FONDAZIONE ITALIANA LINFOMI

Clinical Protocol

Idelalisib plus Obinutuzumab in patients with relapsed/refractory follicular lymphoma: a phase 2, single-arm, multicentric study

ID Study: FIL_GAUDEALIS
EudraCT number: 2018-001229-18

INVESTIGATOR SPONSOR
Fondazione Italiana Linfomi ONLUS (FIL)

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REGISTRATION (SEE CHAPTER 12)	**www.filinf.it**
SAE REPORTING (SEE CHAPTER 17)	**www.drugvigilance.filinf.it**

Version and date of Protocol: Version 2.0 of May 29, 2019

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3. INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

_____
Investigator's Signature Date

_____
Name of Investigator (Typed or Printed)

_____
_____
_____
Institution, Address*

_____
Phone Number*

_____
Investigator-Sponsor Signature* Date
(where required)

_____
Name of Coordinating Investigator (Typed or Printed)

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Institution

* If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s).

4. SYNOPSIS

Study ID	FIL_GAUDEALIS
Eudract N°	2018-001229-18
Title of the study	Idelalisib Plus Obinutuzumab In Patients With Relapsed/Refractory Follicular Lymphoma: A Phase 2, Single-Arm, Multicentric Study.
Phase of the study	Phase II single arm study
Investigational product	Obinutuzumab Idelalisib
Protocol version	Version 2.0 of May 29, 2019
Centers	12 sites within FIL (Fondazione Italiana Linfomi) centres. Coordinating Center: Institute of Hematology, AOU Policlinico S.Orsola-Malpighi, University of Bologna
Study Objectives and Endpoints	<u>Primary Objective</u> To evaluate the efficacy in terms of clinical response in patients treated with combination therapy of idelalisib and obinutuzumab <u>Secondary Objectives</u> • To assess efficacy in terms of progression-free survival (PFS) and overall survival (OS). • To assess the safety of the combination therapy and patients' compliance to treatment; <u>Primary Endpoint</u> Investigator's assessed Overall response rate (ORR) at the end of induction phase of patients treated with a chemo-free combination with obinutuzumab and idelalisib. Overall response rate (ORR) is defined as the proportion of patients with at least a partial response (PR), as defined by 2014 Lugano criteria. <u>Secondary Endpoints</u> - Overall survival (OS) rate; - Progression-free survival (PFS) rate; - patients' withdrawal rate, incidence and nature of any severe adverse events, hospitalization rate throughout the study, and patients' compliance to oral treatment, incidence of any adverse events occurring during and right after treatment
Study design	Single arm, prospective, multi-centric, phase II study. Patients with histologically confirmed follicular lymphoma, in need of a systemic approach and failing (i.e. with refractory disease [no response or response lasting less than 6 months at any previous line of treatment] or with a proven disease relapse) at least 2 previous lines of treatment, including any antibody directed against the CD20 antigen-containing chemotherapy, will undergo a combined chemo-free treatment with obinutuzumab and idelalisib. Obinutuzumab will be administered intravenously at a flat dose of 1000 mg on day 1, 8, 15 of the first cycle, then repeated on day 1 of each subsequent cycle, for 6 cycles (each cycle is completed in 28 days). Idelalisib will be given concomitantly with obinutuzumab and on a daily 150 mg bid schedule. For patients achieving at least a partial response at the end of induction, a maintenance phase with obinutuzumab is scheduled (on day 1 every two months for two years or until progression or unacceptable toxicity, whichever comes first)

	If one of the two drugs has to be permanently discontinued due to any cause, patient may continue treatment with the other agent if it is judged to be a clinical benefit. Patients with at least a stable disease will enter the follow-up phase and will be followed with repeated CT scans every six months for two years or until death/progression occurs (whichever comes firsts). Patients with progressive disease, whenever progression is documented, will enter a survival follow up period of two years after PD was documented. These patients are however considered evaluable for OS.
Duration of the study	1.5 year of enrolment + 6 months of induction + 2 years of maintenance+ 2 years of (survival) follow up (ca. 6,5 years in total)
Number of patients	43 patients (stage I: 15 patients; stage II: 28 patients)
Inclusion criteria	• Relapsed or refractory, histologically confirmed CD20-positive follicular non-Hodgkin's lymphoma, grade 1, 2 or 3a according to WHO 2017 classification. • Age 18 ≥ years • At least 2 prior systemic therapies for follicular lymphoma including both any antibody directed against the CD20 antigen and a chemotherapy combination. • Treatment indications, with the presence of at least one of the following: - bulky disease (nodal or extranodal mass – except spleen – more than 7 cm in its greater diameter or involvement of at least 3 nodal or extranodal sites, each with a diameter equal to or greater than 3 cm); - at least one B-symptom (fever > 38°C of unclear etiology, night sweats, weight loss greater than 10% of body weight in the prior 6 months); - symptomatic splenomegaly; - compression syndrome (i.e. of orbits, ureters, gastrointestinal tract, biliary tract); - lymphoma-related cytopenias (hemoglobin < 10 g/dL and/or platelets < $100 \cdot 10^9$/L and/or neutrophils < $1.5 \cdot 10^9$/L); - pleural or peritoneal serous effusions. - • Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2. • Adequate hematological function, unless abnormalities due to underlying disease, within 28 days prior to signing informed consent, defined as follows: neutrophils > $1.5 \cdot 10^9$/L, platelets > $75 \cdot 10^9$/L, hemoglobin > 8,0 g/dL with transfusion independence. • Capacity and willingness to adhere to study visit schedule and specific protocol procedures. • Willingness to sign a written informed consent. • Compliance with effective contraception without interruption, from 28 days before treatment start up (i.e., during the screening phase) to 18 months after treatment discontinuation, agreeing not to donate the semen during treatment and for 18 months after discontinuation (if the patient is male), or to undergo ongoing pregnancy test during the course of the study (if the patient is female). Birth control methods considered acceptable for the study are those highly effective (IUS, hormonal methods, tubal sterilization, sexual intercourse with a vasectomized male partner) or effective (male condom, diaphragm, cervical cap). According to the usual lifestyle of

	the subjects, if they are not willing to adopt the prescribed contraceptive methods, they have to practice true abstinence for all the period above reported. • Patients must agree to undergo JPJ prophylaxis throughout the treatment period and 2-6 months thereafter (before consulting with Medical Monitor).
Exclusion criteria	• Grade 3b follicular non-Hodgkin's lymphoma or evidence of transformation to high-grade non-Hodgkin's lymphoma. • Central nervous system or leptomeningeal involvement by lymphoma. • Major surgery (excluding any lymph node biopsy) within 28 days prior to signing informed consent. • Seropositivity for HBV or evidence of active infection (HBsAg positivity, or HBsAg negativity with positive anti-HBs/anti-HBc and detectable viral DNA load); if viral load is negative or undetectable, the patient is eligible, provided their HBsAg negativity. • Positive viral HCV RNA • Seropositivity for HIV, regardless of viral load. • Known history of drug induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, on-going extra-hepatic obstruction caused by cholelithiasis, cirrhosis of the liver or portal hypertension • Known history of drug induced pneumonitis • On-going inflammatory bowel disease • On-going alcohol or drug addiction • Life expectancy lower than 6 months. • Prior history of malignancies, other than follicular lymphoma, unless the patient has been free for at least 10 years (exceptions: localized non-melanoma skin cancer ad carcinoma *in situ* of the cervix). • Any of the following laboratory abnormalities: liver enzymes (AST/SGOT and/or ALT/SGPT) > 2.5-fold the upper limit of normal (except of liver involvement by lymphoma); total bilirubin > 1.5 mg/dL (except for patients with known Gilbert's disease or biliary tree compression by lymphoma masses); creatinine clearance < 30 mL/min. • Uncontrolled intercurrent illness. • Known hypersensitivity or allergy to murine products or to any of the medicaments under investigation. • Pregnancy or breastfeeding, or unwillingness to comply with adequate contraception. • Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent the patient from signing the informed consent or which may place the patient at unacceptable risk if participating in the study. • Any evidence of ongoing bacterial, viral and fungal infection. • Known hypersensitivity to the active substances or to any of the excipients. • Concomitant participation into another trial planning experimental therapy.
Study treatment and response criteria	Single arm: Regimen: GAUDEALIS q28 days - Obinutuzumab Dose: 1000 mg IV Day 1, 8, 15 (1st cycle)

<table>
<tr><td></td><td>
- Obinutuzumab Dose: 1000 mg IV Day 1 (2nd cycle onward)
- Idelalisib Dose: 150 mg BID oral Daily (24 weeks)

Obinutuzumab will be administered intravenously at a flat dose of 1000 mg on day 1, 8, 15, of the first cycle, then repeated on day 1 of each subsequent cycle, for 6 cycles in total (each cycle is completed in 28 days). Idelalisib will be given concomitantly with obinutuzumab on a daily 150 mg bid schedule orally and continuously (24 weeks). For patients achieving at least a partial response at the end of induction, a maintenance phase with obinutuzumab is scheduled (on day 1 every two months for two years or until progression or unacceptable toxicity, whichever comes first)
If one of the two drugs has to be permanently discontinued due to any cause, patient may continue treatment with the other agent if it is judged to be a clinical benefit
Overall response rate (ORR) is defined as the proportion of patients with at least a partial response (PR), as defined by 2014 Lugano criteria.
</td></tr>
<tr><td>Assessments schedule</td><td>
Patients will be evaluated before treatment by a staging total body computed tomography (CT) scan (a positron emission tomography (PET) scan is recommended for patients with grade 3A follicular lymphoma), as well with a bone marrow trephine biopsy and molecular evaluation of BCL-2 rearrangement on marrow blood. FL has to be confirmed by histology at relapse. Full blood counts, liver and renal function examinations, lactate dehydrogenase, serum proteins with electrophoresis and immunoglobulin levels will be collected at baseline and before each cycle. Full serological testing for hepatitis B and C virus, human immunodeficiency virus and cytomegalovirus (CMV) will be performed upon patients' enrolment. CT scans will be repeated after induction cycle 3, at EOI, every 3 and 4 months for the first and second year of maintenance, respectively, at treatment completion after 2 years of maintenance or in case of early withdrawal (EOT), at relapse/progression and during follow-up; PET scans are mandatory at baseline, after induction cycle 3 and 6 (EOI), at the end of treatment after 2 years of maintenance or in case of early withdrawal (EOT) and at relapse/progression. At all additional timepoints (including follow-up) PET scans are optional and will be done at clinician discretion only if in accordance with center clinical practice; marrow biopsy and molecular biology examination will be performed only if positive at baseline.
All the responder patients (CR, PR, SD) will enter a follow-up phase and will be followed with repeated CT scans every 6 months for two years (starting from the CT/PET scan performed at the end of treatment) or until death/progression whichever comes first.
Patients with progressive disease, whenever progression is documented, are considered off treatment. Off-treatment patients are however considered evaluable for OS.
</td></tr>
<tr><td>Centralized analyses</td><td>
<table>
<tr><th>TEST</th><th>APPENDIX REF</th><th>REQUIRED</th><th>QUANTITY</th></tr>
<tr><td>Diagnosis Review</td><td>Appendix D</td><td>YES</td><td>1 BLOCK or 20 UNSTAINED SLIDES</td></tr>
<tr><td colspan="4">Upfront centralized diagnosis review is compulsory for treatment start, but the local pathology report is enough to enroll patient.</td></tr>
</table>
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<tr><td>Statistical considerations</td><td>Optimal Simon's two-stage design has been used to calculate the sample size.</td></tr>
</table>

Based on previous clinical experiences, the null hypothesis was set as a true response rate is 55% (response rate of idelalisib single agent), that will be tested against a one-sided alternative response rate of 75% (response of obinutuzumab in combination). Last available clinical response will be considered for patients who will permanently discontinue for any cause both drugs of the experimental combination before the completion of the 6th cycle (planned duration of induction phase). Patients who will have no tumor assessment after the start of therapy will be considered non-responsive.
For the first stage, the accrual will be suspended when 15 patients will have started experimental therapy. If there are 9 or fewer responses in these 15 patients, the study will be stopped.
Otherwise, enrollment will be reopened until 28 additional patients will start experimental therapy, for a total accrual of 43 patients. The null hypothesis will be rejected if 29 or more responses are observed in 43 patients.
This design yields a type I error rate of 5% and power of 80% when the true response rate is 75%

Safety monitoring and stopping rules:
In order to monitor the safety of the treatment in small cohorts of patients, the Bayesian approach of Thall, et al (1995) as extended by Thall and Sung (1998), for monitoring toxicity will be used. We have planned the monitoring of toxicity to ensure that the proportion of patients with non-hematological toxicity (defined as any non-hematological toxicity of grade 3 or higher or treatment interruption for safety reasons or any toxic death) after 3 and 6 cycles of induction is not higher than an acceptable level of 25%. The prior probability of toxicity (25%) is modeled by a beta distribution [Beta (0.5,1.5)]. We will stop the enrolment in the experimental cohort if the posterior probability of the treatment being more toxic than expected is greater than 90%. Patients will be monitored, without suspending the enrollment, according to the following stopping boundaries for toxicity in cohorts of five patients as per assessment every 3 cycles:

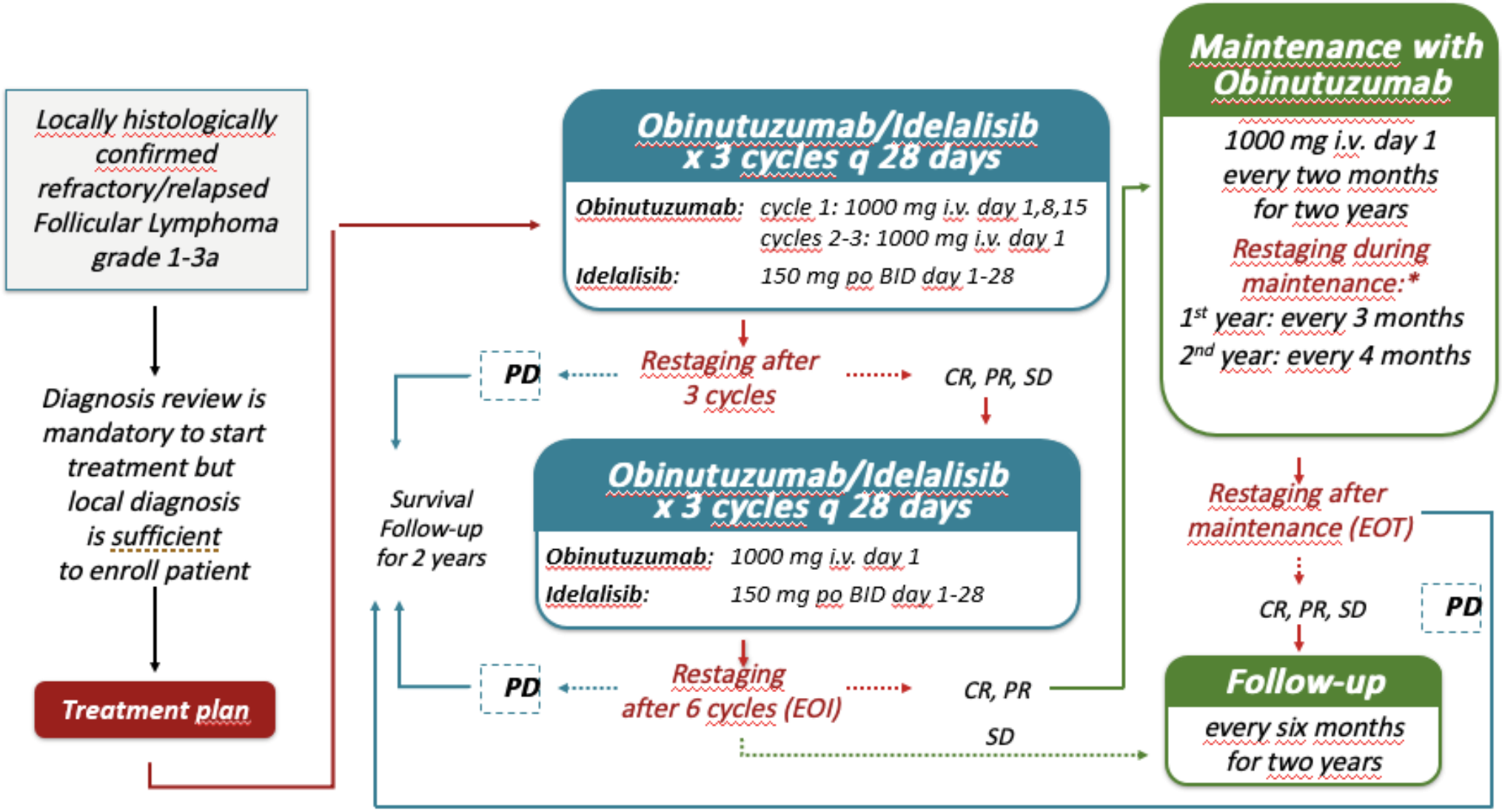
Patients assessed for toxicity	**Stop the enrollment in the cohort if the relevant toxicities are greater or equal to:**
5	3
10	5
15	7
20	9
25	10
30	12
35	13
40	15

Demographics and patients' characteristics will be summarized by descriptive statistics. Point estimates of efficacy and toxicity will be provided with 95% confidence intervals. Overall response rate will be calculated as the sum of complete and partial response rates. Time-to-event endpoints (progression free survival, overall survival) will be estimated by the Kaplan-Meier method. For the safety analyses, both at patient level and at therapy cycle level, summaries of incidence rates (frequency and percentages) of individual adverse events will be reported by type and grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

5. LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
AE	Adverse Event
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
β-HCG	beta-Human Chorionic Gonadotropin
CBC	Complete Blood Cell
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRu	Complete Response unconfirmed
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOI	End of induction (after 6 cycles of GAUDEALIS regimen)
EOT	End of treatment (at the end of maintenance)
FCBP	Female of ChildBearing Potential
FIL	Fondazione Italiana Linfomi
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Review Committee
IMP	Investigational Medicine Product
IP	Investigational Product
ITT	Intent To Treat
IV	Intra Venous
LDH	Lactic DeHydrogenase
LVEF	Left Ventricular Ejection Fraction
MoH	Ministry of Health
MRI	Magnetic Resonance Imaging
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	^{18}F-FDG Positon Emission Tomography
PFS	Progression Free Survival
PK	PharmacoKinetics
PR	Partial Response
PS	Performance Status
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
ULN	Upper Limit of Normal
WHO	World Health Organization

6. STUDY FLOW CHART



* *Patients in PD at any restaging during maintenance will be addressed to Survival follow-up*

7. BACKGROUND

7.1. Disease background

Follicular Lymphoma (FL) is a chronic, indolent but potentially life-threatening malignancy whose natural history is characterized by several periods of remissions ultimately followed by a relapse, which requires sequential treatments with agents that provide alternative mechanisms of tumor control.

There is not a general consensus yet regarding the salvage treatment for patients affected by FL who relapse or show refractoriness to a first line rituximab-containing chemotherapy.

Single agent rituximab, radioimmunotherapy and chemotherapy with bendamustine have received approval for treatment of refractory or relapsed disease.

Single-agent rituximab can offer disease palliation with good tolerability in some patients, but tumor control is not lasting.

Radioimmunotherapy with yttrium90-ibritumomab tiuxetan and iodine131-tositumomab has been limited because of several medical and practical restrictions to the use of these agents.

Bendamustine in combination with rituximab has been evaluated in Europe in 63 patients with relapsed or refractory lymphomas [1]. The overall response rate (ORR) was 90%, with a remarkable complete response (CR) rate of 60%. The median progression-free survival (PFS) was 24 months. A separate study conducted in the United States, Canada and Australia [2] confirmed these results (ORR of 93%, CR rate of nearly 50% and median PFS of 23 months).

7.2. Current therapies for R/R Follicular Lymphoma

Multiple options exist for the treatment of patients with FL who have failed first-line therapy, and the decision of which therapy to use depends on a number of factors, including the prior treatment used, duration of prior response, patient age, comorbid illnesses, and goals of therapy.

Bendamustine

Bendamustine is approved in the United States for use in patients with rituximab-refractory indolent B-cell lymphoma. A pivotal trial in 100 patients reported an ORR of 75% with a median PFS of 9.3 months [3]. The US Food and Drug Administration (FDA)–approved dose of single-agent bendamustine is 120 mg/m^2 given IV on days 1 and 2 of 21-day cycles. Approximately two-thirds of patients required dose modifications or delays, mainly due to cumulative myelosuppression. In addition, most practitioners prefer to administer bendamustine with rituximab. An expert panel has published guidelines on bendamustine dosing when combined with rituximab, and recommends 90 mg/m^2 on days 1 and 2 repeated every 28 days [4]. Lower doses (such as 70 mg/m^2) may be more appropriate in the elderly.

Fludarabine-based regimens

Fludarabine-based regimens are another option for patients who relapse after an alkylator-based therapy. They should be used with caution in heavily pretreated or elderly patients, however, due to immunosuppression.

Radioimmunotherapy

Radioimmunotherapy is also an option for patients with non-bulky, indolent B-cell NHL if the bone marrow is minimally involved. With 90Y ibritumomab tiuxetan, response rates are 70% and response duration is, on average, 11-15 months.

Single-agent rituximab

Single-agent rituximab can be used in relapsed FL, but more patients are becoming rituximab refractory after receiving the drug with primary therapy and as maintenance. For patients who are still rituximab sensitive, it is an attractive option, particularly in the elderly, since after first line they would not tolerate cytotoxic agents.

Obinutuzumab

For patients who are rituximab refractory, the combination of bendamustine and obinutuzumab (type II anti-CD20 monoclonal antibody) was shown to be superior to bendamustine alone, approximately doubling the PFS in a randomized clinical trial [5]. Obinutuzumab is also under investigation in the frontline setting (see *paragraph 7.3.2* for more details).

Idelalisib

A new option for relapsed FL is the phosphatidylinositol 3- kinase d (PI3Kd) inhibitor idelalisib. Idelalisib targets the d isoform of PI3K, an enzyme downstream from the BCR, which eventually signals through AKT and mammalian target of rapamycin. In a phase 2 study of 125 patients with indolent NHL who were refractory to both rituximab and an alkylating agent, idelalisib was administered at a dose of 150 mg twice daily until PD or patient withdrawal [6]. The response rate was 57% with a median duration of 12.5 months. Response rates and duration in the FL subset were similar to the overall population. Grade 3 or higher toxicities included neutropenia (27%), transaminase elevations (13%), diarrhea (13%), and pneumonia (7%). Based upon this data, idelalisib received accelerated approval by the FDA in 2014.

Novel agents under development

A variety of novel agents are under development in FL, including other PI3K inhibitors, immunomodulatory agents, inhibitors of BTK, antibody-drug conjugates, novel anti-CD20 monoclonal antibodies, chimeric antigen receptor T-cell therapy, immune checkpoint inhibitors, inhibitors of nuclear export proteins, and others. An exhaustive review of agents in development is beyond the scope of this review, but examples of novel agents with outcome data in FL are summarized in [7–11]

Stem cell transplantation

High-dose chemotherapy with autoSCT and alloSCT are both useful strategies in the management of FL, particularly for younger patients with high-risk features, such as a brief remission to previous therapy. A review of 904 patients in the International Bone Marrow Transplant Registry who underwent autologous or allogeneic transplantation for FL revealed that durable remissions could be induced with either technique [12]. A lower 5-year recurrence rate with allogeneic transplantations was offset by a higher treatment-related mortality compared with autologous transplantation, leading to similar 5-year survival rates of 51% to 62%. To reduce the treatment-related mortality of alloSCT, most centers now favor a nonmyeloablative strategy in FL.

Results utilizing a nonmyeloablative alloSCT strategy vary widely in the literature. For example, a series of 62 patients treated at the Fred Hutchinson Cancer Center demonstrated a 3-year OS and PFS of 67% and 54%, respectively [13]. Alternatively, a highly selected group (n 547) treated at the MD Anderson Cancer Center achieved an 11-year OS and PFS of 78% and 72%, respectively [14]. There is one small, randomized clinical trial (the Chemotherapy vs Unpurged stem cell transplant vs Purged stem cell transplant [CUP] trial) examining autoSCT vs standard therapy in patients with relapsed FL [15]. The study, conducted in the pre-rituximab era, found improved PFS and a trend toward improved OS with autoSCT. An interesting long-term analysis of patients receiving myeloablative chemotherapy followed by autoSCT comes from investigators at St. Bartholomew's Hospital (London, United Kingdom) and the Dana-Farber Cancer Institute (Boston, MA) [16]. A cohort of 121 patients, with a median follow-up of 13.5 years, was noted to have a plateau in the remission duration curve beginning around year 8. Nearly half of the patients were still in remission at 10 to 15 years, suggesting some patients may be cured. Results were substantially better for patients treated in second remission as opposed to later in the disease course, suggesting the optimal window to consider autoSCT in FL is second or third remission. Later application appears to be associated with diminishing returns, and patients with multiply-relapsed FL are more appropriately considered for alloSCT or novel agents. Trials evaluating autoSCT in first remission do not support its use in that setting [17].

7.3. Study drugs background

7.3.1. Idelalisib

Idelalisib is indicated in combination with rituximab, ofatumumab or bendamustine with rituximab for the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy and for the treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL). Idelalisib should be used only in patients with limited treatment options. Idelalisib is a potent competitive inhibitor of the ATP binding site of the PI3K p110δ catalytic domain, which has been shown to be prominently expressed in cells of hematopoietic origin [18, 19]. Inhibition of

PI3Kδ has been shown to modulate cellular functions including motility, proliferation, survival, and recruitment of additional intracellular signaling enzymes through the B-cell receptor (BCR). B-cell receptor signaling is a central pathologic mechanism in B-cell malignancies in that it promotes leukemia and lymphoma cell survival and proliferation; disruption of BCR signaling can be lethal to malignant B cells. The effects of p110δ on lymphocyte activation/function, cellular proliferation, and protection from apoptosis provide the rationale for targeting this isoform as a therapy for hematologic malignancies.
Idelalisib is an orally bioavailable, new chemical entity with a molecular weight of approximately 415 daltons. Its chemical name is 5-fluoro-3-phenyl-2-[(1S)-1-(9H-purin-6-ylamino)propyl] quinazolin-4(3H)-one). Idelalisib is a chiral compound with a single chiral center at C3. The compound is a single enantiomer with the (S) configuration.
Idelalisib is a new valid option for relapsed FL. In a phase 2 study of 125 patients with indolent NHL who were refractory to both rituximab and an alkylating agent, idelalisib was administered at a dose of 150 mg twice daily until PD or patient withdrawal [6]. The response rate was 57% with a median duration of 12.5 months. Response rates and duration in the FL subset were similar to the overall population. Grade 3 or higher toxicities included neutropenia (27%), transaminase elevations (13%), diarrhea (13%), and pneumonia (7%). Based upon this data, idelalisib received accelerated approval by the FDA in 2014. Efficacy results were confirmed even in a real life context [20].
Idelalisib in combination. with rituximab, bendamustine and or rituximab+bendamustine is also being evaluated in subjects with relapsed/refractory iNHL with an ORR >75% in all the four cohorts (phase I study) [21]. Due to safety signal observed in idealisib combination front-line CLL and early-line relapsed iNHL studies have been terminated as the risk/benefit profile was deemed unlikely to be favorable. Following completion of the CHMP (Committee of Human Medicinal Products) review, the benefit-risk balance of idelalisib in combination with rituximab for the treatment of relapsed CLL, including patients with 17p deletion or TP53 mutation, and idelalisib monotherapy for the treatment of refractory FL remains positive. CHMP concluded that the risk of serious infection is relevant to all indications. Risk minimization measures for serious infections have been implemented, in particular for Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) infection. For further details please consult the last drug Investigator Brochure (IB).

7.3.2. Obinutuzumab

Obinutuzumab (also known as RO5072759, GA101, GAZYVA®, GAZYVARO™) is a humanized glycoengineered type II anti-CD20 monoclonal antibody (moAb). Obinutuzumab was derived by humanization of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to the following characteristics: high-affinity binding to the CD20 antigen, high antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP); low complement-dependent cytotoxicity (CDC) activity; and high direct cell death induction. As of July 2016, obinutuzumab in combination with bendamustine received regulatory approval for the treatment of patients with relapsed/ refractory FL in multiple countries including the US, Switzerland, and the EU.
Obinutuzumab drug substance is manufactured by fermentation of a recombinant mammalian cell line and subsequent purification of the antibody. An antibody-producing cell line was established from a Chinese hamster ovary (CHO) K1 cell line.
In the monotherapy setting (studies BO20999, BO21003, YP25623, and JO21900), the proportion of patients who had a response (CR or PR) at the end of treatment ranged from 28% (11/40 patients) to 58% (7/12 patients). Although these patients had treatment-refractory or relapsed disease and been treated with several prior therapies, some patients in studies BO20999, BO21003 Phase II, and JO21900 achieved a CR by the end-of-treatment assessment. In addition, in study YP25623 one DLBCL patient achieved a CRu and 2 patients achieved a PR. Six of the 13 patients with FL (46%) had a PR; no patient with NHL (DLBCL and FL) achieved a CR.

