Clinical Study Report

Randomized phase II study of treatment with R-CHOP vs Bortezomib-RCAP for young patients with poor IPI diffuse large B-cell lymphoma

Protocol Number: BRCAP-GELTAMO12

EudraCT Number: 2012-005138-12

Clinicaltrials.gov number: NCT01848132

30/Jan/2019

CONFIDENTIAL

Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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1. TITLE PAGE

Study title: Randomized phase II study of treatment with R-CHOP vs Bortezomib.bortezomib-RCAP for young patients with poor International Prognostic Index diffuse large B-cell lymphoma.

Name of test drug: Bortezomib

Indication studied: Diffuse large B-cell lymphoma (DLBCL)

Study description: A prospective, multicentre, phase II randomized clinical trial to evaluate the efficacy and tolerability in young patients with poor IPI diffuse large B-cell lymphoma treated with 6 cycles of subcutaneous bortezomib with R-CAP (R-CHOP without vincristine) vs. the standard regimen of 6 cycles of R-CHOP every 21 days.

Central pathology review was performed in all cases, and samples were classified as germinal centre B-cell-like (GCB) vs. non-GCB subtypes by immunohistochemistry (IHC) (Hans algorithm). Qualitative and quantitative prospective evaluation of the Positron emission tomography-computed tomography (PET/CT), after 2 treatment cycles without modifying the treatment, and after 4 cycles of chemotherapy.

Sponsors: GELTAMO (Grupo Español de Linfoma/Trasplante Autólogo de Médula Ósea)

Protocol Code: BRCAP-GELTAMO12

Clinical Phase: II

Study dates:

Study initiation date: First patient enrolled on 03 October 2013.
Study completion date: Last patient completed on 26 January 2018.

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GCP statement: This study was performed in compliance with ICH Good Clinical Practice (GCP), including the archiving of essential documents

Date of report: 30/Jan/2019

2. SYNOPSIS

NAME OF SPONSOR: GELTAMO (Grupo Español de Linfoma/Trasplante Autólogo de Médula Ósea) **NAME OF FINISHED PRODUCT:** N/A **NAME OF ACTIVE INGREDIENT(S):** BORTEZOMIB	
Title of study	Randomized phase II study of treatment with R-CHOP vs bortezomib-RCAP for young patients with poor International Prognostic Index (IPI) and diffuse large B-cell lymphoma (DLBCL).
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Publication	***Publication in congress:*** ***American Society of Hematology (ASH), 2015:*** Gonzalez-Barca E, Carrillo E, Grande C, Martín A, Coronado M, Montes-Moreno S, Pérez de Oteyza J, Nicolas C, Sancho JM, Palomera L, Lopez J, Lopez-Guillermo A, Peñalver FJ, Hernandez JA, Ramirez MJ, Jarque I, Bargay J, Rodriguez MJ, Canales M, Albo C, Encuentra M, Caballero D, on behalf of the Spanish Group of Lymphoma (Grupo Español de Linfomas y Trasplante de Médula Ósea, GELTAMO). **Phase 2 randomized trial comparing 6 cycles of standard RCHOP chemotherapy vs. 6 cycles of BRCAP (bortezomib, rituximab, cyclophosphamide, Adriamycin, and prednisone) as first line treatment in young patients with poor prognosis diffuse large B-cell lymphoma (DLBCL): Interim analysis.** Blood. 2015;126:1514. ***Sociedad Española de Hematología y Hemoterapia (SEHH), 2016:*** González-Barca E, Carrillo E, Grande C, Martín A, Mercadal S, Domingo E, Coronado M, Montes-Moreno S, Pérez de Oteyza J, Nicolás C, Roncero J, Rodríguez MJ, López J, Palomera LR, Sancho JM, Albo C, Peñalver FJ, López-Guillermo A, Hernández JA, Bargay J, Jarque I, Ramírez MJ, Canales MA, Conde E, Sayas MJ, Caballero D, (Grupo Español de Linfomas y Trasplante de Médula Ósea, GELTAMO). **Resultados preliminares de un ensayo clínico aleatorizado fase 2 de tratamiento de primera línea de pacientes jóvenes con linfoma B difuso de célula grande (LBDCG) de alto riesgo con RCHOP vs Bortezomib-RCAP.** ***American Society of Hematology (ASH), 2016:*** González-Barca E, Carrillo-Cruz E, Grande C, Martín A, Coronado M, MD, Montes-Moreno S, Mercadal S, Roncero JM, Pérez de Oteyza J, Nicolás C, Rodríguez-Salazar MJ, Sancho JM, Palomera L, López-Jiménez J, Albo C, Peñalver FJ, MD, Hernández, JA, López-Guillermo A, Ramírez MJ, Jarque I, Bargay J, Canales M, Conde E, Caballero D. **Phase 2 Randomized Trial Comparing Standard RCHOP Versus BRCAP (bortezomib, rituximab, cyclophosphamide, adriamycin and prednisone) As First Line Treatment in Young Patients with High-Risk Diffuse Large**

	B-Cell Lymphoma (DLBCL). A Study from Spanish Group Geltamo. Blood 2016 128:4201. ***International Conference on Malignant Lymphoma (ICML) Lugano, 2017:*** Gonzalez-Barca E, Carrillo E, Grande C, Martín A, Montes-Moreno S, Coronado M, Mercadal S, Roncero JM, Pérez de Oteyza J, Nicolas C, Rodriguez Salazar MJ, Sancho JM, Palomera L, Lopez J, Albo C, Peñalver FJ, Hernandez JA, Lopez-Guillermo A, Ramirez MJ, Jarque I, Bargay J, Canales M, Conde E, Caballero D. **Phase 2 randomized trial comparing standard RCHOP versus BRCAP as first line treatment in young patients with high-risk DLBCL. A study from Spanish Group GELTAMO.** DOI: 10.1002/hon.2438_49. *Final publication of the trial is currently ongoing.*		
Study period	From: 03 Oct 2013 To: 08 Aug 2018	**Phase of development**	Phase II
Objectives	<u>Primary Objective</u> To evaluate the proportion of patients with event-free survival (EFS) at 2 years in patients diagnosed with DLBCL with an age-adjusted IPI (aIPI) ≥1 with elevated levels of beta-2-microglobulin (above upper normal level [UNL).] <u>Secondary Objectives</u> 1. EFS at 2 years in different biological DLBCL subgroups: germinal centre B-cell-like (GCB) vs. non-GCB. 2. Overall survival (OS) at 2 years in patients diagnosed with DLBCL with an aIPI ≥1 with elevated levels of beta-2-microglobulin (above UNL). 3. Overall response rate and complete remissions in patients diagnosed with DLBCL with an aIPI ≥1 with elevated levels of beta-2-microglobulin (above UNL). 4. Toxicity according to the CTC Common Terminology Criteria for Adverse Events (AE) criteria (version 3.0) of the National Cancer Institute (NCI). 5. To evaluate the predictive value for EFS of interim positron emission tomography–computed tomography (PET/CT) evaluation after 2 and 4 cycles of chemotherapy. 6. To identify clinical and biological prognostic factors for response and survival.		

Methodology	A multicentre, open study with 2 treatment arms: the control arm with 6 cycles of R-CHOP- every 21 days, and the experimental arm with bortezomib subcutaneous on days 1, 8, and 15 of each cycle, rituximab iv, cyclophosphamide, and Adriamycin iv. on day 1 of each cycle, plus prednisone oral on days 1-5, in cycles every 21 days. Central pathology review was performed in all cases, and samples were classified as GCB vs. non-GCB subtypes by immunohistochemistry (IHC) (Hans algorithm). The trial had an optional biological study associated. The samples required were a formalin-fixed paraffin-embedded tissue samples, frozen tissue and peripheral blood, all at the time of diagnosis. PET/CTs were performed at diagnosis, after 2, 4, and 6 cycles (PET2, PET4, and PET6), and were reviewed by at least 3 experts of a central panel in real time. Response was analysed following the visual method with the Deauville scale; for PET2 and PET4, the semi quantitative method was used. Patients with persistent disease after 4 cycles were considered a failure of therapy and were dropped out of the trial. EFS was calculated from diagnosis until an event, defined as death, relapse, progression, or the need for salvage therapy (defined as PET4 or PET6 positive). OS was calculated from diagnosis until death.
Number of patients	● ***Planned:*** 127 ● ***Enrolled:*** 121 patients; 60 in the experimental arm, and 61 patients in the control arm. ● ***Analysed for safety:*** 121 patients ● ***Analysed for efficacy:*** 115 patients
Diagnosis and main criteria for inclusion	**MAIN INCLUSION CRITERIA** 1. Patients diagnosed with primary DLBCL who have never received treatment for this condition. 2. Age between 18 and 70 years. 3. Age-adjusted IPI ≥1, with high levels of beta-2 microglobulin (above UNL). 4. Neoplastic B lymphocytes for CD20 positivity. 5. Eastern Cooperative Oncology Group (ECOG) grade 0-3. 6. More than 12 weeks of life expectancy. 7. Signed informed consent 8. Pregnant nor breastfeeding women. **MAIN EXCLUSION CRITERIA** 1. Patients with central nervous system lymphoma

	2. Transformed follicular lymphoma. 3. HIV-positive patients 4. Positive determination of chronic hepatitis B virus (HBV) infection 5. Positive determination of chronic hepatitis C virus (HCV) infection
Test product, dose, and mode of administration	**Control arm:** 6 cycles of treatment with R-CHOP were be administered: Rituximab intravenously (iv) at a dose of 375 mg/m^2 on day 1, followed by CHOP-type chemotherapy (cyclophosphamide 750 mg/m^2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + vincristine 1.4 mg/m^2 iv (maximum 2 mg) on day 1 + prednisone 100 mg oral on days 1-5). The cycles were administered every 21 days. **Experimental arm:** 6 cycles of treatment with bortezomib administered at a dose of 1.3 mg/m^2 subcutaneous on days 1, 8, 15, followed by rituximab at a dose of 375 mg/m^2 iv on day 1, and of chemotherapy: cyclophosphamide 750 mg/m^2 iv and Adriamycin 50 mg/m^2 iv day 1 + prednisone 100 mg 1-5 oral days The cycles were administered every 21 days.
Duration of treatment	6 cycles, every 21 days.
Criteria for evaluation	**Primary:** Proportion of patients with EFS at 2 years. **Secondary:** ● EFS at 2 years. ● OS at 2 years. ● Complete remission rate. ● Complete remission rate not documented/not confirmed. ● Partial remission rate. ● Stable disease rate, progression. ● Relapsed disease rate. ● Proportion of subjects who received all planned chemotherapy doses on schedule. ● Proportion of cycles of chemotherapy administered in planned doses and on schedule. ● Clinical predictive factors of response. ● Safety endpoints from cycle 1 to 6. ● Prognostic value of PET in terms of survival. ● Biological prognostic factors, including histologic subtype GCB vs. non-GCB.
Statistical methods	**Sample size considerations** The main objective was to compare the efficacy between R-CHOP and bortezomib-RCAP in terms of EFS at 2 years (previously defined). An event was defined as relapse, progression, the need for new antineoplastic treatment, or death from any cause before 2 years. Using the binomial test of 2 proportions and a tail, if the null

	hypothesis in the R-CHOP arm is 55% and expected to be 70% in the bortezomib-RCAP arm, and assuming an alpha error of 0.25 (decide in favour of the experimental arm if the null hypothesis is true) and a beta error of 0.20 (decide in favour of the null hypothesis if the alternative hypothesis is true), it was necessary to enrol 120 patients. If a 5% loss of patients was assumed, the number to be included was 127 patients (50% in each treatment arm).
	
	Statistical considerations
	The analysis was done by intention to treat (ITT). The population consisted of patients who met the criteria for selection and were exposed to at least 1 treatment cycle, regardless of the presence of deviations from the protocol or the patient's withdrawal from the study. The main variable of the study was the proportion of live and event-free patients at 2 years.
	- EXPLORATORY ANALYSIS: All variables were described graphically using the following tools: for categorical variables, frequency tables with sector diagrams; for numerical variables, trend, standard deviations, standard error, mean, median, and limits. Each variable was represented in a box-plot graphic. A bivariate analysis was carried out with the main factors: age, GCB vs. no-GCB, ECOG, and aIPI between the experimental treatment arm and the control arm to verify that these factors do not produce confusion about the main objective.
	- PRIMARY OBJECTIVE: A 1-tailed binomial test was performed to assess whether the bortezomib-RCAP regimen is superior to the control. If the p-value associated with the test was below 0.25, the test was considered to be positive, and the combination was declared to be effective.
	- SECONDARY OBJECTIVE: A logistic regression analysis was performed to find significant factors that can influence the EFS at 2 years. The influence of the subtype was studied histologically as a relevant factor in EFS at 2 years.
	- SURVIVAL ASSESSMENTS:
	  - 2-year EFS: defined as the proportion of patients who were alive with CR from the date of randomisation until 2 years after that date.
	  - EFS: defined as the time that elapsed between the moment of randomisation and the first documented recurrence, progression, or death in the case of no documented recurrence, or the start of a new anti-lymphoma treatment due to refractory or persistent disease. In the EFS analysis, the subjects to whom treatment was discontinued due to adverse effects or other reasons were censored at the time

	that the tumour was evaluated for the last time. - OS: defined as the time between randomisation and death from any cause. In cases where patients withdrew from the trial or were lost to follow-up, they were censored at the date of the last contact. Patients who were still alive at the end of the study were censored at that time. - TOXICITY ASSESSMENTS: Toxicity that appeared in the treatment phase was classified in this report according to the scale of the NCI-CTCAE. *STATISTICAL METHODS* ● Hypothesis testing for descriptive analyses was done using the independent t-test for comparisons between treatment arms for continuous variables, or the Mann-Whitney U test when the variables did not display a normal distribution (assessed using the Kolmogorov-Smirnov test or Shapiro-Wilk test). The chi-square test or, when appropriate, Fisher's exact test, was used in the case of comparisons involving qualitative variables. ● Logistic regression analysis (factors that could influence the EFS at 2 years): Firstly, a univariate analysis was carried out separately for each of the possible explicative variables to decide which variables should be entered in the multivariate models; only those with a statistical association with the dependent variable were selected. The stepwise backward elimination process was used to select the model. In the first step, all possible predictors were entered in the model, and in each step, the variable that was least significant (that is, the one with the largest p-value) was removed, and the model was refitted. Each subsequent step removed the least significant variable in the model until all remaining variables had individual p-values smaller than 0.05. ● For those patients without a date of follow-up, the latest of the following was used as the end of follow-up: date of the end of treatment or the date of the last PET. ● For both time-to-relapse and survival, there was no censoring for reasons other than administrative end of follow-up. ● Progression was extracted from PET2, -4, and -6 (central review) and follow-up visits in variables sg_val_respt_e8_1_c10, sg_val_respt_e8_2_c10, sg_val_respt_e8_3_c10, sg_val_respt_e8_4_c10, sg_val_respt_e8_5_c10, sg_val_respt_e8_6_c10, sg_val_respt_e8_7_c10, and sg_val_respt_e8_7_c10. ● EFS was defined (following protocol) as the time from

randomisation to relapse, progression, start of second line treatment, or death, whichever is earlier.

- OS was defined as the time from randomisation to death.
- Agreement between variables was assessed using the kappa agreement coefficient, interpreted as follows (Altman, 1991):

Value of κ	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

Altman DG. (1991) Practical statistics for medical research. London: Chapman and Hall.

NAME OF SPONSOR: GELTAMO **NAME OF FINISHED PRODUCT**: N/A **NAME OF ACTIVE INGREDIENT(S):** Bortezomib	**INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD** Volume: Page:	**(FOR NATIONAL AUTHORITY USE ONLY)**

SUMMARY CONCLUSIONS

EFFICACY RESULTS

Hundred twenty-one patients were included; the evaluable population per-protocol consisted of 115 patients (diagnosis not confirmed in 6). Fifty-six patients were treated in the experimental arm (BRCAP) and 59 in the control arm (R-CHOP). Median age: 59.8 (range 23.9-71.0), years. Fifty-seven were (49.6%) male. Characteristics at diagnosis: non-GCB subtype: 38/115 (33.0%), IHC co-expression of MYC/BCL2: 50/115 (43.5%), stage III-IV: 108 (94.0%), ≥2 extranodal locations: 62 (71.3%), ECOG 2-3: 38 (33.0%), increased lactate dehydrogenase (LDH): 93 (82.3%), increased beta-2 microglobulin: 71 (71.7%), and aIPI of 3: 28 (24.3%). No differences were found between the arms. Thirty-two (27.8%) patients required pre-phase treatment. The mean relative dose intensity for bortezomib was 98.7%. Twenty seven (25.5%) of 106 patients who completed 4 cycles had a positive PET4 and were withdrawn from the study therapy. ITT CR at the end of therapy (PET4-/PET6-): 31 (55.4%) in BRCAP vs. 27 (45.8.%) in R-CHOP (p=0.431). The proportion of patients who survived free of event at 2 years was 21 (37.5%) in BRCAP vs. 18 (30.5%) in R-CHOP (p=0.214). The proportion of patients with the non-GCB subtype who survives free of event at 2 years was 9 (40.9%) in BRCAP vs. 4 (25.0%) in R-CHOP (p=0.307). After a median follow-up of 28.3 months, the estimated 2-years EFS was 37.5% (95%CI 24.8-50.2) in BRCAP vs. 32.8.% (95%CI 20.7-44.9) in R-CHOP (hazard ratio [HR 1.178] [95% confidence interval (CI 0.748-1.855), p-value=0.479)]), and 2-years OS was 78.3% in BRCAP vs. 68.3% in R-CHOP (HR 1.595 [95% CI 0.793-3.206, p-value=0.190]).

SAFETY RESULTS

In general, treatments were well tolerated, and toxicities were managed with supportive measures. Adverse events (AEs) were recorded and assessed using version 3.0 of Common Toxicity Criteria (NCI-CTCAE).
Neutropenia was the most common AE (any grade) which presented in 52.1% of patients, followed by pain and general disorders (38.8% of cases) and nausea and vomiting along with infections which presented in 38% of patients.
No differences were found between arms in the proportion of patients with any grade AE (95.0% vs. 96.7%; p=0.680), any AE grade ≥3 (73.3% vs. 65.6%; p=0.146), AE related to any treatment (88.3% vs. 73.8%; p=0.041), any AE grade ≥3 related to any treatment (63.3% vs. 49.2%; p=0.117), any serious AE (38.3% vs. 37.7%; p=0.925), SAE related to any treatment (30.0% vs. 26.2%; p=0.645), any haematological AE (65.0% vs. 59.0%; p=0.498), haematological AE grade ≥3 (56.7% vs. 50.8%; p=0.519), non-haematological AE

(91.7% vs. 95.1%, p=0.491), and non-haematological AE grade ≥3 (43.3% vs 34.4vs.%; p=0.315).
Neutropenia grade 4 was the most common AE grade ≥3 which presented in 34.7% of patients; 25 (41.7%) in the experimental arm, and 17 (27.9%) in the control arm.

The BRCAP treatment was feasible, and no major concerns were raised in the trial in terms of the safety of the combination.

CONCLUSION

No significant differences were found between R-CHOP and BRCAP in terms of CR and the proportion of patients free of event at 2 years in this very high-risk population of young DLBCL patients.

DATE OF THE REPORT: 30/Jan/2019

3. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS & DEFINITION OF TERMS

Abbreviation /Acronym	Definition
ADL	Activities of Daily Living
AE	Adverse Event
AEMPS	Agencia Española del Medicamento y Productos Sanitarios
aIPI	International Prognostic Index Adjusted for Age
ALT	Alanine Transaminase
anti-HBc	Anti-core Antibodies
antiHBC	Antibody to Hepatitis B Core Antigen
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BBDD	Database
BIPN	Bortezomib-induced Peripheral Neuropathy
BL	Burkitt lymphoma
BRCAP	Bortezomib, Rituximab, Cyclophosphamide, Adriamycin And Prednisone
Ca	Calcium
CA	Competent Authority
CAPA	Corrective Action Preventive Action
CD	Cluster of Differentiation
CEIm	Comité de Ética de la Investigación con Medicamentos (Independent Ethics Committee of Research with Medicines)
CHL	Classical Hodgkin Lymphoma
CHUVI	C.H.U. de Vigo
CI	Confidence Interval
CIOCC	Centro Integral Oncológico Clara Campal
CMR	Complete Metabolic Response
CMRr	Complete Metabolic Response with residual mass
CNS	Central Nervous System
COV	Close-out Visit

CR	Complete Response
CRAs	Clinicals Researchers Associates
CRO	Contract Research Organization
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTPM	Clinical Trial Project Manager
DFS	Disease Free Survival
DLBCL	Diffuse Large B Cell Lymphoma
DNA	Deoxyribonucleic Acid
EC	Ethical Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG Performance Status
eCRF	Electronic Case Report Form
ECs	Ethics Committee
EDTA	Ethylenediamine Tetraacetic Acid
EFS	Event Free Survival
EMP	Extramedullary Plasmacytomas
EMR	Early Molecular Responder
EORTC	European Organization for Research and Treatment of Cancer
EoT	End of Therapy
ESMO	European Society for Medical Oncology
FDG	Fluorodeoxyglucose
FISH,	Fluorescent In Situ Hybridisation
FL	Follicular Lymphoma
G	Grade
G-CSF	Granulocyte-Colony Stimulating Factor
GCB	Germinal Center B-cell-like
GCB-ABC	Germinal Center B-Cell - Activated B-Cell
GCP	Good Clinical Practice
GELA	French Study Group of the Adult Lymphoma
GELTAMO	Grupo Español de Linfoma Trasplante Autólogo de Médula Ósea
GGT	Gamma-Glutamyl Transferase

H12O	Hospital 12 de Octubre
HBcAb	Hepatitis B Core Antibody
HBsAG	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCA	Hospital Central de Asturias
HCB	Hospital Clínic de Barcelona
HCV	Hepatitis C Virus
HIL	Hospital Infanta Leonor
HIV	Human Immunodeficiency Virus
HJF	Hospital Jerez de la Frontera
HLB	Hospital Lozano Blesa
HLF	Hospital La Fe
HMV	Hospital Marqués de Valdecilla
HRYC	Hospital Ramón y Cajal
HSLL	Hospital Son Llatzer
HUC	Hospital U. Canarias
HUFA	Hospital U. F. Alcorcon
HULP	Hospital U. La Paz
HUS	Hospital U. Salamanca
HUSAL	University Hospital of Salamanca
HVR	Hospital Virgen del Rocío
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICH-GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice
ICML	International Conference on Malignant Lymphoma
ICOB	ICO BADALONA
ICOG	ICO GIRONA
ICOH	ICO L'Hospitalet
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry

IMP	Investigational Medicinal Product
IPI	International Prognostic Index
ISF	Investigator Site File
ITT	Intention To Treat
iv	Intravenous
K	Potassium
LDH	Lactate Dehydrogenase
MiNT	MabThera International Trial
MM	Multiple Myeloma
MZL	Marginal Zone Lymphomas
Na	Sodium
NA	Not Available
NCI	National Cancer Institute
NCI-CTCAE	Common Terminology Criteria for Adverse Events of The National Cancer Institute
ND	Not Determined
NF-κB	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NHL	Non-Hodgkin's Lymphomas
NLPHL	Nodular Lymphocyte Predominant Hodgkin Lymphoma
non-GCB	Non-germinal Center B-cell-like
NRM	Non Relapse Mortality
OPS-OMS	Organización Panamericana De La Salud - Organización Mundial De La Salud Pan American Health Organization - World Health Organization
OR	Odds Ratio
OS	Overall Survival
PMBL	Primary mediastinal B-cell lymphoma
PCR	Polymerase Chain Reaction
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography - Computed Tomography
PETi	Intermediate PET
PIS	Patient Information Sheet
PIs	Principal Investigators
PMD	Progressive Metabolic Disease
PT	Prothrombin Time

PTT	Partial Thromboplastin Time
PVG	Pharmacovigilance
QA	Quality Assurance
R-CAP	Rituximab, Cyclophosphamide, Adriamycin And Prednisone
R-CHOP	Rituximab, Cyclophosphamide, Adriamycin, Vincristine And Prednisone
RDT	Radiotherapy
RMS	Residual Metabolic Disease
RMV	Regular Monitoring Visit
RNA	Ribonucleic Acid
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
sc	Subcutaneous
SD	Standard Deviation
SDV	Source Data Verification
SEHH	Sociedad Española de Hematología y Hemoterapia
SIV	Site Initiation Visits
Std	Standard
SUSARs	Suspected Unexpected Serious Adverse Reactions
SUV	Standardized Uptake Values
TMF	Trial Master File
TNF-α	Tumor Necrosis Factor Alpha
UK	Unknown
UNL	Upper Normal Limit
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell
WT	Wild Type

5. ETHICS AND REGULATORY APPROVAL

5.1. INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and all its amendments and the patient information sheet(s) were reviewed and approved by the appropriate independent ethics committees (ECs) as detailed in table 1 below.

The reference committee for this trial in Spain was Comité de Ética de la Investigación con medicamentos (CEIm) Hospital Universitari de Bellvitge; as reference EC, this committee collated the feedback of implied ECs and oversaw communication with the sponsor. The official positive votes for the initial submission and subsequent amendments are listed in Table 1.

Table 1. Ethics committees

Centre name and number	1. ICO L'Hospitalet (H. Duran i Reynals) 2. H.U. de Salamanca 3. H. Marques de Valdecilla 4. ICO Badalona (H. Germans Trias i Pujol) 5. H. Clinic de Barcelona 6. H.U. 12 de Octubre 7. H.U. Ramón y Cajal 8. H. La Paz 9. H. Fundación Alcorcón 10. HM CIOCC 11. H. Infanta Leonor 12. H.U. Virgen del Rocío 13. H. de Jerez 14. H. Universitario y Politécnico La Fe 15. H. Dr. Peset 16. H.U. Central de Asturias 17. H. Son Llàtzer 18. H. Lozano Blesa 19. H.U. Canarias 20. ICO Girona 21. C.H.U. de Vigo (CHUVI)
Principal investigator	1. Dra. Eva González Barca 2. Dr. Alejandro Martin 3. Dr. Eulogio Conde/Dra. Sonia González de Villambrosia 4. Dr. Juan Manuel Sancho 5. Dr. Armando López Guillermo 6. Dr. Carlos Grande 7. Dr. Javier López Jiménez 8. Dr. Miguel Angel Canales 9. Dr. Francisco Javier Peñalver 10. Dr. Jaime Pérez de Oteyza 11. Dr. Jose Angel Hernandez 12. Dra. Estrella Carrillo Cruz 13. Dra. Mª José Ramírez 14. Dr. Isidro Jarque 15. Dra. Mª José Sayas 16. Dra. Concepcion Nicolas 17. Dr. Joan Bargay 18. Dr. Luis Ramón Palomera 19. Dra. Mª José Rodríguez Salazar

	20. Dr. Josep María Roncero 21. Dra. Carmen Albo
Ethics committee	Comitè Ètic d'Investigació Clínica Hospital Universitari de Bellvitge
Ethics committee chairman	Dr. Francesc Esteve Urbano (Chairman) Dra. Pilar Hereu Boher Dr. Enric Sospedra Martínez Dr. Josep Mª Arnau de Bolós Dra. María Berdasco Menéndez Dr. Enric Condom Mundo Sra. Consol Felip Farrás Dra. Ana María Ferrer Artola Dra. Margarita García Martín Dra. Laura Lladó Garriga Sra. Sonia López Ortega Dra. Cristina Masuet Aumatell Dra. Francesca Mitjavila Villeró Dra. Margarida Nadal Sánchez Dra. Miriam Oms Arias Dr. Joan Josep Queralt Jiménez Dra. Glòria Remesar Navarro Sra. Gemma Martínez Estalella
Date of approval of the final protocol	07 March 2013
Date of approval of amendment 1	04 April 2014
Date of approval of amendment 2	16 April 2016 (evaluated only by the national competent authority, Agencia Española de Medicamentos y Productos Sanitarios/AEMPS)
Date of approval of amendment 3	21 June 2018

5.2. ETHICAL CONDUCT OF THE STUDY

The study was performed in accordance with the current version of the declaration of Helsinki and:

- The International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).
- The Convention on Human Rights and Biomedicine. Oviedo, 4 April 1997. Entry into force: 22 October 1999 (BOE 282, 25.11.99).
- The regulation on adequate protection of personal data according to the Organic Law 15/1999 on personal data protection.
- Act 41/2002 of 14 November 2002, a basic regulating Act on the autonomy of the patient and the rights and obligations in matters of clinical information and documentation.
- The 48th General Assembly Somerset West, South Africa, October 1996, and the 52nd General Assembly, Edinburgh, Scotland, October 2000.
- Law 14/2007, 3 July on Biomedical Research.

