CLINICAL TRIAL PROTOCOL

PROTOCOL NUMBER: GELTAMO IMCL-2015

Sponsor: GEL/TAMO (Grupo Cooperativo Español de Linfoma/Trasplante Autólogo de Médula Ósea)
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PROTOCOL SIGNATURE PAGE

Protocol Number: GELTAMO IMCL-2015

Nº EudraCT: 2015-004158-17

Protocol version: V 3.2 September 16th, 2020

I have read this protocol and agree to conduct this test in accordance with all provisions of the protocol and the Declaration of Helsinki.

Sponsor Signature

Dr. Dolores Caballero

GELTAMO Chairman

Chief Investigator Signature

Dr. Eva Giné Soca

I have read this protocol and agree to conduct this test in accordance with all provisions of the protocol and the Declaration of Helsinki.

Signature

Principal Investigator

Confidential Statement

This document contains confidential information of GEL/TAMO that should not be disclosed to any person other study personnel and members of the Ethics Committee. This information cannot be used for any purpose other than evaluation or implementation of clinical research without the prior written consent of GEL/TAMO

Investigator acceptance

I have read the attached protocol entitled "Multicentric phase II trial to evaluate the efficacy and safety of Ibrutinib in combination with rituximab in patients with indolent clinical forms of Mantle Cell Lymphoma", version 3.2 September 16th, 2020, and I agree to abide all the provisions therein.

I agree to comply with the Tripartite Guideline for Good Clinical Practice.

I accept to ensure that confidential information contained in this document shall not be used for any purpose other than evaluation and conducting clinical research without the prior written consent of GEL/TAMO.

Signature

Principal Investigator	**Date (DD/Mon/AAAA)**

Revision sheet

Version	Date	Modification	Summary of changes	Rationale
1.0	Aug/31th /2015	First version submitted to ECs	NA	
1.1	Nov/20th /2015	First version approved by ECs	Administrative changes	Response to questions raised by the CEIC during the initial evaluation of the study.
1.2	Jun/6th/2016	No-substantial modification	The amended text has been included using bold italics in the following sections. Scheduled of administration is modified: - Section 1: Summary of the protocol, procedure section. -Section 5.2.1: Selection determinations -Procedure table, page 38 The bone marrow biopsy obtained in the previous 6 months and the PET-CT obtained in the 3 months prior to inclusion in the study are accepted as baseline tests. **A broader interval for these baseline tests may be considered for specific cases.** Section 3.4.1: ibrutinib Patients should take 4 capsules of ibrutinib (total dose 560 mg) once daily from D1, Cycle 1. **The capsules should be administered orally with a glass of water, approximately at the same time each day. The capsules should be swallowed whole with water and should not open, break or chew.** Patients should avoid the consumption of foods and beverages containing grapefruit and Seville oranges during the duration of the study due to the inhibition of cytochrome 3A4/5. **If the patient does not take a dose at the scheduled time, he/she can take it as soon as possible at same day and return to normal schedule the next day. The patient should not take extra capsules to make**	The method of administration of Ibrutinib is modified in protocol to be consistent to what is described in the Summary of Product Characteristics (SmPC). This modification is performed because an administrative error is detected in the text of the protocol with reference to the procedure of administration of ibrutinib with respect to what is approved in the SmPC, submitted in protocol evaluation dossier. The type of premedication used prior to infusion of Rituximab is modified in protocol text to be consistent to what is described in the SmPC (presented together with the protocol evaluation dossier) and Sites clinical practice, usually followed for this type of patients. Also, longer interval of time have been accepted for baseline PET and bone marrow biopsy for specific cases, in baseline study procedures. Several typographical errata are corrected.

			up for the missed dose. And Rituximab premedication Seccion 3.4.2: Before the infusion of Rituximab **it is recommended to administer Site common practise pre-medication that includes:** 1. **Antipyretic** 2. **Antihistaminic** 3. Optionally, at the discretion of the investigator, use of glucocorticoids (i.e. methylprednisolone 60 mg iv) as part of the pre-medication and in case of reaction to rituximab Administrative changes.	
2.0	Dec/30th/2016	Substantial modification	The modified text has been included in **bold and italic** and the deleted text is crossed out in the following sections of the protocol (see Table of Changes: Previous-New-Text with detailed changes in each section of the protocol) Update on safety information Selection Criteria	Changes to the protocol are implemented because it is intended to incorporate the new safety information described in the latest edition of the Investigator's Manual, Investigator's Brochure - Edition 10 of the IMP IBRUTINIB whose manufacturer is Janssen Cilag International NV (Commercial Authorisation Number EU/1/14/945/002). In addition, in order to avoid future changes that may be carried out as a result of the periodic safety updates of the Researcher's Manual, it is decided to cross-reference the most current edition of the Investigation Brochure and the Summary of Product Characteristics in corresponding Protocol sections (except for the patient information sheet) where the safety information of the IMP is already contained in the Investigator Brochure. Study selection criteria related to

				lymph node size are modified to facilitate the inclusion of patients with lymph node size less than 3 cm in maximum diameter (instead of 2.5 cm) provided that the Patient does not present criteria for treatment.
			Response definition	Section 5.3.1 response definition and reference number 13 of the protocol “biography” according to modified criteria for evaluating the response for non-Hodgkin's lymphoma because it is intended to use the current response assessment recommendations, according to Lugano classification and Deauville scoring system.
			Concomitant treatments	It is added in the concomitant treatment section the recommendation for the use of antimicrobial prophylaxis, according to Sites local guidelines and patient's risk, (ie pneumonia prophylaxis by pneumocystis with sulfamethoxazole and trimethoprim or equivalent) to maximize the safety of the study, even though there are no formal recommendations at this time.
			Statistical considerations	Section 7 of protocol “Statistical Considerations” is modified to indicate that the second stage of the study will begin when 6 or more complete responses be observed in patients assessed with thoracoabdominal and bone marrow aspirate in the evaluation of sixth month, from the beginning of the therapy (rather than the 12 months initially planned). This change will allow continuing to include patients in the study ensuring adequate treatment efficacy to justify to move to the second stage, but without penalizing excessively the study total recruitment time and reach the total number of foreseen 50 patients. This modification does not affect the periodic patient determinations nor the objectives of the study.
			Administrative changes	Typographical, formatting mistakes are revised and corrected, administrative changes.
3.2	Sep/16th/2	Substantial	The modified text has been	

	020	modification	included in red color and the deleted text is ~~crossed out.~~ Consult separate document (Previous Text - New Text with all the changes detailed in each section of the protocol)	
			Duration of treatment / follow-up	The maximum treatment / follow-up time is extended by 3 more years, from 4 years to a total of 7 years. Clarification of the criteria for treatment interruption is made.
			Study duration	The maximum trial duration is extended from 7 to 10.5 years with no variation in previously described tests and assessment intervals for patients. Clarification is made about the study completion criteria.
			Procedures	Local assessment of marrow status with bone marrow aspiration is indicated as mandatory (rather than optional) during screening and after 12 months to adjust it to standard clinical practice and facilitate the detection and monitoring of the minimum residual disease. Part of these samples will be sent to the central laboratory for biomarker and minimal residual disease studies described in this protocol.
			Administrative changes	Typographical and format errors are rectified and corrected, the reference of the new data protection regulation is updated, the contact point for the notification of security events is updated and the study annexes are updated

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ABBREVIATIONS AND ACRONYMS

SAE	Serious Adverse Event
CRF	Case Report Form
ECOG	Eastern Cooperative Oncology Group
GEL/TAMO	Grupo Español de Linfoma/Trasplante Autólogo de Médula Ósea
IPI	International Prognosis Index
MCL	Mantle Cell Lymphoma
DLBCL	Diffuse large B-cell lymphoma
NHL	No Hodgkin Lymphoma
WHO	World Health Organization
PET	Positron emission tomography
CR	Complete Remission
R-CHOP	Rituximab-CHOP
OR	Overall Response
OS	Overall Survival
PFS	Progression Free Survival
CNS	Central Nervous System
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal

1. STUDY SYNOPSIS

Study Title	Multicentric phase II trial to evaluate the efficacy and safety of Ibrutinib in combination with rituximab in patients with indolent clinical forms of Mantle Cell Lymphoma
Protocol Number:	GELTAMO IMCL-2015
Protocol Version:	3.2 September 16th, 2020
Chief Investigator	Dra. Eva Giné Soca Haematology Department Hospital Clinic de Barcelona C/ Villarroel 170 08036 - Barcelona Tel. +34 932275475
Type of application	Clinical trial of a marketed medicinal product in new indication.
Study phase	Phase II
Indication	Untreated patients with indolent clinical forms of Mantle Cell Lymphoma
Study design	Phase II study with a two-stage design to evaluate efficacy and safety of ibrutinib in combination with rituximab (I+R) in untreated patients with indolent clinical forms of MCL. An extensive biological study will be conducted in order to further characterize this population of MCL patients and evaluate the response obtained with the mutational profile of the tumor.
Number of subjects	50 patients
Study duration	The maximal trial duration will be ~~seven~~ 10,5 years with ~~3~~ 3,5 years of recruitment. The study can stop earlier based on the results obtained in the first 15 recruited patients. Version 3.2: September 16th, 2020
Primary Objectives	1. To assess the efficacy of I+R combination as a therapeutic alternative to immuno-chemotherapy (R-CHOP regimen) in indolent clinical forms of MCL
Secondary Objectives	1. To evaluate the efficacy of I+R combination along time in terms of ORR, PFS, response duration, OS, MRD analysis) 2. To determine the safety and tolerability of ibrutinib in combination with rituximab 3. Biological characterization of indolent clinical forms of MCL and their response to I+R by genomic studies