In the chemotherapy combination studies BO21000 and GAO4915g the proportion of patients achieving a response (CR or PR) was 82% among previously untreated DLBCL patients using Cheson 2007 criteria [22] and exceeded 90% among patients with previously untreated or relapsed/refractory FL. The CR rate was also higher than in the monotherapy studies (35-39% in previously untreated FL, 39-50% in relapsed/refractory FL and 55% in previously untreated DLBCL).
At a pre-planned interim analysis, the pivotal study GAO4753g met its primary objective of showing a difference in IRC-assessed PFS between treatment arms. Treatment with G-bendamustine resulted in a clinically meaningful and statistically significant reduction by 45% in the risk of IRC-assessed PFS (progression or death) compared with bendamustine alone (stratified analysis: HR 0.55, 95% CI [0.40, 0.74]; log-rank p-value ≤ 0.0001).
Furthermore, on 20 May 2016 a pre-planned interim analysis of the pivotal study BO21223 was performed, and the IDMC recommended to unblind and fully analyze the study. The results showed that obinutuzumab-based treatment significantly reduced the risk of disease progression or death (PFS, as assessed by investigator) compared to rituximab-based treatment in patients with previously untreated advanced FL. No new safety signals were detected. EMA has approved obinutuzumab in combination with bendamustine chemotherapy followed by obinutuzumab maintenance in people with FL who did not respond or who progressed during or up to six months after treatment with rituximab or a rituximab-containing regimen.
The approval is based on results from the pivotal phase III GADOLIN study [5, 23] which showed that obinutuzumab plus bendamustine, followed by obinutuzumab alone resulted in a 52 percent reduction (HR=0.48, 95 percent CI 0.34-0.68, p<0.0001) in the risk of disease worsening or death (PFS), compared to bendamustine alone, as evaluated by an independent review committee. As assessed by investigator review, median PFS with the obinutuzumab regimen was more than double that with bendamustine alone (29.2 months vs. 13.7 months; HR=0.48, 95 percent CI 0.35-0.67, p<0.0001). People who received the obinutuzumab regimen also showed a 38 percent reduction (HR=0.62, 95 percent CI 0.39-0.98) in the risk of death (OS) compared to those who received bendamustine alone. For further details please consult the last drug IB.
Obinutuzumab has also been investigated in the frontline setting. The GALLIUM study (clinicaltrials.gov identifier NCT01332968) is an international randomized phase 3 study comparing obinutuzumab plus chemotherapy (with obinutuzumab maintenance) to rituximab plus chemotherapy (with rituximab maintenance) in previously untreated advanced-stage FL. A total of 1202 patients with follicular lymphoma were randomized in the GALLIUM trial (601 patients in each group) [24]. After a median follow-up of 34.5 months, a planned interim analysis showed that obinutuzumab-based chemotherapy resulted in a significantly lower risk of progression, relapse, or death than rituximab-based chemotherapy (estimated 3-year PFS rate of 80.0% and 73.3%, respectively; P = 0.001). No difference emerged between the two groups with respect to other time-to-event endpoints. No significant difference was observed in the rate of response according to CT-based assessment as well. Grade 3-5 adverse events and SAEs were more frequent with obinutuzumab than with rituximab (74.6% vs. 67.8% and 46.1% vs. 39.9%, respectively), but the rates of toxic deaths were similar in the two groups (4.0% and 3.4%, respectively). The most common adverse events were infusion-related events that were considered by the investigators to be largely due to obinutuzumab in 353 of 595 patients and to rituximab in 292 of 597 patients (59.3% and 48.9%, respectively; P<0.001). In conclusion, the GALLIUM trial showed that the replacement of rituximab with obinutuzumab in the context of immunochemotherapy and maintenance therapy in first line resulted in significantly longer PFS, but at the expenses of an higher frequency of high-grade adverse events [24].

8. STUDY RATIONALE

The new frontier in the treatment of FL is the development of non-cytotoxic combination therapies, able to offer to patients a “chemo-free” approach, with the same efficacy of conventional

chemotherapy but less toxicity. The paradigm of this approach is currently represented by the R-square regimen (rituximab + lenalidomide) which has shown an ORR of 77% with a CR rate of 41% [25] in relapsed/refractory FL and is currently under investigation in the frontline setting.
The combination of idelalisib with obinutuzumab would address a persistent unmet medical need with the same non-chemo approach: the design and conduct of this study is supported by knowledge of the natural history and current therapies for the disease, and the information regarding idelalisib and obinutuzumab mechanism of action and safety profile.
Idelalisib is a potent and highly selective, small-molecule, oral inhibitor of the delta isoform of the phosphatidilinositol-3 kinase (PI3Kδ), being able to block the PI3Kδ-AKT signaling and promoting apoptosis, as shown in vitro in lymphoid cell lines and in vivo. Idelalisib has shown an ORR of 56% in heavily pretreated FL patients refractory to both rituximab and alkylating agents, with a CR rate of 14% and a median PFS of 11 months [6]. The potential for clinical efficacy of idelalisib in combination with an anti-CD20 monoclonal antibody in patients with relapsed or refractory indolent non-Hodgkin lymphomas (in particular in FL) is supported by the observed antitumor activity of idelalisib given in combination with rituximab in a phase I study with an ORR of 75% and a CR rate of 22% [21].
Obinutuzumab is a type II glycoengineered humanized anti-CD20 monoclonal antibody. Compared to rituximab, it shows an increased direct cell death induction and antibody-dependent cytotoxicity due to the glycoengineering, with also a superior B-cell depletion effect. It has shown its efficacy as single agent in heavily pretreated relapsed/refractory FL patients with a ORR of 55% and a CR of 9%, being well tolerated and with no dose limiting toxicities [26]. Moreover, it has been also safely and effectively combined with CHOP and FC chemotherapy regimens in the GAUDI study [27], showing remarkable ORR (96% and 93% respectively).

Benefit/Risk balance of the combination idelalisib + obinutuzumab
The association of idelalisib and obinutuzumab is a "chemo-free" therapy with potential good therapeutic efficacy counterbalanced by an acceptable toxicity profile. In particular, the reduced duration of idelalisib administration planned by the study significantly decreases the risk for toxicity previously reported with longer therapy, even if it still maintains the same therapeutic efficacy. Furthermore, idelalisib has a completely different mechanism of action with respect the classic chemotherapy, as well as the addition advantage of the oral administration.

9. STUDY OBJECTIVES

9.1. Primary Objective

- To evaluate the efficacy in terms of clinical response in patients treated with the combination of obinutuzumab and idelalisib.

9.2. Secondary Objective

- To assess efficacy in terms of progression-free survival and overall survival
- To assess the safety and the feasibility of the combination of obinutuzumab and idelalisib.

9.3. Primary Endpoint

Overall response rate (ORR): ORR will be assessed by investigator after the 6th cycle (end of induction phase) of therapy with the combination of obinutuzumab and idelalisib as defined by 2014 Lugano criteria [28]. Last available clinical response will be considered for patients who will permanently discontinue both drugs of the experimental combination before the completion of the 6th cycle (planned duration of induction phase) for any cause. Patients who will have no tumor assessment after the start of therapy will be considered non-responsive.

9.4. Secondary Endpoint

- **Overall survival (OS) rate**, measured from the date of starting therapy to the date of death from any cause. Patients alive and patients who are lost to follow up at the time of the final

analysis will be censored at the date of the last contact. The minimum follow-up time required for OS assessment for all patients will be 2 years.

- **Progression-free survival (PFS) rate**, measured from the date of starting therapy to the date of disease progression, relapse or death from any cause. Responding patients and patients who are lost to follow up will be censored at their last assessment date. Patients who will have no tumor assessment after the start of therapy due to interruption of both drugs will be considered failures at the date of treatment interruption in the PFS analysis. The minimum follow-up time required for PFS assessment for all patients will be 2 years.
- **Treatment safety** through the measurement of: patients' withdrawal rate, incidence, type and grade of any adverse event (AE) and serious adverse event (SAE), hospitalization rate throughout the study, and patients' compliance to oral treatment.

10. STUDY DESIGN

10.1. Overview of study design

This is a prospective, multicenter, single arm, phase II study.
Patients with histologically confirmed FL, in need of a systemic approach and failing (i.e. with refractory disease [no response or response lasting less than 6 months] or with a proven disease relapse) at least 2 previous lines of treatment, including any antibody directed against the CD20 antigen-containing chemotherapy, will undergo a combined treatment of obinutuzumab and idelalisib.
After providing written informed consent, patient will be evaluated for eligibility during a 28-day screening period. In the meanwhile, their bioptic samples will be submitted to the central laboratory designed by FIL to undergo central diagnosis review. If they continue to meet eligibility criteria, they will start the obinutuzumab plus idelalisib regimen and PJP prophylaxis. Histological centralized review is compulsory for treatment start, but the local pathology report is sufficient for patient enrollment.
Obinutuzumab will be administered intravenously at a flat dose of 1000 mg on day 1, 8, 15 of the first cycle, then repeated on day 1 of each subsequent cycle, for a total of 6 cycles (each cycle is completed in 28 days). Idelalisib will be given continuously on a daily 150 mg bid schedule (24 weeks).
If one of the two drugs has to be permanently discontinued due to any cause, patient may continue treatment with the other agent if it is judged to be a clinical benefit.

For patients achieving at least a partial response at the end of induction, a maintenance phase with obinutuzumab is scheduled (on day 1 every two months for two years or until progression or unacceptable toxicity, whichever comes first).

Patients with a stable disease at EOI will enter a follow-up phase and will be followed with repeated CT scans every six months for two years or until progression or death. The same applies to patients in SD at EOT.

Patients with progressive disease, if progression is documented during induction or maintenance phase, are considered off-treatment, but will enter a survival follow up period of two years after treatment discontinuation and will be considered evaluable for OS till study end.
If progression is documented during follow up period, patients will enter a survival follow up period until globally 2 years of follow up are achieved.

Patients who will interrupt therapy (for any reason), if at least in stable disease at time of treatment discontinuation, will enter the follow-up period and will be re-evaluated for response every 6 months for 2 years or until progression/start of new anti-lymphoma therapy/death. If these patients experience progression/start of new lymphoma treatment will be followed up for survival for a total of 2 years from treatment discontinuation. These patients are however considered evaluable for PFS and OS.

Non-responder, relapsing or progressive patients will be treated according to best clinical practice.

These patients are however considered evaluable for OS.

CT scans have to be performed at baseline, after induction cycle 3 and 6 (EOI), every 3 months during the first year of maintenance, every 4 months during the second year of maintenance, at the end of treatment after 2 years of maintenance or in case of early withdrawal (EOT), at relapse/progression and during follow-up.
PET scans are mandatory at baseline, after induction cycle 3 and 6 (EOI), at the end of treatment after 2 years of maintenance or in case of early withdrawal (EOT) and at relapse/progression. At all additional timepoints (including follow-up) they are optional and will be done at clinician discretion only if in accordance with center clinical practice.

10.2. Number of patients

A total of 43 patient will be enrolled in the study: 15 patients at the Stage 1 of the study.
If there are 9 or fewer responses in these 15 patients, the study will be stopped. Otherwise, 28 additional patients will be accrued for a total of 43 patients.

10.3. Duration of the study

Patients will be recruited over 1.5 year + 6 months of induction + 2 years of maintenance and followed for 2 years after the end of the treatment phase (6,5 years).
End of study is defined by the last visit planned by the protocol of the last patient in follow-up that means 2 years after the EOT visit (LPLV). The Final Study Report will be provided after the end of the Study.

11. STUDY POPULATION

11.1. Inclusion criteria

- Relapsed or refractory, histologically confirmed CD20-positive follicular non-Hodgkin's lymphoma, grade 1, 2 or 3A according to the WHO 2017 classification.
- Age ≥ 18 years.
- At least 2 prior systemic therapies for follicular lymphoma including both any antibody directed against the CD20 antigen and a chemotherapy combination.
- Treatment indications, with the presence of at least one of the following:
  - bulky disease (nodal or extranodal – except spleen – mass more than 7 cm in its greater diameter or involvement of at least 3 nodal or extranodal sites, each with a diameter equal to or greater than 3 cm);
  - at least one B-symptom (fever > 38°C of unclear etiology, night sweats, weight loss greater than 10% of body weight in the prior 6 months);
  - symptomatic splenomegaly;
  - compression syndrome (i.e. of orbits, ureters, gastrointestinal tract, biliary tract);
  - lymphoma-related cytopenias (hemoglobin < 10 g/dL and/or platelets < $100 \cdot 10^9$/L and/or neutrophils < $1.5 \cdot 10^9$/L);
  - pleural or peritoneal serous effusions.
  -
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2.
- Adequate hematological function, unless abnormalities due to underlying disease, within 28 days prior to signing informed consent, defined as follows: neutrophils > $1.5 \cdot 10^9$/L, platelets > $75 \cdot 10^9$/L, hemoglobin > 8,0 g/dL with transfusion independence.
- Capacity and willingness to adhere to study visit schedule and specific protocol procedures.
- Willingness to sign a written informed consent.
- Compliance with effective contraception without interruption, from 28 days before treatment start up to 18 months after treatment discontinuation (see paragraph 13.9), agreeing not to donate the semen during treatment and for 18 months after discontinuation (if the patient is male), or to undergo ongoing pregnancy test during the course of the study (if the patient is

female). Birth control methods considered acceptable for the study are those highly effective (IUS, hormonal methods, tubal sterilization, sexual intercourse with a vasectomized male partner) or effective (male condom, diaphragm, cervical cap). According to the usual lifestyle of the subjects, if they are not willing to adopt the prescribed contraceptive methods, they have to practice true abstinence for all the period above reported.
- Patients must agree to undergo JPJ prophylaxis throughout the treatment period and 2-6 months thereafter (before consulting with Medical monitor).