5.3. PATIENT INFORMATION AND CONSENT

All patients provided written informed consent to participate in the study prior to being screened. The transferral of biological samples required previous written informed consent by the patient.

The patient information sheet was submitted to and approved by ECs and the AEMPS; this document detailed the procedures involved in the study (aims, methodology, potential risks, and anticipated benefits), and the investigator explained these to each patient. The patient signed the approved consent form to indicate that the information had been explained and understood. The patient was then allowed time to consider the information presented before signing and dating the informed consent form (ICF) to indicate that they fully understood the information and willingly volunteered to participate in the study. The patient was given a copy of the ICF for their information. The original copy of the ICF was kept in a confidential file in the Investigators' site records. A sample of the patient information sheet and consent form can be found in appendix 15.1.5.

5.4. REGULATORY APPROVAL

The study was performed in compliance with the requirements of the AEMPS. The study gained full regulatory approval on 23 March 2013; GELTAMO was issued with the following EudraCT number: 2012-005138-12. A copy is provided in appendix 15.1.7.

The study gained full approval from the EC on 07 March 2013. A copy is provided in appendix 15.1.6.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table 2 shows the principal study personnel involved.

Table 2. Principal study personnel

Title	Name and affiliation
Coordinating investigator	● Dra. Eva González Barca - Hematología Clínica - Institut Català d'Oncologia ● Dra. Dolores Caballero - Hematología Clínica - Hospital U. de Salamanca ● Dr. Santiago Montes - Anatomía Patológica - Hospital U. Marqués de Valdecilla ● Dra. Mónica Coronado - Medicina Nuclear - Hospital U. La Paz ● Dr. Marcos González - Hematología Clínica - Hospital U. de Salamanca
Sponsor	GELTAMO (Grupo Español de Linfoma Trasplante Autólogo de Médula Ósea)
Project managers	**MFAR Clinical Research** Nerea Lasa Verónica Roca Myriam Peral Ana Márquez
Clinical research associate(s)	**MFAR Clinical Research** Ana Alonso Verónica Roca Sonia Díez Borja Peláez Beatriz Ceballos Alicia Pereira Marina Reyes Sara Fábregas Francisco Roldán Sandra Díaz Joel Rodríguez Cristina Bueno
Medical adviser	Dra. Eva González Barca Hematología Clínica - Institut Català d'Oncologia
Data management	Ana Márquez - MFAR Clinical Research Verónica Roca - MFAR Clinical Research
Trial statistician	Jordi Curto - MFAR Clinical Research

Abbreviation: MFAR, Marketing Farmaceutico S.L.

7. INTRODUCTION

7.1. DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma, and it accounts for 30% to 50% of all non-Hodgkin lymphomas (Salar et al,. Eur J Haematol. 1997; 59: 231-7). Although it is considered a curable disease, 40% of patients do not respond or relapse after the first line of treatment. The International Prognostic Index (IPI) and the IPI adjusted for age (aIPI) are used to identify patients with higher or lower probability of cure (Shipp et al,. N Engl J Med. 1993; 329: 987-94).

For many years, the standard treatment for patients with disseminated DLBCL has been CHOP-type chemotherapy, with which long-term survival is achieved in approximately 40% of patients (Fisher, N Engl J Med. 1993; 329: 580-2. The combination of CHOP with the monoclonal antibody, rituximab, improved the survival of elderly patients with both high- and low-risk IPI (trial of the French group GELA), achieving EFS of 45% and OS of 60% (Coiffier B et al, N Eng J Med 2002; 346: 235-41; Feugier P, et al., J Clin Oncol., 2005; 23: 4117-4126). The R-CHOP combination also proved to be superior to CHOP in young patients with low-risk IPI (MiNT study), with 80% EFS vs. 50% in the CHOP arm (Pfreundschuh et al, Lancet Oncol 2006: 7: 379-91). The German Group compared the effectiveness of the standard treatment CHOP-21 with dense doses CHOP-14 (the drugs were administered every 14 days with the support of granulopoietic growth factors such as granulocyte-colony stimulating factor (G-CSF) in elderly patients, CHOP-14 improved the EFS. After this study, a German trial RICOVER compared, with a factorial design 2x2, 6 vs 8 cycles of CHOP-14 with or without rituximab in elderly patients, and the results again showed that the combination with rituximab improved the EFS (66% vs 47%) (Pfreundschuh et al, Lancet Oncol 2008: 9: 105-16).

7.2. RATIONALE FOR THE STUDY

There is no standard treatment for young patients with DLBCL and high-risk IPI. The survival of these patients remains low, around 40%. First-line treatment with high doses of chemotherapy and rescue with transplantation of autologous hematopoietic precursors have obtained controversial results (Haioun et al,. J Clin Oncol.1997; 15: 1131-7; Gianni A et al,. N Engl J Med,.1997; 336: 1290-97; Milpied N et al,. N Engl J Med. 2004; 350(13): 1287-95; Strehl J et al,. Haematologica. 2003; 88(11): 1304-15). The combination of R-CHOP with new drugs is an attractive approach to treat these patients.

Bortezomib is an inhibitor of proteasomes. Proteasomes are intracellular enzyme complexes that degrade proteins that are ubiquitinated and, therefore, regulate intracellular protein levels. It is involved in intracellular regulation at different levels: the microenvironment, apoptosis, and the cell cycle by inhibiting the NF-κB-VEGF-TNF-α pathway (Kyle & Rajkumar, N Engl J Med. 2004;351:1860-73; Adams, Drug Disc Today. 2003;8:307; Voorhees, et al. Clin Cancer Res. 2003;6:6316-25; Leonard, et al. Int J Cancer, 2006; 119: 971-79). Bortezomib is very active against multiple myeloma and has

also shown efficacy in the treatment of indolent lymphomas (de Vos et al, J Clin Oncol. 2009;27(30):5023-30; Coiffier et al, Lancet Oncol; 2011;12(8):773-84).

In a clinical trial (Dunleavy et al, Blood. 2009;113:6069)-76, it has been shown that bortezomib is also active against DLBCL. It appears that it could be more effective in the activated lymphocyte subtype (ABC subtype) of DLBCL than in the germinal centre subtype (CGG subtype) (Dunleavy et al, Blood. 2009;113: 6069. Lin Z et al, Ann Hematol. 2018; 97:2137-2144). These conclusions are based on a small number of cases and must be reproduced in larger series. Recently another trial has been published in which patients undergoing first-line treatment were receiving a combination of bortezomib and R-CHOP (Ruan et al, J Clin Oncol. 2011; 29(6): 690-7), demonstrating that the combination is feasible. Two large trials combining bortezomib with R-CHOP in DLBCL type ABC (PYRAMID, Lymph 2034); however, both trials are selecting patients according to the immunophenotype, a method that is still poorly reproducible.

In addition, several studies are ongoing in which bortezomib is used subcutaneously instead of intravenously. The results show that the efficacy is the same with less toxicity, there by improving the quality of life of patients. A randomised phase III trial beenwas carried out in patients with relapsed multiple myeloma (MM) to compare the intravenous and subcutaneous formulations, administering the same dose: 1.3 mg/m2 in the conventional scheme on days 1, 4, 8, and 11 in monotherapy with the possibility of adding dexamethasone in case of a suboptimal response after the fourth treatment cycle. The results, published by Moreau et al. showed that the subcutaneous administration of bortezomib is not inferior to intravenous administration; in fact, the overall response and complete remissions rates were similar (42% overall response rate in both arms, and 8% and 6% complete remissions) rates for intravenous and subcutaneous administration, respectively) without differences in time to progression (9.4 months for the intravenous formulation and 10.4 months for the subcutaneous) or OS (Moreau et al,. Lancet Oncol. 2011; 12(5): 431-40). In October 2012, bortezomib was approved by the health authorities for subcutaneous use.

Regarding the methods used for response evaluation and its prognostic value, the results of positron emission tomography-computed tomography (PET/CT.) are controversial The discriminatory value of early PET/CT during treatment in patients with DLBCL with poor prognosis is unclear (Haioun et al:. Blood. 2005; 106: 1376-81). Prospective studies with centralized quantitative and qualitative measurements reviewing are needed.

With all these antecedents, we proposed a phase II randomised clinical trial for young patients with DLBCL with unfavourable IPI, consisting of 6 cycles of subcutaneous bortezomib with R-CAP (R-CHOP without vincristine to avoid the accumulated toxicity of peripheral neuropathy) compared with the standard regimen of 6 cycles of immunochemotherapy R-CHOP every 21 days. We will retrospectively analyse the evolution of patients according to the biological subtype of DLBCL (non-GCB vs GCB). We will also carry out a qualitative and quantitative prospective evaluation of PET/CT after 2 treatment cycles without modifying the treatment and after 4 cycles of chemotherapy.

8. STUDY OBJECTIVES

Primary Objective

To evaluate the proportion of patients with EFS at 2 years in patients diagnosed with DLBCL with an aIPI ≥1 with elevated levels of beta-2 microglobulin (above upper normal level [UNL).]

Secondary Objectives

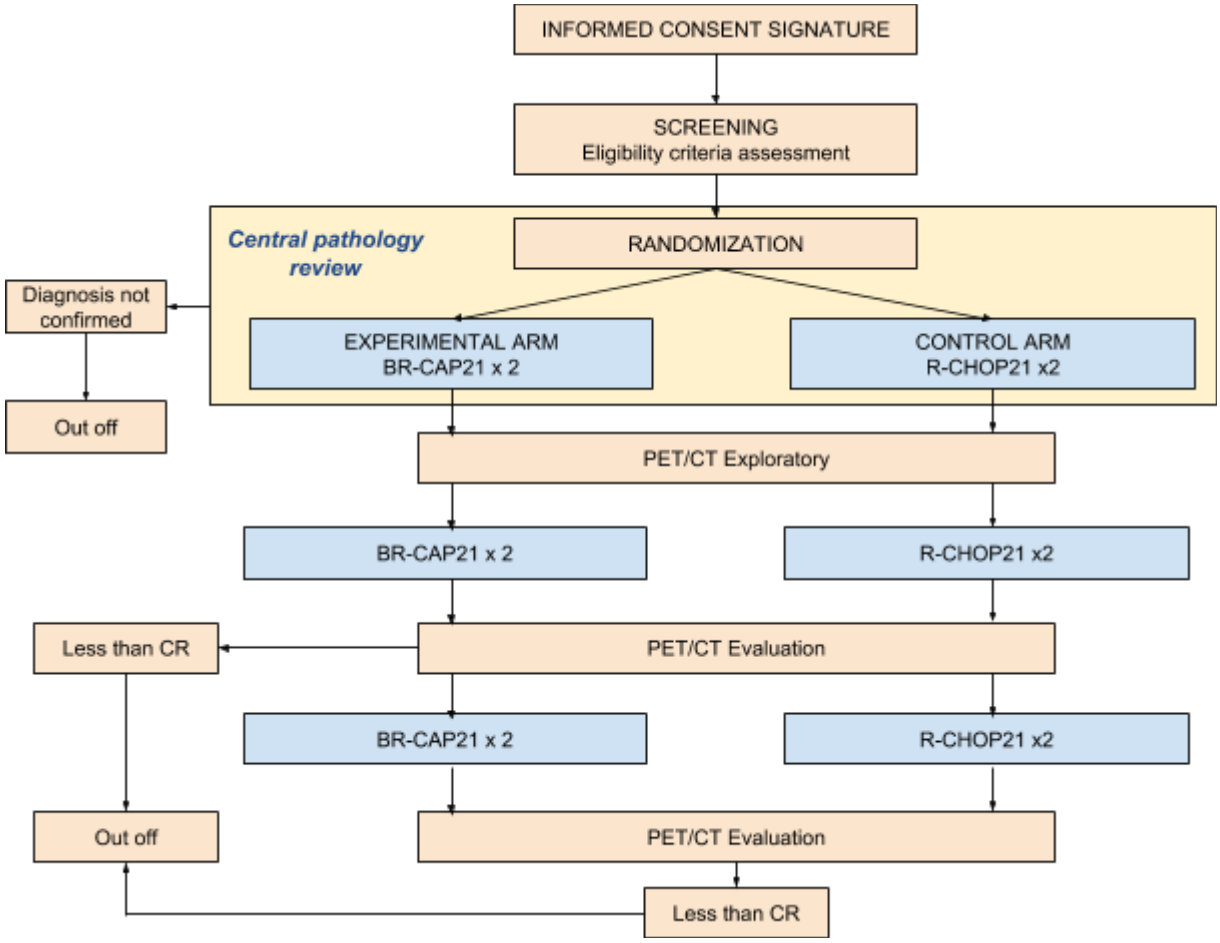
1. EFS at 2 years in different biological DLBCL subgroups: GCB vs. non-GCB.
2. OS at 2 years in patients diagnosed with DLBCL with an aIPI ≥1 with elevated levels of beta-2 microglobulin (above UNL).
3. Overall response rate and complete remissions rates in patients diagnosed with DLBCL with an aIPI ≥1 with elevated levels of beta-2 microglobulin (above UNL).
4. Toxicity according to the Common Terminology Criteria (CTC) for Adverse Events (AE) criteria (version 3.0) of the National Cancer Institute (NCI). http://ctep.cancer.gov/reporting/ctcnew.html).
5. To evaluate the predictive value of interim PET/CT for EFS after 2 and 4 cycles of chemotherapy.
6. To identify clinical and biological prognostic factors for response and survival.

9. INVESTIGATIONAL PLAN

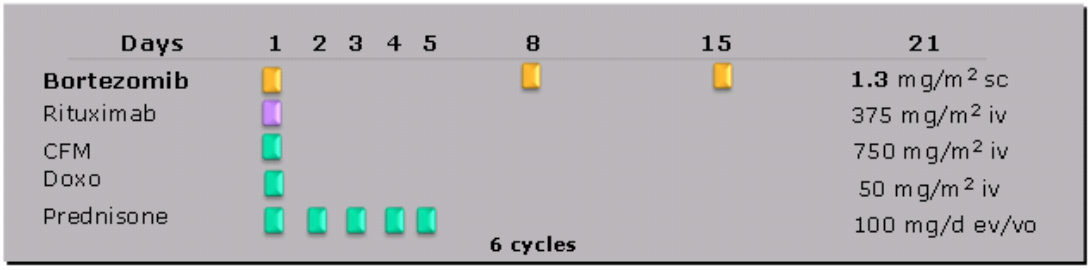
9.1. OVERALL STUDY DESIGN AND PLAN

9.1.1. STUDY FLOWCHART

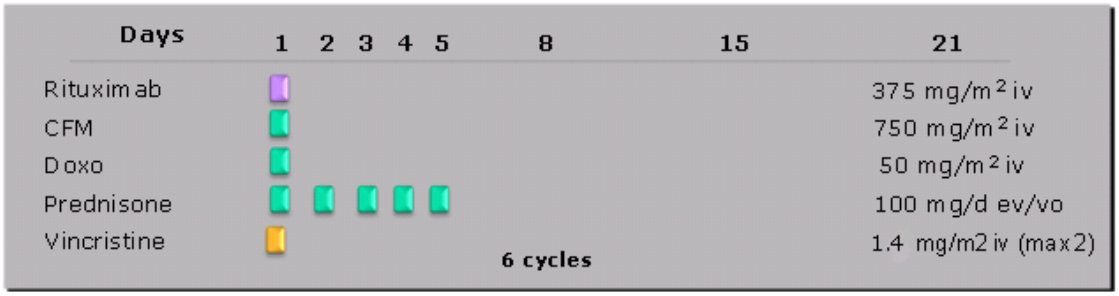
Figure 1. Schematic representation of study protocol



R-B-CAP21



R-CHOP21



9.1.2. STUDY LOCATION

This study was conducted at the following locations:

ICO L'Hospitalet (H. Duran i Reynals)
H.U. de Salamanca
H. Marques de Valdecilla

ICO Badalona (H. Germans Trias i Pujol)
H. Clinic de Barcelona
H.U. 12 de Octubre
H.U. Ramón y Cajal
H. La Paz
H. Fundación Alcorcón
HM CIOCC
H. Infanta Leonor
H.U. Virgen del Rocío
H. de Jerez
H. Universitario y Politécnico La Fe
H. Dr. Peset
H.U. Central de Asturias
H. Son Llàtzer
H. Lozano Blesa
H.U. Canarias
ICO Girona
C.H.U. de Vigo (CHUVI)

Dra. Eva González Barca
Dr. Alejandro Martin
Dr. Eulogio Conde
Dra. Sonia González de Villambrosia
Dr. Juan Manuel Sancho
Dr. Armando López Guillermo
Dr. Carlos Grande
Dr. Javier López Jiménez
Dr. Miguel Ángel Canales
Dr. Francisco Javier Peñalver
Dr. Jaime Pérez de Oteyza
Dr. José Ángel Hernández
Dra. Estrella Carrillo Cruz
Dra. Mª José Ramírez
Dr. Isidro Jarque
Dra. Mª José Sayas
Dra. Concepción Nicolás
Dr. Joan Bargay
Dr. Luis Ramón Palomera
Dra. Mª José Rodríguez Salazar
Dr. Josep María Roncero
Dra. Carmen Albo

9.2. DISCUSSION OF STUDY DESIGN

BRCAP is a multicentre, randomised phase II study that compares the BRCAP experimental treatment to standard, R-CHOP treatment for patients affected by DLBCL. This is a superiority study with the hypothesis that the treatment with BRCAP will exceed R-CHOP treatment in terms of 2-year. The randomisation process was carried out by

assigning treatments contained in sealed envelopes that were opened manually by the person in charge of randomisation in the CRO at the time of receiving an application for inclusion. This procedure guaranteed the impartiality of the operator at all times to perform the randomisation of patients.

In addition, the study design contained a centralized review of diagnoses and an electronic PET web-based platform, both aimed increasing the value of the study results and eliminating the possibility of observer variability in 2 critical aspects of the study: diagnosis per se and imaging disease monitoring.

In the case of patients who consented to donate their samples for the biological substudy, part of the tumor sample (DNA and RNA) was forwarded to the Molecular Biology Unit of the University Hospital of Salamanca (HUSAL) where complementary biological studies were carried out. In addition, peripheral blood samples for other studies were obtained at diagnosis (2 tubes of 10 mL in EDTA).

Stratification of the patients was allowed to guarantee that the clinical variables that were identified a priori as potential confounding factors were conveniently categorized so that the comparison between both treatment arms were equitable regarding the most relevant clinical issues.

The assigned treatment was administered as soon as possible and continued during the 6 cycles as established by the protocol. This allowed a real comparison between the intervention treatment and the standard treatment that was administered in patients with the pathology under study at that time.

The protocol established the performance of a PET-CT evaluation at baseline and at cycle 4 to determine the best alternative treatment for each patient, as those patients who did not present an adequate response to treatment were switched to other therapeutic options, ensuring that patients would receive the best possible treatment. As per standard clinical care, a biopsy was required at month 6 for the purpose of a comparison with the available images to assess the response to treatment.

Recruitment of 127 patients over 2 years was intended; however, the recruitment end date was reached, and it was extended for a few months upon which the final number of patients was considered as sufficient to verify the hypothesis of the study (results are described throughout this document).
Using the binomial test of 2 proportions and a tail, a null hypothesis of 55% was used for R-CHOP arm, and it was estimated that it would be 70% in the bortezomib-RCAP arm; assuming an alpha error of 0.25 and a beta error of 0.20, we needed to include 120 patients. If a 5% loss of patients was assumed, the number to be included was 127 patients (50% in each treatment arm).

Four randomisation lists were generated, one for each stratum, taking into account a uniform distribution. The patients were assigned to each group at a ratio of 1:1 using blocks so that each patient had the same probability of being included in each of the treatment arms. Patients were stratified by:

- aIPI 1-2 vs. aIPI 3
- Eastern Cooperative Oncology Group (ECOG) 0-1 vs. ECOG 2-3

In addition, the following 4 strata were formed:

1. aIPI 1-2/ECOG 0-1
2. aIPI 1-2/ECOG 2-3
3. aIPI 3/ECOG 0-1
4. aIPI 3/ECOG 2-3

During the trial performance, it was detected that the stratification aIPI 3/ECOG 0-1 would not be possible. This is because the maximum score of the aIPI is 3, and the ECOG performance status (PS) is already considered in this index (the IPI is composed of several clinical variables, including ECOG). For that reason, the patients were randomised according to 3 strata:

1. aIPI 1-2/ECOG 0-1
2. aIPI 1-2/ECOG 2-3
3. aIPI 3/ECOG 2-3

At that time, 4 cases were incorrectly randomised in stratum 3 (aIPI 3/ECOG 0-1):

- Patient 11-001 (CIOCC): Experimental arm: after the centralised review was performed on the sample of this patient, the diagnosis of DLBCL was not confirmed.The patient was withdrawn from the trial.
- Patient 05-002 (H. Clinic): Control arm
- Patient 07-006 (H. 12 October): Control arm
- Patient 07-007 (H. October 12): Experimental arm

The Sponsor decided that the patients would continue treatment within the clinical trial in the assigned arm at the time of randomisation, and their data were analysed based on their actual aIPI/ECOG values during the data analysis phase.

9.3. SELECTION OF THE STUDY POPULATION

9.3.1. INCLUSION CRITERIA

1. Patients diagnosed with primary diffuse DLBCL who have never received treatment for this condition.
2. Aged between 18 and 70 years.
3. Age-adjusted IPI ≥1 with high levels of beta-2 microglobulin (above UNL).
4. Neoplastic B lymphocytes for CD20 positivity.
5. ECOG 0-3.
6. More than 12 weeks of life expectancy.
7. Signed informed consent.
8. Women who are not pregnant nor breastfeeding without heterosexual activity during the entire study. Women with heterosexual activity only if they were willing to use 2 methods of contraceptive. The 2 contraceptive methods could be 2 barrier methods or a barrier method combined with a hormonal contraceptive

method to prevent pregnancy, used during the entire study and until 3 months after the study completion.

9.3.2. EXCLUSION CRITERIA

1. Patient previously treated for DLBCL.
2. Patients with central nervous system (CNS) lymphoma.
3. Transformed follicular lymphoma.
4. HIV-positive patients.
5. Positive determination of chronic hepatitis B virus (HBV) infection (defined as positive serology for hepatitis B surface antigen [HBsAg)]. Patients with hidden or previous hepatitis (defined as positive antibodies against the core of the HBV [HBcAb] and HBsAg-negative) were enrolled if undetectable for HBV DNA.
6. Positive results for hepatitis C (antibody serology for hepatitis C virus [HCV]). Patients who were HCV-positive could participate only if the result of the PCR was negative for HCV RNA.
7. History of other primary malignancy with <5 years of complete response (CR) except for basal or squamous cell carcinomas of the skin or cervical carcinoma (in situ).
8. Uncontrolled current illness, e.g., cardiac, pulmonary, neurologic, metabolic, considered to be unrelated to lymphoma.
9. Patients with severe impairment of renal function (creatinine >2.5 UNL) or hepatic function (bilirubin or alanine transaminase [ALT]/aspartate transaminase [AST] >3 UNL), unless it was suspected to be due to the disease.
10. Uncontrolled hypertension (diastolic blood pressure >110 mmHg).
11. Patients with previous history of cardiac disease: ventricular ejection fraction <50%.
12. Patients with severe psychiatric conditions that may interfere with their ability to understand the study (including alcoholism or drug addiction).
13. Pregnant women or breastfeeding women, or adults of childbearing age not using an effective contraception method.
14. Patients with known hypersensitivity to murine proteins or any other component of the study drugs.

9.3.3. WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were free to withdraw from the study at any time without giving a reason. Patients were advised that if they requested to withdraw from the study, at any time during the trial, then this would have no negative consequences.

The principal investigators (PIs) could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered to be detrimental to the well-being of the patient. Patients who withdrew or were withdrawn underwent a final evaluation at the end-of-treatment (EoT) visit. Subjects who withdrew from the clinical trial after signing the ICF (inclusion) were not replaced.

All subjects who discontinued treatment (e.g., due to unacceptable toxicity, PET4 positivity, etc.) underwent follow-up to assess OS.

All withdrawals were fully documented in the case report form (CRF). The PIs documented the date and time of withdrawal and the results of any assessments made at that time. If the patient withdrew because of an adverse event (AE) or a serious adverse event (SAE), details were forwarded to the EC as required. The PIs also forwarded the details to GELTAMO that forwarded the data to regulatory authorities as appropriate.

The main causes for the discontinuation of the investigational product or follow-up were:

- Positive PET4
- Unacceptable toxicity
- PI decision made in favour of patient health
- Death
- Patient decision
- Progressive disease

9.4. TREATMENTS

9.4.1. TREATMENTS ADMINISTERED

Control arm*:* Six cycles of treatment with R-CHOP were administered: Rituximab 375 mg/m2 iv on day 1 followed by CHOP-type chemotherapy (cyclophosphamide 750 mg/m2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + vincristine 1.4 mg/m2 iv (maximum 2 mg) on day 1 + prednisone 100 mg oral on days 1-5). The cycles were administered every 21 days.

Before the infusion of rituximab, the following was administered:

- Paracetamol 1c 500 mg oral
- Diphenhydramine 1c 50 mg oral

The administration of rituximab was performed as an iv infusion. The first infusion was started at a rate of 50 mg/hour, and after the first 30 minutes, the dose could be increased in increments of 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. Subsequent infusions could be administered at an initial rate of 100 mg/hour and increased by 100 mg/hour at intervals of 30 minutes to a maximum of 400 mg/hour.

Experimental arm: Six cycles of treatment with bortezomib were administered subcutaneously at a dose of 1.3 mg/m2 on days 1, 8, and 15, followed by rituximab iv at a dose of 375 mg/m2 on day 1 followed by chemotherapy: cyclophosphamide 750 mg/m2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + prednisone 100 mg oral on days 1-5. The cycles were administered every 21 days.

The administration of bortezomib was determined based on the patient's body surface calculated on day 1 of each cycle according to standard practice, although the Mosteller

formula was recommended. The administered dose was maintained throughout the treatment cycle and was only recalculated at the beginning of the next cycle or if significant weight gain/loss was detected within the cycle (10% with respect to the value of the baseline visit).

The vials were for single administration. The final concentration of the injection for subcutaneous administration was 2.5 mg/mL (3.5 mg bortezomib in 1.4 mL saline). The final concentration of the drug for subcutaneous administration was 2.5 times higher than in the reconstituted solution for iv use. The appropriate amount of bortezomib for subcutaneous administration was dispensed in 1 injection at the proximal lower extremities (femoral region: upper and middle section) or the upper or lower quadrants of the abdominal area (left or right). It was recommended to avoid repeated injection at the same location, and, therefore, injection sites were rotated on the different days of treatment administration.