Primary Endpoints	1. Rate of complete remission (CR) achieved at 12 months of I+R combination.
Secondary Endpoints	1. To determine the overall response rate (ORR) at 12 months, Progression free survival (PFS), duration of response (DOR) and overall survival (OS). 2. To determine the rate of negative minimal residual disease (MRD), the time to obtain a molecular response and the median duration of the molecular response in I+R responding patients. 3. Rates of AEs, SAEs, and SUSARs by CTC grade (Version 4.03) during I+R treatment 4. To assess the health-related quality of life (QOL) during treatment. 5. Genomic studies in indolent clinical forms of MCL (IGHV mutational status, DNA copy-number and whole exome sequencing).
Sample Size	First Stage: 15 patients Second Stage: If at least 6 patients show a complete response during first stage, the study will continue until inclusion of 50 patients.
Summary of subject eligibility criteria	**INCLUSION CRITERIA** 1. Subjects with confirmed diagnosis of Mantle Cell Lymphoma (World Health Organization Classification, WHO 2008). Classical, small-cell variants and marginal-zone variants can be included. 2. Age 18 years or older. 3. Subjects must not have received any prior therapies (excluding diagnostic splenectomy). 4. Asymptomatic patients. 5. Ann Arbor clinical stages I-IV. 6. Eastern Cooperative Oncology Group (ECOG) performance status <2 (0-1). 7. Subjects with a non-nodal MCL presentation with mainly bone marrow or peripheral blood involvement. 8. Other asymptomatic clinical presentations are acceptable in case of low tumor burden, including nodal MCL with lymph node enlargement ≤ 3 cm in the maximum diameter and with low proliferation index (Ki-67 ≤ 30%). 9. The following laboratory values at screening: ▪ Neutrophil count ≥ 1×10e9/L, Hemoglobin level ≥ 100 g/L or platelet count ≥100×10e9/L ▪ Transaminases (AST and ALT) ≤ 3 x ULN ▪ Total bilirubin ≤1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin ▪ Creatinine ≤ 2 x ULN or calculated creatinine clearance ≥ 40 mL/min/1.73 m^2 10. Stable disease without evidence of clinical progression criteria for at least 3 months. Patients in prolonged therapeutic abstention may be included. 11. Women of childbearing potential and men who are sexually

active must be practising a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.

12. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.

13. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

EXCLUSION CRITERIA

1. Aggressive histological variants: blastic and pleomorphic variants (blastoid).
2. Proliferation index measured by Ki-67 > 30%.
3. B-cell monoclonal lymphocytosis with MCL phenotype
4. Eastern Cooperative Oncology Group (ECOG) performance status ≥2.
5. Presence of B symptoms or any relevant symptoms related to the MCL.
6. Nodal clinical forms with lymph node enlargement > 3 cm (maximum diameter).
7. Cytopenias attributable to MCL: Neutrophil count < 1×10e9/L, Hemoglobin level < 100 g/L or platelet count < 100×10e9/L.
8. Organ dysfunction related to MCL including creatinine level > 2 x ULN or altered liver biochemistry (> 3x ULN).
9. Gradual increase in different determinations of serum LDH attributable to MCL that exceeds 20% of the ULN.
10. Known CNS infiltration.
11. Subjects with expected therapy requirement for MCL in a short time (< 3 months)
12. Patients with active hepatitis B or C infection or HIV infection. Positive test results for chronic HBV infection (defined as positive HBsAg serology) or positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing) will be excluded with the following exceptions. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing or antiviral prophylaxis. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible. Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
13. Anticoagulation requirement with vitamin K antagonists.
14. Past medical history of stroke or intracranial haemorrhage within 6 months prior to inclusion.
15. Required medication with strong CYP3A4/5 inhibitors

	16. Any serious comorbidity that makes the patient unacceptable for receiving the treatment. 17. Concomitant or previous malignancies the last 2 years other than basal skin cancer or in situ uterine cervix cancer. 18. Pregnancy or lactation. 19. Major surgery within 4 weeks of inclusion. 20. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification. 21. Vaccinated with live, attenuated vaccines within 4 weeks of randomization. 22. Uncontrolled systemic infection requiring intravenous (IV) antibiotics. 23. 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.
Prohibitions and Restrictions	Ibrutinib will be held in the perioperative period. At least 7 days before and after a major surgical intervention and 3 days before and after a minor intervention.
Dosage and formulation of medication	Subjects will receive the ibrutinib in combination with rituximab according to the following schedule: - Ibrutinib 560 mg daily po for 28 days (cycle one). Continuous cycles until disease progression or unacceptable toxicity. In case of sustained negative MRD (at least for 6 months) after 2 years of continuous therapy, ibrutinib will be discontinued. - Rituximab 375 mg/m^2 iv day 1,8, 15 and 22 (cycle 1, 4 doses). Rituximab 375 mg/m^2 iv, day one of every other cycle for 4 doses (cycle 3, 5, 7 and 9). Ibrutinib will be provided by Janssen.
Study procedures	**<u>A. Prior to treatment initiation (screening):</u>** Within a maximum of 28 days* pre-treatment study test will be performed and then, the medication will be started. ● Informed consent, Clinical History, demographics, physical examination, ECOG, vital signs. ● Local laboratory pathology diagnosis. ● Biochemistry and CBC*. ● Serology, protein electrophoresis and serum immunofixation. ● Coagulation test. ● Pregnancy test (performed on blood or urine) in women of childbearing potential. ● Disease assessment: PET/CT. ● Electrocardiogram.

- Left ventricular ejection fraction (optional, only mandatory in patients with a history of heart disease).
- Bone marrow biopsy.
- Bone marrow aspirate (with local study by flow cytometry and sending for MRD study), ~~optional and recommended in cases exclusively involving bone marrow and peripheral blood.~~

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- Concomitant medication
- Quality of Life questionnaires
- Tumor samples for molecular sub-study and MRD study.

* Baseline laboratory should be done, at the most, in the previous week.

Bone marrow biopsy and PET-CT obtained 6 months and 3 months prior randomization will be accepted as baseline tests. A larger interval for these baseline tests may be considered for specific cases.

B. Treatment phase (up to 12 months from inclusion):

Prior each treatment cycle (monthly visits):

- Anamnesis, physical examination, ECOG, vital signs.
- Biochemistry and CBC.
- Concomitant medication.
- Adverse events.

At 6 months from treatment initiation:

- CT scan.
- ~~Optional~~ Assessing of bone marrow aspirate (with local flow cytometry and sending for MRD study) in forms with exclusively marrow involvement and peripheral blood at diagnosis.
- Assessing of minimal residual disease (MRD) in peripheral blood by RQ-PCR.

At 12 months from treatment initiation, response assessment will be performed:

- Quality of Life questionnaires.
- PET/CT.
- Bone marrow biopsy.
- ~~Optional:~~ Bone marrow aspirate (with local study by flow cytometry and sending for MRD study).

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- Minimal residual disease (MRD) in peripheral blood assessment by RQ-PCR.

C. Treatment and Follow-up phase (from 12 months~~2nd year~~ up to the end of study ~~follow-up~~):

Quarterly visits to be conducted that will include:

- Anamnesis, physical examination, ECOG, vital signs.
- Biochemistry and CBC.
- Concomitant medication.
- Adverse events.

Every 6 months up to ~~4~~ 7 years from the inclusion or end of study ~~follow-up~~):

- CT scans.
- Minimal residual disease (MRD) in peripheral blood assessment by RQ-PCR.

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	D. End of Treatment~~Study~~ Visit: At day 30 after end~~completion~~ of study treatment by any cause: anamnesis, physical examination, ECOG status and vital signs, CBC, biochemistry, CT Scan, minimal residual disease (MRD) in peripheral blood assessment by RQ-PCR, concomitant medication, adverse events, quality of life questionnaires (see section 4.2.3) After the end of treatment visit, the patient will continue to carry out the scheduled evaluations during the follow-up until the end of the study. Version 3.2: September 16th, 2020
Calendar	Inclusion period initiation: May of 2016 End of recruitment: December, 2019~~Mayo of 2019~~ End of Study: December, 2026~~May of 2023~~ Version 3.2: September 16th, 2020
Number of Sites	15 sites

2. RATIONALE AND OBJECTIVES

2.1 RATIONALE

Patients with mantle cell lymphoma (MCL) have a median survival of 3-5 years despite treatment. Indeed, the best therapeutic approach for different patients with MCL remains to be established, coexisting different options of immunochemotherapy regimens which may include autologous transplantation in first-line treatment or rituximab maintenance(2).

Moreover, last years MCL starts to be recognized as a heterogeneous disease both from biological and clinical standpoints. For instance, MCL cases with a non-nodal clinical presentation, usually have distinctive biological features such as SOX-11 negativity, hypermutated IGHV genes and a low number of genetic lesions associated to (11;14). The outcome of these cases is much more favourable compared to conventional MCL, reaching median survivals over 7 to 10 years even receiving less intensive treatments (3-5). In addition to that, up to 30% of the patients with newly diagnosed MCL can be safely deferred from initial therapy until progression (6,7). Therapeutic abstention may be prolonged for more than one year in 50% of cases. These patients usually show longer survivals from the start of treatment compared to patients immediately treated after diagnosis (6). Therefore, all these observations indicate that there are indolent clinical forms in MCL, so its clinico-biological identification is crucial to tailor treatment appropriately. However, at present there is no consensus on the diagnostic criteria or treatment recommendations in cases of indolent MCL. This results in difficulties for the identification of these forms in the clinical practice as well as with a certain therapeutic indefinition, as indolent forms of MCL can be treated either with therapeutic abstention until progression or receive immediate treatment with conventional or more intensive immuno-chemotherapy regimes, which may even include an autologous hematopoietic stem cell transplantation. With the emergence of new biological agents in the therapeutic arsenal of MCL arises the question whether a completely different approach with new drugs and chemotherapy-free could be more appropriate in selected subsets of patients such as indolent MCL forms.

