Clinical Trial Protocol

PROTOCOL GELLC-7

Study drugs: Ibrutinib and Ofatumumab

Protocol title: A multicenter, non-randomized, open label study to evaluate the efficacy and security of Ibrutinib followed by ibrutinib consolidation in combination with ofatumumab in previously untreated patients with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)

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Investigator Coordinator:	Dr. Francesc Bosch Albareda, Dr. Pau Abrisqueta Hospital of Vall d'Hebrón

PROTOCOL SIGNATURE SHEET

Protocol GELLC-7

I have read this protocol and agree to manage and perform this study in compliance with all protocol provisions and in agreement with the ICH Directives on Good Clinical Practice and the Declaration of Helsinki.

Dr. Juan José Lahuerta	_____	_____
(Trial Sponsor´s representative)	Signature	Date
Dr. Francesc Bosch Albareda	_____	_____
(Investigator Coordinator)	Signature	Date
Dr. Pau Abrisqueta	_____	_____
(Investigator Coordinator)	Signature	Date

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Principal Investigator:

_____	_____	_____
Name	Signature	Date

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Name	Signature	Date

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SYNOPSIS

Investigational products	Ibrutinib and ofatumumab
Protocol title	A multicenter, non-randomized, open label study to evaluate the efficacy and security of ibrutinib followed by ibrutinib consolidation in combination with ofatumumab in previously untreated patients with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)
Protocol code	GELLC-7
Phase	II
Study Type	Interventional
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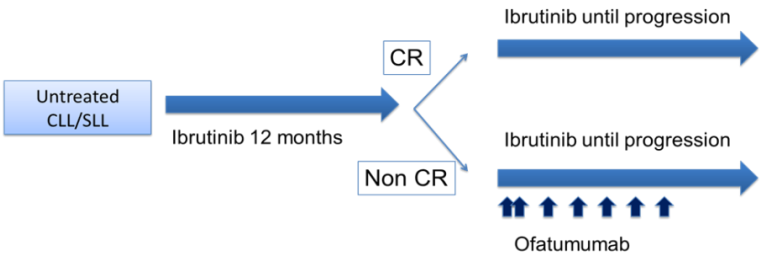
Investigator Coordinators	Dr. Francesc Bosch Albareda Dr. Pau Abrisqueta Hematology Department Vall d'Hebrón Hospital Phone: 934 89 30 00 (ext. 2704) Fax: 934 89 4507
Responsible for monitoring	Adknoma Health Research is the Contract Research Organization (CRO) in charge of monitoring study tasks. The monitor for this trial will be chosen from this company in accordance with study Sponsor. Adknoma Health Researh Martí i Julià, 6-8 Entlo 3ª Dcha. 08034 Barcelona Tel. 93 206 66 66 Fax. 93 206 66 67
Purpose and rational	Based on the promising results obtained with ibrutinib as single agent, the results obtained with ibrutinib in combination with ofatumumab in a previous phase I/IIb study (Jaglowski 2015), and since data from in vitro studies do not support a synergistic effect of the combination of ibrutinib and anti-CD20 mAbs, we propose a chemotherapy-free combined strategy based on ibrutinib monotherapy as front line treatment for patients with CLL, with the addition of a consolidation phase with ofatumumab in patients not attaining CR under ibrutinib in order to improve the quality of their response. Since median time to CR with ibrutinib was nearly 12 months, patients will be evaluated at this time point, and those patients not in CR will add consolidated treatment with Ofatumumab. Thus, this multi-center, non-randomized phase 2 study is designed to evaluate the efficacy and safety of ibrutinib alone or in combination with Ofatumumab in patients no attaining CR under ibrutinib as front-line therapy for patients with chronic lymphocytic leukemia.

Primary endpoint	To determine the complete response rate obtained with the combination of Ibrutinib and ofatumumab. Patients will receive 12 cycles of ibrutinib. Those obtaining a CR will continue with Ibrutinib alone, whereas patients not obtaining a CR will be treated with Ibrutinib and 6 cycles of ofatumumab. For the primary endpoint of the study, response will be evaluated after two months of completing ofatumumab.
Secondary endpoints	• Overall response rate, including partial response with lymphocytosis • Evaluation of minimal residual disease (MRD) • Duration of response and progression-free survival • Safety: type, frequency, and severity of adverse events (AEs) and relationship of AEs to ibrutinib or the combination of ibrutinib and ofatumumab • Response rate in relationship to molecular and genetic prognostic factors • Evaluate biomarkers related to BCR and compensatory signaling pathways and their association with resistance to ibrutinib treatment • Immunological recovery • Overall survival
Study design	Multicenter, non- randomized, open-label, double agent, phase II study of the Spanish Group of CLL (GELLC). Patients with untreated CLL/SLL. Ibrutinib will be administered orally 420 mg (3 x 140 mg capsules) once daily on a continuous schedule on an outpatient basis until disease progression or unacceptable toxicity. After 12 cycles of ibrutinib, patients that do not achieve a complete response (CR) will be treated with the combination of ibrutinib and ofatumumab. Patients in CR after 12 cycles of ibrutinib will continue with ibrutinib alone. Ofatumumab will be administered by IV infusion, 300mg on Day 1 and 1,000 mg on Day 8 of cycle 13, followed by 5 monthly infusions of 1,000 mg (Day 1 of subsequent 28-day cycles for cycles C14, C15, C16, C17, and C18). A treatment cycle will be defined as lasting 28 days. Patients will be treated with ibrutinib, within the study frame, until progression, unacceptable toxicity or cycle C42 of treatment). All patients still on study treatment at the time of cycle C42, or if the study is stopped early, will be transitioned to prescribed ibrutinib.

Study design	**Treatment diagram.** 
Study Population	Physically fit patients with treatment-naïve chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). **Key inclusion criteria:** 1. Adult patients with previously untreated CLL or SLL defined following IWCLL criteria (Hallek, 2008). 2. Must understand and voluntarily sign an informed consent form. 3. Age ≥ 18 years at the time of signing the informed consent form and must be able to adhere to the study visit schedule and other protocol requirements. 4. Must have a documented diagnosis of CLL or SLL [IWCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)] meeting at least one of the following criteria: • Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. • Massive (i.e. > 6 cm below the left costal margin) or progressive or symptomatic splenomegaly. • Massive nodes (i.e. > 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy. • Progressive lymphocytosis with an increase of > 50% over a 2-month period, or lymphocyte doubling time (LDT) of less than 6 months. • A minimum of any one of the following disease-related symptoms: unintentional weight loss ≥ 10% within the previous 6 months, significant fatigue (i.e., ECOG PS 2; cannot work or unable to perform usual activities), fevers of greater than 38.0° C or 100.5F for 2 or more weeks without other evidence of infection, or night sweats for more than 1 month without evidence of infection.

	5. Physically fit patients defined as CIRS < 6 (CIRS Scale, Appendix E). 6. Must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2. 7. All sexually active subjects with the capacity to reproduce (male and female) must use high-efficacy contraceptive methods during the course of the study. These restrictions apply for 12 months after the last dose of ofatumumab or 3 months after the last dose of ibrutinib, whichever happens later. High-efficacy contraceptive methods include: • Total abstinence when consistent with the subject's typical and preferred lifestyle (periodic abstinence [e.g. calendar methods, ovulation, symptothermal and post-ovulation methods] and the withdrawal method are not acceptable contraceptive methods). • Female sterilisation defined as surgical hysterectomy, bilateral oophorectomy, or tubal ligation at least six weeks prior to the study treatment (a simple oophorectomy does not meet the definition of female sterilisation). • Male sterilisation (at least six months before screening). A man who has undergone a vasectomy must be the only partner who is a study subject. • Combination of two of the following methods (a+b or a+c or b+c): a. Use of oral, injected or implanted hormonal contraceptives, or other hormonal contraceptive methods that have a comparable efficacy (failure rate < 1%), for example, hormonal vaginal ring or transdermal hormonal contraceptive. If an oral contraceptive is used, women must use the same pill for a minimum of three months before taking the study treatment. b. Placement of an intrauterine device (IUD) or an intrauterine system (IUS). c. Barrier contraceptive methods: condom or cervical cap (cervical/vault diaphragm or cap) with foam/gel/film/spermicidal cream/vaginal suppository. 8. Female subjects of childbearing potential must have a negative pregnancy test at screening. Females of child bearing potential are defined as sexually mature women

	without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to other causes, including prior chemotherapy, anti-estrogens, or ovarian suppression. **Key exclusion criteria:** 1. Prior treatment for CLL or SLL. 2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form. 3. Systemic infection that has not resolved prior to initiating study treatment in spite of adequate anti-infective therapy. 4. Pregnant or lactating females. 5. Participation in any clinical study or having taken any investigational therapy within 28 days prior to initiating study therapy. 6. Central nervous system (CNS) involvement as documented by spinal fluid cytology or imaging. 7. Prior history of malignancies, other than CLL, unless the patient has been free of the disease for ≥ 3 years. Exceptions include the following: • Basal cell carcinoma of the skin • Squamous cell carcinoma of the skin • Carcinoma in situ of the cervix • Carcinoma in situ of the breast • Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b) 8. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV) infection. 9. Any of the following laboratory abnormalities: • Serum creatinine ≥ 2 x ULN or estimated Glomerular Filtration Rate (Cockroft-GaultAppendix C) ≤ 40 mL/min/1.73m^2 • Absolute neutrophil count (ANC) < 1.0 X 10^9/L, unless secondary to bone marrow involvement by CLL.

	• Platelet count <100,000/mm^3 or <50,000/mm^3 if bone marrow involvement independent of transfusion support in either situation • Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetictransaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) >3 x upper limit of normal (ULN). • Serum total bilirubin > 1.5 x ULN, except in cases of Gilbert's syndrome. 10. Presence of autoimmune haemolytic anemia or autoimmune thrombocytopenia. 11. Disease transformation [i.e. Richter's Syndrome (lymphomas) or prolymphocytic leukemia. 12. Major surgery within the last 28 days prior to registration. 13. History of stroke or intracranial hemorrhage within 6 months prior to enrolment. 14. Currently active, clinically significant cardiovascular disease or a history of myocardial infarction within 3 months prior to enrolment. 15. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists within 28 days of first dose of study drug. 16. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.
Investigational Product Dose/Route/Regimen	• Ibrutinib 420 mg will be administered orally once daily on a continuous schedule until disease progression, unacceptable toxicity or study closure. • Ofatumumab will be administered by IV infusion, 300mg on Day 1 and 1,000 mg on Day 8 of Cycle 13, followed by 5 monthly infusions of 1,000 mg (Day 1 of subsequent 28-day cycles for cycles C14, C15, C16, C17, and C18).

Assessments	**Efficacy:** Response will be assessed after 12 cycles of ibrutinib to determine to continue with ibrutinib alone (patients in CR) or to combine with ofatumumab (patients not in CR). The response to therapy will be assessed after 20 cycles of treatment (2 months after completing ofatumumab) for the primary objective of the study. In addition, the best overall response will be also determined. The best overall response is defined as the best response recorded from the start of treatment until progressive disease/recurrence. The IWCLL guidelines (Hallek, 2008) will be used to measure response in CLL subjects with the modification that isolated treatment related lymphocytosis will not be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines. The best overall response is defined as the best response recorded from the start of treatment until progressive disease/recurrence. Patients will undergo the following assessments during the treatment periods: • Lymph nodes, spleen and liver measurements by physical examination. • Complete blood count (CBC) and differential • Bone marrow aspirate and biopsy for standard histopathology and flow cytometry • MRD assessment by flow cytometry (peripheral blood and bone marrow aspirate) • Computed tomography (CT) scans • ECOG Performance Status • Assessment of constitutional symptoms **Safety:** • Safety will be assessed by AE reporting and standard clinical and laboratory tests (hematology, serum chemistry, and urinalysis). • Toxicity grade is defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) v4.0. **Stopping rules:** • Patients experiencing Grade 4 non-hematologic AEs

	related to study treatment. • Progression of the disease. • Transformation to a more aggressive histology (e.g. Richter's syndrome).
Statistical Analysis	***Sample Size:*** A complete response rate of 13% (CRR reported for ibrutinib as first line therapy in CLL[16]) is assumed as P0 (null hypothesis), and a CRR of 25% (improvement by 12%) is considered as P1 (alternative hypothesis). Applying Simon 2-stage design, (Simon 1989) to obtain 80% power with type I error probability of α=0.05, a maximum number of 76 patients will be required. Anticipating 10% dropouts, 84 patients need to be included. The study will be terminated prematurely if at least 4 complete responses are not observed among the first 28 patients evaluated. The response will be assessed after 20 cycles of treatment (2 months after completing ofatumumab) using the IWCLL guidelines (Hallek, 2008) with the modification that isolated treatment related lymphocytosis will not be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines. Otherwise, the study will continue until a maximum number of 84 patients included. ***Efficacy Analysis:*** <u>Primary endpoint:</u> CRR is defined as the proportion of patients who achieve a CR according to The IWCLL guidelines (Hallek, 2008) as defined in appendix B. CRR will be assessed after 20 cycles of treatment (2 months after completing ofatumumab) for the primary objective of the study. The analysis of CRR will be performed in the ITT population. <u>Secondary Endpoints:</u> ORR is defined as the proportion of patients who achieve a CR, CRi, nPR, or PR over the course of the study. Patients who achieve a PR with lymphocytosis will be included in the ORR. The rate of MRD-negative disease will also be calculated. The IWCLL guidelines (Hallek, 2008) will be used to measure response in CLL subjects with the modification that isolated treatment related lymphocytosis will not be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines.