Pre-phase treatment was allowed in patients with very poor general condition as a result of their lymphoma, with cyclophosphamide 200 mg/m2/day iv infusion for 1 hour on days 1-5 and prednisone 60 mg/m2/day iv or in bolus on days 1-5.

It was recommended to perform CNS prophylaxis in patients with increased serum lactate dehydrogenase (LDH) and more than one extranodal localizations, or in patients with any of the following affections at: paranasal sinuses, Waldeyer's ring, breast, epidural, testicular, or renal space.

For all patients who were anti-HBc (anti-core [Ac]antibodies)-positive, antiviral prophylaxis was recommended during chemotherapy treatment and up to 1 year after the end of treatment. The type of antiviral prophylaxis was selected according to the protocol of each centre. In all these patients, the viral load should be monitored at least every 3 months.

9.4.2. DESCRIPTION OF INVESTIGATIONAL PRODUCTS

RITUXIMAB
- Rituximab concentrate, solution for infusion,
- Dose/route of administration: 375 mg/m² iv.

CYCLOPHOSPHAMIDE
- Cyclophosphamide, powder for solution for injection or iv infusion,
- Dose/route of administration: 750 mg/m² iv.

ADRIAMYCIN
- Adriamycin concentrate, solution for iv infusion,
- Dose/route of administration: 50 mg/m² iv.

PREDNISONE
- Prednisone, tablet,
- Dose/route of administration: 100 mg oral.

BORTEZOMIB

- Bortezomib (experimental arm), powder for solution for injection,
- Dose/route of administration: 1.3 mg/m² sc.

VINCRISTINE
- Vincristine (control am), injectable solution,
- Dose/route of administration: 1.4 mg/m² iv.

9.4.3. METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Control arm with 6 cycles of R-CHOP every 21 days.

Experimental arm with bortezomib subcutaneous on days 1, 8, and 15 of each cycle, rituximab iv, cyclophosphamide iv, adriamycin iv and Adriamycin iv on day 1 of each cycle, and prednisone on days 1-5 oral, in cycles every 21 days.

9.4.4. SELECTION OF DOSES IN THE STUDY

Control arm: 6 cycles of treatment with R-CHOP were administered: Rituximab iv at a dose of 375 mg/m^2 on day 1, followed by CHOP-type chemotherapy (cyclophosphamide 750 mg/m^2 iv on day 1 + Adriamycin 50 mg/m^2 iv on day 1 + vincristine 1.4 mg/m^2 iv (maximum 2 mg) on day 1 + prednisone 100 mg oral days 1-5). The cycles were administered every 21 days.

Before the infusion of rituximab, the following were administered:
- Paracetamol 1c 500 mg oral,
- Diphenhydramine 1c 50 mg oral.

The administration of rituximab was by iv infusion. The first infusion started at a rate of 50 mg/hour; after the first 30 minutes, the dose could be increased in increments of 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. Subsequent infusions could be infused at an initial rate of 100 mg/hour and increased by 100 mg/hour at intervals of 30 minutes to a maximum of 400 mg/hour.

Experimental arm: 6 cycles of treatment with bortezomib administered subcutaneously at a dose of 1.3 mg/m^2 on days 1, 8, and 15, followed by rituximab iv at a dose of 375 mg/m2 on day 1, followed by chemotherapy (cyclophosphamide 750 mg/m2 evion day 1 + Adriamycin 50 mg/m^2 iv on day 1 + prednisone 100 mg oral on days 1-5). The cycles were administered every 21 days.

Before the infusion of rituximab (for both arms), the following were administered:
- Paracetamol 1c 500 mg oral,
- Diphenhydramine 1c 50 mg oral.

The administration of rituximab was by iv infusion. The first infusion started at a rate of 50 mg/hour; after the first 30 minutes, the dose could be increased in increments of 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. Subsequent infusions

could be infused at an initial rate of 100 mg/hour and increased by 100 mg/hour at intervals of 30 minutes to a maximum of 400 mg/hour.

Pre-phase treatment was allowed in patients with very poor general condition due to their lymphoma, with cyclophosphamide 200 mg/m^2/day iv infusion for 1 hour on days 1-5 and prednisone 60 mg//m^2/day iv or in bolus on days 1-5.

It was recommended to perform CNS prophylaxis in patients with increased serum LDH and more than one extranodal location, or in patients with any of the following affections at: paranasal sinuses, Waldeyer's ring, breast, epidural, testicular, or renal space.

For all patients who were anti-HBc (anti-core antibodies)-positive, antiviral prophylaxis was recommended during chemotherapy treatment and up to 1 year after the end of treatment. The type of antiviral prophylaxis was selected according to the protocol of each centre. In all these patients, the viral load should be monitored at least every 3 months.

Dose reduction/delay was allowed according to the general criteria detailed below:

Criteria to apply to each cycle:

- Neutrophils >1,000/µL,
- Platelets > 80,000/µL.

If there was no haematological recovery on day 21 of the cycle, the test was repeated 4 days later (day 25 of the corresponding cycle); if there was still no recovery, it was repeated after 3 days (day 28). In the case of non-recovery, the evaluations were repeated every 7 days until the aforementioned haematological criteria were met.
If haematological recovery was delayed for more than 1 week (i.e. beyond the 28th day of the cycle), the doses of Adriamycin and cyclophosphamide were reduced by 25% in the next cycle.
If haematological recovery was delayed for more than 2 weeks (day 35), the doses of Adriamycin and cyclophosphamide were reduced by 50% in the next cycle.
If for any reason a patient couldn't receive the study treatment for 3 consecutive weeks, the patient was withdrawn from the protocol.

Increasing or reducing doses of rituximab in infusions was not contemplated. Mild or moderate reactions related to perfusion were usually resolved by reducing the rate of perfusion and increasing it when the symptoms improved.

Each day that bortezomib was administered during a cycle (except on day 1), the patient must have:

- Platelets >25,000/µL,
- Neutrophils >500/µL,
- The absence of non-haematological toxicity grade 3-4.

If the above parameters were not met, the dose of bortezomib was suspended. The doses that could not be placed during a cycle, were not re-indicated later in the same cycle.

Doses of bortezomib were reduced if the patient had febrile neutropenia grade ≥3 or neutropenia grade 4 for more than 7 days, a platelet count <10,000/µL, or any non-haematological grade 3 toxicity, excluding neuropathy, which was considered to be related to bortezomib. The dose reductions were the following:

- If the patient received 1.3 mg/m^2, the dose was reduced to 1.0 mg/m^2.
- If the patient received 1.0 mg/m^2, the dose was reduced to 0.7 mg/m^2.
- If the patient received 0.7 mg/m^2, bortezomib was suspended.

No dose re-scaling was allowed after modifications due to haematological toxicity.

Patients with neuralgia or sensory neuropathy related to bortezomib were managed according to Table 3.

Table 3. Management of patients with neuralgia or sensory neuropathy

			Peripheral sensory neuropathy				
			0	1	2	3	4
			Normal	Asymptomatic: loss of deep tendon reflexes or paraesthesia	Moderate symptoms: some limitation of ADL	Serious symptoms: limited autonomy and self-care in ADL	Life threatening: an intervention is urgently needed
Neuralgia	0	None	No action required	No action required	Reduce 1 dose level	Interrupt: reduce 2 dose levels; modify the therapeutic scheme	Withdraw bortezomib
	1	Mild pain	No action required	No action required	Reduce 1 dose level	Interrupt: reduce 2 dose levels; modify the therapeutic scheme	Withdraw bortezomib
	2	Moderate pain: some limitation in ADL	Reduce 1 dose level	Reduce 2 dose levels	Interrupt: reduce 2 dose levels	Interrupt: reduce 2 dose levels; modify the therapeutic scheme	Withdraw bortezomib
	3	Severe pain: limitation of autonomy and self-care in ADL	Interrupt: reduce 2 dose levels; modify the therapeutic scheme	Interrupt: reduce 2 dose levels; modify the therapeutic scheme	Interrupt: reduce 2 dose levels; modify the therapeutic scheme	Withdraw bortezomib	Withdraw bortezomib
	4	Withdraw bortezomib	Withdraw bortezomib	Withdraw bortezomib	Withdraw bortezomib	Withdraw bortezomib	Withdraw bortezomib

Abbreviation: ADL, activities of daily living
Discontinue: interrupt the treatment with bortezomib until the resolution of symptoms of toxicity to grade 1 or better.Modify the therapeutic scheme of bortezomib 3 doses (days 1, 8, and 15) to bortezomib 1 dose on day 1)..Patients treated with doses of 1.3 mg/m^2 of bortezomib that require reduction of 1 dose level should be treated with doses of 1 mg/m^2; if they require reduction of 2 dose levels, they should be treated with doses of 0.7 mg/m^2 (and also modify the therapeutic

scheme if indicated in the table).
Patients treated with doses of 1 mg/m^2 of bortezomib that require reduction of 1 dose level should be treated with doses of 0.7 mg/m^2; if they require reduction of 2 dose levels, they should be treated with doses of 0.7 mg/m^2, and they will always have to modify the therapeutic scheme.
Patients treated with doses of 0.7 mg/m^2 of bortezomib that require reduction of 1 dose level or reduction of 2 dose levels should always modify the therapeutic scheme.

Patients with mild impairment of liver function started treatment with the dose of bortezomib established per protocol (1.3 mg/m^2).

Patients with moderate or severe impairment of hepatic function (bilirubin levels >1.5x ULN, regardless of transaminase levels) started treatment with bortezomib at a reduced dose of 0.7 mg/m^2 in the first cycle with a dose escalation to 1.0 mg/m^2 in subsequent cycles or a dose reduction to 0.5 mg/m^2 depending on the tolerance to the drug, table 4. dose for patients with moderate or severe hepatic toxicity.

Table 4. Management of patients liver dysfunction

Liver impairment	Bilirubin level	Modification of the initial dose
Mild	> 1 x - 1.5 x ULN	None
Moderate	> 1.5x - 3 x ULN	Reduce bortezomib to 0.7 mg / m^2 in the first cycle. Consider escalation of doses to 1.0 mg / m^2 in the following cycles or a dose reduction to 0.5 mg / m^2 depending on tolerance to the drug.
Severe	> 3x ULN (due to infiltration by lymphoma)	

9.4.5. SELECTION AND TIMING OF DOSES FOR INDIVIDUAL PATIENTS

This is a simple randomized study that assigned treatment to a fixed initial dose of BRCAP (experimental arm, days 1, 8 and 15 of the cycle) vs R-CHOP (control arm, administered according to indication), administered parenterally in cycles of 21 days (except for prednisone that was administered orally). The initial dose, premedication, administration speed and frequency of administration were indicated by the trial protocol, as described in section 9.4.4 of this report.

As indicated in section 9.2, the study design included a stratification of patients according to clinical parameters (ECOG and aIPI), but this did not affect the dose or regimen of patients treatment.

The protocol established a reduced initial dose of bortezomib (0.7 mg/m^2) in the experimental arm for patients with moderate or severe hepatic toxicity (see table 4, section 9.4.4). These patients started treatment with bortezomib at 0.7 mg/m^2 in the first cycle, escalating to higher doses (maximum 1.0 mg/m^2) or decreasing to 0.5 mg/m^2, according to patients clinical evolution. For these patients, the maximum dose that could be administered was 1.0 mg/m^2 (1.3 mg/m^2 for the rest of patients) and the minimum was 0.5 mg/m^2 (0.7 mg/m^2 for the rest). It is important to mention that the rest of the

drugs in the BRCAP combination have maintained the initial dose stipulated in the protocol for these patients.

On the other hand, treatment with oral corticosteroids (prednisone 10 mg / day - from day 1 to day 5), was taken by patients at home, in the case they were not admitted to receive parenteral treatment. The protocol only established the dose to be administered, therefore prednisone has been administered according to the local clinical practice in the participating sites, giving the Investigators the instructions to the patients about how and when prednisone should be taken.

As indicated in section 9.4.4, modifications and dose delays were allowed, an algorithm for the management of neuropathies was provided in the protocol, dosing management guidelines for hematological and non-hematological toxicities were also provided.

Finally, the maximum duration of treatment according to the protocol for both arms was 6 cycles every 21 days. The continuity of the treatment depended on the tolerance and the response observed in the patients throughout the study. Treatment was discontinued in case of non-confirmation of diagnosis after centralized review, unacceptable toxicity, if PET 4 was positive or progression. In addition, if a patient could not receive the study treatment for 3 consecutive weeks for any reason, treatment was permanently discontinued.

9.4.6. PRIOR AND CONCOMITANT THERAPY

Concomitant treatment included all prescription and over-the-counter medications used by the patient from 7 days before the start of study treatment until 30 days after the last study treatment. The necessary treatments that the responsible doctor considered appropriate were prescribed for concomitant diseases presented by any patient included in the study. All concomitant medication were reported to the investigator and noted in the relevant eCRF.
Patients who used oral contraceptives, hormone replacement therapy, or other maintenance treatments continued using them.

<u>CNS prophylaxis</u>
CNS prophylaxis was administered with intrathecal chemotherapy only according to the practice of the centre, and its use was documented in the eCRF.

<u>Prophylaxis of hemorrhagic cystitis</u>
Patients were adequately hydrated before and after the administration of cyclophosphamide and advised to urinate frequently. Mesna could be used as prophylaxis, according to the practice of the centre.

<u>Treatment and prophylaxis of neutropenia</u>
In this study, the use of G-CSF was allowed for the treatment of neutropenia.
Primary prophylaxis with G-CSF was recommended according to the guidelines of American Society of Clinical Oncology, European Organization for Research and Treatment of Cancer, and European Society for Medical Oncology (Lyman et al. 2004).

Prophylaxis of reactivation of HBV
Patients with a risk of reactivation of HBV who were HBcAc +, could be treated prophylactically.

Planned radiotherapy
It was not recommended to administer radiotherapy to patients with negative residual PET bulky mass. Patients with PET + masses should be considered having resistant disease; these patients should leave the trial and be managed according to the practice of each centre.

9.4.7. TREATMENT COMPLIANCE

All investigational products were administered by the study investigator or the designated staff member. To ensure drug accountability, the investigator or the designated staff member maintained accurate records of the dates and amounts of drugs received, to whom they were dispensed, and any supplies accidentally or deliberately destroyed, according to local practices.

Patient compliance with the investigational products was recorded in the eCRFs and reviewed by clinical research associates (CRAs) at the time of the monitoring visit, when applicable.

9.5. EFFICACY AND SAFETY VARIABLES

9.5.1. EFFICACY AND SAFETY MEASUREMENTS ASSESSED

Central anatomopathological diagnosis

A centralized anatomopathological reviewing of the GCB vs. non-GCB subtype and other biological analyses were performed in the Pathological Anatomy Service of the Marqués de Valdecilla Hospital, in Santander.
If the centralized review did not confirm the anatomopathological diagnosis, the patient had to leave the protocol to receive the most appropriate treatment outside the trial.

In the case of patients who consented to donate their samples for the biological substudy, part of the tumour sample (DNA and RNA) was forwarded to the Molecular Biology Unit of the University Hospital of Salamanca (HUSAL) where complementary biological studies were carried out. In addition, peripheral blood samples for other studies were obtained at diagnosis (2 tubes of 10 mL in EDTA). For more information see appendix 15.1.3. Biological project.

Performance status
The ECOG PS classifies patients according to their functional impairment, compares the effectiveness of therapies, and assesses the prognosis of patients. ECOG PS was assessed at each visit as a part of the physical examination; only patients with ECOG

PS 0–3 within 7 days prior to treatment initiation were eligible. ECOG PS was measured at subsequent treatment visits on day 1 of each cycle and on subsequent follow-up visits until relapse.

PET-CT (disease status), Appendix 15.1.2. PET project

Response evaluation was conducted according to the revised Cheson 2007 criteria Revised Response Criteria for Malignant Lymphoma. (Chenson et al. J Clin Oncol. 2007 Feb 10;25(5):579-86) every 2 cycles until cycle 6 (included).

All acquisition parameters (2D or 3D, matrix, etc.) complied with a qualification of PET/CT systems for participating in clinical trials. All patients underwent baseline PET/CT before the start of treatment (PET0), as well as 2 other PET/CT scans in the middle of treatment (PET2 and PET4) which were scheduled between days 15 and 20 after the second and the fourth cycle of immunochemotherapy. In addition, all patients underwent a final PET (PET6) after at least 3 weeks after completing treatment.

A centralized review of the PET/CT was carried out:

Qualitative analysis of PET: *PET/CT images were reviewed at dedicated platform. The PET0 was reviewed in each local centre where the study was carried out, following the standard criteria and with the available clinical information (the pathological uptake of fluorodeoxyglucose [FDG] indicates that focal or diffuse uptake is superior to the background activity and is not attributable to physiological uptake). The PET2 and PET4 studies were evaluated without having the clinical information of the patient and were interpreted in a binary way as positive or negative based on the Deauville 5-point scale.*

Deauville Scale:
1. Non uptake,
*2. Uptake ≤ mediastinum**,*
3. Uptake > mediastinum but ≤ liver,
4. Uptake moderately greater than the liver,
5. Uptake markedly greater than the liver and/or new lesions,
X new areas of uptake probably not related to lymphoma.

***NOTE: if the activity of the mediastinal vascular pool is ≥ the liver activity, then the activity of the lesion should be compared with that of the liver (uptake of the lesion < liver corresponds to score 2, uptake of the lesion = liver corresponds to score 3).*

A PETi (intermediate PET) was considered positive if the uptake of the residual disease was moderate or markedly greater than that of the liver (Deauville >3). A PETi was considered negative if the uptake of the residual disease was inferior or similar to that of the liver (Deauville ≤3). Only the result of PET4 was decisive for a change of treatment.

Semiquantitative analysis of PET

The maximum standardised uptake values (SUVs) were calculated by body weight.

SUVmax is defined as the highest SUV value in the hypermetabolic lesion with the highest uptake of FDG. For each PET study, the tumour lesion with the most intense uptake of FDG was identified among all the hypermetabolic foci using a gradient colour scale. The most active volumetric region bewas determined by calculating the

corresponding SUVmax. To calculate ΔSUVmax, the most active region in any region or organ in PET2 and PET4 was compared with that in PET0, even if the location in PET2 or PET4 differs from the location in PET0. The SUVmax between PET0 and PET2 (ΔSUVmaxPET0-2) and between PET0 and PET4 (ΔSUVmaxPET0-4) were calculated.
PET2 was defined as positive if the ΔSUVmaxPET0-2 was <66% and negative if it was >66%. PET4 was considered positive if the ΔSUVmaxPET0-4 was <70% and negative if it was >70%.
Only the result of PET4 could change the therapeutic scheme.
In case the results of the qualitative and quantitative assessment differed from each other in the PET2 and PET4, the semiquantitative analysis was decisive to determine a positive or negative study.

Final response
PET6 was analysed qualitatively or visually using the Deauville 5-point scale. The determination of remission status at the end of treatment was made considering the metabolic and morphological findings of the PET/CT following the latest proposals of experts (Menton, 2012): as follows
Complete metabolic response:

- Deauville 1, 2, or 3 with or without residual mass and without evidence of the involvement of the bone marrow, spleen, or other extralymphatic organs.
- Complete metabolic response with residual mass was called CMRr, being necessary to record the size of the mass.

Residual metabolic disease:

- Deauville 4 or 5 and residual mass of any size (without new lesions).

Progressive metabolic disease (PMD):

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

<u>CT scan (disease status)</u>
The thorax, abdomen, pelvis, and other disease locations were subjected to radiological imaging by CT scan during the follow-up until relapse.
Disease relapse assessment was maintained in these subjects every 3 months during the first year, every 6 months during the second year, and every year during years 3-5 of follow-up, or until relapse or the end of the trial.

<u>Bone marrow biopsy</u>
Bone marrow biopsy was performed at baseline to confirm if the bone marrow was infiltrated.
A new bone marrow biopsy was mandatory to confirm the CR if the bone marrow was previously infiltrated.

<u>Electrocardiogram (ECG)</u>
ECG analysis was performed at baseline (during patient selection) and after trial initiation following PI criteria. Clinical evaluations of all ECG reports were performed by PIs.
The ejection fraction was optional (only mandatory in patients with a history of heart disease).

Clinical examination

Physical examination included the assessment of the following: general appearance, clinical assessment of the injection site, ECOG PS, and an analysis of respiratory, cardiovascular, abdominal, pelvic, skin, head and neck, lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities), and neurological systems.

Vital signs

Height was assessed at screening only. Weight was assessed at screening and repeated if it significantly changed according to the PI. Blood pressure and temperature were included during the measurement of vital signs. The date of collection and measurement was recorded on appropriate eCRFs and medical records. Any clinically significant changes in vital signs were recorded as AEs.

Safety

AEs were recorded and assessed continuously (at each visit) throughout the trial until the final outcome or at the 30-day follow-up safety visit (EoT visit). All ongoing AEs at the EoT visit were monitored and followed up by the investigator until stabilisation or until the outcome was known unless the subject was documented as “lost to follow-up”. Adverse drug reactions were followed up at least until 30 days after the last study treatment administration.

The sponsor sent appropriate safety notifications to health authorities in accordance with applicable laws and regulations. In accordance with ICH-GCP, the sponsor informed the investigators of “findings that could adversely affect the safety of subjects, impact the conduct of the trial, or alter the approval/favourable opinion of the IEC to continue the trial”. In particular, and in line with respective regulations, the sponsor informed the investigator, health authorities, and ECs of AEs that were both serious and unexpected and were considered to be related to the administered product (suspected unexpected serious adverse reactions [SUSARs]) in an expedited manner.

Laboratory tests

Sites provided a list of laboratory normal ranges, and any changes in these normal ranges during the trial were forwarded to the sponsor. Blood samples were collected for clinical laboratory tests following the timing detailed in the schedule of assessments.

Haematology

Haematology determinations were performed at baseline and before treatment administration. They were also performed at the EoT visit and at each follow-up visit to monitor patient safety. Haematology tests included haemoglobin, platelets, white blood cell (WBC) count, and WBC differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

Serum chemistry

Serum chemistry determinations were performed at baseline and at each cycle of treatment on day 1 before treatment administration. They were also performed at the EoT visit and at each follow-up visit to monitor patient safety. Basal serum chemistry tests included creatinine, urea, uric acid, sodium, potassium, calcium, glucose, total

proteins, proteinogram, albumin, determination of G immunoglobulin (IgG), IgA, and IgM, bilirubin, alkaline phosphatase, gamma-glutamyl transferase, AST, ALT, LDH, and serum beta-2 microglobulin.
The rest of the serum chemistry tests included basic biochemistry with LDH and serum beta-2 microglobulin.

Coagulation
Tests for prothrombin time, partial thromboplastin time and fibrinogen were performed at baseline.

Serological determination of HBV, HCV, and HIV
Patients who tested positive for HIV, HCV, or active chronic HBV were not eligible for inclusion in the trial.
Patients with hidden or previous hepatitis (defined as positive antibodies against HBcAb and HBsAg-negative) could be enrolled if undetectable for HBV DNA.
Patients who were HCV-positive could participate only if the result of the PCR was negative for HCV RNA.

Pregnancy
Women of childbearing potential underwent a serum or urine pregnancy test prior to investigational treatment initiation.
Additional pregnancy tests were performed at the discretion of the investigators to rule out pregnancies.

Epidemiological questionnaire
A survey with clinical data of interest for biological projects (e.g. personal history, infectious infections, autoimmunity and family history of haematological neoplasms) was performed at baseline.

Table 5 shows the schedule of examinations and procedures for overall study period.

Table 5. Schedule of examinations and procedures

Study determination	Basal: Previous to the start of treatment	During the treatment	At the end of treatment	Follow-up		
	Day -28 and day 0	Before each cycle	60 days after completing the cycle*	1st year	2nd year	3rd- 5th year
Informed consent	**X**					
Inclusion / exclusion criteria	**X**					
Date of birth, date of diagnosis, clinical history	**X**					
Anamnesis/Physical examination (including ECOG and vital signs)	**X**	**X** *weekly*	**X**	**X** *every 3 months*	**X** *every 3 months*	**X** *every 6 months*
Local anatomopathological diagnosis (1)	**X**					
Complete blood count (2)	**X**	**X** *weekly*	**X**	**X** *every 3 months*	**X** *every 3 months*	**X** *every 6 months*
Biochemistry (3)	**X**	**X**	**X**	**X** *every 3 months*	**X** *every 3 months*	**X** *every 6 months*
Coagulation (4)	**X**					
Serology (HIV, HBV, and HCV)	**X**					
Pregnancy test (urine or blood)	**X**					
Image tests (5)	**X**	**X** *It will be carried out as close as possible to the start of the 3rd and 5th cycle*	**X**	**X** *every 3 months*	**X** *every 6 months*	**X** *Annual*
Electrocardiogram	**X**					
Ejection fraction: optional (only mandatory in patients with a history of heart disease)	**X**					
Bone marrow biopsy	**X**		**X** (6)			
Peripheral blood samples (7)	**X**					
Concomitant medication	**X**	**X**	**X**			

Adverse events		**X** *weekly*	**X**	**X**	**X**	**X**
Survey (data of interest for biological projects)	**X**					
Others (8)			**X**			

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

**If a patient ends the treatment prematurely, an end-of-treatment visit will be* performed *at that moment which will include: anamnesis,* a *physical examination, adverse events and concomitant medication, blood count, basic biochemistry with* lactate dehydrogenase *and serum beta-2-microglobulin, assessment of ECOG status*, *and vital signs.* The *reason for ending the treatment* will be registered, and t *data of the last evaluation of the response to* treatment *will be used.*

(*1*) *centralized review of the* paraffin tissue *sample from anatomopathological diagnosis* and the *histological* subtype *GCB* vs. *non-GCB.* will be performed *For this test, the 28-day period is not strict*, i.e., *anatomopathological results of biopsies performed within the last 3 months will be accepted as valid. A frozen sample of the* tumour *must be stored in the* centre *at day-time (see annex III of biological samples)*.

If the centralized review does not confirm the diagnosis, the patient must* withdraw from *the protocol.

(2: (hemoglobin) Includes haemoglobin, leukocytes with differential count, and platelets.

The baseline analysis should be performed within 7 days prior to the start of treatment. The analytics carried out before each cycle cannot be performed more than 48 hours before the cycle.

(3: Basal) Baseline: creatinine, urea, uric acid, sodium, potassium, calcium, glucose, total proteins, proteinogram, albumin, determination of IgG, IgA, and IgM, bilirubin, AST, ALT, LDH, and serum beta-2 microglobulin.

Other analyticals: basic biochemistry with LDH and serum beta-2 microglobulin.

The baseline analysis should be performed within 7 days prior to the start of treatment. The analytics carried out before each cycle cannot be performed more than 48 hours before the cycle.

(4) PT, PTT and fibrinogen.

(*5*) *Baseline: PET/*CT.

*During treatment: PET/*CT which *will be carried out as close as possible to the beginning of the third and fifth treatment cycles.*

*End of treatment: PET/*CT.

Follow-up:

- *1st year: Axial abdominal CT scan and pelvic thoracic CT, cervical if clinically indicated (every 3 months),*
- *2nd year: abdominal and pelvic thoracic CT, cervical if clinically indicated (every 6 months),*
- *3rd-5th year: abdominal and pelvic thoracic CT scan, cervical if clinically indicated ()annually.*
- *All the information of the PET project can be found in Annex 4 of the protocol.*

(6) Bone marrow biopsy to confirm CR if the bone marrow was previously infiltrated.

