Multicentric Phase II Trial to Evaluate the Efficacy and Safety of Ibrutinib in Combination With Rituximab, Gemcitabine, Oxaliplatin and Dexamethasone Followed by Ibrutinib Maintenance in Patients With Refractory/Relapsed Non-GCB Diffuse Large B-cell Lymphoma Non Candidates to ASCT

CLINICAL TRIAL PROTOCOL

CODE: [redacted]

Sponsor: [redacted]

Coordinator Researchers: [redacted]

Monitoring: [redacted]

SIGNATURE PAGE PROTOCOL

Protocol Number: [redacted]

Ollie # EudraCT: [redacted]

Protocol version: 2, October 21, 2016

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

Signature of the sponsor

[redacted]

Signature of the Coordinating Investigator:

[redacted] [redacted]

I have read this protocol and agree to carry out this trial in accordance with all the provisions of the protocol and in accordance with the Declaration of Helsinki.

Principal Investigator: .....
Name:

Confidentiality Statement

This document contains confidential information of [redacted] that should not be disclosed to anyone other than the study staff and members of the Ethics Committee. This information cannot be used for any other purpose than the evaluation or conduct of clinical research without the prior written consent of [redacted]

Investigator Acknowledgment

I have read the attached protocol entitled “Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM”, version: 2, October 21, 2016, and I agree to comply with all the provisions stipulated therein.

I agree to act in accordance with the Tripartite Guide for Good Clinical Practice standards.

I agree to ensure that the confidential information contained herein is not used for any purpose other than the evaluation and conduct of clinical research, without the prior written consent of [redacted].

Signature

Principal investigator	Date (DD/month/YYYY)

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ABBREVIATIONS

AAG	Adverse Event serious
CRD	Notebook data collection
ECOG	oncological Cooperative East*(EasternCooperative Oncology*Group)
MRD	minimal residual disease
GEL / OCA	Group Spanish Lymphoma / Autologous Bone Marrow
HC	Hemogram complete
HLA	human leukocyte antigen*(human leukocyte antigen*)
DLBCL	diffuse large B Cell
NHL	nonHodgkin
ULN	upper limit of normal
WHO	World Health Organization
PET	positron emission tomography*(positron emission tomography)*
RAN	absolute neutrophil count
RC	complete remission
PR	***Partial response***
EE	***Stable disease***
RG	overall response
R-GEMOX	Rituximab-GEMOX
SG	Survival overall
SLA	free survival events
SLP	freeSurvival progression
CNS	Central nervous system
ASCT	autologous stem cell transplant
TFT	time to treatment failure
TRG	overall response rate

(V Version 2: October 21, 2016)

0. GENERAL INFORMATION

Study Title	Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM
Protocol number	[redacted]
Protocol version	2.0 dated October 21, 2016
Chief investigators	[redacted]
Application type	Clinical trial of a drug marketed in a new indication.
Phase of the study	Phase II
Indication	Diffuse large B-cell lymphoma (DLBCL) Primary
objective	1. To assess the efficacy of the IR-GEMOX-dexa combination as salvage treatment in patients with refractory or relapsed non-GCB diffuse large B-cell lymphoma , in terms of overall response rate (ORR).
Secondary objectives	**1.** To assess the efficacy of the combination of IR-GEMOX-dexa followed by ibrutinib as maintenance treatment in terms of secondary endpoints (complete remission [CR], overall survival [OS], event-free survival [EFS], survival progression-free [PFS] and duration of response). **2.** To determine the safety and tolerability of ibrutinib in combination with R-GEMOX-dexa. **3.** To determine the safety and tolerability of ibrutinib as maintenance treatment. **4.** Identify clinical and biological prognostic factors that influence response and survival rates. **5.** Establish a correlation between mutational status and response and survival. **6.** Evaluate the relationship of PET/TC results with biological markers.

	7. Establish a correlation between HLA polymorphisms and response and survival. **8.** Establish a correlation between minimal residual disease (MRD) at the end of treatment (6-8 cycles of IR-GEMOX) with the response observed in PET/TC and survival.
Study design	Phase II multicentre clinical trial to evaluate the efficacy and safety of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin and dexamethasone followed by ibrutinib as maintenance treatment in patients with treatment-resistant or relapsed non-GCB DLBCL who are not candidates for treatment. receive an autologous stem cell transplant (ASCT). An extensive biological study will be carried out in order to further characterize this population of patients with DLBCL and establish a correlation between the response obtained and the biological profile of the tumor. In addition, centralized PET/TC reviews will be carried out.
Primary endpoint	1. Overall response rate (complete remission + partial response) of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin, and dexamethasone.
Secondary endpoints	1. CR rate during the induction and maintenance phases. 2. Conversion rate from EE or PR to PR or CR during the maintenance phase 3. Duration of the response. 4. Progression free survival. 5. event-free survival. 6. overall survival. 7. Safety and tolerability of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin, and dexamethasone. 8. Safety and tolerability of ibrutinib as maintenance treatment. 9. Influence of clinical and biological prognostic factors on response and survival rates. 10. Establish a correlation between mutational status and response and survival. 11. Establish a correlation between HLA polymorphisms and response and survival. 12. Establish a correlation between the response observed in the PET/TC and the biological markers. 13. Establish a correlation between MRD at the end of treatment (6 - 8 cycles of IR-GEMOX) with the response observed in PET/TC, PFS and OS.

Sample size:	Inclusion of a total of 62 patients during an approximate period of 24 months.
Summary of patient eligibility criteria	**INCLUSION CRITERIA** 1. Patients with confirmed histological diagnosis of diffuse large B-cell lymphoma. 2. Patients 18 years of age or older. 3. Non-germinal center B cell subtype (non-GCB) according to the Hans algorithm (local laboratories). Centralized evaluation will be performed to confirmB cell subtype ***non-germinal center(non-GCB)*** , but a negative result will not exclude the patient from the study if ***clinical benefit (CR, PR, or SE) is obtained*** after the study. 4th cycle. ***(Version 2: October 21, 2016)*** 4. Recurrent or refractory disease after: ● At least one prior line of treatment, including rituximab in combination with chemotherapy; or, ● After a previous ASCT; or, ● Following allogeneic transplant with reduced-intensity conditioning, unless the patient is receiving immunosuppressive drugs or has graft-versus-host disease at the time of study enrollment. (Resistance to treatment is defined as the inability to achieve CR after treatment latest.) 5. Functional status of the *Eastern Cooperative Oncology Group* (ECOG) ≤ 2. 6. FDG PET basal demonstrating positive lesions (Deauville 4 or 5) compatible with the anatomical tumor locations defined on CT. 7. Hematological values should be within the following limits: a. Absolute neutrophil count (ANC) ≥1000/µl regardless of growth factor treatment. b. Platelets ≥100,000/µL or ≥50,000/µL in case of bone marrow involvement, regardless of transfusion therapy in either situation. 8. Biochemical values within the following limits: a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of normal (ULN). b. Total bilirubin ≤1.5 times the ULN, unless the increase in bilirubin is due to Gilbert's syndrome or non-hepatic in origin. c. Serum creatinine ≤2 times the ULN or estimated creatinine clearance (CCr) ≥30ml/min. 9. Females of reproductive capacity and sexually active males must use a highly effective method of contraception during and after the study, in accordance with local regulations regarding the use of contraceptive

methods for participants in clinical trials. Men must agree not to donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. In males, these restrictions apply for 3 months after the last dose of study drug.

10. Females of reproductive capacity must have a negative serum (beta-human chorionic gonadotropin [pregnancy test atβ-potentialhCG]) or urine screening. Pregnant or lactating women cannot participate in this study.
11. Signature (or signature of the legal representative) of an informed consent document indicating that they understand the purpose and procedures required by the study and express their desire and ability to participate in the study.

EXCLUSION CRITERIA

1. Previous malignancy other than DLBCL, with the exception of adequately treated basal cell carcinoma and squamous cell carcinoma, cervical cancer *in situ,* or other tumors that have not recurred for at least 2 years or will not limit survival to <2 years (Note: these cases should be discussed with the principal investigator).
2. Autologous stem cell transplant candidates.
   NOTE: Young patients who have received more than one line of treatment and are refractory may be considered ineligible for autologous stem cell transplantation and are therefore eligible for this study.
   (Version 2: October 21, 2016)
3. Life-threatening disease, condition, or organ dysfunction that, in the opinion of the investigator, could compromise patient safety, interfere with the absorption and metabolism of ibrutinib, or pose an undue risk to treatment outcomes. study.
4. Significant cardiovascular disease, such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months prior to screening, or any class 3 or 4 heart disease *New York Heart Association*.
5. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small intestine or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete intestinal obstruction.
6. Treatment with any immunotherapy, chemotherapy, radiation therapy or experimental treatment within 3 weeks prior to the first dose of the drug of the study (allowed the use of corticosteroids for symptoms related to

	the disease as indicated in paragraph **3**.7). ***(Version 2: October 21, 2016)*** 7. Prior treatment with ibrutinib or other BTK inhibitors. 8. Central nervous system (CNS) involvement by lymphoma. 9. History of stroke or intracranial hemorrhage in the 6 months prior to inclusion. 10. Need for anticoagulation with warfarin or equivalent vitamin K antagonists. 11. Need for treatment with potent CYP3A inhibitors (see the ***"Potential for Drug-Drug Interactions" section of the Investigator's Manual). (Version 2: October 21, 2016)*** 12. Grade ≥2 toxicity (except alopecia) related to prior anticancer therapy, including radiation. 13. History of human immunodeficiency virus (HIV) infection, active hepatitis C virus infection (HCV; positive RNA polymerase chain reaction [PCR]), or active hepatitis B virus infection (HBV; DNA PCR positive) or any active uncontrolled systemic infection requiring IV antibiotics Patients with negative HBV PCR are allowed to be included. 14. Major surgery within 4 weeks prior to the first dose of study drug. 15. Administration of live attenuated vaccines in the 4 weeks prior to inclusion. 16. Pregnancy or lactation.
Medication formulation and administration	schedule Patients will receive ibrutinib in combination with R-GEMOX-dexa followed by ibrutinib as maintenance treatment, according to the following schedule: <u>Induction phase:</u> - Patients will initially receive 4 cycles every 14 days of ibrutinib + RI-GEMOX-D, consisting of: ● 375 mg/m^2 rituximab iv on day 1. ● 1000 mg/m^2 Gemcitabineiv on day 1 or 2 (at investigator's discretion). ● 100 mg/m^2 oxaliplatin on day 1 or 2 (after gemcitabine administration). ● Dexamethasone 20 mg orally or IV on day 1 and orally on days 2 and 3. ● Ibrutinib 560 mg daily for 14 days. Patients who show ***clinical benefit*** (PR, CR ***or EE)*** will receive 2 (in the case of CR) or 4 (in the case of PR ***or EE)*** additional cycles of 14 days each. ***If the centralized review does not confirm the diagnosis of non-GCB type DLBCL, the patient may continue in the clinical trial if the local investigator and trial coordinators consider that the patient is benefiting from the clinical trial***.

	(Version 2: October 21, 2016) <u>Maintenance phase:</u> After the induction phase, patients will receive 560mg ibrutinib daily. Continuous cycles for up to 2 years, until disease progression or unacceptable toxicity occurs (whichever comes first). Patients with an inferior response to ***EE*** after the induction phase and patients experiencing disease progression at any time during induction should complete the study. The PET/TC will be reviewed by thePET platform [redacted] (see annex VI). Treatment decisions will be made pursuant to centralized review. [redacted] is providing both the drug ibrutinib and the funding for the study. ***(Version 2: October 21, 2016)***
Study Procedures	***<u>A. Prior to Initiation of Treatment: No later</u>*** than 28 days* (8 days for CBC and chemistry) prior to initiation of treatment, baseline data should be determined and obtained. the following clinical and biological data: ● Informed consent. ● Clinical history, concomitant medication, demographic data, physical examination, ECOG. ● Height, weight and vital signs. ● Local histological diagnosis. Obtaining a tumor biopsy at the start of the study is recommended, especially in cases of recurrence. Paraffin-embedded blocks of biopsies will be sent for central diagnostic validation and biological studies (see Annex VII). A centralized evaluation will be performed to confirm the subtype ***non-GCB*** before administration of the 4th cycle. ***(Version 2: October 21, 2016);*** ● Complete blood count (CBC). ● Biochemistry: creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, protein electrophoresis, albumin, IgG, IgA, and IgM, bilirubin, alkaline phosphatase, GGT, AST, ALT, LDH, and β2-microglobulin. ● Basal coagulation: PT, aPTT, fibrinogen. ● Serology: HBV (including HBsAg, HBsAc, and HBcAc; HBV DNA in cases with positive serology), HCV, HIV.

- Pregnancy test (carried out on blood or urine) in women of reproductive capacity.
- Disease assessment: PET/TC.
- Electrocardiogram.
- Left ventricular ejection fraction (optional, mandatory only in patients with a history of heart disease).
- Bone marrow biopsy.
- Peripheral blood samples for biological studies (see Annex VII).
- Questionnaires on comorbidities (see Annex X).

An extensive biological study will be performed in order to further characterize this population of DLBCL patients with AUC and to evaluate the response obtained with the mutational profile of the tumor. In the event that patients agree to participate in the biological study, peripheral blood, paraffin-embedded blocks from the original diagnostic lymph node biopsy, and lymph node biopsy performed at the time of recurrence (if available) are sent to a central laboratory to perform phenotypic subtyping tests, molecular studies, mutational spectrum, and determination of the cell of origin using NanoString technology (NanoString Technologies, WA, USA) (13).

***The baseline analysis must be performed, at most, in the previous week.*

B. During treatment with IR-GEMOX-dexa:

1. Before each cycle of treatment:
   - History, physical examination, ECOG, vital signs.
   - CH and biochemistry (creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, albumin, bilirubin, alkaline phosphatase, GGT, AST, ALT and LDH).
   - Concomitant medication.
   - Adverse events.
2. Evaluation of the response during induction:
   - PET/TC 10-14 days after the start of the 4th cycle).
   - Peripheral blood samples for MRD studies (see Annex VII).

C. Evaluation of response at the end of induction:

21-35 days after the start of the 6th or 8th cycle:

- History, ECOG, physical examination, concomitant medication, adverse events.
- GH and biochemistry (creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, protein electrophoresis, albumin, IgG, IgA and IgM, bilirubin, alkaline phosphatase, GGT, AST, ALT, LDH and microglobulin β2).

- PET/TC.
- Bone marrow biopsy (in case of infiltrate at the time of inclusion in the study).
- Peripheral blood samples for MRD studies (see Annex VII).

D. Maintenance treatment:

Visits will be made every 8 weeks, which will include the following:

- History, physical examination, ECOG, vital signs.
- Biochemistry and HC.
- Concomitant medication.
- Adverse events.

An evaluation of response will be performed:

- chest, abdominal and pelvic TC every 6 months. PET/TC in case of suspected recurrence or progression or to confirm CR.
- Peripheral blood samples for MRD studies (see Annex VII), at the same time as imaging evaluations.

E. End of Treatment Visit:

On day 30 after completion or discontinuation of study treatment:

- History, physical examination, ECOG, vital signs.
- Biochemistry and HC.
- Concomitant medication.
- Adverse events.
- Reason for termination of treatment.
- PET/TC to assess response, if not done in the last 3 months.
- Peripheral blood samples for MRD studies (see Annex VII).

F. Follow-up visits (PFS):

Visits will be made every three months until disease progression is observed or until the end of the study, which will include the following:

- History, physical examination, ECOG, vital signs.
- Biochemistry and HC.
- Monitoring of adverse events.
- Thoracic, abdominal, and pelvic TC every 6 months for the first 2 years. PET/TC in case of suspected recurrence or progression or to confirm CR.
- Peripheral blood samples for MRD studies (see Annex VII), at the same time as imaging evaluations.

G. Follow-up Visits (OS):

	• Data on overall survival.
Calendar	Presentation: December 2015 Start of inclusion: March 2016 inclusion: April 2018 End date ofEnd date of the study: September 2020 Presentation of results: ***to be determined (Version 1.2: July 7, 2016)***

1. REVISION SHEET

Version	Date	Detail/ Modification	Summary of changes	Justification
1.0	-	1st Version presented to the CEIC	NA	-
1.1	4/Jan/2016	1st Version approved by the CEIC	Administrative changes.	Response to the questions raised by the CEIC during the initial evaluation of the study.
1.2	7/Jul/2016	Non-substantial modification	Screening and Inclusion Procedure Section **3.4**: The recommended premedication in relation to Rituximab is detailed. ***(Version 2: 2016-Oct-21)*** Pg. 28: Grade ≥3 Neutropenia (ANC <1 x 10^9/L [ie, <1000/mm^3]) with infection or fever. Translation errors and administrative changes.	The inclusion procedure will be carried out through an online platform 24/7, specific to this study. Annex XII is incorporated. The recommended pre-medication is unequivocally clarified based on the Technical Sheet and clinical practice of each center. Page 28: Conforms to the criteria NCI-CTCAE(version 4.03) Translation errors and administrative changes
2.0	21/Oct/2016	Substantial modification	Update of the safety information	changes are being implemented to incorporate new safety information described in the latest edition of the Investigator's Manual, Investigator's Brochure - Edition 10 for the investigational drug IBRUTINIB whose manufacturer is [redacted] *1/14/945/002).* In order to prevent the safety

			Clarification in one of the inclusion criteria	information detailed in the protocol from becoming out of date as a result of regular safety updates to the Investigator's Manual, it is decided to make direct reference to the most current edition of this manual and to the Summary of Product Characteristics at the points of the protocol (except for the patient information sheet) where the safety information of the investigational product is already collected in accordance with said manual. A clarification has also been added to one of the study's exclusion criteria to emphasize the possibility of including young patients who are not candidates for autologous transplantation because they have received more than one line of treatment and are refractory. This aspect was not explicitly reflected in the patient selection criteria, although it was implicitly contemplated in the following exclusion criteria: *Candidates for autologous stem cell transplantation*.
			Medication of the protocol / concomitant treatments	Section 3.4 (Protocol Medication) is amended to state that adequate G-CSF prophylaxis should be given after cycles of chemotherapy to reduce the duration of neutropenia and the incidence of febrile neutropenia. Because this treatment is performed routinely in patients receiving R-GemOX-type regimens and, therefore, in the patients included in this trial, this modification is made to recommend the specific regimen to be followed during chemotherapy cycles with the The objective is to do it in the same way in all the patients in the trial, although the regimen recommended in the specific protocols (if any) of each center may be used.
			Treatment Plan	Due to the fact that the tumor samples must be evaluated for centralized review of the histopathological diagnosis in the Pathological Anatomy Service of the [redacted] in the first place and then in the [redacted] to determine the cell of origin (GCB vs. ABC-like DLBCL) by the 20-gene digital stringent expression test (NanoString), the NanoString cell of origin assignment result may not be available at the time the patient receives the 4th cycle of the study's R-GemOx scheme. As a consequence, the sponsor has decided that the assessment of the decision to continue in the trial at the end of the 4th cycle of treatment be made based on the result obtained in the

				centralized review reflected in the histopathological diagnosis report of the service of [redacted] In this way, the sections of the protocol that refer to the treatment plan after the 4th cycle are modified as detailed below: ● Those patients in Complete Remission (CR), Partial Response (PR) or Stable Disease (SE), and with centralized review report confirming the diagnosis of non-germinal center B-cell (non-GCB) DLBCL, they may continue to receive trial treatment according to the criteria established in section 3.3 (Treatment plan). ● Those patients in Progression must abandon the trial treatment. ● Those patients with a centralized review report that does not confirm the local diagnosis of non-GCB DLBCL, may continue to receive the treatment of this study within the clinical trial as long as the investigator of the center confirms that the patient is obtaining a clinical benefit and improvement of their disease as a consequence of the administration of the study treatment. These cases will be discussed with the study coordinators and the center investigator must inform the patient of the centralized diagnosis, as well as confirm the patient's decision to continue in the clinical trial.
			GemOx Adjustment	Based on the experience of the group [redacted] with the R-GemOx-Dexa regimen and the results obtained in a previous clinical trial in the same study population (5), it was decided to modify section 3.5.3 (GemOx dose adjustments) where the criterion of the number of platelets that the patient must present to receive the next cycle of GemOx is indicated: from 70,000 / µl it is extended to 50,000 / µl.
			Typographical/Formatting Protocol errors	Finally, typographical and formatting errors are rectified and corrected.

2. RATIONALE AND OBJECTIVES

2.1 RATIONALE

The use of highly effective rituximab treatments for the treatment of diffuse large B-cell lymphoma (DLBCL) makes recovery more difficult for patients with relapse or resistance to treatment (1, 2). In addition, patients who are elderly or have significant comorbidities, who are therefore not candidates for high-dose consolidation treatment, have a worse prognosis (3). In this context, prospective studies evaluating new salvage treatments are essential.

The combination of rituximab, gemcitabine, and oxaliplatin (R-GEMOX) is an effective salvage regimen for patients with relapsed or refractory DLBCL, with a favorable toxicity profile for noncompliant and/or noncompliant patients. elderly (3, 4). A phase II trial included 49 patients with relapsed (DLBCL who were*n*= 6) or refractory (*n*= 43)not candidates for ASCT. The median age was 69 years. After four cycles, 21 patients (44%) had complete remission (CR) and 8 (17%) partial response (PR), resulting in an overall response rate (ORR) of 61%. However, patients previously exposed to rituximab had significantly worse ORR (23% vs. 65%; *p*= 0.004), as well as significantly worse progression-free survival (PFS) (median 4 months vs. 11 months; median 4 months vs. 11 months; *p*=0.02) than patients who have not received prior treatment with rituximab (3). Therefore, new therapeutic regimens are needed for these patients, and GEMOX could be a good therapy for new combinations with targeted treatments (4,5).

Using gene expression profiling (PEG), DLBCL can be divided into prognostically important subgroups, with germinal center B cell (GCB), activated B cell (ABC) gene expression profiling or type 3 (6,7). The GCB type group has a significantly better survival than the ABC type group. The type 3 group is heterogeneous and not well defined, but has a similar poor outcome to the type ABC group. The initial requirement for fresh frozen tissue biopsies and microarray technology has been shown to be an obstacle to the implementation of molecular subtyping of cell of origin (CDO) in routine clinical practice. To overcome these obstacles, several algorithm-based immunohistochemical (IHC) studies have been proposed (8,9,10). However, these are limited by their binary nature (not identifying the 10% to 15% of unclassified biopsies by PEG), as well as significant interlaboratory and interobserver variability. These factors have contributed to the presence of important discrepancies in the literature regarding the prognostic significance of the CDO subtypes determined by IHC (11,12,13). Recent improvements in technology have provided the opportunity to use formalin-fixed paraffin-embedded tissue (TFFIP) biopsies to obtain reliable PEG (14). The feasibility of applying digital gene expression to analyze TFFIP samples for CDO assignment has recently been published. The Lymph2Cx trial identified groups of patients with significantly different outcomes after R-CHOP treatment, independent of IPI score, and was shown to be a reliable test, with excellent agreement in CDO assignment between different laboratories (15 ,16).