	PFS is defined as the time from the date of treatment initiation to confirmed disease progression (assessed by IWCLL 2008 criteria, with modification for treatment-related lymphocytosis) or death from any cause, whichever occurs first. Patients who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Patients who start new anticancer therapy before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of the new anticancer therapy. OS is defined as the time from the date of treatment initiation to death due to any cause. Patients who are known to be alive or whose survival status is unknown will be censored at the last date the patient is known to be alive. Distribution of PFS and OS will be summarized using the Kaplan-Meier estimate of median and its corresponding 95% confidence interval (CI). ***Safety Analysis:*** Data from all subjects who receive at least one dose of the study drugs will be included in the safety analyses and analysed as treated. Study medication exposure will be summarized including duration of study medication, total dose taken, and dose reductions or treatment delays. Adverse events, vital sign measurements, clinical laboratory measurements, and concomitant medications will be also summarized. AEs will be classified using the NCI CTCAE (v 4.0). Subsets of AEs to be summarized include serious AEs (SAEs), events of all CTCAE grade severities, events classified as NCI CTCAE grade 3 or higher, suspected treatment-related AEs, suspected unexpected serious adverse reactions (SUSARs), and events that resulted in withdrawal of study medication. Laboratory data will be summarized according to the NCI CTC severity grade.
Study Calendar	• The study will start in the second quarter of 2017 and the total duration of the study will be approximately 67 months with an enrolment period of 18 months. • Estimated median treatment duration for each patient: 42 months. • Follow-up duration for each patient: 30 days after the last dose of study drug. • Patient enrolment (FPFV-LPFV): Jun2017 – Dec2018 • The screening phase of each patient will be from 0 to 28 days.

	• Treatment period duration (FPFT-LPLV): Jun2017 – Jun2022 • Planned study termination: (clinical cut-off): 6 months after last visit (follow-up) of the last evaluable patient included in the study, that is, Dec2022.

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List of abbreviations

ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CIRS	Cumulative Illness Rating Score
CLL	chronic lymphocytic leukemia
CR	complete remission (response)
CRi	CR with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
del 17p	deletion on the short arm of chromosome 17
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	human immunodeficiency virus
IB	investigator's brochure
IC50	half maximal inhibitor concentration
INR	International Normalized Ratio
ITT	intent to treat
IV	intravenous
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDT	lymphocyte doubling time
LN	lymph node
MREC	Medical Research Ethics Committee
MRD	minimal residual disease
MRI	magnetic resonance imaging

NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
nPR	nodular partial remission (response)
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PR	partial response
PT	prothrombin time
QTc	corrected QT interval
RBC	red blood cell
REB	Research Ethics Board
SAE	serious adverse event
SEER	Surveillance Epidemiology and End Results
SLL	small lymphocytic lymphoma
SPD	sum of the products of diameters
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

1. Background and Rationale

1.1 Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

CLL is the most common form of adult leukemia in the developed world. The estimated 2010 prevalence in the United States (US) was approximately 106,000 individuals (SEER 2010). A population-based study found that more than half of the cases presented at over 70 years of age (Brenner 2008). CLL is characterized by an accumulation of monoclonal mature B cells (CD5+/CD23+) in the blood, bone marrow, and secondary lymph organs. These cells are constantly being stimulated by their BCR, as well as by interactions with their microenvironment (Chiorazzi 2005). According to the World Health Organization (WHO), SLL, a disease with similar pathological findings but without the lymphocytosis, is considered to be a manifestation of the same underlying disorder as CLL (Campo 2011).

Once diagnosed with CLL or SLL, patients can have a variable course—some not requiring treatment for more than a decade and others requiring more urgent treatment, particularly those with clinically symptomatic disease (Gribben 2011). According to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines, the following features are indications for therapy: progressive marrow failure (manifested by anemia or thrombocytopenia), massive or progressive splenomegaly (6 cm or greater), massive or progressive lymph nodes (10 cm or greater in the longest diameter), progressive lymphocytosis with a rapid lymphocyte doubling time occurring in less than 6 months, worsening autoimmune cytopenias resistant to corticosteroids or other standard treatment, and constitutional symptoms (Hallek 2008).

1.2 Standard Treatment

The past decade has seen significant advancement in the treatment of CLL. The addition of cyclophosphamide to fludarabine further improved response rates and PFS compared with fludarabine alone, but at the cost of increased toxicity (Flinn 2000, O'Brien 2001, Eichhorst 2006; Flinn 2007). A number of new agents have been evaluated and approved for the treatment of patients with CLL, such as alemtuzumab, bendamustine, ofatumumab, and rituximab. Chemo-immunotherapy regimens containing a nucleoside analog and an anti-CD20 agent have markedly improved outcomes when used as initial therapy in young otherwise healthy patients requiring treatment. Treatment of patients with CLL with chemoimmunotherapy results in high response rates including many cases with no detectable minimal residual disease (MRD), and a prolonged duration of response. However, some genetic abnormalities, principally deletion of 17p13.1 have poor response to these regimens, and patients with unmutated immunoglobulin variable region heavy chain genes have shorter remissions than those with mutated genes. (Tam 2008, Hallek 2010, Bosch 2009) Furthermore, all patients eventually relapse and because of this CLL remains an incurable disease. In addition, standard chemoimmunotherapy combinations, mainly fludarabine, cyclophophamide and rituximab (FCR), are associated with significant toxicities and sustained

immunosuppression in a significant proportion of patients.(Tam 2008) Thus, despite these advances, additional treatment options are desirable.

1.3 Ibrutinib Background

Ibrutinib is an orally administered first-in-class small molecule selective inhibitor of Bruton's tyrosine kinase (BTK) currently under investigation in B-cell malignancies including chronic lymphocytic leukemia (CLL) and the related small lymphocytic lymphoma (SLL). In vitro, ibrutinib inhibited purified BTK and selected members of the kinase family with 10-fold specificity compared with off-target kinases.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulins that make up the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation including immunoglobulin chain rearrangement and somatic mutation is tightly regulated, and it is thought that B-cell lymphomas and CLL result from mutations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies (Meeker 1985; Kuppers 2005; Gururajan 2006).

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease, X-linked agammaglobulinemia, and the mouse genetic immunodeficiency disease, X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signalling and a failure to generate mature B cells. The BTK protein is expressed in most hematopoietic cells with the exception of T cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signalling in B cells (Satterthwaite 2000).

B cell receptor (BCR) signaling has emerged as a key factor for the survival of CLL tumor cells. Bruton's tyrosine kinase (BTK) is a critical factor of this pathway and its function is essential to promote survival of CLL cells through the activation of several important pathways, including AKT, ERK, and NF-κB. (Craxton 1999, Tomlinson 2001, Petro 2000, Petro 2001) In addition, BTK is important to homing and adhesion of CLL cells to lymph nodes and bone marrow, where CLL cells receive survival and protecting signals from the microenvironment. (Spaargaren 2003, Burger 2011) Ibrutinib is an orally, potent inhibitor of the BTK that covalently binds to its cysteine-481 amino acid. Data from preclinical studies have shown that ibrutinib is able to inhibit important survival pathways of CLL cells as ERK and NF-κB signaling, and also tumor-cell migration. (Honigberg 2010, Herman 2011, Ponader 2012) A phase 1 study of ibrutinib showed a fairly acceptable safety profile and clinical antitumor activity in patients with relapsed or refractory B-cell malignancies. (Advani 2013) These results were confirmed in a phase 1b–2 study of ibrutinib in relapsed or refractory CLL patients where an overall response rate of 71% with an additional nearly 20% of partial response with lymphocytosis was observed.

Importantly, the response was independent of clinical and genomic risk factors, including 17p13.1 deletion. Progression-free survival (PFS) and overall survival (OS) at 26 months were 75% and 83%, respectively. Toxic effects were mild; predominantly grade 1-2 diarrhea, fatigue and upper respiratory tract infections. (Byrd 2013) Recently a phase 3 trial showed significantly improved PFS, OS and response rate in comparison with ofatumumab in patients with previously treated CLL. (Byrd 2014) As front line therapy, ibrutinib have shown an overall response rate of 71% with a two year estimated PFS of 96.3% (95% CI 76.5 – 99.5%) in elderly patients with CLL. Median time to initial response was 1.9 months (1.8–4.6); median time to best response was 5.9 months (1.9–8.3) and median time to complete response was 12.4 months (9.1–14.7). (O'Brien 2014)

1.4 Ofatumumab background

Ofatumumab is an immunoglobulin G1κ (IgG1κ) human monoclonal antibody that specifically recognizes a distinct epitope encompassing both large and small extracellular loops on the human CD20 molecule expressed on B cells [Teeling, 2006] and binds to this site with high affinity with a dissociation half-life of approximately 3 hours [Teeling, 2004]. Ofatumumab induces more efficient complement-dependent cytotoxicity (CDC) mediated cell lysis *in vitro*, compared to rituximab, especially in low CD20 density cells [Teeling, 2004].

In a Phase I dose-ranging trial of ofatumumab for the treatment of relapsed or refractory CLL (Study Hx-CD20-402), subjects were given ofatumumab Weekly for 4 Weeks [100 mg + 3 x 500 mg (n=3), 300 mg + 3 x 1000 mg (n=3), and 500 mg + 3 x 2000 mg (n=27)]. Among the subjects in the highest dose group, 48% achieved at least a partial response (PR) [Coiffier, 2008]. The maximum tolerated dose (MTD) was not reached. Adverse events were limited to Grade 1-2 infusion reactions, Grade 4 neutropenia (7% of patients), and non-opportunistic Grade 1-2 infections (51% of patients). The pivotal trial (Study Hx-CD20-406), in subjects with fludarabine-refractory CLL (refractory to both fludarabine and alemtuzumab (n=59), or refractory to fludarabine and with bulky lymphadenopathy for whom alemtuzumab is not suitable (n=79)) evaluated 300 mg + 7 x 2000 mg for eight Weekly doses, followed by four monthly 2000 mg doses. The investigator-determined overall objective response rate of patient's refractory to fludarabine and alemtuzumab was 42%, with a median duration of response of 6.5 months. The best response was PR. In this study, ofatumumab was generally well tolerated. The most frequently reported adverse events (>15% frequency) were pyrexia, diarrhea, fatigue, cough, neutropenia, anaemia and pneumonia. There were no unexpected safety findings. The results of this pivotal study served as the basis of approval for ofatumumab in the United States and Europe for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. A Phase II study in patients with previously untreated CLL (Study Hx-CD20-407) compared ofatumumab at two dose levels in combination with fludarabine and cyclophosphamide. The primary endpoint was complete response rate, evaluated during treatment and 3 months after the last dose. Subjects were randomised into one of two ofatumumab dose groups; either 500 mg (N=31) or 1000 mg (N=30), on Day 1, with fludarabine 25 mg/m2 and cyclophosphamide 250 mg/m2 on Days 2 through 4. Six courses were given at 4-Week intervals. Results demonstrated an overall response rate of 75% with a CR of 41%. There were no unexpected safety findings reported during treatment and within 30

Days after the last infusion. The most common adverse events of Grade 3 or 4 (>10%) were leukopenia and neutropenia [Wierda, 2011]. The results from this study show the activity of ofatumumab in combination with chemotherapy in patients with previously untreated CLL.

Ofatumumab, a human anti-CD 20 antibody, is currently indicated for the treatment of CLL in patients who are refractory to fludarabine and alemtuzumab. The 300 mg initial ofatumumab dose followed by up to 6 monthly 1000 mg doses, has been selected based on preclinical data, clinical population pharmacokinetic modelling, and prior and ongoing clinical experience with ofatumumab in studies Hx-CD20-402 [Hagenbeek, 2008], Hx- CD20-406 [Wierda, 2011], and Hx-CD20-407 [Wierda, 2011]. Preclinical data suggest that ofatumumab plasma concentrations >10 µg/mL are sufficient to suppress peripheral B-cell recovery in cynomolgus monkeys as well as to suppress tumour cell growth in Daudi tumour-bearing SCID mice [Bleeker, 2008]. A nonlinear mixed-effects model for ofatumumab pharmacokinetics was developed based on the pharmacokinetic data from the Phase I study Hx-CD20-402 in 33 patients with relapsed or refractory CLL and was used to simulate ofatumumab concentrations using the proposed dosing regimen [Hagenbeek, 2008]. Based on administration of an initial two dose Cycle of 300 mg infusion on Day 1 followed by 1000 mg on Day 8 and subsequent monthly dosing with 1000 mg ofatumumab on Day 1 of each Cycle, the probability of maintaining plasma ofatumumab concentrations >10 µg/mL was approximately 90% or greater by the end of the second Cycle, throughout the remainder of the six-Cycle dosing period, and for four Weeks after the last dose. Thus, a dosing schedule with a first infusion of 300 mg and subsequent infusions of 1000 mg at Week 2 and at 4-Week intervals starting at Week 5 is expected to achieve prolonged maintenance of plasma concentrations >10 µg/mL in a high proportion of subjects with CLL.