(7) See Annex 3 for biological samples

(8) All the tests that were initially altered by the presence of lymphoma will be repeated.

9.6. DATA QUALITY ASSURANCE

Central reviewing of the anatomopathological diagnosis was performed as an additional quality assurance (QA) procedure for the most critical eligibility criteria of the clinical trial. Locally anatomopathological diagnosis was accepted for patient inclusion to prevent a delay in treatment initiation; however, patients for whom the anatomopathological diagnosis could not be confirmed upon central reviewing (but who were locally assessed as DLBCL) were systematically excluded following the recommendations to initiate other treatments.

To ensure the feasibility of performing all determinations on the tumour tissue samples, the quality of tumour tissue samples was systematically reviewed by the central laboratory in Hospital Universitario Marqués de Valdecilla. Patients with no suitable tumour samples maintained their participation in the clinical.

For QA of the data, all members of the trial were required to be trained in GCP, clinical trial legislation, pathology, and protocol-related issues. Data quality control procedures included the need for the CRA to confirm that the data were handled appropriately by the investigator staff and that trial documentation (management templates, spreadsheets, eCRF, and sample handling), both at the beginning of the trial and when changes in the team were introduced, was properly handled.

For this trial, 4 procedures for data QA were set in place:

1. Training of CRAs in pathology: performed by the Clinical Trial Project Manager (CTPM) using the training materials available from the CRO and other materials provided by the sponsor. Several meetings took place between the coordinating investigator and CRO staff during the trial.
2. Training of CRAs in study procedures: performed by the CTPM through training materials available from the CRO and the study protocol.
3. Training of research teams: Training of site staff was maintained throughout the study, and training to staff was provided whenever the need was identified by the study monitor and was mandatory at the following times:
    a. Site initiation visits (SIVs): SIV is the first exposure of the site team to the study. During these visits, the most important aspects of the trial were presented using a deck of slides previously validated by the trial coordinating investigator. The presentation included the justification of the project, the objectives, eligibility criteria, study procedures, reference to ICH-GCP (informed consent procedure, inclusions, pharmacovigilance, and protocol deviations management), drug management, the identification of CRAs, and all relevant issues.
    b. Routine monitoring visits: Follow-up monitoring visits are vital because they allow CRAs to maintain contact with the site staff and to verify adherence to the protocol, ICH-GCP, and site regulations. Therefore, whenever necessary, CRAs provided training to the study team at the site; training was mandatory when there were changes in the members of the research team, in cases of substantial amendments to the protocol,

patient information sheet, or study procedures, and in case of major protocol deviations. The source data validation of critical variables was performed according to the monitoring plan agreed to with the sponsor.

4. Protocol, study documents, consultation, and data management
    a. Protocol: The protocol was developed from the protocol synopsis approved by the study partner using the template provided by the AEMPS and after several reviewing and validation steps by the sponsor, the biostatistician, coordinating investigators, and the coordinating team. Once the protocol was approved by the sponsor, it was submitted along with other documentation to the EC and AEMPS for evaluation. The protocol and/or synopsis was distributed to the sites to confirm their participation. Once the study was approved, trial documentation was distributed to the sites. Any comments or queries received by the CRA were recorded in the QA log, available on the study trial master file (TMF). Recording of this feedback is critical because it could identify points of improvement in the protocol and issues that could lead to protocol amendments.
    b. Study documents: Includes study forms, the TMF, investigator site file (ISF) model report, etc. All improvements proposed by the teams were evaluated and implemented if necessary.
    c. Inquiries: Any comments, questions, answers, and details of the concerned managing person were recorded in the QA log. This system is very effective to ensure uniformity of approach when addressing issues from the centre as requested.
    d. Data management: The preparation of the CRF included a review by the coordinating investigator and study statistician to confirm that the variables to collected and the methods of collection were suitable for the study. The reviewing of the CRF and guidelines for finalising the CRF were explained at the SIV.
    e. Source data verification: Study data were collected by investigator and staff using eCRFs that were reviewed during monitoring visits. CRAs reviewed data collected in eCRFs and their consistency with the source data.

The source data were defined according to GCP as “all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial”.

Source documents were defined according to GCP as “original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-ray images, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)”.

Source documentation is the medical record of the subject before, during, and after the trial. It confirms the eligibility criteria of the subject in the given trial. It documents the

progress of the subject from consenting until the subject completes the study. It records the accountability of the investigational product dispensed, consumed, and returned by the subject. It serves as the complete medical record of the subject with reference to the treating physician at any point in time.

Finally, it forms a strong foundation for the data that get transcribed into a CRF, which ultimately gets translated into a clinical study report (CSR).

The monitoring plan included SIVs, 4 regular monitoring visit (RMV), and close-out visits (COVs) During RMVs, CRAs reviewed the source data (Table 6) in those sites with a high number of patients (more than 3 patients).A risk-based approach was used to select patients to be reviewed (patients that experienced an SAE, had protocol deviation, or had pending issues). Patients were also randomly selected from sites according to the same risk-based approach.

Table 6. Source Data Verification schedule

Form	Variables
Baseline	Date of birth, ICF, ECOG, aIPI, diagnosis date, staging, CD20 status, histological subtype, LDH, -beta-2 microglobulin, haemoglobin, platelets, and neutrophils
AEs	Grade and need of SAE communication
PET/CT	All variables: date, central review, and local review
Cycles	Start date, treatment given, and number of cycles
End of treatment	End date and reason EoT, disease evaluation
Overall survival	Date and reason, disease evaluation
Follow-up	Date, patient status, and disease evaluation
Follow-up overall survival	Date and patient status
Death	Date of death and reason

Abbreviations: ICF, informed consent form; ECOG, Eastern Cooperative Oncology Group; aIPI, age-adjusted International Prognostic Index; LDH, lactate dehydrogenase; SAE, serious adverse event; EoT, end-of-treatment

If all the aforementioned variables were reviewed by the CRA for all patients included in the site, then dose modifications and minor toxicities were also reviewed.
Data cleaning: All inconsistent data were queried to the site, and all responses were answered by the site in writing; the corresponding fields in the eCRFs were amended, and new data were collected in the database. All changes were tracked in the corresponding audit trail of the eCRF.

9.7. STATISTICAL METHODS PLANNED IN THE PROTOCOL & DETERMINATION OF SAMPLE SIZE

9.7.1. STATISTICAL AND ANALYTICAL PLANS

Primary Endpoint:
Proportion of patients with EFS at 2 years.

Secondary endpoints:

- EFS at 2 years
- OS at 2 years
- Complete remission rate
- Complete remission rate not documented/not confirmed
- Partial remission rate
- Stable disease rate or progression of disease rate.
- Relapsed disease rate
- Proportion of subjects who received all planned chemotherapy doses on schedule
- Proportion of cycles of chemotherapy administered in planned doses and on schedule
- Clinical predictive factors for response
- Safety endpoints from cycle 1-6
- Prognostic value of PET in terms of survival
- Biological prognostic factors, including histologic subtype GCB vs. non-GCB

Statistical considerations

The analysis was done by intention to treat (ITT). The population consisted of patients who met the criteria of selection and were exposed to at least 1 treatment cycle, regardless of the presence of deviations to the protocol or the patient's withdrawal from the study. The main variable of the study was the proportion of live and event-free patients (EFS) at 2 years.

- EXPLORATORY ANALYSIS All the variables were described graphically using the following tools: for categorical variables frequency tables with sector diagrams. For numerical variables trends, standard deviations, standard error, mean, median and limits. Each variable was represented in a box-plot graphic. A bivariate analysis was carried out with the main factors: age, GCB vs. no-GCB, ECOG, and aIPI between the experimental treatment arm and the control arm to verify that these factors did not produce confusion about the main objective.

- PRIMARY OBJECTIVE: A 1-tailed binomial test was performed to assess whether the bortezomib-RCAP regimen was superior to the control. If the p-value associated with the test was below 0.25, we considered the test to be positive, and we declared the combination to be effective.

- SECONDARY OBJECTIVE: A logistic regression analysis was performed to identify significant factors that can influence the EFS at 2 years. The influence of the subtype was studied histologically as a relevant factor in EFS at 2 years.

- SURVIVAL ASSESSMENTS
    - 2-year EFS: defined as the rate of patients who were alive with CR from the date of randomisation until 2 years after that date.
    - EFS: defined as the time that elapsed between the moment of randomisation and the first documented recurrence, progression, or death in the case of no documented recurrence, or the start of a new anti-lymphoma treatment due to refractory or persistent disease. In the EFS analysis, the subjects to whom the treatment was discontinued due to AEs or other reasons were censored at the time that the tumour was evaluated for the last time.
    - OS: defined as the time between randomisation and death from any cause. In cases where patients withdrew from the trial or were lost to follow-up, they were censored at the date of the last contact. Patients who were still alive at the end of the study were censored at that time.

- TOXICITY ASSESSMENTS: Toxicities that appeared in the treatment phase were classified in this report according to the NCI-CTCAE.

STATISTICAL METHODS

- Hypothesis testing for descriptive analyses was performed using the independent t-test for comparisons between the arms of treatment in continuous variables or the Mann-Whitney U test when the variables did not display a normal distribution (assessed using the Kolmogorov-Smirnov test or the Shapiro-Wilk test). The chi-square test or, when appropriate, Fisher's exact test was used in the case of comparisons involving qualitative variables.
- Logistic regression analysis (factors that could influence the EFS at 2 years): Firstly, a univariate analysis was carried out separately for each of the possible explicative variables to decide which variables were to be entered in the multivariate models; only those with a statistical association with the dependent variable were selected. A stepwise backward elimination process was used to select the model. In the first step, all possible predictors were entered in the model, and in each step, the variable that was least significant (that is, the one with the largest p-value) was removed, and the model was refitted. Each subsequent step removed the least significant variable in the model until all remaining variables had individual p-values smaller than 0.05.
- For patients without a date of follow-up, the latest of the following was used as the end of follow-up: the date of the "end of treatment", or the date of the last PET.
- For both time-to-relapse and survival, there was no censoring for reasons other than the administrative end of follow-up.
- Progression was extracted from PET2, -4, and-6 (central review) and follow-up visits in variables sg_val_respt_e8_1_c10, sg_val_respt_e8_2_c10, sg_val_respt_e8_3_c10, sg_val_respt_e8_4_c10, sg_val_respt_e8_5_c10,

sg_val_respt_e8_6_c10, sg_val_respt_e8_7_c10, sg_val_respt_e8_7_c10.

- EFS was defined (following protocol) as the time from randomizations to relapse, progression, start of second line, or death, whichever is earlier.
- OS was defined as the time from randomisation to death.
- Agreement between variables was assessed using the kappa agreement coefficient, interpreted as shown in Table 7 (Altman, 1991):

Table 7. Assessment of agreement using kappa

Value of κ	Strength of agreement
<0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

Altman DG. (1991) Practical statistics for medical research. London: Chapman and Hall.

9.7.2. DETERMINATION OF SAMPLE SIZE

The main objective was to compare the efficacy between R-CHOP and bortezomib-RCAP in terms of EFS at 2 years (previously defined). An event was defined as relapse, progression, the need for a new antineoplastic treatment, or death from any cause at 2 years.
Using the binomial test of 2 proportions and a tail, if the null hypothesis in the R-CHOP arm is 55%, and we expected it to be 70% in the bortezomib-RCAP arm, and assuming an alpha error of 0.25 (decides to favour the experimental arm if the null hypothesis is true) and a beta error of 0.20 (decides in favour of the null hypothesis if the alternative hypothesis is true), it was necessary to include 120 patients. If a 5% loss of patients was assumed, the number to be included was 127 patients (50% in each treatment arm).

9.8. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.8.1. PROTOCOL AMENDMENTS

The initially approved protocol version was version 2.0 (15 Feb 2013); amendments to this version were made throughout the study as detailed below:

1. Amendment 1: Version 2.0 (15 Feb 2013) was amended to version 3.0 (7 Jan 2014). The following modifications were made:

- Section 0 (General information):

- The information referring to the time foreseen to reach the sample number of patients was updated.
- It was clarified that the baseline analysis should be performed within a week prior to the start of treatment.
- The information was standardized, stating that during the basal phase a pregnancy test should be performed.
- The information standardized was to record that the biochemistry performed prior to the beginning of each cycle should include values for LDH and beta2--microglobulin.
- It was specified that if the centralized review could not confirm the anatomopathological diagnosis, the patient should abandon the protocol.

- Section 2.3 (Protocol medication):
  - The information was standardized to record that it was recommended to perform antiviral prophylaxis for those patients who were Anti-HBc-positive.

- Section 2.5.1 (Conditions to start a new cycle of treatment and modification of CHOP doses):
  - It was specified that patients should withdraw from the protocol if they could not receive study treatment for a period of 3 consecutive weeks.

- Section 2.6 (Concomitant treatments):
  - The information was standardized to record that concomitant treatments should be collected from 7 days before starting the treatment until 30 days after the last treatment.

- Section 3 (Patient selection):
  - The information referring to the time foreseen to reach the sample number of patients was updated.

- Section 3.2 (Exclusion criteria):
  - Exclusion criteria no. 15 and no. 16 were eliminated to avoid duplication with exclusion criteria no. 9 and no. 10.

- Section 3.3 (Withdrawal criteria):
  - The information was standardized to record that patients with a complete absence of response according to PET evaluation after the 6th cycle of treatment, should withdraw from the trial.

- Section 4.2.1 (Pre-treatment study tests):
  - The information was standardized, including the pregnancy test as a test to be performed at baseline.
  - The information was standardized to record that the biochemistry performed prior to the beginning of each cycle should include values for LDH and beta2--microglobulin.

- Section 4.5 (Scheme of procedures):

- Information was standardized, including the pregnancy test as a test to be performed at baseline.
- It was clarified that the visit at the end of the treatment should be made 60 days after completing the cycle.
- It was clarified that the baseline analysis should be performed within a week prior to the start of treatment.

- Section 5.3 (Qualification of an adverse event):
  - Two exceptions were included for the 24h-hour expedited notification of Serious Adverse Events (SAE s) for this trial.

- Annex 2 (Patient Information sheet and Informed Consent):
  - It was clarified that if the centralized review did not confirm the anatomopathological diagnosis, the patient should abandon the protocol - Annex 3 (Biological project).
  - It was specified that in extraordinary situations, a second extraction of a peripheral blood sample may be necessary.
  - Dr. Miguel Alcoceba was included as a collaborator for the biological project at the University Hospital of Salamanca - Annex 6 (Patient information sheet for the collection of biological samples and their use in biological studies in the context of a clinical trial),

2. For this trial, 2 additional substantial amendments were performed:
   - On 16 Apr 2015, to notify a labelling modification of the investigational medical product.
   - On 21 June 2018, a change of PI at site H. Marques de Valdecilla took place.

10. STUDY POPULATION

10.1. DISPOSITION OF PATIENTS

Figure 2. Patient disposition

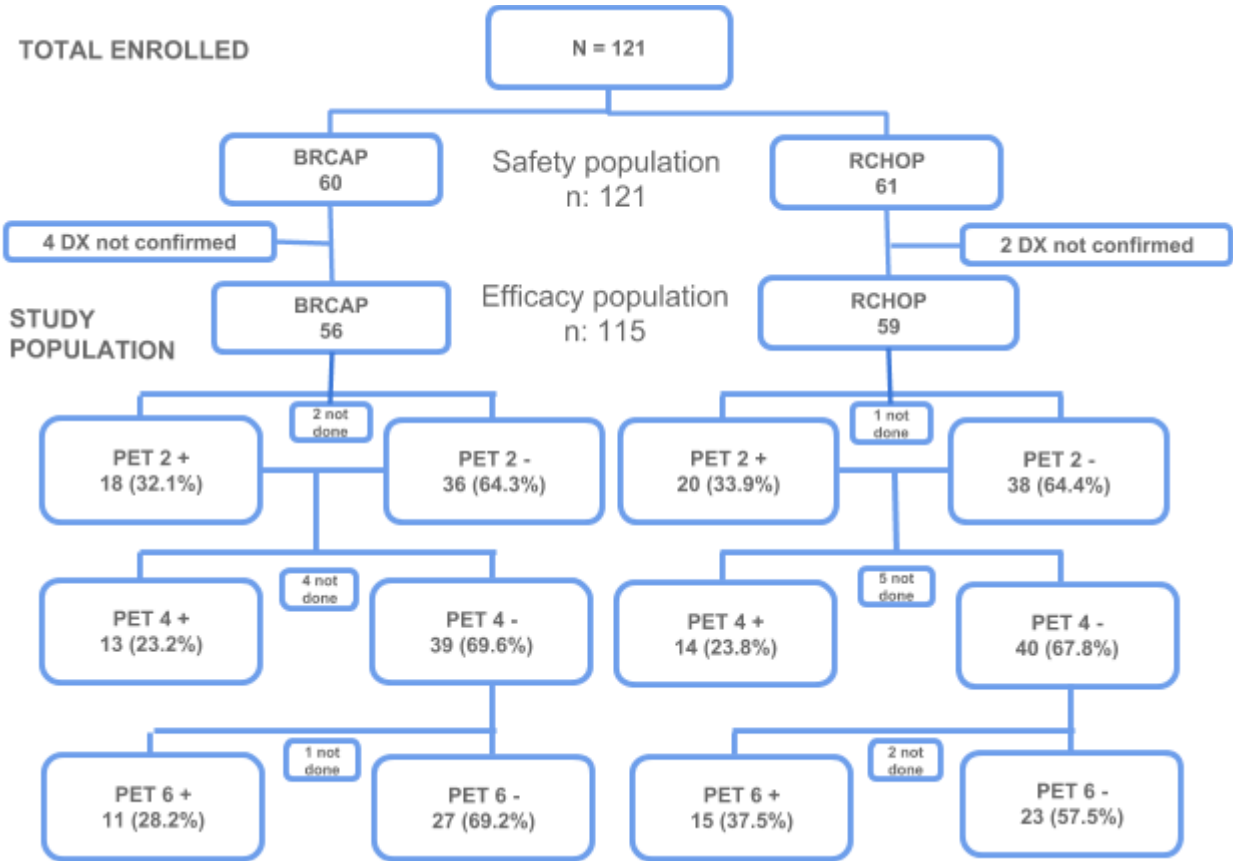


Table 8. Eligible patients by arm and hospital

	Experimental	Control	Total
	N (%)	N (%)	N (%)
ICO-L'HOSPITALET (ICOH)	10 (17.9)	15 (25.4)	25 (21.7)
C.H.U. DE VIGO (CHUVI)	1 (1.8)	2 (3.4)	3 (2.6)
CIOCC	0 (0.0)	5 (8.5)	5 (4.3)
H. 12 DE OCTUBRE (H12O)	6 (10.7)	6 (10.2)	12 (10.4)
H. CENTRAL DE ASTURIAS (HCA)	4 (7.1)	2 (3.4)	6 (5.2)
H. CLINIC DE BARCELONA (HCB)	1 (1.8)	2 (3.4)	3 (2.6)
H. INFANTA LEONOR (HIL)	1 (1.8)	2 (3.4)	3 (2.6)

H. DE JEREZ (HJF)	2 (3.6)	0 (0.0)	2 (1.7)
H. LOZANO BLESA (HLB)	2 (3.6)	1 (1.7)	3 (2.6)
H. LA FE (HLF)	1 (1.8)	0 (0.0)	1 (0.9)
H. MARQUES DE VALDECILLA (HMV)	1 (1.8)	1 (1.7)	2 (1.7)
H. RAMON Y CAJAL (HRYC)	1 (1.8)	3 (5.1)	4 (3.5)
H. SON LLATZER (HSLL)	1 (1.8)	1 (1.7)	2 (1.7)
H. U. CANARIAS (HUC)	5 (8.9)	0 (0.0)	5 (4.3)
H. U. F. ALCORCON (HUFA)	2 (3.6)	1 (1.7)	3 (2.6)
H. U. LA PAZ (HULP)	2 (3.6)	0 (0.0)	2 (1.7)
H. U. SALAMANCA (HUS)	5 (8.9)	5 (8.5)	10 (8.7)
H. VIRGEN DEL ROCIO (HVR)	6 (10.7)	9 (15.3)	15 (13.0)
ICO BADALONA (ICOB)	2 (3.6)	2 (3.4)	4 (3.5)
ICO GIRONA (ICOG)	3 (5.4)	2 (3.4)	5 (4.3)
Total	56 (100.0)	59 (100.0)	115 (100.0)

Table 9. Reasons for ineligibility

	Study subject ID	Hospital	Reason for ineligibility
1	02-008	HUS	Diagnostic: DLBCL + FL 3A
2	23-004	CHUV	Diagnostic: DLBCL with PMBL + CHL
3	15-002	HLF	Diagnostic: Follicular Lymphoma B - 3A
4	20-003	HLB	Diagnostic: Follicular Lymphoma B low grade
5	22-004	ICOG	Diagnostic: MZL
6	11-001	CIOCC	Diagnostic: NLPHL

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CHL, classical Hodgkin Lymphoma; PMBL, Primary mediastinal B-cell lymphoma; MZL, marginal zone lymphoma; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma.

There were 9 patients who were considered eligible and were included in the study; however, their sample were not available for centralized review (Table 10).

Table 10. Eligible patients without sample for centralized review

	Study Subject ID	Hospital	Reason for ineligibility
1	05-002	HCB	Without sample for centralized review.
2	05-003	HCB	Without sample for centralized review

3	07-003	H12O	Without sample for centralized review The sample received after the initial study is compatible with infiltration by lymphoma B.
4	07-006	H12O	Without sample for centralized review
5	08-002	HRYC	Without sample for centralized review
6	09-002	HULP	Without sample for centralized review
7	13-005	HVR	Without sample for centralized review
8	13-007	HVR	Without sample for centralized review
9	18-002	HCA	Without sample for centralized review

A total of 133 patients signed the ICF for participating in the trial; 12 failed the screening and were not enrolled.

The disposition of enrolled patients is detailed in table 11, randomization was 1:1, and the accrual of the trial ended by the time pre-specified in the protocol (24 months after the first inclusion). During that time, 121 patients out of 127 (initially planned) were enrolled as 120 cases needed to be recruited in this study, therefore, the accrual was finalized.

Patient disposition was well balanced with an almost equal distribution between the control vs. the experimental arm (60 vs. 61), all 121 patients initiated study treatment and were considered for safety analysis. However, after central reviewing of diagnosis, 6 patients were excluded (2 (3.3%) in the control arm and 4 (6.7%) in the experimental arm). Thus, 115 patients were considered for efficacy analysis in the ITT population (defined as patients who fulfilled the inclusion criteria and received at least 1 dose of the study treatment); no differences were found between study arms in the proportion of ineligible patients (p=0.439).

At the database cut-off, all eligible patients (n=115) had completed their participation in the trial, either because they had completed the follow-up of 2 years indicated in the protocol, or any of the events indicating the end of the study were present (death, loss of follow-up, or withdrawal of informed consent). It is relevant to mention that the number of deaths in the control arm was higher than in the experimental arm (20 vs. 13). In addition, 18 patients reached the 2 years of follow-up in the control arm, while 21 did in the experimental arm, indicating a trend in favour of the experimental arm.

Table 11. Disposition of patients

	Control Arm	Experimental Arm	Total
Patients enrolled	61	60	121
Received at least one cycle of study treatment	61	60	121
Evaluable patients	59	56	115
End of study (evaluable population)	59	56	115

Death	20	13	33
Lost to follow-up	3	0	3
Study completion (24 months of follow-up)	35	43	77
Withdraw informed consent	1	0	1

10.2. PROTOCOL DEVIATIONS

Table 12 specifies details of deviations from the study protocol by type and frequency of findings.

All protocol deviations were discussed with sites, codified, and escalated to Trial Coordinators with the corresponding associated information and severity assessment; when applicable, protocol deviation was reported to the competent authority (CA) according to current regulation, and corrective and preventive actions (CAPA) was applied in each instance.

Table 12. Protocol deviations

Deviation type	***Total***
Procedures	172
Efficacy criteria	70
Informed consent form	44*
Safety	30
Eligibility criteria	19
Other	5

**All findings with informed consents were managed and notified according to the current legal regulations.*

The most repeated findings were associated with incomplete completion concerning for consent of biological samples (17 opportunities), re-consent using updated versions of the ICF (9 incidents detected), 9 incidents were recorded related to incomplete completion of the ICF fields (patient/investigator data, etc.), 3 patients signed obsolete versions of the ICF, in 4 cases the co-investigator was not included in the signature and delegation list and a non spanish speaker patient signed an informed consent that he could not understand but he got a translation by a/n (profesional) interpreter. Full details of the protocol deviations can be found in Appendix 15.1.10.

11. EFFICACY EVALUATION

11.1. DATA SETS ANALYSED

The analysis was carried out by ITT analysis (n=115). The population analysed was composed of those patients who met the selection criteria and were exposed to at least 1 treatment cycle, regardless of the presence of deviations from the protocol or their withdrawal from the study.

All patients fulfilling the eligibility criteria (115 patients) were included in the study database. Hundred twenty-one patients received at least 1 dose of treatment and were considered for safety analysis; 6 patients were declared as non-eligible and were excluded from efficacy analyses.

11.2. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 13 shows the demographics of the patients participating in the trial.

In the comparison between the arms of the baseline characteristics, the distribution by gender, age, PS, and aIPI (among others) was balanced between both treatment arms; only nodal affectation statistical significant differences between the study arms: in the experimental arm, 52 patients (92.9%) had nodal affectation vs. 44 patients (74.6%) in the control arm (p=0.012).