Recent studies indicate that new therapeutic agents have selective activity on the ABC and GCB subtypes (17,18,19). Ibrutinib, an oral Bruton tyrosine kinase inhibitor, is a potent killer of ABC-type

DLBCL cell lines *in vitro* and in xenografts (20). It exhibits monotherapy activity in relapsed and refractory B-cell malignancies, with few toxic side effects (21,22,23,24). In a phase I study, patients with relapsed or refractory B-cell malignancies had a 60% overall response, with 16% of patients in complete remission when given ibrutinib (25). In patients with relapsed DLBCL, ibrutinib showed preferential activity against tumors with the ABC subtype, with a 37% response, with very little activity (5% response) in the GCB subtype (26). Ibrutinib has also been evaluated in combination with immunochemotherapy. In a phase I-II study, ibrutinib was combined with R-CHOP in patients with previously untreated CD20-positive B-cell non-Hodgkin's lymphoma. In the dose escalation phase (part 1), patients with diffuse large B-cell lymphoma, mantle cell lymphoma, or follicular lymphoma were included. Patients received ibrutinib 280 mg, 420mg, or 560mg daily in combination with an R-CHOP regimen every 21 days. The safety of the recommended phase II dose was subsequently evaluated in a dose-expansion population composed of patients with newly diagnosed diffuse large B-cell lymphoma (Part 2). Thirty-three patients were included (Part 1: 17; Part 2: 16) and 32 received treatment with ibrutinib plus R-CHOP (one patient withdrew from the Part 2 cohort). The maximum tolerated dose was not reached and the recommended dose in phase II of ibrutinib was 560mg daily. The most common grade 3 or higher adverse events were neutropenia (73% [24 of 33 patients]), thrombocytopenia (21% [seven patients]), and febrile neutropenia and anemia (18% each [six patients]). The most frequently reported serious adverse events were febrile neutropenia (18% [six patients]) and hypotension (6% [two patients]). Thirty (94%) of the 32 patients who received one or more doses of the combination treatment achieved an overall response. All 18 patients with diffuse large B-cell lymphoma who received the recommended dose in phase II had an overall response. For those patients subtyped and treated with the recommended dose in phase II, five (71%) of the seven patients with germinal center B-cell subtype and two (100%) patients with B-cell subtype non-germinal center presented a complete response (27). These results demonstrate that ibrutinib is well tolerated when added to immunochemotherapy, and that it may improve responses in patients with B-cell non-Hodgkin's lymphoma.

Taking these data together, we hope that the combination of ibrutinib with R-GEMOX-dexa may be effective and well tolerated.

Therefore, we propose a phase II, multicenter, open-label, non-randomized study to assess the safety and efficacy of the combination of ibrutinib with rituximab, gemcitabine, oxaliplatin, and dexamethasone followed by ibrutinib as maintenance treatment for the salvage treatment of patients with relapsed or refractory non-GCB DLBCL who are not candidates for stem cell transplantation.

2.2 OBJECTIVES

Primary

1. To assess the efficacy of the combination (IR-GEMOX-dexa) as salvage treatment in patients with refractory or relapsed non-GCB DLBCL, in terms of overall response rate (ORR).

Secondary

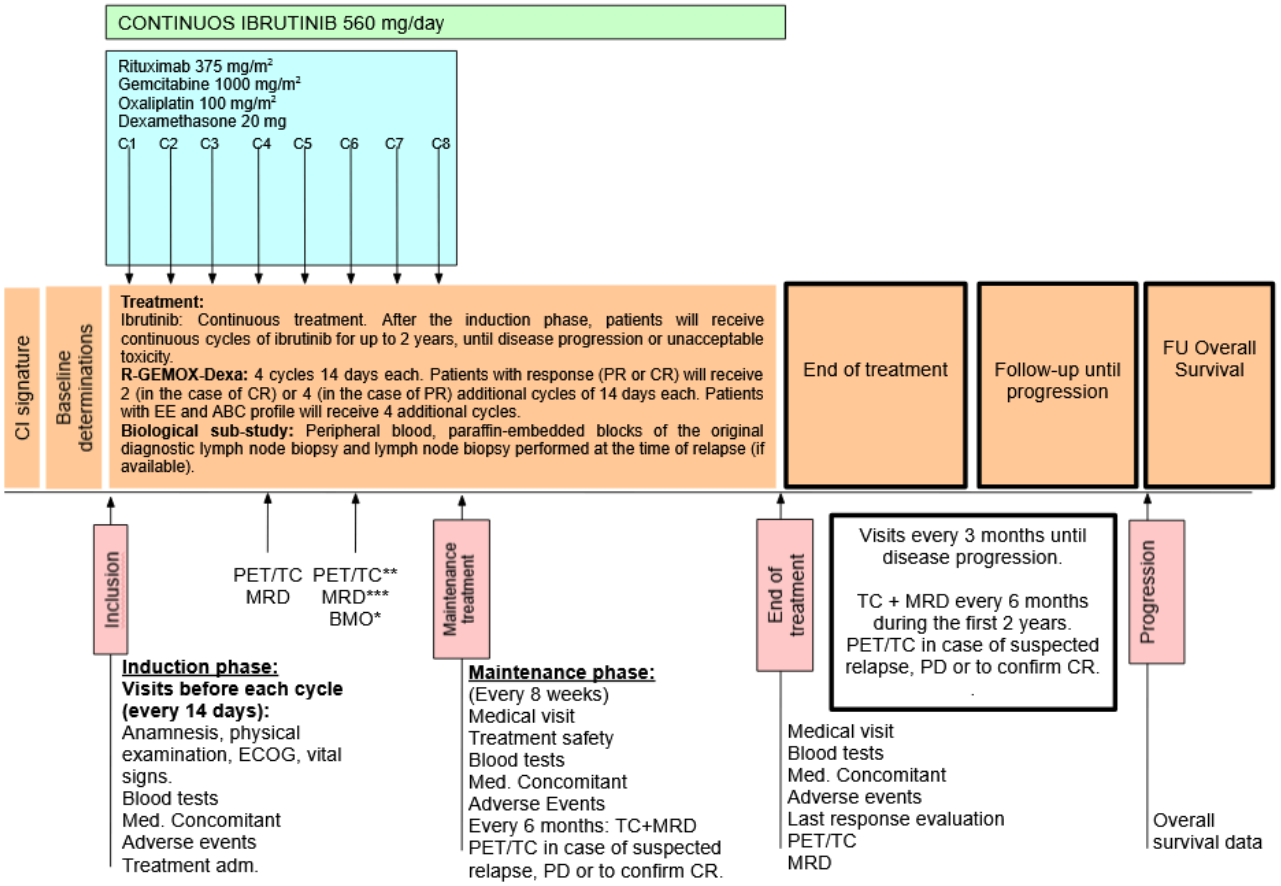
1. To assess the efficacy of the combination of IR-GEMOX-dexa followed by ibrutinib as maintenance treatment in terms of secondary endpoints (complete remission (CR), overall survival (OS), event-free survival (EFS), of progression [PFS] and duration of response).
2. To determine the safety and tolerability of ibrutinib in combination with R-GEMOX-dexa.
3. To determine the safety and tolerability of ibrutinib as maintenance treatment.
4. Identify clinical and biological prognostic factors that influence response and survival rates.
5. Establish a correlation between mutational status and response and survival.
6. Evaluate the relationship of PET/TC results with biological markers.
7. Establish a correlation between HLA polymorphisms and response and survival.
8. Establish a correlation between minimal residual disease (MRD) at the end of treatment (6-8 cycles of IR-GEMOX) with the response observed in PET/TC and survival.

3. STUDY DESIGN AND TREATMENT DESCRIPTION

3.1 DEVELOPMENT PHASE

Phase II exploratory clinical trial.

3.2 STUDY DIAGRAM



* In case of infiltration at the time of enrollment in the study
** PET/TC after the 4th cycle and at the end of the 6th or 8th cycle of IR-GEMOX
*** MRD studies in peripheral blood at the end of the 6th or 8th cycle of IR-GEMOX

3.3 TREATMENT PLAN

Patients will receive ibrutinib in combination with R-GEMOX-dexa followed by ibrutinib as maintenance treatment, according to the following schedule:

Induction phase:

- 375 mg/m^2 rituximab iv on day 1.
- 1000 mg/m^2 gemcitabine iv on day 1 or 2 (at investigator's discretion).
- 100 mg/m^2 oxaliplatin on day 1 or 2 (after gemcitabine administration).
- Dexamethasone 20 mg orally or IV on day 1 and orally on days 2 and 3.
- Ibrutinib 560 mg daily for 14 days.

Evaluation of response will be done after the 4th cycle (10-14 days after the start of the 4th cycle). Patients who show ***clinical benefit*** (RP, CR ***or EE)*** will receive 2 (in the case of CR) or 4 (in the case of PR ***or EE)*** additional cycles of 14 days each. Evaluation of response will be done after the 6th or 8th cycle (21-35 days after the start of the 6th or 8th cycle).
Those patients with a centralized review report that does not confirm the diagnosis local non-GCB DLBCL, may continue to receive the treatment of this study according to the previous response criteria within the clinical trial as long as the investigator of the center confirms that the patient is obtaining a clinical benefit and improvement of their disease as a consequence of the administration of the study treatment. These cases will be discussed with the study coordinators and the center investigator must inform the patient of the centralized diagnosis, as well as confirm the patient's decision to continue in the clinical trial.

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Maintenance phase:
After the induction phase, patients who present a response will receive ibrutinib 560mg daily. Continuous cycles for up to 2 years, until disease progression or unacceptable toxicity occurs (whichever comes first).
Patients with an inferior response to ***EE*** after the induction phase and patients experiencing disease progression at any time during induction should terminate treatment. The PET/TC will be reviewed by the PET platform [redacted] (see annex VI). Treatment decisions will be made pursuant to centralized review.

(*Version 2: October 21, 2016)*

This clinical trial includes:

- Centralized review of response by imaging. See annex VI.
- Central histological review of the diagnosis. See annex VII.
- Associated biological projects. See annex VII.

1. Patient selection procedure:

Before starting the selection period, informed consent must be obtained from the patient, using the latest version in force throughout the study. The different procedures performed as part of the patient's usual clinical treatment (eg, blood tests, diagnostic imaging tests, etc.) and performed before the signing of the informed consent may be used for screening or considered baseline if these Tests were performed as specified in this protocol. Once the informed consent has been signed, each patient will be assigned a selection number (selection code). Each center will receive in the investigator's center file the selection form in which the default numbers for selection are assigned. This document must always remain at the study center under the custody of the research team. This screening number will identify the patients during the period between signing the informed consent and inclusion in the study.

2. *Procedures **screening and** inclusion of the patient:*

The procedure for screening and inclusion will be made through the following platform: [redacted] from [redacted] it will be provided usernames and passwords to researchers and people assigned by them to the performance of the procedure. Through the registration of patients on the platform, an email confirming the screening or inclusion will be automatically generated.
It is important to remember that the patient will not be able to receive treatment until the center has received the inclusion confirmation email that the system generates automatically.
For the correct fulfillment of the procedure, Annex XII is attached.

3.4 PROTOCOL MEDICATION

1. 560mg ibrutinib daily for 14 days during induction cycles. Maintenance phase: continuous cycles until disease progression or unacceptable toxicity occurs (maximum of 2 years).

Supply of ibrutinib: ibrutinib will be supplied by the sponsor, through [redacted]. Ibrutinib (4 capsules for a 560mg dose) should be administered orally with a glass of water, at approximately the same time each day. The capsules must be swallowed whole with water and must not be opened, broken or chewed. Avoid consumption of grapefruit and blood orange during treatment with ibrutinib. If the 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 additional capsules to make up for a missed dose.
Ibrutinib is authorized by the EMA, but not for the indication proposed in this protocol.

2. R-GEMOX-dexa; 4 cycles every 14 days:
    - rituximab 375mg/m^2 iv on day 1.
    - 1000mg/m^2 Gemcitabineiv (30-minute infusion) on day 1 or 2.
    - 100mg/m^2 Oxaliplatin(3-hour infusion) on on day 1 or 2 (after gemcitabine administration).
    - Dexamethasone 20mg orally or IV on day 1 and orally on days 2 and 3.

*Patients with ***clinical benefit*** (PR, CR, ***or EE***) will receive 2 (for CR) or 4 (for the case of PR ***or EE***) additional cycles of 14 days each.

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Before the infusion of rituximab, it ***is recommended to administer the usual pre-medication of each center that includes:***

- ***Antipyretic***
- ***Antihistamine***
- Optionally, and at the investigator's discretion, use of glucocorticoids (eg, methylprednisolone 60 mg IV) as part of pretreatment and if a reaction to rituximab occurs.

Rituximab will be administered intravenously. The first infusion will start at a rate of 50mg/hour. If well tolerated, increments of 50 mg/hour can be made every 30 minutes, up to a maximum of 400mg/hour. Subsequent infusions can be given at an initial rate of 100mg/hour, with increments of up to 100mg/hour at 30-minute intervals to a maximum of 400mg/hour.

Rituximab supply: Rituximab, a treatment marketed and used in an authorized indication, will be supplied by the participating hospital through the local supply procedure.

Prior to oxaliplatin infusion, the following should be administered:

- Appropriate antiemetic therapy (anti-5HT3).

The patient will be warm and away from cold drafts.
Likewise, every effort will be made to keep the extremity being infused warm. Dexamethasone can be associated with Polaramine, and the infusion can be slowed down from 4 to 6 hours in patients who experience some type of previous reaction and present late vomiting.
In order to reduce the duration of neutropenia and the incidence of neutropenia febrile after each cycle of chemotherapy, prophylaxis with G-CSF should be administered according to the protocols established in each center (except for contraindications or intolerance). One of the following guidelines is recommended (as applicable):

- ***Administer between days +2 and +4 (of the cycle) G-CSF at a dose of 300 µgr/Kg up to a total of 6 -8 days.***
- ***Administer between days +2 and +4 (of the cycle) Pegfilgrastim 6 mg, single dose.***

(***Version 2: October 21, 2016)***

3.4.1 Possible adverse events of ibrutinib

Possible adverse events of ibrutinib, The information regarding contraindications, warnings, special precautions for use, as well as possible interactions with other drugs, ***should be consulted in:***

- Latest version of the Investigator's Manual available in the archive of the investigator's center.
- **Latest version of the** Summary of Product Characteristics (SPC), available in the file of the investigator's center or on the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=
pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

3.4.2 Possible adverse events of other drugs used in the study

For the rest of the drugs administered to the patients in the study, information regarding contraindications, warnings, special precautions for use, as well as possible interactions, available at:

- Summary of Product Characteristics (SPC), available in the file of the investigator's center or on the EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

3.5 DOSE ADJUSTMENTS

3.5.1 Adjustments of ibrutinib

Treatment with ibrutinib should be interrupted in the following cases:

- Non Toxicity hematological d and grade ≥3.
- Grade ≥3 neutropenia (ANC <1 x 10^9/L [ie, <***1,000*** /mm^3]) with infection or fever. ***(Version 1.2: July 7, 2016)***
- Grade 4 neutropenia (ANC <0.5 x 10^9/l [ie, <500/mm^3]).
- Grade 3 thrombocytopenia (platelets <50 x 10^9/L [ie, <50,000/mm^3]) in the presence of major bleeding (ie, ≥ Grade 2 bleeding).
- Grade 4 thrombocytopenia (platelets <25 x 10^9/L [ie, <25,000/mm^3]).
- ***Other significant toxicities not reflected in the previous points if the investigator considers that the risk of administering Ibrutinib outweighs the benefits.***
  (*Version 2: October 21, 2016)*

Once symptoms of toxicity have resolved to grade 1 or baseline (recovery), ibrutinib treatment may be resumed at the starting dose. If toxicity recurs, the daily dose should be reduced by one capsule (140mg). If necessary, a second dose reduction of 140 mg may be considered. If such toxicities persist or recur after two dose reductions, the drug should be discontinued. Study drug may be withheld for up to 21 consecutive days. Study drug administration should be permanently discontinued in the event of toxicity lasting more than 21 days, unless site investigators consider that the benefit of continuing ibrutinib treatment outweighs the risk.

Recommended dose modifications are described below:

Modifications to ibrutinib dose	
Appearance of the same adverse event	**Action**
First	Interrupt study drug until recovery to ≤ Grade 1 or baseline; can be reset to the original dose level.
Second	Interrupt study drug until recovery to ≤ Grade 1 or baseline; restart at a lower dose level (3 capsules [ie 420mg daily]).
Third	Interrupt study drug administration until recovery to ≤ Grade 1 or baseline; restart at a lower dose level (2 capsules [ie 280mg daily]).
Fourth	The study drug is suspended.

Dosage level	**Dose**
0	560mg/día
-1	420mg/día
-2	280mg/día
Ibrutinib suspension	

Missed dose

If dose is not taken at scheduled time, it can be taken as soon as possible on the same day with a return to normal schedule the next day . The patient should not take additional capsules to make up for a missed dose.

Special warnings and precautions for use

The following study documents should be consulted:

- Latest version of the Investigator's Manual available on file at the investigator's center.
- Latest version of the Summary of Product Characteristics (SPC), available in the file of the investigator's center or on the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl = pages / medicines / landing / epar_search.jsp & mid = WC0b01ac058001d124

(version*2: October 21, 2016)*
3.5.2 Titration of rituximab

No possibility of modifications contemplated by the dose. Mild or moderate infusion reactions usually resolve by slowing the infusion rate and increasing it when symptoms improve.
Patients should be closely monitored for the onset of cytokine release syndrome. The infusion should be stopped immediately in patients who develop any evidence of serious reactions, especially severe dyspnoea, bronchospasm or hypoxia. Evidence of tumor lysis syndrome should then be evaluated, including appropriate laboratory tests and, in the case of evidence of pulmonary infiltration, with a chest X-ray. The infusion should not be restarted until complete remission of all symptoms and normalization of laboratory values and chest X-ray results. From this point on, the infusion can be resumed at half the rate of the previous infusion. If the same serious adverse reactions are observed a second time, the decision to terminate treatment should be discussed with the lead study investigatorinvestigation@ .net case-by-case basis.
Anaphylactic and hypersensitivity reactions have been reported to occur following iv administration of murine proteins, usually occurring within the first few minutes of infusion. Drugs used to combat hypersensitivity reactions, ie, epinephrine, antihistamines, and corticosteroids, should be available for immediate use in case an allergic reaction occurs during administration. The clinical manifestations of anaphylaxis may resemble those 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, discontinuation of antihypertensive treatments within 12 hours prior to infusion should be considered. Cases of angina pectoris or cardiac arrhythmias such as atrial flutter and fibrillation, heart failure and/or myocardial infarction have been reported in patients treated with rituximab. Therefore, careful monitoring should be performed in patients with a history of heart disease and/or chemotherapy-associated cardiotoxicity.
Cases of reactivation of hepatitis B, including cases of fulminant hepatitis, have been observed in patients who were treated with rituximab with cytotoxic chemotherapy. When rituximab is used in combination with cytotoxic chemotherapy, patients with a history of hepatitis B should be closely monitored for signs of active hepatitis B virus infection and antiviral therapy initiated if clinically indicated (see section 2.7).
The prepared solution must be administered as an intravenous infusion through a specific line. It should not be administered as a direct or rapid intravenous infusion.

3.5.3 GEMOX dose adjustments

Before each cycle, an analytical follow-up will be carried out, with which the following criteria will be established to be applied in the following cycle:

- Neutrophils >1000/µl
- Platelets > ***50,000/µl***

(*Version 2: October 21, 2016)*

If the patient does not show hematological recovery on day 14 of the cycle, a new analysis will be performed every 7 days until the patient's recovery.
If haematological recovery is delayed for more than one week, the gemcitabine and oxaliplatin dose will be reduced by one level (-1) in the next cycle.
If haematological recovery is delayed for more than two weeks, gemcitabine and oxaliplatin doses will be reduced by 2 levels (-2) in the next cycle.
If for any reason the patient is unable to receive study treatment for 3 consecutive weeks, treatment should be discontinued after discussion with the study chief investigator.
Patients experiencing grade 4 non-hematologic toxicity will be withdrawn from the study if the toxicity is deemed unacceptable by the investigator's team.

Dose modifications - non-hematologic toxicity	
GRADE	DOSAGE LEVEL
0-2	0
3	-1
4	-2

Dose modifications - liver or kidney failure				
	Bilirrubin		Creatinine	
	2,0-4,0	>4	1,5 - 2,0	>2
Gemcitabine	-1	-2	-1	-2
Oxaliplatin	0	0	-1	-2

Oxaliplatin dosage level	**Dose**
0	100mg/m^2
-1	80mg/m^2
-2	65mg/m^2

Gemcitabine dosage level	**Dose**
0	1000mg/m^2

-1	800mg/m^2
-2	650mg/m^2

3.5.4 Protocol modifications based on toxicity (phase)

Pre-inclusionToxicity will be thoroughly evaluated in the first 4 induction cycles with the IR-GEMOX regimen in the first 6 - 12 patients included in the study, such that if a minimum of 3 of 6 or 6 of 12 patients experience any ≥3 grade hematologic toxicity and/or dose level reductions are required, the dose schedule would be modified. the following eligible patients in this study (ibrutinib level -1, gemcitabine and oxaliplatin). Should these dose modifications be made after enrollment of the first 6 and 12 patients in the study, 2 additional cohorts of 6 and 12 patients will be enrolled. Toxicities occurring in the first 4 cycles of these cohorts will be reassessed. If the regimen is considered toxic for this patient population, the study will be closed.

3.6 TREATMENT WITHDRAWAL CRITERIA

1. Disease Progression: Patients who progress will discontinue treatment but will continue to attend study visits for treatment and long-term follow-up.
2. Patients with a response less than ***EE*** after 4 cycles of induction phase.
3. Unacceptable toxicity.
4. Researcher's decision.
5. Refusal of the patient to continue with the study treatment.

(***Version 2: October 21, 2016)***

3.7 CONCOMITANT TREATMENTS

Concomitant treatments include all prescription and non-prescription drugs or treatments used by the patient from 7 days before starting study treatment to 30 days after the last medication of the studio. The doctor responsible for the treatment will prescribe the necessary treatments for the concomitant diseases presented by any patient included in the study. The patient must inform the investigator and record all concomitant medication in the corresponding CRDe.

Patients undergoing treatment with oral contraceptives, hormone replacement therapy or other maintenance treatments should continue with this treatment.

to. Pretreatment Steroids Steroid use

Is permitted up to 10 days prior to the start of study treatment (ie, up to 100mg prednisone or equivalent). If steroids are given, they should be given after screening radiologic evaluation, baseline laboratory evaluations, and baseline performance status assessment.

b. Treatment and prophylaxis for neutropenia

G-CSF should be administered as primary prophylaxis for neutropenia (unless contraindicated or intolerable), as indicated in section 3.4 of this protocol.

(*Version 2: October 21, 2016)*

c. Hepatitis B reactivation prophylaxis hepatitis B

Patients who are surface antigen positive or antinuclear antibody positive should receive appropriate prophylaxis according to local standards.

d. Antimicrobial prophylaxis

The use of antimicrobial prophylaxis (eg, prophylaxis for *Pneumocystis pneumonia* with sulfamethoxazole and trimethoprim or equivalent) is recommended, according to institutional guidelines.

It is allowed for the **central nervous system prophylaxis** in accordance with local guidelines. CNS prophylaxis with iv methotrexate is not allowed

f. The use of **erythropoietic drugs** when the hemoglobin level is <10 g/dl and will be discontinued when the level is >12g/dl.

g. Prohibited Concomitant Medications Concurrent

Anychemotherapy, antineoplastic immunotherapy, experimental treatment, or radiation therapy is prohibited. The use of corticosteroids when administered as premedication or to treat rituximab infusion-related reactions or contrast medium allergies, as well as short courses (<14 days) of corticosteroid therapy for medical reasons not related to cancer, is permitted. (eg, treatment for autoimmune cytopenias), in doses not to exceed 100mg/day of prednisone or equivalent. In contrast, corticosteroid doses equivalent to >20mg/day of prednisone are not allowed; routine pre-infusion medication with corticosteroid doses >100mg prednisolone (or equivalent) intravenously is not permitted.

g. Invasive procedures:

The following guidelines should be applied perioperatively for patients who require surgery or an invasive procedure while receiving ibrutinib:

- For surgery or invasive procedures requiring sutures or staples for closure, ibrutinib should be discontinued at least 7 days before the intervention and It will be administered for at least 7 days after the procedure or intervention, and will be resumed at the discretion of the

investigator when the surgical wound is reasonably healed, without serohematic drainage or the need for drainage tubes.