Among the new drugs under development, Ibrutinib is showing an impressive efficacy in relapsed and refractory patients (8-9), which has led to its approval by the FDA and EMA agencies, in this context. Ibrutinib alone is able to induce 68% of responses in heavily pre-treated patients with MCL, including up to 21% of complete responses. The median time to achieve a CR was of 5.5 months (2-12 months). Moreover, ibrutinib in combination with rituximab appears to be a feasible and highly effective treatment in the relapse and refractory setting. The overall response rate was superior to 85%, including CR in 38% of cases. Moreover, MCL patients with a lower proliferation index (Ki-67 < 50%) achieved CR in up to 48% of the cases.

These promising results provide an excellent opportunity of treating in front-line selected MCL patients with a chemo-free approach, probably this resulting in a more efficient and less toxic manner of treating these patients. In this sense, we hypothesize that MCL cases with an indolent clinical presentation, not requiring the immediate initiation of therapy, would be excellent candidates to receive Ibrutinib in combination with rituximab in first line treatment.

Likewise, this trial offers an unbeatable platform to comprehensively and prospectively study the biological characteristics of this selected group of patients, which will allow to improve their future clinical-biological identification and to deepen the knowledge of the response and resistance mechanisms. to new drugs. For this reason it has been contemplated to associate an extensive and complete molecular study, which includes the total sequencing of exomes from these patients.

MCL similarly to what has been observed in other lymphoproliferative disorders, could show subclonal heterogeneity even at diagnosis and this fact might condition the ulterior clinical behaviour of the tumor (10). In addition, there has been recently described the involvement of the alternative NF-kB pathway in the resistance of BCR inhibitors by the identification of several mutations in NF-kB regulatory genes that confer resistance to these biological agents (11).

This observation enhances the need of collecting fresh samples in the setting of well-designed trials to elucidate the role of new therapies in these patients. As peripheral blood is involved in a

meaningful proportion of MCL patients (12), this allows the collection of both tumor and normal DNA and RNA, in an easy and convenient way. Therefore, peripheral blood has been selected as primary source for the biologic study.

Finally, we think that patients with asymptomatic MCL and clinically stable for at least 3 months, including forms with a non-nodal presentation but also selected nodal cases with a low tumor burden, would be excellent candidates to receive a frontline combination of Ibrutinib and rituximab. An extensive biological characterization of these cases is planned in order to try to improve its identification in the future and to evaluate the impact of molecular features on responses to treatment and relapse. This effort will help clinicians to better recognize indolent MCL and also will facilitate the design of a specific therapeutic approach to these patients.

2.2 OBJECTIVES

Primary

1. To explore the efficacy of I+R combination as a therapeutic alternative to immuno-chemotherapy (R-CHOP regimen) in indolent forms of MCL by assessing the rate of complete responses achieved at 12 months of treatment.

Secondary

1. To evaluate the efficacy of I+R combination along time in terms of secondary endpoints (ORR at 12 months, PFS, response duration, OS, MRD analysis)

2. To determine the safety and tolerability of ibrutinib in combination with rituximab (including evaluation of health-related quality of life (QOL))

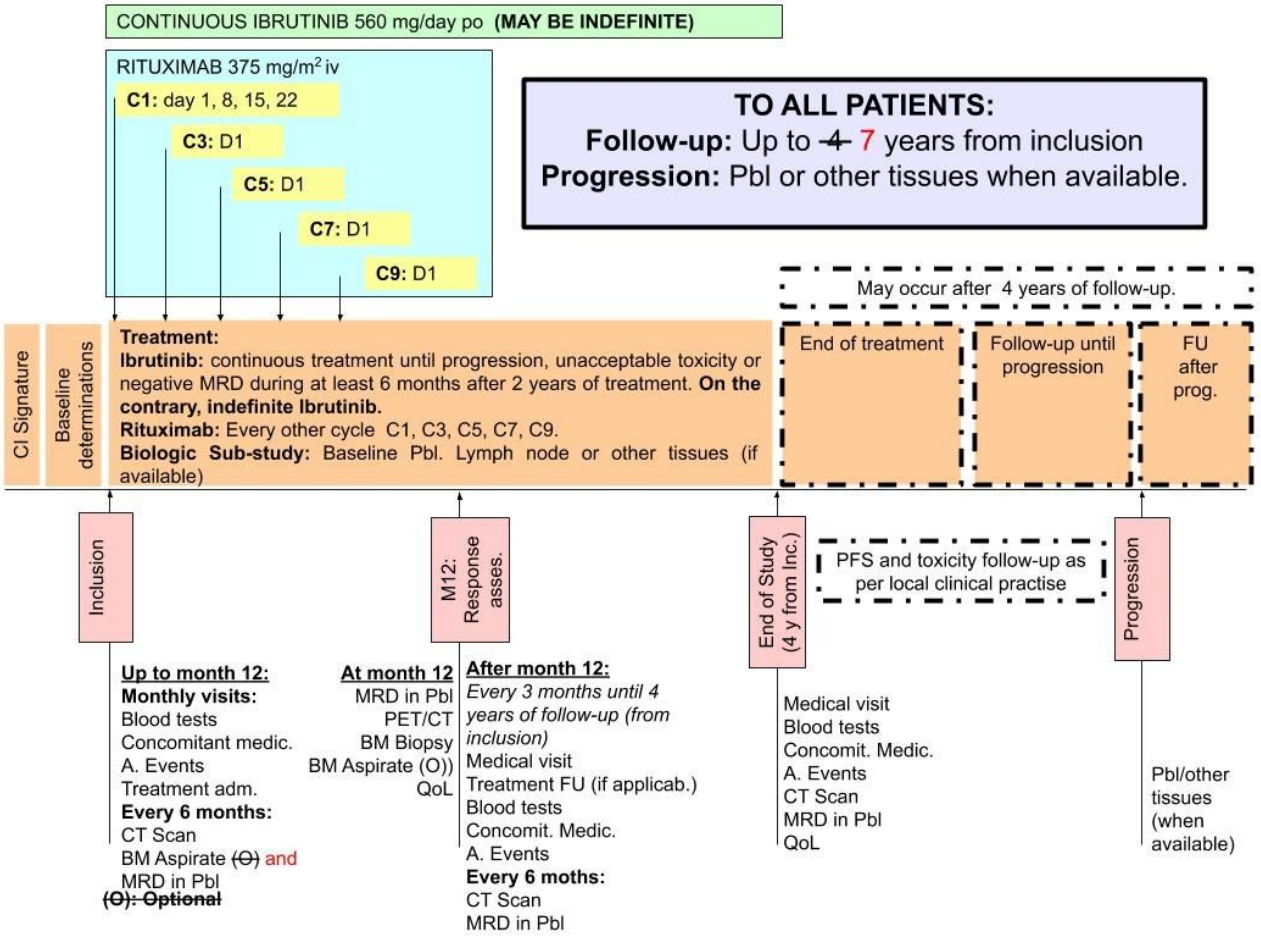
3. Biological characterization of indolent forms of MCL and their response to I+R by genomic studies

3. STUDY DESIGN AND TREATMENT DESCRIPTION

3.1 DEVELOPMENT PHASE

Phase II exploratory clinical trial.

3.2 STUDY SCHEMA



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3.3 TREATMENT PLAN

Subjects will receive ibrutinib in combination with rituximab according to the following schedule:

- Ibrutinib 560 mg daily po for 28 days (cycle one). Continuous cycles until disease progression or unacceptable toxicity. In case of sustained negative MRD (at least for 6 months) after 2 years of continuous therapy, ibrutinib will be discontinued.
- Rituximab 375 mg/m^2 iv day 1,8, 15 and 22 (cycle 1, 4 doses). Rituximab 375 mg/m^2 iv, day one of every other cycle for 4 doses (cycle 3, 5, 7 and 9).

This clinical trial includes:

- Central review of response by imaging.
- Histological central laboratory review of diagnosis.
- Biological Associated Project.

Within a maximum of 28 days pre-treatment study test will be performed (except BMO and PET-CT, that are admissible if are obtained within six months and three months respectively in patients with clinical stability) and then the medication is started. Tests to be performed and related details are described in section 4.2 of this protocol.

1. Patient Screening Procedure:

Before starting the selection period, the patient's informed consent should be obtained, using the latest version in force throughout the entire trial. Different procedures performed as part of routine clinical management of the patient (e.g., blood tests, imaging tests, etc.) and made before the informed consent signature can be used for selection or basal if these tests were carried out as specified in this protocol. Once the informed consent is signed, a screening number will be assigned to each patient (screening code). Each site will receive in the Investigator Site File, the screening form in which default numbers are assigned for the screenings. This document must always remain in study site in the custody of the research team. This selection number will identify patients during the period from informed consent signature to the inclusion in the study.

2. Patient Inclusion Procedure:

After confirming that a patient is a candidate for inclusion in this study (inclusion / exclusion criteria), the inclusion (registration) procedure should be done centralized in MFAR.

The recruitment period will be of ~~3~~ 3.5 years (~~expected~~ from May~~January~~ 2016 to December~~January~~ 2019).

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The patient inclusion procedure is described below:

1. Complete and sign the inclusion form for the patient (the registration form must be signed by a clinical Principal Investigator or designated, appropriately identified in the signature list and registration delegation of responsibilities).
2. Send the completed and signed form to:

MFAR, S.L.

FAX (+ 34 93 253 11 68) o e-mail a investigacion@mfar.net

3. MFAR, will carry out the registration process of the patient.
4. MFAR Will reply to sites, sending both by fax and email the inclusion confirmation

form for the patient. The inclusion confirmation form contains the patient code for this study, which will identify the patient throughout the trial.

5. Once the site staff has received form MFAR the inclusion confirmation form, the patient can start study treatment.

3.4 PROTOCOL MEDICATION

3.4.1. Ibrutinib

Ibrutinib 560 mg daily po for 28 days (cycle one). Continuous cycles until disease progression or unacceptable toxicity. In case of sustained negative MRD (at least for 6 months) after 2 years of continuous therapy, ibrutinib will be discontinued.