Table 13. Demographics of study patients (I)

		Experimental (n=56)	Control (n=59)	Total	p-value
		N (%)	N (%)	N (%)	
Gender	**Male**	27 (48.2)	30 (50.8)	57 (49.6)	*0.778 (1)*
	Female	29 (51.8)	29 (49.2)	58 (50.4)	
Performance Status ECOG	**0-1**	36 (64.3)	41 (69.5)	77 (67.0)	*0.553 (1)*
	≥2	20 (35.7)	18 (30.5)	38 (33.0)	
Age >60 years	**<60 years**	32 (57.1)	26 (44.1)	58 (50.4)	*0.161 (1)*
	≥60 years	24 (42.9)	33 (55.9)	57 (49.6)	
Adenopathies	**Yes**	35 (62.5)	37 (62.7)	72 (62.6)	*0.981 (1)*
	No	21 (37.5)	22 (37.3)	43 (37.4)	
Hepatomegaly	**Yes**	4 (7.1)	6 (10.2)	10 (8.7)	*0.743 (2)*
	No	51 (91.1)	52 (88.1)	103 (89.6)	
	ND	0 (0.0)	1 (1.7)	1 (0.9)	
	UK	1 (1.8)	0 (0.0)	1 (0.9)	
Splenomegaly	**Yes**	8 (14.3)	13 (22.0)	21 (18.3)	*0.451 (2)*

	No	44 (78.6)	45 (76.3)	89 (77.4)	
	NA	1 (1.8)	0 (0.0)	1 (0.9)	
	ND	1 (1.8)	1 (1.7)	2 (1.7)	
	UK	2 (3.6)	0 (0.0)	2 (1.7)	
Lymphomas Other	**Yes**	15 (26.8)	20 (33.9)	35 (30.4)	*0.480 (2)*
	No	40 (71.4)	39 (66.1)	79 (68.7)	
	ND	1 (1.8)	0 (0.0)	1 (0.9)	
Histological Subtype (Baseline)	**GCB**	46 (82.1)	51 (86.4)	97 (84.3)	*0.839 (2)*
	No GCB	8 (14.3)	7 (11.9)	15 (13.0)	
	ND	1 (1.8)	1 (1.7)	2 (1.7)	
	UK	1 (1.8)	0 (0.0)	1 (0.9)	
CD20 expression	**Yes**	56 (100.0)	59 (100.0)	115 (100.0)	---
Bone marrow infiltration	**Positive**	13 (23.2)	10 (16.9)	23 (20.0)	*0.452 (2)*
	Negative	39 (69.6)	47 (79.7)	86 (74.8)	
	ND	4 (7.1)	2 (3.4)	6 (5.2)	
Clinical Stage	**I**	1 (1.8)	0 (0.0)	1 (0.9)	*0.228 (2)*
	II	5 (8.9)	1 (1.7)	6 (5.2)	
	III	14 (25.0)	17 (28.8)	31 (27.0)	
	IV	36 (64.3)	41 (69.5)	77 (67.0)	
Extranodal Affectation	**Yes**	42 (75.0)	45 (76.3)	87 (75.7)	*0.874 (1)*
	No	14 (25.0)	14 (23.7)	28 (24.3)	
Extranodal Affectation Number	**1**	13 (31.0)	12 (26.7)	25 (28.7)	*0.659 (1)*
	2 or more	29 (69.0)	33 (73.3)	62 (71.3)	
	Total	42 (100.0)	45 (100.0)	87 (100.0)	
Nodal Affectation	**Yes**	52 (92.9)	44 (74.6)	96 (83.5)	*0.012 (2)*
	No	3 (5.4)	13 (22.0)	16 (13.9)	
	ND	1 (1.8)	2 (3.4)	3 (2.6)	
aIPI	**1-2 (Low medium-High medium score)**	41 (73.2)	46 (78.0)	87 (75.7)	*0.553 (1)*
	3 (High score)	15 (26.8)	13 (22.0)	28 (24.3)	
Symptoms B	**Yes**	25 (44.6)	21 (35.6)	46 (40.0)	*0.395 (2)*
	No	31 (55.4)	37 (62.7)	68 (59.1)	
	ND	0 (0.0)	1 (1.7)	1 (0.9)	
High LDH	**Yes**	48 (87.3)	45 (77.6)	93 (82.3)	*0.178 (1)*
	No	7 (12.7)	13 (22.4)	20 (17.7)	
	Total	55 (100.0)	58 (100.0)	113 (100.0)	
High B2-micro	**Yes**	33 (70.2)	38 (73.1)	71 (71.7)	*0.752 (1)*
	No	14 (29.8)	14 (26.9)	28 (28.3)	
	Total	47 (100.0)	52 (100.0)	99 (100.0)	
Antibodies HIV	**Negative**	56 (100.0)	57 (96.6)	113 (98.3)	*0.496 (2)*

	ND	0 (0.0)	2 (3.4)	2 (1.7)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
HbsAg	**Negative**	56 (100.0)	58 (98.3)	114 (99.1)	*1.000 (2)*
	ND	0 (0.0)	1 (1.7)	1 (0.9)	
Hepatitis C	**Negative**	56 (100.0)	58 (98.3)	114 (99.1)	*1.000 (2)*
	ND	0 (0.0)	1 (1.7)	1 (0.9)	
Prephase (Cycle 1 - D1)	**Yes**	16 (28.6)	16 (27.1)	32 (27.8)	*1.000 (1)*
	No	35 (62.5)	38 (64.4)	73 (63.5)	
	UK	5 (8.9)	5 (8.5)	10 (8.7)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; aIPI, age-adjusted International Prognostic Index; LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; HbsAg, hepatitis B surface antigen. ND: Not Determined. 1: Chi-square test; 2: Fisher's exact test

Table 14. Demographics of study patients (II)

	Experimental			**Control**			**Total**			**p-value**
	N	**Mean (SD)**	**Median (min-Max)**	**N**	**Mean (SD)**	**Median (min-Max)**	**N**	**Mean (SD)**	**Median (min-Max)**	
Age (years)	56	56.2 (10.0)	58.1 (28.9-71.0)	59	58.3 (11.0)	60.8 (23.9-71.0)	115	57.3 (10.6)	59.8 (23.9-71.0)	*0.166 (2)*
Nodal Affectation Number	52	7.0 (5.8)	5.0 (1.0-26.0)	43	6.7 (4.6)	6.0 (1.0-18.0)	95	6.8 (5.3)	5.0 (1.0-26.0)	*0.851 (2)*
Leukocytes Value	56	8.5 (4.2)	7.9 (1.0-20.9)	59	7.8 (3.4)	7.4 (2.4-16.7)	115	8.1 (3.8)	7.6 (1.0-20.9)	*0.310 (1)*
Lymphocytes Value	56	1.6 (1.1)	1.3 (0.2-5.0)	59	1.3 (0.9)	1.1 (0.1-5.3)	115	1.4 (1.0)	1.1 (0.1-5.3)	*0.146 (2)*
Haemoglobin Value	56	116.6 (20.7)	118.5 (70.0-156.0)	59	116.2 (23.6)	116.0 (12.2-161.0)	115	116.4 (22.2)	117.0 (12.2-161.0)	*0.926 (1)*
Platelets Value	56	295.7 (144.5)	254.0 (37.0-680.0)	59	333.7 (224.9)	259.0 (111.0-1574.0)	115	315.2 (190.2)	259.0 (37.0-1574.0)	*0.576 (2)*
LDH Value	56	532.0 (410.2)	366 (142.0-2467.1)	59	453.6 (267.1)	388 (125.7-1298.0)	115	491.8 (345.0)	383.2 (125.7-2467.1)	*0.432 (2)*

Abbreviations: SD, standard deviation; LDH, lactate dehydrogenase. 1: t-test for independent samples; 2: Mann-Whitney U test

11.3. CENTRAL REVIEW OF DISEASE DIAGNOSTICS

No statistically significant differences were found between the study arms concerning the variables defining central review for disease diagnosis (Table 15).

Table 15. Central review of disease diagnostics (I)

		Experimental	Control	Total	p-value
		N (%)	N (%)	N (%)	
Confirmed diagnosis	**Yes**	53 (94.6)	53 (89.8)	106 (92.2)	*0.491 (2)*
	UK	3 (5.4)	6 (10.2)	9 (7.8)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
Definitive centralized diagnosis	**DLBCL**	48 (85.7)	48 (81.4)	96 (83.5)	*0.780 (2)*
	DLBCL +FL 3B	1 (1.8)	0 (0.0)	1 (0.9)	
	BL rich in cells T and histiocytes	1 (1.8)	3 (5.1)	4 (3.5)	
	LF 3B	2 (3.6)	0 (0.0)	2 (1.7)	
	BL mediastinum	1 (1.8)	1 (1.7)	2 (1.7)	
	PMBL	0 (0.0)	1 (1.7)	1 (0.9)	
	No (tumoral necrosis CD20)	0 (0.0)	1 (1.7)	1 (0.9)	
	No tissue sample available	2 (3.6)	3 (5.1)	5 (4.3)	
	Unknown/Diagnosis not confirmed	1 (1.8)	2 (3.4)	3 (2.6)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
Phenotype GCB-ABC	**GCB**	30 (53.6)	36 (61.0)	66 (57.4)	*0.501 (2)*
	NO-GCB	22 (39.3)	16 (27.1)	38 (33.0)	
	NA (no sample available for centralized review)	3 (5.4)	6 (10.2)	9 (7.8)	
	UK	1 (1.8)	1 (1.7)	2 (1.7)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
MYD88L265P	**Wild-type (WT)**	9 (16.1)	6 (10.2)	15 (13.0)	*0.491 (2)*
	NA (no sample available for centralized review)	3 (5.4)	6 (10.2)	9 (7.8)	
	UK	44 (78.6)	47 (79.7)	91 (79.1)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
MYC IHC %	**0**	3 (5.4)	3 (5.1)	6 (5.2)	*0.969 (2)*
	<5	2 (3.6)	2 (3.4)	4 (3.5)	
	10	3 (5.4)	3 (5.1)	6 (5.2)	
	20	5 (8.9)	5 (8.5)	10 (8.7)	
	30	4 (7.1)	6 (10.2)	10 (8.7)	
	40	7 (12.5)	11 (18.6)	18 (15.7)	
	50	5 (8.9)	2 (3.4)	7 (6.1)	
	60	8 (14.3)	6 (10.2)	14 (12.2)	

	70	3 (5.4)	4 (6.8)	7 (6.1)	
	80	3 (5.4)	4 (6.8)	7 (6.1)	
	90	3 (5.4)	1 (1.7)	4 (3.5)	
	100	2 (3.6)	1 (1.7)	3 (2.6)	
	UK	8 (14.3)	11 (18.6)	19 (16.5)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
BCL2 IHC %	**0**	6 (10.7)	4 (6.8)	10 (8.7)	*0.053 (2)*
	<5	0 (0.0)	2 (3.4)	2 (1.7)	
	10	1 (1.8)	4 (6.8)	5 (4.3)	
	20	2 (3.6)	4 (6.8)	6 (5.2)	
	30	0 (0.0)	1 (1.7)	1 (0.9)	
	40	1 (1.8)	0 (0.0)	1 (0.9)	
	50	9 (16.1)	5 (8.5)	14 (12.2)	
	60	4 (7.1)	2 (3.4)	6 (5.2)	
	70	5 (8.9)	0 (0.0)	5 (4.3)	
	80	8 (14.3)	7 (11.9)	15 (13.0)	
	90	4 (7.1)	13 (22.0)	17 (14.8)	
	100	9 (16.1)	6 (10.2)	15 (13.0)	
	UK	7 (12.5)	11 (18.6)	18 (15.7)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
C-MYC (≥40%) and BCL2 (≥50%) IHC	**Yes**	29 (51.8)	21 (35.6)	50 (43.5)	*0.181 (1)*
	No	19 (33.9)	24 (40.7)	43 (37.4)	
	UK	8 (14.3)	14 (23.7)	22 (19.1)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
CD30 IHC %	**0**	28 (50.0)	23 (39.0)	51 (44.3)	*0.335 (2)*
	<5	5 (8.9)	13 (22.0)	18 (15.7)	
	10	2 (3.6)	0 (0.0)	2 (1.7)	
	20	5 (8.9)	3 (5.1)	8 (7.0)	
	30	2 (3.6)	2 (3.4)	4 (3.5)	
	40	1 (1.8)	0 (0.0)	1 (0.9)	
	50	3 (5.4)	1 (1.7)	4 (3.5)	
	60	1 (1.8)	2 (3.4)	3 (2.6)	
	80	2 (3.6)	2 (3.4)	4 (3.5)	
	90	0 (0.0)	1 (1.7)	1 (0.9)	
	UK	7 (12.5)	12 (20.3)	19 (16.5)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
CD30 (≥20%)	**Yes**	14 (25.0)	11 (18.6)	25 (21.7)	*0.297 (2)*
	No	34 (60.7)	33 (55.9)	67 (58.3)	
	UK	8 (14.3)	15 (25.4)	23 (20.0)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
FISH CMY	**Normal**	24 (42.9)	27 (45.8)	51 (44.3)	*0.829 (2)*

	Rearranged (translocation)	5 (8.9)	3 (5.1)	8 (7.0)	
	No hybridization	2 (3.6)	1 (1.7)	3 (2.6)	
	Gain/Amplification	1 (1.8)	2 (3.4)	3 (2.6)	
	Gain/Amplification and Rearranged (translocation)	1 (1.8)	0 (0.0)	1 (0.9)	
	Not evaluable/No tissue/UK	23 (41.1)	26 (44.1)	49 (42.6)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
FISH BCL2	**Normal**	27 (48.2)	25 (42.4)	52 (45.2)	
	Rearranged (translocation)	8 (14.3)	5 (8.5)	13 (11.3)	
	No hybridization	0 (0.0)	1 (1.7)	1 (0.9)	*0.661 (2)*
	Gain/Amplification	1 (1.8)	1 (1.7)	2 (1.7)	
	Not evaluable/No tissue/UK	20 (35.7)	27 (45.8)	47 (40.9)	
FISH BCL6	**Normal**	20 (35.7)	15 (25.4)	35 (30.4)	
	Rearranged (translocation)	10 (17.9)	12 (20.3)	22 (19.1)	
	No hybridization	2 (3.6)	1 (1.7)	3 (2.6)	
	Gain/Amplification and Rearranged (translocation)	1 (1.8)	0 (0.0)	1 (0.9)	*0.530 (2)*
	Not evaluable/No tissue/UK	23 (41.1)	31 (52.5)	54 (47.0)	

Abbreviations: UK, unknown; DLBCL, diffuse large B-cell lymphoma; FL 3B, follicular lymphoma 3B; BL, B lymphoma, ; PMBL, Primary mediastinal B-cell lymphoma; GCB, germinal centre B-cell; WT, wild type NA, not available; IHC, immunohistochemistry; MYC; BCL2,; FISH, fluorescent in situ hybridisation
1: Chi-square test; 2: Fisher's exact test

Table 16. Central review of disease diagnostics (II)

	Experimental			**Control**			**Total**			**p-value**
	N	**Mean (SD)**	**Median (min-Max)**	**N**	**Mean (SD)**	**Median (min-Max)**	**N**	**Mean (SD)**	**Median (min-Max)**	
MYC IHC %	48	45.6 (28.0)	45.0 (0.0-100.0)	48	41.9 (25.7)	40.0 (0.0-100.0)	96	43.8 (26.8)	40.0 (0.0-100.0)	*0.509 (2)*
BCL2 IHC %	49	61.8 (32.3)	70.0 (0.0-100.0)	48	59.6 (36.4)	80.0 (0.0-100.0)	97	60.7 (34.2)	70.0 (0.0-100.0)	*0.916 (2)*
CD30 IHC %	49	12.6 (21.4)	0.0 (0.0-80.0)	47	12.9 (23.8)	5.0 (0.0-90.0)	96	12.7 (22.5)	0.0 (0.0-90.0)	*0.725 (2)*

Abbreviations: SD, standard deviation; IHC, immunohistochemistry. 1: T-test for independent samples; 2: Mann-Whitney U test

Agreement between histological subtype diagnoses was measured using Cohen's' kappa, a statistic that measures the inter-rater agreement for categorical items by taking

into account the agreement may be occurring by chance. Note that 13 patients had any of these 2 variables missing. A variable was assessed using the kappa agreement Kappa coefficient (Table 17) (Altman, 1991):

Table 17. Assessment of agreement using kappa

Value of κ	Strength of agreement
B < 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

The agreement between hospital and centralized diagnoses was, “fair” with κ=0.231 (p=0.003) (Table 18).

Table 18. Agreement between external (hospital) and centralized diagnosis

		Centralized diagnosis				
		GCB	No GCB	Total	Measure of Agreement Kappa	p-value
		N (%)	N (%)	N (%)		
Hospital diagnosis (eCRF/external)	GCB	62 (60.8)	28 (27.5)	90 (88.2)	0.231	0.003
	NO-GCB	3 (2.9)	9 (8.8)	12 (11.8)		
	Total	65 (63.7)	37 (36.3)	102 (100.0)		

Abbreviations: GCB, germinal centre B-cell; eCRF, electronic case report form

For the patients described in Table 19 (n=31), no agreement was reported for their diagnosis.

Table 19. Patients without agreement in diagnosis

	ID	Hospital	Arm (Baseline)	Histological Subtype (Baseline)	Phenotype GCB-ABC
1	01-004	ICOH	Control	GCB	NO-GCB
2	01-008	ICOH	Control	GCB	NO-GCB
3	01-009	ICOH	Experimental	GCB	NO-GCB
4	01-010	ICOH	Control	GCB	NO-GCB
5	01-011	ICOH	Experimental	GCB	NO-GCB
6	01-012	ICOH	Control	GCB	NO-GCB
7	01-013	ICOH	Experimental	GCB	NO-GCB

8	01-021	ICOH	Control	GCB	NO-GCB
9	01-028	ICOH	Control	GCB	NO-GCB
10	02-007	HUS	Control	GCB	NO-GCB
11	02-009	HUS	Control	GCB	NO-GCB
12	02-010	HUS	Control	GCB	NO-GCB
13	04-003	ICOB	Experimental	GCB	NO-GCB
14	07-002	H12O	Experimental	GCB	NO-GCB
15	07-005	H12O	Experimental	GCB	NO-GCB
16	07-007	H12O	Experimental	GCB	NO-GCB
17	07-008	H12O	Experimental	GCB	NO-GCB
18	07-009	H12O	Control	GCB	NO-GCB
19	07-011	H12O	Experimental	GCB	NO-GCB
20	11-004	CIOCC	Control	GCB	NO-GCB
21	12-002	HIL	Control	No GCB	GCB
22	13-008	HVR	Experimental	GCB	NO-GCB
23	13-009	HVR	Experimental	GCB	NO-GCB
24	13-013	HVR	Control	GCB	NO-GCB
25	13-017	HVR	Experimental	No GCB	GCB
26	14-001	HJF	Experimental	GCB	NO-GCB
27	14-002	HJF	Experimental	GCB	NO-GCB
28	19-001	HSLL	Experimental	No GCB	GCB
29	20-001	HLB	Experimental	GCB	NO-GCB
30	21-002	HUC	Experimental	GCB	NO-GCB
31	23-002	CHUV	Experimental	GCB	NO-GCB

Abbreviation: GCB, germinal centre B-cell

11.4. MEASUREMENTS OF TREATMENT COMPLIANCE

Table 20 shows information regarding treatments received by patients. In general, treatment was well tolerated in evaluable patients in the trial after receiving at least 1 dose of study treatment (n=115).

The patients were randomized to receive RCHOP (n=59) vs. bortezomib-RCAP (n=56). The median number of bortezomib-R-CAP cycles was 6 (minimum - maximum: 1–6) cycles; it was the same for the median number of R-CHOP cycles.
These data show that both treatment distribution and duration were similar for BR-CAP and R-CHOP, reflecting that the combination is feasible (no additive toxicity was documented).

Treatment was completed (6 cycles) in 79 patients (39 experimental , 40 control). Of the 115 eligible patients, 36 (17 experimental, 19 control) received 4 cycles or fewer of the combination. Reasons for these premature discontinuations are detailed below:

1. PET4-positive: 27 patients in total: experimental arm 13, control arm 14 (01-003, 01-007, 01-010, 01-020, 01-021, 01-022, 01-024, 02-001, 02-002, 02-003, 02-007, 02-011, 05-002, 05-005, 11-006, 13-001, 13-010, 18-001, 18-003, 18-004, 18-006, 19-002, 20-001, 20-002, 20-004, 21-001, and 21-005).
2. Investigator decision: 3 patients in the experimental arm (01-027: double hit and high tumour burden; 08-004: due to possible bortezomib rifabutin interaction; and 13-017: due to double hit results).
3. Death: 1 patients in the control arm 1 (01-016).
4. ICF withdrawal: 1 patient in the control arm (22-003).
5. Progressive disease: 2 patients in total: 1 patient in the control arm (23-001) and 1 patient in the experimental arm (07-001).
6. SAE: 1 patient in the control arm (23-003).
7. 1 patient due to a pulmonary adenocarcinoma (01-026).

Table 20. Measurements of treatment compliance

	Total (n=121)
Treatment disposition	
Patients randomized	121
Received at least one injection (safety population)	115
Efficacy population	115
Treatment allocation	
R-CHOP (control arm)	59
B-R-CAP (experimental arm)	56
End of Treatment - reasons	
Complete protocol treatment	79
PET4 positive	27
Investigator decision	3
Progressive disease	2
Death	1
Patient decision - ICF withdraw	1
Pulmonary adenocarcinoma	1
SAE	1

Abbreviations: ICF, Informed Consent Form SAE, serious adverse event

11.5. STUDY DURATION

The total duration of the study, considering the period between obtaining the approvals until the last visit of the last patient, was 58 months.

The study was approved by the AEMPS on 23 Mar 2013 and the reference EC on 07 Mar 2013. The first centre was activated on 21 May 2013; all the centres were activated and open to accrual on 23 July 2014. The first patient was included on 03 Oct 2013 and the last patient on 26 Jan 2016.

The first patient started treatment on 03 Oct 2013 (start of risk exposure period); the date of administration of the last patient who received treatment in the study was 16 May 2016. Overall, the period of treatment exposure was 3.9 months.

Regarding the follow-up of patients, the last visit of the last patient was on 22 Jan 2018, closing the database of the study on 22 Jan 2018 with the median follow-up of 28.3 months.

The End of Study communication was made on 25 Sept 2018, after having clarified all data inconsistencies with centres and having performed the close-out visits.

11.5.1. STATISTICAL/ANALYTICAL ISSUES

11.5.1.1. HANDLING OF DROPOUTS OR MISSING DATA

A total of 121 patients were included in the study. Of these patients, 6 were excluded from the efficacy and safety analysis for the reasons reported in Table 21. All the eligible patients reported the administration of at least 1 infusion of study treatment and were considered for safety analysis.

Table 21. Patients excluded from efficacy and safety analysis

Patient	Hospital	Reason for the exclusion from the analysis
11-001	CIOCC	Patient 11-001 was randomised into the trial and started treatment on 03 Oct 2013, with a local diagnosis of DLBCL .On 13 Nov 2013, centralised review performed on the sample of this patient did not confirm the diagnosis of DLBCL. Diagnosis centralised review: lymph node with Hodgkin's lymphoma B, predominantly nodular lymphocytic type.
02-008	H. U. Salamanca	Patient 02-008 was randomised into the trial and started treatment on 28 Sep 2015 with a local diagnosis of DLBCL. On 27 Oct 2015, centralised review performed on this patient's sample did not confirm the diagnosis of DLBCL. Diagnosis of the centralised review: “lymph node with DLBCL (60% GCB phenotype) and 3A follicular lymphoma area 3 (40%)”.
22-004	ICO Girona	Patient 22-004 was randomised into the trial and began treatment on 02 Nov 2015 with a local diagnosis of DLBCL. On 18 Dec 2015, the centralised review performed on the sample of this patient did not confirm the diagnosis of DLBCL. Diagnosis of the revision: "lymphatic centralised review nodal with B lymphoma of the

		marginal zone (GANGLIONAR)".
20-003	H. Lozano Blesa	Patient 20-003 was randomised into the trial and started treatment on 05 Feb 2015 with a local diagnosis of DLBCL. On 06 Mar 2015, the revision centralised performed on the sample of this patient did not confirm the diagnosis of DLBCL. Diagnosis of the centralised review: “tissue cylinder with B-lymphoma suggestive of low-grade follicular lymphoma of diffuse pattern”.
15-002	H. Universitario y Politécnico La Fe	Patient 15-002 was randomised into the trial and started treatment on 06 May 2015 with a local diagnosis of DLBCL. On 29 May 2015, the centralised review performed on this patient's sample did not confirm the diagnosis of DLBCL. Diagnosis of the revision centralised review: “follicular B lymphoma grade 3A”.
23-004	Complejo Hospitalario Universitario de Vigo	Patient 23-004 was randomizeds into the trial and started treatment on 20 Nov 2015 with a local diagnosis of center DLBCL. On 02 Dec 2015, the centralised review performed on the sample of this patient did not confirm the diagnosis of DLBCL. Diagnosis of the centralised review: “lymph node biopsy with diffusely large unclassifiable B-cell lymphoma, with intermediate features between diffuse mediastinal B-lymphoma and Hodgkin's lymphoma”.

Abbreviation: DLBCL, diffuse large B-cell lymphoma

The clinical database was exported from Openclinica. The central biological review database was received from Dr. Santiago Montes (H. Marqués de Valdecilla), and central PET review was received from Dra. Mónica Coronado (H. La Paz).

All inconsistencies, missing values, or clarifications were managed by CRAs at each site, and resolution issues were documented in the database, in eCRFs, and in writing with a query form (when applicable).

For evaluation of response to treatment, 40 patients did not have documented relapse at database cut-off; therefore, their data were censored at the last available image test. The differences between the events at 24 months and the end of follow-up are presented in Table 22.

Table 22. Differences between events at 24 months and at the end of follow-up

Patient	EFS >24 months	EFS End follow-up	Reason
01-013	Event-free	Event	This patient had an event after 24 months
08-001	Event	Event-free	The last follow-up of this patient is was around 22 months.
22-003	Event	Event-free	This patient withdrew informed consent after PET2 without presenting with an event.

Abbreviation: EFS, event-free survival

By the time of database closure, 82 patients were alive; these patients were censored at the date of their last follow-up visit.

11.5.2. TABULATION OF INDIVIDUAL RESPONSE DATA

All demographic and relevant baseline data were collected (gender, date of birth, diagnosis date, localisation, disease status). The diagnosis was centrally reviewed to ensure that only DLBCL patients were analysed.

Baseline LDH level was systematically analysed according to sites' local procedures and normal ranges. Beta-2 microglobulin levels were not available for 7 patients (3 patients from H. Salamanca and 4 from H. 12 de Octubre).

Treatment administration data were available for 115 patients analysed for efficacy; the start/end date of treatment and the number of cycles administered were recorded in the eCRF. The reasons ending treatment were also recorded and categorised.

Response to treatment was recorded for each imaging test, taking into account the information provided by sites and the central PET review.

Progression/relapse date, progression/relapse reason (when applicable), and progression/relapse censored (and the corresponding comments field) were populated with the information provided by the sites.

Finally, patient status (alive, lost to follow-up, or dead) was systematically updated until database closure. Date of death or censoring, reason for death, and other comments were included in the database.

The safety database created for this study included data on all evaluable patients receiving at least 1 dose of study treatment. AEs with grades ≥3, SAEs, and suspected unexpected serious adverse reactions (SUSARs) were analysed.

Reconciliations among the safety database, SAEs, and SUSARs were performed periodically.

11.6. EFFICACY EVALUATION

11.6.1.TWO-YEAR EVENT FREE SURVIVAL (Primary endpoint)

Two-year EFS was the rate of patients who were alive and in CR from the date of randomisation up to 2 years after that date.

As required in the protocol, the primary objective was analysed using a *One-tailed binomial test* to assess whether the bortezomib-RCAP regimen was superior to the control. If the p-value associated with the test was below 0.25, is consider the test as to be positive, and the combination was declared to be effective. To calculate the 1-tailed binomial test, Epidat 4.2 was used (Epidat: software for epidemiological analysis of data; version 4.2, July 2016; Consellería de Sanidade, Xunta de Galicia, Spain; Organización

Panamericana de la Salud (OPS-OMS); Universidad CES, Colombia. Available at: http://www.sergas.es/Saude-publica/EPIDAT).

According to the methodology proposed in the protocol, the difference in percentage between arms was statistically significant at a threshold of 0.25, in which case the test could be considered as positive.

Table 23. EFS at 24 months with CR in the first 24 months

	Experimental	Control	% difference and 75% Confidence Interval	p-value
	N (%)	N (%)	N (%)	
EFS>24 months and CR during 1st 24m	21/56 (37.5%)	18/59 (30.5%)	7.0% (0.0%, 17.1%)	*0.214 (1)*

Abbreviation: EFS, event-free survival. 1: 1-sided binomial test

The primary endpoint has also been analysed using the usual methodology: comparing between arms the proportions of patients who are alive and in complete response from the date of randomization until 2 years after that date using the Chi-square test, assuming statistical differences under the threshold of 0.05 and reporting at 95% confidence intervals for the proportions.

No statistical significant differences were found between the study arms in the rate of patients who are alive and in complete response from the date of randomization until 2 years after that date: 37.5% of patients in the experimental arm vs. 30.5% in the control arm (p=0.429) (Table 23 and 24).