The pivotal Phase II study Hx-CD20-406 demonstrated that as monotherapy, ofatumumab is an active, well-tolerated treatment providing clinical improvement for very poor-prognosis CLL subjects [Wierda, 2011]. Additionally Study Hx-CD20-407 which compared ofatumumab at two dose levels in combination with fludarabine and cyclophosphamide (FC) for the treatment of previously untreated subjects, demonstrated treatment activity and a good safety profile [Wierda, 2011]. Although both ofatumumab doses demonstrated activity and similar OR rates in the previously untreated CLL subjects, the CR rate without CT scan confirmation was higher in the 1000 mg group than in the 500 mg group. In both treatment groups, ofatumumab displayed a safety profile similar to that previously seen with FC combined with other anti-CD20 antibody regimens in untreated subjects with CLL. The overall incidence of Adverse Events (AE) and the degree of myelosuppression were similar between the 2 treatment groups.

1.5 Rationale for Trial

Despite these promising results, complete responses under treatment with ibrutinib are not frequently achieved. Thus, strategies to improve the rate and quality of response could improve the outcome of the patients with CLL. The favorable safety profile of ibrutinib may facilitate its use in combination with other agents for the treatment of CLL. Data on a phase II trial of ibrutinib plus rituximab and on a phase I trial of the combination ibrutinib, rituximab and bendamustine reported favorable toxicity profiles. (Burger 2014, Barrientos 2013) In

addition, the capacity of ibrutinib to egress the leukemic cells from their protective niches into peripheral blood may become CLL cells more exposed and vulnerable for chemotherapy or monoclonal antibodies (mAbs) treatments. However, recent data from in vitro studies suggest that ibrutinib could impair the cell-mediated antitumor activities of anti-CD20 mAbs, including dependent NK-cell mediated cytotoxicity through the inhibition of ITK (interleukine 2 inducible TK), and also anti-CD20 mAb-mediated phagocytosis by macrophages and polymorphonuclear neutrophils. (Kohrt 2014, Bojarczuk 2014, Da Roit 2014) Interestingly, complement-dependent cytotoxicity (CDC) activity seems not be significantly affected by ibrutinib thus favoring its combination with anti-CD20 mAbs with strong CDC capacity. (Da Roit 2014) Ofatumumab is a human anti-CD20 mAb with more potent CDC than rituximab, even in cells with low CD20 expression levels, including CLL cells and complement-resistant B-cell lines. The potent CDC with ofatumumab may be a result of the close proximity of the small-loop binding site to the cell surface, potentially leading to more effective deposition of complement on the cell surface. (Beum 2008, Pawluczkowycz 2009) In a phase II study, ofatumumab as single agent achieved an overall response rate of 58% and 47% in patients with fludarabine and alemtuzumab-refractory CLL, and patients with fludarabine-refractory CLL with bulky lymphadenopathy, respectively. (Wierda 2010)

Although pre-clinical studies have reported that ibrutinib can inhibit Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) that can be observed with monoclonal anti-CD20 antibodies, these findings have not been clinically corroborated, which suggests that the pre-clinical findings cannot be translated directly to clinical context. Clinical data from various studies on CLL that combined ibrutinib with anti-CD20 antibodies rituximab and ofatumumab consistently showed additive activity with the combination regimen compared to ibrutinib or monoclonal anti-CD20 antibody administered as monotherapy (Jaglowski 2015 and Burger 2014).

Furthermore, the complement-dependent cytotoxicity (CDC) observed in vitro with ofatumumab is not affected by ibrutinib (Da Roit F 2015). And because ibrutinib induces tissue lymphocytes to exit into peripheral blood where the complement is abundant, its combination with a monoclonal anti-CD20 antibody that mediates the CDC can be an effective combination.

The safety data from a phase I/IIb study that combines ofatumumab with ibrutinib in patients with relapsing CLL/SLL showed that this combination was well tolerated and no dose-limiting toxicity was observed. The most frequent adverse effects observed with the combination (diarrhoea, reactions related to the infusion, contusion/bruising, upper respiratory infection) were consistent with the safety profile of the individual drugs in previous trials (Jaglowski 2015).

Based on the promising results obtained with ibrutinib as single agent, the results obtained with ibrutinib in combination with ofatumumab in a previous phase I/IIb study (Jaglowski 2015), and since data from in vitro studies do not support a synergistic effect of the combination of ibrutinib and anti-CD20 mAbs, we propose a chemotherapy-free combined strategy based on ibrutinib monotherapy as front line treatment for patients with CLL, with the addition of a consolidation phase with ofatumumab in patients not attaining CR under ibrutinib in order to improve the quality of their response. Since median time to CR with

ibrutinib was nearly 12 months, patients will be evaluated at this time point, and those patients not in CR will add consolidated treatment with ofatumumab. Thus, this multi-center, non-randomized phase 2 study is designed to evaluate the efficacy and safety of ibrutinib alone or in combination with ofatumumab in patients no attaining CR under ibrutinib as front-line therapy for patients with chronic lymphocytic leukemia.

The initial dose of 300 mg of ofatumumab, followed by up to 6 monthly doses of 1000 mg, was selected based on pre-clinical data, the pharmacokinetic model of the clinical population, and the previous and current clinical experience with ofatumumab in the studies Hx-CD20-402 [Hagenbeek, 2008], Hx-CD20-406 [Wierda, 2011] and Hx-CD20-407 [Wierda, 2011].

In this study, when using it in combination and as a consolidation of the response to ibrutinib, a short 6-cycle regimen was considered.

2. Study Objectives

2.1 Primary Endpoint

The primary endpoint of the study is to determine the complete response rate obtained with the combination of Ibrutinib and ofatumumab. Patients will receive 12 cycles of ibrutinib. Those obtaining a CR will continue with Ibrutinib alone, whereas patients not obtaining a CR will be treated with Ibrutinib and 6 cycles of ofatumumab. For the primary endpoint of the study, response will be evaluated after two months of completing ofatumumab.

The IWCLL guidelines (Hallek, 2008) will be used to measure response in CLL subjects with the modification that isolated treatment related lymphocytosis will not be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines.

2.2 Secondary Endpoints

The secondary endpoints of the study include:

- Overall response rate, including partial response with lymphocytosis
- Evaluation of minimal residual disease (MRD)
- Duration of response and progression-free survival
- Safety: type, frequency, and severity of adverse events (AEs) and relationship of AEs to ibrutinib or the combination of ibrutinib and Ofatumumab
- Response rate in relationship to molecular and genetic prognostic factors
- Evaluate biomarkers related to BCR and compensatory signaling pathways and their association with resistance to ibrutinib treatment
- Immunological recovery
- Overall survival

3. Study Design

3.1 Global design

Multicenter, non- randomized, open-label, double agent, phase II study in patients with untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) to determine the complete response rate obtained with the combination of Ibrutinib and ofatumumab.

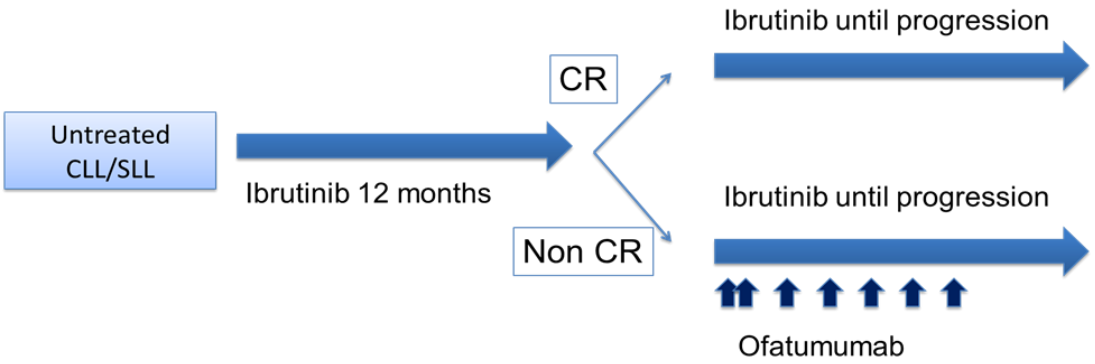
Approximately, 84 patients will be included in the study. The study will be terminated prematurely if at least 4 complete responses are not observed among the first 28 patients evaluated. The response will be assessed after 20 cycles of treatment (2 months after completing ofatumumab) using the IWCLL guidelines (Hallek, 2008) with the modification that isolated treatment related lymphocytosis will not be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines. Otherwise, the study will continue until a maximum number of 84 patients included.

3.2 Trial Plan

Periods of patient participation in the study:

- **Screening Phase:**
  The screening phase includes the screening visit. After providing the written Informed Consent form to participate in the study, patients will be evaluated for eligibility during a screening period of 28 days (Days -28 to 0).
- **Treatment Phase:**
  Ibrutinib 420 mg will be administered orally once daily on a continuous schedule until disease progression or unacceptable toxicity. A treatment Cycle will be defined as lasting 28 days. At 12 cycles patients that not achieve a complete response (CR) will be consolidated with the combination of ibrutinib and Ofatumumab. Patients in CR after 12 cycles of ibrutinib will continue with ibrutinib alone.
  Ofatumumab will be administered by IV infusion, 300mg on Day 1 and 1,000 mg on Day 8 of Cycle 13, followed by 5 monthly infusions of 1,000 mg (Day 1 of subsequent 28-day cycles for cycles C14, C15, C16, C17, and C18).
  Patients will be treated with ibrutinib until progression, unacceptable toxicity or cycle C42 of treatment.
  All patients still on study treatment at the time of cycle C42, or if the study is stopped early, will be transitioned to prescribed ibrutinib.
- **Suspected Disease Progression:**
  A visit should be performed at the time of suspected disease progression. If it is confirmed treatment will be sttoped.
- **End-of-Treatment:**
  An End-of-Treatment visit will be performed within 30 days (+ 3 days) after the discontinuation of treatment for any reason. The visit should be conducted prior to starting a new anticancer treatment.

- **Follow-up for Progression (Pre-PD) :**
  Patients who discontinue study treatment without confirmed progression will continue to be followed for progression every 4 months (± 7 days) for the first 24 months from start of treatment, then every 6 months (± 7 days) until progression or study closure.



Safety will be assessed by AE reporting and standard clinical and laboratory tests (hematology, serum chemistry, and urinalysis). Toxicity grade is defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) v4.0.
During the treatment phase, the following stopping rules will apply:

- Patients experiencing Grade 4 non-hematologic AEs related to study treatment.
- Progression of the disease.
- Transformation to a more aggressive histology (e.g. Richter's syndrome).

3.3 Randomization

Not applicable

3.4 Blinding

Not applicable.

4. Selection of Patients

4.1 Inclusion Criteria

Physically fit patients with treatment-naïve chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

1. Adult patients with previously untreated CLL or SLL defined following IWCLL criteria (Hallek, 2008).

2. Must understand and voluntarily sign an informed consent form.

3. Age ≥ 18 years at the time of signing the informed consent form and must be able to adhere to the study visit schedule and other protocol requirements.

4. Must have a documented diagnosis of CLL or SLL [IWCLL guidelines for diagnosis and treatment of CLL (Hallek, 2008)] meeting at least one of the following criteria:

   - Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia.
   - Massive (i.e. > 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
   - Massive nodes (i.e. > 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
   - Progressive lymphocytosis with an increase of > 50% over a 2 month period, or lymphocyte doubling time (LDT) of less than 6 months.
   - A minimum of any one of the following disease-related symptoms: unintentional weight loss ≥ 10% within the previous 6 months, significant fatigue (i.e., ECOG PS 2; cannot work or unable to perform usual activities), fevers of greater than 38.0° C or 100.5F for 2 or more weeks without other evidence of infection, or night sweats for more than 1 month without evidence of infection.

5. Physically fit patients defined as CIRS < 6 (CIRS Scale, Appendix E).

6. Must have an Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.

7. All sexually active subjects with the capacity to reproduce (male and female) must use high-efficacy contraceptive methods during the course of the study. These restrictions apply for 12 months after the last dose of ofatumumab or 3 months after the last dose of ibrutinib, whichever happens later. High-efficacy contraceptive methods include:

   - Total abstinence when consistent with the subject's typical and preferred lifestyle (periodic abstinence [e.g. calendar methods, ovulation, symptothermal and post-ovulation methods] and the withdrawal method are not acceptable contraceptive methods).

- Female sterilisation defined as surgical hysterectomy, bilateral oophorectomy, or tubal ligation at least six weeks prior to the study treatment (a simple oophorectomy does not meet the definition of female sterilisation).

- Male sterilisation (at least six months before screening). A man who has undergone a vasectomy must be the only partner who is a study subject.

- Combination of two of the following methods (a+b or a+c or b+c):

    a. Use of oral, injected or implanted hormonal contraceptives, or other hormonal contraceptive methods that have a comparable efficacy (failure rate < 1%), for example, hormonal vaginal ring or transdermal hormonal contraceptive. If an oral contraceptive is used, women must use the same pill for a minimum of three months before taking the study treatment.

    b. Placement of an intrauterine device (IUD) or an intrauterine system (IUS).

    c. Barrier contraceptive methods: condom or cervical cap (cervical/vault diaphragm or cap) with foam/gel/film/spermicidal cream/vaginal suppository.