11.2. Exclusion criteria
- Grade 3b follicular non-Hodgkin's lymphoma or evidence of transformation to high-grade non-Hodgkin's lymphoma.
- Central nervous system or leptomeningeal involvement by lymphoma.
- Major surgery (excluding any lymph node biopsy) within 28 days prior to signing informed consent.
- Seropositivity for HBV or evidence of active infection (HBsAg positivity, or HBsAg negativity with positive anti-HBs/anti-HBc and detectable viral DNA load); if viral load is negative or undetectable, the patient is eligible, provided their HBsAg negativity.
- Positive viral HCV RNA.
- Seropositivity for HIV, regardless of viral load.
- Known history of drug induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), alcoholic liver disease, non-alcoholic steatohepatitis, primary biliary cirrhosis, on-going extra-hepatic obstruction caused by cholelithiasis, cirrhosis of the liver or portal hypertension.
- Known history of drug induced pneumonitis.
- On-going inflammatory bowel disease.
- On-going alcohol or drug addiction.
- Life expectancy lower than 6 months.
- Prior history of malignancies, other than follicular lymphoma, unless the patient has been free for at least 10 years (exceptions: localized non-melanoma skin cancer ad carcinoma in situ of the cervix).
- Any of the following laboratory abnormalities: liver enzymes (AST/SGOT and/or ALT/SGPT) > 2.5-fold the upper limit of normal (except of liver involvement by lymphoma); total bilirubin > 1.5 mg/dL (except for patients with known Gilbert's disease or biliary tree compression by lymphoma masses); creatinine clearance < 30 mL/min.
- Uncontrolled intercurrent illness.
- Known hypersensitivity or allergy to murine products or to any of the medicaments under investigation.
- Pregnancy or breastfeeding, or unwillingness to comply with adequate contraception.
- Any serious medical condition, laboratory abnormality or psychiatric illness that would prevent the patient from signing the informed consent or which may place the patient at unacceptable risk if participating in the study.
- Any evidence of ongoing bacterial, viral and fungal infection.
- Known hypersensitivity to the active substances or to any of the excipients.
- Concomitant participation into another trial planning experimental therapy.

12. PATIENTS ENROLLMENT
12.1. Informed consent
The Investigator(s) must obtain informed consent of a patient or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP). Documentation that informed consent occurred prior to the patient's entry into the study and of the informed consent process should be recorded in the patient's source documents. Subjects will be informed that their participation is

voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his/her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. The subject will be given sufficient time to read the informed consent form and the opportunity to ask questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of the subject's dated signature. After having obtained the consent, a copy of the informed consent form must be given to the subject.
The original consent form signed and dated by the patient and by the person consenting the patient prior to the patient's entry into the study must be maintained in the Investigator's study files and a copy given to the patient. In addition, if a protocol is amended and the changes impact on the content of the informed consent, the informed consent must be revised. Patients participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent. The revised consent form signed and dated by the patient and by the person consenting the patient must be maintained in the Investigator's study files and a copy given to the patient.

12.2. Patient registration and data collection
Following confirmation of eligibility and written informed consent, patients should be registered online at *www.filinf.it*, in the dedicated section. An email of confirmation will be sent to the local investigator to coordinating investigator of the study and to the FIL Trial office staff. The electronic Case Report Forms (CRFs) for data collection could be reached in the restricted area of the FIL website by authorized users.

13. TREATMENT
13.1. IDELALISIB
Idelalisib will be provided in tablets intended for oral administration. Each tablet contains 150 mg or 100 mg of active idelalisib. The 150-mg tablets will be used for initial therapy; the 100-mg tablets are provided for use by those subjects who require a dose reduction. The 150-mg tablets are pink, film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, red iron oxide, polyethylene glycol, talc, polyvinyl alcohol (PVA), and titanium dioxide. The 100-mg tablets are orange, film-coated, and include the following inactive excipients: microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, sodium starch glycolate, magnesium stearate, yellow iron oxide, polyethylene glycol, talc, PVA, and titanium dioxide.

13.1.1. Supplier
Idelalisib tablets will be supplied free of charge by Gilead Sciences (Zydelig®).

13.1.2. Receipt of study drug
The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by FIL or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Study drug accountability records must also be maintained that include the subject number to whom the study drug was dispensed, the date, quantity and lot number of the study drug dispensed.

13.1.3. Preparation, reconstitution and administration
Idelalisib will be provided in bottles. Each bottle contains 60 tablets (4-week supply plus a modest overage) of one of the relevant dose strengths (150 mg, 100 mg) and a polyester coil. Bottles are white and are made of high-density polyethylene. Each bottle is closed with a white, continuous-thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Each bottle will have a unique number. The clinic staff will be responsible for dispensing idelalisib. It is planned that drug will be dispensed at 12-week intervals. Study drug may be dispensed at alternate intervals at the discretion of the investigator. Tablets should be dispensed in the original bottles provided.

13.1.4. Storage and handling

Bottles containing tablets of idelalisib should be stored at controlled room temperature (ie, ~25°C, with a range of 15 to 30°C). While stability of study drug tablets stored at controlled room temperature has been confirmed, brief excursions to temperatures as low as -20°C or as high as 40°C (eg, during shipping) will not adversely affect the drug.
The clinic staff will write the subject number on each bottle that is dispensed. Immediately before dispensing, the clinic staff will write the bottle number for each dispensed bottle in the study drug administration record corresponding to the subject number.
The disposition of idelalisib should be documented from the time of receipt at the site through subject dispensing and return.
Study personnel must ensure that all study drug is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics or allow the study drug to be used other than as directed by this protocol.

13.1.5. Unused study drug supplies

Idelalisib should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject should be recorded in the study drug accountability records. Patients will be instructed to return empty bottles or unused capsules. Unused or returned study drug will be destroyed locally in compliance with local pharmacy destruction procedures and drug disposition must be appropriately documented in the study file. If any study drug is lost or damaged, its disposition should be documented in the source documents. Records documenting the date of study drug shipping or destruction, relevant lot numbers, and amount shipped or destroyed should be maintained.

13.2. OBINUTUZUMAB

13.2.1. Supplier

Obinutuzumab will be supplied free of charge by F. Hoffmann-La Roche AG (Gazyvaro™).

13.2.2. Preparation, reconstitution and administration

Obinutuzumab is provided as a single dose 1000 mg liquid concentrate for infusion containing of 25 mg/mL obinutuzumab. The 1000 mg dose is supplied in 50 mL glass vials containing 40 mL of the 25 mg/mL liquid concentrate. In addition to the drug substance, the liquid is also composed of histidine/histidine-HCl, trehalose and poloxamer 188. Obinutuzumab should be prepared by a healthcare professional using aseptic technique. The required amount of liquid concentrate should be drawn from the vial and diluted in PVC or non-PVC polyolefin infusion bags containing sterile, nonpyrogenic 0.9% aqueous sodium chloride (NaCl) solution. Other diluents such as dextrose (5%) solution should not be used.

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. Do not use an additional in-line filter because of potential adsorption.
The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light. For clinical formulation-specific and batch-specific instructions and information on in-use stability, see the packaging label.

Administration of First and Subsequent Infusions of Obinutuzumab are shown in table below:

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

13.2.3. Receipt of study drug

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by FIL or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Study drug accountability records must also be maintained that include the subject number to whom the study drug was dispensed, the date, quantity and lot number of the study drug dispensed.

13.2.4. Storage and handling

The recommended storage conditions for obinutuzumab drug product are between 2°C and 8°C, protected from light.

13.2.5. Unused study drug supplies

Patients will be instructed to return empty bottles or unused capsules. Unused or returned study drug will be destroyed locally in compliance with local pharmacy destruction procedures and drug disposition must be appropriately documented in the study file. If any study drug is lost or damaged, its disposition should be documented in the source documents.

13.3. Treatment schedule and design

All eligible patients will undergo a combined treatment with obinutuzumab and idelalisib for 6 cycles (each cycle is completed in 28 days).

1st CYCLE

- Obinutuzumab Dose: 1 g IV Day 1, 8, 15
- Idelalisib Dose: 150 mg oral BID Daily

2nd – 6th CYCLE

- Obinutuzumab Dose: 1 g IV Day 1

- Idelalisib Dose: 150 mg oral BID Daily

If one of the two drugs has to be permanently discontinued due to any cause, patient may continue treatment with the other agent if it is judged to be a clinical benefit.

Maintenance
For patients achieving at least a partial response at the end of induction, a maintenance phase with obinutuzumab is scheduled (on day 1 every two months for two years or until progression or unacceptable toxicity, whichever comes first)

13.4. Premedication
13.4.1. Idelalisib
Idelalisib does not require specific premedications or supporting medications. However, patients must undergo JPJ prophylaxis throughout the treatment period and 2-6 months thereafter (before consulting with Medical monitor) and must undergo two-weeks CMV monitoring starting from baseline.

13.4.2. Obinutuzumab
All obinutuzumab infusions should be administered after premedication with oral acetaminophen and an antihistamine. The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for infusion-related reactions (IRRs), if deemed appropriate by the investigator, and should be administered prior to the obinutuzumab infusion. On Cycle 1 Day 1, it is recommended that oral prednisone, prednisolone, or methylprednisolone be given within 12 hours as a premedication but at least 60 minutes prior to the obinutuzumab infusion.
Premedication with prednisone or prednisolone is mandatory in patients who had an IRR and should continue until IRRs no longer occur during antibody infusion.
If it is the strong preference of the investigator or of the site (e.g., for logistical reasons) or if the patient is at increased risk for an IRR (high tumor burden, high peripheral lymphocyte count), the administration of obinutuzumab infusion can be split over 2 days. In all parts of the study, obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available, and patients should be under the close supervision of the investigator at all times.
The commonly experienced IRRs have been characterized by fever, chills, flushing, nausea, vomiting, hypotension, hypertension, fatigue, and 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 v. 5.0, 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 the 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 may be a predisposing factor for the development of IRRs.
IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions.

13.5. Prophylactic measures

Prevention of infections
Fatal and/or serious infections occurred in patients treated with idelalisib monotherapy or in combination with rituximab or with unapproved combination therapies. The most common infections were pneumonia, sepsis, and febrile neutropenia. Treatment with idelalisib should not be initiated in patients with any evidence of ongoing systemic bacterial, fungal, or viral infection. Treat infections prior to initiation of idelalisib therapy.

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 or fatal Pneumocystis jirovecii pneumonia (PJP) or cytomegalovirus (CMV) occurred in <1% of patients treated with idelalisib. Provide PJP prophylaxis during treatment with idelalisib. Regular clinical and laboratory monitoring for CMV infection is recommended in patients with history of CMV infection or positive CMV serology at the start of treatment with idelalisib.

Treatment-emergent Grade 3 or 4 neutropenia occurred in patients treated with idelalisib monotherapy or in combination with rituximab or with unapproved combination therapies.
Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with obinutuzumab administration.
In case of Grade 3 or 4 neutropenia blood counts should be monitored at least every 2 weeks for the first 6 months of therapy, and at least weekly in patients while neutrophil counts are less than 1.0, until neutrophil values return to at least Grade 2.
Use of 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) [29], European Organisation for Research and Treatment of Cancer (EORTC) [30], and European Society for Medical Oncology (ESMO) [31] guidelines, namely for patients who are ≥ 60 years old and/or with comorbidities.
Patients with Grade 3 to 4 neutropenia lasting more than one week are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered.

Thrombocytopenia
Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. Fatal hemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of hemorrhage in patients treated with obinutuzumab. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. 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.
Patients treated with concomitant medication, which could possibly worsen thrombocytopenia-related events (e.g., platelet inhibitors and anticoagulants), may be at greater risk of bleeding when the platelet count is < 20,000/μL. When possible, replace prior therapy with Vitamin K antagonists, such as warfarin, with low-molecular weight heparin (LMWH) or new oral anticoagulants (NOACs) before Cycle 1 Day 1.
Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.

Tumor lysis syndrome (TLS) Prophylaxis
TLS has been reported with obinutuzumab administration. Patients with a high tumor burden, including patients with a lymphocyte count ≥ 25 × 10^9/L are at increased risk for TLS and severe IRRs. All patients with peripheral blood lymphocyte count of ≥ 25 × 10^9/L or bulky adenopathy must receive prophylaxis for TLS prior to the initiation of study treatment. This includes appropriate hydration, consisting of fluid intake of approximately 3 L/day, starting 1−2 days prior to the first dose of obinutuzumab, and administration of allopurinol (300 mg/day orally) or a suitable alternative (i.e., rasburicase) treatment, starting at least 12 − 24 hours prior to the first infusion of

obinutuzumab (Cycle 1, Day 1). All patients should then be carefully monitored during the initial weeks of treatment. Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts ≥ 25 × 10^9/L) before the second and subsequent infusions of obinutuzumab should receive continuous TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Worsening of Preexisting Cardiac Condition
In patients with underlying cardiac disease and treated with obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias, including atrial fibrillation and tachyarrhythmia, have been observed. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution to prevent a potential fluid overload.

13.6. Patients HBV positive
Not included in this study as per inclusion/exclusion criteria.

13.7. Patients HCV positive
Not included in this study as per inclusion/exclusion criteria.

13.8. Patients HIV positive
Not included in this study as per inclusion/exclusion criteria.

13.9. Contraception
Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.
Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 18 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- Practice effective barrier contraception during the entire study treatment period and through 18 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)

Birth control methods considered acceptable for use in the trial

Highly effective methods	Additional effective methods
Levonorgestrel-releasing intrauterine system (IUS)	Male condom
Hormonal methods (Ovulation inhibitory progesterone-only pills (i.e. desogestrel); Medroxyprogesterone acetate depot; Implant	Diaphragm

Tubal sterilization	Cervical Cap
Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by two negative semen analyses	

13.10. Excluded/admitted concomitant medication

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, and nutritional supplements) used by a patient from 7 days prior to the screening evaluation to the end of study visits. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. Concomitant use of hematopoietic growth factors is allowed in accordance with instructions provided in the package inserts.

Idelalisib

CYP3A inducers

Idelalisib exposure may be reduced when co-administered with CYP3A inducers such as rifampicin, phenytoin, St. John's wort (Hypericum perforatum), or carbamazepine. Since a reduction in idelalisib plasma concentrations may result in decreased efficacy, co-administration of idelalisib with moderate or strong CYP3A inducers should be avoided.

CYP3A substrates

The primary metabolite of idelalisib, GS-563117, is a strong CYP3A4 inhibitor. Thus, idelalisib has the potential to interact with medicinal products that are metabolized by CYP3A, which may lead to increased serum concentrations of the other product that may increase their systemic exposures and increase or prolong their therapeutic activity and adverse reactions. When idelalisib is co-administered with other medicinal products, the Summary of Product Characteristics (SmPC) for the other product must be consulted for the recommendations regarding co-administration with *CYP3A4 inhibitors.*

Concomitant treatment of idelalisib with CYP3A substrates with serious and/or life-threatening adverse reactions (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, midazolam, triazolam) should be avoided and alternative medicinal products that are less sensitive to CYP3A4 inhibition should be used if possible.

