Official Title: A Non-Interventional, Retrospective and Prospective, Multicenter, Single Arm Study Evaluating the Effectiveness and Safety of Obinutuzumab in Patients with Previously Untreated Advanced Follicular Lymphoma

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STATISTICAL ANALYSIS PLAN For NON-INTERVENTIONAL STUDIES

TITLE:	**A NON-INTERVENTIONAL, RETROSPECTIVE AND PROSPECTIVE, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFECTIVENESS AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA**
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PLAN PREPARED BY:	[redacted]
DATE FINAL:	N.A.
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STATISTICAL ANALYSIS PLAN APPROVAL

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

Statistical Analysis Plan (version 1.0) has been amended to align it to the protocol Version 2.0 released on 23 May 2021 and to implement other changes regarding an additional interim analysis.

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1. BACKGROUND AND STUDY OBJECTIVES

1.1 BACKGROUND

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative tumours with varying behaviour and treatment-response patterns (Armitage 1993).

NHL is the most common hematologic malignancy in adults.

The majority of NHLs (also known as malignant lymphoma) are of B-cell origin and are characterized by the expression of a membrane antigen, CD20, which is important in cell cycle initiation and differentiation (Anderson et al. 1984).

NHL can be divided into aggressive and indolent NHL.
Indolent NHLs are a heterogeneous group of malignant lymphomas and account for about one-third of all NHLs.

Follicular lymphoma (FL) is the second most common lymphoma and is the most common subtype of indolent B-cell lymphomas diagnosed in the United States and Western Europe, accounting for approximately 35% of all NHLs, and 70% of indolent lymphomas (Swerdlow et al. 2008).

The clinical course of indolent NHL is characterized by remission and relapse (Gallagher et al. 1986).

Patients who are diagnosed without symptoms can be observed without treatment for several years. However, treatment is required when the patient presents with symptoms at diagnosis or develops symptoms during observation (Izutsu 2014).

Treatment modalities for FL include chemotherapy, radiotherapy and immunotherapy against CD20, and stem cell transplantation, but a standard treatment approach for FL has not been established.

Currently, the first-line treatment for FL is rituximab in combination with chemotherapy, followed by maintenance therapy with rituximab every two months for two years, as demonstrated by results of the PRIMA study (Salles et al, 2011). This regimen had determined a satisfactory result in most of treated patients, with a 10-year progression free survival of 51%.
Despite these encouraging results, therapy for FL is not curative and presents with a chronic course (i.e. remitting-relapsing), with progressively shorter remissions and with increased risk of developing a transformation of the disease, i.e. the transition from an indolent malignant lymphoma to a more aggressive type of lymphoma. The majority of patients will ultimately die from progressive disease.

Therefore, the introduction of new agents that may potentially alter the natural history of the disease is of great interest.

Obinutuzumab is a recombinant monoclonal humanized and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes.

Obinutuzumab has been evaluated in a wide-ranging program of clinical trials in patients with B-cell malignancies. Efficacy as monotherapy has been reported in patients with relapsed/refractory indolent and aggressive NHL (Salles et al. 2012; Salles et al. 2013) and in chronic lymphocytic leukemia (CLL) of B-cell origin (Cartron et al. 2014). Improved outcomes have also been noted when Obinutuzumab has been added to chemotherapy in patients with B-cell NHL (Radford et al. 2013).

In the phase III study (the GALLIUM trial), in patients with previously untreated indolent NHL, Obinutuzumab-based chemotherapy resulted in a significantly lower risk of progression, relapse, or death and in a superior progression-free-survival (PFS) than rituximab-based chemotherapy (Marcus et al. 2017).
A further analysis (Seymour et al, 2018) of the progression of disease at 2 years (POD24) and its impact on overall survival (OS) has shown that treatment with Obinutuzumab plus chemotherapy was associated with a marked reduction of POD24 compared to rituximab-based chemotherapy.