7. Female subjects of childbearing potential must have a negative pregnancy test at screening. Females of child bearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to other causes, including prior chemotherapy, anti-estrogens, or ovarian suppression.

4.2 Exclusion Criteria

1. Prior treatment for CLL or SLL.

2. 2. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form.

3. Systemic infection that has not resolved prior to initiating study treatment in spite of adequate anti-infective therapy.

4. Pregnant or lactating females.

5. Participation in any clinical study or having taken any investigational therapy within 28 days prior to initiating study therapy.

6. Central nervous system (CNS) involvement as documented by spinal fluid cytology or imaging.

7. Prior history of malignancies, other than CLL, unless the patient has been free of the disease for ≥ 3 years.

   Exceptions include the following:

   - Basal cell carcinoma of the skin

- Squamous cell carcinoma of the skin
- Carcinoma in situ of the cervix
- Carcinoma in situ of the breast
- Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b)

8. Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV) and/or Hepatitis C Virus (HCV) infection.

9. Any of the following laboratory abnormalities:

   - Serum creatinine ≥ 2 x ULN or estimated Glomerular Filtration Rate (Cockroft-GaultAppendix C) ≤ 40 mL/min/1.73m^2
   - Absolute neutrophil count (ANC) < 1.0 X 10^9/L, unless secondary to bone marrow involvement by CLL.
   - Platelet count <100,000/mm3 or <50,000/mm3 if bone marrow involvement independent of transfusion support in either situation
   - Serum aspartate aminotransferase (AST)/serum glutamic-oxaloacetictransaminase (SGOT) or alanine transaminase (ALT)/serum glutamate pyruvate transaminase (SGPT) >3 x upper limit of normal (ULN).
   - Serum total bilirubin > 1.5 x ULN, except in cases of Gilbert's syndrome.

10. Presence of autoimmune haemolytic anemia or autoimmune thrombocytopenia.

11. Disease transformation [i.e. Richter's Syndrome (lymphomas) or prolymphocytic leukemia.

12. Major surgery within the last 28 days prior to registration.

13. History of stroke or intracranial haemorrhage within 6 months prior to enrolment.

14. Currently active, clinically significant cardiovascular disease or a history of myocardial infarction within 3 months prior to enrolment.

15. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists within 28 days of first dose of study drug.

16. Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.

5. Treatments

5.1 Ibrutinib

Ibrutinib is provided as hard gelatin capsules containing 140 mg of Ibrutinib. The capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All formulation excipients are compendial and are commonly used in oral formulations.

The recommended storage condition for Ibrutinib capsules is controlled room temperature.

Ibrutinib is currently approved in Europe for the treatment of previously untreated adult patients with chronic lymphocytic leukaemia (CLL) or those who have received at least one prior therapy; for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL); and in adult patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy.

5.1.1 Dosage and Administration

Ibrutinib 420 mg (3 x 140-mg capsules) is administered orally once daily with approximately 240 mL of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. Each dose of Ibrutinib should be taken at least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time each day. The use of strong CYP3A4/5 inhibitors/inducers, and grapefruit and Seville oranges (due to CYP3A4/5 inhibition) should be avoided for the duration of the study.

If a dose is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose.

Ibrutinib is received typically on an outpatient basis. Ibrutinib will be dispensed to patients in bottles at each visit. Unused Ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone.

5.1.2 Dose Hold, Reduction, or Discontinuation

Treatment with Ibrutinib should be held for any unmanageable, potentially study drug-related toxicity that is Grade 3 or higher in severity.

Study drug may be held for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days.

The actions of Table 1 should be taken for the following toxicities:

- Grade 4 ANC (<500/µL) for >7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded in CRF.)
- Grade 3 or 4 platelets (<50,000/µL); or, in patients with baseline thrombocytopenia, a platelet decrease of 50-74% from baseline in presence of bleeding
- Grade 4 Platelets (<25,000/µL); or, in patients with baseline thrombocytopenia, decrease of >75% from baseline or <20,000/µL, whichever is higher.
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy, or any other Grade 4 toxicity and any unmanageable Grade 3 toxicity.

Table 1: Drug Discontinuation Actions for ibrutinib Occurrence

	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (280 mg daily)
3rd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (140 mg daily)
4th	Discontinue ibrutinib

5.1.3 Treatment-related Lymphocytosis

Treatment-related lymphocytosis, for the purposes of this protocol, is defined as an elevation in blood lymphocyte count of ≥50% compared to baseline and ≥5,000/µL that occurs in the setting of improvement in at least one other disease-related parameter including lymph node size, spleen size, hematologic parameters (hemoglobin or platelet count), or disease-related symptoms. Given the known mechanism of action of BCR-inhibiting agents including ibrutinib, treatment-related lymphocytosis is an expected and frequent pharmacodynamics phenomenon observed with initiation (or re-initiation) of ibrutinib. ibrutinib associated treatment-related lymphocytosis generally occurs within the first weeks of therapy, peaks within the first few months, and resolves slowly. As clarified by the authors of the IWCLL guidelines (Hallek 2012) and outlined in the NCCN NHL 2012 guidelines, patients with isolated lymphocytosis in the setting of improvement in other disease parameters should not be considered to have progressive disease (Cheson 2012). Asymptomatic treatment-related lymphocytosis should also not be considered an AE. Patients with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

Specifically, upon initiation of treatment, a transient phase of increase in lymphocyte counts (ie, ≥50% increase from baseline and above absolute count 5,000/µL), often associated with reduction of lymphadenopathy, has been observed in most patients (75%) with relapsed/ refractory CLL/SLL and some patients (33%) with relapsed/refractory mantle cell lymphoma (MCL) treated with ibrutinib monotherapy. This observed transient lymphocytosis is usually not associated with an adverse event and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and resolves within a median of 7.1 weeks in the MCL and 18.7 weeks in the CLL patients.

5.1.4 Warnings, Precautions, and Adverse Effects

Ibrutinib is contraindicated in subjects with clinically significant hypersensitivity to the compound itself or to the excipients in its formulation. Ibrutinib has not been used in subjects with biliary obstruction, acute hepatitis, severe liver failure, or severely impaired renal function; the use of ibrutinib should be avoided in subjects with these conditions. The use of strong CYP3A4/5 inhibitors or inducers, grapefruit, and Seville oranges should be avoided for the duration of the study. Use of preparations containing St. John's Wort is contraindicated in patients treated with Ibrutinib.

5.1.5 Guidelines for ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for patients who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguinous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.
- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

5.2 Ofatumumab

Ofatumumab is a human monoclonal antibody (IgG1) that binds specifically to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule.

Ofatumumab in combination with chlorambucil or bendamustine is indicated for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy or treatment of CLL in patients who are refractory to fludarabine and alemtuzumab.

Ofatumumab will be provided to sites by Novartis. The contents of the label will be in accordance with all applicable regulatory requirements. Under normal conditions of handling and administration, ofatumumab is not expected to pose significant safety risks to site staff. Site staff should take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Site staff should notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request. Adequate precautions must be taken to avoid direct contact with ofatumumab.

The recommended storage condition for Ofatumumab is:

- Store and transport refrigerated (2°C – 8°C).
- Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- For storage conditions after dilution of the medicinal product: from a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions

5.2.1 Ofatumumab Pre-infusion Medications

Pre-medication before each ofatumumab infusion should be given 30 minutes to 2 hours prior to ofatumumab treatment. Pre-medication can be administered through the same IV access used for the ofatumumab infusion. Pre-medication with acetaminophen and antihistamine will be required for all infusions of ofatumumab. Pre-medication with steroid will be required for the 300mg and 1000 mg infusion of ofatumumab in Cycle 13 (first cycle of ofatumumab). If there are no severe infusion reactions following the 1st 1000 mg infusion, investigators will be allowed to use their discretion whether steroid pre-medication is required for further Cycles (See Table 2). Pre-medication dosing is as follows:

- Acetaminophen (PO) equivalent to approximately 1000 mg, or the local standard of care.
- Antihistamine (IV or PO) equivalent to approximately 50 mg diphenhydramine.
- Glucocorticoid (IV) equivalent to approximately 50 mg prednisolone.

Table 2 Pre-medication Requirements Prior to Ofatumumab Infusions

Infusion #	Acetaminophen (iv or po) 1000mg or equivalent	Antihistamine (iv or po) iphenhydramine 50mg or equivalent	Glucocorticoid (iv) Prednisolone or equivalent
1st	**X**	**X**	50 mg
2nd	**X**	**X**	50 mg
3rd - 7th	**X**	**X**	0–50 mg[a]

a. If the 2nd infusion has been completed without the subject experiencing any Grade ≥ 3 AEs, pre-medication with glucocorticoid may be reduced or omitted before the 3rd to 7th infusion, at the Investigators discretion.

5.2.2 Ofatumumab Dosage and Administration

Ofatumumab is a clear liquid concentrate solution for infusion presented in glass vials. Ofatumumab will be infused intravenously on Day 1 (300 mg) and Day 8 (1000 mg) in the 13 cycle (1st Cycle of ofatumumab), followed by up to a maximum of 5 further 1000 mg infusions, every 28 Days, at the 1st Day of each Cycle. The ofatumumab infusions will be prepared in 1000 mL Sodium Chloride (NaCl) sterile, pyrogen free 0.9% NaCl to yield a 0.3 mg/mL and 1 mg/mL ofatumumab concentration for the first and subsequent infusions, respectively.

Ofatumumab should be given for up to 6 Cycles, however in the following instances, ofatumumab may be given for fewer than 6 Cycles:

1. If the subject demonstrates disease progression.

2. If a subject cannot tolerate the ofatumumab and is unable to receive further treatment with ofatumumab, the subject should stop further ofatumumab treatment. The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and eCRF.

5.2.3 Ofatumumab Treatment Schedule

5.2.3.1 ***First Infusion of 300 mg Ofatumumab***

The initial rate of the first infusion of 300 mg ofatumumab (0.3 mg/mL) should be 12 mL/hour (hr). If no infusion reactions occur, the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/hr, according to Table 3. If this schedule is followed, the infusion duration will be approximately 4.5 hours.

Table 3 Infusion Rate at Initial Ofatumumab Infusion

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

5.2.3.2 *Subsequent Infusions of 1000 mg Ofatumumab*

If the previous infusion has been completed without Grade ≥ 3 infusion-associated AEs, the subsequent infusion of 1000 mg (1 mg/mL) can start at a rate of 25 mL/hr and should be doubled every 30 minutes up to a maximum of 400 mL/h, according to Table 4.

The duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with Grade ≥ 3 infusion associated AEs, the subsequent infusion should start at a rate of 12 mL/hour according to Table 3.

Table 4 Infusion Rate at Subsequent Ofatumumab Infusions

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

During infusions the subject should be monitored closely and appropriate measurements should be performed whenever judged necessary.

No dose reductions or modifications for ofatumumab are permitted.

5.2.4 Management of Infusion Reactions

5.2.4.1 *Mild and Moderate Intensity Adverse Events (Grade 1 and 2)*

If the investigator judges a Grade 1 or 2 AE to be related to the infusion, the infusion may be temporarily slowed or interrupted. When the subject's condition is stable, the infusion can be restarted according to the judgment of the investigator.

Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hr, for the first infusion or 25 mL/hr for subsequent infusions, before the pause, the infusion should be restarted at 12 mL//hr, for the first infusion, or 25 mL/hr for subsequent infusions.

Hereafter, the infusion rate may be increased according to the judgment of the investigator or in the manner described in Table 3 and Table 4.

5.2.4.2 ***Severe Intensity Adverse Events (Grade ≥3)***

If the investigator judges a Grade ≥ 3 AE to be related to the infusion, the infusion must be interrupted and the appropriate clinical intervention begun. When the AE decreases to Grade < 3, the investigator may restart the infusion. Upon restarting the infusion, the infusion rate must be 12 mL/hr for the first infusion or 25 mL/hr for subsequent infusions, and may subsequently be increased according to the judgment of the investigator or as described in Table 3 and Table 4.

If the severity of the AE does not resolve to Grade < 3 despite adequate clinical intervention, or the same AE increases to Grade ≥ 3 on three occasions during one infusion, the subject should be withdrawn from further ofatumumab treatment.

5.3 Treatment Accountability and Compliance

Patients will be instructed on how to use Ibrutinib. Patient compliance with the ibrutinib will be assessed by the investigator or designee at each visit using direct questioning, examination of patient diaries, and capsule counts and will be recorded in the pharmacy binder. Compliance will be verified by the sponsor or designee and will be recorded in the study pharmacy binder.

Patient compliance with the Ofatumumab is not applicable; it is administered by the investigator or designee in the study site.

Pharmacy service and, in an extraordinary way, the investigator, is the responsibility to ensure the maintenance of an updated record of the availability of the drug under study in each study site where the investigational product is registered and stored.

The registers or notebooks shall comply with the applicable regulations and directives and shall include:

- Amount received and located at the storage location.
- Amount currently stored.
- ID number or batch number.
- Dates and initials of the person responsible for the entries and exits in the inventory of the drug.
- Quantity dispensed
- Amount transferred to another area for dispensing or storage.
- Disposition of medication outside the study (eg loss, wasted, broken).
- Amount returned to the sponsor, if applicable.