Obinutuzumab

Patients who experience infusion-related temperature elevations of > 38.5°C (> 101.3°F) or other minor infusion-related symptoms may be treated symptomatically with acetaminophen/paracetamol (≥ 500 mg) and/or H1 and H2 histamine-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, β2-agonists, and/or corticosteroids) as clinically indicated according to standard clinical practice. For patients enrolled on obinutuzumab-containing regimens, it is recommended that corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) be given as premedication within 12 hours of, but at least 60 minutes prior to, the obinutuzumab infusion on Cycle 1 Day 1. After the first obinutuzumab infusion, additional glucocorticoids are allowed at the investigator's discretion. For patients who did not experience infusion-related symptoms with their previous infusion, premedication at subsequent infusions may be omitted at the investigator's discretion.

Infusion reaction prophylaxis with medications (e.g., acetaminophen/paracetamol, antihistamines, and/or corticosteroids) may be instituted at any point in the study if it is determined to be in the best interest of the patient on the basis of the observation of IRRs in patients already enrolled in the study. Patients with Grade 3 hypotension or fever must be premedicated prior to retreatment.

Patients with hypotension requiring vasopressor support or with Grade 3 wheezing, hypoxia, or generalized urticaria must be permanently discontinued from study treatment.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy
- Radiotherapy
- Immunotherapy including immunosuppressive therapy
- Radioimmunotherapy
- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Biologic agents (other than hematopoietic growth factors, which are allowed if clinically indicated and used in accordance with instructions provided in the package inserts).
- Any therapy intended for the treatment of lymphoma

Patients who require the use of any of these agents will be discontinued from all study treatment.

13.11. Warnings

Idelalisib
WARNING: FATAL AND SERIOUS TOXICITIES: HEPATIC, SEVERE DIARRHEA, COLITIS, PNEUMONITIS, INFECTIONS, and INTESTINAL PERFORATION

- Fatal and/or serious hepatotoxicity occurred in 16% to 18% of idelalisib-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue idelalisib as recommended (see *paragraph 13.12*).
- Fatal and/or serious and severe diarrhea or colitis occurred in 14% to 20% of idelalisib-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue idelalisib as recommended (see *paragraph 13.12*).
- Fatal and/or serious pneumonitis occurred in 4% of idelalisib-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue idelalisib as recommended (see *paragraph 13.12*).
- Fatal and/or serious infections occurred in 21% to 48% of idelalisib-treated patients. Monitor for signs and symptoms of infection. Interrupt idelalisib if infection is suspected (see *paragraph 13.12*).
- Fatal and serious intestinal perforation can occur in idelalisib -treated patients across clinical trials. Discontinue idelalisib for intestinal perforation (see *paragraph 13.12*).

Obinutuzumab
WARNING: HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B Virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients receiving CD20-directed cytolytic antibodies, including obinutuzumab. Screen all patients for HBV infection before treatment initiation. Monitor HBV-positive patients during and after treatment with obinutuzumab. Discontinue obinutuzumab and concomitant medications in the event of HBV reactivation (see *paragraphs 13.5* and *13.12*).
- Progressive Multifocal Leukoencephalopathy (PML) including fatal PML, can occur in patients receiving obinutuzumab (see *paragraphs 13.5* and *13.12*).

13.12. Dose modification and Toxicity Management

Idelalisib

See Table and paragraphs below for dose modification instructions for specific toxicities related to idelalisib. For other severe or life-threatening toxicities related to idelalisib, withhold drug until toxicity is resolved. If resuming idelalisib after interruption for other severe or life- threatening toxicities, reduce the dose to 100 mg twice daily. Discontinue idelalisib permanently for recurrence of other severe or life-threatening idelalisib-related toxicity upon rechallenge.
No dose modification is required for lymphocytosis, which has been observed in some patients taking idelalisib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings.

Dose Modifications for Toxicities Due to Zydelig

Pneumonitis	**Any symptomatic pneumonitis**		
	Discontinue Zydelig in patients with any severity of symptomatic pneumonitis		
ALT/AST	**>3-5 × ULN**	**>5-20 × ULN**	**>20 × ULN**
	Maintain Zydelig dose. Monitor at least weekly until <1 x ULN.	Withhold Zydelig. Monitor at least weekly until ALT/AST are <1 x ULN, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Bilirubin	**>1.5-3 × ULN**	**>3-10 × ULN**	**>10 × ULN**
	Maintain Zydelig dose. Monitor at least weekly until <1 x ULN.	Withhold Zydelig. Monitor at least weekly until bilirubin is <1 x ULN, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Diarrhea*	**Moderate diarrhea**	**Severe diarrhea or hospitalization**	**Life-threatening diarrhea**
	Maintain Zydelig dose. Monitor at least weekly until resolved.	Withhold Zydelig. Monitor at least weekly until resolved, then may resume Zydelig at 100 mg BID.	Discontinue Zydelig permanently.
Neutropenia	**ANC 1.0 to <1.5 $\cdot 10^9$/L**	**ANC 0.5 to <1.0 $\cdot 10^9$/L**	**ANC <0.5 $\cdot 10^9$/L**
	Maintain Zydelig dose.	Maintain Zydelig dose. Monitor ANC at least weekly.	Interrupt Zydelig. Monitor ANC at least weekly until ANC ≥0.5 Gi/L, then may resume Zydelig at 100 mg BID.
Thrombocytopenia	**Platelets 50 to <75 $\cdot 10^9$/L**	**Platelets 25 to <50 $\cdot 10^9$/L**	**Platelets <25 $\cdot 10^9$/L**
	Maintain Zydelig dose.	Maintain Zydelig dose. Monitor platelet counts at least weekly.	Interrupt Zydelig. Monitor platelet count at least weekly. May resume Zydelig at 100 mg BID when platelets ≥25 Gi/L.
Infections	**Grade 3 or higher sepsis or pneumonia**		
	Interrupt Zydelig until infection has resolved.		
	Evidence of CMV infection or viremia		
	Interrupt Zydelig in patients with evidence of active CMV infection of any grade or viremia (positive PCR or antigen test) until the viremia has resolved. If Zydelig is resumed, monitor patients by PCR or antigen test for CMV reactivation at least monthly.		
	Evidence of PJP infection		
	Interrupt Zydelig in patients with suspected PJP infection of any grade. Permanently discontinue Zydelig if PJP infection is confirmed.		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; ULN, upper limit of normal; CMV, cytomegalovirus; PCR: polymerase chain reaction; PJP: *Pneumocystis jirovecii* pneumonia

*Moderate diarrhea: increase of 4–6 stools per day over baseline; severe diarrhea: increase of ≥7 stools per day over baseline.

Serious Infections

Monitor patients on idelalisib for signs and symptoms of infection, and interrupt idelalisib for Grade 3 or higher infection.

Serious and fatal infections have occurred with idelalisib, including opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV). These infections have most frequently occurred the first 6 months of idelalisib treatment.

All subjects will receive trimethoprim-sulfamethoxazole or other established for PJP throughout the treatment with idelalisib. Prophylaxis should continue until the CD4+ T-cell count is documented >200 cells/µl following the end of treatment. Interrupt idelalisib in patients with suspected PJP infection of any grade, and permanently discontinue idelalisib if PJP infection of any grade is confirmed.

Subjects have to be monitored each 15 days starting from day 1 for CMV throughout the course of idelalisib treatment (CMV PCR or antigen test). If unequivocal clinical or laboratory evidence of CMV infection is present, the subject has to discontinue idelalisb until the viremia has resolved and udergo effective antiviral treatment according to established clinical guidelines.

If idelalisb is subsequently resumed, patients should be monitored by PCR or antigen test for CMV reactivation at least monthly.

Patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new respiratory symptoms promptly.

Hepatoxicity

Withhold idelalisib in the event of a Grade 3 or 4 aminotransferase elevation (ALT/AST ≥5 ULN). Once values have returned to Grade 1 or below (ALT/AST ≤3 ULN), resume idelalisib at 100 mg twice daily.

If the event dose not recur, the dose can be escalated to 150 mg twice daily after consulting with the Medical Monitor. If the event recurs, withhold until return to Grade 1 or below, after which re-initiation may be considered after consulting with the Medical Monitor.

Avoid concurrent use of idelalisib with other drugs that may cause liver toxicity.

Severe Diarrhea/Colitis

Withhold idelalisib for diarrhea of Grade 3 or 4. Once diarrhea has returned to Grade 1 or below, resume idelalisib at 100 mg daily. If the diarrhea does not recur, the dose can be re-escalated to 150 mg twice daily after consulting with the Medical Monitor.

Avoid concurrent use of idelalisib and other drugs that cause diarrhea.

Intestinal Perforation

Fatal and serious intestinal perforation occurred in idelalisib-treated patients. At the time of perforation, some patients had moderate to severe diarrhea. Advise patients to promptly report any new or worsening abdominal pain, chills, fever, nausea, or vomiting. Discontinue idelalisib permanently in patients who experience intestinal perforation.

Pneumonititis

Fatal and serious pneumonitis occurred in patients treated with idelalisib. Clinical manifestations included interstitial infiltrates and organizing pneumonia. Time to onset of pneumonitis ranges from <1 to 15 months. Monitor patients on idelalisib for pulmonary symptoms. In patients taking idelalisib who present with pulmonary symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation, withhold

idelalisib until the etiology has been determined. If symptomatic pneumonitis or organizing pneumonia is diagnosed, initiate appropriate treatment with corticosteroids.
Once pneumonitis has resolved and if re-treatment is deemed eligible for Medical Monitor, resumption of treatment at 100 mg twice daily can be considered.

Severe cutaneous reactions
Fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred in patients treated with idelalisib. If SJS or TEN is suspected, interrupt idelalisib until the etiology of the reaction has been determined. If SJS or TEN is confirmed, permanently discontinue idelalisib.
Other severe or life-threatening (Grade ≥3) cutaneous reactions, including dermatitis exfoliative, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash, and skin disorder, have been reported in idelalisib-treated patients. Monitor patients for the development of severe cutaneous reactions and withhold idelalisib Once cutaneous reaction has returned to Grade 1 or below, resume idelalisib at 100 mg twice daily. If reaction do not recur, the dose can be re-escalated to 150 mg twice daily after consulting with the Medical Monitor.

Anaphylaxis
Serious allergic reactions, including anaphylaxis, have been reported in patients on idelalisib. In patients who develop serious allergic reactions, discontinue idelalisib permanently and institute appropriate supportive measures.

For more details, please refer to *Appendix E* or the IB.

Obinutuzumab
There will be no obinutuzumab dose modification in this study. Consider treatment interruption if patients experience an infection, Grade 3 or 4 cytopenia, or a ≥ Grade 2 non-hematologic toxicity. Any NCI CTCAE (v. 5.0) toxicity Grade ≥ 3 in severity that is deemed related to obinutuzumab treatment will require interruption of study treatment until resolution to Grade ≤ 2 or ≥ 80% of baseline, whichever is lower.
Resumption of obinutuzumab treatment may be considered in patients with resolution of toxicities to Grade ≤ 1 within 2 weeks at the discretion of the investigator, after consultation with the Medical Monitor. Failure of such toxicities to resolve after 2-week delay in study treatment will require permanent discontinuation of obinutuzumab.
Continuation of study treatment following dose delays beyond 2 weeks will require consultation with and approval of the Medical Monitor based on an assessment of the benefit-risk analysis of continuing to delay study treatment.
Patients in whom toxicities have not resolved (i.e., to Grade ≤ 1 or ≥ 80% of baseline) may have their study treatment delayed by up to 2 weeks. If all study drug−related toxicities have resolved to Grade≤ 1 or ≥ 80% of baseline, the patient may resume idelalisib and obinutuzumab dosing on the regular every−28−day schedule.
Patients who do not fulfill the criteria for dosing after the additional 2 weeks have elapsed may be discontinued from study treatment and be followed for safety outcomes. Exceptions on the basis of ongoing clinical benefit may be allowed following a careful assessment and discussion of risk versus benefit with the patient by the investigator and approval from the Medical Monitor. In addition, delay of therapy because of toxicities not attributed to study drug may not require discontinuation and will be discussed with the Medical Monitor.

Progressive Multifocal Leukoencephalopathy
A “black-box” warning for obinutuzumab states that JC viral infection (including fatal) that resulted in PML with destructive infection of oligodendrocytes of the CNS white matte have been reported in patients treated with anti-CD20 therapies, including rituximab and obinutuzumab. The diagnosis of

PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common.
Some syndromes regarded as cortical (e.g., aphasia or visual-spatial disorientation) can occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA).
Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the diagnosis and management of PML.

Management of Infusion Reactions (IRRs)
Obinutuzumab can cause severe and life-threatening infusion reactions, mostly on Day 1 of obinutuzumab infusion. Infusion reactions can also occur with subsequent infusions. Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g., bronchospasm, larynx and throat irritation, wheezing, laryngeal edema). The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills. Patient premedication for IRRs is highly recommended (see *paragraph 13.4.2*)

If a patient experiences an infusion reaction of any grade during infusion, adjust the infusion as follows:
- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy.
- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently discontinue treatment if patients experience a Grade 3 infusion-related symptom at rechallenge.
- Grade 1–2 (mild to moderate): Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.

For patients with preexisting cardiac or pulmonary conditions, monitor more frequently throughout the infusion and the post-infusion period since they may be at greater risk of experiencing more severe reactions. Hypotension may occur as part of the obinutuzumab infusion reaction. Consider withholding antihypertensive treatments for 12 hours prior to, during each obinutuzumab infusion, and for the first hour after administration until blood pressure is stable. For patients at increased risk of hypertensive crisis, consider the benefits versus the risks of withholding their antihypertensive medication as is suggested here.

Hypersensitivity Reactions Including Serum Sickness
Hypersensitivity reactions have been reported in patients treated with obinutuzumab. Signs of immediate-onset hypersensitivity included dyspnea, bronchospasm, hypotension, urticaria and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported, with symptoms that include chest pain, diffuse arthralgia and fever. Hypersensitivity reactions may be difficult to clinically distinguish from infusion related reactions. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped, and

treatment permanently discontinued. Patients with known hypersensitivity reactions to obinutuzumab, including serum sickness, must not be retreated.

