed CR rates at end of induction
- Summary of Investigator-assessed CR rates at end of induction
- Summary of IRC-assessed CR rates at end of induction including PET
- Summary of Investigator-assessed CR rates at end of induction including PET

APPENDIX 1 (cont'd)
Closed Reports

- Summary of MRD results
- Summary of OR rates at end of induction
  - By IRC including and excluding PET
  - By investigator including and excluding PET

Efficacy Interim Analyses for PFS

The following list outlines the outputs that will be provided at interim efficacy analyses. Details will be given in the interim SAP.

- Investigator-assessed PFS summary
  - Stratified and non-stratified
- Investigator-assessed Kaplan-Meier plot
- IRC-assessed PFS summary
  - Stratified and non-stratified
- IRC-assessed Kaplan-Meier plot
- OS summary and Kaplan-Meier plot (only at second efficacy IA)
  - Stratified and non-stratified
- Complete and overall response rates at end of induction

Appendix 2
Open Reports

The following data will be included in open reports (treatment arms combined):

- Recruitment rates
- Patient disposition – stratification factors
- Protocol violations/data problems