- Amount destroyed at the study site, if applicable.
- Samples sent to third parties for bioavailability / bioequivalence, if applicable.

The sponsor or designee will provide forms to facilitate inventory control if the staff of the research center does not have an established system that meets those requirements.

Pharmacy service and, in an extraordinary way, the investigator, is the responsibility to maintain addecuate storage conditions and temperature monitoring.

Upon completion or termination of the study, all unused and / or partially used drug should be returned or destroyed as per Sponsor's instructions.

5.4 Concomitant Medications

5.4.1 Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Patients at Risk for Tumor Lysis Syndrome

Patients with more than one of the following factors are considered to be at increased risk of tumor lysis syndrome:

- Serum creatinine ≥ 1.5 x ULN
- WBC count ≥ 50 x 109/L (or 50,000/mm3)
- Uric acid > ULN

Such patients should be considered for hydration and treatment with a uric acid lowering agent (xanthine oxidase inhibitor allopurinol or Uloric [febuxostat] +/- rasburicase) according to the drug product's package insert before continuing treatment with Ibrutinib, as well as for frequent monitoring for tumor lysis-associated signs and symptoms.

5.4.2 Concomitant Medications to be Used with Caution

CYP Inhibiting/Inducing Drugs

Ibrutinib is metabolized primarily by CYP3A4/5. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, Cmax and AUC0-last, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤ 2-fold in 37 patients treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 patients not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 patients treated

with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing PCI-32765 dose to 140 mg or withhold treatment temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Co-administration of ibrutinib with strong CYP3A inducers (such as carbamazepine and rifampin) decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered and if needed, the Medical Monitor may be contacted.

Antiplatelet Agents and Anticoagulants

There have been reports of hemorrhagic events in patients treated with ibrutinib. These include minor hemorrhagic events like contusion, epistaxis, and petechiae; and major hemorrhagic events including gastrointestinal, intracranial hemorrhage, and hematuria. It is not clear whether or not these events are attributable to ibrutinib; however, it is possible that treatment with the study drug could increase the risk of bruising and bleeding.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Ibrutinib should be used with caution in patients requiring other anticoagulants or medications that inhibit platelet function. Patients receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising, and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided.

5.4.3 Other Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited during the Treatment Phase of the study. Localized, hormonal, or bone sparing treatment for non-B-cell malignancies may be considered with approval of the Medical Monitor. Corticosteroids at dosages equivalent to prednisone >20 mg/day administered consecutively for 7 days or longer are not allowed. Prednisone >100 mg/day or corticosteroid equivalent is prohibited. If a patient develops autoimmune complications of CLL/SLL requiring prednisone >20 mg/day (or corticosteroid equivalent), study drug should be held and the case discussed with the medical monitor.

Erythropoietic growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and sargramostim are also prohibited for the first 6 months of study treatment. However, initiation of erythropoietic growth factors (eg, erythropoietin), platelet growth factors (eg, thrombopoietin) and/or sargramostim can be considered after 6 months on study based on the indication outlined in the respective package inserts.

Because of the risk of infection, administration of live attenuated vaccines should be avoided during and after treatment with ofatumumab, until B cell counts are normalized.

5.5 Packaging and labeling

Ibrutinib (until cycle C42) and Ofatumumab (cycle C13, 14, 15, 16, 17 and 18) will be provided by the sponsor to the sites:

- Ibrutinib will be supplied on behalf of the sponsor, by Janssen through B & C and distributed by the latter to the centers, free of charge for conducting the clinical trial.
- Ofatumumab will be supplied on behalf of the sponsor, by Novartis through Farmavenix and distributed by the latter to the centers, free of charge for conducting the clinical trial.

Ibrutinib is provided as hard gelatin capsules containing 140 mg of Ibrutinib. The capsules are packaged in opaque high-density polyethylene (HDPE) plastic bottles.

Ofatumumab 100 mg and 1000 mg concentrate for solution for infusion is provided as Clear Type I glass vial with a latex-free bromobutyl rubber stopper and aluminium over-seal, containing 5 ml and 50 ml respectively, of concentrate for solution for infusion. It is available in packs of 3 vials.

Ibrutinib and Ofatumumab will be labeled with the Sponsor name and address, strength, lot number and customary investigational medicinal product (IMP) regulatory statements.

Medication labels will comply with the legal requirements and be printed in the local language. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

5.6 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her study site number and patient number. The study site number is assigned by the Sponsor to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, the patient number will not be reused. If the patient fails to be started the administration of study drug for any reason, the reason will be entered on the Screening Log, and the Demography CRF should also be completed.

6. Visit schedule and assessments

The study flow is in Appendix A. These assessments are also described below.

Before study entry, throughout the study, and at the follow-up evaluations, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and efficacy assessments. Clinical evaluations and laboratory assessments may be repeated more frequently if clinically indicated.

6.1 Informed Consent

The patient must first read, understand, and sign the Medical Research Ethics Committee (MREC)-approved informed consent form confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. In addition, patients must sign all approved ICF amendments per the applicable MREC's guidelines during the course of the study.

6.2 Assessments by Visit

6.2.1 Screening phase

The following eligibility assessments will be performed within 28 days prior to study treatment initiation unless otherwise noted:

- Informed consent
- Medical history
- Concomitant medications (within 28 days prior to study treatment initiation, including over-the-counter drugs, vitamins, herbal supplements)
- Adverse events
- Height
- Physical examination, vital signs, weight, and ECOG performance status
- Clinical Stage Rai/Binet
- Radiologic examination by CT of the neck, chest, abdomen, and pelvis (magnetic resonance imaging [MRI] if CT is contraindicated) (within 6 weeks prior to study treatment initiation)
- Bone marrow biopsy and aspirate should be performed at Screening or up to 90 days before the first dose of study drug (mandatory only if cytopenias).
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)

- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell [RBC] count, and reticulocytes)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Coagulation panel (prothrombin time/INR and activated partial thromboplastin time)
- Creatinine clearance (by Cockcroft-Gault equation)
- Cytogenetic, CLL FISH panel (within 3 months)
- Serum Quantitative Inmunogloubulins (IgA, IgG, IgM)
- Coombs test
- B2-microglobulin
- Hepatitis serologies
- Genetic/molecular prognostic factors
- 12-lead ECG
- Review of eligibility criteria
- Blood for inmunophenotyping (for diagnosis), TP53 mutations and IGVH mutation status
- Pregnancy test (For women of childbearing potential only)

6.2.2 Treatment Phase

6.2.2.1 ***Predose Baseline (Day 1 of Cycle 1)***

The following procedures will be performed in the 3 days before dosing at the Day 1 of Cycle 1 Visit, unless otherwise noted. Screening tests may be used as baseline tests if done in the 7 days before the first dose of study drug. These procedures may be performed on Day 1 of Cycle 1 prior to the first dose of study drug.

- Confirm eligibility
- Cumulative Illness Rating Scale (CIRS)
- Concomitant medications
- Adverse events
- Study drug compliance review (study drug instruction and how to take study drug)
- Physical examination, vital signs, weight, and ECOG performance status

- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Clinical stage (Rai / Binet)
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid) and β2-microglobulin.
- Dispense study drug (ibrutinib)

6.2.2.2 ***Cycles 1–2***

The following procedures will be performed on Day 8 and 15 of Cycle 1, and Days 1 and 15 of Cycle 2 (± 3 days):

- Concomitant medications
- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration)
- Physical examination, vital signs, weight, and ECOG performance status
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)

The following procedures will be performed on Day 1 of Cycle 2:

- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Clinical stage (Rai / Binet)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Overall response assessment
- Dispense study drug (ibrutinib)

6.2.2.3 ***Cycles 3–11***

The following procedures will be performed on Day 1 of Cycles 3 through 11 (± 3 days):

- Concomitant medications

- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration)
- Physical examination, vital signs, weight, and ECOG performance status
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Clinical stage (Rai / Binet)
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Serum Quantitative Immunoglobulins (IgA,IgG, IgM) (every odd cycle)
- CT/MRI Scan (Cycle 3 only)
- Overall response assessment
- Dispense study drug (ibrutinib)

6.2.2.4 ***Cycle 12***

Between cycle 12 and cycle 13, the disease must be evaluated.

The following procedures will be performed:

- Concomitant medications
- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration)
- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Clinical stage (Rai / Binet)
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)

- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Radiologic examination by CT of the neck, chest, abdomen, and pelvis (MRI if CT is contraindicated)
- Bone marrow biopsy and aspirate should be performed to confirm complete remission/response (CR). Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; MRD should be also analyzed in peripheral blood.
- Overall response assessment
- Serum immunoglobulins (IgA, IgG, and IgM)

6.2.2.5 ***Cycle 13***

The following procedures will be performed on Days 1 and 8 of Cycle 13 (± 3 days):

- Concomitant medications
- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration)
- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)

The following procedures will be performed on Day 1 of Cycle 13:

- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Clinical stage (Rai / Binet)
- Overall response assessment
- Dispense study drug (ibrutinib and ofatumumab)

6.2.2.6 ***Cycles 14–19***

The following procedures will be performed on Day 1 (± 3 days):

- Concomitant medications
- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration)
- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Clinical stage (Rai / Binet)
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Serum quantitative Immunoglobulins (IgA, IgG, IgM) (every odd cycle)
- Overall response assessment
- Dispense study drug (ibrutinib and ofatumumab (except cycle 19))

6.2.2.7 ***Cycle 20***

Disease must be evaluated.

The following procedures will be performed:

- Concomitant medications
- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration)
- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Clinical stage (Rai / Binet)
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)

- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Radiologic examination by CT of the neck, chest, abdomen, and pelvis (MRI if CT is contraindicated)
- Bone marrow biopsy and aspirate should be performed to confirm complete remission/response (CR). Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; MRD should be also analyzed in peripheral blood.
- Overall response assessment
- Flow cytometry-based blood assays
- Serum immunoglobulins (IgA, IgG, and IgM)
- Dispense study drug (ibrutinib)

6.2.2.8 ***Cycles 21 Through Treatment Termination***

The following procedures will be performed on Day 1 of every odd cycle (for Cycles 21, 23, 25, 27 and 29), then every 3 cycles (beginning Cycle 31) until progression or study closure (± 3 days):

- Concomitant medications
- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration), as relevant
- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Clinical stage (Rai / Binet)
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Dispense study drug (ibrutinib only, maximum 3-cycle supply)

- Bone marrow aspirate should be performed in any time point during follow-up when the MRD peripheral blood analyses become negative. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; MRD should be also analyzed in peripheral blood. Patients in CR should be followed every 6 months for MRD by peripheral blood flow cytometry and in patients with negative CR and MRD in BM, every 12 months and at the time that the patient presents data with suspicion of relapse
- Overall response assessment
- Serum immunoglobulins (IgA, IgG, and IgM)
- Dispense study drug (ibrutinib)
- Pregnancy test (only for women of childbearing potential) 5 months after the last dose of ofatumumab (Day 1 of cycle 23).

6.2.3 Suspected Disease Progression

The following procedures should be performed at the time of suspected disease progression:

- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Concomitant Medication
- Adverse Events
- Clinical stage (Rai / Binet)
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Radiologic examination by CT of the neck, chest, abdomen, and pelvis (MRI if CT is contraindicated)
- Overall response assessment
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)
- Serum immunoglobulins (IgA, IgG, and IgM)

6.2.4 End-of-Treatment Safety Visit

The tests listed below will be performed within 30 days (+ 3 days) after the discontinuation of treatment for any reason. The visit should be conducted prior to starting a new anticancer treatment.

- Concomitant medications

- Adverse events
- Study drug compliance review (review of study drug diary and evaluation of contents of study drug containers from home administration), as relevant
- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Clinical stage (Rai / Binet)
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/ discomfort due to splenomegaly including satiety, anorexia)
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and uric acid)
- Serum immunoglobulins (IgA, IgG, and IgM)
- Overall Response Assessment
- Pregnancy test (only for women of childbearing potential)

6.2.5 Follow-up for Progression (Pre-PD)

Patients who discontinue study treatment without confirmed progression will continue to be followed for progression every 4 months (± 7 days) for the first 24 months from start of treatment, then every 6 months (± 7 days) until progression or study closure. Required information is as follows:

- Physical examination (including focused ocular questions), vital signs, weight, and ECOG performance status
- Concomitant medication
- Adverse Events
- Clinical stage (Rai / Binet)
- Serum chemistry
- Serum Quantitative Immunoglobulins (IgA, IgG, IgM)
- Disease-related symptoms (weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including satiety, anorexia)
- Bone marrow aspirate should be performed in any time point during follow-up when the MRD peripheral blood analyses become negative. Marrow collected to confirm CR should

have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; MRD should be also analyzed in peripheral blood. Patients in CR should be followed every 6 months for MRD by peripheral blood flow cytometry and in patients with negative CR and MRD in BM, every 12 months and at the time that the patient presents data with suspicion of relapse

- Overall response assessment
- Hematology (WBC count with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes)
- Anticancer therapies initiated

6.3 Description of Procedures

6.3.1 Confirmation of Eligibility

Perform all necessary procedures and evaluations to document that the patient meets each eligibility criterion.