Patients should take 4 capsules of ibrutinib (total dose 560 mg) once daily from D1, Cycle 1. The capsules should be administered orally with a glass of water, approximately at the same time each day. The capsules should be swallowed whole with water and should not open, break or chew. Patients should avoid the consumption of foods and beverages containing grapefruit and Seville oranges during the duration of the study due to the inhibition of cytochrome 3A4/5.

If the patient does not take a dose at the scheduled time, he/she can take it as soon as possible at same day and return to normal schedule the next day. The patient should not take extra capsules to make up for the missed dose.

Ibrutinib supply: Ibrutinib will be supplied by the Sponsor, through Janssen Laboratory.

3.4.2. Rituximab

Rituximab 375 mg/m^2 iv day 1,8, 15 and 22 (cycle 1, 4 doses). Rituximab 375 mg/m^2 iv, day one of every other cycle for 4 doses (cycle 3, 5, 7 and 9).

Before Rituximab infusion, it is recommended to administer Site local practise pre-medication that includes: se recomienda administrar pre-medicación habitual de cada centro que incluya:

1. Antipyretic

2. Antihistaminic

3. Optionally, up to the investigator's discretion the use of glucocorticoids (i.e.: methylprednisolone 60 mg iv) as part of the pre-treatment and in case of rituximab reaction.

Rituximab administration will be done by intravenous infusion. The prepared solution should be administered as an intravenous infusion through a dedicated line. It should not be administered as an intravenous push or bolus. The first infusion will begin at a rate of 50 mg/hour after the first 30 minutes, it could be done increments of 50 mg / hr every 30 minutes to a maximum of 400 mg/hour. Subsequent infusions can be infused at an initial rate of 100 mg / hr being increased to 100 mg / hour at intervals of 30 minutes to a maximum of 400 mg / hour.

Rituximab supply: Rituximab, treatment commercially available and indicated in all MCL national and European guidelines will be provided by participating Hospital through the local supply procedure, after positive vote of the EC and Institution Conformity.

3.4.3 Ibrutinib possible adverse events

The following information detailed the possible adverse events of Ibrutinib. It should also consider the information regarding contraindications, warnings, precautions for use and possible interactions with other drugs, available at:

- Last version of Investigator Brochure available at Investigator Site File.

- Last Version of Summary of Product Characteristics (SmPC), available at the Investigator Site File or at EMA website:

http://www.ema.europa.eu

3.4.4 Possible adverse events of other drugs used in the trial

For the rest of drugs administered to trial subjects, it should be considered the information regarding contraindications, warnings, precautions for use and possible interactions, available at:

- Summary of Product Characteristics (SmPC), available at the Investigator Site File or at EMA website:

http://www.ema.europa.eu

3.5 DOSE ADJUSTMENTS

3.5.1. Ibrutinib Dose adjustments

Ibrutinib therapy should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), Ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, the once daily dose should be reduced by one capsule (140 mg). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue the medicinal product.

Recommended dose modifications are described below:

Dose level	Dose
0	560 mg/day
-1	420 mg/day
-2	280 mg/day
Discontinue Ibrutinib	

Missed dose

If a dose is not taken at the scheduled time, 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.

3.5.2 Rituximab dose adjustment

The increase or reduction in dose infusions is not contemplated. Mild or moderate infusion-related reactions usually resolve by reducing the infusion rate and increasing it when symptoms improve.

Patients should be closely monitored for detecting the start of a cytokine release syndrome. The infusion should immediately stop in patients who develop any evidence of severe reactions, especially severe dyspnoea, bronchospasm or hypoxia. Then it should be evaluated the evidence of tumor lysis syndrome including appropriate laboratory tests, and evidence of pulmonary infiltration by chest radiography. No patient infusion should be restarted until complete resolution of all symptoms, and normalization of laboratory values and chest x-ray results. From that moment, the infusion may initially restarted at most half the rate of previous infusion. If the same severe adverse reactions would be presented for a second time, the decision to stop treatment, it should be discussed with the trial chief Investigator (investigacion@mfar.net), on a case by case basis.

It has been reported that, following IV administration of murine proteins, anaphylactic and hypersensitivity reactions can be observed, which typically occur during the first minutes of the infusion. It is convenient to have for immediate use, drugs used to combat hypersensitivity reactions, i.e., epinephrine, antihistamines and corticosteroids, in case an allergic reaction occurs during administration. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Since hypotension may occur during rituximab infusion, it should be considered to withhold anti-hypertensive medicines 12 hours prior to the infusion. It has been described angina pectoris or cardiac arrhythmias such as flutter and atrial fibrillation, heart failure or myocardial infarction in patients treated with rituximab. Therefore, patients with a history of cardiac disease and/or cardiotoxic chemotherapy, should be closely monitored.

Reactivation of hepatitis B, which included cases of fulminant hepatitis in patients who were treated with rituximab with cytotoxic chemotherapy have been observed. When rituximab is used in combination with cytotoxic chemotherapy, patients with a history of hepatitis B should be closely monitored for signs of active infection by the hepatitis B virus, and start antiviral treatment if clinically indicated.

3.6 TREATMENT WITHDRAWAL CRITERIA

In the event of sustained negative MRD (at least 6 months) after 2 years of continuous treatment, the investigator should withdraw ibrutinib treatment.

In addition, the investigator, for reasons of medical urgency, must withdraw the patient from the study treatment according to the following criteria:

1. Disease Progression: Patients that present progression will discontinue the treatment
2. Unacceptable toxicity

~~3. Negative MRD at least for 6 months after 2 years of treatment~~

3.~~4.~~ Patient non-compliance~~Investigator decision~~

4. ~~5.~~ Patient rejection to continue study treatment

Patients who complete treatment will undergo the end-of-treatment testing and evaluation schedule as described in section 5.2.4

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3.7 CONCOMITANT TREATMENTS

Concomitant treatments include all prescription and non-prescription drugs used by the patient from 7 days before starting the study treatment until 30 days after the last study medication. The attending physician will prescribe the necessary treatments appropriate to concomitant diseases presented by any patient included in the study. The patient must inform to the investigator and record all concomitant medications in the relevant eCRF.

Patients using oral contraceptives, hormone replacement therapy or other maintenance treatments, should continue using it.

a. Treatment and prophylaxis for neutropenia

In this study the use of G -CSF to treat neutropenia is allowed.

Primary prophylaxis with G -CSF is recommended under the guidelines of ASCO, EORTC, ESMO and(15).

b. Hepatitis B reactivation prophylaxis

Lamivudine or other antiviral treatments have to be considered to patients at risk of reactivation of hepatitis B (i.e. HBcAc+).

c. Antimicrobial prophylaxis

It is recommended the use of antimicrobial prophylaxis (ie pneumonia prophylaxis by pneumocystis with sulfamethoxazole and trimethoprim or equivalent), according to Sites local guidelines

3.7.1 Ibrutinib Interaction with other medicinal products and other forms of interaction

You can obtain detailed information in:

- Last version of Investigator Brochure available at ISF
- Last version of Summary of Product Characteristic available at ISF and at EMA website:

https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_es.pdf

3.7.2 Rituximab Interaction with other medicinal products and other forms of interaction

It should take into account information on possible interactions with other drugs for other therapeutic drugs referred to in the trial scheme, available at:

Summary of product characteristics available at the investigator site file or at EMA website:

http://www.ema.europa.eu

4. PATIENT ELIGIBILITY CRITERIA

4.1 INCLUSION CRITERIA

1. Subjects with confirmed diagnosis of Mantle Cell Lymphoma (World Health Organization Classification, WHO 2008). Classical, small-cell variants and marginal-zone variants can be included.
2. Age 18 years or older.
3. Subjects must not have received any prior therapies (excluding diagnostic splenectomy).
4. Asymptomatic patients.
5. Ann Arbor clinical stages I-IV.
6. Eastern Cooperative Oncology Group (ECOG) performance status <2 (0-1).
7. Subjects with a non-nodal MCL presentation with mainly bone marrow or peripheral blood involvement.
8. Other asymptomatic clinical presentations are acceptable in case of low tumor burden, including nodal MCL with lymph node enlargement ≤ 3 cm in the maximum diameter and with low proliferation index (Ki-67 ≤ 30%).
9. The following laboratory values at screening:
    - Neutrophil count ≥ 1×10e9/L, Hemoglobin level ≥ 100 g/L or platelet count ≥ 100×10e9/L
    - Transaminases (AST and ALT) ≤ 3 x ULN
    - Total bilirubin ≤ 1.5 x ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
    - Creatinine ≤ 2 x ULN or calculated creatinine clearance ≥ 40 mL/min/1.73m^2
10. Stable disease without evidence of clinical progression criteria for at least 3 months. Patients in prolonged therapeutic abstention may be included.
11. Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. For males, these restrictions apply for 3 months after the last dose of study drug.
12. Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [ß-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
13. Sign (or their legally-acceptable representatives must sign) an informed consent document indicating that they understand the purpose of and procedures required for the study, including biomarkers, and are willing to participate in the study.

4.2 EXCLUSION CRITERIA

1. Aggressive histological variants: blastic and pleomorphic variants (blastoid).
2. Proliferation index measured by Ki-67 > 30%.
3. B-cell monoclonal lymphocytosis with MCL phenotype.
4. Eastern Cooperative Oncology Group (ECOG) performance status ≥2.
5. Presence of B symptoms or any relevant symptoms related to the MCL.
6. Nodal clinical forms with lymph node enlargement > 3 cm (maximum diameter).
7. Cytopenias attributable to MCL: Neutrophil count < 1×10e9/L, Hemoglobin level < 100 g/L or platelet count < 100×10e9/L.
8. Organ dysfunction related to MCL including creatinine level > 2 ULN or altered liver biochemistry (> 3x ULN).
9. Gradual increase in different determinations of serum LDH attributable to MCL that exceeds 20% of the ULN.
10. Known CNS infiltration.
11. Subjects with expected therapy requirement for MCL in a short time (< 3 months).
12. Patients with active hepatitis B or C infection or HIV infection. Positive test results for chronic HBV infection (defined as positive HBsAg serology) or positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing) will be excluded with the following exceptions. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing or antiviral prophylaxis. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible. Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
13. Anticoagulation requirement with vitamin K antagonists.
14. Past medical history of stroke or intracranial haemorrhage within 6 months prior to inclusion.
15. Required medication with strong CYP3A4/5 inhibitors.
16. Any serious comorbidity that makes the patient unacceptable for receiving the treatment
17. Concomitant or previous malignancies the last 2 years other than basal skin cancer or in situ uterine cervix cancer.
18. Pregnancy or lactation.
19. Major surgery within 4 weeks of inclusion.
20. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification.
21. Vaccinated with live, attenuated vaccines within 4 weeks of randomization.
22. Uncontrolled systemic infection requiring intravenous (IV) antibiotics.
23. 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.