- For minor procedures (such as central line placement, core needle biopsy, thoracentesis, or paracentesis), ibrutinib should be stopped at least 3 days before the procedure and not restarted for at least 3 days after the procedure. In the case of bone marrow biopsies performed while the subject is on ibrutinib treatment, interruption of ibrutinib treatment will not be necessary.
- For procedures in emergency situations, administration of ibrutinib should be withheld after the procedure and until the surgical wound is reasonably healed, for at least 7 days following emergency surgery.

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

The following study documents should be consulted:

- Latest version of the Investigator's Manual available on file at the investigator's site.
- Latest version of the Summary of Product Characteristics (SPC), available in the file of the investigator's center or on the EMA website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

(***Version 2: October 21, 2016)***

3.7.2 Interaction of rituximab/gemcitabine/oxaliplatin/dexamethasone with other medicinal products and other forms of interaction

Information on the possible interactions with other drugs of other therapeutic drugs indicated in the study schedule, available at:

Summary of product characteristics available on file with the investigator's center or on the EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

4. PATIENT ELIGIBILITY

CRITERIA 4.1 INCLUSION CRITERIA

1. Patients with confirmed histological diagnosis of diffuse large B-cell lymphoma. Patients ≥18 years of age.
2. Non-germinal center B cell subtype (non-GCB) according to Hans' algorithm (local laboratories).
   Centralized evaluation will be performed to confirmB cell subtype ***non-germinal center(non-GCB)***, but a negative result will not exclude the patient from the study if ***clinical benefit (CR, PR, or SE) is obtained*** after the study. 4th cycle.
   (***Version 2: October 21, 2016)***
3. Recurrent or refractory disease after:
   - At least one prior line of treatment, including rituximab in combination with chemotherapy; or,
   - After a previous TACM; or,
   - Following allogeneic transplant with reduced-intensity conditioning, unless the patient is receiving immunosuppressive drugs or has graft-versus-host disease at the time of study enrollment.

   (Resistance to treatment is defined as the inability to achieve CR after treatment latest.)
4. Performance status *Eastern Cooperative Oncology Group* (ECOG) ≤2.
5. PET with baseline FDG showing positive lesions (Deauville 4 or 5) consistent with the anatomical tumor locations defined on CT.
6. Hematological values should be within the following limits:
   a. Absolute neutrophil count (ANC) ≥1000/µl regardless of growth factor treatment.
   b. Platelets ≥100,000/µL or ≥50,000/µL in case of bone marrow involvement independent of transfusion therapy in either situation.
7. Biochemical values within the following limits:
   a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of normal (ULN).
   b. Total bilirubin ≤1.5 times the ULN, unless the increase in bilirubin is due to Gilbert's syndrome or non-hepatic in origin.
   c. Serum creatinine ≤2 times the ULN or estimated creatinine clearance (CCr) ≥30ml/min.
8. Females of reproductive potential and sexually active males must use a highly effective method of contraception during and after the study, in accordance with local regulations regarding the use of contraceptive methods for participants in clinical trials. Men must agree not to donate sperm during and after the study. For females, these restrictions apply for 1 month after the last dose of study drug. In males, these restrictions apply for 3 months after the last dose of study drug.

9. Females of reproductive age must have a negative serum (beta-human chorionic gonadotropin [pregnancy test atβ-potentialhCG]) or urine screening. Pregnant or lactating women cannot participate in this study.
10. Signature (or signature of the legal representative) of an informed consent document indicating that they understand the purpose and procedures required by the study and express their desire and ability to participate in the study.

4.2 EXCLUSION CRITERIA

1. Prior malignancy other than DLBCL, with the exception of adequately treated basal cell carcinoma and squamous cell carcinoma, cervical cancer *in situ,* or other tumors that have not recurred for at least 2 years or will not limit survival to <2 years (Note: these cases should be discussed with the principal investigator).
2. Autologous stem cell transplant candidates.
   NOTE: Young patients who have received more than one line of treatment and are refractory may be considered ineligible for autologous stem cell transplantation and are therefore eligible for this study.
   (***Version 2: October 21, 2016)***
3. Life-threatening disease, condition, or organ dysfunction that, in the opinion of the investigator, could compromise patient safety, interfere with the absorption and metabolism of ibrutinib, or pose an unreasonable risk to treatment outcomes. study.
4. Significant cardiovascular disease, such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months prior to screening, or anyclass 3 or 4 heart disease *New York Heart Association*.
5. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small intestine or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete intestinal obstruction.
6. Treatment with any immunotherapy, chemotherapy, radiotherapy, or experimental treatment within 3 weeks prior to first dose of study drug (corticosteroids permitted for disease-related symptoms and as noted in section **3.7**). **(*Version 2: October 21, 2016)***
7. Prior treatment with ibrutinib or other BTK inhibitors.
8. Central nervous system (CNS) involvement by lymphoma.
9. History of stroke or intracranial hemorrhage in the 6 months prior to inclusion.
10. Need for anticoagulation with warfarin or equivalent vitamin K antagonists.
11. Need for treatment with potent CYP3A inhibitors (see the ***"Potential for Drug-Drug Interactions" section of the Investigator's Manual). (Version 2: October 21, 2016)***
12. Grade ≥2 toxicity (except alopecia) related to prior anticancer therapy, including radiation.
13. History of human immunodeficiency virus (HIV) infection, active hepatitis C virus infection (HCV; positive RNA polymerase chain reaction [PCR]), or active hepatitis B virus infection (

HBV; DNA PCR positive) or any active uncontrolled systemic infection requiring IV antibiotics Patients with negative HBV PCR are allowed to be included.

14. Major surgery within 4 weeks prior to the first dose of study drug.
15. Administration of live attenuated vaccines in the 4 weeks prior to inclusion.
16. Pregnancy or lactation.

4.3 STUDY COMPLETION CRITERIA

Investigators should encourage patients to complete the trial; however, patients may voluntarily withdraw from the trial at any time. The investigator may also, at his discretion, withdraw patients from this trial or the sponsor may suspend the trial.

The causes of premature withdrawal from the study must be documented in the data collection notebook (CRF) as:

- Closure/termination of the trial.
- Patient lost follow-up.
- Researcher's decision.
- Withdrawal of informed consent from the patient.
- Important deviation from the protocol, when appropriate.
- Death.

The date of withdrawal from the study and the reason for withdrawal must be recorded on the CRF. Subsequent treatment and follow-up until death will be determined by ensuring the patient's medical care in accordance with clinical practice. In the event of death, an autopsy certificate with cause of death should be obtained, if possible.

Note: Patients who discontinue the study for any reason cannot be re-enrolled.

5. CONDUCT OF THE STUDY AND ASSESSMENT OF RESPONSE

5.1 STUDY

ENDPOINTS Primary endpoint:

1. Overall response rate (complete remission + partial response) of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin, and dexamethasone.

Secondary endpoints:

1. CR rate during the induction and maintenance phases.
2. Conversion rate from EE or PR to PR or CR during the maintenance phase.
3. Response duration.

4. Progression free survival.
5. event-free survival.
6. overall survival.
7. Safety and tolerability of ibrutinib in combination with rituximab, gemcitabine, oxaliplatin, and dexamethasone.
8. Safety and tolerability of ibrutinib as maintenance treatment.
9. Influence of clinical and biological prognostic factors on response and survival rates.
10. Establish a correlation between mutational status and response and survival.
11. Establish a correlation between HLA polymorphisms and response and survival.
12. Establish a correlation between the response observed in the PET/TC and the biological markers.
13. Establish a correlation between MRD at the end of treatment (6-8 cycles of IR-GEMOX) with the response observed in PET/TC, PFS and OS.

5.2 CONDUCT OF THE STUDY

All the data of patients included in the study will be collected in the data collection notebook (CRD). Active patient monitoring includes history, physical examination, laboratory tests, ECOG status, vital signs, assessment of adverse events, and concomitant medication.
Information on adverse events and concomitant medication will be collected up to 30 days after the last administration of study medication. In the case of serious adverse events (and related to concomitant medication), the data recording will be extended until the SAE has resolved or is considered clinically stable according to medical criteria.
When a patient completes the protocol procedures, no additional diagnostic tests will be performed, only survival data will be collected.
The tests and evaluations that will be carried out in the different periods of the study are detailed below.

5.2.1 *Before the start of treatment:*

Within a maximum period of 28 days* (8 days for complete blood count and biochemistry) before the start of treatment, the following clinical and biological data must be determined and obtained:

- Informed consent.
- Clinical history, concomitant medication, demographic data, physical examination, ECOG.
- Height, weight and vital signs.
- Local histological diagnosis. Obtaining a tumor biopsy at the start of the study is recommended, especially in cases of recurrence. Paraffin-embedded blocks of biopsies will be sent for central diagnostic validation and biological studies (see Annex VII). A centralized evaluation will be carried out to confirm the subtype ***non-GCB*** before administration of the 4th cycle.
  (*Version 2: October 21, 2016)*

- Complete blood count (HC).
- Biochemistry: creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, protein electrophoresis, albumin, IgG, IgA, and IgM, bilirubin, alkaline phosphatase, GGT, AST, ALT, LDH, and β2-microglobulin .
- Basal coagulation: PT, aPTT, fibrinogen.
- Serology: HBV (including HBsAg, HBsAc, and HBcAc; HBV DNA in cases with positive serology), HCV, HIV.
- Pregnancy test (carried out on blood or urine) in women of reproductive capacity.
- Disease assessment: PET/TC.
- Electrocardiogram.
- Left ventricular ejection fraction (optional, mandatory only in patients with a history of heart disease).
- Bone marrow biopsy.
- Peripheral blood samples for biological studies (see Annex VII).
- Questionnaires on comorbidities (see Annex X).

An extensive biological study will be performed in order to further characterize this population of DLBCL patients with AUC and to evaluate the response obtained with the mutational profile of the tumor. In the event that patients agree to participate in the biological study, peripheral blood, paraffin-embedded blocks from the original diagnostic lymph node biopsy, and lymph node biopsy performed at the time of recurrence (if available) are sent to a central laboratory to perform phenotypic subtyping tests, molecular studies, mutational spectrum, and determination of the cell of origin using NanoString technology (NanoString Technologies, WA, USA) (13). The biological studies will be coordinated by [redacted]

5.2.2 Tests and determinations during treatment

1. During treatment with IR-GEMOX-dexa:

Before each cycle of treatment:

- History, physical examination, ECOG, vital signs.
- CH and biochemistry (creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, albumin, bilirubin, alkaline phosphatase, GGT, AST, ALT and LDH).
- Concomitant medication.
- Adverse events.

Evaluation of response during induction:

- PET/TC 10-14 days after the start of the 4th cycle).
- Peripheral blood samples for biological studies (see Annex VII).

2. Evaluation of response at the end of induction:

21-35 days after the start of the 6th or 8th cycle:

- History, ECOG, physical examination, concomitant medication, adverse events.
- CH and biochemistry (creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, protein electrophoresis, albumin, IgG, IgA and IgM, bilirubin, alkaline phosphatase, GGT, AST, ALT, LDH and β2 -microglobulin).
- PET/TC.
- Bone marrow biopsy (in case of infiltrate at the time of inclusion in the study).
- Peripheral blood samples for MRD studies (see Annex VII).

3. Maintenance treatment:

Visits will be made every 8 weeks, which will include the following:

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

An evaluation of response will:

- Be performed a TC scan of the chest-abdominal-pelvic (and cervical if clinically indicated) will be performed every 6 months. PET/TC, if clinically indicated, in case of suspected recurrence or progression or to confirm CR.
- Peripheral blood samples for biological studies (see Annex VII), at the same time as imaging evaluations.

5.2.3 End of treatment visit (30 +/- 5 days)

On day 30 after completion or discontinuation of study treatment:

- History, physical examination, ECOG, vital signs.
- Biochemistry and HC.
- Concomitant medication.
- Adverse events.
- Reason for termination of treatment.
- PET/TC to assess response, if not done in the last 3 months.
- Peripheral blood samples for biological studies (see Annex VII).

5.2.4 Follow-up until progression (after the end of treatment)

Visits will be made every three months until disease progression is observed or until the end of the study and will include the following:

- History, physical examination, ECOG, vital signs.
- Biochemistry and HC.
- Monitoring of adverse events.

- A thoracic-abdominal-pelvic (and cervical if clinically indicated) TC scan will be performed every 6 months for the first 2 years. PET/TC, if clinically indicated, in case of suspected recurrence or progression or to confirm CR.
- Peripheral blood samples for biological studies (see Annex VII), at the same time as imaging evaluations.

5.2.5 Post-progression:

- follow-upOverall survival follow-up (alive/dead/lost to follow-up).

5.3 RESPONSE AND TOXICITY CRITERIA

Response to treatment will be assessed according to the Lugano Response Evaluation Criteria for Non-Hodgkin's Lymphoma (28).

5.3.1 Response definitions

Response will be classified according to the 2014 criteria of Cheson et al. (see annex IX). The PET/TC will be reviewed by the PET platform [redacted] (see Annex VI). Treatment decisions will be made pursuant to centralized review.

5.3.2 Assessment of toxicity

Toxicity will be classified according to theCommon Terminology Criteria for Adverse Events *National Cancer Institute* (CTCAE V 4.03).

5.4 TREATMENT AFTER COMPLETION OF THE STUDY

In the event of therapeutic failure and subsequent withdrawal from the protocol treatment program, each center will apply the treatment they consider most appropriate.

5.5 STUDY PROCEDURES

The following pages summarize the procedures that will be carried out in each of the study stages:

tests	***Before treatment initiation***	**Induction phase**	***End of induction period***	**Maintenance phase**	**End of study visit study**	**Follow-up unt progression**
	Day -28 and day 0	***Before each cycle (every 14 days)***	***21 - 35 days after the start of the 6th or 8th cycle***	***(every 8 weeks for 2 years)***	***30 days after completion of treatment***	
Informed consent	X					
Inclusion/exclusion criteria	X					
Date of birth, date of diagnosis, medical history, weight, height	X					
History/physical examination (including ECOG status and vital signs)	X	X	X	X	X	X
Local histological diagnosis (1)	X					
Complete blood count (CBC) (2)	X	X	X	X	X	X
Biochemistry (3)	X	X	X	X	X	X
Coagulation (4)	X					
Serology *(HIV, hepatitis B and C) (5)*	X					
Pregnancy test (in urine or blood)	X					
PET/TC	X	X *Perform 10 - 14 days after start of the 4th cycle*	X	X If clinically indicated or to confirm CR	X If not performed in the last 3 months	X If clinically indicated
TC (6)				X Every 6 months	***(Version 1.2: July 7, 2016)***	X Every 6 month during the first years

tests	***Before treatment initiation***	**Induction phase**	***End of induction period***	**Maintenance phase**	**End of study visit study**	**Follow-up unt progression**
	Day -28 and day 0	***Before each cycle (every 14 days)***	***21 - 35 days after the start of the 6th or 8th cycle***	***(every 8 weeks for 2 years)***	***30 days after completion of treatment***	
Electrocardiogram	X					
Ejection fraction: optional *(8)*	X					
Bone marrow biopsy	X		*X (in case of infiltrate at the time of inclusion in the study)*			
Concomitant medication.	X	X	X	X	X	
Adverse events.		X	X	X	X	X
Follow-up of overall survival						
Comorbidity questionnaires	X					
Initial diagnosis paraffin-embedded block (Version 1.2: July 7, 2016)	***X***					
Lymph node biopsy at recurrence (if available)	X					
(7) Blood peripheral	X	*10 - 14 days after the start of the 4th cycle*	X (for MRD studies)	X	X	X

1: Obtaining a tumor biopsy at the start of the study is recommended, especially in cases of recurrence. Paraffin-embedded blocks of biopsies will be sent for central diagnostic validation and biological studies (see Annex VII).

2: Hemoglobin, leukocytes with leukocyte formula and platelets. The baseline determination must be made in the ***8 (Version 1.2: July 7, 2016)*** days prior to the start of treatment. Determinations made before each of the cycles must be made ***within*** 48 hours before the cycles. ***(Version 1.2: July 7, 2016)***

3: Basal period and at the end of induction: creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, protein electrophoresis, albumin, IgG evaluation, IgA and IgM, bilirubin, alkaline phosphatase, GGT, AST, ALT, LDH and ***$\beta_2$mi***croglobulina ***(version 1.2: July 7,***2016).The baseline determination must be made within 8 days prior to the start of treatment.

Rest of the study: creatinine, urea, uric acid, Na, K, Ca, Mg, glucose, total protein, albumin, bilirubin, alkaline phosphatase, GGT, AST, ALT and LDH. Determinations made before each of the cycles must be made *within* 48 hours before the cycles. ***(Version 1.2: July 7, 2016)***

4: PT, TTP, fibrinogen.

5: Including HBsAg, HBsAc and HBcAc; HBV DNA in cases with positive serology.

6: TC chest, abdominal and pelvic, cervical (if clinically indicated).

7: Peripheral blood samples for MRD studies, at the same moments as the imaging evaluations.

8: Only mandatory in patients with a history of heart disease.

6. REPORTING OF ADVERSE EVENTS

The monitoring of the safety of the study will be governed by the provisions of the EU Directive 2001/20/EU and the detailed guide on obtaining, verifying and reporting adverse reactions/events that have appeared in clinical trials. They are medicines for human use.
The sponsor, through the lead study investigator, will assess the reported serious adverse events (SAEs) and determine the predictability of the reported events using available safety documents. In addition, it will urgently report all SAEs that are considered "suspected unexpected serious adverse reaction, SRAGI" to the competent authorities, with the help of the monitor and the center's staff.
Notification to the competent authorities (drug agencies, reference EC, local EC and other local competent bodies, according to local guidelines) and principal investigators of any reportable event is the responsibility of the sponsor, within the time limits established by local regulations (Suspicion of serious and unexpected adverse reactions must be reported to the competent authorities and the relevant Ethics Committees as soon as possible, within a maximum of 15 days from the time the sponsor first becomes aware; this period is reduced to 7 days in the event of SARS fatal and life-threatening).
All adverse events that occurred during the clinical trial (in the case of SAE, from the signing of the informed consent) and up to 30 days after the last dose of study medication must be recorded in the CRD. In the case of serious adverse events (SAEs), the data record will be extended until the SAE has resolved or is considered clinically stable, based on medical judgment.

6.1 DEFINITIONS

6.1.1 Definition and classification of adverse events

Adverse event
Adverse event is any adverse medical event in a patient in a clinical study who has been administered a drug (investigational or not). An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unexpected sign (including an abnormal result), symptom or disease temporarily associated with the use of a medicine (clinical investigational or non-investigational product), considered or not related to the aforementioned drug (product in the clinical investigation phase or that is not in the investigation phase). (International Conference on Harmonization [ICH] definition).
This includes the appearance of new symptoms or worsening in severity or frequency from baseline or abnormal results of diagnostic procedures, including laboratory abnormalities.
Note: the sponsor collects the adverse events that appear from the signing of the FCI (see section 5.3.1., All adverse events, during the time of the last record of adverse events).

Serious adverse event

Serious adverse event, according to the guidelines of the ICH and the EU on Pharmacovigilance with medicinal products for human use, is any untoward medical event that, at any dose:

- Causes death.
- It is potentially deadly.
- (The patient was at risk of death at the time of the event. It does not refer to an event that hypothetically could have caused death if it had been more intense.)
- Requires hospitalization or extension of an existing hospitalization.
- Causes persistent or significant disability/incapacity.
- It is a congenital anomaly.
- It is a suspicion of transmission of any infectious agent through a drug.
- Is medically important.*

*Medical and scientific criteria will be applied to decide whether expedited notification is also appropriate in other situations, such as a major medical event that is not immediately life-threatening and does not result in death or hospitalization of the patient , but may endanger the patient or require medical intervention in order to avoid one or more of the other outcomes included in the definition above. These should also be considered serious.

6.1.2 Adverse event definitions and classifications

Unlisted adverse event (unexpected) reference safety information

An adverse event is considered unlisted if its nature or intensity is not consistent with the corresponding product's reference safety information. For ibrutinib, the predictability of an adverse event will be determined based on whether or not it has been listed in the Investigator's Manual.

Drug-Related Adverse Event

An adverse event is considered to be drug-related if attribution is possible, likely, or very likely, based on the definitions provided below.

Definitions of attribution

No related

An adverse event that is unrelated to the use of the drug.

Equivocal

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or where the temporal relationship indicates that a causal relationship is unlikely.

Possible

An adverse event that could be due to the use of the drug. An alternative explanation, for example concomitant drug(s) or concomitant disease(s), is not conclusive. The temporal relationship is reasonable, and therefore a causal relationship cannot be ruled out.

Probable

An adverse event that could be due to the use of the drug. The temporal relationship is indicative (eg demonstrated by withdrawal). An alternative explanation, for example concomitant drug(s) or concomitant disease(s), is less likely.

Very likely

An AE that is listed as a possible adverse reaction and cannot be reasonably justified by an alternative explanation, e.g. concomitant drug(s) or concomitant disease(s). The temporal relationship is highly indicative (eg demonstrated by withdrawal and reintroduction).

Criteria for determining intensity

An evaluation of the degree of intensity will be made using the NCI-CTCAE criteria (version 4.03). The investigator must use clinical judgment in assessing the severity of events not directly experienced by the patient (eg, laboratory abnormalities).

6.2 SPECIAL REPORTING SITUATIONS

Safety events of concern with a Sponsor Study Drug that may require urgent reporting and/or safety evaluation include, but are not limited to:

- Sponsor Study Drug Overdose.
- Suspected abuse/misuse of a study drug by the sponsor.
- Unintentional or accidental exposure to a sponsor's study drug.
- Medication errors involving a sponsor's product (with or without patient exposure to the sponsor's study drug, eg, name confusion).

Special notification situations must be recorded in the CRD. Any special notification situation that meets the criteria for a serious adverse event should be recorded on the serious adverse events page of the CRD.

6.3 PROCEDURES

6.3.1 All adverse events

All adverse events and special notification situations, whether serious or not, will be reported from the time the signed and dated ICF is obtained and until the last procedure related to the patient's study (which may include contact for security follow-up). Serious adverse events, including those reported spontaneously to the investigator within 30 days of the last dose of study drug, must be reported.

All events that meet the definition of a serious adverse event are recorded as serious adverse events, regardless of whether they are protocol-specific assessments.
All adverse events, regardless of severity, intensity, or suspected relationship to study drug, must be recorded using medical terminology in the original document and on the CRD. Whenever possible, diagnoses should be provided when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and cold should be reported as "upper respiratory infection"). Investigators must record their opinion regarding the relationship of the adverse event to the study treatment on the CRF. All necessary measures for the treatment of adverse events will be recorded in the original documentation.
The sponsor assumes the responsibility of making the pertinent notification of adverse events to the health authorities. The sponsor will also notify [redacted] of all unlisted (unexpected) serious adverse events related to the use of the study drug. The sponsor must notify these events to the Clinical Research Ethics Committee (CEIC) that has approved the protocol, unless the CEIC requires and documents something different.