Table 24. EFS at 24 months with CR in the first 24 months

		Experimental	Control	Total	p-value
		N (%, CI 95%)	N (%, CI 95%)	N (%, CI 95%)	
EFS>24 months and CR during 1st 24m	**No**	35 (62.5%, 49.8;75.2)	41 (69.5%, 57.7;81.2)	76 (66.1%, 57.4;74.7)	*0.429 (1)*
	Yes	21 (37.5%, 24.8;50.2)	18 (30.5%, 18.8;42.3)	39 (33.9%, 25.3;42.6)	
	Total	56 (100.0%)	59 (100.0%)	115 (100.0%)	

1: Chi-square test

11.6.1.1 EFS According to GCB (Centralized review)

In patients with phenotype GCB (n=66, centralized review), no statistical significant differences were found between the study arms in the rate of patients who are alive and in complete response from the date of randomization until 2 years after that date: 26.7% of patients in the experimental arm vs. 36.1% in the control arm (p=0.412) (Table 25).

Table 25. EFS at 24 months with CR in the first 24 months. Phenotype GCB (n=66)

		Experimental	Control	Total	p-value
		N (%, CI 95%)	N (%, CI 95%)	N (%, CI 95%)	
EFS>24 months and CR during 1st 24m	**No**	22 (73.3%, 57.5;89.2)	23 (63.9%, 48.2;79.6)	45 (68.2%, 56.9;79.4)	*0.412 (1)*
	Yes	8 (26.7%, 10.8;42.5)	13 (36.1%, 20.4;51.8)	21 (31.8%, 20.6;43.1)	
	Total	30 (100.0%)	36 (100.0%)	66 (100.0%)	

1: Chi-square test; 2: Fisher's exact test

11.6.1.2 EFS According to no-GCB (Centralized review)

In patients with phenotype no-GCB (n=38, centralized review), no statistical significant differences were found between the study arms in the rate of patients who are alive and in complete response from the date of randomization until 2 years after that date: 40.9% of patients in the experimental arm vs. 25% in the control arm (p=0.307) (Table 26).

Table 26. EFS at 24 months with CR in the first 24 months. Phenotype NO-GCB (n=38)

		Experimental	Control	Total	p-value
		N (%, CI 95%)	N (%, CI 95%)	N (%, CI 95%)	
EFS>24 months and CR during 1st 24m	**No**	13 (59.1%, 38.5;79.6)	12 (75.0%, 53.8;96.2)	25 (65.8%, 50.7;80.9)	*0.307 (1)*
	Yes	9 (40.9%, 20.4;61.5)	4 (25.0%, 3.8;46.2)	13 (34.2%, 19.1;49.3)	
	Total	22 (100.0%)	16 (100.0%)	38 (100.0%)	

1: Chi-square test; 2: Fisher's exact test

11.6.2. SECONDARY ANALYSIS

As required in the protocol, a *logistic regression analysis* was performed to identify significant factors that can influence the EFS at 2 years. The influence of the histological subtype was studied as a relevant factor in EFS at 2 years. Firstly, a univariate analysis was carried out separately for each of the possible explicative variables to decide which variables were should be entered in the multivariate models; only those with a statistical association with the dependent variable were selected. A stepwise backward elimination process was used to select the model. In the first step, all possible predictors were entered into the model, and in each subsequent step, the variable that was least significant (that is, the one with the largest p-value) waswas removed, and the model was refitted. This was repeated until all remaining variables had individual p-values, smaller than 0.05.

In the univariate logistic regression analysis, the following variables showed statistical significance (p<0.05): Lymphomas Other (Baseline), Extranodal Affectation (Baseline), Nodal Affectation (Baseline), high LDH and C-MYC (≥40%), and high BCL2 (≥50%) IHC (Table 27).

Table 27. EFS and CR at the end of treatment

PFS>24m and CR at the end of treatment						
Variables	**Categories**	**No N (%)**	**Yes N (%)**	**Total N (%)**	**OR (95% CI)**	**p-value**
Arm (randomised)	Experimental	35 (46.1)	21 (53.8)	56 (48.7)	1.37 (0.63-2.96)	0.429
	Control	41 (53.9)	18 (46.2)	59 (51.3)	1	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Gender (Baseline)	Male	35 (46.1)	22 (56.4)	57 (49.6)	1.52 (0.70-3.30)	0.294
	Female	41 (53.9)	17 (43.6)	58 (50.4)	1	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Performance Status ECOG (Baseline)	0-1	51 (67.1)	26 (66.7)	77 (67.0)	0.98 (0.43-2.23)	0.962
	≥2	25 (32.9)	13 (33.3)	38 (33.0)	1	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Age >60 years	<60 years	37 (48.7)	21 (53.8)	58 (50.4)	1.23 (0.57-2.67)	0.600
	≥60 years	39 (51.3)	18 (46.2)	57 (49.6)	1	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Adenopathies (Baseline)	Yes	49 (64.5)	23 (59.0)	72 (62.6)	0.79 (0.36-1.75)	0.564
	No	27 (35.5)	16 (41.0)	43 (37.4)	1	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Hepatomegaly (Baseline)	Yes	8 (10.5)	2 (5.1)	10 (8.7)	0.47 (0.09-2.31)	0.349
	No	67 (88.2)	36 (92.3)	103 (89.6)	1	
	ND	1 (1.3)	0 (0.0)	1 (0.9)		
	UK	0 (0.0)	1 (2.6)	1 (0.9)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Splenomegaly (Baseline)	Yes	14 (18.4)	7 (17.9)	21 (18.3)	0.94 (0.34-2.56)	0.897
	No	58 (76.3)	31 (79.5)	89 (77.4)	1	
	NA	1 (1.3)	0 (0.0)	1 (0.9)		
	ND	2 (2.6)	0 (0.0)	2 (1.7)		
	UK	1 (1.3)	1 (2.6)	2 (1.7)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		

Lymphomas Other (Baseline)	Yes	29 (38.2)	6 (15.4)	35 (30.4)	1	0.013
	No	46 (60.5)	33 (84.6)	79 (68.7)	3.47 (1.29-9.30)	
	ND	1 (1.3)	0 (0.0)	1 (0.9)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Histological Subtype (Baseline)	GCB	62 (81.6)	35 (89.7)	97 (84.3)	1.55 (0.46-5.24)	0.479
	No GCB	11 (14.5)	4 (10.3)	15 (13.0)	1	
	ND	2 (2.6)	0 (0.0)	2 (1.7)		
	UK	1 (1.3)	0 (0.0)	1 (0.9)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Phenotype GCB-ABC (centralized review)	GCB	45 (59.2)	21 (53.8)	66 (57.4)	0.90 (0.38-2.09)	0.802
	NO-GCB	25 (32.9)	13 (33.3)	38 (33.0)	1	
	NA	5 (6.6)	4 (10.3)	9 (7.8)		
	UK	1 (1.3)	1 (2.6)	2 (1.7)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
CD20 expression (Baseline)	Yes	76 (100.0)	39 (100.0)	115 (100.0)	---	---
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Bone marrow infiltration (Baseline)	Positive	18 (23.7)	5 (12.8)	23 (20.0)	0.55 (0.18-1.62)	0.275
	Negative	57 (75.0)	29 (74.4)	86 (74.8)	1	
	ND	1 (1.3)	5 (12.8)	6 (5.2)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Clinical Stage (Baseline)	I	1 (1.3)	0 (0.0)	1 (0.9)	0.00 (---)	1.000
	II	4 (5.3)	2 (5.1)	6 (5.2)	1.10 (0.19-6.45)	0.912
	III	18 (23.7)	13 (33.3)	31 (27.0)	1.59 (0.67-3.77)	0.288
	IV	53 (69.7)	24 (61.5)	77 (67.0)	1	0.769
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Clinical Stage (Baseline)	I-II	5 (6.6)	2 (5.1)	7 (6.1)	0.77 (0.14-4.15)	0.759
	III-IV	71 (93.4)	37 (94.9)	108 (93.9)	1	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Extranodal Affectation (Baseline)	Yes	62 (81.6)	25 (64.1)	87 (75.7)	1	0.042
	No	14 (18.4)	14 (35.9)	28 (24.3)	2.48 (1.03-5.95)	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Extranodal Affectation Number (Baseline)	1	18 (29.0)	7 (28.0)	25 (28.7)	0.95 (0.34-2.67)	0.923
	2 or more	44 (71.0)	18 (72.0)	62 (71.3)	1	
	Total	62 (100.0)	25 (100.0)	87 (100.0)		

Nodal Affectation (Baseline)	Yes	71 (93.4)	25 (64.1)	96 (83.5)	1	<0.001
	No	3 (3.9)	13 (33.3)	16 (13.9)	12.31 (3.24-46.79)	
	ND	2 (2.6)	1 (2.6)	3 (2.6)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
aIPI (Baseline)	1-2	54 (71.1)	33 (84.6)	87 (75.7)	2.24 (0.82-6.10)	0.114
	3 (High score)	22 (28.9)	6 (15.4)	28 (24.3)	1	
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Symptoms B (Baseline)	Yes	33 (43.4)	13 (33.3)	46 (40.0)	1	0.272
	No	42 (55.3)	26 (66.7)	68 (59.1)	1.57 (0.70-3.52)	
	ND	1 (1.3)	0 (0.0)	1 (0.9)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
High LDH	Yes	66 (89.2)	27 (69.2)	93 (82.3)	1	0.011
	No	8 (10.8)	12 (30.8)	20 (17.7)	3.67 (1.35-9.97)	
	Total	74 (100.0)	39 (100.0)	113 (100.0)		
Antibodies HIV (Baseline)	Negative	75 (98.7)	38 (97.4)	113 (98.3)	---	---
	ND	1 (1.3)	1 (2.6)	2 (1.7)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
HbsAg (Baseline)	Negative	75 (98.7)	39 (100.0)	114 (99.1)	----	---
	ND	1 (1.3)	0 (0.0)	1 (0.9)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Hepatitis C (Baseline)	Negative	75 (98.7)	39 (100.0)	114 (99.1)	---	---
	ND	1 (1.3)	0 (0.0)	1 (0.9)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
C-MYC (≥40%) and BCL2 (≥50%) IHC	Yes	39 (51.3)	11 (28.2)	50 (43.5)	1	0.014
	No	23 (30.3)	20 (51.3)	43 (37.4)	3.08 (1.26-7.57)	
	UK	14 (18.4)	8 (20.5)	22 (19.1)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
CD30 (≥20%)	Yes	15 (19.7)	10 (25.6)	25 (21.7)	1.57 (0.60-4.08)	0.357
	No	47 (61.8)	20 (51.3)	67 (58.3)	1	
	UK	14 (18.4)	9 (23.1)	23 (20.0)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		
Prephase (cycle 1 D1)	Yes	25 (32.9)	7 (17.9)	32 (27.8)	1.000	0.132
	No	46 (60.5)	27 (69.2)	73 (63.5)	2.10 (0.80-5.49)	
	UK	5 (6.6)	5 (12.8)	10 (8.7)		
	Total	76 (100.0)	39 (100.0)	115 (100.0)		

Abbreviations: EFS, event-free survival; CR, complete response; OR, odds ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ND, not determined; UK, unknown; NA, not available; GCB, germinal centre B-cell; aIPI, age-adjusted International Prognostic Index; LDH, lactate dehydrogenase; HIV, human immunodeficiency virus; HbsAg, hepatitis B surface antigen.

The multivariate logistic regression analysis started entering the variables that showed statistical significance (p<0.05) in the univariate logistic regression analysis. According to the clinician criteria the following variables were not entered in the multivariate model: lymphomas other, extranodal affectation and Nodal affectation (Table 28).

Table 28. Multivariate logistic regression of EFS at 24 months with CR (I)

PFS>24m and CR at the end of treatment			
Variables	Categories	OR (95% CI)	p-value
High LDH	Yes	1	0.004
	No	7.95 (1.94-32.62)	
C-MYC (≥40%) and BCL2 (≥50%) IHC	Yes	1	0.054
	No	2.56 (0.98-6.64)	
Constant		0.23	<0.001

Abbreviations: EFS, event-free survival; CR, complete response; OR, odds ratio; CI, confidence interval.

11.6.2.1. Event-free survival

EFS was defined as the time that elapsed between the randomisation date and the first documented recurrence, progression, or death (in the case of no documented recurrence), or the start of a new anti-lymphoma treatment due to refractory or persistent disease. In the EFS analysis, the subjects to whom the treatment were discontinued due to AEs or other reasons were censored at the time that the tumour was evaluated for the last time.

At 6 months from the start of the treatment, the EFS was 64.3% in the experimental arm (confidence interval [CI] 95%: 51.8% to 76.8%) and 56.9% in the control arm (CI95% 42.4 to 68.4%).

At 12 months from the start of the treatment, the EFS was 50% in the experimental arm (CI95%: 36.9 to 63.%) and 36.2% in the control arm (95% CI: 23.8% to 48.6%).

The median EFS was 11.37 months (95% CI 0.0 to 27.33) in the experimental arm and 6.31 months (95% CI 2.95 to 9.68) in the control arm. No statistically significant differences were found between the arms of treatment (p=0.477) (Table 29).

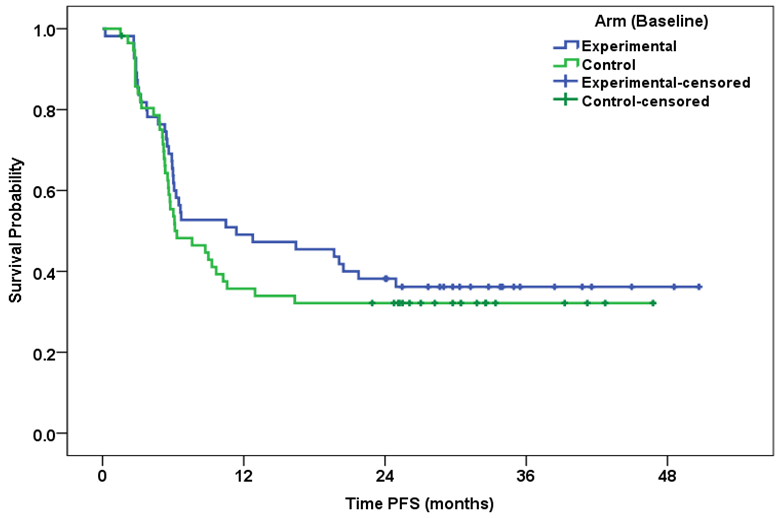
Table 29. EFS according to arm treatment

EFS		N events	N patients at risk	% Proportion of cumulative estimated survival	CI 95%
At 6 months	Experimental	20	36	64.3	(51.8,76.8)
	Control	25	33	55.4	(42.4,68.4)
At 12 months	Experimental	28	28	50.0	(36.9,63.1)
	Control	37	22	36.2	(23.8,48.6)
At 24 months	Experimental	35	21	37.5	(24.8,50.2)
	Control	39	19	32.8	(20.7,44.9)
At 36 months	Experimental	36	6	35.5	(22.9,48.1)
	Control	39	6	32.8	(20.7,44.9)
At 48 months	Experimental	36	2	35.5	(22.9,48.1)
	Control	39	2	32.8	(20.7,44.9)

	Arm	N (%) events	Median (months)	Min-Max	Standard error	CI 95%	p-value (1)
EFS	Experimental	36 (64.3%)	11.37	0.2-50.7	8.14	(0.00;27.33)	*0.477*
	Control	39 (66.1%)	6.31	1.5-46.8	1.72	(2.95;9.68)	
	Overall	75 (65.2%)	8.73	0.2-50.7	1.93	(4.95;12.50)	

1: Log-rank test

Figure 3. EFS according to arm treatment (Kaplan-Meier curve)



A total of 40 patients (34.8%) were alive without event at the end of follow-up, not finding statistically significant differences between arms (35.7% in experimental and 33.9% in control, p=0.838) (Table 30).

Table 30. Events during follow-up

		Experimental	Control	Total	p-value
		N (%, CI 95%)	N (%, CI 95%)	N (%, CI 95%)	
EFS	Alive without event	20 (35.7%, 23.2;48.3)	20 (33.9%, 21.8;46.0)	40 (34.8%,26.1;43.5)	
	Event	36 (64.3%, 51.7;76.8)	39 (66.1%, 54.0;78.2)	75 (65.2%,56.5;73.9)	*0.838*
	Total	56 (100.0%)	59 (100.0%)	115 (100.0%)	

1: Chi-square test; 2: Fisher's exact test

Table 31. Type of events (EFS)

		Experimental	Control	Total	p-value
		N (%, CI 95%)	N (%, CI 95%)	N (%, CI 95%)	
EFS	Event at PET 4	7 (19.4%, 6.5;32.4)	8 (20.5%, 7.8;33.2)	15 (20.0%, 10.9;29.1)	
	Event at PET 6	11 (30.6%, 15.5;45.6)	15 (38.5%, 23.2;53.7)	26 (34.7%, 23.9;45.4)	
	Progression disease after treatment	7 (19.4%, 6.5;32.4)	5 (12.8%, 2.3;23.3)	12 (16.0%, 7.7;24.3)	
	Recurrence of lymphoma during 5 years of follow-up	2 (5.6%, -1.9;13.0)	1 (2.6%, -2.4;7.5)	3 (4.0%, -0.4;8.4)	*0.949 (2)*
	2nd line (new treatment)	7 (19.4%, 6.5;32.4)	8 (20.5%, 7.8;33.2)	15 (20.0%, 10.9;29.1)	
	Exitus	2 (5.6%, -1.9;13.0)	2 (5.1%, -1.8;12.1)	4 (5.3%, 0.2;10.4)	
	Total	36 (100.0%)	39 (100.0%)	75 (100.0%)	

1: Chi-square test; 2: Fisher's exact test

In those patients that presented an event (n=75), the median time between the randomizations date and the event date was 5.6 months; we did not find a statistically significant difference between the arms (5.9 months in the experimental arm and 5.8 months in the control arm, p=0.277 (Table 32).

Table 32. Time until event (months)

	Experimental			Control			Total			p-value
	N	Mean (SD)	Median (min-Max)	N	Mean (SD)	Median (min-Max)	N	Mean (SD)	Median (min-Max)	
Time until event (months)	36	8.2 (6.7)	5.9 (0.2-24.9)	39	5.8 (3.1)	5.3 (1.5-16.3)	75	7.0 (5.2)	5.6 (0.2-24.9)	*0.277*

Abbreviation: SD, standard deviation. 1: Mann-Whitney U test

11.6.2.2 Overall survival (OS)

OS was defined as the time between randomisation and death from any cause. In cases

where patients withdrew from the trial or were lost to follow-up, they were censored at the date of the last contact. The patients who were still alive at the end of the study were censored at that time.

At 6 months from the start of the treatment, the OS was 96.4% in the experimental arm (95% CI 91.5% to 101.3%) and 94.9% in the control arm (95% CI 89.2% to 100.6%).

At 12 months from the start of the treatment, the OS was 87.5% in the experimental arm (95% CI 78.8% to 96.2%) and 82.7% in the control arm (95% CI: 72.9% to 92.5%).

The median OS was not reached in either of the arms. The mean OS was 41.6 months (95% CI 37.26% to 45.97%) in the experimental arm and 35 months (95% CI 30.72% to 39.27%) in the control arm. No statistically significant differences were found between the arms of treatment (p=0.186; Table 33).

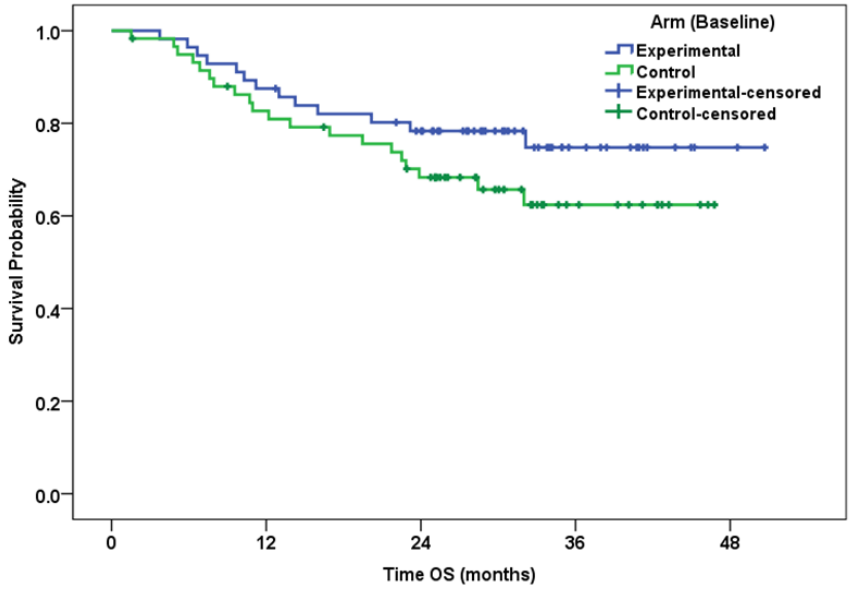
Table 33. OS according to arm treatment

OS		N events	N patients at risk	% Proportion of cumulative estimated survival	CI 95%
At 6 months	**Experimental**	2	54	96.4	(91.5,101.3)
	Control	3	55	94.9	(89.2,100.6)
At 12 months	**Experimental**	7	49	87.5	(78.8,96.2)
	Control	9	48	82.7	(72.9,92.5)
At 24 months	**Experimental**	12	41	78.3	(67.4,89.2)
	Control	18	37	68.3	(56.2,80.4)
At 36 months	**Experimental**	13	13	74.8	(62.4,87.2)
	Control	20	11	62.4	(48.8,76.0)
At 48 months	**Experimental**	13	2	74.8	(62.4,87.2)
	Control	20	0	0.0	(0.0,0.0)

	Arm	N (%) events	Median (months)	Mean (months)	Min-Max	Standard error (mean)	CI 95% of the mean	p-value (1)
OS	**Experimental**	13 (23.2%)	---	41.6	3.7-50.7	2.22	(37.26;45.97)	*0.186*
	Control	20 (33.9%)	---	35.0	1.5-46.8	2.18	(30.72;39.27)	
	Total	33 (28.7%)	---	39.5	1.5-50.7	1.66	(36.24;42.75)	

Abbreviations: OS, overall survival; CI, confidence interval. 1: Log-rank test

Figure 4. OS according to treatment arm (Kaplan-Meier curve)



A total of 82 patients (71.3%) were alive at the end of follow-up; we did not find a statistically significant difference between the arms (76.8% in the experimental arm and 66.1% in the control arm, p=0.206) (Table 34).

Table 34. Deaths during follow-up

		Experimental	Control	Total	p-value
		N (%, CI 95%)	N (%, CI 95%)	N (%, CI 95%)	
Overall survival	Alive	43 (76.8%, 65.7;87.8)	39 (66.1%, 54.0;78.2)	82 (71.3%, 63.0;79.6)	*0.206 (1)*
	Death	13 (23.2%, 12.2;34.3)	20 (33.9%, 21.8;46.0)	33 (28.7%, 20.4;37.0)	
	Total	56 (100.0%)	59 (100.0%)	115 (100.0%)	

Abbreviation: CI, confidence interval. 1: Chi-square test; 2: Fisher's exact test

Of the 33 patients that died, 24 (72.7%) had died of lymphoma and 9 from other reasons (27.3%) (Tables 35 and 36).

Table 35. Causes of death

			Experimental	Control	Total	p-value
			N (%, CI 95%)	N (%, CI 95%)	N (%, CI 95%)	
Death	Due to lymphoma		9 (69.2%, 44.1;94.3)	15 (75.0%, 56.0;94.0)	24 (72.7%, 57.5;87.9)	*0.393 (2)*
	Other		4 (30.8%, 5.7;55.9)	5 (25.0%, 6.0;44.0)	9 (27.3%, 12.1;42.5)	
		Total	13 (100.0%)	20 (100.0%)	33 (100.0%)	

Abbreviation: CI, confidence interval. 1: Chi-square test; 2: Fisher's exact test

Table 36. Other causes of death during follow-up

		Experimental arm	Control arm	Total
		N (%)	N (%)	N (%)
Other type of death	Aspergillosis pulmonary	0 (0.0%)	1 (5.0%)	1 (3.0%)
	Unknown	0 (0.0%)	1 (5.0%)	1 (3.0%)
	Multiorgan refractory failure to treatment by shock of origin ethnic pulmonary	0 (0.0%)	1 (5.0%)	1 (3.0%)
	Respiratory infection and lymphoma progression at the pulmonary level	0 (0.0%)	1 (5.0%)	1 (3.0%)
	Advanced high-grade lymphoma b. Constitutional syndrome. Tumour intestinal obstruction. Tumour ascites (lymphomatosis perit.)	0 (0.0%)	1 (5.0%)	1 (3.0%)
	Pneumonia	1 (7.7%)	0 (0.0%)	1 (3.0%)
	Severe sepsis in a neutropenic patient	1 (7.7%)	0 (0.0%)	1 (3.0%)
	Septic shock secondary to bacteraemia per kpc post-transplant	1 (7.7%)	0 (0.0%)	1 (3.0%)
	Unknown	1 (7.7%)	0 (0.0%)	1 (3.0%)

In those patients that died (n=33), the median time between the randomizations date and the date of death was 11.2 months; we did not find a statistically significant difference between the arms (11.2 months in the experimental arm and 11.6 months in the control arm, p=0.763) (Table 37).

Table 37. Time until death (months)

	Experimental			Control			Total			p-value
	N	Mean (SD)	Median (min-Max)	N	Mean (SD)	Median (min-Max)	N	Mean (SD)	Median (min-Max)	
Time until death (months)	13	13.4 (8.0)	11.2 (3.7-32.1)	20	14.3 (8.7)	11.6 (1.5-32.0)	33	13.9 (8.3)	11.2 (1.5-32.1)	0.763

Abbreviation: SD, standard deviation. 1: Independent Samples t-Test

11.6.2.3. Time of follow-up

Overall the total number of patients (n=115), the median time of follow-up (the difference between the randomisation and the last date of follow-up or death) was 28.3 months; we did not find a statistically significant difference between the arms (29.4 months in the experimental arm and 26.1 months in the control arm, p=0.208 (Table 38).

Table 38. Time to follow-up

	Experimental			Control			Total			p-value
	N	Mean (SD)	Median (min-Max)	N	Mean (SD)	Median (min-Max)	N	Mean (SD)	Median (min-Max)	
Time until loss of follow-up/ death (months)	56	28.3 (11.4)	29.4 (3.7-50.7)	59	25.5 (12.3)	26.1 (1.5-46.8)	115	26.9 (11.9)	28.3 (1.5-50.7)	0.208

Abbreviation: SD, standard deviation

11.6.2.4. Responses at the end of treatment

No statistically significant difference was found in the response at the end of treatment between the study arms, p =0.431 (Table 39).