4.3 PROHIBITIONS AND RESTRICTIONS

The following guidance should be applied during the perioperative period for subjects 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 serosanguineous 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.

4.4 PREMATURE DISCONTINUATION~~END~~ OF STUDY CRITERIA

It will encourage patients to comply with the treatment, visits and procedures scheme until the end of the study is reached as described in section 5.2.5 ~~complete the trial~~, however, patients can voluntarily leave the trial at any time.

~~The investigator may also, at its discretion, withdraw patients from this trial, or the Sponsor may discontinue the trial.~~

The reasons for premature study discontinuation by the patient should be documented in the case report form (CRF) as:

- ~~The trial is closed/ended.~~
- Patient lost of follow up.
- ~~Investigator decision.~~
- Patient informed consent withdrawal .
- ~~Major protocol deviation, when applicable.~~
- Death.

Both the date of withdrawal from the study and the cause of withdrawal will be recorded in the CRF.

Post-treatment and follow-up up to death will be determined ensuring the patient's medical care according to clinical practice. In case of death, it should as far as possible, to obtain the certificate with the cause of death.

Note: Patients who leave the trial for any reason, will not be enrolled again.

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5. STUDY DEVELOPMENT AND RESPONSE ASSESSMENT

5.1 STUDY ENDPOINTS

Primary Endpoint:

1. Rate of complete remission (CR) achieved at 12 months with Ibrutinib in combination with Rituximab. All the patients will be evaluated with PET-CT and bone marrow biopsy at that point and the international response criteria will be applied (13).

Secondary Endpoints:

1. Overall Response Rate (ORR) achieved at 12 months.
2. Progression Free Survival.
3. Response Duration.
4. Rate of negative Minimal residual disease (MRD) at 12 months, time to obtain a molecular response, duration of molecular response. Prognostic value of MRD status.
5. Overall survival.
6. Rates of AEs, SAEs and SUSARs by CTC grade (Version 4.03) during I+R treatment.
7. To assess the health-related quality of life (QOL) during treatment.
8. Genomic studies in indolent clinical forms of MCL (IGHV mutational status, DNA copy-number and whole exome sequencing).

5.2 STUDY DEVELOPMENT

All data of patients included in the study will be collected in the case report form (CRF).

The active monitoring of patients includes anamnesis, physical examination, laboratory tests, ECOG status, vital signs, adverse events assessment and concomitant medication.

Data on adverse events and concomitant medications will be collected up to 30 days after the last study medication administration. In the case of serious adverse events (and related concomitant medication) registration should be extended until the SAE is resolved or is considered as clinically stable by medical judgment.

When a patient terminates study or terminate study treatment due to disease progression, ~~finalizes protocol procedures, no additional diagnostic tests will be performed, only~~ survival and progression/relapse data will be collected (when applicable) until the end of the study as described in section 5.2.6. The study is divided into 3 phases: a Screening phase, a Treatment Phase, and a Treatment and Follow-up phase.

Tests and evaluations to be performed in different periods of the study are detailed below.

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5.2.1 Screening Phase:

Within a maximum of 28 days* prior to treatment initiation, it should be determined and collected the following clinical and laboratory data:

- Informed consent.
- Date of birth, date of diagnosis, medical history and concomitant medication.
- Physical examination, ECOG and vital signs.
- Quality of Life questionnaires.
- Local laboratory pathology diagnosis. The tissue FFPE block or slides will be sent to the central pathology laboratory to confirm the diagnosis and the Ki-67 proliferation rate whenever possible. The timeline of 28 days for the central review is not strict.
- CBC (hemoglobin, leucocytes with differential count and platelets).
- Biochemistry: creatinine, urea, uric acid, Na, K, Ca, glucose, total protein, protein electrophoresis, albumin, IgG assessment, IgA and IgM, bilirubin, alkaline phosphatase, GGT, AST, ALT, LDH and β2 seric microglobulin, serum immunofixation.
- Coagulation; TP, TTP, fibrinogen.
- Pregnancy test (performed on blood or urine) in women of childbearing potential.
- Hepatitis B and C (including anti-core VBH) and HIV serology.
- Disease assessment by PET/CT.
- Electrocardiogram.
- Left ventricular ejection fraction (optional, only mandatory in patients with a history of heart disease).
- Bone marrow biopsy.
- Bone marrow aspirate (with local study by flow cytometry and sending to MRD determination) ~~is optional, but recommended in cases exclusively involving bone marrow and peripheral blood.~~
- Concomitant medication.
- Tumor samples for molecular sub-study and MRD study. It will be obtained 30-50 ml of peripheral blood for shipment to central laboratory. Other territories will be considered based on clinical presentation, availability of samples (exceeding from diagnosis) and method of sample preservation.

* Baseline laboratory should be performed within 7 prior days at the most. The PET-CT and BMB obtained within 3 and 6 months prior to enrolment in the study respectively, will be accepted as a baseline examination in patients who meet study eligibility criteria. A broader interval may be considered for these baseline tests according to specific cases

** If the central review does not confirm the pathological diagnosis, the patient must be withdrew from the study.

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5.2.2 Study procedures during treatment phase

5.2.2.1 Before each treatment cycle (monthly the first year of treatment, thereafter every 3 months):

- Anamnesis, physical examination, ECOG, vital signs.
- Biochemistry and CBC.
- Adverse events and Concomitant medication

5.2.2.2 At 6 months from treatment initiation, in addition to states in section 5.2.2.1 "before each treatment cycle", when applicable:

- CT scan of chest, abdomen, pelvis and other involved sites if applicable
- Consider bone marrow aspirate (with study by flow cytometry) in forms with exclusively marrow involvement and peripheral blood at diagnosis.
- Assessing of minimal residual disease (MRD) in peripheral blood by RQ-PCR.

5.2.2.3 At 12 months from treatment initiation in addition to states in section 5.2.2.1 "before each treatment cycle", when applicable:

- Quality of Life questionnaires.
- PET/CT.
- Bone marrow biopsy.
- ~~Optional~~: Bone marrow aspirate (with local study by flow cytometry and sending for MRD determination).
- Minimal residual disease (MRD) in peripheral blood assessment by RQ-PCR.

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5.2.3. Treatment and Follow-up Phase

From month 12 or from completion of treatment without disease progression and up to 7 ~~4~~ years from patient inclusion in addition to states in section 5.2.2.1 "before each treatment cycle", when applicable:

- CT scan every 6 months.
- Minimal residual disease (MRD) in peripheral blood assessment by RQ-PCR every 6 months.

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5.2.4 End of Study Visit (30+/- 5 days)

An End of Treatment~~Study~~ Visit will be scheduled within 30 days after the last dose of study drug for all subjects, except for reasons of death or withdrawal of consent for study participation. (see section 5.2.5)

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The following procedures will apply:

- Anamnesis, physical examination, ECOG status and vital signs.
- Quality of life questionnaires.
- CBC, biochemistry.
- Adverse events and concomitant medication.
- CT scan (not necessary if the previous determination was obtained within the last three months and there is no clinical change that justifies it).
- Minimal residual disease (MRD) in peripheral blood assessment by RQ-PCR (not necessary if the previous determination was obtained within the last three months and there is no clinical change that justifies it).
- Obtain new tumor sample from peripheral blood, when applicable (in case of progression or relapse).

5.2.5. End of study

Participation in the study will end when any of the following occurs:

- The patient completes 7 years of treatment or follow-up since inclusion in the study,
- Progression during treatment or in the follow-up phase,
- Loss of follow-up or death
- Withdrawal of consent by the patient during the treatment or follow-up phase

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5.2.6 Follow- up post-progression or End of Study

Follow-up by routine clinical practice of progression (if applicable) and / or survival (alive / death / loss to follow-up) until trial closure~~Overall Survival follow up (Live/Dead/lost of follow-up).~~

5.3 RESPONSE AND TOXICITY CRITERIA

Treatment response will be assessed according to the International Response Criteria for Non-Hodgkin Lymphoma (13).

5.3.1 Response definitions

The response obtained will be classified according to the 2014 criteria of Cheson et al. (13) (see Annex VII). The PET / CT will be reviewed by GELTAMO PET platform.

5.3.2 Response assessment:

Percentage of complete remissions at 12 months: is defined as the percentage of patients who are alive and in complete response at 12 months from the date of treatment initiation. All patients will be evaluated with PET- CT and bone marrow biopsy at that time.

Overall response rate: Proportion of patients who experienced PR or CR.

Progression free survival (PFS): defined as the time between start of treatment and the first documentation of recurrence, progression, or death in the event of no documented recurrence, or start of a new anti – lymphoma treatment, due a refractory or persistent disease.

Response duration: is defined as the time from the documentation of tumor response to disease progression or death, in the event of no documented recurrence, or start of a new anti – lymphoma treatment because of refractory or persistent disease.

Overall survival (OS): is defined as the time between the start of treatment and death from any cause. Patients that are withdrawn from the trial or lost of follow-up, will be censored with the date of last contact. Patients who are still alive at the end of the study will be censored at that time.