6.3.2 Serious Adverse Events

Study site personnel must notify [redacted] of all serious adverse events that occur during the course of the study within 24 hours of becoming aware of the event.

All serious adverse events that have not resolved at the end of the study or when the patient ends their participation in the study should until:

- be followed upThe event is resolved.
- The event stabilizes.
- The event returns to baseline, if baseline value/state is available.
- The event is attributable to agents other than the study drug or to factors unrelated to the conduct of the study It is
- unlikely that additional information can be obtained (patient or healthcare professional refusal to provide further information, loss to follow-up after showing due diligence with efforts to keep track).

Suspected transmission of an infectious agent by a drug will be reported as a serious adverse event. Any event requiring hospitalization (or prolonged hospitalization) that occurs during the course of a patient's participation in a study will be reported as a serious adverse event, except hospitalizations for the following reasons:

- Hospitalizations not indicated to treat acute illness or adverse events (eg, for social reasons, such as pending admission to a long-term care facility).
- Surgery or procedure scheduled prior to study inclusion (must be documented on CRF).

Note: hospitalizations scheduled before the signing of the FCI will not be considered as SAEs, nor those in which the condition for which the hospitalization was scheduled has not worsened. Any AE that results in an extension of the originally scheduled length of hospitalization will be reported as a new AE.

- Disease progression will 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 meet the definition of a serious adverse event.
- A standard procedure for administration of study treatment will not be reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of treatment delivery will be reported as a serious adverse event.
- The administration of a blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such a transfusion remains a serious adverse event that should be reported.
- A procedure for investigations related to the protocol/investigation (e.g., surgery, imaging tests, endoscopy, laboratory sampling, bone marrow sampling, blood sampling for pharmacokinetics or biomarkers). Hospitalization or prolonged hospitalization for a complication of such procedures remains a serious adverse event that should be reported.
- Prolongation of hospitalization for technical, practical or social reasons in the absence of an adverse event.
- A scheduled procedure prior to study inclusion (must be documented on CRF). Prolonged hospitalization for a complication considered to be possibly related to the study drug remains a serious adverse event that should be reported.

6.3.3 Adverse events of interest

Standard safety monitoring of specific adverse events, or groups of adverse events, will be performed as part of the monitoring activities performed. These events will be reported to [redacted] within 24 hours of becoming aware of them, regardless of severity (eg, serious and non-serious adverse events), following the procedure described above for SAEs, and will require further data collection.

6.3.3.1 Major hemorrhage

A major hemorrhage is defined as any bleeding episode of grade 3 or greater intensity, or leading to one of the following: intraocular hemorrhage resulting in loss of vision, the need for transfusion of 2 or more units of red blood cells or equivalent amount of blood, hospitalization or prolonged hospitalization.

6.3.3.2 Intracranial hemorrhage

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

6.3.4 Other malignant neoplasms

In addition to routine reporting of all AEs, all malignancies, including solid tumors, skin cancer, and hematologic malignancies, must be reported during study treatment and during protocol-specified follow-up periods, including post-treatment follow-up. progression for determination of overall survival.

6.3.5 Pregnancy

Study site personnel must notify [redacted] of all initial reports of pregnancy within 24 hours of becoming aware of the event. Abnormal pregnancy outcomes (eg miscarriage, stillbirth and congenital anomaly) are considered serious adverse events and should be reported as a serious adverse event. Study treatment will be discontinued in any patient who becomes pregnant during the study.

Because the effect of study drug on sperm is unknown, pregnancies of partners of male study participants will be reported to study site personnel within 24 hours of knowledge of the event.

Follow-up information will be required on the outcome of the pregnancy, as well as on any postnatal sequelae of the newborn.

6.4 MANAGEMENT OF PRODUCT QUALITY COMPLAINTS

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling or packaging, that is, any dissatisfaction with respect to the identity, quality, durability or reliability of a product, including its labeling or the integrity of the package. A PCR may have some effect on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PCR data from clinical trials is critical to the protection of patients, investigators, and the sponsor, and is mandated by health agencies around the world.

6.4.1 Procedures

Study site personnel must notify [redacted] all CPRs within 24 hours of knowledge of the event.

If the defect is combined with a serious adverse event, the research staff must report the PCR to [redacted] in accordance with the reporting timelines for serious adverse events. A sample of the suspected product should be retained for possible further investigation, if requested by [redacted].

6.5 NOTIFICATION OF PREGNANCY

The pregnancy of a female patient or the partner of a male patient, not being a serious adverse event in itself, should be managed immediately also as an SAE. It must be registered and notified with a specific form for pregnancy events and must be notified immediately (within 24 hours of knowledge), even if a voluntary or spontaneous termination occurs, describing the details of the birth and the presence or absence of a defect in the fetus or a congenital anomaly.

Potential effects on spermatogenesis: Pregnancies that occur in the partner of a male patient should also be reported within 24 hours using the specific pregnancy form and should be followed

until the end of the pregnancy, even if there is an interruption voluntary or spontaneous, describing the details of the birth and the presence or absence of any defects in the fetus or a congenital anomaly. The pregnant partner of the patient will also be instructed to contact their doctor immediately.

In order to carry out monitoring of clinical data during pregnancy, authorization must be requested from the pregnant woman, either a study patient or the partner of a study patient, which will be documented by signing a “Rapid Disclosure Consent”. medical data during pregnancy. This form will not be sent to the monitor/CRO, but will be kept on file with the rest of the study documentation at the center.

6.6 CONTACT INFORMATION FOR NOTIFICATIONS OF SAE, PREGNANCY, DEATH AND QUALITY CLAIMS

7.STATISTICAL CONSIDERATIONS

7.1 CALCULATION OF SAMPLE SIZE

Using a 23% as the baseline overall response rate for R-GEMOX in relapsed or refractory DLBCL patients previously exposed to R(3), sample size calculation assumes 80% power (beta is 20%) to detect a significant improvement greater than 25% and an alpha level of significance of 0.05, for a one-sided exact test of a single proportion. Assuming a target ORR of 48% and a dropout rate of 10%, it will be necessary to include 62 patients.

7.2 STATISTICAL ANALYSIS

The analysis populations are defined as:
- Population of all treated patients: defined as all patients receiving at least 1 dose of study drug.
- Evaluable Responder Population: Defined as all patients who have measurable disease at baseline, receive at least 1 dose of study drug, and have at least 1 adequate post-baseline disease evaluation. An adequate evaluation of the disease is defined as having sufficient evidence to correctly indicate whether or not disease progression has occurred. Patients who have died due to progression are also considered to have an adequate evaluation.
- Safety population: defined as all patients receiving at least 1 dose of study drug, which is the same definition as for the population of all treated patients.
- Patient information: the distribution of the populations of all treated patients and of those with evaluable response will be provided. Information regarding the distribution of patients will be summarized, including the number of patients receiving treatment, completing the trial, and withdrawing treatment, as well as the reason for withdrawal. Baseline demographics and characteristics will be summarized.
- Efficacy analysis: the final analysis of the primary endpoint, ORR (CR + PR) after 4 cycles, can be carried out 4 months after the last patient enrollment, and will be based on the population of all patients treated. Response rates with confidence intervals (95% interval) will be presented. ORR will be assessed according to local and centralized PET/TC assessments.

Overall survival, PFS, event-free survival, and duration of response are defined as follows (Cheson et al., 2007):

- Overall survival (OS): defined as the time between entry in the trial and death from any cause. It will be analyzed using the Kaplan-Meier method. Data from patients withdrawing from the study or not available for follow-up will be censored at the date of last contact.
- Progression free survival. It is defined as the time elapsed from the inclusion of the first patient in the study until the progression of the disease or death due to any cause.

• Event-free survival. It is defined as the time elapsed from trial inclusion to lymphoma progression, treatment failure, or death from any cause. It will be analyzed using the Kaplan-Meier method.
• Response duration. It will be calculated from the date when there is an indication of CR or PR until the date of recurrence or progression of the disease. It will be analyzed using the Kaplan-Meier method.

8. ETHICAL CONSIDERATIONS

8.1 GENERAL CONSIDERATIONS

This study will be carried out in accordance with the requirements of the «Declaration of Helsinki» adopted at the 18th General Assembly of the World Medical Association held in Helsinki, Finland, in June 1964, and all relevant reviews. The standards of Good Clinical Practice (GCP) published by the working group on the Efficacy of Medicines of the European Union (1990) (CPMP/ICH/135/95) and the regulatory requirements and applicable laws in the country will also be applied. in which the study is carried out.

In accordance with Directive 95/46 of the European Parliament and Directive 2001/20/EC, which establish the requirements for conducting a clinical trial, the information obtained during the clinical trial may only be used by the sponsor of the clinical trial. in order to evaluate the results according to the regulations indicated above.

8.2 WRITTEN INFORMED CONSENT

It is the obligation of the investigator to obtain written informed consent from patients (in accordance with the requirements of the European Clinical Trials Directive), before including a patient in the study, or when necessary, before evaluating the patient's eligibility for the study.
Each patient or their legal representative must, in terms of the provisions of the European Directive on clinical trials, freely give their informed consent in writing after having received oral and written information about the objectives of the study, the procedures that will be performed, the possible anticipated benefits, drawbacks, and risks, possible therapeutic alternatives, and your rights and responsibilities. The patient or their representative must be informed that their participation is voluntary and that they can withdraw at any time without consequence. It will also be informed that the sponsor, its representatives and the competent authorities will have access to the clinical data.
The investigator will be responsible for providing each patient or their representative with a Patient Information Sheet and an Informed Consent Form authorized by the corresponding Ethics Committee.

If the patient agrees to participate in the study, the patient or their legal representative must sign the consent form. The investigator must also sign and date this form, indicating that informed consent has been obtained and that the patient has had an opportunity to ask questions and these have been answered appropriately.
The patient or their representative will receive a copy of the Patient Information Sheet and the signed informed consent form.
The investigator will file in the patient records of each patient the original signed and dated informed consent forms. No patient can participate in the study until the signing of the informed consent.

8.3 DATA CONFIDENTIALITY

The confidentiality of the data of each patient will be respected at all times, complying with the requirements established in Law 15/99 on the protection of personal data and in RD 1720/2007 of December 21. With the In order to guarantee the confidentiality of the study data in accordance with Directive 95/46 of the European Parliament and Directive 2001/20/EC, personal and clinical data may only be accessed by the study sponsor or its designated personnel, for purposes of monitoring/audit, the researcher and team of collaborators, the Ethics Committee of the research center, or the one that supervises the center, and relevant health authorities.
Study patients will be identified by a unique code made up of the center number (two digits) and a consecutive number in chronological order of inclusion (two digits).
The researcher will inform the study patients that the data obtained in this study will be kept and analyzed by computer and that the European regulations regarding computerized data management will be followed. Data protection is described in the written patient information sheet.
The investigator agrees that the sponsor has the right to use the results of the clinical trial, including the forms or copies of the CRD. In order to allow the use of the information obtained in this clinical study, the investigator understands his obligation to offer the results of the analyzes and all the information developed during the study to the sponsor.

8.4 CLINICAL TRIAL INSURANCE

The study will have an insurance policy that will cover all possible damages that patients may suffer as a result of the evaluated product, in accordance with the applicable legislation in the country in which the study is carried out.

8.5 PRESENTATION TO THE EC

This protocol and all the required documentation will be submitted for evaluation to the relevant Ethics Committee, following the procedure established in current European regulations and the instructions of the health authorities in the countries where the study is carried out.

The study will not begin until the CEIC gives its positive vote and the competent authority is available for the study, and until other local requirements established by current legislation are met. The investigator will provide the sponsor with a copy of the relevant documents.
The Ethics Committee and the relevant health authorities will be informed of all changes in the protocol that may affect the safety of patients or the development of the study and of serious and unexpected reactions and other information that may alter the design of the study or imply a risk to patients. The corresponding approvals/authorizations will be obtained in the event of substantial modifications to the protocol, as established in the European Directive and the guidelines in force.

9. PRACTICAL CONSIDERATIONS

9.1 RESPONSIBILITIES UNDER GCP REGULATIONS

The sponsor, monitor and investigators will comply with the responsibilities established in GCP regulations.

9.1.1 INVESTIGATOR

1. Agree and sign the study protocol.
2. Know in depth all the characteristics of the study drugs.
3. Obtain informed consent from patients prior to inclusion in the study.
4. Ensure that appropriate medical care is provided to the patient in the event of any adverse event (including clinically significant laboratory values) related to the study.
5. Collect, record and report data correctly.
6. Immediately notify the sponsor of all SAEs and unexpected adverse events.
7. Accept the responsibility that all persons involved in the study will respect the confidentiality of any information about study patients.
8. Keep the Ethics Committee regularly informed about the facts of the study.
9. Take responsibility for the preparation of the final report of the study, providing its acceptance and signature.

9.1.2 SPONSOR

1. The sponsor is responsible for implementing and maintaining quality assurance and control systems with written SOPs so that trials are performed and data generated, documented (registered) and reported in accordance with the protocol , GCP standards and applicable regulatory requirements.
2. Sign the protocol and any modifications to it with the pertinent investigator.
3. Select the most appropriate investigator based on their qualifications and availability of resources, and ensure the investigator's agreement to conduct the study as specified in the protocol.

4. Provide all available basic and clinical information on the investigational product and keep it updated throughout the study.
5. Request the report of the Clinical Research Ethics Committee and the authorization of the Spanish Agency for Medicines and Health Products and send the notification or request, as appropriate and without prejudice to the notification of the autonomous communities, in the event of any modification or breach of the protocol , discontinuation of the trial and including the reasons for discontinuation of treatment.
6. Provide investigational medicinal products free of charge and ensure that they have been prepared in accordance with good manufacturing standards and that they have been properly packaged and labeled. The sponsor is also responsible for the conservation of the investigational products, as well as for keeping the records of their manufacturing process and quality control, keeping the records of the supplied investigational products and guaranteeing that the center where the study is carried out establishes a procedure for the correct handling, conservation and use of the investigational products supplied.

In exceptional cases, other supply routes may be agreed with the centre.

1. Designate the monitor who will supervise the performance of the trial.
2. Notify the health authorities and the Clinical Research Ethics Committees involved in the trial of serious or unexpected adverse events, according to the procedures established in the European and local directives.
3. Immediately inform the investigator and the Clinical Research Ethics Committee of any relevant new information that becomes available during the trial.
4. Provide compensation to patients in the event of study-related injury or death. Provide legal and economic coverage to the researcher, except for those damages resulting from malpractice or negligence on the part of the researcher.
5. Agree with the researcher on the assignment of responsibilities for data processing, reporting and publication of results. In any case, the sponsor is responsible for preparing the final or partial reports of the trial and their presentation to the competent authorities.
6. The sponsor will have a point of contact, where the patients of the trial can obtain more information about it, which may be delegated to the investigator.

9.1.3 MONITOR

The Sponsor delegates the monitoring tasks to [redacted].

a) Work according to the sponsor's standard operating procedures, visit the investigator before, during and after the study to monitor compliance with the protocol and ensure that all data is recorded and reported correctly and completely, and that informed consent is obtained of all patients prior to inclusion in the study.
b) Guarantee that both the investigators and the centers where the trial will be carried out are suitable for this purpose throughout the trial.

c) Ensure that both the principal investigator and all personnel assisting the investigator are duly informed and ensure immediate communications between the investigator and the sponsor at all times.
d) Verify that the researcher complies with the authorized protocol and all its modifications.
e) Check that the storage, dispensing, return and documentation of the supply of products in the clinical investigation phase are safe and adequate.
f) Submit written reports to the sponsor after each monitoring visit and after all relevant contacts with the investigator.

9.2 MODIFICATIONS AND DEVIATIONS OF THE PROTOCOL

After reviewing and signing the protocol, neither the investigator nor the sponsor may make modifications or changes without the written consent of both.
In case of any modification or change of the protocol once signed, this modification must be discussed and agreed between the principal investigator and the sponsor, and be signed by both parties. Protocol modifications must form an integral part of the original protocol. The Ethics Committee must be informed of all changes to the protocol that may affect the safety of patients or the development of the study. In case of relevant modifications, approval of the modification must be obtained, in accordance with European and local regulations, before applying said modifications.

9.3 MONITORING

A team of monitors designated by the sponsor will periodically monitor the study to ensure that the rights and well-being of patients are protected, that the protocol is followed, that applicable regulations and ethical requirements are met, that all documentation is available in the centers and that the data is collected accurately.
The investigator must provide the monitor with access to patient charts, study records, CRFs, original signed informed consent forms, and all original documents.
Any deficiencies observed during the monitoring visits will be discussed with the investigator and an agreement will be reached on the corrective measures to be applied.

9.4 DATA MANAGEMENT

All data (personal, clinical, economic, derived from biological material) obtained from patients will be treated in accordance with Directive 95/46/EC of the European Parliament and of the Council, dated October 24, 1995 regarding the protection of natural persons with regard to the processing of personal data. In accordance with said legislation, patients may exercise their rights of access, modification, opposition and cancellation of their data, for which they must contact the clinical study

doctor. The content of the CRFs, as well as the documents generated during the study, will be considered strictly confidential and will not be disclosed to third parties.
The investigator must keep a detailed record of all persons involved in the study.
The investigator will collect and record the study data in the medical records of each patient and will then transfer the information to the CRFs provided by the sponsor. All data must be fully, promptly, accurately and intelligibly recorded in the CRD.
The investigator must date and sign each of the CRDs in the specific field of the CRDe.
The investigator must keep all the original documentation (analytical results, treatment sheets, signed informed consent, etc.).
The data recorded in the CRD will be reviewed and analyzed; the database data will also be checked for inconsistencies. Questionable, inconsistent, or incomplete data will be resolved by the investigator in writing and the correction will be recorded in the CRF audit trail.
Computerized data correction procedures will apply.

9.5 FILING OF STUDY DOCUMENTATION

It is the investigator's responsibility to ensure that the trial file is maintained at the study center. In this study, the file will contain the following documentation, among others:

1. Study protocol, current and previous versions, review and/or modifications (when applicable).
2. Patient information sheet and consent form, revision and/or modifications (when applicable).
3. Researcher commitment.
4. Contract for clinical research.
5. CV of the investigator and sub-investigators.
6. Positive vote of the CE to carry out the study and modifications (when applicable) and the rest of the relevant communications with the CE.
7. Authorization from the CA to carry out the study and modifications (when applicable) and the rest of the relevant communications with the CA.
8. Correspondence between the investigators, the EC and the sponsor related to this study.
9. Annual reports and security reports.
10. Laboratory normality intervals, where the necessary determinations in this study will be detailed. Laboratory quality certification.
11. PEI documentation (count forms, conservation, etc.).
12. Updated clinical study staff signature list and task delegation record.
13. Patient identification list, for patients included in the study.

The investigator must keep the patient identification list and all signed informed consents on file for at least 15 years after the end of the trial. Any original information related to the study that allows the verification of the inclusion and exclusion criteria, including the clinical history, a copy of all the

data collection notebooks and the documents for its use of the product in the clinical phase must be kept for the maximum time interval allowed in the center.

9.6 CONTROL AND QUALITY GUARANTEE

The study will be supervised by monitors from [redacted]. The study monitor will contact the investigators on a regular basis. In these contacts, the progress of the study will be discussed with the investigator and it will be verified that the CRDs are completed in full and consistently. The study monitor (and, when requested, a representative of the sponsor) will also check the informed consent forms.
With proper supervision and ensuring confidentiality, the investigator will allow the sponsor's representative or study monitor to compare the data entered into the CRF with the original data at the study site (source documents) and to observe study procedures in order to verify compliance with the study protocol.

9.7 INSPECTION AND AUDIT

Quality assurance audits may be carried out at any time during the trial or after its completion. In addition, the relevant authorities may review the study in the terms established in European and local regulations.
At the request of the monitor, the auditor, the Ethics Committee or the health authorities, the investigator must provide direct access to all the documentation related to the clinical trial.

9.8 PREMATURE TERMINATION OF THE STUDY

The sponsor may, at any time, suspend the participation of an investigator in the study. In the event that an investigator's participation in a study is suspended, the sponsor shall promptly and in writing inform the CEIC and the AC of the reason(s) for the suspension.
Reasons for premature study termination may include, but are not limited to:

- New available information justifying that continuation of the study is not feasible.
- Unsatisfactory inclusion in terms of quantity or quality.
- Collection of inaccurate or incomplete data.
- Protocol breach.

9.9 ECONOMIC ASPECTS OF THE TRIAL

The economic aspects of the study will also be sent to the CEIC for evaluation at the time of presentation of the protocol.

9.10 PUBLICATION POLICY

The sponsor and the researchers agree to publish the results of this study. All publications and presentations proposed by the investigators or their team and collaborators derived from or related to the study must be sent to the sponsor for review before being sent for publication or presentation.
In the publications, the signing authors will be ordered according to the number of patients included, from highest to lowest.
If the proposed publication or submission contains patentable material, which, in the opinion of the sponsor, ensures intellectual property protection, the publication or submission may be delayed for a reasonable period of time to achieve this protection.

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ANNEXES:

I. List of participating centers
II. Patient information sheet and consent form for the study
III. Patient information sheet and consent form for the molecular substudy
IV. Patient information sheet and consent form for Biobank
V. ECOG
VI. Performance Status NCI CTCAE Criteria V4.03
VII. PET/TC
VIII. Centralized Review Biological Substudy
IX. Lugano Response Evaluation Criteria for Non-Hodgkin Lymphoma (28)
X. Comorbidity Questionnaire (CIRS and GAH)
XI. Ibrutinib SmPC
XII. ***Procedure of Screening and Inclusion (Version 1.2: July 7, 2016)***

I. List of participating centers

The list of participating centers will be provided in a separate document.

II. Patient Information Sheet and Study Consent Form – Version 2.0, October 07, 2016

Patient Information Sheet

Study Title: Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM
EudraCT:
Protocol number:
Sponsor:

Coordinators:
:
Dr/a..... ..... .
Hospital: .... Contact telephone number:..... .....

Dear patient:

Your doctor has invited you to participate in the clinical trial entitled "Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM", which could improve the treatment strategy for their disease. This study is carried out (sponsor) by the group . The drugs will be provided by the Legal Sponsor of the study, the , which has signed an agreement with which will provide the investigational drug Ibrutinib and is the funding entity for this clinical trial.

Before you decide to participate, it is important that you understand why the study is being done and what your participation entails. Please take the time to carefully read the following information, which you can discuss with others if you wish. Ask your doctor if anything is not clear or if you need more information. Please take the time you need to decide if you want to participate in this study. You can also discuss the study with your GP or others before making a decision.

You decide whether or not you want to participate. If you decide to participate, you will be asked to sign the consent form attached to this sheet and a copy will be given to you to keep.
You are not required to participate. If you decide to participate, you are completely free to withdraw at any time and without giving any reason. The fact that you decide to withdraw at any time or that you decide not to participate without having to justify this decision will not affect the care you receive in the future. If you decide not to participate, the study doctor will explain the best available standard treatment.
In cases like yours, the most commonly used treatments are R-GEMOX combination chemotherapy, other regimens used in young patients, such as (DHAP (dexamethasone, cytarabine, and platinum), ESHAP (etoposide, methylprednisolone, cytarabine, and platinum) or ICE (ifosfamide, carboplatin and etoposide), but at low doses, or other chemotherapeutic agents alone. In this case, your doctor will consider the advantages and disadvantages of these drugs, and jointly decide the best alternative.
The doctor in charge of This study is at your entire disposal to answer any questions you may have. If you agree to participate, it is mandatory to sign this Informed Consent Form. This signature is confirmation that you freely agree to participate in this study. The signature does not release your doctor nor to the sponsor of his responsibilities with respect to you
During the study, your doctor will provide you with any new information that may affect your decision.
We inform you that the research team will not receive any financial compensation for conducting this clinical trial in which you are offered to participate.
In addition, this study does not contemplate the payment of extraordinary expenses to patients. If for any particular reason, they occur, the Sponsor will only cover those extraordinary expenses that have been previously agreed with the Sponsor and have been approved by the same.