Overall, Obinutuzumab has an acceptable safety profile as emerged from clinical trials. Infusion-related Reactions (IRRs) were the most common AEs throughout all clinical trials (Edelmann et al. 2016). They comprised of various symptoms such as hypotension or hypertension, tachycardia, dyspnea, pyrexia, chills, nausea, vomiting, diarrhea, flushing and headache coinciding with drug infusion. However, IRRs mainly occurred during the first infusion and almost always resolved with slowing or interrupting the infusion and/or upon steroid administration.
Obinutuzumab has also received the approval from the European Medicines Agency (EMA) for use in combination with chemotherapy, followed by Obinutuzumab maintenance therapy in patients with previously untreated advanced follicular lymphoma.

This observational study has been planned to evaluate the effectiveness of Obinutuzumab in combination with chemotherapy in previously untreated advanced FL patients, in the real world setting in Italy.
The study will allow to collect real-life data in a significant number of Italian patients and thus will allow to verify in routine practice the effectiveness and safety management in 50 reference sites all over the country.

1.2 STUDY OBJECTIVES

This study aims to evaluate the effectiveness and safety of Obinutuzumab in patients with previously untreated advanced follicular lymphoma (FL) treated with Obinutuzumab in routine clinical care.

1.2.1 Effectiveness Objectives

The primary effectiveness objective of this study is as follows:

1) To evaluate the effectiveness of Obinutuzumab in combination with chemotherapy in previously untreated advanced follicular lymphoma (FL) patients, in the real world setting as measured by the proportion of patients relapsed within 24 months from start of therapy (POD24).

The secondary effectiveness objectives of this study are as follows:

2) To evaluate the progression free survival (PFS) at 2 and 3 years;
3) To evaluate the overall and complete response rates at mid and end of induction, and during and after maintenance therapy (including the complete response rate at 30 months [CR30]), as per clinical practice, with and without 18F-fluorodeoxyglucose – positron emission tomography (FDG-PET);
4) To describe patient/disease characteristics and the second line regimens prescribed for patients who progressed after first line therapy during the overall study duration and within 24 months from start of therapy (POD24);
5) To explore the effectiveness of Obinutuzumab in different patient subgroups, stratified by follicular lymphoma International Prognostic Index (FLIPI) – intermediate and high, ECOG performance status (PS), age at study entry, chemotherapy backbone choice, hepatitis infection (history of past/resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), presence of autoimmune disease, history of renal failure and liver failure.

1.2.2 Safety Objectives

The safety objectives of this study are as follows:

1) To evaluate the safety of Obinutuzumab in a real-world setting.

1.2.3 Other/Exploratory Objectives

1) To describe the treatment pattern in first and second line of treatment;
2) To evaluate methods applied to tumour and response evaluations according to used guidelines and clinical practice;
3) To evaluate the FDG-PET response at end of induction and end of maintenance, as per clinical practice;
4) To evaluate the Quality of life;
5) To evaluate the presence of B symptoms;
6) To explore effectiveness of Obinutuzumab in real world setting;
7) To explore prescription profile;
8) To explore COVID-19 impact on therapy adherence

2. STUDY DESIGN

2.1 DESCRIPTION OF STUDY DESIGN

This is a retrospective and prospective primary data collection and secondary data use, non-interventional, multi-center, national (involving approximately 50 Italian centers) study.

Patients should be included after the start of treatment with Obinutuzumab and chemotherapy, including newly diagnosed FL patients. Patients included should have performed at least 2 cycles of induction treatment with Obinutuzumab and chemotherapy within 1 year from beginning of treatment and will be followed up 3.5 years from the start of treatment.

For each patient, the study will consist of a period of 42 months which can include:
- an induction treatment period (approximately 6 months) in which patients will receive Obinutuzumab and chemotherapy;
- a maintenance treatment period (approximately 24 months) in which patients will receive Obinutuzumab monotherapy;
- a follow-up period of one year, after the last Obinutuzumab administration, or up to 3.5 years after start of the treatment for early discontinued patients.

A schedule of activities is provided in Appendix 1.