Minimal residual disease negative rate: is defined as the proportion of subjects who are MRD negative (ie, less than the lower limit of detection for the MRD assay). All patients with a valid MRD result (negative or positive) will be included in this analysis.

5.3.3 Toxicity assessment

Toxicity appeared during any phase of treatment will be classified according to the Common Toxicity Criteria of the National Cancer Institute (CTC AE V 4.03).

5.4 TREATMENT AFTER END OF STUDY

In case of treatment failure and subsequent protocol treatment schedule withdrawal, each institution shall apply the treatment they consider most appropriate.

5.5. STUDY PROCEDURES

Study procedures in the present protocol will include CT scans, positron emission tomography (PET) using (18F)-fluorodeoxyglucose (FDG), bone marrow biopsy and aspirate, minimal residual disease assessment, central pathology and PET review, genomic studies and patient-reported outcomes.

1.- Image Assessments:

- CT scans of chest, abdomen, pelvis and any other location where disease is present must be performed at screening and at scheduled timepoints (see following tables). Patients who discontinue treatment prior to disease progression must continue to have regularly scheduled CT assessments until completing the study follow-up.
- PET scan: Whole body FDG-PET must be performed at screening and a 12 months of treatment to assess response. A centralized review of the PET scan will be done following the International Response Criteria for Non-Hodgkin Lymphoma (13).

Both separate CT scan and PET scan or combined PET/CT scanner will be accepted.

2.- Pathology Assessments:

- **Central laboratory pathology review:** The tissue FFPE block or slides from the diagnosis will be sent to the central pathology laboratory to confirm the diagnosis and variants of MCL. The Ki-67 proliferation rate will be confirmed or determined whenever possible. The timeline of 28 days for the central review is not strict.

- **Bone marrow assessment:** Bone marrow biopsy must be obtained during screening and at 12 months when assessing the response obtained to treatment to confirm CR. IHC studies will be performed according to local laboratory pathology practice and in case of intermediate samples by morphology only. Bone marrow aspirates must~~are optional and may~~ be considered in addition to bone marrow biopsy.

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3.- Biomarkers and Minimal Residual Disease Assessments.

Blood samples for biomarker determination in the genomic sub-study will be collected during screening and in case of disease progression or relapse. Genomic studies including whole-exome sequencing are planned. Samples from other territories may be collected according to its availability (exceeding samples after diagnosis) and the method of preservation.

In addition, blood samples and bone marrow aspirates will be obtained at the times described in the table of procedures in this section for monitoring minimal residual disease by means of quantitative real-time chain reaction polymerase (qRT-PCR).

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4.- Patient-Reported Outcomes

QLQ 30 and FACT-LYM questionnaires will be used for reporting the patient's outcome at screening and at 12 months of treatment.

In the following pages are summarized the procedures to be conducted in each of the stages of the study:

Study tests	*Prior treatment initiation*	First year of treatment	From second to seventh ~~fourth~~ year of treatment or follow-up	End of treatment ~~study~~ visit	Post-progression follow-up or end of study
	Day -35 y day 0	*Before each cycle (monthly)*	*Every 3 months until end of study*	*30 days after end of treatment*	
Informed Consent	X				
Inclusion/exclusion criteria	X				
Date of birth, date of diagnosis, clinical history	X				
Anamnesis/ Physical Examination (including ECOG and vital signs)	X	X	X	X	
Local anatomic-pathological diagnosis (1)	X				
Complete blood count (CBC). (2)	X	X	X	X	
Biochemistry (3)	X	X	X	X	
Coagulation (4)	X				
Serology *(HIV, hepatitis B and C)*	X				
Pregnancy Test (Urine or blood)	X				
PET/CT (5)	X	X *To be performed at 12 months from treatment initiation*			
CT Scan (6)		X every 6 months	X every 6 months	X	
Electrocardiogram	X				
Ejection fraction: optional. *(only mandatory in patients with history of cardiopathy)*	X				
Bone marrow biopsy (7)	X	X *To be performed at 12*			

		months from treatment initiation			
Bone marrow aspirate with flow cytometry ~~(optional)~~	X	X *To be ~~assessed~~ performed at 6 and 12 months from treatment initiation*			
MRD assessment in peripheral blood by RQ-PCR	X* (initial study)	X every 6 months	X every 6 months	X	
Concomitant medication	X	X	X	X	
Adverse events		X	X	X	
PRO (QOL questionnaires)	X	X *To be performed at 12 months from treatment initiation*		X	
Overall survival follow up					X
Biological Sub-study (mandatory peripheral blood)					
Tumor sample (8)	X				X (if progression)

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1: The classic, small and marginal cell MCL variants may be included after central pathology review (not strict 28 days).

2: Haemoglobin, leucocytes with differential count and platelets. Baseline determination should be done within 7 days before treatment initiation. Determinations performed before each of the cycles should be done within 72 hours before cycles.

3: Baseline (and response evaluation in 12 months, without serology): creatinine, urea, uric acid, Na, K, Ca, glucose, total protein, protein electrophoresis, albumin, IgG assessment, IgA and IgM, bilirubin, alkaline phosphatase, GGT, AST, ALT, LDH and β2 seric microglobulin, serum immunofixation.

Other biochemistry: Basic biochemistry with LDH. Baseline determination should be done within 7 days before treatment initiation. Determinations performed before each of the cycles should be done within 72 hours before cycles.

4: PT, APTT, fibrinogen.

5: Period of 28 days for Baseline PET/CT is not strict: PET/CT performed within 3 months prior patient inclusion will be accepted. A broader interval may be considered for the baseline determination in specific cases.

6: Chest, abdomen and pelvis CT scan, cervical (if clinically indicated).

7: Baseline bone marrow biopsy (BMB): For this test 28 days is not strict and BMB obtained within 6 months prior to patient inclusion with stable disease will be accepted. A broader interval may be considered for the baseline determination in specific cases.

8: Peripheral blood samples will be obtained prior to initiation of treatment for obtaining purified samples of tumor and non-tumor paired cells for the biological sub-study. In other territories, exceeding diagnosis samples may be used, based on availability and means of conservation. Always when possible, a new tumor sample will be obtained, either in tissue and/or peripheral blood, in patients who have progressive or relapsing disease to carry out the second part of the sub-study that will focus on the study of Ibrutinib resistance mechanisms.

6. ADVERSE EVENTS NOTIFICATION

The safety monitoring of the trial will follow what is established by EU Directive 2001/20/EU and the detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use.

The Sponsor, through the study Chair investigator, will assess reported serious adverse events (SAE) will determine the expectedness of events reported using available safety documents and will communicate expeditiously those SAEs that are “suspected unexpected serious adverse reaction – SUSAR” to competent authorities, with the help of the monitor and site staff.

The notification to the competent authorities (drug agencies, reference EC, Local EC, and other local competent bodies, according local guidelines) and principal investigators of any reportable event is the responsibility of the Sponsor, within in the time limits established by the local regulations (suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor, this period is reduced to 7 days in case of fatal and life-threatening SUSARs).

All adverse events during the conduction of the clinical trial (in the case of SAE from informed consent signature) and up to 30 days after the last dose of study medication, should be recorded in the CRF. In the case of serious adverse events (SAE) registration lasts until the AAG is resolved or deemed clinically stable, by medical judgment.

6.1 DEFINITIONS

6.1.1 Definition and categorization of Adverse Events

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 unfavourable 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 (refer to Section 5.3.1., All Adverse Events, for time of last adverse event recording).

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.

6.1.2 Adverse Event Definitions and Classifications

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 Investigator's Brochure.

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.

Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by de-challenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by de-challenge and re-challenge).

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 (e.g., laboratory abnormalities).

6.2 Special Reporting Situations

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

- Overdose of a sponsor study drug.
- Suspected abuse/misuse of a sponsor study drug.
- Inadvertent or accidental exposure to a sponsor study drug.
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, e.g., name confusion).
- Suspicion of the transmission of any infectious agent.

Special reporting situations should be recorded in the CRF and the Sponsor must be notified via fax (FAX: 93 253 11 68) by recording the information on the serious adverse events form. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page and the CRF.

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6.3 Procedures

6.3.1 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.

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 (e.g., 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 will also report to Janssen all serious adverse events that are unlisted (unexpected) and associated with the use of the study drug. The sponsor must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

6.3.2 Serious Adverse Events

All serious adverse events occurring during the study must be reported to the Sponsor (see section 6.6, contact details for notification)~~Janssen~~ by study-site personnel within 24 hours of their knowledge of the event.

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 (e.g., 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 that were 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 is 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 fulfil the serious adverse event definition.
- A standard procedure for protocol therapy administration will not be reported as a serious

adverse event. 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. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). 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.

6.3.3 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 (see section 6.6, contact details for notification)~~Janssen~~ within 24 hours of awareness irrespective of seriousness (i.e., serious and non-serious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

6.3.3.1 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: intra-ocular 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.

6.3.3.2 Intracranial Hemorrhage

Any intracranial hemorrhage adverse event, including subdural haematoma/hemorrhage, epidural haematoma/hemorrhage and intra-cerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

6.3.4 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.

6.3.5 Pregnancy

All initial reports of pregnancy must be reported to the Sponsor (see section 6.6, contact details for notification)~~Janssen~~ by the study-site personnel within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (e.g., spontaneous abortion, stillbirth, and congenital anomaly) are considered serious adverse events and must be reported as a Serious Adverse Event. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their

knowledge of the event.

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

6.4 PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labelling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labelling 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.

6.4.1 Procedures

All initial PQCs must be reported to the Sponsor (see section 6.6, contact details for notification)~~Janssen~~ by the study-site personnel within 24 hours after 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 (see section 6.6, contact details for notification)~~Janssen~~ according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the Sponsor.~~Janssen.~~

6.5. PREGNANCY NOTIFICATION

The pregnancy of a female patient or partner of a male patient, not being itself a serious adverse event, it should be also expeditiously managed like a SAE. It should be registered and notified with a specific form for pregnancy events and reported on an expedited basis (within 24 hours since first knowledge), even a voluntary or spontaneous discontinuation occurs, describing the details of the birth and presence or absence of a defect in the foetus or a congenital abnormality.