1. WHAT IS THE OBJECTIVE OF THE STUDY?

Your doctor has diagnosed you with refractory or recurrent non-GCB diffuse large B-cell lymphoma. The standard treatment for your disease usually includes different options based on a combination with rituximab. However, there is currently no treatment that can be considered the gold standard for treatment-resistant or recurrent diffuse large B-cell lymphoma of the non-GCB type. For this reason, we invite you to participate in this study in which we will evaluate the efficacy of ibrutinib in combination with rituximab-GEMOX-dexamethasone as a therapeutic alternative in diffuse large B-cell lymphoma.
It is an investigational medicine so it may not benefit you or even harm you.

two. WHAT IS THE MECHANISM OF ACTION OF IBRUTINIB?

Ibrutinib works by blocking Bruton's tyrosine kinase, a protein in the body that helps these cancer cells grow and survive. By blocking this protein, ibrutinib helps kill and reduce the number of cancer cells. It also slows down the worsening of cancer.

3. WHAT IS THE PLAN STUDY?

This study plans to include approximately 62 patients with treatment-resistant or recurrent diffuse large B-cell lymphoma of the non-GCB type who are not candidates for autologous transplantation

(ASCT) in different centers [redacted]. The study is divided into different periods that include the selection of candidates, the treatment period and follow-up.

1. Do you meet all the criteria to participate?

If you agree to participate in this clinical study and after signing the Informed Consent Form, you will go to a study visit with your doctor, in which you will be asked questions about your disease, the treatments you have received, your medical history and associated treatments . Some tests will also be done, which mainly include: clinical examination, blood tests, urine tests, an EKG, imaging tests (PET/TC), a bone marrow biopsy, and a centralized review of your tumor sample where the initial diagnosis was made to confirm the diagnosis. You will also be asked to give your consent to collect biological blood and tumor samples necessary to carry out additional biological tests, which will allow better definition of certain characteristics of your disease, and the detection of traces of disease using techniques that are more sensitive than the usual ones (determinations of minimal residual disease (MRD)).

Some of these tests are allowed to be done within 28 days before the start of treatment; According to the detailed conditions of the protocol, it will not be necessary to perform them for inclusion in the study.

Your participation in this study will depend on the results of these tests. If the tests performed during the screening period indicate that you can participate in the study, you will have a visit that will finally confirm the opportunity to start the study treatment.

2. Treatment period You

will receive ibrutinib in combination with R-GEMOX-dexa according to the following schedule:

<u>Induction phase:</u>

- Patients will initially receive 4 cycles of 14 days each of ibrutinib + R-GEMOX-D, consisting of:

560 mg of ibrutinib per day;

375 mg/m^2 rituximab intravenously (iv) on day 1;

1000 mg/m^2 gemcitabine iv on day 1 or 2;

100 mg/m^2 oxaliplatin on day 1 or 2;

Dexamethasone 20 mg IV on day 1 and orally on days 2 and 3.

If you respond to treatment, you will receive 2 or 4 additional cycles of 14 days each.

Maintenance phase:

After the induction phase, you will receive 560 mg of ibrutinib per day. Continuous cycles until disease progression or unacceptable toxicity occurs (maximum of 2 years).

If you do not respond to treatment after the first 4 cycles, or experience disease progression at any time during the induction phase, maintenance treatment will be discontinued.

For each patient, the clinical study will last a maximum of 4 years from the date of inclusion. However, the monitoring of the status of your disease will be carried out indefinitely, in accordance with normal practice.
Clinical and laboratory determinations will be made every 14 days until the end of treatment with the IR-GEMOX cycles. During the maintenance phase every 8 weeks and after the end of treatment, every 3 months until the end of the study follow-up, unless otherwise indicated by your doctor's discretion.
PET/TC will be performed after the 4th and 6th or 8th cycle of IR-GEMOX and at the end of treatment. In addition, they will also be performed in case of suspicion of relapse or progression to confirm the response. The PET/TC studies will be reviewed by a group of nuclear medicine experts ([redacted] PET platform).
During maintenance treatment, TC scans will be performed every 6 months. Also, if clinically indicated, during follow-up every 6 months in the first 2 years.
EMR studies will be performed on peripheral blood at the end of the 6th or 8th cycles of IR-GEMOX, and at the same time that imaging studies are performed (if you are also participating). in biological substudies).
Bone marrow biopsy will be obtained at the end of IR-GEMOX treatment, if necessary.

You will also be asked to give your informed consent to collect biological samples necessary to perform the associated biological substudy. This participation is optional, and such consent will be given to you separately.

3. Termination of study treatment and follow-up period

You may discontinue your participation at any time without prejudice and without affecting the treatment you require. If you or your study doctor decide to discontinue study treatment, follow-up will continue unless you decide to completely withdraw your consent for the study.

At the end of the treatment period, a follow-up visit will be made 30 days later. Thereafter, you will continue to have visits every 3 months and/or regular contacts until the end of the trial. In the event of disease progression, your doctor will discuss with you the best treatment for you.

In addition to the visits provided for in the protocol, your doctor may ask you to attend additional visits to monitor your condition, based on his or her clinical judgment and/or normal clinical practice.

The interruption of participation, by the Principal Investigator or the Sponsor, can only be carried out in cases that are clinically justified or legally provided for. The trial may be terminated prematurely for the following reasons: New information available justifying that continuation of the trial is not feasible, unsatisfactory inclusion, collection of inaccurate or incomplete data or non-compliance with the trial protocol.

Your trial doctor may withdraw you from this study for not complying with the instructions given to you (for example, not attending the scheduled visits), because you need a treatment not allowed by the protocol, because you do not consider it to be better for your health or welfare or because

the study is canceled. If this occurs, you will be informed of the reason for the termination. In either case, you will continue to receive appropriate medical care for your illness.

4. YOUR RESPONSIBILITY DURING THE STUDY

You must go to the study center for each scheduled visit and to inform your doctor of any changes in your health and any symptoms you may feel, even if you think they are not related to the treatment of the study. study.
In addition, you will need to take the study medication as prescribed. You must return all unused treatments as well as empty containers at each visit. *It is also very important that you tell your doctor about any other medications you are taking and those you take during the study. Study treatment may interfere with your medications. Your doctor has a list of all the medicines that you should avoid or take with caution.*

During the study, you will be asked not to take any herbal preparations or other alternative medications. Some treatments should not be taken concomitantly with the study drug (eg, chemotherapy, immunotherapy, hormonal treatment).

5. REPRODUCTIVE EFFECTS

The effects of ibrutinib on the developing fetus are unknown, therefore pregnant or lactating women cannot participate in this study. No one knows yet what risks there may be. Some medicines cause women to have babies prematurely (early) or their children to be born with defects.

If you are able to have children, you must use highly effective birth control while taking study treatment, and for 1 month for women or 3 months for men, after you stop taking study treatment , to prevent pregnancy in both you and your partner. A "highly effective method of contraception" is defined as a method that has a low failure rate (i.e., less than 1% per year) if used consistently and correctly and includes implants, injectables, dual-hormonal contraceptive pill, some intrauterine devices (IUDs), sexual abstinence (defined as abstinence from all aspects of sexual activity), or having an infertile partner. If you are using hormonal contraceptives, such as birth control pills or contraceptive devices, a second barrier method of contraception (eg, condoms) should be used.

Note: Some birth control pills may not be effective when certain medications are taken. If you have any questions about this, please discuss them with the study doctor.

Keep in mind that even if you use an acceptable birth control method, you can still get pregnant.

Males: If your partner becomes pregnant while taking study treatment or 3 months after the last dose of ibrutinib, you must notify study staff. Study staff will discuss this further with you. You should not donate sperm while taking the study drug and for 3 months after you stop taking it.

Women: If you become pregnant while taking study treatment or 1 month after the last dose of ibrutinib, you must notify study staff. If you become pregnant during the study, you must stop taking the study treatment immediately. The sponsor will continue to collect information about the pregnancy and the birth of your child even after you have stopped study treatment.

In the event of a pregnancy, both parents must give prior authorization for access to the data of the pregnancy and the baby in a consent separate from and subsequent to the current one, validated by the CEIC.

6. WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS?

If your condition is getting worse, if side effects become severe, or if new information indicates that this treatment is not in your favor, your doctor will notify you and discuss alternative treatment with you.

You may develop side effects during your participation in this study. You should tell the study doctor about any side effects you develop.

6.1. Side effects of ibrutinib:

The following side effects have been reported by patients who have received ibrutinib in clinical studies.

The most common side effects, occurring in at least 1 in 5 patients, have been:

- Increased frequency of loose or liquid stools (diarrhea)
- Muscle and joint pain
- ***Neutropenia***
- Bruising
- Skin rash
- Nausea

(Version 2.0, October 21, 2016)

Side effects that have been seen in at least 1 in 10 patients include:

- Mouth
- sores Sinus infection
- Fever
- Low white blood cells (the cells that help fight infection)

- Low platelets (the cells that help blood to clot)
- Constipation
- Swelling of the hands or feet
- Joint pain
- Vomiting
- Skin infection
- Pneumonia
- Headache
- Muscle spasms High
- blood pressure

(Version 2.0, October 21, 2016)

Side effects that have been observed at least in 1 in 100 patients, include:

- ***Dizziness***
- ***Urinary tract infection***
- ***Nosebleed***
- ***Petechiae (small bright red spot that appears on the skin) him because of a hemorrhage)***
- ***Cutaneous***
- ***Basal carcinoma***
- ***Squamous cell carcinoma***
- ***Broken nails (Onychoclasis)***
- ***Interstitial lung disease***
- Blurred vision
- Increased level of uric acid in the blood
- ***Lack of fluids in the body (dehydration)***
- Abnormal heart rhythm (atrial fibrillation) High number
- of white blood cells
- low white blood cells with fever
- skin redness
- Increasing the level of lymphocytes
- extended severe infection throughout the body

version 2.0, October 21, 2016)

side effects that have been observed at least 1of 1000 patients, include:

- ***Unusual levels of chemicals in the blood caused by the rapid breakdown of cancer cells, which can lead to changes in kidney function, abnormal heart rhythms, or seizures. (Tumor lysis syndrome)***
- ***Itchy skin rash (Urticaria)***
- ***Bleeding around the brain (subdural hematoma)***

- ***Swelling of the face, lips, mouth, tongue or throat (angioedema)***
- ***Severe increase in white blood cell count which may cause cells to aglomerate (leukostasis syndrome)***
- ***Severe blistering and peeling skin rash, particularly around the mouth, nose, eyes, and genitals (Stevens-Johnson syndrome)***
- ***Liver failure***

(Version 2.0, October 21, 2016)

Most of these side effects has been mild to moderate in intensity; however, serious side effects have also occurred. Some of these have been serious enough to lead to study drug discontinuation, dose modification or reduction, patient hospitalization, disability, and sometimes death.
You should tell your doctor or study team about any adverse reaction you experience. The study doctor may give you medicine to help treat side effects and keep them from getting worse. The study doctor may also decide to stop ibrutinib treatment for a short time or reduce your dose to allow you to recover from side effects.

Bleeding
It is possible to may experience bruising or nosebleeds during treatment with ibrutinib.
Serious internal bleeding, such as bleeding in the stomach, intestines or brain, can occur very rarely, some cases being fatal. If you are taking other medicines or supplements that increase the risk of bleeding, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), or medicines used to prevent or treat blood clots or stroke, ibrutinib may increase this risk. Anticoagulants, such as warfarin or other vitamin K antagonists, should not be taken concomitantly with ibrutinib. The use of supplements such as fish oil or vitamin E preparations should be avoided while taking ibrutinib. Contact the study doctor if you develop signs or symptoms of serious bleeding, such as blood in the stool or urine, or bleeding that lasts for a long time or that you cannot control.

Effects on the heart
Heartbeat disturbances (atrial fibrillation and/or atrial flutter) have been reported in patients treated with ibrutinib, ***especially also in those patients with heart disease, increased blood pressure, acute infections, or who had abnormal heartbeats in the past***. Atrial fibrillation and atrial flutter are a common form of heartbeat disturbance. The heartbeat may be fast or irregular and cause symptoms such as palpitations, dizziness, weakness, feeling light-headed, or shortness of breath. You must notify the study doctor immediately if you experience any of these symptoms while participating in the study.

(Version 2.0, October 21, 2016)

Infections
You may experience viral, bacterial or fungal infections during treatment with ibrutinib. ***Some of these infections have led to hospitalizations and death.*** Contact the study doctor if you develop fever, chills, weakness, confusion, body aches, cold or flu-like symptoms, tiredness, or shortness of breath, as these could be signs of an infection.

A rare viral disease in the brain that is usually fatal: progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with ibrutinib in combination with rituximab and in patients who had previously received rituximab treatment. If you experience symptoms such as weakness, paralysis, vision loss, and/or impaired speech, please notify the study doctor immediately.

(Version 2.0, October 21, 2016).

Lymphocytosis and leukostasis

It is possible to experience an increased number of lymphocytes, a type of white blood cell, in your blood (lymphocytosis). This can happen in the first few weeks of treatment and you should not assume that this increase in white blood cells means that your disease is getting worse. This increase can be sustained for several weeks or months. The increase in white blood cells in the bloodstream can alter blood flow and cause bleeding or clots (leukostasis). Isolated cases of such events have been reported in patients treated with ibrutinib. The study doctor will monitor your blood count and may give you additional treatment as needed. You can ask the study doctor what the test results mean.

Decreased blood cell counts

Marked decreases in white blood cell, red blood cell and platelet counts (neutropenia, anemia and thrombocytopenia) have been reported in patients treated with ibrutinib. If you develop symptoms such as fever, weakness, or frequent bruising and/or bleeding, please notify the study doctor immediately.

Allergic Reactions

Some people experience allergic reactions to drugs. Severe allergic reactions can be life-threatening. If you have an allergic reaction to ibrutinib you may experience a skin rash, difficulty breathing, wheezing, sudden low blood pressure with dizziness, swelling around the mouth, throat or eyes, a racing heart and/or sweating.

Before starting treatment with the study drug, you must tell the study doctor if you have any allergies to any drugs. You should inform the study doctor immediately if you experience any of the allergic symptoms listed.

Skin rash

Frequent cases of maculopapular skin rash (red, flat areas of skin with small bumps) have been reported in patients treated with ibrutinib alone or in combination with other medicinal products. Most skin rashes are mild to moderate in intensity and begin 2-3 weeks or later after initiation of ibrutinib.

Rarely, severe skin rash (over 50% of the body) or rash with blisters and peeling skin, which may include open ulcers or sores in the mouth or other areas (Stevens-Johnson syndrome), have been reported. This reaction could be life-threatening. You should notify your study doctor immediately if you develop a rapidly spreading rash, or if you notice any peeling of the skin, with or without ulcers or mouth sores.

Cutaneous Carcinoma and Other cancers

Cutaneous carcinoma (basal cell carcinoma and squamous cell carcinoma) have been reported more frequently and possibly related to ibrutinib treatment. Other types of cancer have been seen in patients who have been treated with ibrutinib. These include skin cancer, solid tumors, and various types of blood cancers. The causal relationship with ibrutinib is unknown. You will need to tell the study doctor if you develop a new cancer during your stay in the study.

(Version 2.0, October 21, 2016).

Tumor lysis syndrome (TLS)

Unusual levels of chemicals in the blood caused by rapid breakdown of cancer cells have been observed during cancer treatment and sometimes even without treatment. This can cause changes in kidney function, an abnormal heartbeat, or seizures. The study doctor may perform blood tests for TLS.

Hypertension

Common cases of hypertension have been reported in patients treated with ibrutinib. Sometimes, patients with high blood pressure may have headaches, dizziness, nervousness, sweating, trouble sleeping, flushing of the face, or nosebleeds, but in some cases, there may be no symptoms and they may go unnoticed. After starting ibrutinib, your doctor may check your blood pressure regularly. The study doctor should know if you have any of the symptoms of high blood pressure which could mean that you have developed high blood pressure or that your high blood pressure is getting worse. The study doctor may adjust existing antihypertensive medications and/or initiate antihypertensive treatment where appropriate.

(Version 2.0, October 21, 2016).

Hepatic failure

Rare cases of hepatic failure have been reported in patients treated with ibrutinib. ***Symptoms of liver failure include yellowing of the eyes and skin (jaundice), itchy skin, dark urine, gray or clay-colored stools, confusion, nausea, loss of appetite, fatigue, or diarrhea. You should tell your study doctor immediately if you have any of these symptoms that may indicate liver disease. The study doctor may be able to diagnose and provide you with the necessary medical care.***

(Version 2.0, October 21, 2016).

Interstitial lung

Interstitial lung disease is a group of lung diseases in which tissues become inflamed and can be damaged. Interstitial lung disease is not associated with infections (e.g. bacteria, viruses, fungi) and cases have been reported in patients treated with ibrutinib. You should tell your doctor if you have a cough, any signs of new or worsening respiratory symptoms, such as shortness of breath or difficulty breathing.

(Version 2.0, October 21, 2016).

Interference with other medications

Some foods, such as grapefruit juice or bitter oranges, can interfere with the way the body processes ibrutinib. This interference could make the concentrations of ibrutinib in the body too high or too low. It's also possible that taking the study drug with your regular medications or supplements, including fish oil, vitamin E, or other vitamins, could change the way those regular medications or supplements work. It is very important that you avoid drinking grapefruit juice and bitter oranges and that you tell the study doctor about any medications, supplements, or herbal products (such as St. John's wort) that you are taking during the study. You should notify the study doctor immediately of any side effects to avoid possible harm.

Suspension of treatment for any type of surgical intervention

Ibrutinib may increase the risk of bleeding in any surgical intervention. Ibrutinib should be discontinued at least 3 to 7 days before and after an intervention, depending on the type of intervention and the risk of bleeding. Please contact the study doctor if you have any type of surgery scheduled. For emergency procedures, administration of ibrutinib should be withheld (interrupted) after the procedure until the surgical wound is sufficiently healed (without suppuration).

Contact your study doctor as soon as possible and he or she will tell you when to stop ibrutinib and when to start treatment again after surgery.

In addition to the risks listed above, there may be unknown or unexpected side effects associated with the use of ibrutinib. You will be duly informed, verbally or in writing, of any new information, findings, or changes in the way the research will be conducted that may influence your willingness to continue participating in the study.

You may experience some, all, or none of the ibrutinib side effects listed. Study doctors and nursing staff will monitor you closely for side effects. You may receive medications or other treatments to prevent or reduce some of these effects. You should tell your doctor or study staff immediately if you experience any side effects. You should also tell them if you have any other health problems or how you feel during the study, whether or not you think they are related to the study drug.

You should get medical help and contact your doctor or study staff if you experience any of these side effects or others during the study.

6.2. Side effects R-GEMOX-Dexa

Your doctor will explain the adverse effects of the drugs used in this clinical trial (Rituximab, Gemcitabine, Oxaliplatin and Dexamethasone), all of them marketed in Spain and used in the treatment of Lymphomas.

Data on the combination of ibrutinib and rituximab-GEMOX-dexa are limited and no relevant problems have been reported to date.

7. WHAT ARE THE BENEFITS OF PARTICIPATING IN THE STUDY?

With your participation in this study, you will receive ibrutinib, the study drug, along with rituximab-GEMOX-dexa. This treatment may be effective and well tolerated, but there is no guarantee that this will be the case, as this is an exploratory trial, you may not derive any clinical benefit from the trial.

However, the information obtained from this study will help improve the treatment of other patients with your disease in the future.

8. WHAT ARE MY RIGHTS AND THE LEGAL PROVISION OF THIS STUDY?

Medical research is strictly regulated by law. Legal provisions guarantee a series of rights. Please read this section carefully.

Insurance and compensation system:

The sponsor has contracted insurance with the company [redacted] in accordance with Spanish Law 29/2006, of July 26, on guarantees and rational use of medicines and health products and Royal Decree 223/2004, of February 6, which regulates clinical trials with medicines to cover the risks related to their participation in this study.

We inform you that it is possible that your participation in this clinical trial may modify the general and particular conditions (coverage) of your insurance policies (life, health, accident...), therefore, we recommend that you contact your company and inform you of your participation in it to determine if it could affect your current insurance policy, validated by the CEIC.

Approval of the competent authorities:

This protocol has been approved by the Spanish Medicines Agency and has obtained the favorable opinion of the Ethics Committee of [redacted] as CEIC of Reference, implying the Approval of the Ethics Committees of all the participating centers. The last task is to verify if the conditions related to your protection and your rights have been respected, as well as to verify your rights and well-being as a participant in a clinical trial in accordance with Law 15/1999 on the Protection of Personal Data. Personnel and Royal Decree 1720/2007.

Right to anonymity

Your identity will never be revealed. The data obtained as part of the investigation will remain completely anonymous.

Your medical information, identified by a code, as well as data about your lifestyle, since it is data necessary for research and your ethnicity, will be protected following local standards and regulations.

No individual patient will be identified at the time of publication of the results.

The data collected in the study will be identified by a code and only the study doctor or collaborators will be able to relate it to you and your medical history. Therefore, your identity will not be revealed except in case of medical emergency or legal requirement.

Right to confidentiality

The transmission and communication of data will be carried out under the rules of professional secrecy. None of the people who have access to this data will be able to disclose or reveal said information.
Access to your personal information will be restricted to the study doctor and his collaborators, health authorities, the Clinical Research Ethics Committee and the study monitors and auditors, who will be subject to the duty of secrecy inherent to their profession, when they need it, they will be able to verify the data and procedures of the study, but always maintaining their confidentiality in accordance with current legislation. By signing this document, you are allowing direct access to your medical records to the persons mentioned in this same paragraph, accredited for it. The sponsor of this study will in no case have access to your personal data or know your identity.

In the event that the data is sent to third countries, the level of protection established by Spanish Legislation will be maintained. Your data will be anonymized prior to sending it to avoid any type of identification that may be related to you.

Right to data protection

In accordance with current regulations on data protection, you expressly consent to the inclusion of data from your clinical history as well as those resulting from your participation in this study in a personal data file under the responsibility of [redacted] that has invited you to participate in this clinical trial. The treatment, communication and transfer of your personal data will be adjusted at all times to the provisions of Organic Law 15/1999, of December 13, on the protection of personal data and its development regulations. Know that in addition to the doctor who treats you, there may be other agents who access your personal data when they need it to check the data and procedures of the study, but always maintaining their confidentiality in accordance with current legislation."
In all the publications that are generated with the results of the clinical trial,will appear
no identifying information about you(Name, surnames, social security number, address...).

Rights of access, rectification, cancellation and opposition
The provisions of the Data Protection Law 15/1999 guarantee access to databases relating to your data and right of opposition and rectification. This right must be claimed from your doctor who knows your identity.
The trial data may be consulted in the Spanish Registry of Clinical Trials, intended for the knowledge of patients and health professionals.

Access to medical records
You can also access directly or through a doctor of your choice to all medical information under the provisions of local regulation.

Right to information
If you have any questions about this study, ask your study doctor, who will provide you with any information you need about the study drug or your participation.