2.2 DATA SOURCES

Patients' data will be recorded on eCRFs. Data from patient notes should be entered on the CRF as soon as they become available. Data will be collected from patients' records as kept by their attending physicians during daily clinical practice. Initial treatment/pre-treatment data are collected retrospectively. Data will be collected as availability in source document.

Regarding Patient-reported Outcome (PRO), patients will use an electronic PRO (ePRO) device to capture PRO data at in-person clinic visits. In case patient is not able to complete the electronic questionnaires, e.g. due to technical issues, the PRO data will be completed by patient in paper records and later transferred into the electronic system by site staff. In case any survival follow-up contact is conducted by phone or in case of patient’s compromised reading ability (e.g illiterate patients/ vision issues, etc) the PRO data for that visit will be collected in an interview performed by a trained site staff (via telephone or face-to-face, depending on how visit occurs), recorded in paper records (source document) and then transferred in electronic system.

2.3 PRIMARY OUTCOME MEASURES

Progression of disease at 2 years (POD24), defined as the time from the date of treatment initiation with Obinutuzumab until the first documented progression of disease

or death due to disease progression, whichever occurs first, within 24 months from the start of treatment with Obinutuzumab. Patients who have no disease progression and have not died due to disease progression or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death due to disease progression occurs prior to their first scheduled tumor assessment. Patients who die for reasons not related to the disease progression within 24 months from the treatment start with Obinutuzumab will be excluded from the statistical analysis of the endpoint.

2.4 SECONDARY OUTCOME MEASURES

2.4.1 Secondary Effectiveness Outcome Measures

- Progression free survival (PFS) at 2 and 3 years, defined as the time from the date of treatment initiation until the first documented progression of disease measured by routine clinical care or death from any cause, whichever occurs first. Patients who have no disease progression and have not died or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Time to next treatment (TTNT), defined as the Time to initiation of subsequent systemic anti-cancer therapy following initiation of Obinutuzumab containing therapy. Patients not starting a subsequent systemic anti-cancer therapy will be censored at the date of the last study visit;
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause. Patients who still alive at the time of analysis and patients who are lost to follow-up will be censored at their last time known to be alive;
- Correlation between POD24 and OS;
- TTLCB, defined as the time from first dose to loss of clinical benefit as assessed by the treating physician (single or multiple reasons possible: e.g. disease progression, deterioration in ECOG PS, death, other). Patients who do not loss clinical benefit will be censored at the date of the last study visit. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Overall response rate (ORR);
- Complete response (CR);
- Complete response at 30 months (CR30);

- Duration of response (DoR) measured per clinical practice, defined as the time from first documentation of CR or partial response (PR) (whichever occurs first) until disease progression, as evaluated by the physician according to routine clinical practice or death. Patients who have no disease progression and have not died or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last;
- Time to response, defined as the time from first dose of Obinutuzumab to first documented response as assessed in clinical routine. Patients without response at the time of analysis and patients who are lost to follow-up will be censored at the date of their last tumour assessment. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Rate of patients with stable disease (SD);
- Effectiveness of Obinutuzumab in different patient subgroups, stratified by FLIPI (intermediate/high), ECOG-PS, age at study entry, hepatitis infection (history of past/resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), chemotherapy backbone choice, presence of autoimmune disease, history of renal failure and liver failure.

2.4.2 Secondary Safety Outcome Measures

- Incidence, nature, seriousness, severity and relatedness of all adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI);
- Infusion related reactions (IRRs) management at each center as per clinical practice;
- Clinical laboratory abnormalities;
- Vital signs.