Table 39. Response at the end of treatment

		Experimental	Control	Total	p-value
		N (%)	N (%)	N (%)	
Confirmed diagnosis	**Complete remission**	31 (55.4)	27 (45.8)	58 (50.4)	*0.431 (2)*
	Partial remission	9 (16.1)	15 (25.4)	24 (20.9)	
	Stable disease	0 (0.0)	1 (1.7)	1 (0.9)	
	Relapse/PD	13 (23.2)	15 (25.4)	28 (24.3)	
	UK/ND/NA	3 (5.4)	1 (1.7)	4 (3.5)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	

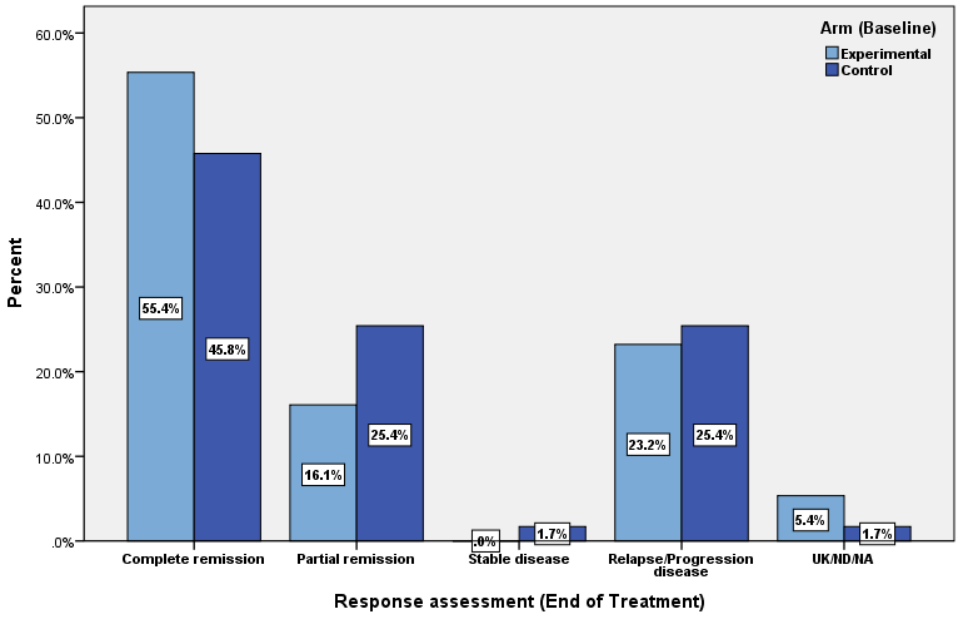
Abbreviations: UK, unknown; PD, progressive disease; ND, not determined; NA, not available. 1: Chi-square test; 2: Fisher's exact test

Response at the end of treatment was not available for 4 patients (Table 40).

Table 40. Patients without response at the end of treatment

	ID	Hospital	Arm (Baseline)	Response assessment (End of Treatment)	Comments
1	01-016	ICOH	Control	UK/ND/NA	
2	01-027	ICOH	Experimental	UK/ND/NA	29/12/2015 Anatomic Pathology report, fish result: translocation of c-MYC and BCL-2. Assessment: young patient with a double hit DLBCL and elevated tumour load, candidate for treatment according to the burkimab protocol.
3	08-004	HRYC	Experimental	UK/ND/NA	
4	21-003	HUC	Experimental	UK/ND/NA	

Figure 5. Response at the end of treatment



11.6.2.4.1. Centralized review of PET4 and PET6

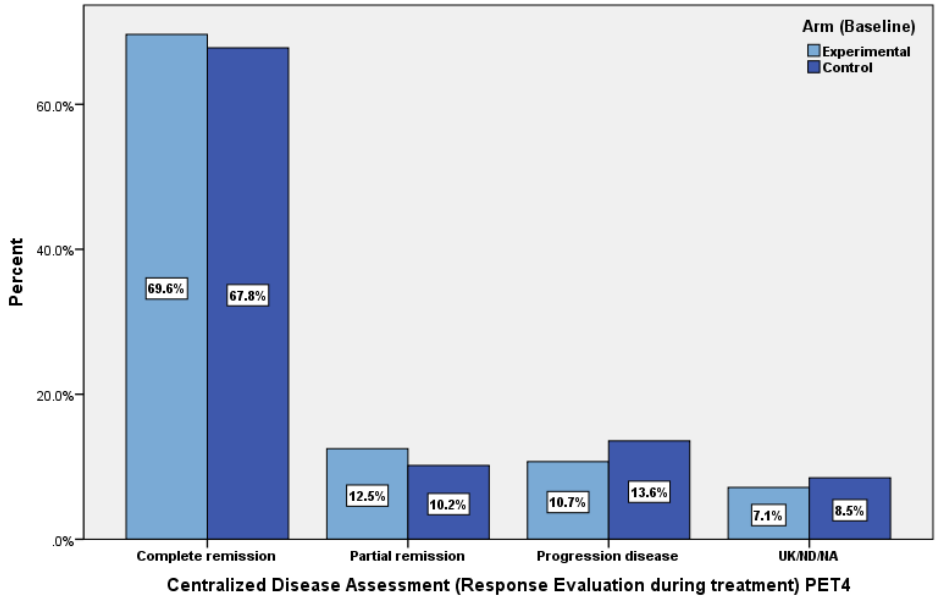
No statistically significant differences were found regarding response at the centralised disease assessment of PET4 between the study arms, p=0.961 (Table 41).

Table 41. Response at PET4 according to the centralised review

		Experimental	Control	Total	p-value
		N (%)	N (%)	N (%)	
Centralized Disease Assessment (Response Evaluation during treatment) PET4	**Complete remission**	39 (69.6)	40 (67.8)	79 (68.7)	*0.961 (2)*
	Partial remission	7 (12.5)	6 (10.2)	13 (11.3)	
	Progression disease	6 (10.7)	8 (13.6)	14 (12.2)	
	UK/ND/NA	4 (7.1)	5 (8.5)	9 (7.8)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	

Abbreviations: UK, unknown; ND, not determined; NA, not available. 1: Chi-square test; 2: Fisher's exact test

Figure 6. Response at PET4 according to the centralised review



No statistically significant differences were found in the response at PET6 according to the visual Deauville scale (p=0.580) between the study arms.

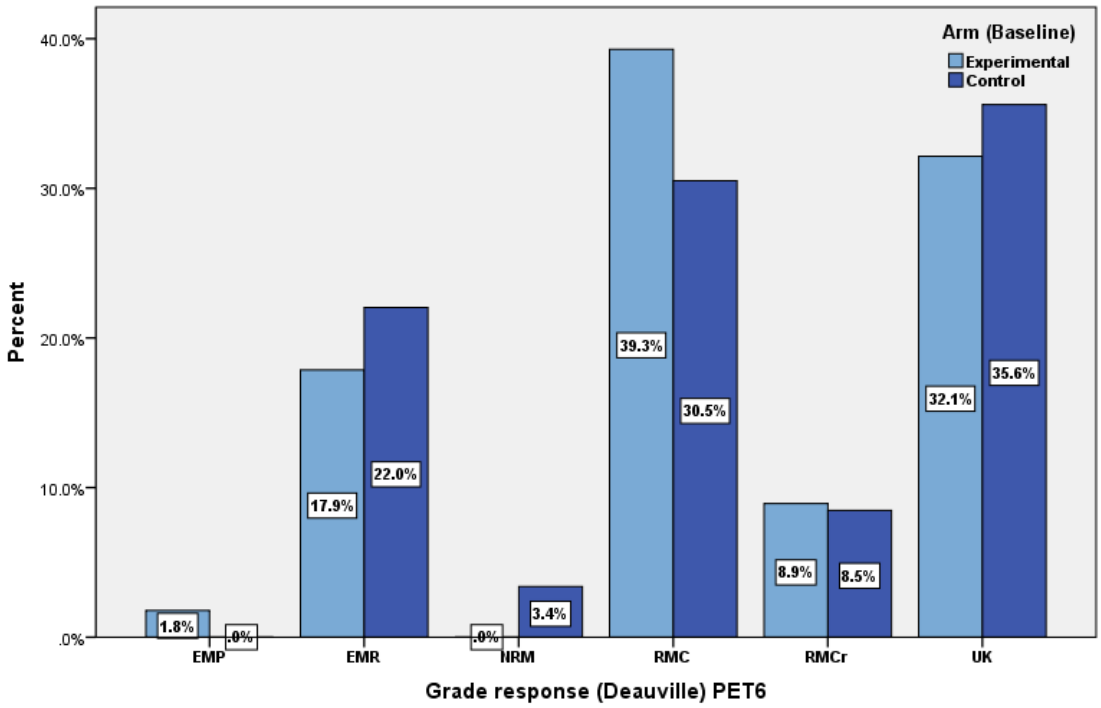
No statistically significant differences were found in the grade response at PET6 according to the Deauville scale (p=0.665) between the study arms (Table 42).

Table 42. Response at PET6 according to the centralised review

		Experimental	Control	Total	p-value
		N (%)	N (%)	N (%)	
Result PET visual (Deauville) PET6	**Positive**	11 (19.6)	15 (25.4)	26 (22.6)	*0.580 (1)*
	Negative	27 (48.2)	23 (39.0)	50 (43.5)	
	NA	18 (32.1)	21 (35.6)	39 (33.9)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	
Response Grade (Deauville) PET6	**EMP**	1 (1.8)	0 (0.0)	1 (0.9)	*0.665 (2)*
	EMR	10 (17.9)	13 (22.0)	23 (20.0)	
	NRM	0 (0.0)	2 (3.4)	2 (1.7)	
	RMC	22 (39.3)	18 (30.5)	40 (34.8)	
	RMCr	5 (8.9)	5 (8.5)	10 (8.7)	
	NA	18 (32.1)	21 (35.6)	39 (33.9)	
	Total	56 (100.0)	59 (100.0)	115 (100.0)	

1: Chi-square test; 2: Fisher's exact test

Figure 7. Response at PET6 according to the centralised review



11.6.2.5. Diagnostic test: EFS

Receiver operating characteristic (ROC) curves were calculated as a discrimination measure. The curves were constructed by computing the sensitivity and specificity of increasing numbers of ΔSUV (%) for PET4. Obtaining an area of 1 would represent a perfect test while area of 0.5 represents a failed test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system:

- 0.90-1 = excellent
- 0.80-0.90 = good
- 0.70-0.80 = fair
- 0.60-0.70 = poor
- 0.50-0.60 = fail

To select the optimal cut-off according to the sensitivity and specificity, the Youden Index and the minimum distance to the upper left corner (where sensitivity=1 and specificity=1), were calculated using the formula :

$$\sqrt{((1\text{-sensitivity})^2+(1\text{-specificity})^2)}$$

(see details at http://www.medicalbiostatistics.com/roccurve.pdf)

11.6.2.5.1. Diagnostic test: EFS SUV (%) for PET4

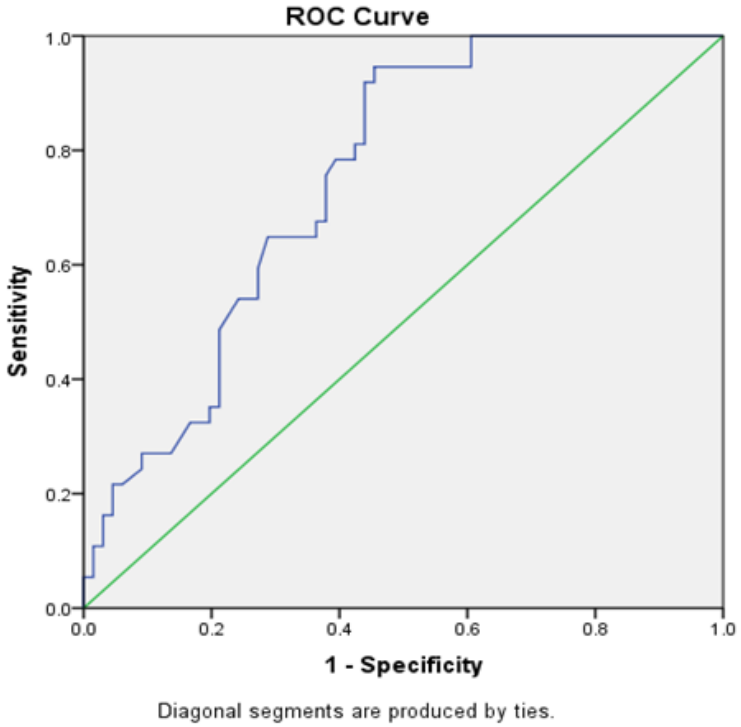
The area under the curve (AUC) obtained using SUV PET4 as a diagnostic test for EFS was 0.751 (fair accuracy with a 95% CI 0.66 to 0.84), and the optimal threshold obtained varied between 80.30 and 81.25 for ΔSUV (%) depending on the method (Table 43).

Table 43. AUC for EFS vs.ΔSUV (%) PET4

Area Under the Curve					
Area	**Std. Error**	**p-value**		**Confidence Interval 95%**	
0.751	0.047	<0.001		(0.66;0.84)	
Change SUV (%) PET4	**Sensitivity**	**1-Specificity**	**Specificity**	**Youden J index Max(Sensitivity+Specificity-1)**	**Min(Optimal' threshold point)**
80.30	0.946	0.455	0.545	***0.491***	0.458
80.80	0.919	0.455	0.545	0.464	0.462
81.25	0.919	0.439	0.561	0.480	***0.447***

Abbreviations: Std, standard; SUV, standard uptake value

Figure 8. ROC curve: AUC for EFS vs. ΔSUV (%) PET4



11.6.2.5.2. Diagnostic test: EFS SUV (%) PET6

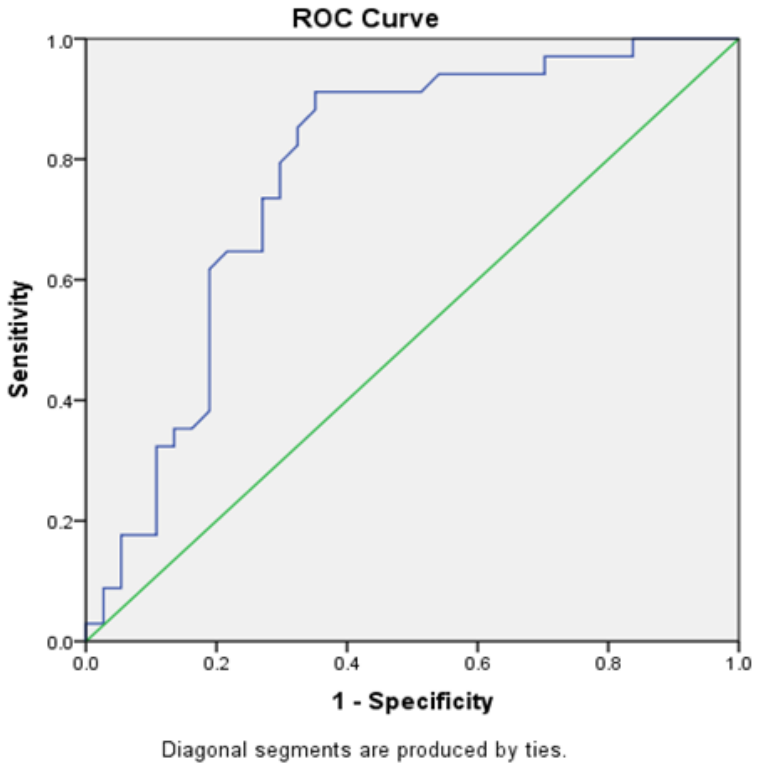
The AUC obtained using SUV PET6 as the diagnostic test for EFS was 0.777 (fair accuracy with a 95% CI 0.66 to 0.89), and the optimal threshold obtained by both methods coincided with a value of 84.75 for ΔSUV (%) PET6 (Table 44).

Table 44. AUC for EFS vs. ΔSUV (%) PET6

Area Under the Curve					
Area	**Std. Error**	**p-value**	**Confidence Interval 95%**		
0.777	0.057	<0.001	(0.66;0.89)		
Change SUV (%) PET6	**Sensitivity**	**1-Specificity**	**Specificity**	**Youden J index Max(Sensitivity+Specificity-1)**	**Min(Optimal' threshold point)**
84.45	0.912	.378	0.622	.533	0.389
84.75	0.912	.351	0.649	***.560***	***0.362***
85.45	0.882	.351	0.649	.531	0.371

Abbreviations: AUC, area under the curve; EFS, event-free survival; SUV, standard uptake value, Std, standard

Figure 9. ROC curve: AUC for EFS vs. ΔSUV (%) PET6



FACTORS ASSOCIATED WITH EFS

A Cox regression analysis is performed to find significant factors that can influence the EFS. Firstly a univariate analysis will be carried out separately for each one of the possible explicative variables to decide which variables are entered in the multivariate models; only those with a statistical association with the dependent variable will be selected. Backward elimination stepwise process will be used to select the model. In the first step all possible predictors will be entered in the model and in each step, the variable that is least significant (that is, the one with the largest P value) will be removed and the model will be refitted. Each subsequent step will remove the least significant variable in the model until all remaining variables have individual P values smaller than 0.05.

In the univariate Cox regression analysis the following variables showed statistical significance (p<0.05): Lymphomas Other (Baseline), Extranodal Affectation (Baseline), Nodal Affectation (Baseline), High LDH and C-MYC (≥40%) and BCL2 (≥50%) IHC (Table 45).

Table 45. Univariate Cox regression of the EFS

		Event/Total (%)	HR	95.0% CI HR	p-value
Arm (Baseline)	**Experimental**	36/56 (64.3)	1.000		
	Control	39/59 (66.1)	1.178	(0.748;1.855)	0.479
Gender (Baseline)	**Male**	35/57 (61.4)	1.000		
	Female	40/58 (69.0)	1.164	(0.739;1.832)	0.513
Performance Status ECOG (Baseline)	**0-1**	49/77 (63.6)	1.000		
	>=2	26/38 (68.4)	1.095	(0.680;1.762)	0.709
Age >60 years	**<60 years**	36/58 (62.1)	1.000		
	>=60 years	39/57 (68.4)	1.150	(0.731;1.810)	0.546
Adenopathies (Baseline)	**No**	26/43 (60.5)	1.000		
	Yes	49/72 (68.1)	1.180	(0.734;1.900)	0.494
Hepatomegaly (Baseline)	**Yes**	7/10 (70.0)	1.000		
	No	67/103 (65.0)	1.177	(0.540;2.566)	0.682
Splenomegaly (Baseline)	**No**	57/89 (64.0)	1.000		
	Yes	14/21 (66.7)	1.004	(0.559;1.801)	0.990
Lymphomas Other (Baseline)	**No**	46/79 (58.2)	1.000		
	Yes	28/35 (80.0)	1.874	(1.169;3.005)	0.009
Histological Subtype (Baseline)	**GCB**	61/97 (62.9)	1.000		
	No GCB	11/15 (73.3)	1.336	(0.703;2.542)	0.377

Phenotype GCB vs. No-GCB	**GCB**	43/66 (65.2)	932		
	NO-GCB	26/38 (68.4)	1.000	(0.573;1.517)	0.777
CD20 expression (Baseline)	**Yes**	75/115 (65.2)			
Bone marrow infiltration (Baseline)	**Negative**	56/86 (65.1)	1.000		
	Positive	18/23 (78.3)	1.375	(0.808;2.339)	0.241
Clinical Stage (Baseline)	**I**	1/1 (100.0)	1.000		0.191
	II	3/6 (50.0)	0.103	(0.010;1.031)	0.053
	III	19/31 (61.3)	0.135	(0.017;1.058)	0.057
	IV	52/77 (67.5)	0.177	(0.024;1.338)	0.094
Clinical Stage (Baseline	**I-II**	4/7 (57.1)	1.000		
	III-IV	71/108 (65.7)	1.233	(0.450;3.378)	0.684
Extranodal Affectation (Baseline)	**No**	13/28 (46.4)	1.000		
	Yes	62/87 (71.3)	1.931	(1.059;3.520)	0.032
Extranodal Affectation Number (Baseline)	**2 or more**	43/62 (69.4)	1.000		
	1	19/25 (76.0)	1.192	(0.694;2.046)	0.524
Nodal Affectation (Baseline)	**No**	3/16 (18.8)	1.000		
	Yes	70/96 (72.9)	5.874	(1.845;18.701)	0.003
aIPI (Baseline)	**3 (High score)**	23/28 (82.1)	1.000		
	1-2 (Low medium-High medium score)	52/87 (59.8)	1.627	(0.993;2.664)	0.053
Symptoms B (Baseline)	**No**	42/68 (61.8)	1.000		
	Yes	32/46 (69.6)	1.160	(0.731;1.839)	0.529
High LDH	**No**	8/20 (40.0)	1.000		
	Yes	65/93 (69.9)	2.326	(1.115;4.853)	0.025
C-MYC (>=40%) Y BCL2 (>=50%) IHC	**No**	23/43 (53.5)	1.000		
	Yes	39/50 (78.0)	1.912	(1.140;3.207)	0.014
CD30 (>=20%)	**No**	46/67 (68.7)	1.000		
	Yes	15/25 (60.0)	1.363	(0.761;2.443)	0.297

The multivariate Cox regression analysis started entering the variables that showed statistical significance ($p<0.05$) in the univariate Cox regression analysis. According to the clinician criteria the following variables were not entered in the multivariate model: aIPI (Baseline), lymphomas other, extranodal affectation and Nodal affectation (Table 46).

Table 46. Multivariate Cox regression of the EFS (all factors with p-value<0.1 in univariate)

		HR	95.0% CI HR	p-value
High LDH	**No**	1.000		
	Yes	4.338	(1.344;14.000)	0.014
C-MYC (>=40%) Y BCL2 (>=50%) IHC	**No**	1.000		
	Yes	1.637	(0.970;2.762)	0.065

FACTORS ASSOCIATED WITH OS

A *Cox regression analysis* is performed to find significant factors that can influence the OS. Firstly a univariate analysis will be carried out separately for each one of the possible explicative variables to decide which variables are entered in the multivariate models; only those with a statistical association with the dependent variable will be selected. Backward elimination stepwise process will be used to select the model. In the first step all possible predictors will be entered in the model and in each step, the variable that is least significant (that is, the one with the largest P value) will be removed and the model will be refitted. Each subsequent step will remove the least significant variable in the model until all remaining variables have individual P values smaller than 0.05.

In the univariate Cox regression analysis only the variable Lymphomas Other (Baseline) showed statistical significance (p<0.05) (Table 47).

Table 47. Univariate Cox regression of the OS

		Event/Total (%)	HR	95.0% CI HR	p-value
Arm (Baseline)	**Experimental**	13/56 (23.2)	1.000		
	Control	20/59 (33.9)	1.595	(0.793;3.206)	0.190
Gender (Baseline)	**Male**	14/57 (24.6)	1.000		
	Female	19/58 (32.8)	1.349	(0.676;2.691)	0.396
Performance Status ECOG (Baseline)	**0-1**	23/77 (29.9)	1.000		
	>=2	10/38 (26.3)	0.823	(0.392;1.729)	0.606
Age >60 years	**<60 years**	12/58 (20.7)	1.000		
	>=60 years	21/57 (36.8)	1.906	(0.938;3.876)	0.075
Adenopathies (Baseline)	**No**	10/43 (23.3)	1.000		
	Yes	23/72 (31.9)	1.506	(0.717;3.165)	0.280
Hepatomegaly (Baseline)	**Yes**	3/10 (30.0)	1.000		

	No	29/103 (28.2)	0.980	(0.298;3.218)	0.973
Splenomegaly (Baseline)	**No**	28/89 (31.5)	1.000		
	Yes	3/21 (14.3)	0.391	(0.119;1.288)	0.123
Lymphomas Other (Baseline)	**No**	17/79 (21.5)	1.000		
	Yes	16/35 (45.7)	2.530	(1.277;5.011)	0.008
Histological Subtype (Baseline)	**GCB**	25/97 (25.8)	1.000		
	No GCB	6/15 (40.0)	1.805	(0.739;4.407)	0.195
Phenotype GCB-ABC	**GCB**	18/66 (27.3)	1.015		
	NO-GCB	11/38 (28.9)	1.000	(0.479;2.150)	0.969
CD20 expression (Baseline)	**Yes**	33/115 (28.7)			
Bone marrow infiltration (Baseline)	**Negative**	26/86 (30.2)	1.000		
	Positive	7/23 (30.4)	1.075	(0.466;2.479)	0.865
Clinical Stage (Baseline)	**I**	1/1 (100.0)	1.000		0.190
	II	1/6 (16.7)	0.062	(0.004;1.024)	0.052
	III	9/31 (29.0)	0.116	(0.014;0.963)	0.046
	IV	22/77 (28.6)	0.115	(0.015;0.897)	0.039
Clinical Stage (Baseline)	**I-II**	2/7 (28.6)	1.000		
	III-IV	31/108 (28.7)	0.994	(0.238;4.156)	0.994
Extranodal Affectation (Baseline)	**No**	6/28 (21.4)	1.000		
	Yes	27/87 (31.0)	1.590	(0.656;3.852)	0.305
Extranodal Affectation Number (Baseline)	**2 or more**	16/62 (25.8)	1.000		
	1	11/25 (44.0)	1.805	(0.837;3.890)	0.132
Nodal Affectation (Baseline)	**No**	2/16 (12.5)	1.000		
	Yes	30/96 (31.3)	2.720	(0.650;11.385)	0.171
aIPI (Baseline)	**3 (High score)**	24/87 (27.6)	1.000		
	1-2 (Low medium-High medium score)	9/28 (32.1)	1.104	(0.513;2.376)	0.799
Symptoms B (Baseline)	**No**	20/68 (29.4)	1.000		
	Yes	13/46 (28.3)	0.919	(0.457;1.848)	0.813
High LDH	**No**	4/20 (20.0)	1.000		
	Yes	27/93 (29.0)	1.552	(0.543;4.437)	0.412
C-MYC (>=40%) Y BCL2 (>=50%) IHC	**No**	9/43 (20.9)	1.000		
	Yes	15/50 (30.0)	1.521	(0.665;3.480)	0.320
CD30 (>=20%)	**No**	20/67 (29.9)	1.000		
	Yes	3/25 (12.0)	2.897	(0.860;9.755)	0.086

After excluding (According to the clinician criteria) the following variables from the multivariate model: aIPI (Baseline), lymphomas other, extranodal affectation and Nodal affectation, none variable showed statistically significance in the univariate models (all p-values>0.05).

12. SAFETY EVALUATION

12.1. EXTENT OF EXPOSURE

Safety assessments included patient history and physical examinations, vital signs, ECOG PS, AEs, blood chemistry, and blood counts which were performed at each visit. AE severity was graded according to the NCI-CTCAE, version 3.0. Relation of AEs to bortezomib or chemotherapy (definitely, probably, possibly, unlikely, or unrelated) were assessed by the PI at each site.

The median duration of the study treatment was 6 cycles (1–6); 1 patient (23-003, control arm) prematurely discontinued treatment (after 3 cycles) due to ischemic heart disease related to doxorubicin.

12.2. ADVERSE EVENTS (AEs)

12.2.1. BRIEF SUMMARY OF ADVERSE EVENTS

A total of 121 patients received at least 1 infusion of study treatment and were included in the safety analysis. The analysis was performed considering the worst grade of reported AE per patient and considering a sample size of 121 patients.

A total of 116 patients (95.9%) presented any AEs, and 84 (69.4%) presented with grade 3 and grade 4 AEs.

Statistically significant differences were found between arms in the proportion of patients who presented AEs related to any treatment: 88.3 in the experimental arm vs 73.8 in the control arm (p=0.041) (Table 48).

No differences were found between arms in the proportion of patients with: any Adverse Event (95% vs 96.7, p=0.680), any Adverse Event grade ≥3 (73.3% vs 65.6, p=0.146), any AE grade ≥3 related to any treatment (63.3 vs 49.2%, p=0.117), any SAE (38.3% vs 37.7%, p=0.925), SAE related to any treatment (30.0% vs 26.2%, p=0.645), any haematological AE (65% vs 59%, p=0.498), haematological AE grade ≥3 (56.7% vs 50.8%, p=0.519), non-haematological AE (91.7% vs 95.1%, p=0.491) and non-haematological AE grade ≥3 (43.3% vs 34.4%, p=0.315).