Potential effects on spermatogenesis: pregnancies that occur in the partner of a male patient should also be notified within 24 hours by the specific form of pregnancy and followed until the end, although a voluntary or spontaneous discontinuation occurs, describing details of the birth and the presence or absence of a defect in the foetus or a congenital abnormality. It will also indicate to the patient pregnant couple that should immediately contact her doctor.

To carry out the monitoring of clinical data in pregnancy, it should be requested pregnant authorization either in case of study patient or partner of a male patient, which will be documented with the signing of the "Express consent to disclosure medical data on pregnancy". This form should not be sent to the monitor / CRO, but will be kept on file with the other study documentation at the Site.

6.6. CONTACT DATA FOR SAE, PREGNANCY, DEATH AND QUALITY CLAIMS NOTIFICATIONS, SPECIAL SITUATION REPORTS

DEPARTAMENTO DE INVESTIGACIÓN MFAR, S.L.

Fax: +34 93 253 11 68

e-mail: investigacion@mfar.net

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7. STATISTICAL CONSIDERATIONS

Our study proposal is looking for a therapeutic alternative to conventional immunochemotherapy (R-CHOP) in clinically indolent MCL.

This phase II study will explore the feasibility of Ibrutinib plus Rituximab combination in this subset of patients evaluating its capacity of inducing a high response rate with a favourable toxicity profile. In addition, an extensive biological study of the cases will be conducted in order to explore clinic-biological correlations.

We hypothesize that for a CR rate of 30% usually achieved with R-CHOP, the combination of Ibrutinib plus Rituximab will be able to exceed this proportion in 20%.

We propose a Phase II study with a two-stage design with error probabilities α and β of 0.10 and 0.2 respectively. The optimal design will have an expected sample size of 50 patients (at least 46 patients evaluable for response).

The first stage will consist of 15 patients. If 5 or less complete responses are observed the trial is terminated, otherwise accrual can continue to a total of 50 patients.

For Primary Analysis we plan the evaluation of CR rate at 6 months from the start of therapy. All the patients will be evaluated with Thoracoabdominopelvic CT and bone marrow aspirate at that point. If 5 or less complete responses are observed among the first 15 patients recruited and evaluated, the trial will be terminated.

8. MOLECULAR SUB-STUDY

Peripheral blood samples will be collected prior the start of therapy in order to obtain DNA and RNA purified of tumor samples and DNA and RNA of paired non tumor samples. IGHV mutational assessment and genomic studies including whole exome sequencing (WES) and the analysis of DNA copy number alterations will be conducted in those pretreatment samples.

Lymph node or other tissue biopsies (either frozen or FFPE tissue) diagnostic of MCL will be collected when available to perform histological review, create a TMA and to obtain tumor DNA and RNA in order to expand the genomic studies especially in those cases without peripheral blood involvement.

A new tumor sample collection either in peripheral blood and/or tissue will be obtained whenever possible in those patients presenting progressive or relapsed disease to I+R in other to allow conducting second time-point WES studies. These studies will focus particularly in the study of the mechanisms of ibrutinib resistance.

9. ETHICAL CONSIDERATIONS

9.1 GENERAL CONSIDERATIONS

This study will be conducted in conformity with the requirements of the "Declaration of Helsinki" adopted by the 18th World Medical Association General Assembly held in Helsinki, Finland, June 1964 and relevant revisions. The Good Clinical Practice (GCP) issued by the working group on the Efficacy of Medicinal Substances of the European Union (1990) (CPMP/ICH/135/95) and applicable regulatory requirements and laws on the country where the Trial is taking place.

According to Directive 95/46 of the European parliament and 2001/20 /EC by which the requirements to perform a clinical trial are established, the information obtained in the course of the clinical trial, will only be able to be used by the clinical trial sponsor to evaluate the results according to the mentioned regulation.

9.2 WRITTEN INFORMED CONSENT

Is the obligation of de Investigator to obtain a written informed consent of the subjects (according to the requirements according the European directive of Clinical Trials), before including a patient in the trial, or when needed, before assessing the eligibility of subject for the study.

Each subject or her/his legal representative will be required in the terms established in European Directive for clinical trials, granting free written informed consent after receiving oral and written information about the trial objectives, procedures to follow, the possible benefits, drawbacks and expected risks, possible therapeutic alternatives as well as their rights and responsibilities. The patient or his representative must be informed that their participation is voluntary and they can withdraw at any time without incurring any consequences. It should also be informed that the Sponsor, their representatives and competent authorities will have access to clinical data.

The Investigator will be responsible for providing each subject or her/his representative a Patient Information Sheet and Informed Consent Form approved by the relevant ethics committee.

If the patient agrees to participate in the study, itself or her/his legal representative must sign the consent form. The investigator must also sign and date this form, thus indicating that it has obtained informed consent and that the patient has had the opportunity to ask questions and these have been properly answered.

The patient or her/his representative will receive a copy of the Patient Information Sheet and the informed consent form signed.

The Investigator will archive in the patient records of each subject the original informed consent forms signed and dated. No patient may participate in the study until signing the informed consent.

9.3 DATA CONFIDENTIALITY

The confidentiality of the data of each patient will be respected at all times. In order to warrant the confidentiality of study data according to Regulation (EU) No. 2016/679 General Data Protection (RGPD), and Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights~~Directive 95/46 of the European parliament and 2001/20/EC~~, personal and clinical data can only be accessed by the Sponsor of the study or its designated staff, for monitoring/auditing purposes, the investigator and team of collaborators, the Ethics Committee of the investigational site, or the one overseeing the centre, and pertinent Health Authorities.

Study subjects will be identified by a unique code consisting in site number (two digits) and

consecutive number according to chronological order of recruitment (two digits).

The investigator will inform the study subjects that data obtained in this trial will be stored and analysed by computer and that the European regulations on the management of computerized data will be followed. Data protection is described in the patient information sheet in writing.

The Investigator accepts that the Sponsor has the right to use the results of the clinical trial, including CRF forms or copies thereof. To allow the use of information obtained in the clinical trial, the investigator understands that he is obligated to provide full test results and all information developed during the study to the Sponsor.

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9.4 CLINICAL TRIAL INSURANCE

The trial will have an insurance policy that will cover all possible damages that patients may suffer as a result of product tested, according to local applicable laws in the country where the study is conducted.

9.5 EC SUBMISSION

This protocol and all required documentation will be submitted for evaluation to the relevant Ethics Committee following the procedure established in current European regulation and the instructions of health authorities in the countries where the trial takes place.

The study will not begin until the EC positive vote and Competent Authority be available for the study, and other local requirements established by current legislation are met. The Sponsor will provide the Investigator with a copy of the relevant documents.

The Ethics Committee and the relevant health authorities will be informed of all changes to the protocol that may affect the safety of the subjects or the conduct of the trial and the severe and unexpected reactions and other information that may alter the design of the study or imply a risk for the patients. The corresponding approvals/authorizations will be obtained In the case of substantial amendments to the protocol, according to what is established in European Directive and guidelines.

10. PRACTICAL CONSIDERATIONS

10.1 RESPONSIBILITIES ACCORDING TO GCPs

The Sponsor, monitor and investigators will comply the responsibilities established in the GCPs.

10.1.1 Investigator

a) To agree and sign the study protocol.

b) To know in depth all study drugs characteristics.

c) To obtain informed consent of subjects before inclusion in the trial.

d) To ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory valued, related to the trial.

e) To collect, register and notify data in a correct way.

f) To notify immediately to the sponsor all SAE and unexpected adverse events.

g) To take responsibility that all people involved in the trial will respect the confidentiality of any information about the study subjects.

h) To keep the Ethics Committee regularly informed on the facts of the study.

i) To take co-responsibility on the elaboration of the final study report, providing his/her agreement and signature.

10.1.2 Sponsor

a) The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

b) To sign with the respective investigator the protocol and any amendment to the protocol.

c) To select the most suitable investigator based on the investigator's qualifications and availability of resources, and to assure the investigator's agreement to conduct the trial as specified in the protocol.

d) To provide all available basic and clinical information on the investigational medicinal product and maintain it updated throughout the duration of the trial.

e) To request the report by the Clinical Research Ethics Committee and authorization by the Spanish Agency for Medicines and Medical Devices and to submit notification or application, as appropriate and without prejudice to notification of autonomous communities, in the event of any amendment or violation of the protocol, discontinuation of the trial and reasons for discontinuation.

f) To provide the investigational medicinal products at no cost and to ensure that they have been prepared according to good manufacturing practice and are suitably packaged and labeled. The sponsor is also responsible for the storage of investigational products and for keeping records of their manufacture and quality control, to keep records of the investigational medicinal products supplied and to ensure that the site where the trial is conducted establishes a procedure for correct handling, storage and use of investigational medicinal products delivered.

In exceptional cases, other means of supply may be agreed with the site.

g) To appoint the monitor who shall supervise the performance of the trial.

h) To notify health authorities and Clinical Research Ethics Committees involved in the trial of any unexpected or serious adverse events in accordance with the procedures established in European and local directive.

i) To inform promptly the investigator and Clinical Research Ethics Committee of any new relevant information that becomes available during the trial.

j) To provide compensation for the subjects in the event of trial-related injury or death. To provide legal and financial cover for the investigator, except for claims resulting from malpractice or negligence by the investigator.

k) To agree with the investigator on the allocation of responsibilities for data processing, preparation of reports, and publication of results. In any case, the sponsor is responsible for preparing final or partial reports of the trial and submitting them to the appropriate authorities.

l) The sponsor shall provide a contact point, where the trial subjects may obtain further information about the trial, which may be delegated on the investigator.