During the course of the study, you have the right to be informed about this research. Your doctor will provide you with any new information that may affect your decision.

Right to withdraw from the study

You can withdraw your consent at any time without having to justify the reason and end your participation in the study. In order to ensure and preserve your safety, we will ask that you inform the study doctor of your decision immediately. In this case and if you wish, your doctor will offer you an appropriate treatment.

Right of access to global research results

Your participation in this study favors the improvement of biological and medical knowledge. You will be able to know the global results of this study. The design of the protocol and its results will be published and made available on at least one public website such as the Spanish Registry of Clinical Trials (https://reec.aemps.es/reec/faces/buscador/index.xhtml) and/or the American database (https://www.clinicaltrials.gov), intended for the knowledge of patients and professionals Of the health.

The results of the study will be published in a scientific journal and presented at international scientific conferences.

Informed consent form

Study title: *Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM*
EudraCT: [redacted]
Protocol number: [redacted]
Sponsor: [redacted]
Coordinators: [redacted]

I, the undersigned (name, surname): ……

The doctor……of the Hospital .... has provided me with all the information I have requested about the conditions of the treatment, its duration, its effectiveness and its side effects. I have had the opportunity to ask all the questions necessary to understand the study.

I understand that my participation in the study is completely voluntary and that I can withdraw my consent at any time without providing a reason. Deciding not to participate or to withdraw from the study will not harm or have any effect on my future treatment. My consent does not relieve the researchers of their responsibilities. I retain all my rights guaranteed by law.

I understand that my doctor can withdraw me from the study at any time if he or she thinks it is in my best interest.

Based on the conditions specified in the “Patient Information Form” of this document.

My participation in this study is completely voluntary	YES ☒ NO ☒
I freely accept that samples may be obtained and processed for research purposes:	YES ☒ NO ☒
- A sample of the tumor (for centralized review)	YES ☒ NO ☒

Date: Date:

Signature of the patient : Researcher's signature:

Name and surnames: ***Name and surnames:***

III. Molecular Substudy Patient Information Sheet and Consent Form

Translational Research - OPTIONAL - Patient Information Sheet

Study Title: "Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM"

EudraCT: [redacted]

Protocol number: [redacted]

Sponsor: [redacted]

Coordinators: [redacted]

Substudy coordinators:

- Central review of molecular and histopathological diagnostic studies: [redacted]

- Analysis of the mutational spectrum of 45 genes and evaluation of MRD in patients with treatment-resistant or recurrent diffuse large B-cell lymphoma included in the phase II clinical study [redacted]

- Evaluation of the cell of origin (germinal center B versus activated) in patients with treatment-resistant or relapsed diffuse large B-cell lymphoma included in the phase II [redacted]

Estimated /a patient:

Your doctor has invited you to participate in the biological substudies of the study entitled **«***Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM***»**, which could improve the strategy treatment of your illness. This study is carried out (sponsor) by the group [redacted].

Before you decide to participate, it is important that you understand why the study is being done and what your participation entails. Please take the time to carefully read the following information, which you can discuss with others if you wish. Ask your doctor if anything is not clear or if you need more information. Please take the time you need to decide if you want to participate in this study.

You decide whether or not you want to participate. If you decide to participate, you will be asked to sign the consent form attached to this sheet and a copy will be given to you to keep.

You are not required to participate in this substudy. If you decide to participate, you are completely free to withdraw at any time and without giving any reason. Your decision to withdraw at any time will not affect the care you receive in the future.

The doctor in charge of this study is at your entire disposal to answer any questions you may have. If you agree to participate in this sub-study, it is mandatory to sign this Informed Consent Form. This signature is confirmation that you freely agree to participate in this study. Signature does not relieve your physician or sponsor of their responsibilities to you.

Why have I been invited to participate?

Along with the clinical part of the study, [redacted], an in-depth biological study is also planned to characterize this population of patients with diffuse large B-cell lymphoma (DLBC) and to evaluate the response obtained with the tumor mutational profile. Clinical studies as [redacted] offer the ideal platform for biological studies, because patients receive treatment and followup evenly; therefore, the integration of these clinical data with biological characteristics results in high-quality information with reduced bias.

The goal of these substudies is to see if we can discover biomarkers in the blood or tumor tissue that could identify in the future which patients will benefit from the study treatment. This will not affect your treatment, but may provide prognostic information about your disease. It will also be evaluated if we can identify markers in the blood in early stages that show the progression of the disease (recurrence) before it can be seen in diagnostic imaging tests. This would allow clinicians to modify and/or select the best treatment alternatives for diffuse large B-cell lymphoma in the future. It is important to keep in mind that you, as the patient donor of the biological samples, are not expected to derive any direct benefit from participation in this substudy.

Blood and tumor samples from patients participating in clinical studies, such as the [redacted], are extremely valuable as accurate clinical information is obtained on the patients themselves. This information, including information about whether the tumor responds to treatment or if the disease comes back in the future, can be used along with information obtained in the laboratory to help answer questions about diffuse large B-cell lymphoma and its treatment.

How is this study carried out?

This study will involve testing blood samples and preserving tissue samples (left over from diagnosis). Of course, this will only be done with your permission. You may refuse to participate in this part of the study without affecting your participation in the rest of the study or your relationship with your doctor.

It is stated that for their participation in this substudy, it is not necessary to collect extraordinary biopsies, in relation to the main study. The extra samples will be obtained from archival material or surplus samples obtained from routine clinical practice procedures will be used. Biological sample requirements are outlined below:

- Lymph node biopsy or other tissue biopsies for diagnosis of DLBCL at baseline.
- Lymph node biopsy at time of relapse (if available).

Peripheral blood will be obtained prior to the start of study treatment, at the same time as imaging studies, and in the event of recurrence of disease after study treatment. Blood samples will be obtained at the same time blood samples are obtained under your usual care, whenever possible.
The samples will be sent to [redacted], to perform phenotypic subtyping tests, molecular studies, mutational spectrum and determination of the cell of origin using NanoString technology (NanoString Technologies, WA, USA) associated with this clinical study.

What will happen to me if I decide to participate?
If you choose to participate, blood samples and tissue biopsies will be sent to the central laboratory for substudy determinations.
These samples will be handled by specialized technical personnel who will ensure the precise quality conditions for subsequent studies. The personal data collected about you will be confidential and processed in accordance with Organic Law 15/1999 on the Protection of Personal Data and the current legislation on Biomedical Research (Law 14/2007 on Biomedical Research) and the Royal Decree 1716/2011, of November 8, which establishes the basic requirements for authorization and operation of biobanks for biomedical research purposes, treating them only in accordance with the objectives described in this document, so any relationship between the sample and your personal identity is strictly confidential. The results obtained from the different studies carried out with the samples may be published in scientific journals, but your identity or data that identifies you or may identify you will never be provided.
These additional tests will not affect your treatment in any way. If you decide not to participate in the collection of samples for laboratory research, this will not affect your participation in the clinical part of the [redacted] or your relationship with your doctor.

Any unused sample portions will be retained until the material is depleted in case new research is developed in the future that may help us better understand the response of DLBCL to these treatments. The criteria contained in Royal Decree 1716/2011, of November 8, which establishes the basic requirements for authorization and operation of biobanks for biomedical research purposes, will be met. For this, will be presented for additional informed consent to the biobank of the [redacted]Valdecilla,which will be where the remaining samples of the determinations made in these hospitals will be stored. The surplus of the material sent to the [redacted] be returned to the Hospital of origin once the determinations of the study have been completed. These samples will also be used for other future studies related to DLBCL. Any of these studies must be authorized by the Ethics Committees. We cannot describe in this document all the possible tests that can be performed on the preserved samples and if you are not comfortable with this aspect, you can not participate.
This research will be based in laboratories associated with the clinical study sites, but may involve collaboration with commercial companies (including drug/pharmaceutical companies) or other institutions. You will not receive any financial compensation for your participation in this study.

Will this study help patients in the future?

This substudy will provide us with important information about the most appropriate way to treat patients in the future.

What will be the side effects of this study?

Side effects in addition to those experienced in routine practice are not expected.

However, blood samples will often, but not always, be obtained at the same time that blood tests are required in normal practice.

What other risks can I run if I participate?

You may be contacted to request additional sample collection.

The risks related in this substudy will be the same as in normal clinical practice in terms of blood extraction: hematoma and/or local swelling in the extraction area.

What are the possible benefits of participating in the study?

The information obtained from this substudy will help us decide the best form of treatment for patients with your disease in the future. It could also provide prognostic information about your disease.

What happens if new information appears?

During the study, your doctor will provide you with any new information that may affect your decision. Sometimes, during the course of a research project, new information becomes known about the disease being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your doctor will arrange your further treatment.

It is possible that, due to the conduct of this study, the results obtained may have implications for you and your family. You can refuse to know these results. In addition, if you decide not to be informed of these results, in the event that these may affect your family, the study doctor may contact them. If you decide to learn about study results that may affect your family, you will be advised to let them know.

If you want to know the results, the study doctor will provide you and your family with genetic counseling or refer you to a place where genetic counseling can be offered.

Who organizes and finances the research?

This study is organized by the group [redacted], sponsor of the [redacted].

Will the confidentiality of my information be protected?

All samples will be encrypted (all information that could identify you will be removed). This means that the samples will be identified by a numerical code, not by your name, and neither you nor your family members will be identified or contacted. No individual patient will be identified at the time of publication of the results.

If you decide to participate in this clinical study, information will be collected and entered into a study database. The scientific and medical staff of the group medical [redacted] and those who work for them in conducting the study may need to review yours to ensure that the study is being carried out correctly, but your confidentiality will be protected at all times. The REC or the

national health authorities may review your medical notes (related to this study) and the study information to verify that the study is being carried out correctly.

Your GP will be informed about your participation in this study, although all information collected about you during the study will be kept strictly confidential.

What will happen to the results of the research study?

The results of this clinical research study will be published in a major scientific journal. The results will also be presented at international clinical and scientific conferences. No information on individual patients will be provided in these publications or presentations of results. You or your family may request a copy of the published results.

Who has reviewed this study?

This substudy has been reviewed and has obtained the favorable opinion of a reference Ethics Committee and has the approval of the national health authority in which the study is carried out. If you require more information, you should contact your physician in charge of the trial.

Thank you for taking the time to read this information sheet and for considering your participation in this clinical study.

If you have any questions about your disease or clinical trials, please discuss them with your doctor.

Names and contact telephone numbers:

……

…… ……

…… ……

……

Research Consent Form Translational

Study Title: Ensayo clínico fase II multicéntrico para evaluar la eficacia y la seguridad de ibrutinib en combinación con rituximab, gemcitabina, oxaliplatino y dexametasona seguido de ibrutinib como tratamiento de mantenimiento en pacientes con linfoma difuso de células B grandes de tipo no GCB resistente al tratamiento o recidivante no candidatos a recibir un TACM
EudraCT: [redacted]
Protocol number: [redacted]
Sponsor: [redacted]
Coordinators: [redacted]

Substudy coordinators:
- Central review of molecular studies and histopathological diagnosis: [redacted]
- Analysis of the mutational spectrum of 45 genes and evaluation of MRD in patients with treatment-resistant or recurrent diffuse large B-cell lymphoma included in the phase II clinical study [redacted]
- Evaluation of the cell of origin (germinal center B versus activated) in patients with treatment-resistant or relapsed diffuse large B-cell lymphoma included in the phase II [redacted]

Me, the undersigned (name, surname): ……
The doctor…… of the Hospital. .....I has provided all the information I have requested about the p RAFT Translational biological research associated with the study [redacted] and have had the opportunity to perform all the questions necessary to understand the study.
I understand that my participation in the study is completely voluntary and that I can withdraw my consent at any time without providing a reason. Deciding not to participate or to withdraw from the study will not harm or have any effect on my future treatment.
I grant my authorization to use part of my biological samples left over from the diagnosis and the extraction and donation of 50mL of peripheral blood to participate in the research project defined in this document.

Based on the conditions specified in the "Patient Information Form" of this document

My participation in this study is completely voluntary	YES ☒ NO ☒
I freely accept that samples may be obtained and processed for research purposes:	YES ☒ NO ☒
- Biopsy Lymph node or other tissue biopsies for biological substudy	YES ☒ NO ☒
- Peripheral blood	YES ☒ NO ☒
- Lymph node biopsy at time of relapse	YES ☒ NO ☒

Date:_____
Patient's first and last name:
_____

Patient's signature:

_____

Date: _____
IP name and surname(s):
_____

Investigator's signature:

_____

IV. Patient information sheet and consent form for Biobank

INFORMED CONSENT DOCUMENT

Project/Clinical Trial: **CODE PROTOCOL:** [redacted]

Principal Clinical Investigator: [redacted]

Biological Project Managers: [redacted]

Information to the Participant

Purpose and description of the process

This document is to request your written authorization for the donation of part of the remaining sample of diagnostic tissue, in order to incorporate your sample into a Biobank that exists at the [redacted]L (tissue node, [redacted]) and use said surplus in a biomedical research project related to cancer. It is important that you read this informed consent form carefully, that you understand its content and its purpose and that, where appropriate, ask all the questions you think necessary about it.

The advancement of science and medicine requires that research be carried out on tissues, both healthy and pathological, in association with clinical data on their process, treatment and evolution. This advance is especially important in the field of cancer, since it is the second leading cause of death in the world. The main way to obtain these tissues that allow biomedical research are the leftover samples of the extractions that are made for diagnostic purposes. Part of the tissue or blood sample is no longer necessary for the corresponding study and to establish a diagnosis and is therefore normally destroyed.

As a patient, you can donate the remainder of your sample so that, instead of being destroyed, it can be used in biomedical research related to cancer, incorporating the sample into a Biobank. The purpose of the donation is to provide researchers with tissue or blood so that they can develop advances in the field of knowledge about cancer, in particular about its appearance, evolution and treatment.

The consent that you now give for the use in research of this excess tissue, which would otherwise be discarded, does not imply any additional risk or inconvenience for you since you are only going to authorize its use in a research project and incorporation into a Biobank. .

The donation of this surplus tissue is voluntary, so if you give your consent for its use, you can revoke it at any time. In the event of this revocation, this will not entail any change in the relationship with your doctor or any damage to your diagnosis/treatment and/or follow-up. In case of revocation, your sample will no longer form part of the investigation, although the data obtained up to that moment will form part of it.

The current project to which this consent refers has been evaluated and accepted by an independent and accredited Ethics Committee and Scientific Committee. The objectives of the present study refer to the identification of biological markers useful in the diagnosis and possibly prognosis of patients with aggressive post-transplant B-cell lymphoma.

Altruistic nature of the donation

The donation is altruistic in nature by law, so you will not obtain any economic benefit from it now or in the future. However, the insights gained from studies carried out on your sample and many others can help medical advancement, and thus other people.

Data protection and confidentiality

The personal data collected about you will be confidential and processed in accordance with Organic Law 15/1999 on the Protection of Personal Data and the current legislation regarding biomedical research, treating them only in accordance with the objectives described in this document, so any relationship between the sample and your personal identity is strictly confidential. The results obtained from the different studies carried out with the samples may be published in scientific journals, but your identity or data that identifies you or may identify you will never be provided.

At the time that you consent to the use of surplus samples for the purposes of applied research described, said surplus will be subjected to a dissociation process. In other words, you will only be identified by a number and/or a code containing all your data duly coded, so the researchers involved will never know your identity or any data that could identify you; however, they may, in any case, access other data such as their gender or age, but always maintaining due confidentiality in accordance with current legislation. Files with identification will have restricted access.

Likewise, once the sample has been incorporated into the biobank, your personal data will be incorporated into an automated confidential file, duly registered with the Spanish Data Protection Agency, in accordance with the terms established in Organic Law 15/1999 on Data Protection. Personal Data, whose ownership corresponds to the [redacted], in order to manage the use of the surplus assigned by you for the research purposes described in this document, being able to exercise at any time, the rights of access, rectification, cancellation or opposition, recognized by the aforementioned regulations on the protection of personal data, by contacting the person in charge of the tissue node [redacted] or at the following e-mail address: [redacted]

With this consent, the Hospital's specialists may consult your clinical history, only in the event that it is necessary to update the information associated with your samples.

Information on the results of the study

The data obtained from the analysis of the sample will be archived, and will form part of the study/research project and will be maintained during its development. The methods used in Biomedical research are usually different from those approved for clinical practice, so they should not be considered of clinical value to you. However, in the event that these investigations provide data that could be both clinically and genetically relevant for you and of interest to your health or that of your family, they will be communicated to you if you deem it appropriate. Likewise, relevant information could be obtained for your family, it will be up to you to decide whether or not you want to communicate it. If you want such relevant information to be communicated to you, you must enter it in the box that appears at the end of this sheet.

The samples

We also request your consent, so that if, there are surplus tissue after the end of the study, these can be used in other research projects. Any project for which Biobank samples are used will be previously approved by an accredited Scientific and Ethical Committee.

We thank you for your selfless collaboration with the advancement of science and medicine and, especially, in reference to research on the appearance, development and treatment of cancer.

INFORMED CONSENT DOCUMENT for biological study

Project/Clinical Trial: **CODE PROTOCOL:** [redacted]

Clinical Principal Investigator: [redacted]

Biological Project Managers: [redacted]

Informed Consent

PATIENT DATA	
Surnames	
Name	
Address	
DNI or similar:	*Hospital:* *Medical record number:*
I declare under my responsibility that I have read the Participant Information Sheet about the aforementioned study and agree to participate in it. I have been given a copy of the Participant Information Sheet and a copy of this Informed Consent (current page), dated and signed. The characteristics and objective of the study and the possible benefits and risks of the study have been explained to me. I have been given time and opportunity to ask questions. All questions were answered to my complete satisfaction. I know that the confidentiality of my data will be maintained, as long as they are not essential for the development of the project. I give my consent voluntarily and I know that I am free to withdraw from the study at any time, for any reason, and without it having any effect on my future medical treatment.	
I authorize the use of possible surpluses in other related projects	YES ⛀ NO ⛀
I authorize to be contacted in case more information is needed	YES ⛀ NO ⛀
Date	*Signature*

Data of the person providing the information and the consent form	
Name and surnames	*Signature*

More information provide in a stand alone document

V. ECOG functional status

GRADE	ECOG FUNCTIONAL STATUS
0	Fully active, capable of carrying out all pre-disease activities without limitations.
1	Restriction of physically strenuous activities, but the person can walk and perform tasks of a sedentary or restful nature, e.g. light housework or office tasks.
2	Ambulatory and able to carry out personal care but unable to carry out any work activity. Up for more than 50% of waking hours approximately
3	Person is only capable of self-care limited, confined to bed or chair for more than 50% of waking period.
4	Completely disabled, unable to perform personal care of any kind, totally confined to bed or chair.
5	Death

VI. NCI CTCAE Criteria V4.03

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

VII. Centralized review of PET/TC

CENTRALIZED REVIEW PROTOCOL.

Image Subcommittee of the [redacted] group.

Justification

PET/TC performed midway through treatment has proven to be a tool of great prognostic value in patients with DLBCL, being capable of early classifying patients as good or poor responders (1). For this reason, numerous clinical trials are studying the use of new therapeutic strategies based on the results of early PET/TC; that is, escalate or de-escalate the treatment based on the individual metabolic response of each patient (2).

In recent years, there have been numerous advances in the field of molecular imaging, especially aimed at agreeing and unifying the criteria for evaluating and interpreting PET/TC studies. Thus, at the First International Workshop held in Deauville, France, in 2009 (3), a visual assessment method (Desauville 5-point scale) was adopted to assess intermediate PET (PET). In addition, with the aim of improving the visual assessment in the interpretation of the PETi in the DLBCL, the use of quantitative analysis was proposed. The most widely used quantitative index is the Standardized Uptake Value (SUV), which relates the dose of FDG administered to the patient's weight. The change in maximum SUV ([redacted]SUVmax) in tumor tissue before and after treatment can be used to measure the degree of response (4-8).

The Deauville criteria and quantification by [redacted]SUV in patients with DLBCL have already been validated (9). The latest expert consensus in Lugano reflects the mid-term and end-of-treatment endpoints (10).

Since 2014, the group[redacted] has had a group of nuclear medicine experts in the centralized assessment of PET/TC studies in clinical trials using the latest international recommendations (10).

In the present work, thegroup [redacted], made up of nine nuclear medicine doctors, will carry out a qualitative and quantitative prospective centralized assessment of the PET/TC studies performed before the start of treatment as well as after the fourth cycle (the latter being decisive for the number of cycles to be administered) and the final PET/TC after completing the treatment to assess the remission status.

Objectives

- Evaluate the relationship of metabolic parameters with biological markers.
- Identify the best interpretation criteria for PET/TC studies (visual or quantitative) to predict survival.
- To study the prognostic value of metabolically negative residual lesions.
- Measure the degree of agreement between the reviewers, which will be calculated by

Cohen's K coefficients and Krippendorf's α.

- To study the feasibility of centralized calculation of tumor metabolic volume in baseline PET/TC (VMT0) and to establish its prognostic value.

Material and methods

PET/TC study protocol

All acquisition parameters must comply with the QTC (qualification of PET/TC systems for participating in clinical trials).

All patients will undergo a baseline PET/TC scan before starting treatment (PET0), as well as another PET/TC scan after the fourth cycle of IR-GEMOX (PET4), which will be scheduled between days 10 and 14 after said cycle. cycle. In addition, all patients will undergo a final PET/TC after the sixth or eighth cycle (PET6 or PET8) at least three weeks after completing treatment.

All PET/TC studies of each patient will be performed in the same chamber and with the same acquisition protocol.

The preparation of the patient, injection of FDG and acquisition of the studies will be carried out following the recommendations of the EANM (11).

Transfer of images and PET Network

The TC and PET studies with attenuation correction, anonymized, will be sent to the central platform [redacted] in DICOM PART 10 format within 72 hours of acquisition.

The centralized review panel will be composed of 9 expert nuclear medicine doctors. Each of them will carry out a blind and independent evaluation of all the studies.

For each patient, a centralized review of PET0 and PET4 will be performed. In the centralized review process, each nuclear medicine doctor will fill out a clinical form that will be available on the platform [redacted]. The final result of the PET/TC study will be sent back to the investigator. Finally, the PET6/PET8 will also be reviewed within a week after receiving the images.

Qualitative analysis of PET

PET0 will be informed in each local center where the study is performed, following the standard criteria and with the available clinical information (a pathological uptake of FDG is that focal or diffuse uptake greater than the background activity, not attributable to physiological uptake).

PET4 studies will be centrally assessed without having the patient's clinical information available, and will be interpreted binary as positive or negative based on the 5-point Deauville scale.

Deauville scale (3)

no uptake
uptake ≤ mediastinum **
uptake > mediastinum but ≤ liver
uptake moderately greater than liver
uptake markedly greater than liver and/or new lesions
X new areas of uptake probably not related to lymphoma

PET4 will be considered positive if the uptake of residual disease is moderately or markedly greater than that of the liver (Deauville >3). PET4 will be considered negative if the uptake of residual disease is less than or similar to that of the liver (Deauville ≤3).
The result of the PET4 will be decisive for the change of treatment.