6.3.2 Medical History

Collect and record the patient's complete history including concurrent medical signs and symptoms within 28 days of first dose with study drug will also be recorded based upon available documents and patient history. Disease history, including the date of initial diagnosis, and Rai and Binet staging.

6.3.3 Adverse Events

All medical occurrences that meet the accepted regulatory definition of AE must be recorded from the time the informed consent form is signed until 30 days after the last dose of study drug. Laboratory abnormalities designated clinically significant by the Investigator will also be recorded as AEs. Serious Adverse Events (SAEs) and AEs of special interest will be reported to the sponsor within 24 hours of awareness and will require enhanced data collection.

6.3.4 Physical Examination, Vital Signs, Height and Weight and ECOG performance status scale

Physical examinations should include height (screening only) and weight, examination of the skin, eyes (with specific questions focused on ocular symptoms), ears, nose, throat, lungs, heart, abdomen, extremities, and lymphatic system. The lymphatic system examination will include bidimensional measurements of palpable lymph nodes and measurement of spleen and liver sizes by centimeters below the costal margin on the respective side.

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature.

ECOG performance status scale:

GRADE	ECOG PERFORMANCE STATUS

GRADE	ECOG PERFORMANCE STATUS
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

6.3.5 Clinical Stage Rai/Binet

Rai Staging System					
	Lymphocytosis	**Adenophaty**	**Hepato/splenomagaly**	**Hemoglobin**	**Platelets**
0	+	-	-	≥ 11g/dL	≥ 100x103/µl
I	+	+	-	≥ 11g/dL	≥ 100x103/µl
II	+	(+/-)	+	≥ 11g/dL	≥ 100x103/µl
III	+	(+/-)	(+/-)	< 11g/dL	≥ 100x103/µl
IV	+	(+/-)	(+/-)	>< 11g/dL	< 100x103/µl

Binet Staging Syste				
	Lymphocytosis	**Adenophaty regions**	**Hemoglobin**	**Platelets**
A	+	<3 regions	≥ 10g/dL	≥ 100x103/µl
B	+	≥ 3 regions	≥ 10g/dL	≥ 100x103/µl
C	+	(+/-)	<10g/dL ó <100x103/µl	

6.3.6 Disease-related Symptoms

Disease-related symptoms including fatigue, night sweats, fever, weight loss, symptoms of splenomegaly (abdominal pain/discomfort including early satiety), and anorexia will be assessed and recorded in the patient records.

6.3.7 Electrocardiogram (ECG)

Patients should have a 12-lead ECG done at Screening and in Cycle 12. Abnormalities should be included in the medical history, as appropriate.

6.3.8 Concomitant Medications

All medications and products (i.e., growth factors, blood supportive products) from 14 days before the start of study drug administration through 30 days after the last dose of study drug must be recorded.

After a patient discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until patient death or closure of the study.

6.3.9 Cumulative Illness Rating Scale (CIRS)

The CIRS is a measure of comorbid medical conditions. As an individual ages, the number of comorbid medical conditions increases, which can impact treatment tolerance to anti-cancer therapy (Welch 1996). A geriatric modification of CIRS, CIRS-G, was created to reflect common comorbidities of the elderly, with an emphasis on chronic problems and limitation in function (Miller 1992).

This rating scale defines the extent to which organs and systems are affected, without referring to specific diseases (Appendix E).

6.3.10 Hepatitis Serologies

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody. If Hepatitis B core antibody or Hepatitis B surface antigen is positive, then Hepatitis B PCR to quantitate Hepatitis B DNA must be performed. DNA PCR needs to be confirmed negative prior to inclusion in the study in patients who are Hepatitis B core antibody positive or Hepatitis B surface antigen positive. Per published guidelines (NCCN 2012) or institutional guidelines, patients should be closely monitored for hepatitis B reactivation. Obtaining repeated hepatitis B PCR every 3 months for the first 12 months after first dose of study drug in order to monitor for reactivation of hepatitis B is recommended.

6.3.11 Hematology

Hematology will be evaluated by local laboratory and will include a complete blood count (CBC) with white blood cell differential (with manual 5-part differential, platelets, hemoglobin, hematocrit, red blood cell count, and reticulocytes).

6.3.12 Coagulation Panel

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening using a local laboratory.

6.3.13 Serum Chemistry

Serum chemistry will be evaluated by a local laboratory and will include albumin, alkaline phosphatase, ALT, AST, BUN, calcium, creatinine, glucose, lactate dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, and uric acid.

6.3.14 Creatinine clearance (Cockcroft-Gault)

Creatinine clearance will be evaluated by local laboratory according to the appendix C.

6.3.15 Serum Immunoglobulin and β2-microglobulin

Quantitative immunoglobulin (IgG, IgM, IgA) levels and serum β2-microglobulin (screening only) will be evaluated by local laboratory.

6.3.16 Coombs test

Coombs test will be evaluated by local laboratory.

6.3.17 Computed Tomography (CT) Scans

CT scans of the neck, chest, abdomen, and pelvis will be performed. MRI may be used to evaluate sites of disease that cannot be adequately imaged using CT (in cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations). If MRI is required for any other reason, this must first be discussed with the study medical monitor.

6.3.18 Bone Marrow Aspirate and Biopsy

A unilateral bone marrow aspirate and biopsy must be obtained at Screening or up to 90 days before the first dose of study drug (mandatory only in cases with cytopenias). Subsequently, a bone marrow aspirate and biopsy should be obtained to confirm CR, at disease evaluation in cycle 12 or cycle 20, distinguish autoimmune and treatment-related cytopenias, and for biomarker assessments. In addition, bone marrow aspirate should be performed in any time point during follow-up when the MRD peripheral blood analyses become negative. Marrow collected to confirm CR should have MRD assessed by flow cytometry on the aspirate. MRD should be also analyzed in peripheral blood. Patients in CR should be followed every 6 months for MRD by peripheral blood flow cytometry and in patients with negative CR and MRD in BM, every 12 months and at the time that the patient presents data with suspicion of relapse. The analysis of MRD will be performed in the department of Hematology of University Hospital of Salamanca

6.3.19 Cytogenetic, CLL FISH Panel

Within 90 days prior to the first dose of study drug the cytogenetic profile by using the standard CLL FISH probes to detect abnormalities in chromosomes 13q, 12, 11q, and 17p must be evaluated.

6.3.20 Overall Response Assessment

Overall response assessment will include evaluation of physical exams, recording of symptoms, hematological evaluations, and radiographic evaluations per the schedule of assessments.

6.3.21 Overall Survival

After progression, patients will be followed to assess survival status and receipt of subsequent anticancer therapy until death, withdrawal by patient, loss to follow-up, or study termination by Sponsor, whichever comes first.

6.3.22 Blood for immunophenotyping (for diagnosis), TP53 mutations, and IGVH mutation status

This analysis will be performed in the department of Hematology of Vall d'Hebron Hospital. The sample shipping instructions are specified in Appendix C of this protocol.

6.3.23 Pregnancy test

In women of childbearing potential, a test should be done to rule out pregnancy during the screening period, 5 months after the last dose of ofatumumab (Day 1 of Cycle 23) and within 30 days after completing the last dose of ibrutinib (End-of-treatment visit).

7. Main Efficacy Evaluations

Disease evaluations include:

- Physical examination (which will focus on the presence/absence of size increase/ decrease in lymph nodes, liver, and spleen)
- Disease-related symptoms
- Hematologic parameters by CBC performed at a local laboratory
- Radiographic evaluation (CT or MRI scan of the neck, chest, abdomen, and pelvis)
- Bone marrow aspirate and biopsy with MRD by flow cytometry if there is evidence of CR in the other response parameters; patients in CR will be followed by peripheral blood MRD every 6 months

7.1 Suspected Disease Progression

The schedule of assessments is provided in Appendix A. Any suspected case of disease progression will prompt procedures performed in a Suspected Disease Progression visit. Disease progression should be confirmed with a CT scan (or MRI, if CT is contraindicated) and should be reported to the sponsor within 24 hours of discovery. If disease progression is suspected based on the results of a single examination (including CT scan) or a single laboratory parameter, this finding should be confirmed by a subsequent evaluation at least 2 weeks later.

7.2 Guidelines for Disease Evaluation

Objective response will be categorized as CR, CR with incomplete bone marrow recovery (CRi), nPR, partial response (PR), stable disease, or progressive disease—all based upon IWCLL criteria (Hallek 2008). Patients who achieve PR in all parameters except lymphocyte count will be considered a PR with lymphocytosis, for the purposes of the protocol. All responses must be maintained for at least 2 months to be considered confirmed. CRs must be confirmed by bone marrow biopsy and aspirate.

Detailed definitions of all categories of response are in Appendix B.

Given the known mechanism of action of BCR-inhibiting agents, including ibrutinib, and the treatment-related lymphocytosis frequently observed during treatment with ibrutinib, isolated treatment-related lymphocytosis (in absence of other clinical, CT, or laboratory evidence of disease progression) will not be considered progressive disease. This approach is supported by both the authors of the IWCLL 2008 guidelines (Hallek 2012, Cheson 2012) and the NCCN.

8. Safeting, Monitoring and Reporting

8.1 Adverse Event Definitions and Classifications

8.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event may therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF. (8.2.1)

8.1.2 Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

8.1.3 Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an adverse event will be determined by whether or not it is listed in the current Investigator's Brochure.

For Ofatumumab the expectedness of an adverse event will be determined by whether or not it is listed in the current SmPC.

8.1.4 Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed below.

8.1.5 Attribution Definitions

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

- Not suspected: The temporal relationship of the adverse event to IP administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Suspected: The temporal relationship of the adverse event to IP administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

8.1.6 Severity Criteria

An assessment of severity grade will be made using the NCI-CTCAE (version 4.03). The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

AEs that are not defined in the NCI CTCAE should be evaluated for severity / intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible

- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

- Grade 5 = Death - the event results in death]

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as “serious” which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject’s life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

8.1.7 Special Reporting Situations

Safety events of interest on a study drugs that may require expedited reporting and/or safety evaluation include, but are not limited to:

Overdose of study drug

Suspected abuse/misuse of study drug

Inadvertent or accidental exposure to a study drug

Medication error involving a product (with or without subject/patient exposure to the study drugs, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

8.2 Reporting Procedures

8.2.1 All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety).

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported to the sponsor. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor must report these events to the appropriate Medical Research Ethics Committee (MREC) that approved the protocol unless otherwise required and documented by the MREC.

In adition, the sponsor will also report to Janssen and Novartis all serious adverse events and adverse events of interest, listed and unlisted (unexpected) and associated or not associated with the use of their study drug.

8.2.2 Serious Adverse Events

All serious adverse events occurring during the study must be reported to the sponsor by study-site personnel within 24 hours of their knowledge of the event using the SAE Report Form, or approved equivalent form.

Send SAEs to:
Adknoma Health Research
Departamento de Farmacovigilancia
FAX: +34 93 206 66 67

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization have to be reported as a new serious adverse event.
- Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.
- A standard procedure for protocol therapy administration will not be reported as a serious adverse event, however an hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.
- The administration of blood or platelet transfusion will not be reported as a serious adverse event, however an hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling) will not be reported as a serious adverse event, however an hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an adverse event
- A procedure planned before entry into the study (must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the study drug remains a reportable serious adverse event.

8.2.3 Adverse Events of Interest

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities. These events will be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.

Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

Other Malignancies

In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

8.2.4 Pregnancy

All initial reports of pregnancy, suspected pregnancy, or positive pregnancy test in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the Pregnancy Reporting Form or an approved equivalent form.

Any subject who becomes pregnant during the study must discontinue further study treatment.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Consent to report information regarding pregnancy outcomes from the female partners of any males who took study drug in this study should be obtained.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Sponsor immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported within 24 hours of the

Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

8.2.5 Expedited Reporting of Adverse Events

8.2.5.1 *Reporting to Regulatory Authorities and the Ethics Committee*

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 IP 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 IP as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator.

8.2.5.2 *Immediate reporting by Investigator to Sponsor and Sponsor to the appropriate pharmaceutical company*

The investigator will inform the Sponsor of all SAEs within 24 hours in order that the sponsor can fulfill their regulatory reporting obligations within the required timeframes.

Contact details for SAE reporting:
Adknoma Health Research
Departamento de Farmacovigilancia
FAX: 93 206 66 67

The Sponsor will supply the pharmaceutical companies (Janssen and Novartis) with a copy of all SAEs reports which involve exposure to corporate products 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), or whether it is related or not to the study drug.

8.3 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.

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event. The Sponsor will inform the pharmaceutical companies (Janssen and Novartis) 24 hours of being made aware of the event.

If the defect is combined with a serious adverse event, the investigational staff must report the PQC to the Sponsor according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation.

9. Withdrawal of Patient from Treatment or Study

Investigators are encouraged to keep a patient experiencing clinical benefit on study treatment unless significant toxicity puts the patient at risk or routine noncompliance puts the study outcomes at risk.