Tumor Lysis Syndrome (TLS)
Tumor lysis syndrome (TLS), including fatal cases, has been reported in patients receiving obinutuzumab. During the initial days of obinutuzumab treatment, monitor the laboratory parameters of patients considered at risk for TLS. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. Refer to *paragraph 13.5*.

Infections
Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. Patients with a history of recurring or chronic infections may be at increased risk of infection.
A “black-box” warning for obinutuzumab states that reactivation of hepatitis B as well as other serious viral infections (e.g., infections caused by cytomegalovirus, Varicella zoster virus, herpes simplex virus, JC virus, and HCV) that were new, reactivated, or exacerbated 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 SCT. The risk of such infections with obinutuzumab is unknown.

Thrombocytopenia
Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. In patients with Grade 3 or 4 thrombocytopenia, monitor platelet counts more frequently until resolution and consider subsequent dose delays of obinutuzumab. Transfusion of blood products (i.e., platelet transfusion) may be necessary. Consider withholding concomitant medications, which may increase bleeding risk (platelet inhibitors, anticoagulants), especially during the first cycle.
In the event of severe thrombocytopenia (platelet count < 10,000/μL) and/or symptomatic bleeding (irrespective of platelet count) in patients who are not receiving concomitant anticoagulants or platelet inhibitors: Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves. If Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).
In the event of thrombocytopenia with platelet count < 20,000/μL and/or symptomatic bleeding (irrespective of platelet count) in patients who are receiving concomitant anticoagulants or platelet inhibitors:

- Hold obinutuzumab until thrombocytopenia or symptomatic bleeding resolves. If Cycle 1 Day 8 is delayed, then skip Day 8 and administer Day 15 as previously scheduled (if thrombocytopenia or symptomatic bleeding has resolved). If Cycle 1 Day 15 is delayed, then skip Day 15 dosing and administer Cycle 2 Day 1 of obinutuzumab as scheduled (if thrombocytopenia or symptomatic bleeding has resolved).
- For patients who are on LMWH or NOACs, when platelet count < 20,000/μL develops, reduce the dose of LMWH or NOACs used.
- For patients who are on platelet inhibitors when thrombocytopenia with platelet count < 20,000/μL develops, consideration should be given to temporarily pausing the use of platelet inhibitors.

Neutropenia
Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab. Monitor patients with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of

developing infection. Consider administration of granulocyte colony-stimulating factors (GCSF) in patients with Grade 3 or 4 neutropenia.
Consider dose delays in the case of Grade 3 or 4 neutropenia. Patients with severe and long lasting (> 1 week) neutropenia are strongly recommended to receive antimicrobial prophylaxis until resolution of neutropenia to Grade 1 or 2. Consider antiviral and antifungal prophylaxis.
In the event of febrile neutropenia or neutropenia with infection, hold obinutuzumab until febrile neutropenia or neutropenia with infection resolves.

- If Cycle 1 Day 8 is delayed long enough that the patient is approaching Day 15, then skip Day 8 and administer Day 15 as previously scheduled (if infection or fever has resolved)
- If Cycle 1 Day 15 is delayed long enough that the patient approaching Cycle 2, then skip Day 15 dosing and administer Cycle 2 Day 1 as scheduled (if infection or fever has resolved).

Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment) and/or prolonged (lasting longer than 28 days).

For more details please refer to *Appendix F* or drug IB.

14. REMOVAL OF SUBJECTS FROM TREATMENT AND/OR STUDY

14.1. Discontinuation from study treatment

A patient should discontinue treatment if any of the following occurs:

- completed treatment as per protocol
- unacceptable toxicity that does not allow to give the protocol treatment
- progression, relapse or death at anytime
- refusal of the patient to further cooperate (at any time and for any reasons)
- investigator's decision that the protocol treatment is not anymore in the best interest of the patient

Subject study participation may be ended due to any of the following reasons:

- Initiation of anti-neoplastic therapy in the absence of progression
- Disease progression
- Withdrawal of consent
- Significant subject noncompliance with study drug administration, study procedures, or study requirements
- Investigator's decision to remove the subject from the study, in consultation with the Medical Monitor
- Pregnancy
- The subject is lost to follow-up
- Death

Discontinuation of the study at the request of the Sponsor, a regulatory agency, or an independent ethics committee (IEC).
Patients who discontinue treatment for any cause will continue to be followed for two years for OS. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.
Study drug may be discontinued in the following instances, in consultation with the Medical Monitor:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Objective evidence based of PD
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study

14.2. Withdrawal of subjects from the study

- Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate CRF page.
- Criteria for subject withdrawal include (but are not limited to):
  - death,
  - toxicity
  - violation of inclusion criteria
  - lost to follow up
- Subject study participation may be ended due to any of the following reasons:
  - Initiation of anti-neoplastic therapy in the absence of progression
  - Disease progression
  - Withdrawal of consent
  - Significant subject noncompliance with study drug administration, study procedures, or study requirements
  - Investigator's decision to remove the subject from the study, in consultation with the Medical Monitor
- Pregnancy
- The subject is lost to follow-up
- Death
- Discontinuation of the study at the request of Sponsor, a regulatory agency, or an institutional review board or independent ethics committee (IRB/IEC)

14.3. Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.
If the patient explicitly states his/her wish not to contribute further data to the study, the assigned FIL Study Coordinator should be informed, and the withdrawal of consent should be documented by the investigator in the patient's case report form. Information from subsequent ambulatory visits, laboratory or instrumental assessments and any other information on the patient status after consent withdrawal won't be collected in the data base or used for analysis However, both clinical data collected until patient's withdrawal as well as the data coming from the central review will still be considered as available for the study analysis.

14.4. Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time site investigator must document attempts to contact the patient either by phone or letter.

14.5. Premature termination of the study

The sponsor reserves the right to stop the trial at any time, in accordance with the DSMB. The investigators will be informed of this decision in writing.
The same applies to any investigator willing to discontinue his/her participation to the trial. The investigator must immediately inform the sponsor in writing of this decision.

15. STUDY PROCEDURES TIMEPOINTS

15.1. Screening period

within 28 days prior to Study Cycle 1 Day 1

All subjects will be screened for study eligibility including:

- Confirmed relapsed/refractory FL*
  ***** Histological centralized review is compulsory for start of treatment, but the local pathology report is sufficient for patient enrollment*
- Medical History;
- Physical Examination;
- Height, Weight;
- ECOG;
- Vital Signs;
- B symptoms;
- Hematology including Hemoglobin, Platelets, White blood cell count (WBC) with differential;
- Blood chemistry including creatinine, total bilirubin, LDH, AST, ALT, serum proteins with electrophoresis, immunoglobulin levels;
- Electrocardiogram;
- LVEF by either bi-dimensional echocardiogram or cardiac scintigraphy (MUGA);
- Measurable lesion assessment on CT scan of neck, chest, abdomen and pelvis, to be performed with and without contrast;
- FDG-PET scan (mandatory)
- Pregnancy test (if applicable);
- A bone marrow biopsy with immunohistochemical evaluation;
- Local molecular evaluation of BCL-2 rearrangement on marrow blood;
- Viral tests including HIV, HBsAg, HBsAb, HBcAb, HBV DNA and HCV (HCV RNA required for patient who are HCV antibody positive);
- Monitoring for CMV infection;
- Concomitant medications.

15.2. Treatment period (Induction)

Before each course of chemotherapy (within 24 hours prior to Day 1):

- Physical Examination, including weight;
- ECOG;
- Vital Signs;
- B-symptoms;
- Hematology including Hemoglobin, Platelets, White blood cell count (WBC) with differential;
- Blood chemistry including creatinine, total bilirubin, LDH, AST, ALT, serum proteins with electrophoresis, immunoglobulin levels;
- AE assessment;
- Pregnancy test (if applicable);
- Concomitant medications.

At days 8 and 15 during the first cycle:

- Vital Signs;
- Hematology including Hemoglobin, Platelets, White blood cell count (WBC) and neutrophils;
- Blood chemistry including creatinine, total bilirubin, LDH, AST, ALT;
- AE assessment

15.3. Assessment for restaging

after III* course and at EOI:

- Measurable lesion assessment on CT scan of neck, chest, abdomen and pelvis, to be performed with and without contrast;
- FDG-PET scan (mandatory);
- Bone marrow biopsy only if positive at baseline.

Patients who achieve a response less than stable disease after first restaging or at EOI are considered out of treatment and will be shifted to survival follow up
*Within 7 days before cycle IV day 1

Clinical and Laboratory CMV infections monitoring: Every two weeks starting from C1D1.
Prophylaxis for PJP: all patients will receive PJP prophylaxis during idelalisib treatment and for 2 to 6 months after stopping treatment; patients have to be monitored for respiratory signs and symptoms.

15.4. EOT phase

at 4-6 weeks after last treatment administration

- Physical Examination;
- ECOG;
- Vital Signs;
- Hematology including Hemoglobin, Platelets, White blood cell count (WBC) with differential;
- Blood chemistry including creatinine, total bilirubin, LDH, AST, ALT, serum proteins with electrophoresis, immunoglobulin levels;
- Pregnancy test (if applicable);
- Electrocardiogram;
- LVEF by either bi-dimensional echocardiogram or cardiac scintigraphy (MUGA);
- Measurable lesion assessment on CT scan of neck, chest, abdomen and pelvis, to be performed with and without contrast (unless the subject already has had per-protocol assessments ≤4 weeks prior);
- FDG-PET scan (mandatory) unless the subject already has had per-protocol scan ≤4 weeks prior;
- Bone marrow biopsy only if positive at baseline;
- Molecular evaluation of BCL-2 rearrangement on marrow blood only if positive at baseline;
- Drug accountability
- AEs assessment
- Recording of concomitant medications.

Subjects lost to follow up should be recorded as such on the eCRF. All subjects who discontinue study treatment, including those who refuse to return for a final visit, should be contacted for a list of antineoplastic therapies received after discontinuation of study treatment.

15.5. Maintenance period

every 3 months for the first year and every 4 months for the second year
Maintenance phase begins after the end of induction and continues until 2 years or PD documentation or unacceptable toxicity, whichever comes first only for patients who achieve at least PR at EOT.

- Physical Examination;
- ECOG;
- Vital Signs;
- Clinical Laboratory Evaluations;
- CT scan of neck, chest, abdomen and pelvis, to be performed with and without contrast (counting months with a ±7 days range from EOT imaging evaluation);

- FDG-PET scans during maintenance are optional and will be performed at clinician discretion only if in accordance to the site clinical practice.

15.6. Follow up period

(every 6 months)

- For patients in SD at the EOI restaging (ie for patients who not continue with maintenance phase).
- For patients in SD, PR or CR at the end of maintenance phase.

The follow up phase continues until 2 years, PD or a new anti-lymphoma therapy, whichever comes first. If any of the above occurs, patients will enter the survival follow up period till the completion of two years globally.

- Physical Examination;
- ECOG;
- Vital Signs;
- Pregnancy test (if applicable);
- Clinical Laboratory Evaluations;
- FDG-PET and CT scan of neck, chest, abdomen and pelvis, to be performed with and without contrast (counting months with a ±7 days range from EOT imaging evaluation);
- FDG-PET scans during follow-up are optional and will be performed at clinician discretion only if in accordance to the site clinical practice.

15.7. Survival Follow up

For patients in PD or for patients who start a new anti-lymphoma treatment. Every 3 months until 2 years (counting follow up phase too if applicable) or until study closure whichever comes first. Survival follow up can be performed with a telephone contact too and the investigator must report: disease status, patients' status (dead or alive and date of death, new anti-lymphoma therapy).

15.8. Early withdrawn (EW)

discontinuation from study treatment

- Physical Examination;
- ECOG;
- Vital Signs;
- Hematology including Hemoglobin, Platelets, White blood cell count (WBC) with differential;
- Blood chemistry including creatinine, total bilirubin, LDH, AST, ALT, serum proteins with electrophoresis, immunoglobulin levels;
- Pregnancy test (if applicable);
- Electrocardiograms;
- LVEF by either bi-dimensional echocardiogram or cardiac scintigraphy (MUGA);
- Measurable lesion assessment on CT scan of neck, chest, abdomen and pelvis, to be performed with and without contrast unless the subject already has had per-protocol scan ≤4 weeks prior;
- FDG-PET scan (mandatory) unless the subject already has had per-protocol scan ≤4 weeks prior;
- Drug accountability
- AEs assessment
- Recording of concomitant medications.

15.9. Schedule of assessments

	Screening	Treatment (Induction)						Restaging after 3 cycles, EOI, EOT, EW	Maintenance[g]	FU[e]	OS- FU
		Cycle 1			Cycle 2-6						
	-28 to D1	D1	D8	D15	D1	D8	D15				
Informed consent	X										
Inclusion/Exclusion	X										
Medical History	X										
Height	X										
Weight	X	X	X	X	X						
Physical exam	X	X	X	X	X			X	X	X	
Pregnancy test	X	X	X	X	X			X	X	X	
Vital signs	X	X	X	X	X			X	X	X	
ECOG	X	X	X	X	X			X	X	X	
Hematology	X	X	X	X	X			X	X	X	
Chemistry	X	X	X	X	X			X	X	X	
Virology	X										
12-lead ECG	X							X [h]			
Tumor biopsy [b]	X										
CT of neck, chest, abdomen, pelvis	X							X [f]	X [f]	X [f]	
FDG-PET	X							X [f]	X [f]	X [f]	
LVEF measurement	X							X [h]			
BM biopsy	X							X [a]	X [a]	X [a]	
BCL-2 rearrangement	X							X [ah]			
B symptoms	X	X	X	X	X			X	X	X	
Idelalisib		BID									
Obinutuzumab		X	X	X	X				X [g]		
CMV monitoring [c]	X			X	X		X				

	Screening	Treatment (Induction)						Restaging after 3 cycles, EOI, EOT, EW	Maintenance[g]	FU[e]	OS- FU
		Cycle 1			Cycle 2-6						
	-28 to D1	D1	D8	D15	D1	D8	D15				
PJP prophylaxis [d]		X	X	X	X	X	X	X			
Survival follow up contact											X
Concomitant medications	Recorded from screening through 30 days after the last dose of treatment.										
Adverse event reporting		Recorded from first dose of study drug through 30 days after the last dose of treatment.									
Serious adverse event	Reported from signing of the informed consent from through last patient last visit										

[a] only if positive at baseline/previous assessment;
[b] Histological centralized review is compulsory for treatment start, but the local pathology report is sufficient for patient enollment;
[c] Every two weeks starting from C1D1;
[d] All patients will receive prophylaxis for PJP during idelalisib treatment and for 2 to 6 months after stopping treatment; patients have to be monitored for respiratory signs and symptoms;
[e] Every 6 months for 2 years only for CR, PR or SD patients at the end of treatment until PD, unacceptable toxicity or a new anti-lymphoma therapy;
[f] FDG-PET scan is mandatory at baseline, after induction cycle 3, at the EOI, at the end of treatment after 2 years of maintenance or in case of early withdrawal (EOT) and at relapse/progression, unless the subject already has had per-protocol scan ≤4 weeks prior; all additional PET scans (every 3 months during the first year of maintenance, every 4 months during the second year of maintenance and during follow-up) are optional and will be done at clinician discretion only if in accordance to the site clinical practice;
[g] obinutuzumab on day 1 every two months, procedures every 3 months for first year and every 4 months for the second year;
[h] only EOI and EOT.