2.5 OTHER OUTCOME MEASURES

Other variables of interest are below:

- Patient/disease characteristics: age, sex, ECOG PS, Ann Arbor staging, FLIPI (intermediate/high), medical history and history of FL, comorbidities, physical examination and vital signs;
- Treatment pattern:
  - Time from diagnosis to start of treatment with Obinutuzumab;
  - Duration of treatment with Obinutuzumab;
  - Dose modifications;
  - Treatment discontinuation;
  - Prophylaxis medications;
  - Type of chemotherapy chosen in association with Obinutuzumab;
  - Second line regimens prescribed for patients who progressed within two years after starting first line therapy;

  - Time to initiation of subsequent systemic anti-lymphoma therapy following initiation of Obinutuzumab containing therapy;
  - Adherence to treatments
- Quality of life: EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L); Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym);
- Presence of B symptoms;
- Concomitant medication prescribed or in current use from the start of therapy with Obinutuzumab until discontinuation of the treatment;
- FDG-PET response at end of induction and end of maintenance, as per clinical practice. When PET is not performed, the alternative routine tumor assessment method will be collected;
- Differences in patient/disease characteristics and treatment pattern/adherence pre- and post- COVID19 pandemic.

2.6 DETERMINATION OF SAMPLE SIZE

Sample size of this clinical study is selected based on feasibility.

Sample size is justified for the primary effectiveness endpoint POD24 treated as binary variable. A sample size of 300 evaluable patients will allow estimation of the two-sided 95% confidence interval with a width equal to 7.9% (precision 3.95%) of the POD24 when the expected percentage is equal to 13%.
The Clopper-Pearson's formula has been used for the computation.

Moreover, a sample size of 300 evaluable patients will allow estimation of the two-sided 95% confidence interval with a width equal to 9.4% (precision 4.70%) of the PFS rate at 3 years (treated as binary variable) when the expected percentage is equal to 80%.

3. STATISTICAL METHODS

The statistical analysis will be performed using the R Statistical Software (Foundation for Statistical Computing, Vienna, Austria) version 3.6.0 or higher.

This is not a hypothesis testing study but an exploratory study with predefined precision of estimates for key efficacy and safety parameters; there are no formal statistical hypotheses tests to be tested, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Data will be summarized using appropriate descriptive statistics. Categorical data will be presented as frequencies and percentages. For continuous data, arithmetic mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum will be presented. The 95% confidence interval of the observed proportions (calculated using either the Clopper-Pearson methodology, or the Poisson distribution, for frequencies below 10%) will be provided.

3.1 ANALYSIS POPULATIONS

The following populations will be considered for data analysis:

Effectiveness population
Effectiveness analysis population includes all patients who are enrolled and have received at least two cycles of Obinutuzumab.

Safety population
Safety analysis population includes all patients who are enrolled.

Screening failures are not considered for the analyses.

3.2 EFFECTIVENESS ANALYSIS

Effectiveness analysis population includes all patients who are enrolled and have received at least two cycles of Obinutuzumab.

In general, the time to endpoint will be defined as an interval between the date of enrolment (date of first visit) and date of first occurrence of the event. For patients who are event free, the censoring time will be calculated as a time interval between date of enrolment and the patient`s final contact with available data concerning the event. The estimates and graphical presentation will be performed via Kaplan-Meier approach.

Logistic regression will be performed on the rate of endpoints in order to test the impact of covariates, i.e. age, sex, ECOG PS, Ann Arbor staging, FLIPI, hepatitis infection

(history of past/ resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), chemotherapy backbone choice, medical history and history of FL, comorbidities.

Exploratory analysis between different medical treatments given or subgroup analysis will be performed using Cox regression model and including relevant covariates.

Corresponding 95% confidence intervals (CIs) will be provided for all statistical estimates.

3.2.1 Primary Outcome Measures

The primary endpoint is progression of disease at 2 years (POD24).

POD24 will be analyzed according to the survival analysis methods. The quartiles with their 95% confidence interval (estimated using Kaplan-Meier methods and Greenwood's formula) will be presented. Kaplan-Meier plots with a 95% CI will be prepared. Estimates for the survivor function will be obtained by the Kaplan-Meier approach.

Moreover, the POD24 will be analyzed as binary variable. Number and percentage of patients with its 95% CI for POD24 will be calculated.