10.1.3 Monitor

Monitoring task are delegated by the Sponsor to MFAR.

a) To work according to sponsor standard operating procedures, visit the investigator before, during and after the trial to control adherence to the protocol and assure that all data are correctly and completely recorded and reported, and that informed consent is obtained from all subjects prior to their enrolment in the trial.

b) To ensure that both the investigators and the sites where the trial is to be conducted are adequate for this purpose for the duration of the trial.

c) To ensure that both the principal investigator and all staff assisting the investigator are adequately informed and to ensure communications between the investigator and sponsor promptly at all times.

d) To check that the investigator complies with the protocol and all approved amendments.

e) To check that the storage, dispensing, return and documentation of the supply of investigational medicinal products are safe and appropriate.

f) To submit written reports to the sponsor after each monitoring visit and after all relevant contacts with the investigator.

10.2 PROTOCOL AMENDMENTS AND PROTOCOL DEVIATIONS

After the protocol is reviewed and signed, neither the investigator nor the Sponsor can make changes or alterations without the written consent of both.

If it is needed to perform any modification or alteration to the protocol one it has been signed, this modification should be discussed and agreed between the principal investigator and the sponsor, and signed by both parties. The amendments to the protocol should form an integral part of the original protocol. The ethics committee must be informed of all amendments to the protocol that may affect the safety of the subjects or the conduct of the trial. In case of relevant amendments the approval of the amendment should be obtained, in accordance of European and Local regulations, before implementing such modifications.

10.3 MONITORING

A team of monitors appointed by the Sponsor will monitor the study regularly to ensure the safeguarding of rights and welfare of patients, the protocol is followed accordingly, the applicable standards and ethical requirements are meets, all necessary documentation is available in Sites and the data is collected accurately.

The Investigator must grant access to the monitor to subjects medical records, study records, CRF, signed original informed consent forms and all source data documents.

Any deficiency observed during monitoring visits will be discussed with the investigator, reaching agreement on the corrective measures to be implemented.

10.4 DATA MANAGEMENT

All data (personal, clinical, economic, derived from biologic material) obtained from patients will be handled according to the Regulation (EU) No. 2016/679 General Data Protection (RGPD), and Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights~~Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data~~. According to such legislation, patients will be able to exert their rights to access, modification, opposition and cancellation of their data, for which the clinical trial physician must be addressed. The content of the CRFs, as well as the documents generated during the study will be considered strictly confidential and not revealed to third parties.

The investigator should keep detailed records of all subjects involved in the trial.

The investigator should collect and record data from the study in the medical records of each subject and then, transfer the information to the CRF provided by the Sponsor. All data must be completely recorded, without delay, accurately and intelligible in the CRF.

The investigator should date and sign each of the CRF in the specific field of the eCRF.

The researcher should keep all the original documentation (lab results, treatment sheets, signed Informed Consent, etc.).

Data recorded in the CRF will be reviewed and analysed; data from the database will also be reviewed to detect inconsistencies. Doubtful, inconsistent or incomplete data will be queried to the investigator in written and correction will be tracked in the audit trail of the CRF.

Correction procedures of computerized data will be applied.

10.5 STUDY DOCUMENTATION ARCHIVING

It is the responsibility of the investigator to ensure the maintenance of trial file in the study site. For this trial the file will contain, but not be limited to, the following documentation:

1. Protocol Study, current and previous version, revision and/or amendments (when applicable);

2. Patient information sheet and consent form, revision and/or amendments (when applicable);

3. Investigator commitment;

4. Contract for clinical research;

5. Investigator and sub-investigators CV;

6. EC Positive Vote for the trial and amendments (when applicable) and other relevant communications with the EC;

7. CA approval for the trial and amendments (when applicable) and other relevant communications with the CA;

8. Correspondence between Investigators, EC and Sponsor related to this trial;

9. Annual reports and safety reports;

10. Normal laboratory ranges, in which the determinations required in this trial be detailed. Quality certification for this laboratories;

11. IMP documentation (accountability forms, conservation, etc.);

12. Updated Clinical Trial Staff Signature list and delegation log;

13. Subject identification list, for patients enrolled in the trial.

The investigator should file the subject identification list and all signed informed consent for at least 15 years after completion of the trial. Any original information related to the study that allow the verification of the criteria for inclusion and exclusion, including medical records, a copy of all case report forms and documents for use of investigational product should be stored for the maximum time allowed by the Site.

10.6 QUALITY CONTROL AND QUALITY ASSURANCE

The study will be overseen by MFAR, SL monitors. The study monitor will contact investigators periodically. In these contacts the progress of the study will be discussed with the investigator and will be checked that CRFs are filled out in full and consistently manner. Study Monitor (and, when requested, a representative from the sponsor) will also check the informed consent forms.

With a proper supervision and guarantee of confidentiality, the investigator will allow to the representative of the sponsor or to the study monitor to compare the data entered in the CRF with the original data in the study site (source documents), and to observe the study procedures in order to verify the study protocol compliance.

10.7 INSPECTION AND AUDITING

Audits of quality assurance may be performed at anytime during the trial or after completion. Also, the study may be inspected by the relevant authorities on the terms established in the European and local regulations.

Upon request of the monitor, auditor, ethics committee or regulatory authorities, the investigator should provide direct access to all documents related to the clinical trial.

10.8 STUDY EARLY TERMINATION

The Sponsor may, at any time, suspend the participation of an investigator in the study. In the event that the participation of an Investigator on a study be suspended, the Sponsor will inform promptly and in writing to the EC and CA about the reason or reasons for the suspension.

The study early termination may be due, among others, the following reasons:

- New information available that justify that the continuation of the study is not feasible.
- Unsatisfactory recruitment in terms of quantity or quality.
- Data collection inaccurate or incomplete.
- Protocol non compliance.

10.9 FINANCIAL ASPECTS OF THE TRIAL

Financial aspect of the trial will be submitted to EC for evaluation at the protocol submission.

10.10 PUBLICATION POLICY

The Sponsor and Investigators are committed to publish the results of this study. All publications and presentations proposed by the Investigators or his/her staff and associates resulting from or related to the study, should be submitted to the Sponsor for timely review before being submitted for publication or presentation.

In publications the signing authors will be sorted by number of patients included, from highest to lowest accrual.

If the proposed publication or presentation contains patentable material, which, in the Sponsor opinion, guarantees the protection of intellectual property, it may delay any publication or presentation for a reasonable period of time in order to achieve such protection.

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ANNEXES

I. List of participating Sites

II. Study Patient Information Sheet and Consent Form

III. Molecular Sub-study Patient Information Sheet and Consent Form

IV. ECOG Performance Status

V. NCI CTCAE V4.0

VI. SmPC of Ibrutinib

VII. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification (13)

APPENDIX I. Participating Sites

A list of participating sites will be available as an independent document.

APPENDIX II. Patient Information Sheet and Informed Consent Form

The current Patient Information and Study Informed Consent sheets are available as a separate document.

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APPENDIX III. Sheet Patient Information and Informed Consent molecular substudy

The current Patient Information and Study Informed Consent sheets are available as a separate document.

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APPENDIX IV. 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 housework, 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	Death.

APPENDIX V. NCI CTCAE V4.0

Version 4.0 of CTC is available at:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

A paper copy is included in the investigator's site file.

APPENDIX VI. Ibrutinib SmPC

The current Ibrutinib SmPC is available as a separate document.

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ANNEX VII. *Revised Criteria for Response Assessment*

Lugano Criteria for Response Assessment for Non-Hodgkin Lymphoma (13)

Response and Site	**PET-CT–Based Response**	**CT–Based Response**
Complete	Complete metabolic response	Complete radiologic response
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target ganglia / ganglion masses should cecrease by ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non Measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Back to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial radiologic response
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings	≥ 50% decrease in SPD of up to 6 measurable target nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5mm × 5mm as the default value.

	indicate residual disease	When no longer visible, 0 × 0 mm. For a node> 5mm × 5mm, but smaller than normal, use the actual measurement for the calculation.
Non Measured lesions	Not applicable	Absent / normal, regress, but no increase
Organ enlargement	Not applicable	None
New lesions	None	Not applicable
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant measurable nodes and extranodal sites; criteria for disease progression are not met
Non Measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target	Score 4 or 5 with an increase in	A single node / lesion must be

nodes/nodal masses	intensity of uptake from baseline and/or	abnormal with: LDi> 1.5 cm and ≥50% increase from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions> 2 cm In the setting of splenomegaly, splenic length should increase by> 50% of the extent of its previous increase beyond the baseline (eg, a 15 cm spleen should increase to> 16 cm). If there is no previous splenomegaly, it should increase at least 2 cm from the initial value New or recurrent splenomegaly
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	
Non Measured lesions	None	New progression or clear progression of unmeasured pre-existing lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved injuries. A new node> 1.5 cm on any axis. A new extranodal site> 1.0 cm in any axis; if it is <1.0 cm in any axis, its presence must be unequivocal and attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent alteration

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

* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if performed at the time of an interim examination. However, in trials involving PET investigating de-escalation, it may be preferable to consider a score of 3 as an inadequate response (to avoid

insufficient treatment). Measured dominant lesions: Up to six of the largest dominant nodes, lymph node masses, and extranodal lesions selected to be clearly measurable in two diameters. The nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-ganglionic lesions include solid organ lesions (eg, liver, spleen, kidneys, lungs), gastrointestinal involvement, skin lesions, or those seen on palpation. Unmeasured lesions: Any disease not selected as a measure, dominant disease, and truly evaluable disease should be considered unmeasured. These sites include all nodes, lymph node masses, and extranodal sites that were not selected as dominant or measurable or that do not meet the measurability requirements but are still considered abnormal, as well as truly evaluable disease, which is any site of suspected disease that may be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or at extranodal sites (eg, gastrointestinal tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with a complete metabolic response, but should not be greater than normal physiologic uptake. Surrounding (e.g., with spinal activation as a result of chemotherapy or myeloid growth factors).