9.1 Discontinuation of Treatment

Study treatment must be discontinued under the following circumstances:

- Progressive disease
- Withdrawal of consent for treatment by patient
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or the best interest of the patient)
- Study termination by Sponsor
- Adverse event for which continued study treatment would be detrimental
- Lost to follow-up
- Pregnancy in female subjects or partners of male subjects
- Death

An End-of-Treatment visit will be performed within 30 days (+ 3 days) after the discontinuation of treatment for any reason. The visit should be conducted prior to starting a new anticancer treatment.

9.2 Withdrawal from the Study

Withdrawal from the study (including all follow-up requirements) will occur under the following circumstances:

- Withdrawal of consent for follow-up by the patient
- Lost to follow-up
- Death

In case a patient is lost to follow-up, every possible effort must be made by the study site personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow-up must be documented in the patient's records.

When a patient withdraws before completing the study, the reason for withdrawal must be documented in the source documents. Efforts will be made to obtain partial withdrawal of consent in order to continue to collect survival data on all patients who were randomized in the study.

10. Stadistical Methods and data Analysis

10.1 Population for analysis

The efficacy analysis will include all the population by intention-to-treat (ITT). To be evaluable for efficacy, patients must have baseline evaluation of disease status, received at least one complete cycle of treatment and at least one follow-up evaluation of disease status.

The safety analyses of treatment administration will include all patients that receive at least one dose of study treatment.

Only those patients who complete twenty cycles of the study (C1 - C20) will be considered evaluable for the purpose of determining the primary endpoint.

10.2 Endpoints

10.2.1 Primary Endpoint

Complete response rate according to IWCLL criteria (Hallek 2008).

10.2.2 Secondary Endpoints

Efficacy

- ORR defined as the proportion of patients who achieve CR, CRi, nPR, or partial response (PR) per IWCLL 2008 criteria over the course of the study
- Rate of MRD-negative CRs
- OS and Progression-Free Survival (PFS) will be included as a secondary where progressive disease (PD), or death are defined as events.

Safety

- Incidence of AEs and changes in laboratory variables, vital signs, and ECG

10.2.3 Exploratory Endpoints

- Response rate in relationship to molecular and genetic prognostic factors
- Evaluate biomarkers related to BCR and compensatory signaling pathways and their association with resistance to ibrutinib treatment
- Immunological recovery

10.3 Statistical methods

10.3.1 Efficacy analysis

Primary endpoint

CRR is defined as the proportion of patients who achieve a CR according to The IWCLL guidelines (Hallek, 2008) as defined in appendix B. CRR will be assessed after 20 cycles of treatment (2 months after completing ofatumumab) for the primary objective of the study. The analysis of CRR will be performed in the ITT population.

Secondary Endpoints

ORR is defined as the proportion of patients who achieve a CR, CRi, nPR, or PR over the course of the study. Patients who achieve a PR with lymphocytosis will be included in the ORR. The rate of MRD-negative disease will also be calculated. The IWCLL guidelines (Hallek, 2008) will be used to measure response in CLL subjects with the modification that isolated treatment related lymphocytosis will not be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines.

PFS is defined as the time from the date of treatment initiation to confirmed disease progression (assessed per IWCLL 2008 criteria, with modification for treatment-related lymphocytosis) or death from any cause, whichever occurs first. Patients who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. Patients who start new anticancer therapy before documentation of disease progression will be censored on the date of the last adequate disease assessment that is on or before the start date of the new anticancer therapy.

OS is defined as the time from the date of treatment initiation to death due to any cause. Patients who are known to be alive or whose survival status is unknown will be censored at the last date the patient is known to be alive.

Distribution of PFS and OS will be summarized using the Kaplan-Meier estimate of median and its corresponding 95% confidence interval (CI).

10.3.2 Safety analysis

Data from all subjects who receive at least one dose of the study drugs will be included in the safety analyses and analyzed as treated. Study medication exposure will be summarized including duration of study medication, total dose taken, and dose reductions or treatment delays.

Adverse events, vital sign measurements, clinical laboratory measurements, and concomitant medications will be also summarized.

AEs will be classified using the NCI CTCAE (v 4.0). Subsets of AEs to be summarized include serious AEs (SAEs), events of all CTCAE grade severities, events classified as NCI CTCAE grade 3 or higher, suspected treatment-related AEs, suspected unexpected serious adverse reactions (SUSARs), and events that resulted in withdrawal of study medication. Laboratory data will be summarized according to the NCI CTC severity grade.

10.4 Sample-Size Considerations

A complete response rate of 13% (CRR reported for ibrutinib as first line therapy in CLL[16]) is assumed as P0 (null hypothesis), and a CRR of 25% (improvement by 12%) is considered as P1 (alternative hypothesis). Applying Simon 2-stage design, (Simon 1989) to obtain 80% power with type I error probability of α=0.05, a maximum number of 76 patients will be required. Anticipating 10% dropouts, 84 patients need to be included. The study will be terminated prematurely if at least 4 complete responses are not observed among the first 28 patients evaluated. The response will be assessed after 20 cycles of treatment (2 months after completing ofatumumab) using the IWCLL guidelines (Hallek, 2008) with the modification that isolated treatment related lymphocytosis will not be considered as disease progression as recommended by the IWCLL 2008 guideline clarification (Hallek 2012) and the National Comprehensive Cancer Network (NCCN), 2012 guidelines. Otherwise, the study will continue until a maximum number of 84 patients included.

The primary efficacy analyses will be based on the intention to-treat population (ITT) which includes all enrolled subjects. The primary end point is the complete response rate determined according to The IWCLL guidelines (Hallek, 2008). Primary and secondary endpoints will be analyzed by means of standard descriptive and exploratory inferential statistical methods.

10.5 Reporting statistical plan deviations

All deviations from the original statistical analysis plan are included in the final clinical trial report.

10.6 Data monitoring committee

A regular data monitoring will be performed by the study Sponsor and investigators coordinators.

11. ETHICS

11.1 Good Clinical Practice

The study will be conducted according to the International Conference on Harmonisation and Good Clinical Practice (ICH-GCP) and applicable regulatory requirements. The Investigators are fully acquainted with the proper use of the study drug as described in the protocol and in the current Investigator's Brochure. The essential documents will be kept for demonstrating the validity of the study and the integrity of the data gathered. The main files should be established at the start of the study, be kept during this study and kept according to the relevant regulations.

11.2 Ethical considerations

The study will be conducted according to the ethical guidelines of the Declaration of Helsinki (http://www.wma.net/en/30publications/10policies/b3/) and EU Directives. The Medical Research Ethics Committee (MREC) will review all documentation relevant to the study for the purpose of protecting the rights, safety and well-being of the patients. The study will be only performed at the centers for which approval has been obtained by the MREC. The Investigator will provide the MREC with the protocol, current Investigator's Brochure, Informed Consent, advertising (if appropriate), written information provided to patients, updates related to safety, annual progress reports, and any change in these documents.

11.3 Patient information and Informed Consent

Once the complete study is explained, written Informed Consent will be obtained from the patient, legal guardian or representative before starting participation in the study. The method for obtaining and documenting the Informed Consent and its contents must be in compliance with the International Conference on Harmonisation related to the good clinical practice and all relevant regulatory requirements.

11.4 Patient confidentiality

In order to respect patient privacy, patients will be identified by patient number in all case report forms, study drug accountability logs, study reports and communications. The Investigator will provide the inspectors and possible auditors or designees and regulatory authorities access to the source medical records of the patient so that they can review the data contained in the case report forms and audit the data gathering process. Confidentiality will be kept and the identity of the patients will not be disclosed as far as permitted by the law and relevant regulations, among which, the Organic Act 15/1999 of 13 December on data protection.

11.5 Protocol compliance

The investigators will undertake the study in compliance with the protocol provided by Pethema Foundation, once approval or favorable opinion are obtained from the MREC and the

relevant regulatory authorities. The protocol should not be modified without consent from the Pethema Foundation. Protocol amendments require written approval or favorable opinion from the MREC prior to implementation, unless the amendment is required to prevent immediate risks for patients. The MREC can provide, if the relevant regulatory authorities permit it, a review and approval or favorable decision as soon as possible for making minor changes in the studies ongoing that have obtained approval or a favorable decision from the appropriate MREC. The Pethema Foundation will submit all protocol amendments to the regulatory authorities according to the current regulations.

When an immediate protocol deviation is required to prevent immediate risks for the patients, the Investigator will contact the Pethema Foundation representative, if the circumstances permit it, to discuss the measures planned to adopt. Any protocol deviation must be documented in detail in the CRF and the original documentation.

11.6 Early study discontinuation

This study may be discontinued early if, in the Sponsor's opinion, there is sufficient reasonable cause. The investigators will receive a written notice where the discontinuing party documents the reason for the study discontinuation.

The circumstances warranting study discontinuation include, among others:

- Determination of unexpected, substantial or unacceptable risks for the patients.
- Inability to enroll an acceptable number of patients.
- Inadequate compliance with protocol requirements.
- Plans for modifying, cancelling or discontinuing the development of the study drug.

11.7 Data registering and storage

The Investigator will keep all study records in compliance with ICH-GCP requirements and current regulations.

11.8 Responsibility and insurance

The Sponsor has taken out an insurance policy covering, in its terms and conditions, the liability for damages caused to participants and derived from this research, performed fully in compliance with both the scientific protocol and the applicable law and professional standards. The insurance company is HDI HANNOVER INTERNATIONAL (SPAIN), SEGUROS Y REASEGURADOS, S.A with its registered address in Madrid, C/ Luchana. 23 6º; Policy number being: 08054309-14266.

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13. Appendices

Appendix A: Schedule of Assessments

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)											Suspected PD	End-of-Treatment	Pre-PD FU[b]
		Cycle 1			Cycle 2		Cycles 3–11	Cycle 12	Cycle 13		Cycles 14 –19	Cycle 20	Cycles 21–Term			
		D1 (baseline)[a]	D8	D15	D1	D1 5	D1	D1	D1	D8	D1	D1	D1[d]	Any time	Within 30 D after treatment	q 4 mos, then q 6 mos[c]
Study Visit Windows	-28 to 0 days	± 3 days						Between D1 C12 and D1 C13	± 3 days			Between D1 C20 and D1 C21	± 3 days	Any time	+ 3 days	± 7 days
Procedures																
Informed consent	X															
Confirm eligibility	X															
Medical history	X															
Cumulative Illness Rating Scale (CIRS)		X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam, vital signs, weight, ECOG	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical stage (Rai / Binet)	X	X		X		X	X	X	X		X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X		X		X	X	X	X		X	X	X	X	X	X
Creatinine clearance (Cockcroft-Gault)	X															

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)												Suspected PD	End-of-Treatment	Pre-PD FU[b]
		Cycle 1			Cycle 2		Cycles 3–11	Cycle 12	Cycle 13		Cycles 14 –19	Cycle 20	Cycles 21–Term			
		D1 (baseline)[a]	D8	D15	D1	D1 5	D1	D1	D1	D8	D1	D1	D1[d]	Any time	Within 30 D after treatment	q 4 mos, then q 6 mos[c]
Study Visit Windows	-28 to 0 days	± 3 days						Between D1 C12 and D1 C13	± 3 days			Between D1 C20 and D1 C21	± 3 days	Any time	+ 3 days	± 7 days
Procedures																
Cytogenetic, CLL FISH panel	X															
Serum Quantitative Immunoglobulins (IgA,IgG, IgM)	X						(X)[f]	X			(X)[f]	X	X	X	X	X
Coombs test	X															
B2-microglobulin	X															
Hepatitis serologies[o]	X															
Coagulation panel	X															
12-lead ECG	X							X								
Any new anticancer therapy																X
Disease assessment:																
CT/MRI scan	X[g]						X[h]	X				X		X		
Bone marrow biopsy, aspirate and MRD PB by flow cytometry[l]	X							(X)				(X)	(X)			(X)
Disease-related symptom	X	X		X		X	X	X		X		X	X	X	X	X

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)												Suspected PD	End-of-Treatment	Pre-PD FU[b]
		Cycle 1			Cycle 2		Cycles 3–11	Cycle 12	Cycle 13		Cycles 14 –19	Cycle 20	Cycles 21–Term			
		D1 (baseline)[a]	D8	D15	D1	D1 5	D1	D1	D1	D8	D1	D1	D1[d]	Any time	Within 30 D after treatment	q 4 mos, then q 6 mos[c]
Study Visit Windows	-28 to 0 days	± 3 days						Between D1 C12 and D1 C13	± 3 days			Between D1 C20 and D1 C21	± 3 days	Any time	+ 3 days	± 7 days
Procedures																
Overall response assessment					X		X	X	X		X	X	X	X	X	X
Blood for immunophenotyping (for diagnosis), *TP53* mutations, and *IGVH* mutation status[j]	X															
Pregnancy test[p]	X												(X)		X	
Dispense study drug (Ibrutinib)		X		X	X	X	X	X	X	X	X	X	X			
Study Drug compliance review (Ibrutinib)		X[l]		X	X	X	X	X	X	X	X	X	X		X	
Study drug administration (Ofatumumab)[m]									X	X	X					
Overall survival[n]															(X)	

D = day; Term = treatment termination; d/c = discontinuation; PD = progressive disease; FU = follow-up; (x) = not all visits or all subjects

[a] To be collected pre-dose, unless otherwise specified

[b] For patients who have discontinued study treatment without confirmed progression

[c] Every 4 cycles, then every 6 cycles (beginning Cycle 30) until progression or study closure

[d] Every odd cycle until cycle 29, then every 3 cycles (beginning Cycle 31) until progression or study closure

[e] AEs are reported from the time the patient signs the Informed Consent Form until 30 days following last dose of study drug. In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events for the duration of the study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

[f] Every odd cycle

[g] Baseline CT scan can be performed up to 6 weeks prior to the first dose of study drug

[h] Cycle 3 only

[i] Bone marrow biopsy and aspirate should be performed at Screening or up to 90 days before the first dose of study drug (mandatory only if cytopenias), and to confirm complete remission/response (CR) at disease evaluation in cycle 12 or cycle 20. In addition, bone marrow aspirate should be performed in any time point during follow-up when the MRD peripheral blood analyses become negative. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; MRD should be also analyzed in peripheral blood. Patients in CR should be followed every 6 months for MRD by peripheral blood flow cytometry and in patients with negative CR and MRD in BM, every 12 months and at the time that the patient presents data with suspicion of relapse. The analysis of MRD will be performed in the department of Hematology of University Hospital of Salamanca

[j] These analysis will be performed in the department of Hematology of Vall d'Hebron Hospital

[k] Physical examinations should include height (screening only)

[l] Cycle 1 D1 (Baseline): patient should be instructed in how to take study drug (Ibrutinib)

[m] Ofatumumab will be administered by IV infusion, 300mg on Day 1 and 1,000 mg on Day 8 of Cycle 13, followed by 5 monthly infusions of 1,000 mg (Day 1 of subsequent 28-day cycles for cycles C14, C15, C16, C17, and C18).