Logistic regression analysis will be performed to assess which variables are predictive of POD24. To identify factors associated with POD24, logistic regression analysis will be performed with backwards selection (removing factors with $P > 0.05$). Univariable associations between factors and POD24 will be calculated by using the Chi-square test.

In the analysis of POD24 will be excluded patients who die within 24 months from the treatment start with Obinutuzumab for reasons not related to the disease progression.

3.2.2 Secondary Outcome Measures

Time-to-event outcomes (PFS at 2 and 3 years, TTNT, OS, TTLCB, duration of response, and time to response) will be analyzed according to the survival analysis methods. The quartiles will their 95% confidence interval (estimated using Kaplan-Meier methods and Greenwood's formula) will be presented. Kaplan-Meier plots with a 95% CI will be prepared. Estimates for the survivor functions for all time to event endpoints will be obtained by the Kaplan-Meier approach.

Cox regression analysis will be used to assess which variables are predictive of OS as well as to evaluate the association between early POD and OS from a risk-defining event, that is, survival from time of POD for early progressors or from 2 years after diagnosis.

Response rates (ORR, CR, CR30 and rate of patients with stable disease) will be presented with the number and proportions of responders and non-responders together with two-sided, 95% Clopper-Pearson CIs.

3.3 SAFETY ANALYSES

Safety analysis population includes all patients who are enrolled.

3.3.1 Adverse events

Adverse events are those with start date beyond or equal to the date of first administration of Obinutuzumab and until 185 days after the last Obinutuzumab dose intake or until starting a new anti-cancer therapy (whichever occurs first). After this period AEs that are believed to be related to prior study drug treatment will be collected.

All adverse events will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus version 22 or higher. Summary statistical tables including frequency counts and percentages and the number of adverse events will be produced.

Data will be listed by study site, patient number, and study day. Events occurring on or after treatment on Day 1 (treatment-emergent adverse events - TEAEs) will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 grade. In addition, SAEs, including deaths, will be listed separately and summarized.

AEs leading to treatment discontinuation will be listed.

Infusion related reactions (IRRs) and adverse events of special interest (AESI) will be summarized by descriptive statistics and will be listed.

3.3.2 Laboratory and vital signs

Relevant laboratory and vital signs (*Systolic and diastolic blood pressure, Heart rate, Body temperature*) data will be displayed by time.
Additionally, all laboratory data will be summarized by grade with use of NCI CTCAE v5.0.

For each parameter the change from baseline to each post-baseline visit will be calculated.
All medications reported will be coded using the WHO-DRL Dictionary version 2018 or higher and classified according to 3rd level ATC level subgroup and Preferred Term.
The following vital signs, when performed as per clinical practice, will be captured in the eCRF:
- Systolic and diastolic blood pressure (mmHg)

- Heart rate (bpm)
- Body temperature (°C)

For each variable the change from baseline to each post-baseline visit will be calculated.

3.4 SENSITIVITY ANALYSES

No sensitivity analyses are planned.

3.5 OTHER ANALYSES

All exploratory endpoints will be analyzed using descriptive statistics only.

In particular, the following other analyses will be performed:

Use of Obinutuzumab in real world setting
Descriptive statistics for the use of Obinutuzumab in the real world setting will be performed.
At least the following conditions will be considered in the analysis:

- Not performing obinutuzumab administration on Day 8 and Day 15 in Cycle 1 (without safety reasons)
- Maintenance period: administration of obinutizumab in an interval superior to 10 days from the expected date (every 2 months per label). NOTE: An analysis will be performed to assess if this condition will have impact on efficacy parameters (PFS/ POD24) and to explore the delay reason (COVID-19 or others)
- All the chemotherapy scheme used with Obinutuzumab in real world setting

Prescription profile
Obinutuzumab prescription profile and chemotherapy backbone choice by Italian region, age range, patient's profile and site dimension (outlying sites/universities, etc.)

Impact of COVID-19
The COVID-19 impact will be evaluated in terms of:

- Safety (infections and COVID-19 related events)
- Maintenance delay or interruption due to pandemic status
- Therapy interruption due to patient's complications caused by COVID-19

3.6 HANDLING OF MISSING DATA

There will be no missing value handling mechanisms and missing data will not be imputed.