16. SAFETY MEASUREMENTS AND PARAMETERS

16.1. Safety measurements

All patients who have received at least one dose of study medication will be considered the Analysis Population and will be evaluated for toxicity from the time of their first drug administration. When toxicity occurs, it should be graded according to the NCI Common Toxicity Criteria, version 5.0.

16.2. Safety parameters

Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

An overdose, accidental or intentional, whether or not it is associated with an AE, or abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. If an overdose is associated with an AE, the overdose and adverse event should be reported as separate terms.

Serious Adverse Events (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (t*he term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)*
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a medically significant event
- Is a suspected transmission of any infectious agent via a medicinal product.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriated in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.

The term “severe” is a measure of intensity, thus a severe AE is not necessarily serious. For example, “nausea of several hours” duration may be severe but may not be clinically serious.

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.

- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form on www.drugvigilance.filinf.it must be completed.
For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An unlisted adverse event, the nature or severity of which is not consistent with the applicable product information. For an investigational drug, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure of experimental drug. For drugs with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the SmPC.

Severity
The intensity of the toxicities, AE or SAE will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system version 5.0 in the toxicity categories that have recommended grading.
AEs not listed on this grading system will be graded according to the five-point system below:

Mild (grade 1)	Discomfort noticed but no disruption of normal daily activity
Moderate (grade 2)	Discomfort sufficient to reduce or affect normal daily activity
Severe (grade 3)	Incapacitating with inability to work or perform normal daily activity
Life-threatening (grade 4)	Substantial risk of dying at time of event
Death (grade 5)	Fatal

Causality
The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- Not related. An adverse event that is not related to the use of the investigational product.
- Unlikely/Doubtful. An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- Possible. An AE that might be due to the use of the investigational product. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- Probable. An AE that might be due to the use of the investigational product. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).
- Definite/Very likely. An AE that is listed as a possible adverse event reaction, and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).
- Not assessable: there is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

16.3. Serious Adverse Events reporting rules

All events that meet one or more criteria of seriousness (see above) occurred after the informed consent signature until the end of the study or early withdrawal for any cause, regardless of the relationship to the study treatment, will be reported as SAE.
After this time, SAE that occurs, during the follow-up period, if considered related to the study medication, will be reported.
Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all SAEs and his opinion as to whether the SAE can be related to the study drugs.
General SAE reporting rules:

- Any episode of any grade of toxicities, which meets one of the seriousness criteria, must be reported as “Serious Adverse Event” in the appropriate SAE form.
- Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as “Serious Adverse Event”.
- “Alopecia” toxicity (any grade) will never be reported as “Serious Adverse Event”.

All AEs that occur from the first dose of study drug administration up to 30 days following the last dose of investigational product will be reported.
All SAEs that occur between the study informed consent signature and until the LPLV will be notified to the sponsor, using the FIL Serious Adverse Event reporting rules. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All AEs and SAEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded in the CRF in accordance to the CTCAE criteria v 5.0. They must be recorded using medical terminology (MedDRA version 21.1).

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

Obligations of the Investigator
Investigators must record also in the CRF their opinion concerning the relationship of the adverse event to the study therapy. All measures required for adverse event management must be recorded in the source document.
Investigators must submit reports of all SAEs, regardless of attribution to the Sponsor within 24 hours of learning of the events.
For initial SAE investigators should record all case details that can be gathered on a SAE form that must be completed directly online through the FIL web site: www.drugvigilance.filinf.it

The initial report must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up SAE form as soon as it becomes available and/or upon request.
The Investigator(s) must keep copies of all SAE information on file. All SAEs that have not resolved upon discontinuation of the patient’s participation in the study must be followed until either the event resolves completely, stabilizes/resolves with sequelae, or returns to baseline (if a baseline value is available).

The FIL Pharmacovigilance will supply Gilead Sciences and F. Hoffmann-La Roche AG [Pharmaceutical Company] with a copy of all SAEs which involve exposure to a Gilead Sciences and F. Hoffmann-La Roche AG product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC).

The FIL Pharmacovigilance will provide Gilead Sciences and F. Hoffmann-La Roche AG with a copy of the development safety update report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committees.

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Adverse Events of Special Interest (Immediately Reportable to the Sponsor)
Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).
Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law and based on the following observations:
  - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of any of the study treatment components is suspected.

- TLS of any grade, irrespective of causality
- Second malignancies.

Obligations of the Sponsor
The Sponsor will inform relevant Regulatory Authorities and Ethics Committees:

- Of all relevant information about serious unexpected adverse events suspected to be related to the study drugs that are fatal or life-threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will be subsequently be submitted within an additional eight days
- Of all other serious unexpected events suspected to be related to the study drugs as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

16.4. Pregnancy
Females of Childbearing Potential
Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug are considered events to be reported immediately to FIL Pharmacovigilance on the appropriate Pregnancy Form:

e-mail: drugvigilance@filinf.it
Fax: +39.0131.263455

If the subject is on study drug, the study drug is to be discontinued immediately.
The exposure of any pregnant female (e.g. caregiver or pharmacist) to study drug is also an immediately reportable event.
The female should be referred to an obstetrician/gynecologist preferably one experienced in reproductive toxicity for further evaluation and counseling.
The Investigator will follow the female subject until completion of the pregnancy and must notify FIL immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (i.e., spontaneous or therapeutic abortion) the Investigator should report the abnormal outcome as a SAE within 24 hours of the Investigator's knowledge of the event through www.drugvigilance.filinf.it.
All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator(s) suspects is related to the in-utero exposure to the study drug should also be reported to FIL within 24 hours of the Investigator's knowledge of the event through www.drugvigilance.filinf.it.

Male patients
If a female partner of a male patient taking study drug becomes pregnant, the male patient taking study drug should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.
If a pregnancy related event is reported in a female partner of a male subject, the investigator should determine whether the female partner is willing to release her medical information to FIL Pharmacovigilance and allow the pregnancy related event to be followed-up to completion.

16.5. Follow up of AEs and SAEs
Any SAE should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported should be sent to the FIL as soon as information becomes available via www.drugvigilance.filinf.it.
All AEs must be documented, and the outcome must be followed-up until the return to normal or consolidation of the patient's condition.
Subjects withdrawn from the study due to any AE will be followed at least until the outcome is determined even if it implies that the follow-up continues after the patient has left the trial.

16.6. Product Quality Complaint Handling
A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

Procedures
All initial PQCs must be reported to Gilead Sciences/F. Hoffmann-La Roche AG by the study-site personnel within 24 hours after being made aware of the event.
If the defect is combined with a SAE, the investigational staff must report the PQC to Gilead Sciences/F. Hoffmann-La Roche AG according to the SAE reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Gilead Sciences/F. Hoffmann-La Roche AG.

17. STATISTICAL CONSIDERATIONS

17.1. Sample size
Optimal Simon's two-stage design [32] has been be used to calculate the sample size.
The null hypothesis that the true response rate is 55% (response rate of idelalisib single agent) [6] will be tested against a one-sided alternative response rate of 75% (response of obinutuzumab in combination) [23]. Last available clinical response will be considered for patients who will permanently discontinue for any cause both drugs of the experimental combination before the completion of the 6th cycle (planned duration of induction phase).
For the first stage, the accrual will be suspended when 15 patients will have started experimental therapy. If there are 9 or fewer responses in these 15 patients, the study will be stopped.
Otherwise, enrollment will be reopened until 28 additional patients will start experimental therapy for a total of 43. The null hypothesis will be rejected if 29 or more responses are observed in 43 patients.

This design yields a type I error rate of 5% and power of 80% when the true response rate is 75%.

17.2. Safety monitoring and stopping rules

In order to monitor the safety of the treatment in small cohorts of patients, the Bayesian approach of Thall, et al. [33], as extended by Thall and Sung [34], for monitoring toxicity will be used. We have planned the monitoring of toxicity to ensure that the proportion of patients with non-hematological toxicity defined as any non-hematological toxicity of grade 3 or higher after 3 and 6 cycles of induction was not higher than an acceptable level of 25%. The prior probability of toxicity (25%) is modeled by a beta distribution [Beta (0.5,1.5)]. We will stop the enrolment in the experimental cohort if the posterior probability of the treatment being more toxic than expected is greater than 90%. Patients will be monitored, without suspending the enrollment, according to the following stopping boundaries for toxicity in cohorts of five patients as per assessment every 3 cycles:

Patients Enrolled	Stop the enrollment in the cohort if the relevant toxicities are greater or equal to:
5	3
10	5
15	7
20	9
25	10
30	12
35	13
40	15

Demographics and patients' characteristics will be summarized by descriptive statistics. Point estimates of efficacy and toxicity will be provided with 95% confidence intervals. Overall response rate will be calculated as the sum of complete and partial response rates. Time-to event endpoints (progression free survival, overall survival) will be estimated by the Kaplan-Meier method. For the safety analyses, frequency of toxicities will be reported by type and grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).

17.3. Statistical analysis plan

Analysis population

Both efficacy and safety analyses will be conducted on all patients receiving at least one dose of planned therapy.

Adverse Events

All adverse events will be listed. The focus of AE summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an AE that occurs or worsens in the period from the first dose of study drugs to 30 days after the last dose of study drug. AEs that occur before the first dose of study treatment or >30 days after the subject has been discontinued from study treatment will be included in data listings.

AEs will be classified using MedDRA version 21.1 with descriptions by System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 5.0, whenever possible. If a CTCAE criterion does not exist for a specific type of adverse event, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the study drug will be categorized as related or unrelated.

A subject who reports multiple treatment emergent AEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade.

AE descriptions will be presented by decreasing frequency for a given System Organ Class and Preferred Term.

Separate listings and summaries will be prepared for the following types of treatment-emergent adverse events:

- Study-drug-related (idelalisib or obinutuzumab) adverse events
- AEs that are Grade ≥3 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug (idelalisib or obinutuzumab) discontinuation
- SAE (with categorization of the primary reason that the adverse event is considered serious, e.g., death, hospitalization, etc)

18. INDEPENDENT DATA SAFETY MONITORING BOARD (DMSB)

The FIL on its own initiative and responsibility set up an independent external DSMB. The DSMB consist in Experts independent from the sponsor.
The aim of the DSMB is to assess, at intervals (every 3 cycles) during the course of the trial, the progress of the trial, the trial safety data and the trial outcome data with a view to recommending whether the trial should continue, be modified or be terminated.

The DSMB will be composed by:

- Three independent clinicians with expertise in the treatment of FL
- The biostatistician of the study
- An independent statistician with expertise in the methodology of clinical trials and data analysis.

Roles of DSMB (suggested, not exclusive):

- To monitor evidence for treatment harm (toxicity).
- To decide whether to recommend changes to the protocol.
- To decide whether to recommend that the trial continues to recruit participants or whether recruitment should be terminated.
- To review final analysis of the data.
- To discuss final data with PI and the sponsor.

Timing of Analyses

Interim Analyses

The DSMB will have access to serious adverse events requiring expedited reporting and will be provided with accumulating safety data on a regular basis. An interim safety review will be conducted by the DSMB at ~3 months after the first subject is enrolled. Thereafter, interim safety reviews will be performed by the DSMB at intervals of ~3 months, according to the availability of the safety monitoring results; the specific frequency of these reviews will depend upon the rate at which the trial is enrolled, the nature of any emerging safety signals, and monitoring recommendations from the DSMB. At each review, all available safety data will be summarized and evaluated. The analyses will offer opportunities to assess early for evidence of substantial clinical benefit.

Planned meetings:

Three face-to-face meetings that include preparation, working time during the meeting, transport time and writing reports.
Three call conferences that include preparation, working time during the meeting, transport time and writing reports.

Following each review, each meeting and each call conference, the DSMB will prepare a report and may recommend changes in the conduct of the trial.

19. INDEPENDENT EXTERNAL PATHOLOGY REVIEW

An independent pathologist panel will review the lymph node/tumor biopsy, as well as any available bone marrow biopsy or other diagnostic material for upfront confirmation of the diagnosis of cases classified by local pathologist as FL. The investigative site must submit the requested samples as part of the screening phase to allow for a histological review. Histological centralized review is compulsory for treatment start, but the local pathology report is sufficient for patient

enrollment A confirmation of diagnosis of FL will be made by an expert pathologist and his staff The review process will be organized according to the procedures described in *Appendix D*.

20. GOOD CLINICAL PRACTICE, QUALITY CONTROL AND QUALITY ASSURANCE

20.1. Monitoring, Audits and Inspections

During the study the monitoring will be prevalently made by e-mail and telephone. The field monitor will visit the site, when needed, mainly in presence of data incongruity, to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice and the progress of enrolment. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. FIL Safety Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

20.2. Investigator(s) responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice. The investigator must give the monitor access to relevant records to confirm the above.

The Investigator(s) is responsible for keeping a record of all patients who sign an Informed Consent Form and are screened for entry into the study. For those patients who fail screening the reason(s) for exclusion must be recorded in the patient's source documents.

No procedure/assessment/measurement/test other than those outlined here, or in the schedule of study assessments, is to be performed without the prior written approval of Principal Investigator, or unless deemed by the investigator(s) as necessary for the patient's medical care. Investigator(s) and/or authorized designee(s) must enter study data onto electronic CRFs supplied by FIL. The data on the CRF will be recorded in an anonymous manner to protect the patient's identity by using a unique identifier that will prevent personal identifiable information.

The Investigator(s), or a designated member of the Investigators' staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the patient's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The CRFs must be completed as soon as possible after the patient's visit, but no later than prior to each monitoring visit and be made available to the FIL representative(s) so that the accuracy and completeness may be checked.