Semiquantitative analysis of PET

Maximum SUV values will be calculated by body weight.
SUVmax is defined as the highest SUV value in the hypermetabolic lesion with the highest FDG uptake. For each PET/TC study, the tumor lesion with the most intense FDG uptake will be identified among all the hypermetabolic foci using a color gradient scale. The most active volumetric region will be determined, calculating the SUVmax on it. To calculate ΔSUVmax, the most active region in any region or organ in PET4 will be compared to that in PET0, even if the location in PET 4 differs from the location in PET0. The SUVmax between PET0 and PET4 (ΔSUVmaxPET0-4) will be calculated (12).
Positive PET4 is defined if ΔSUVmax PET0-4 is <70% and negative if ΔSUVmax PET0-4 is ≥70%.
In the event that the results of the qualitative and quantitative assessment differ from each other in the PET4, the semi-quantitative analysis will be decisive to consider the study positive or negative.
The PET4 result will determine the number of cycles to be administered: in the case of complete remission (CR), patients will receive 2 more cycles; partial response (PR): 4 more cycles; stable disease (SE): 4 more cycles; progression: they will exit the trial.

Final response

PET6/PET8 should be analyzed qualitatively or visually following the 5-point Deauville scale. The definition of the remission state at the end of the treatment will be carried out taking into account the metabolic and morphological findings of the PET/TC, following the latest proposals from the experts (10):

Complete metabolic response (CMR):

Deauville 1, 2,3 , with or without residual mass and without evidence of involvement of the bone marrow, spleen or other extra lymphatic organs.

The CMR with residual mass should be called rMCR, and the size of the mass must be recorded.

Residual metabolic disease (RMD):

Deauville 4 or 5 and residual mass of any size (no new lesions).

Progressive metabolic disease (PMD):

Deauville 4 or 5 and new hypermetabolic foci of FDG compatible with lymphoma or increased uptake of previously existing foci corresponding to disease and/or ≥50% increase in the sum of the product of the diameters of the masses .

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VII. Biological Substudy

An extensive biological study will be performed in order to further characterize this non-GCB DLBCL patient population and evaluate the response obtained with the mutational profile of the tumor. In the event that patients agree to participate in the biological study, peripheral blood, paraffin-embedded blocks from the original diagnostic lymph node biopsy, and lymph node biopsy performed at the time of recurrence (if available) are sent to a central laboratory to perform phenotypic subtyping tests, molecular studies, mutational spectrum, and determination of the cell of origin using NanoString technology (NanoString Technologies, WA, USA) (13). The biological studies will be coordinated by [redacted]

1. CENTRAL REVIEW OF MOLECULAR AND HISTOPATHOLOGICAL DIAGNOSTIC STUDIES

2. ASSESSMENT OF CELL OF ORIGIN (GERMINAL CENTER B VS ACTIVATED) IN PATIENTS WITH TREATMENT-RESISTANT OR RECURRENT DIFFUSE LARGE B-CELL LYMPHOMA INCLUDED IN THE PHASE II STUDY [redacted]

3. MUTATIONAL SPECTRUM ANALYSIS OF 45 GENES AND EVALUATION OF MRD IN PATIENTS WITH TREATMENT-RESISTANT OR RECURRENT DIFFUSE LARGE B-CELL LYMPHOMA INCLUDED IN THE PHASE II CLINICAL STUDY ([redacted] GUIDELINE) (No EUDRACT [redacted])

1. REVIEW oF CENTRAL AND MOLECULAR STUDIES Histopathological diagnosis

[redacted]

1.1 BIOLOGICAL SAMPLES:

Is planned to collect different types of biological samples from patients enrolled in the clinical trial:
It requires tissue blocks from diagnostic lymph node/extranodal incisional or excisional biopsies. Biopsies using thick except needles are recommended that the clinical situation indicates that the only safe means to obtain diagnostic tissue[25].
Each patient will have to sign a specific informed consent form for the molecular studies included in this protocol.

- Diagnostic sample fixed in formalin and included in paraffin (FFIP). The FFIP tissue in which the diagnosis of DLBCL is established. At least one FFIP block is required for central review and further study. If two or more samples are available from a patient obtained at different times, all representative samples should be evaluated.

- Representative neoplastic tissue frozen at the time of diagnosis. At least one block of frozen neoplastic tissue to obtain DNA and RNA. The samples must be representative of the neoplastic tissue. Representative sections should contain > 80% neoplastic cells and allow sufficient DNA and RNA (0.5 - 1 g each) to be obtained for molecular studies. These samples must be obtained from the majority of patients included in the study, included in OCT medium and stored at -80 ºC until shipment.

- Peripheral blood (non-neoplastic) from the patient at any time during the study. Two EDTA tubes with 10 ml of peripheral blood without any particular treatment.

All biological samples available from the patient at the time of diagnosis (FFIP, frozen) will be sent immediately after the patient's inclusion in the clinical trial for central diagnostic review (see below). The shipment of the BP will be made after the extraction procedure.

All shipments will be coordinated by the staff of [redacted], together with the [redacted] of the clinical centers included in the study. The patient must sign a specific informed consent related to biological studies.

After receipt, the samples will be coded with an Id number associated with the biological project. All personal data in relation to the patient will be included in a database, which complies with the

personal data protection law. The samples will be processed for the different objectives in the different associated laboratories:

Central review of histopathological diagnosis and extended diagnostic tests: [redacted]

Molecular studies. [redacted]

All samples (FFIP, frozen tissue, BP and derivatives (extracted RNA and DNA, histological and immunohistochemical samples, tissue microarrays) will be stored in the [redacted]

1.2. CENTRAL HISTOPATHOLOGICAL DIAGNOSTIC REVIEW

Diagnostic samples from all Patients included in the trial will be evaluated by a group of hematopathologists from [redacted]A diagnosis will be established based on the current WHO classification of hematolymphoid neoplasms[1]The group of standard diagnostic markers will include: Hematoxylin-eosin and IHC: CD20, CD3, CD30, CD10, BCL6, BCL2, MUM1, C-MYC, KI67

Immunohistochemistry will be performed by automated methods and using monoclonal antibodies and optimized visualization methods All IHC results will be evaluated in the diagnostic context in a semi-quantitative way and the cases will be classified according to the algorithms already published[5, 8, 1 0, 12, 26].

A diagnostic report will be generated for each case within ten days of receipt of the diagnostic FFIP sample and sent to the clinical coordinator.

1.3. EXTENDED DIAGNOSTIC PANEL

Tissue microarrays (TMA) (60 representative samples in duplicate in each TMA) will be constructed with the tissue obtained from the FFIP blocks.[27] An expanded set of biomarkers will be performed on TMA samples:

Immunohistochemistry: A set of 15-20 monoclonal antibodies will be tested.

- Fluorescent *in situ* hybridization (FISH) for the detection of translocations including: IGH, C-MYC, BCL6, BCL2, IRF4, PAX5 and tp53 (17p) deletions.

1.4. MUTATIONAL PROFILE

DNA will be extracted from FFIP diagnostic tumor tissue and processed to allow targeted NGS sequencing using Illumina/Miseq equipment [redacted].

Contact information:

[redacted]

[redacted] smontes@humv.es
[redacted]

2. ASSESSMENT OF CELL OF ORIGIN (GERM CENTER B *VERSUS* ACTIVATED) IN PATIENTS WITH RESILIENT DIFFUSE LARGE B-CELL LYMPHOMA TO TREATMENT OR RECIDENT INCLUDED IN THE PHASE II STUDY [redacted]

[redacted]

November 11, 2015

Background

Diffuse large B-cell lymphoma (DLBCL) is the type of most common lymphoma in Western countries, accounting for 35-50% of cases. Although considered a single category in the WHO classification, DLBCL represents a heterogeneous group of lymphomas classified together on the basis of morphology, immunophenotype, genetic alterations, as well as clinical behavior. Ten years ago, the distinction of DLBCL into categories of cell of origin (CDO) based on gene expression patterns reminiscent of germinal center B cell group (GCB group) and activated B cell group (ABC group), as defined by the gene expression microarray (PEG) technique, showed crucial biological, prognostic, and possibly therapeutic implications.[1] Thus, ABC-type DLBCL exhibits unique alterations, including constitutive activation of the NFkB pathway, poor response to conventional treatment, and poor survival compared to CGB-type DLBCL.[2-3] In addition, the classification into groups based on the CDO is increasingly important due to the emergence of new treatments that have selective biological activity in one of the groups. This is the case of ibrutinib: several studies suggest that this drug has a high selective activity in patients with ABC-type DLBCL.[4-5]

DLBCL treatment outcomes have improved significantly after the introduction of rituximab (R) in CHOP-type regimens and is now the gold standard treatment. However, even with current immunochemotherapy, approximately 30-40% of patients will relapse or ultimately progress.[6] Rescue treatment in patients with relapse/resistant to treatment shows clearly insufficient results and the use of new drugs is warranted. A phase II study will begin in a few months to determine the efficacy of ibrutinib in combination with R-GEMOX-dexa. A clinical trial in patients with relapsed/refractory DLBCL is an excellent target to conduct a biological side project and gain insight into the biology of the disease. It would be of special interest to know the CDO of tumor cells.

The original method for defining PEG groups used microarrays of RNA derived from frozen tissue. This technique is not feasible in routine clinical practice, since paraffin-embedded tissue is usually available. For this reason, different attempts to develop immunohistochemical algorithms that capture information related to PEG have been evaluated. However, neither algorithm provided high reproducibility in clinical practice.[7] More recently, the same consortium that designed the GCB/ABC classification, the *Lymphoma and Leukemia Molecular Profiling Project*, has developed a 20-gene digital strict expression test (NanoString) for CDO assignment (Lymph2Cx assay), which can be used on formalin-fixed and paraffin-embedded samples. This test was validated in an independent cohort and is currently marketed in clinical practice.[8,9]

In summary, we are proposing a parallel biological project related to the current clinical trial [redacted], with the main objective of determining the ODCs of tumors.

Objectives

- To determine the CDO (GCB-type DLBCL *versus* ABC) in patients with relapsed/refractory DLBCL included in the phase II clinical trial [redacted]

- Establish a correlation between the CDO and the main clinical and biological characteristics, the response to treatment and the outcome of the patients.

Methods (summary)

1. Samples: 62 tumor samples (paraffin-embedded tissue) at diagnosis; in addition, 15 - 20 tumor samples at the time of recurrence (biopsy at the time of recurrence is not mandatory, but recommended).

3. Nucleic acid extraction from paraffin-embedded material.

4. Determination of cell of origin using the Lymph2Cx assay, as described in the recent LLMPP publication (Scott et al., Blood 2014;123:1214-7), using NanoString technology (NanoString Technologies, WA, USA). 200 ng of RNA were used to determine gene expression levels.

5. Statistical Considerations: The primary endpoint of the trial is RESPONSE to treatment; therefore, the main objective of the biological project will be to establish the relationship between CDO and the mutational spectrum with response to treatment with RI-GEMOX-dexa. The main clinical characteristics at the time of diagnosis and recurrence, and the outcome (progression-free and overall survival) will also be analyzed.

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3. SPECTRUM ANALYSIS OF 45 GENES AND ASSESSMENT OF MRD IN PATIENTS WITH TREATMENT-RESISTANT OR RECURRENT DIFFUSE LARGE B-CELL LYMPHOMA INCLUDED IN THE PHASE II CLINICAL STUDY (GUIDELINE [redacted]) (No EUDRACT [redacted])

[redacted]

[redacted]

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November 1, 2015

Background

Diffuse cell lymphoma Large B lymphoma (DLBCL) is an aggressive lymphoma that represents ~40% of all NHL in adults, most of which are classified as "not otherwise specified" (NOS) according to the 2008 WHO classification. DLBCL NOS is a heterogeneous group of lymphomas , subclassified as germinal center B cell (GCB) or activated B cell (ABC or non-GCB) phenotype based on cellular origin.[1,2] Despite improved treatment and the introduction of rituximab, up to 40% of DLBCL patients relapse and die due to disease progression.[4-6] In addition, the recurrence rate is similar in the two DLBCL groups, suggesting the existence of additional oncogenic events that influence treatment resistance.[7] Rescue treatment in patients with relapse/resistance to treatment shows clearly insufficient results and the use of new drugs is warranted. A clinical trial in patients with relapsed/refractory DLBCL is an excellent target to conduct a biological side project and gain insight into the biology of the disease. Of special interest would be to know the mutational spectrum of DLBCL tumor cells.

Recently, the most frequently mutated genes have been described using next generation sequencing (NGS) in patients with DLBCL, which has led to the description of new genetic mutations together with the frequently mutated genes described in these entities [7-10] Thus, several genes are more common in GCB-type DLBCL (eg, CREBB, EZH2, MLL2), while others are specific to or more common in non-GCB-type DLBCL (loss of CDKN2A/B, mutations in TNFAIP3, MYD88 or CARD11), with biological, prognostic and possibly therapeutic implications.[7-8] In addition, many of these genes are part of the same cellular pathway, so presumably the alteration of any of these genes would trigger the alteration of the entire pathway, with a possible implication in the prognosis. However, studies looking at the clinical role of gene mutations are very limited.[11-13] The

study of mutations in these genes and these pathways would be of special interest in studying the effect of these mutations on the response to different drugs, as well as in the identification of possible new targets or in the individualized treatment of these pathologies . In this context, mutations in different genes in the NF-κB pathway (eg, BTK, TRAF2, BIRC3, PLCγ2, MYD88, CD79A/B, etc.) have been shown to alter the response to ibrutinib in different disorders B-cell lymphoproliferative disorders, including DLBCL.[14-17]

In addition to mutations, monitoring of circulating tumor DNA as minimal residual disease (MRD) in patients with DLBCL has been shown to be a reliable tool for predicting premature treatment failures as well as recurrence from remission.[18,19] Finally, we have shown that the HLA-B44 supertype could define a subgroup of patients who do not respond to R-CHOP regimens.[20] Therefore, the study of this HLA supertype in a clinical trial would be of interest.

In summary, we propose a parallel biological project related to the clinical trial [redacted] with the main objective of evaluating the mutational spectrum of the included cases; furthermore, our aim was to establish a correlation between the presence of MRD and response, and to assess the role of the HLA-B44 supertype in response and outcome.

Objectives

- To evaluate the mutational spectrum of 45 genes in patients with relapsed/resistant DLBCL included in the phase II clinical trial [redacted]
- Evaluate the minimal residual disease (MRD) in the DLBCL included in the clinical trial.
- To study the HLA status in non-tumor samples in the DLBCL included in the clinical trial.
- Establish a correlation between the mutational spectrum, the MRD and the HLA status and the main clinical and biological characteristics, the response to treatment and the outcome of the patients.

Methods (summary)

1. Samples:

Mutational spectrum: 62 tumor samples at diagnosis; also, when available, tumor samples when recurrence occurs. The use of fresh frozen tissue or good quality DNA extracted from fresh frozen tissue is recommended; paraffin-embedded tissue should be a second option.

MRD. Identification of MRD targets: The tumor sample at diagnosis will be used for amplification of IgH and IgK rearrangements in order to select the most appropriate MRD targets for each patient (VDJ, DJ or IgK).

Follow-up: Plasma will be obtained from two x 10 cc peripheral blood (PB) samples in EDTA tubes for MRD studies on each follow-up date (at the same times as imaging studies). Plasma must be obtained at each center within four hours of SP collection, in order to avoid contamination with DNA from circulating leukocytes. The plasma and the remaining cells (circulating leukocytes) will be sent separately to Salamanca, where DNA from these two fractions will be isolated. MRD will be

assessed at the PET/TC reassessment after 4 cycles and at the end of the induction period. MRD monitoring will be carried out at each control CT, in accordance with the protocol and from the end of treatment during the first two years.
HLA: non-tumorous or low tumor burden peripheral blood sample. The same samples can be used for HLA analysis as for MRD studies. In case a new sample is needed, 1 x 10 cm sample can be obtained ^{3} of SPin an EDTA tube at any time during the project.

2. Mutational status of 45 relevant or possibly relevant genes in DLBCL determined by Miseq (Illumina) and confirmed by Sanger sequencing. These genes are the following:
ARID1A, B2M, BCL2, BCL6, BIRC3, BTK, CARD11, CCND3, CD79A, CD79B, CREBBP, EBF1, EP300, EZH2, FBXO11, FOXO1, GNA13, GNAI2, HIST1H1B, HIST1H1C, HIST1H1D, HIST1H1E, IRF8, MEF2B, MLL2, MYC, MYD88, NOTCH1, NOTCH2, P2RY8 PCLO, PIM1, PLCγ2, POU2F2, S1PR2, SOCS1, SPEN, STAT3, tbl1xr1, TET2, TNFAIP3, TNFRSF14, TP53, TRAF2, TRAF3

3. rearrangements IgH (VDJ and DJ) and IgK at the time of diagnosis will be analyzed using PCR, in accordance with concerted action by BIOMED-2[21] in order to select the most suitable MRD targets. MRD in circulating leukocytes will be evaluated using the BIOMED-2 strategy, while plasma samples will be evaluated by high-throughput sequencing. The selected target will be evaluated in follow-up samples at the time of reassessment after cycle 4, at the end of the induction period, and at each control TC scan for the first two years. MRS studies will be analyzed in both circulating leukocytes and circulating plasma tumor DNA at each follow-up. The results of the MRD will be compared with those of the TC/PET studies.

4. HLA-B typing at the low resolution level will be performed by PCR-SSO and Luminex XYP, in accordance with the standards of the European Federation for Immunogenetics. The presence of the HLA-B44 supertype will be evaluated as previously published.[20] Briefly, patients with at least one HLA-B*18, HLA-B*37, HLA-B*40, HLA-B*41, HLA-B*44, HLA-B*45, or HLA-B allele *50 are considered positive for the presence of the supertype.

5. Statistical considerations: the objective of the biological project will be to establish the relationship between MRD, mutational spectrum and HLA status with the response to the study [redacted], progression-free survival and overall survival.

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IX. Revised criteria for response assessment

Assessment Criteria Lugano Response Assessment Criteria for Non-Hodgkin Lymphoma (28)

Response and location	**Response based on PET/TC**
Complete	Complete metabolic response
Lymphatic and extralymphatic nodes	Score 1, 2, or 3 with or without a residual mass in 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation in the spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), the uptake it may be higher than in normal mediastinum and/or liver. Under these circumstances, the complete metabolic response can be inferred if the uptake at the initial sites of involvement is not higher than the surrounding normal tissue, even if the tissue exhibits high physiological uptake.
unmeasured injuries	Not applicable
Increasing the size of the organs	Not applicable
New injuries	None
Bone Marrow	No evidence of FDG avidity in bone marrow
Partial	Partial metabolic response
lymph nodes and extralymphatic	Rating 4 or 5 † with reduced uptake compared to those with basal mass(es) and residual mass(es) of any size. At mid-treatment, these results suggest that the disease is responding At the end of treatment, these results are indicative of residual disease
unmeasured injuries	Not applicable
Increasing the size of the organs	Not applicable
New injuries	None
Bone marrow	Residual uptake greater than uptake in bone marrow normal, but reduced compared to baseline (diffuse uptake consistent with reactive changes from chemotherapy). If there are persistent focal bone marrow changes in the setting of a nodal response, consideration should be given for further examination with MRI or biopsy or an interval scan.

No response or stable disease	No metabolic response
Target lymph nodes/nodal masses, extranodal lesions	Score of 4 or 5 no significant change in FDG uptake from baseline to mid- or end of treatment
unmeasured injuries	Not Applicable
Increase the size of the organs	Not Applicable
New injuries	None
Bone marrow	No change from baseline
Disease progression	Metabolic disease progression
Individual lymph nodes/target lymph node masses	Score of 4 or 5 with an increase in uptake intensity over baseline period
Extranodal injuries	New areas of FDG avidity consistent with lymphoma at mid- or end-of-treatment assessment
unmeasured injuries	Ninguna
New injuries	New areas of FDG avidity consistent with lymphoma rather than another etiology (e.g. infection, inflammation). If uncertain as to the etiology of new lesions, a biopsy or interval scan may be considered.
Bone marrow	New or recurrent areas of FDG avidity.

X. Questionnaire on comorbidities

CIRS SCALE

General principles of scoring

Each patient's disease must be classified in the appropriate section. If there are several diseases in the same section, only the most severe is scored.

Level 0: No past minor problems or injuries: childhood illnesses (chickenpox), minor surgery (fully healed carpal tunnel, cesarean section), healed uncomplicated fractures, other past problems already resolved without sequelae or complications (pneumonia)

Level 1: Any current medical problem that causes mild discomfort or disability, or has an occasional exacerbation, having only a minor impact on morbidity (asthma controlled with bronchodilators, occasional heartburn relieved with antacids). Medical problems that are not currently active but were significant in the past (kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy)

Level 2: Medical conditions that require daily treatment or first-line therapy (asthma controlled with inhaled steroids, gastro-oesophageal reflux treated with daily medication, osteoarthritis that requires non-steroidal anti-inflammatory drugs,…) and/or have moderate disability or morbidity

Level 3: Chronic conditions that are not controlled with first-line therapy (asthma that corticosteroid therapy, symptomatic angina despite medical regimens, symptomatic heart failure or uncontrolled hypertension despite a complex therapeutic regimen) and/or ongoing significant but not severe disability

Level 4: Any acute condition requiring immediate treatment or hospitalization (unstable angina, acute myocardial infarction, stroke, but also bladder obstruction) and/or extremely severe problems, organ failure (end-stage kidney disease requiring dialysis, oxygen-dependent chronic obstructive pulmonary disease, end-stage heart failure); severe sensory impairment (nearly complete blindness or deafness; being in a wheelchair) and/or severely impaired quality of life; severe functional disability; delusion due to medical (organic) conditions

Neoplasm evaluation

Level 1: Cancer diagnosed in the remote past, without evidence of recurrence or sequelae in the last 10 years or skin cancer excised in the past without important sequelae (other than melanoma).

Level 2: There is no evidence of recurrence or sequelae in the last 5 years.

Level 3: Required chemotherapy, radiation, hormone therapy, or surgery for cancer within the past 5 years.

Level 4: Recurrent malignancy or metastasis (other than lymph nodes) or palliative treatment phase.

These ratings will be made in the appropriate organ category for a given neoplasm.

HEART

In this category, only heart and coronary diseases will be taken into account (not vascular): coronary artery disease, heart failure, valvular heart disease, heart disease secondary to hypertension, endocarditis, myocarditis, pericarditis, arrhythmias (extrasystoles , bundle branch blocks, atrial fibrillation), malignant tumors of the heart. The functional impact must also be considered, for example, NYHA II heart failure has a different value between dependent and independent people.

0. No problem

1. Past myocardial infarction (more than 5 years ago); occasional angina pectoris [exertional], asymptomatic valvular disease

2. Medication-compensated congestive heart failure (NYHA I-II); daily medications for angina pectoris, left ventricular hypertrophy, atrial fibrillation, bundle branch block, daily antiarrhythmic drugs (including for prophylaxis), valvular disease requiring medical treatment

3. Previous myocardial infarction (less than 5 years ago) , abnormal stress test; coronary artery bypass surgery or other heart surgery (valve replacement), moderate congestive heart failure (NYHA II-III), or complex medical treatment; bifascicular block, pericardial effusion, or pericarditis

4. Acute coronary syndrome, unstable angina, or acute myocardial infarction; intractable congestive heart failure (NYHA III-IV acute or chronic); marked restriction of normal activities of daily living secondary to cardiac function

HYPERTENSION

Considering only the severity of hypertension, organ damage (complications) should be considered within the respective categories.