3.7 LIMITATIONS OF THE RESEARCH METHOD

This study will be conducted in approximately 50 sites in Italy and will reflect the standard of care in place in the selected investigational study sites. Therefore, caution should be used in the generalisation of data collected in this study.

Furthermore, the design of the trial may be associated with further limitations:

- the possible bias in patients' selection due to the uncontrolled design of the trial may have impact on results;
- as when entering in the initial patient's treatment/pre-treatment data are collected retrospectively, missing data might occur in the retrospective period as well the distribution of missing data might be different across the participating investigational sites;
- pooling of prospective and retrospective data collection will be done even though not equivalent and this needs to be taken into consideration when interpreting the results;
- COVID19 pandemic may have impact on routine clinical care.

3.8 INTERIM, FINAL ANALYSES AND TIMING OF ANALYSES

An interim analysis will be performed approximately one year after the first patient is included in the study in order to evaluate safety data (particularly, infections and events COVID related), demographic data (including potentially differences in patient enrolled pre- or post- COVID19 pandemic), FLIPI, treatment choices (obinutuzumab prescription profile and chemotherapy backbone choice per Italian region, per age range, per patient's profile and site dimension - outlying sites/ universities, etc.), impact of COVID19 over maintenance delay and treatment adherence.

A second interim analysis will be performed approximately two years after the first patient included in the study in order to evaluate safety and primary, and secondary effectiveness data (including POD24), and the impact of COVID-19 on the patients management.. Tables template for second interim analysis is reported in Appendix 3.

The final analysis will be performed at the end of the study.

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Appendix 1
Data Collection Overview for Primary Data Collection (as per Standard of Care)

Data Collection (available data will be collected; no additional diagnostic or monitoring procedures will be applied to patients outside of routine clinical practice)	Enrolment visit [a]	Retrospective Data collection	Prospective Data Collected during Treatment Period (Induction and maintenance period)	Follow-up period [b]
Informed consent[c]	x			
Diagnosis confirmation (clinical stage, histology)		x		
Target Population	x	x		
Medical history and demographic data		x		
Concomitant treatments/medications[d]	x	X	x	
Treatment with Obinutuzumab	(x)[c]	(x)[c]	x	
Prophylaxis medication	x	x	x	
Laboratory assessments[e]	x	x	x	
Pregnancy test	x[f]	x[f]	x[f]	
Physical examination and Vital signs	x	x	x	
ECOG	x	x	x	x
B symptoms	x	x	x	x
QoL (Quality of life: EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L); Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym) [g]	x		x	x
Chemotherapy regimen	x	x	x	
AEs/SAEs/IRR/ADR	x		x	x[k]
Retrospective Safety data collection		x[h]		
Tumor assessments	x	x	x	x
Ann Arbor	x	x		
FLIPI score assessment[i]	x	x		
BM evaluation	x	x	x	x
Response rate[j]	x	x	x	x
New anti-cancer therapy and survival status after end of treatment				x

[a] Items Concomitant treatments/medications, Treatment with obinutuzumab, Pregnancy test. Physical examination and Vital signs, Prophylaxis medication and Chemotherapy regimen apply only for patients still

on treatment at the time of enrollment as part of their standard procedures for treatment. In case of patients enrolled after treatment completion, these data will be collected as indicated in the Retrospective column and the prospective information will be collected as described in the Follow-up period.

[b] Approximately one-year follow-up after last dose of Obinutuzumab administration, as per clinical practice, or for patients that early discontinue the treatment up to 3.5 years after first treatment administration or until withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy. For patients that discontinue treatment before completing induction or maintenance, the follow up parameters can be collected in accordance with current patient's schedule visit and not every 2 months.

[c] Patients included should have performed at least 2 cycles of induction treatment with Obinutuzumab and chemotherapy, within 1 year from beginning of treatment

[d] Including any medication used by the patient from 7 days prior to starting treatment with obinutuzumab.