[n] After progression, patients will be followed up to assess survival status and receipt of subsequent anticancer therapy until death, withdrawal by patient, loss to follow-up, or study termination by Sponsor, whichever comes first.

[o] DNA PCR needs to be confirmed negative prior to inclusion in the study in patients who are Hepatitis B core antibody positive or Hepatitis B surface antigen positive. Per published guidelines (NCCN 2012) or institutional guidelines, patients should be closely monitored for hepatitis B reactivation. Obtaining repeated hepatitis B PCR every 3 months for the first 12 months after first dose of study drug in order to monitor for reactivation of hepatitis B is recommended.

[p] Pregnancy test: In women of childbearing potential, a test should be done to rule out pregnancy during the screening period, 5 months after the last dose of ofatumumab (Day 1 of Cycle 23) and within 30 days after completing the last dose of ibrutinib (End-of-treatment visit).

Appendix B: Definitions of Response (Hallek 2008)

Complete Response (CR)

All of the following are required for a CR:

- No significant lymphadenopathy (> 1.5 cm) by CT or palpable on examination (if not scannable)
- No hepatosplenomegaly by CT
- No constitutional symptoms, defined as: no fever > 38ºC for ≥ 2 weeks without evidence of infection, no unintentional ≥ 10% body weight loss within last 6 months, no night sweats for > 1 month without evidence of infection, and no fatigue (ECOG performance score ≥ 2) interfering with work or usual activities
- ANC > 1500/µL, platelets > 100,000/µL, and hemoglobin > 11.0 g/dL
- Lymphocyte count < 4.0 x 10^9/L

Marrow aspirate and biopsy must be performed after all other criteria meet the definition of CR. To define a CR, the marrow sample must be at least normocellular for age, with < 30% of nucleated cells being lymphocytes. B-lymphoid nodules should be absent. In addition, in patients who meet the CR criteria, MRD by flow cytometry should be performed to evaluate MRD status.

Complete Response with an Incomplete Marrow Recovery (CRi)

CRi is defined as a CR with an incomplete recovery of the patient's bone marrow. Bone marrow must be hypocellular. Patients who have a CRi fulfill criteria for a CR, but continue to have persistent anemia, thrombocytopenia, or neutropenia due to drug toxicity in the bone marrow and not due to any evidence of CLL.

Nodular Partial Response (nPR)

Nodular partial response (nPR) is a response where patients meet criteria for a CR, but the bone marrow biopsy shows that there are still B-lymphoid nodules present. These nodules are residual disease and therefore the patient is termed an nPR.

Partial Response (PR)

A ≥ 50% drop in lymphocyte count from baseline or ≤ 4.0 x 10^9/L is required for a PR and the following is observed in a criterion evaluable at baseline:

- ≥ 50% decrease in the sum products of the perpendicular diameters of up to 6 lymph nodes by CT or, if only one measurable lymph node at baseline, a ≥ 50% decrease in the longest diameter of the single lymph node by CT AND no increase in any other lymph node by CT. Note: In a small lymph node < 2cm, an increase of < 25% is not considered to be significant.
- No new enlarged lymph nodes by CT or physical examination

- ≥ 50% decrease in the enlargement of spleen and/or liver size from baseline or normalization by CT

Plus a response in at least one of the following criteria independent of growth factor support or transfusion.* If all criteria are normal at baseline, they must remain normal to be considered a PR:

- ANC > 1500/µL or ≥ 50% improvement over baseline
- Platelets > 100,000 or ≥ 50% improvement over baseline
- Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline

* Note: For a criterion to be considered a response, it must have been evaluable at baseline.

PR with Lymphocytosis

Patient exhibits lymphocytosis but the following are observed in a criterion evaluable at baseline:

- ≥ 50% decrease in the sum products of the perpendicular diameters of up to 6 lymph nodes by CT or, if only one measurable lymph node at baseline, a ≥ 50% decrease in the longest diameter of the single lymph node by CT AND no increase in any other lymph node by CT. Note: In a small lymph node < 2cm, an increase of < 25% is not considered to be significant.
- No new enlarged lymph nodes by CT or physical examination.
- ≥ 50% decrease in the enlargement of liver or spleen size from baseline or normalization by CT.

Plus a response in at least one of the following criteria independent of growth factor support or transfusion.* If all criteria are normal at baseline, they must remain normal to be considered a PR:

- ANC > 1500/µL or ≥ 50% improvement over baseline
- Platelets > 100,000/µL or ≥ 50% improvement over baseline
- Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline

* Note: For a criterion to be considered a response, it must have been evaluable at baseline.

Stable Disease

Not meeting criteria for CR, CRi, nPR, PR, PR with lymphocytosis, or progressive disease.

Progressive Disease

At least ONE of following:

- New enlarged nodes > 1.5 cm, new hepatomegaly, or new splenomegaly

- ≥ 50% increase from nadir in existing lymph node (must reach > 1.5 cm in the longest diameter) or ≥ 50% increase from nadir in sum of product of diameters of multiple nodes
- ≥ 50% increase from nadir in enlargement of liver or spleen
- ≥ 50% increase from baseline in lymphocyte count (and to ≥ 5000/µL) unless considered treatment-related lymphocytosis
- New cytopenia (hemoglobin or platelets) attributable to CLL. The progression of any cytopenia (unrelated to autoimmune cytopenia or bleeding), as documented by a decrease of hemoglobin levels from baseline by more than 2 g/dL or to < 10.0 g/dL, or by a decrease of platelet counts from baseline by more than 50% or to < 100,000/µL in the presence of active CLL defines disease progression. When applicable, a marrow biopsy should demonstrate an infiltrate of clonal CLL cells.
- Unequivocal progression for non-target lesions
- Transformation to a more aggressive histology (eg, Richter's Syndrome). Whenever possible, this diagnosis should be established by lymph node biopsy.

Suspected progressive disease must be confirmed by a serial examination at least 2 weeks later.

Measurable Disease

Patients must have at least 1 measurable site of disease to participate in this study. Measurable sites of disease are defined as lymph nodes or lymph node masses. Each measurable site of disease must be greater than 1.5 cm in its longest diameter. Measurement must be determined by imaging evaluation.

Patients may have a previously irradiated area from a malignancy prior to development of CLL. Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If there are tumor lesions in previously irradiated areas and progression has occurred, these lesions will be considered measurable. If tumor lesions in previously irradiated areas are present and have been stable, then these lesions are not considered measurable. If tumor lesions in previously irradiated areas progress during the study, then disease progression will be considered as having occurred, provided progression is confirmed.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures, as appropriate, including peripheral blood counts.

Richter's Transformation

Richter's syndrome is lymphomatous transformation to a more aggressive histology in a patient with CLL or SLL and is most often characterized by the development of high-grade NHL or Hodgkin's disease. Symptoms of Richter's transformation can include new or progressive

lymphadenopathy or organomegaly, fever, loss of weight and muscle mass, and other health problems. Richter's transformation can be suggested by a CT/PET scan, but must be confirmed with a biopsy (ie, lymph node) demonstrating the histologic transformation.

Minimal Residual Disease

MRD is defined as < 1 CLL cell per 10,000 leukocytes, as assessed by flow cytometry of a bone marrow aspirate and biopsy or peripheral blood sample.

Bone marrow biopsy and aspirate should be performed at Screening or up to 90 days before the first dose of study drug (mandatory only if cytopenias), and to confirm complete remission/response (CR) at disease evaluation in cycle 12 or cycle 20. In addition, bone marrow aspirate should be performed in any time point during follow-up when the MRD peripheral blood analyses become negative. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry on the aspirate; MRD should be also analyzed in peripheral blood. Patients in CR should be followed every 6 months for MRD by peripheral blood flow cytometry and in patients with negative CR and MRD in BM, every 12 months and at the time that the patient presents data with suspicion of relapse. The analysis of MRD will be performed in the department of Hematology of University Hospital of Salamanca

Appendix C: Sample collection

Blood samples will be collected from all subjects for determination of TP53 mutations, IGVH mutational status, and for flow citometry centralized diagnosis and MRD analysis according to Appendix A table.

The determination of TP53 mutations, and IGVH mutational status will be performed in the department of Hematology of Vall d'Hebron Hospital

The analysis of MRD by flow cytometry will be performed in the department of Hematology of University Hospital of Salamanca

Patients will be asked to donate the remaining part of any blood samples taken for central lab assessment at the Vall d'Hebron Hospital laboratories for later scientific research. Patients may participate in the main study without donating their left-over for research.

Left-over samples for additional research will be frozen in the laboratory of the department of Hematology , located at the University Hospital of Vall d'Hebron, Barcelona. Because scientific knowledge is continuously advancing and analytical techniques are continuously improving, it is currently not clear exactly what analyses will be done and which techniques will be used. However, it is certain that the research will be aimed only at improving the understanding and treatment of CLL. Decisions on the research to be conducted on stored samples will be made by the GELLC group. All information, including any genetic information obtained from research on the left-over blood samples, will remain confidential. Research samples will be stored securely but in a way that allows samples to be retrieved from the laboratories and destroyed, if needed (for example, if a patient wishes to withdraw his/her blood samples).

The following residual samples will be collected for research purposes: Residual serum and blood samples extracted under the study protocol for central lab assessment (any remaining blood from the TP53, and IGVH analyses) The Informed Consent Form will contain a separate section that addresses participation in the Vall Hebron storage of leftover samples. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason. Fill a separate, specific section in the Inform Consent Form will be required to document a patient's agreement to provide optional samples. The investigator should document whether or not the patient has given consent. Patients who give consent to provide leftover samples have the right to revoke such consent at any time without having to provide any reason for it. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Monitor and Sponsor in writing of the patient's wishes.

In this study samples will be treated in accordance with Law 14/2007 of 3 July, on Biomedical Research. A code will be assigned to the samples so the patients will not be identified. Only the study investigators will have access to this code.

For more information on the processing and shipping of biological samples, please refer to the "***Sample Shipping Manual***". This manual is provided in a separate document.

Appendix D: Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance

For serum creatinine concentration in mg/dL:

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

+ age in years, weight (wt) in kilograms

Appendix E: CIRS Scale (Cumulative Illness Rating Scale)[1]

Please bear in mind that the organ system affected by the disease being studied is not included in this rating scale.
If there are two or more illnesses or disorders of one organ system, the most severe illness or impediment should be evaluated.

ORGAN SYSTEMS	**Specify the illness (if applicable)** **Specify the most serious illness**	SCORE
Cardiac		0 – 1 – 2 – 3 – 4
Vascular		0 – 1 – 2 – 3 – 4
Respiratory		0 – 1 – 2 – 3 – 4
Eyes, ears, nose and throat		0 – 1 – 2 – 3 – 4
Upper gastrointestinal		0 – 1 – 2 – 3 – 4
Lower gastrointestinal		0 – 1 – 2 – 3 – 4
Hepatic and Pancreatic		0 – 1 – 2 – 3 – 4
Renal		0 – 1 – 2 – 3 – 4
Genitourinary		0 – 1 – 2 – 3 – 4
Musculoskeletal and cutaneous		0 – 1 – 2 – 3 – 4
Neurological		0 – 1 – 2 – 3 – 4
Endocrine, metabolic and breast		0 – 1 – 2 – 3 – 4
Psychiatric		0 – 1 – 2 – 3 – 4
TOTAL		

CIRS Comorbidity Classification

Score	
0	Not affected. Organs and systems not compromised.
1	Mild, does not interfere with normal activity, excellent prognosis.
2	Moderate, interferes with habitual activity, good prognosis.
3	Severe, debilitating, urgent surgical intervention, guarded prognosis.
4	Extremely severe, compromises life, severe prognosis.

[1] Adapted from Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968 May;16(5):622-6.