Table 48. Safety variables

Variables	Categories	Experimental N (%)	Control N (%)	Total N (%)	p-value
AE (any)	No	3 (5.0)	2 (3.3)	5 (4.1)	0.680 (2)
	Yes	57 (95.0)	59 (96.7)	116 (95.9)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
AE grade ≥3	No	16 (26.7)	21 (34.4)	37 (30.6)	0.146 (1)
	Yes	44 (73.3)	40 (65.6)	84 (69.4)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
AE related to any treatment	No	7 (11.7)	16 (26.2)	23 (19.0)	0.041 (1)
	Yes	53 (88.3)	45 (73.8)	98 (81.0)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
AE related to Bortezomib	No	14 (23.3)			----
	Yes	46 (76.7)			
	Total	60 (100.0)			
AE grade ≥3 related to any treatment	No	22 (36.7)	31 (50.8)	53 (43.8)	0.117(1)
	Yes	38 (63.3)	30 (49.2)	68 (56.2)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
AE grade ≥3 related to Bortezomib	No	30 (50.0)			----
	Yes	30 (50.0)			
	Total	60 (100.0)			
SAE	No	36 (60.0)	38 (62.3)	74 (61.2)	0.925 (2)
	Yes	23 (38.3)	23 (37.7)	46 (38.0)	
	UK	1 (1.7)	0 (0.0)	1 (0.8)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
SAE related to any treatment	No	42 (70.0)	45 (73.8)	87 (71.9)	0.645 (1)
	Yes	18 (30.0)	16 (26.2)	34 (28.1)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
SAE related to Bortezomib	No	43 (71.7)			----
	Yes	17 (28.3)			
	Total	60 (100.0)			
Haematological AE	No	21 (35.0)	25 (41.0)	46 (38.0)	0.498 (1)
	Yes	39 (65.0)	36 (59.0)	75 (62.0)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
Non haematological AE	No	5 (8.3)	3 (4.9)	8 (6.6)	0.491 (1)

	Yes	55 (91.7)	58 (95.1)	113 (93.4)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
Haematological AE grade ≥3	No	26 (43.3)	30 (49.2)	56 (46.3)	0.519 (1)
	Yes	34 (56.7)	31 (50.8)	65 (53.7)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	
Non haematological AE grade ≥3	No	34 (56.7)	40 (65.6)	74 (61.2)	0.315 (1)
	Yes	26 (43.3)	21 (34.4)	47 (38.8)	
	Total	60 (100.0)	61 (100.0)	121 (100.0)	

1: Chi-square test; 2: Fisher's exact test

The main undesirable effect at any grade was neutropenia which occurred in 63 (52.1%) patients, pain and general disorders in 47 patients (38.8%), nausea and vomiting in 46 patients (38.0%), and infections in 46 patients (38.0%) followed by pain musculoskeletal/soft tissue (36.4%), asthenia (36.4%), respiratory disorders (34.7%) and febrile neutropenia (27.3%) (Table 49).

Table 49. Every AE (ordered by frequency)

	Experimental N (%)	Control N (%)	Total N (%)
Neutropenia	34 (56.7%)	29 (47.5%)	63 (52.1%)
Pain and General disorders	21 (35.0%)	26 (42.6%)	47 (38.8%)
Nausea and vomiting	27 (45.0%)	19 (31.1%)	46 (38.0%)
Infection	23 (38.3%)	23 (37.7%)	46 (38.0%)
Pain Musculoskeletal/Soft tissue	19 (31.7%)	25 (41.0%)	44 (36.4%)
Asthenia	20 (33.3%)	24 (39.3%)	44 (36.4%)
Respiratory disorders	20 (33.3%)	22 (36.1%)	42 (34.7%)
Febrile neutropenia	18 (30.0%)	15 (24.6%)	33 (27.3%)
Fever	15 (25.0%)	17 (27.9%)	32 (26.4%)
Constipation	15 (25.0%)	17 (27.9%)	32 (26.4%)
Mucositis	12 (20.0%)	17 (27.9%)	29 (24.0%)
Gastrointestinal disorders	13 (21.7%)	14 (23.0%)	27 (22.3%)
Diarrhea	12 (20.0%)	14 (23.0%)	26 (21.5%)
Anemia	13 (21.7%)	13 (21.3%)	26 (21.5%)
Plaquetopenia	13 (21.7%)	7 (11.5%)	20 (16.5%)
Neuropathy	8 (13.3%)	11 (18.0%)	19 (15.7%)
Cephalea	9 (15.0%)	10 (16.4%)	19 (15.7%)
Vascular disorders	7 (11.7%)	10 (16.4%)	17 (14.0%)
Cardiac disorders	7 (11.7%)	10 (16.4%)	17 (14.0%)

Metabolic/Lab. disorders	8 (13.3%)	8 (13.1%)	16 (13.2%)
Anorexia	7 (11.7%)	9 (14.8%)	16 (13.2%)
Skin disorders	7 (11.7%)	8 (13.1%)	15 (12.4%)
Vasovagal	7 (11.7%)	7 (11.5%)	14 (11.6%)
Neurological disorders	6 (10.0%)	8 (13.1%)	14 (11.6%)
Edema	5 (8.3%)	9 (14.8%)	14 (11.6%)
Lymphopenia	5 (8.3%)	7 (11.5%)	12 (9.9%)
Anxiety	7 (11.7%)	3 (4.9%)	10 (8.3%)
Renal/Genitourinary	4 (6.7%)	5 (8.2%)	9 (7.4%)
Paresthesia	2 (3.3%)	6 (9.8%)	8 (6.6%)
Insomnia	3 (5.0%)	5 (8.2%)	8 (6.6%)
Infusional reaction	6 (10.0%)	2 (3.3%)	8 (6.6%)
Eye disorders	6 (10.0%)	2 (3.3%)	8 (6.6%)
Dyspepsia	6 (10.0%)	2 (3.3%)	8 (6.6%)
Constitutional Symptoms	6 (10.0%)	2 (3.3%)	8 (6.6%)
Rash	6 (10.0%)	1 (1.6%)	7 (5.8%)
Allergic Reaction	3 (5.0%)	4 (6.6%)	7 (5.8%)
Hepatotoxicity	3 (5.0%)	3 (4.9%)	6 (5.0%)
Sweating	2 (3.3%)	3 (4.9%)	5 (4.1%)
Rectorragie/Hemorrhoids	1 (1.7%)	4 (6.6%)	5 (4.1%)
Herpes Zoster	4 (6.7%)	1 (1.6%)	5 (4.1%)
Somnolence	3 (5.0%)	1 (1.6%)	4 (3.3%)
Pleural effusion	2 (3.3%)	2 (3.3%)	4 (3.3%)
Leukopenia	2 (3.3%)	2 (3.3%)	4 (3.3%)
Herpes	1 (1.7%)	3 (4.9%)	4 (3.3%)
Dysgeusia	3 (5.0%)	1 (1.6%)	4 (3.3%)
Tumor lysis syndrome	3 (5.0%)	0 (0.0%)	3 (2.5%)
Musculoskeletal/Soft tissue	1 (1.7%)	2 (3.3%)	3 (2.5%)
Endocrine disorders	0 (0.0%)	3 (4.9%)	3 (2.5%)
Contusion	1 (1.7%)	2 (3.3%)	3 (2.5%)
Secondary Neoplasm	1 (1.7%)	1 (1.6%)	2 (1.7%)
Renal toxicity	1 (1.7%)	1 (1.6%)	2 (1.7%)
Abdominal distension	1 (1.7%)	1 (1.6%)	2 (1.7%)
Vomiting	1 (1.7%)	0 (0.0%)	1 (0.8%)
Hypovolemic Shock	0 (0.0%)	1 (1.6%)	1 (0.8%)

Severe metabolic acidosis	0 (0.0%)	1 (1.6%)	1 (0.8%)
Possible rabdomiolisis	0 (0.0%)	1 (1.6%)	1 (0.8%)
Pancytopenia	0 (0.0%)	1 (1.6%)	1 (0.8%)
Nodule	1 (1.7%)	0 (0.0%)	1 (0.8%)
No valid	1 (1.7%)	0 (0.0%)	1 (0.8%)
Nausea/vomiting	0 (0.0%)	1 (1.6%)	1 (0.8%)
Lymphocele	1 (1.7%)	0 (0.0%)	1 (0.8%)
Gouty arthropathy	0 (0.0%)	1 (1.6%)	1 (0.8%)
Fall	0 (0.0%)	1 (1.6%)	1 (0.8%)
Erectile dysfunction	0 (0.0%)	1 (1.6%)	1 (0.8%)
Disorders of the auditory system	1 (1.7%)	0 (0.0%)	1 (0.8%)
Dermatology/Skin	1 (1.7%)	0 (0.0%)	1 (0.8%)
Chest wall pain	1 (1.7%)	0 (0.0%)	1 (0.8%)
Ascites	1 (1.7%)	0 (0.0%)	1 (0.8%)

Table 50 contains all the AE grade ≥3. Neutropenia G4 was the most common AE grade ≥3 presented in 34.7% of the patients.

Table 50. Every AE grade ≥3

	Experimental N (%)	Control N (%)	Total N (%)
Anemia - G3	5 (8.3%)	1 (1.6%)	6 (5.0%)
Anorexia - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Cephalea - G3	2 (3.3%)	0 (0.0%)	2 (1.7%)
Eye disorders - G3	1 (1.7%)	0 (0.0%)	1 (0.8%)
Febrile neutropenia - G3	12 (20.0%)	7 (11.5%)	19 (15.7%)
Febrile neutropenia - G4	6 (10.0%)	3 (4.9%)	9 (7.4%)
Gastrointestinal disorders - G3	0 (0.0%)	3 (4.9%)	3 (2.5%)
Gastrointestinal disorders - G4	1 (1.7%)	1 (1.6%)	2 (1.7%)
Pain and General disorders- G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Infection - G3	4 (6.7%)	4 (6.6%)	8 (6.6%)
Infection - G4	0 (0.0%)	1 (1.6%)	1 (0.8%)
Infusional reaction - G3	2 (3.3%)	1 (1.6%)	3 (2.5%)
Leukopenia - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Leukopenia - G4	1 (1.7%)	0 (0.0%)	1 (0.8%)
Lymphopenia - G3	2 (3.3%)	2 (3.3%)	4 (3.3%)

Lymphopenia - G4	3 (5.0%)	3 (4.9%)	6 (5.0%)
Mucositis - G3	2 (3.3%)	2 (3.3%)	4 (3.3%)
Nausea and vomiting - G3	0 (0.0%)	2 (3.3%)	2 (1.7%)
Neurological disorders - G3	1 (1.7%)	0 (0.0%)	1 (0.8%)
Neuropathy - G3	0 (0.0%)	2 (3.3%)	2 (1.7%)
Neutropenia - G3	7 (11.7%)	10 (16.4%)	17 (14.0%)
Neutropenia - G4	25 (41.7%)	17 (27.9%)	42 (34.7%)
Pain Musculoskeletal/Soft tissue - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Pancytopenia - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Plaquetopenia - G3	5 (8.3%)	2 (3.3%)	7 (5.8%)
Plaquetopenia - G4	3 (5.0%)	1 (1.6%)	4 (3.3%)
Pleural effusion - G3	1 (1.7%)	0 (0.0%)	1 (0.8%)
Secondary Neoplasm - G4	0 (0.0%)	1 (1.6%)	1 (0.8%)
Tumor lysis syndrome - G3	2 (3.3%)	0 (0.0%)	2 (1.7%)
Vasovagal - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)

12.2.2. TREATMENT-RELATED ADVERSE EVENTS

A total of 121 patients received at least 1 dose of infusion of study treatment and were included in the safety analysis. A total of 98 patients (81.0%) presented with AEs related to study treatment; 68 (56.2%) patients presented grade 3 and 4 AEs related to the study treatment.

The analysis of AEs related to bortezomib showed that a total of 46 (76.7%) patients presented any grade AEs; 30 (50.0%) patients presented grade 3 and 4 AEs. No grade 5 toxicities were reported. Table 51 contains all the AE related (toxicities) ordered by frequencies. Neutropenia was the most common AE related presented in 38.8% of the patients.

Table 51. Every AE related (toxicities ordered by frequency)

	Experimental N (%)	Control N (%)	Total N (%)
Neutropenia	28 (46.7%)	19 (31.1%)	47 (38.8%)
Febrile neutropenia	14 (23.3%)	12 (19.7%)	26 (21.5%)
Nausea and vomiting	15 (25.0%)	5 (8.2%)	20 (16.5%)
Anemia	9 (15.0%)	6 (9.8%)	15 (12.4%)
Plaquetopenia	10 (16.7%)	4 (6.6%)	14 (11.6%)
Neuropathy	7 (11.7%)	6 (9.8%)	13 (10.7%)
Infection	4 (6.7%)	8 (13.1%)	12 (9.9%)

Asthenia	7 (11.7%)	5 (8.2%)	12 (9.9%)
Lymphopenia	4 (6.7%)	5 (8.2%)	9 (7.4%)
Pain and General disorders	8 (13.3%)	1 (1.6%)	9 (7.4%)
Infusional reaction	6 (10.0%)	2 (3.3%)	8 (6.6%)
Fever	4 (6.7%)	4 (6.6%)	8 (6.6%)
Diarrhea	4 (6.7%)	4 (6.6%)	8 (6.6%)
Respiratory disorders	4 (6.7%)	3 (4.9%)	7 (5.8%)
Mucositis	3 (5.0%)	4 (6.6%)	7 (5.8%)
Skin disorders	2 (3.3%)	4 (6.6%)	6 (5.0%)
Pain Musculoskeletal/Soft tissue	3 (5.0%)	2 (3.3%)	5 (4.1%)
Gastrointestinal disorders	1 (1.7%)	4 (6.6%)	5 (4.1%)
Allergic Reaction	2 (3.3%)	3 (4.9%)	5 (4.1%)
Rash	4 (6.7%)	0 (0.0%)	4 (3.3%)
Vasovagal	3 (5.0%)	0 (0.0%)	3 (2.5%)
Vascular disorders	1 (1.7%)	2 (3.3%)	3 (2.5%)
Paresthesia	1 (1.7%)	2 (3.3%)	3 (2.5%)
Neurological disorders	2 (3.3%)	1 (1.6%)	3 (2.5%)
Leukopenia	2 (3.3%)	1 (1.6%)	3 (2.5%)
Hepatotoxicity	1 (1.7%)	2 (3.3%)	3 (2.5%)
Constitutional Symptoms	2 (3.3%)	1 (1.6%)	3 (2.5%)
Tumor lysis syndrome	2 (3.3%)	0 (0.0%)	2 (1.7%)
Dyspepsia	2 (3.3%)	0 (0.0%)	2 (1.7%)
Constipation	2 (3.3%)	0 (0.0%)	2 (1.7%)
Cephalea	1 (1.7%)	1 (1.6%)	2 (1.7%)
Renal/Genitourinary	1 (1.7%)	0 (0.0%)	1 (0.8%)
Renal toxicity	1 (1.7%)	0 (0.0%)	1 (0.8%)
Rectorrhagia/Hemorrhoids	0 (0.0%)	1 (1.6%)	1 (0.8%)
Pancytopenia	0 (0.0%)	1 (1.6%)	1 (0.8%)
Metabolic/Lab. disorders	0 (0.0%)	1 (1.6%)	1 (0.8%)
Herpes Zoster	0 (0.0%)	1 (1.6%)	1 (0.8%)
Edema	0 (0.0%)	1 (1.6%)	1 (0.8%)
Dysgeusia	0 (0.0%)	1 (1.6%)	1 (0.8%)
Cardiac disorders	1 (1.7%)	0 (0.0%)	1 (0.8%)
Anxiety	1 (1.7%)	0 (0.0%)	1 (0.8%)

Table 52 contains all the AE related (toxicities) grade ≥3. Neutropenia G4 was the most common AE related grade ≥3 presented in 26.4% of the patients.

Table 52. Every AE related (toxicities) grade ≥3

	Experimental N (%)	Control N (%)	Total N (%)
Anemia - G3	3 (5.0%)	1 (1.6%)	4 (3.3%)
Febrile neutropenia - G3	10 (16.7%)	5 (8.2%)	15 (12.4%)
Febrile neutropenia - G4	4 (6.7%)	2 (3.3%)	6 (5.0%)
Gastrointestinal disorders - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Gastrointestinal disorders - G4	0 (0.0%)	1 (1.6%)	1 (0.8%)
Infection - G3	1 (1.7%)	2 (3.3%)	3 (2.5%)
Infection - G4	0 (0.0%)	1 (1.6%)	1 (0.8%)
Infusional reaction - G3	2 (3.3%)	1 (1.6%)	3 (2.5%)
Leukopenia - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Leukopenia - G4	1 (1.7%)	0 (0.0%)	1 (0.8%)
Lymphopenia - G3	2 (3.3%)	2 (3.3%)	4 (3.3%)
Lymphopenia - G4	2 (3.3%)	3 (4.9%)	5 (4.1%)
Nausea and vomiting - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Neurological disorders - G3	1 (1.7%)	0 (0.0%)	1 (0.8%)
Neuropathy - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Neutropenia - G3	6 (10.0%)	6 (9.8%)	12 (9.9%)
Neutropenia - G4	20 (33.3%)	12 (19.7%)	32 (26.4%)
Pancytopenia - G3	0 (0.0%)	1 (1.6%)	1 (0.8%)
Plaquetopenia - G3	3 (5.0%)	2 (3.3%)	5 (4.1%)
Plaquetopenia - G4	2 (3.3%)	0 (0.0%)	2 (1.7%)
Tumor lysis syndrome - G3	2 (3.3%)	0 (0.0%)	2 (1.7%)

12.3. SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

Overall, 46 patients (38.3% experimental vs. 37.7% control) presented with at least 1 SAE of any grade; related to any treatment: 30.0% vs. 26.2%. No grade 5 SAEs were reported. Treatment was withdrawn in 1 patient due to ischemic heart disease related to doxorubicin. Two patients were withdrawn due to an infection: 1 case due to pulmonary aspergillosis (related to prednisone) and the other was due to pneumonia (not related to the study treatment).

A total of 9 patients presented with grade 4 SAEs related to the study medication. Grade 4 febrile neutropenia was observed in 6 patients, and most of these patients (5 out of 6) recovered within 7 days. Thrombopenia (n=1), neutropenia (n=1), leucopenia (n=1), infection (n=1), and gastrointestinal disorders (n=1) related to study treatment were also reported.
Febrile neutropenia was the most common grade 3 SAE (n=17), related to the study treatment in 15 cases. Infections and infestations was the second most reported grade 3 SAE (n=8) related to the study treatment in 3 cases. Moreover, grade 3 SAEs of gastrointestinal disorders were reported in 3 patients; 1 case was related to the study treatment, and 2 cases of tumour lysis syndrome were both related to het study treatment.
One patient presented a secondary neoplasm not related to study treatment. More information is provided in Appendix 15.2.2.

12.4. DEATHS

At the time of database closure, 33 deaths were reported in the trial. For 2 cases, causes of death were not reported; 31 patients died due to other reasons described below.
Among these 31 patients, 24 deaths (69.2% in the experimental arm vs. 75.0% in the control arm) were related to lymphoma according to the PI; in the remaining 7 patients, the following events were identified as causes death:

- Pulmonary aspergillosis
- Multiorgan refractory failure to treatment due to shock of ethnic pulmonary origin
- Respiratory infection and lymphoma progression at the pulmonary level
- Advanced high-grade lymphoma constitutional B syndrome; tumour intestinal obstruction and tumour ascites (peritoneal lymphomatosis)
- Pneumonia
- Severe sepsis in a neutropenic patient
- Septic shock secondary to bacteraemia per kpc post-transplant

A total of 2 patients died while receiving study treatment or within 30 days after receiving the last dose of study treatment (EoT); in both these cases, reasons for death according to the were pneumonia unrelated to the study treatment and pulmonary aspergillosis related to prednisone (Table 53).

Table 53. Possibly treatment-related deaths

Patient number	Event	Treatment	Investigator casual relationship to IMP	Timeframe regarding treatment	SUSAR
01-016	Pulmonary aspergillosis	R-CHOP	Prednisone	19 days	No

Abbreviation: SUSAR, suspected unexpected serious adverse event

12.5. CLINICAL LABORATORY EVALUATION

At SIVs, normal laboratory ranges and laboratory certification were recorded for each site. Baseline laboratory evaluations of patients were systematically reviewed by CRAs to monitor eligibility.

According to the protocol, blood tests included the following:

- Haematology tests: haemoglobin, platelets, WBC count, and WBC differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

- Biochemistry tests: creatinine, urea, urate, sodium, potassium, calcium, glucose, total proteins, albumin, (depending on the centre's standard practice), LDH, beta-2 microglobulin, AST, ALT,and total bilirubin.

Only at baseline: monoclonal component, IgG, IgA, IgM, serology, and coagulation.

After study initiation, all clinical laboratory evaluations were performed by PIs at each visit according to the protocol and following their local practice. All parameters of laboratory tests were characterised by PIs as "normal, ""abnormal without clinical relevance," and "abnormal with clinical relevance".
CRAs reviewed the corresponding laboratory evaluations when monitoring AEs and SAEs.

Clinical laboratory toxicities were collected in the corresponding eCRF forms; they are described in the AE section of this CSR. A descriptive analysis of recorded laboratory AEs along with the percentage of incidence (%) are presented both as general AEs and categorised as SAEs and SUSARs.

12.5.1. VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Baseline vital signs, physical examinations, and other observations related to safety were systematically reviewed by CRAs in patients to monitor their eligibility criteria.

According to the protocol, the following determinations regarding vital signs, physical examinations, and other observations related to safety were performed:

- Blood pressure and temperature measurements
- Weight and height
- ECOG PS
- Physical examination
- ECG characterised as "with or without" significant alteration
- Pregnancy test

After study initiation, evaluations were performed by principal investigators at each visit

according to the protocol and following their local practice. CRAs reviewed the corresponding evaluations when monitoring AEs and SAEs.

Data on ECOG PS were available for all patients enrolled in the trial.

Non-haematological toxicities were recorded in the corresponding eCRFs, and are described in the AEs section of this CSR. A descriptive analysis of recorded AEs along with the percentage of incidence (%) are presented both as general AEs and categorised as SAEs and SUSARs.

12.6. CONCOMITANT MEDICATION USE

Throughout the trial, investigators prescribed concomitant medication or treatment considered necessary to provide adequate supportive care, with the exception of other investigational products.

Baseline concomitant medications were recorded in the eCRF and included all drugs received within 30 days before study treatment initiation.

Concomitant medications were also recorded up to 30 days after the last dose of the study treatment. A follow-up of the concomitant medications used for clinically significant AEs was performed until the AEs resolved or were considered stable.

CRAs reviewed concomitant medications when monitoring AEs and SAEs.

No relevant data regarding concomitant medications were observed by the sponsor. Therefore, they are not reported in this CSR.

13. DISCUSSION AND OVERALL CONCLUSIONS

Survival of patients with DLBCL and high IPI has been widely evidenced as poor; treatments alternatives for this high risk population are still limited when the aim is to avoid relapse. Stratification of patients according evidenced prognostic factors has been defined as a helpful strategy for treatment selection. For this study, the age-adjusted IPI score and type of DLBCL (activated B cell-like/ABC) were considered for selecting patients a population of study who are considered of high risk/unfavourable prognosis; willing to evaluate if the addition of the proteasome inhibitor bortezomib to the RCAP regimen can be at least comparable with the standard of care, R-CHOP.

Results of this study have been assessed based on two different groups of treatment that were followed for a median 28.3 months, overall, clinically comparable at baseline except for nodal affectation that was statistically more frequent in the experimental arm, 92.9% vs. 74.6%, but, of note, not significantly different when median number of affected nodes were summarized and compared, 5.0 vs. 6.0).

Combination of R-CHOP with new drugs is an attractive approach, along with performing an early evaluation with PET/CT after 2 to 4 cycles and change induction therapy if a complete response is not achieved. Analysis of the two-arm designed study with 121 patients divided into two arms (R-CHOP vs. BRCAP) has shown that, overall, no statistical significant differences were observed when comparing the total number of patients with complete response (CR) nor the proportion of patients free of event after 2 years since start of treatment and event-free survival, all when intention-to-treat population was analyzed and also when patients were classified based on GCB or no-GCB phenotype. These similarities were also evident when patients were summarized and compared based on treatment arm and phenotype.
Univariate and multivariate analysis on factors with possible association with EFS + complete response at 24 months allowed to consider that nodal affectation at baseline and a high LDH value might be statistically associated with the probability of not reaching complete response nor of been free of event. On the other hand, overall survival (mean/sd: 34.03/2.84 months) was not associated with a particular characteristic at baseline, nor treatment arm.

Of note, 27 patients were reported as positive at time of PET4, so treatment was adapted as intended by protocol. As per protocol, the PET4 and PET6 evaluation was proposed as a possible prognosis factor for EFS and OS and evaluated for sensitivity and specificity through ROC curves based on the SUV change, showing in both cases, a fair and comparable accuracy. Post-therapy response assessment through PET has been subject of several analyses and guidelines (Kobe C et al. *PET/CT for Lymphoma Post-therapy Response Assessment in Hodgkin Lymphoma and Diffuse Large B-cell Lymphoma.* Semin Nucl Med. 2018; 48:28-36. Casasnovas RO et aL. *FDG-PET-driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study.* Blood. 2017; 130:1315-1326. Islam et al. *PET-derived tumor metrics predict DLBCL response and progression-free survival.* Leuk Lymphoma. 2019; 4:1-7) and considered as a better predictive tool that contrast-enhanced CT scan for therapeutic decision making (Le Gouill et al. *Interim PET-driven strategy in de novo*

diffuse large B-cell lymphoma: do we trust the driver? Blood. 2017; 129:3059-3070).

Furthermore, subcutaneous administration of bortezomib has been tested in multiple myeloma with similar response to treatment (*Mu SD et al. Subcutaneous versus Intravenous Bortezomib Administration for Multiple Myeloma Patients: a Meta-analysis. Curr Med Sci 2018; 38:43-50*), but a much more largely decreased incidence of adverse events such as grade 3 thrombocytopenia or bortezomib-induced peripheral neuropathy (BIPN). The pharmacokinetic profile of intravenous bortezomib is characterized by a two-compartment model with a rapid distribution phase followed by a longer elimination phase and a large volume of distribution (*Tan CRC et al, Clinical Pharmacokinetics and Pharmacodynamics of Bortezomib, 2019;58:157-168*). The main mechanism of action of bortezomib, that goes through inhibition of chymotrypsin-like site of the 20S proteolytic core within the 26S proteasome, induces cell-cycle arrest and apoptosis, whether it is intravenous or subcutaneously. This homogeneity is also observed when frequency of adverse events in this trials, that is comparable to the available data on intravenous administration of the drug.

Results of this study allow to conclude that there are no significant differences on efficacy or safety of treatment with R-CHOP or with BRCAP in this very high-risk population of young DLBCL patients.

14. TABLES, FIGURES AND GRAPHS

Tables and figures are included in the corresponding sections of this CSR.

In appendix 15.3 “Graphs” include the following tables, figures and graphs:

- Characteristics baseline graphs
- Safety analysis graphs

15. APPENDICES

15.1 STUDY INFORMATION

15.1.1. Last version of Protocol including amendments

15.1.2. PET project study plan

15.1.3. Biomarkers project study plan

15.1.4. Case Report Form

15.1.5. Last version of Subject Information documents

- General patient information sheet and informed consent, version 3.0_07JAN2014
- Patient information sheet and consent form for biological samples, version 3.0_07JAN2014

15.1.6. Ethics Committees positive vote

15.1.7. Regulatory Approval

15.1.8. Randomisation Code Listing

15.1.9. Publications based on the study

15.1.10 Protocol deviation Listing

15.2. PATIENT DATA LISTINGS

15.2.1. Listing of Adverse Events by Patient

15.2.2. Listing of Severe Adverse Events

15.2.3. Individual patient data of efficacy

15.3. GRAPHS