[e] Laboratory tests will include: haematology (WBCs and differential count [at least neutrophils and monocyte %], RBCs, haemoglobin, haematocrit, platelet count) and blood chemistry (creatinine, beta-2 microglobulin, LDH, AST, ALT).

[f] Data collected if performed per clinical practice as clinically indicated.

[g] QoL will be completed prospectively period, every 2 cycles in induction treatment phase and every 2 months during maintenance treatment phase. For further instructions over QoL completion please refer to section 6.6.1. PRO questionnaires (FACT-Lym, EQ-5D) should be administered prior to any treatment assessments. PRO questionnaires should also be administered at first assessment after report of disease progression.

[h] AEs/SAEs/IRR/ADR that occur prior ICF signature should be reported in eCRF as available; however only the event preferred term as per CTCAE vs 5.0 is required as Individual Case Safety Report are not applicable. Prospective safety that must be fully assessed and reported by study physician including assessment of seriousness (see Section 8.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

[i] FLIPI score (age, number of nodal sites, LDH level, haemoglobin, stage) or FLIPI2 (age, beta-2 microglobulin, bone marrow involvement, longest diameter of largest involved node, haemoglobin) collected at diagnosis.

[j] Response will be collected at mid of the induction (between 10 and 14 weeks after the start of treatments), end of the induction (at the day of cycle 6 until 1 month later) during maintenance (1 year after the start of treatment, i.e. from 10 to 14 months after the start of treatment; 2 years after the start of treatment, i.e. from 22 to 26 months after the start of treatment; 3 years after the start of treatment, i.e. from 34 to 38 months after the start of treatment), at the end of maintenance and at Follow-up as per clinical practice, as well as at any tumor assessment that shows disease progression, CR or CRu during induction or maintenance. The assessment of tumor response will be based on standard Cheson criteria and the Deauville 5-point scale (Appendix 6) (*Younes et al. 2017*).

[k] All adverse events data available in medical records after start of the treatment should be reported until 185 days after the last obinutuzumab dose or until starting a new anti-cancer therapy (whichever occurs first). After this period AEs that are believed to be related to prior study drug treatment will be collected.

Appendix 2
List of Planned Outputs

Output for baseline descriptive analyses

- Summary of demographic characteristics
- Listing of demographic characteristics
- Summary of history of treatment with Obinutuzumab and chemotherapy
- Summary of follicular lymphoma characteristics
- Summary of clinical staging pre treatment
- Summary of FLIPI/FLIPI2 (at treatment start)
- Summary of medical history (other than FL)
- Listing of medical history (other than FL)
- Summary of physical examination
- Listing of physical examination abnormalities
- Summary of vital signs and ECOG
- Listing of vital signs and ECOG
- Summary of hematology, blood chemistry and serology
- Summary of tumor assessment and target and not target lesions
- Listing of target and not target lesions
- Summary of bone marrow evaluation

Output for effectiveness analyses

- Results regarding POD24
- Results regarding PFS
- Results regarding TTNT
- Results regarding OS
- Results regarding TTLCB
- Results regarding ORR
- Results regarding CR
- Results regarding CR30
- Results regarding duration of response
- Results regarding time to response
- Results regarding SD
- Results regarding effectiveness of Obitunuzumab in patient subgroups

Output for safety analyses

- Summary of Adverse Events and IRRs
- Listing of Adverse Event and IRRs
- Summary of clinical laboratory abnormalities during the study
- Summary of vital signs during the study

Output for exploratory analyses

- Summary of treatment pattern

- Summary regarding method applied to tumour response evaluation (e.g. FDG-PET)
- Summary about quality of life information from questionnaire
- Summary of presence of B symptoms during the study
- Summary regarding effectiveness in off-labels
- Summary regarding COVID19 impact on therapy mainteinance
- Summary of concomitant medication
- Listing of concomitant medication

Appendix 3
Tables template for second interim analysis

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