0. NormotensionBorderline

1. hypertension, hypertension compensated by salt restriction and weight loss, drug-free (when drug therapy is indicated, but patient is not on medication, score is at least 2)

2.Daily antihypertensive medications: hypertension controlled by one drug therapy (including fixed-dose combinations)

3. Hypertension requiring two or more drugs for control

4.Malignant hypertension, or hypertension not controlled by a complex therapeutic regimen

VASCULAR -HEMATOPOIETIC

Arterial disease: carotid atherosclerosis, peripheral arterial disease (PAD), aneurysms (each site);
Venous disease: venous insufficiency, varicose veins, deep vein thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension;
Hematopoietic disease: anemia, leukopenia, thrombocytopenia, hematological neoplasms;
Lymphopoietic disease: chronic lymphatic edema, lymphoma, diseases of the spleen and thymus;
Immune disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

0. No problem

1. Venous insufficiency, varices, lymphedema, carotid stenosis <70%, hemoglobin 10-12 g/dl (in women), 12-14 g/dl (in men), anemia of chronic "inflammatory" disease

2. Prior DVT, a symptom of atherosclerosis (claudication, murmur, amaurosis fugax, absent pedal pulse), or daily medications (eg, antiplatelet medications); EAP-IIa IIb by Fontaine; carotid stenosis >70%; aortic aneurysm <4 cm; hemoglobin 10.8 g/dl (in women), 10-12 g/dl (in men), anemia secondary to iron, vitamin B12, or folate, or chronic renal failure; total white blood cells (white blood cells) 2,000 to 4,000/mmc, mild thrombocytopenia (50,000-150,000/mmc)

3. DVT or recent DVT (<6 months ago), two or more symptoms of atherosclerosis (see above); Fontaine III or recent PAD / previous angioplasty (with or without stent); hemoglobin <8 g/dl (in women), <10 g/dl (in men), dyserythropoietic anemia; white blood cells <2000/mmc; Severe thrombocytopenia (<50,000/mmc)

4. Pulmonary embolism (acute or recent/previous), atherosclerosis requiring surgical intervention (eg, aortic aneurysm >4 cm, symptomatic carotid stenosis >70%, Fontaine IV PAD, or amputation due to vascular causes, etc.); recent/previous vascular surgery, any hematological or vascular neoplasm (including multiple myeloma)

In the case of immunological disease, the score should be assigned taking into account blood abnormalities, stage of organ damage and/or functional disability (2: symptoms controlled by daily medications, 3: symptoms are not adequately controlled; 4: symptoms impossible to control or poor prognosis for a short time).

RESPIRATORY

This category includes COPD, asthma, emphysema, restrictive interstitial lung diseases, malignant tumors of the lung and pleura, pneumonia, and tobacco use as well.

0. No problem

1. Recurrent episodes of acute bronchitis, asthma currently treated with on-demand inhalers when needed; smoker of more than 10 but less than 20 pack-years.

2. Instrumental diagnosis of COPD or interstitial lung disease (X-rays, CT, spirometry); daily on-demand inhalers (≤ 2 pharmacological classes), two or more episodes of pneumonia in the last 5 years, smoker of more than 20 but less than 40 pack-years.

3. Dyspnea on exertion secondary to limited respiratory capacity, not well controlled by daily medications; oral steroids required for lung disease; daily PRN inhalers (3 pharmacological classes), acute pneumonia treated on an outpatient basis

4. Chronic oxygen supplementation, respiratory failure requiring assisted ventilation, or previous (at least one episode); any pulmonary or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered a disease, and is classified according to *pack-years in life*:

Number of packs of cigarettes smoked per day X number of years smoked in a lifetime

For example: 20 cigarettes/day (1 pack of tobacco) X 1 year = 1 pack-year

Former smokers should also be ranked, but those who have been smoke-free in the past 20 years deserve a rating lower than smoking

Examples:
A. Patient smoking 20 cigarettes/day (1 pack) for 25 years = 25 pack-years - CIRS score: 2
B. Patient smoking 40 cigarettes/day (2 packs) for 25 years = 50 pack-years - CIRS score: 3
C. Former smoker of 20 cigarettes/day (1 pack) for 25 years, quit 5 years ago - CIRS score: 2
D. Former smoker of 20 cigarettes/day (1 pack) for 25 years, left 20 years ago - CIRS results: 1

COPD classification could be more specific when instrumental data (objective tests) are available: blood gasses, forced expiratory volume in 1 second (FEV1), etc

EYES, EARS, NOSE AND THROAT AND LARYNX

To simplify the potential complexity of this category it was decided to score according to severity of disability generated by sensory diseases (degree of limited autonomy and communication) and avoid qualifying each type of pathology. Sensory alterations should be classified **after** instrumental correction (corrective lenses, hearing aids, etc.)
Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology
Ears: otitis, dizziness, any cause of hearing impairment
Nose and throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignant tumors
Larynx: dysphonia, acute and chronic laryngitis, malignant tumors

0. No problem

1. Visual acuity corrected with glasses, mild hearing loss, chronic sinusitis

2. Difficulty in reading newspapers or driving despite wearing glasses; hearing aid required; chronic sinus complaints requiring medication, vertigo/dizziness requiring daily medication

3. Severely low vision, partially blind (escort required to venture out, unable to read newspaper); severe hearing impairment; laryngeal dysphonia (non-neurological dysarthria)

4. Functional blindness/deafness: unable to read, recognize familiar face; laryngectomy (all causes, especially malignancies); surgical intervention required for vertigo; aphonia secondary to deterioration of the larynx.

UPPER GASTROINTESTINAL SYSTEM

This category includes from the esophagus to the duodenum and the pancreatic tree: dysphagia, gastroesophageal reflux, hiatal hernia, esophageal diverticula, any type of gastritis (consider H. pylori eradication or not), gastric/duodenal ulcer, pancreatitis acute or chronic, malignant tumors (gastric lymphoma).
Note that type 1 diabetes is classified under "metabolic".

0. No problems

1. Hiatal hernia, gastritis or gastroesophageal reflux requiring medication on demand; previous ulcer (more than 5 years ago); previous H. Pylori eradication treatment (more than 5 years ago)

2. Daily proton pump inhibitor/antacid medications; documented gastric or duodenal ulcer or H.Pylori eradication therapy within 5 years

3. Active gastric or duodenal ulcer; positive fecal occult blood test, any swallowing disturbance or dysphagia, chronic pancreatitis requiring pancreatic enzyme supplementation for digestion; previous episode of acute pancreatitis

4. Any type of neoplasms (see "Evaluation Neoplasms"), previous gastric surgery due to cancer, history of perforated ulcer (gastric surgery not due to cancer); melena/profuse bleeding from the upper gastrointestinal tract, acute pancreatitis

LOWER GASTROINTESTINAL SYSTEM

Includes the rest of the digestive system, from the small intestine to the anus: Whipple's disease, diverticulosis, irritable bowel, malignancies. Constipation is also scored by type and frequency of laxatives needed, or history of retention.

0. No problems, prior appendectomy, prior hernia repair (no complications)

1. Constipation managed with on-demand medications, active hemorrhoids, intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adhesions, laparocele, etc.), irritable bowel syndrome (few symptoms).

2. Constipation requiring daily bulk laxatives (psyllium, polycarbophil, Sterculia, guar gum, etc), or laxatives; diverticulosis (anterior diverticulitis), inflammatory bowel disease in medication remission (more than 5 years ago).

3. Intestinal impaction/diverticulitis in the last year, daily use of stimulants (irritants) or osmotic laxatives (bisacodyl, senna, glycerol, docusate sodium, lactulose, polyethylene glycol) or enemas, chronic intestinal inflammation in remission with medications (less than 5 years)

4. Recurrent diverticulitis, active inflammatory disease; current impaction; hematochezia/active bleeding from the lower GI tract; colon carcinoma

LIVER AND BILIARY TREE

Includes liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, idiopathic, autoimmune), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignant tumors. As the hepatobiliary system is difficult to assess through physical examination, laboratory results should be used.

0. No problem

1. History of hepatitis (actually with normal transaminase values), cholecystectomy

2. Cholelithiasis, chronic hepatitis or previous hepatitis (less than 5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with Mildly elevated transaminases (< 3 times normal values), excessive alcohol use in the last 5 years (assess in "psychiatric", too)normal values).

3. Chronic hepatitis or any other liver disease with marked elevation of transaminases (> 3 times normal values), elevated levels of bilirubin

4. Acute cholecystitis, biliary obstruction, active hepatitis and liver cirrhosis; any carcinoma of the liver or biliary tree

RENAL

This category is exclusive to the kidneys: kidney stones, acute/chronic renal failure, glomerulonephritis, nephrotic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma.
Bence-Jones proteinuria should not be considered in multiple myeloma.

0. No problem

1. Asymptomatic kidney stones; passage of kidney stones in the last ten years; pyelonephritis in the last 5 years, renal cysts without hematuria

2. Serum creatinine >1.5 but <3 mg/dl without diuretic or antihypertensive medications (especially ACE inhibitors or RAAS blockers), kidney stones requiring daily medicationsdl

3. Serum creatinine >3 mg/dl or >1.5 mg/dl in conjunction with diuretics, antihypertensives, or bicarbonate therapy; active pyelonephritis, nephrotic syndrome; colic symptoms treated as outpatient

4. Dialysis required, renal carcinoma, colic symptoms requiring hospitalization

GENITOURINARY

Ureters, bladder, urethra.
Genitals, prostate, testicles, penis, seminal vesicles.
Uterus, ovaries. *The mammary gland is classified under "metabolic".*
This category includes all GU tract impediments: urethral or bladder stones, benign prostatic hypertrophy (BPH), urinary tract infections (UTIs), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

0. No problems

1. Stress incontinence, BPH without urinary symptoms, hysterectomy or ovariectomy (uterine fibroid, benign tumor)

2. Cervico-vaginal pathology (or two consecutive abnormalities), frequent UTIs (3 or more in the last year) in women or UTIs current, urinary incontinence (not stress) in women; BPH with urinary symptoms (frequency, urgency, hesitancy); status post TURP; any urinary diversion procedure, catheter, bladder stones

3. Prostate cancer in situ (for example, found on purpose during TURP), vaginal bleeding, cervical carcinoma in situ, hematuria (any cause), urinary incontinence (non-stress) in men; bladder polyps

4. Acute urinary retention; current urosepsis; any GU carcinoma, except anterior

MUSCULOSKELETAL-TEGUMENTARY

This is a very broad category, including: osteoarthritis, osteoporosis, bone fractures; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized

skin cancers, rheumatoid arthritis and polymyalgia rheumatica, muscle lesions (rotator cuff, long head of biceps); pressure ulcers; any dermatological disease.
The qualifications of this category are strictly linked to the disability that it causes, for the evaluation of the degree of disability, they refer to basic and instrumented activities.

NOTE: Rate the severity of each illness based on the level of disability caused by the same illness in this category, without taking into account disability caused by other illnesses. For example: a patient affected by both osteoarthritis and hemiplegia from a previous attack has a high level of disability, but you should mark 2 for disability due to osteoarthritis (in this category) and 4 for disability due to stroke (in this category). neurological category); for a patient with rheumatoid arthritis deformans and a previous attack with no remaining results, note 4 disability from arthritis (in this category) and 2 disability from stroke (in the neurological category).

0. No problems

1. Requires on-demand medications for osteoarthritis (NSAIDs) or has slightly limited IADLs due to joint pathologies; excised skin cancer (except melanoma), skin infections requiring antibiotics within a year

2. Daily anti-osteoarthritis medications (NSAIDs) or use of assistive devices or some limitation in IADLs (previous arthro-prostheses or fractures treated with low level of remaining disability), osteoporosis without vertebral fractures; daily medications for chronic skin conditions (including local, such as psoriasis or pressure ulcers); non-metastatic melanoma, daily rheumatoid arthritis medications (except steroids) with low level of disability

3. Osteoarthritis with moderate level of disability on IADLs; chronic steroid treatment required for arthritic conditions or joint deformities or severe disabilities; osteoporosis with vertebral compression fractures

4. Wheelchair for musculoskeletal disease; severe joint deformities or severe use disability; osteomyelitis; any neoplasm of bone, muscle or connective tissue (see section "Classification Neoplasms"); metastatic melanoma.

Fractures and/or arthro-prostheses (both recent and old) have to be classified according to the level of disability they cause (considering the results as well), in order to avoid confusion about possible classifications of different fractures or joints. The same for muscle diseases.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

This category includes "somatic" pathologies of the central and peripheral nervous system: any type of cerebrovascular accident, neurodegenerative diseases (Parkinson's disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. The severity and prognosis of the disease, but also the functional impairment caused by the disease, must be carefully estimated.

0. No problems (or decreased seizures in childhood)

1. Frequent headaches requiring on-demand medications without impairment of advanced ADLs; Previous TIA (one case); Previous existence of epilepsy, really untreated, without seizures for more than 10 years.

2. Chronic daily headache requiring medication (even for prophylaxis) or with advanced regular deterioration in advanced ADLs (bed rest, work abandonment, etc.); True TIA or more than one prior TIA, prior stroke with no significant residual, neurodegenerative diseases of mild intensity (see above), treated and well controlled; drug-controlled epilepsy.

3. Previous stroke with residual mild dysfunction (hemiparesis, dysarthria), and any neurosurgical procedure; neurodegenerative diseases of moderate severity (see above) not well controlled by medication, epilepsy under treatment but with periodic seizures.

4. Acute or previous cerebrovascular accident with serious residual dysfunctions (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy), serious neurodegenerative diseases (see above) causing disability in ADLs, neurological coma .

Alzheimer's disease and dementia should not be classified in this category (psychiatric and behavioral illnesses): Alzheimer's disease should appear only in psychiatric disorders; if the dementia is due to vascular and/or mixed dementia and/or other neurological problems (for example, Parkinson's disease), they should be approved in both the “neurological” and “psychiatric” categories at the appropriate severity level, taking into account in this category stroke and multi-infarct encephalopathy responsible for cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (also systemic infections and poisoning)

Type 1 and type 2 diabetes (organ damage must be considered in the respective categories, as well as hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; It also includes hypo- and hyperthyroidism, hypo- and hyperparathyroidism, adrenal

pathology (Cushing's or Addison's disease), hypogonadism, hypopituitarism, etc. Neoplasms of these glands, both benign (such as thyroid nodules) and malignant (such as thyroid or adrenal cancer, vipoma, etc.) are also included.
Even if it is an exocrine gland, the breast is included in this category because the authors did not find a more suitable category, which also includes breast cancer.
It also includes: electrolyte disorders, sepsis, systemic infections (such as tuberculosis, syphilis, AIDS) classified according to their severity and the functional deterioration they cause (see general indications) and poisoning (chronic by metals or acute by pesticides or carbon monoxide).

0. No problems

1. Diabetes and/or dyslipidemia compensated by diet, moderate obesity (BMI 30-35 kg/m2), hypothyroidism on replacement therapy (L-thyroxine); hyperthyroidism caused by surgically treated Plummer's adenoma.

2. Diabetes compensated with oral hypoglycemic agents or insulin (hemoglobin A1c <7%), dyslipidemia well controlled by daily medications (LDL-C below the recommended target according to individual global cardiovascular risk), moderate obesity (BMI 35-45 kg/m2) , hyperthyroidism (Basedow, Plummer) with pharmacological treatment; asymptomatic or surgically treated hyperparathyroidism, fibrocystic breast disease.

3. Diabetes not well compensated by therapy (hemoglobin A1c 7-8.5%, presence of complications), dyslipidemia not well controlled (LDL-C higher than the recommended goal according to individual global cardiovascular risk, for example, LDL-C > 100 mg/dl in patients with myocardial infarction or stroke), severe obesity (BMI > 45 kg/m2), symptomatic hyperparathyroidism (eg, hypercalcemia), adrenal insufficiency replacement therapy, any electrolyte disturbance requiring hospitalization .

4. Uncontrolled diabetes (hemoglobin A1c > 8.5%) or diabetic ketoacidosis or hyperosmolar nonketotic coma in the past year, uncontrolled genetic dyslipidemia, acute adrenal insufficiency during hormone replacement therapy, any tumor of the thyroid, breast, or adrenal gland (see "Evaluation Neoplasms").

NOTE: When the patient is not being treated with drug therapy for diabetes or dyslipidemia but should be treated for optimal control of disease (eg, hemoglobin A1c > 7%, total cholesterol > 250 mg/dL), score the pathology according to the laboratory values, which is what really defines its severity.

PSYCHIATRIC AND BEHAVIORAL ILLNESSES

This category includes both dementia and behavioral disorders (psychosis, anxiety, depression, agitation) and all pre-existing and/or unrelated psychiatric disorders of dementia. Since this is the only category that analyzes the mental state of the patient (all others refer to the physical state), it is very important to evaluate it by carefully considering the additional instructions derived from the Comprehensive Geriatric Assessment (MMSE, Geriatric Depression Scale, Neurological Inventory). -Psychiatry if available).

0. No psychiatric problems or history of the same

1. minor psychiatric conditions or history of the same: previous (occasional) psychiatric treatment without hospitalization, case of major depression and/or use of antidepressants for more than 10 years without hospitalization, occasional use from minor tranquilizers (eg, benzodiazepines, including as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).

2. A history of major depression (according to DSM-IV criteria) in the last 10 years (treated or not); mild dementia (MMSE 20-25), upon admission to the Department of Psychiatry for any reason; history of substance abuse (more than ten years ago, including alcoholism).

3. Current major depression (according to DSM-IV criteria) or more than two prior episodes of major depression in the past 10 years, moderate dementia (MMSE 15-20), current and regular use of daily antianxiety medications (including such as hypnotherapy for insomnia), substance abuse or dependence currently or in the last ten years (according to DSM-IV criteria); requires daily antipsychotic medication; previous suicide attempt.

4. Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient treatment (psychiatric emergency, such as suicide attempt or severe depression for the purpose of suicide, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse, severe agitation of dementia); severe dementia (MMSE <15); delirium (acute confusion or altered mental status for medical (organic) reasons): in this case the medical cause should also be coded in its own category with the appropriate level of severity).

(Version 1.2: July 7, 2016)

Psychiatric consultation could be requested for this category; dementia and depression, the most frequent diseases in the elderly, can be marked in detail with the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse, and all the rest) has to be rated according to the level of functional impairment or disability it causes.

ASSESSMENT LIST

Medical history

1. Calendar of events and/or interventions (how long ago did you have surgery for ..., how long ago did you have a myocardial infarction or stroke, etc.) and assessment of functional impairment
2. drug list*(fundamental),*including laxatives and tranquilizers (including hipno-inductivos)
3. Symptoms of atherosclerotic disease (TIA, angina, claudication, amaurosis)
4.diagnosis *etiologic* (reasonably reliable) of anemia
5. degree of vascular stenosis or aneurysm dimension (by Doppler and/or ultrasound and/or TC data, if available)
6. Information about your smoking (how many cigarettes per day for how many years? *when did you stop?*)
7. Wearing glasses? With this help, is the patient able to read a newspaper? Do you need a companion to go on an adventure?
8. Any hearing aids? (It should evaluate the possibility of communicating with the patient)
9. "History peptic" of the patient (including prior therapy for H. pylori eradication)
10. Urinary symptoms incontinence, indwelling catheter (including BADL - *basic activities daily life*)

Physical exam

a. Height (m^2) and weight (kg) (*measured*, not reported, if possible) to calculate BMI
b. Blood pressure, heart rate, heart murmurs, peripheral arterial pulses
c. Joint pain or limited passive stiffness (Non-x-ray based diagnosis of osteoarthritis)
d. Neurological sequelae (dysarthria/aphasia, hemiparesis/hemiplegia)

Baseline laboratory values

• Complete blood count: hemoglobin, leukocytes and platelets
• Creatinine, electrolytes
• Cholesterol levels (total, HDL) and triglycerides
• AST, ALT, fractionated bilirubin

• Thyroid function and vitamin serum B12 (when indicated)
• Hemoglobin A1c (for diabetics)

GAH

Geriatric assesement for Hematology

polypharmacy
number of concomitant drugs
Putting number of drugs

MOOD DURING tHE LAST WEEK
During the last week, he felt depressed ...
<3
days> 3 days

SUBJECTIVE HEALTH STATE
In general, compared to other people your age,
would you say your health is...
Excellent
Very good
Good
Fair
Poor

ACTIVITIES OF DAILY LIVING
You need help with your daily life YES NO You have a
caregiver YES NO You
have Difficulty buying personal items YES NO
Difficulty managing money YES NO
Difficulty walking YES NO
Difficulty performing daily tasks light domestics YES NO
NUTRITION
Weight (kg)
Height (m)
BMI
Have you lost weight in the last 3 months?
No
Between 1 and 3 kg

More than 3 kg
I don't know
Have you eaten less than usual in the last 3 months
due to loss of appetite, digestive problems or
difficulty chewing and/or swallowing?
No
Somewhat less
Much less
WALKING SPEED
How long does it take for the patient to walk there
and back? (m/sec)
MENTAL STATUS
What is today's date? Correct Incorrect
What day of the week is today? Correct Incorrect
What is your phone number? Correct Incorrect
What is your age? Correct Incorrect
When were you born? Correct Incorrect
What is the name of the president of the government? Correct Incorrect
What was the name of the previous president of the government? Correct Incorrect
What are your mother's last names? Correct Incorrect
Starting at 20, subtract 3 by 3,
until reaching the end
Correct Incorrect

COMORBIDITY AND HABITS
Diabetes mellitus YES NO
Cancer YES NO
Pulmonary disease YES NO
Heart failure YES NO
Smoking YES NO/EX-SMOKER

XI. Ibrutinib SmPC

Summary of product characteristics, available on file at the investigator's center or on the EMA website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

XII. Screening and Inclusion Procedure

REGISTRATION OF USERS IN THE ONLINE SCREENING/INCLUSION PLATFORM:

1.- Registration of users:

The screening and inclusion process must be carried out by IP, CoIP (doctors) or personnel designated by the IP conveniently identified in the Signature List. After the start visit, the link to the inclusion platform will be sent to the IP along with his username and password as the person responsible for the inclusion of patients (in the event that there are Collaborating Researchers identified in the Signature List, they will also be provided with the access data).

Link to the platform: [redacted]

2.- Generation of private password:

To comply with BPC, once the IP/Co-IP accesses the username and password provided by [redacted] ***for the first time, the system will ask you to change the password.***

IMPORTANT: ***The password assigned from*** [redacted] ***expires (approximately one week), therefore it is recommended that users generate the private password as soon as possible after receiving temporary access.***

From this moment on, the user will keep the same access data for all the inclusion platforms [redacted] ***that are generated.***

3. Patient RegistrationPatient:

3.1Screening (must be performed by the Center, IP or CoIP or assigned personnel):

IMPORTANT: The patient must have signed the informed consent to start the screening process.

Link to the platform: [redacted]

1.- Access the screening form by clicking on 

2.- Once accessed, the user must enter the screening date, signature of the informed consent and the patient's date of birth. Click on “save”.

3.- The system will request confirmation for what must be clicked on "accept" and the system will automatically assign the screening number for the patient.

4.- After showing the screening number on the screen, both the hospital team registered on the platform (indicated by the center at the start visit) and the team [redacted] ***will receive a confirmation email of the patient in screening.***

3.2- Inclusion of patients (must be carried out by the Center, PI or CoIP or designated personnel):

Once all the screening tests have been carried out and confirm that the patient meets all the eligibility criteria, the PI/Co-PI or designated personnel must perform the inclusion process before starting the study treatment.

Link to the platform: [redacted]

1.- Click on "Edit"  ***of the patient in screening that you want to include.***
2.- Complete if the patient meets the eligibility criteria (checkbox).
3.- Once the form has been properly completed, click on "save", the system will request confirmation of the patient's inclusion, click on "accept", the system will assign the patient's number automatically and send the confirmation of inclusion by email to all persons identified at the start visit as recipients of the opt-in confirmation notification. (Version 1.2: July 7, 2016)