21. ETHICAL AND REGULATORY STANDARDS

21.1. Independent Ethics Committee Review Approval

This study will be conducted according to the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients (see: http://www.wma.net/e/policy/b3.html for more information). The review of this protocol by the IEC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Patients and Part 56 Institutional Review Boards. Before implementing this study, the protocol, the proposed informed consent form and other information to patients, must be reviewed by a properly constituted IEC. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to

FIL before the study initiation. The names and occupations of the chairman and the members of the IEC must be supplied to FIL.
The FIL as sponsor of the study, together with site Investigator(s), will be responsible for preparing documents, where ever applicable, for submission to the relevant IEC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.
A copy of the IEC approval for the protocol and the Informed Consent is to be provided to FIL and site Investigator(s). The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.
The Investigator(s) is responsible for notifying the FIL Safety Monitoring Office and the IEC of any serious deviations from the protocol, or anything else that may involve added risk to patients.
Any advertisements used to recruit patients for the study must be reviewed and approved by FIL and the IEC prior to use.
Before the start of the study, the FIL will provide the IEC with current and complete copies of the following documents:

1. final protocol and, if applicable, amendments
2. informed consent form (and any other written materials to be provided to the subjects)
3. Investigator's Brochure (or equivalent information) and amendments
4. information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
5. investigator's curriculum vitae or equivalent information (unless not required, as documented by IEC)
6. any other documents that the IEC requests to fulfil its obligation.

During the study the FIL according with site investigators will send the following documents to the IEC for their review and approval, where appropriate:

1. protocol amendments
2. revision(s) to informed consent form and any other written materials to be provided to subjects
3. revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
4. Investigator's Brochure amendments or new edition(s)
5. summaries of the status of the study (at least annually or at intervals stipulated in guidelines of the IEC)
6. reports of adverse events that are serious, unexpected and associated with the investigational drug
7. new information that may affect adversely the safety of the subjects or the conduct of the study
8. deviations from or changes to the protocol to eliminate immediate hazards to the subjects
9. report of deaths of subjects under the investigator's care
10. notification if a new investigator is responsible for the study at the site
11. any other requirements of the IEC

21.2. Protocol Amendments Approval

Any amendment to this protocol that seems appropriate, as the study progresses will be submitted to the IEC for written approval before the implementation of the amended version. The written signed approval from the IEC should refer specifically to the investigator(s) and to the protocol number and title and mention any amendment numbers that are applicable. Amendments that are administrative in nature do not require IEC approval but will be submitted to the IEC for information purposes.

22. ADMINISTRATIVE PROCEDURES

22.1. Curriculum vitae

An updated copy of the curriculum vitae of each investigator and sub-investigator will be provided to the FIL Start Up prior to the beginning of the study.

22.2. Confidentiality agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of FIL.
They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of FIL.
It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.
The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

22.3. Record retention in investigating centers

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.
However national regulations should be taken into account, the longest time having to be considered.
For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes according to the applicable laws and regulations on Clinical Trials.
Any center will notify the sponsor before destroying any data or records.

22.4. Ownership of data and use of the study results

The sponsor has the ownership of all data and results collected during this study. In consequence the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of any country.

22.5. Authorship

The first results of the trial will be published after complete data collection and evaluation of the primary endpoint. Partial or preliminary results can be published beforehand. Publication is to be initiated by the chairmen in charge of the study with approval of coordinators.
Any publication in the form of a lecture, poster or article must be before approved by the Scientific Committee of FIL.
The authors will be proposed (according to the updated FIL publication rules) by the chairmen in charge of the study, approved by coordinators and finally decided by the Steering Committee of the study.
All study data and publications are the property of the FIL.

22.6. Insurance coverage

The Investigator-sponsor of the Study must ensure that adequate insurance coverage is available to the patients, in accordance with the ICH Guidelines of Good Clinical Practice. Such coverage must extend to all damages deriving from the study, to the Protocol Study exclusion of those attributable to wilful misconduct or negligence of the institution or investigator. A copy, or excerpt, or insurer’s certificate, attesting the existence and amount of such coverage at least for the duration of the study must be supplied as part of the study documentation to the review and approval of the IEC.
A specific insurance with company HDI Global SE has been concluded for patients enrolled in this study. No extra expenses, neither for therapies nor for clinical or laboratory procedures can be asked or expected to be paid by SSN or patients.

22.7. Protocol amendments procedures

It is specified that the appendices attached to this study and referred to in the main text of this study, form an integral part of the study.

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the FIL.
Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended to this study.
Approval/advice of amendments by Ethics Review Committee and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.
If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval/advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.
In some instances, an amendment may require a change to a consent form. The investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

23. DATA HANDLING AND RECORD KEEPING

23.1. Data/documents

The investigator(s) must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; patient's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; patient files) and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, filed and retained.

23.2. Data Management

Data will be entered into the clinical database as per FIL SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary, in the form of a Data Clarification Form (DCF) or a query. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

23.3. Retention of Records

The investigator(s) must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation includes, but is not limited to, protocols, case report forms, advertising for patient participation, adverse event reports, patient source data, correspondence with health authorities and IECs, informed consent forms, investigator(s) curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor must be consulted if the investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period. The investigator(s) must retain study records for the time period according to local laws or requirements, whichever is longer. The monitor will inform the investigator(s) of the dates for retention. All study documents should be made available if required by relevant health authorities.

24. PRIVACY OF PERSONAL DATA

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. These data must be collected and processed with

adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.
The investigator-sponsor ensures that the personal data will be:

1. processed fairly and lawfully
2. collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
3. adequate, relevant, and not excessive in relation to said purposes
4. accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject before collection of data. Such consent should also address the transfer of the data to other entities and to other countries. The subject has the right to request through the investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.
Patients will be registered in the study via web site prior to any study related procedure and after signing informed consent.
The name of the patient will not be asked for not recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify and must be included on all case report form.

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26. APPENDICES

APPENDIX A: ECOG PERFORMANCE STATUS

SOURCE: *Oken MM et al, Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX B: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

In the present study, adverse events and/or adverse drug reactions will be recorded according to the: **Common Terminology Criteria for Adverse Events (CTCAE), version 5.0**.
Click on CTCAE, version 5.0 to download the document in pdf.

APPENDIX C: Response assessment by CT and PET scans

SOURCE: *Cheson et al., J Clin Oncol. 2014 Sep 20;32(27):3059-68* [28].

Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX D: PATHOLOGY REVIEW GUIDELINES

Every center participating to the study will provide the central laboratory with material used to perform local diagnosis of FL relapsed, or that used for the more recent biopsy in the case of refractory patients. The investigative site must submit the requested samples as part of the screening phase to allow for an upfront histological review. Central review is mandatory to start treatment, even if patients can be entered in the study according to local diagnosis.

Samples shipment will be set up by FIL.

For each patient, a formalin-fixed paraffin embedded (FFPE) tissue block should be provided to the central laboratory. Sites are encouraged to provide a block, since some nuclear antigens to be tested are labile, and the risk for false negative results on cut sections is high.
The block will be promptly returned to the local site upon completion of the central review process.

In the case a block is absolutely not available, the site can choose one on the two following options:

a) to send 20 unstained sections;
b) to send one H&E or GIEMSA stained slide from each block, and all immunostains performed for local diagnosis plus 15 unstained sections. The institution's H&E, GIEMSA and immunostains will be returned promptly after the review is done.

In both cases, an anonymized copy of the local diagnostic reports, including the description, the final diagnosis, and the immunohistochemical and/or flow cytometry results and molecular results, if done, are also to be also provided.

Tests to be performed at central laboratory

Standard panel:
CD20, CD5, CD10, BCL6, IRF4/MUM1, CD23, BCL2 (if negative with monoclonal antibody 124, to be tested also with E17 and SP66), LMO2, MYC, P53 and KI-67.

Differential diagnosis:
In the case of problems of differential diagnosis with marginal lymphoma, IRTA1 and MNDA will be also assessed.

Special cases:
In some particular types of FL cases, it could be difficult rendering a definite diagnosis relying on the results of the above reported tests: in these cases, FISH analysis (e.g., disease presenting with *IRF4* rearrangement or double hits) and/or molecular assessments (e.g., *TP53* mutations or Ig rearrangement) will be done.

Central diagnosis review FIL laboratory:
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The laboratory has entered into an agreement with FIL to carry out the centralized review of the samples of patients registered in the trial.

APPENDIX E: REFERENCE SAFETY INFORMATION FOR IDELALISIB

Serious Expected Terms Associated with idelalisib Coded by MedDRA version 21.1)
IB edition 19 of 27 September 2018.

SOC	SARs	Frequency
Blood and lymphatic system disorders	Neutropenia	Common
Gastrointestinal disorders	Diarrhea	Common
	Colitis	Common
Investigations	Transaminases increased	Uncommon
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Common
	Organising pneumonia[a]	Uncommon
Skin and subcutaneous tissue disorders	Dermatitis exfoliative	Rare
	Rash generalised	Uncommon
	Rash maculo-papular	Uncommon
General disorders and administration site conditions	Pyrexia	Very common
Infections and Infestations	*Pneumocystis jirovecii* pneumonia	Common
	Cytomegalovirus infection	Uncommon

SOC = system organ class; SARs = serious adverse reactions
Frequencies are defined as follows: very common (≥ 10%); common (≥ 1% and < 10%); uncommon (≥ 0.1% and < 1%); rare (≥ 0.01% and < 0.1%).
a SAR identified through postmarketing surveillance.

APPENDIX F: REFERENCE SAFETY INFORMATION FOR OBINUTUZUMAB

(Serious Expected Terms Associated with obinutuzumab Coded by MedDRA version 21.1)
IB edition 13; study pool = 3745 patients; Data cut-off date = 14 Mar 2018

MedDRA PT	(Cumulative Clinical Trial Exposure = 3745) All SARs	Comment
Injury, poisoning and procedural complications SOC		
Infusion related reaction *	234	
Blood and lymphatic system disorders SOC		
Neutropenia *	290	
Thrombocytopenia*	114	
Anaemia *	32	
Leukopenia *	41	
Febrile neutropenia	320	
Lymphopenia	4	
Haemolytic anaemia	2	
Cardiac disorders SOC		
Atrial fibrillation *#	29	In the context of worsening of pre-existing cardiac condition
Cardiac failure *#	13	In the context of worsening of pre-existing cardiac condition
Acute coronary syndrome #	5	In the context of worsening of pre-existing cardiac condition
Angina pectoris #	2	In the context of worsening of pre-existing cardiac condition
Myocardial infarction #	14	In the context of worsening of pre-existing cardiac condition
Supraventricular tachycardia #	2	In the context of worsening of pre-existing cardiac condition
Acute myocardial infarction #	2	In the context of worsening of pre-existing cardiac condition
Cardiac failure acute #	2	In the context of worsening of pre-existing cardiac condition
Cardiac failure congestive #	4	In the context of worsening of pre-existing cardiac condition
Sinus tachycardia #	3	In the context of worsening of pre-existing cardiac condition
Tachycardia #	7	In the context of worsening of pre-existing cardiac condition
Gastrointestinal disorders SOC		
Diarrhoea *	26	
Colitis *	10	
Intestinal perforation *	3	
Nausea	16	In the context of infusion related reactions
Vomiting	18	In the context of infusion related reactions
Constipation *	3	
Neutropenic colitis	2	
General disorders and administration site conditions SOC		
Pyrexia *	169	
Asthenia *	4	
Chest pain *^	4	In the context of worsening of cardiac condition
Chills	17	In the context of infusion related reactions
Fatigue	19	In the context of infusion related reactions
Chest discomfort	3	In the context of worsening of cardiac condition
Infections and infestations SOC		
Upper respiratory tract infection *	15	
Sinusitis *	6	
Urinary tract infection *	26	
Herpes zoster *	22	
Pneumonia *	167	
Influenza *	13	
Pharyngitis *	3	
Lung infection *	42	
Atypical pneumonia	4	
Hepatitis B reactivation *	9	
Herpes zoster disseminated	3	
Neutropenic infection	9	
Pneumonia bacterial	3	
Pneumonia fungal	4	
Respiratory tract infection	14	
Sinusitis fungal	2	
Progressive multifocal leukoencephalopathy *	6	
Hepatitis B	2	
Herpes virus infection	4	
Lower respiratory infection	9	
Pneumonia haemophilus	2	
Pneumonia psedomonal	2	

MedDRA PT	(Cumulative Clinical Trial Exposure = 3745) All SARs	Comment
Respiratory, thoracic and mediastinal disorders SOC		
Cough *^	7	
Dyspnoea	27	In the context of worsening of cardiac condition or in the context of infusion related reactions
Oropharyngeal pain *	2	
Metabolism and nutrition disorders SOC		
Tumour lysis syndrome *	116	
Hypokalaemia *	5	
Musculoskeletal and connective tissue disorders SOC		
Back pain *	4	
Pain in extremity *	2	
Vascular disorders SOC		
Hypertension *	6	
Hypotension	30	In the context of infusion related reactions
Orthostatic hypotension	2	In the context of infusion related reactions
Investigations SOC		
White blood cell count decreased *	2	
Neutrophil count decreased *	25	
Platelet count decreased	9	
Immune system disorders SOC		
Anaphylactic reaction	9	
Hypersensitivity	9	
Anaphylactic shock	2	
Drug hypersensitivity	2	
Nervous system disorders SOC		
Syncope	13	In the context of infusion related reactions
Headache *	7	In the context of infusion related reactions
Dizziness ^	4	In the context of worsening of cardiac condition or in the context of infusion related reactions
Neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC		
Squamous cell carcinoma of skin *	4	

* denotes PTs that are ADRs listed in the company core data sheet and Summary of Product Characteristics of obinutuzumab

# denotes PTs in the context of risk of pre-existing cardiac condition. PTs were retained on the basis of significant medical history suggestive of worsening of a pre-existing cardiac condition.

^ denotes PTs that also falls in the SOC Cardiac disorders and have been reported as serious more than once in clinical trials with obinutuzumab

MedDRA version: 21.0

Cut-off date for data extraction: 30 April 2018

The reason of the difference of the events listed in IB and EU SmPC is the following:

- AEs that occurred with a higher frequency (≥2% difference) in the obinutuzumab arm compared to the relevant comparator arm in CLL (indication from study BO21004) or in NHL (indication in studies GAO4753g and BO21223) are listed in EU SmPC