OSPEDALE SAN RAFFAELE
ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

SINGLE-CENTER, RETROSPECTIVE STUDY AIMED TO PERFORM A MOLECULAR CHARACTERIZATION OF AGGRESSIVE B-CELL LYMPHOMAS (DIFFUSE LARGE B-CELL LYMPHOMA, HIGH-GRADE B-CELL LYMPHOMA WITH MYC AND BCL2 AND/OR BCL6 TRANSLOCATIONS, HIGH-GRADE B-CELL LYMPHOMA NOT OTHERWISE SPECIFIED) AND TO OBSERVE THE CLINICAL PATIENTS' OUTCOMES ACCORDING TO THE 2017 WHO CLASSIFICATION

Protocol Acronym: CHARTHER

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Sponsor: IRCCS Ospedale San Raffaele

Authorized Sponsor Representative: Fabio Ciceri

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Principal Investigator: Andrés J.M. Ferreri, MD
Lymphoma Unit, Dept. of Onco-Hematology
IRCCS Ospedale San Raffaele, Milan, Italy

Co-Principal Investigator:
Maurilio Ponzoni, Prof
Pathology Unit
IRCCS San Raffaele Scientific Institute, Milan, Italy

Co- Investigator:
Lorenza Pecciarini, MS
Pathology Unit
IRCCS San Raffaele Scientific Institute, Milan, Italy

PROTOCOL SIGNATURE PAGE

Study Title: SINGLE-CENTER, RETROSPECTIVE STUDY AIMED TO PERFORM A MOLECULAR CHARACTERIZATION OF AGGRESSIVE B-CELL LYMPHOMAS (DIFFUSE LARGE B-CELL LYMPHOMA, HIGH-GRADE B-CELL LYMPHOMA WITH MYC AND BCL2 AND/OR BCL6 TRANSLOCATIONS, HIGH-GRADE B-CELL LYMPHOMA NOT OTHERWISE SPECIFIED) AND TO OBSERVE THE CLINICAL PATIENTS' OUTCOMES ACCORDING TO THE 2017 WHO CLASSIFICATION

Protocol Acronym: CHARTHER

Protocol Version and Date: Version 1, Date 21/03/2022

The undersigned has read and understood all the aspects of the protocol detailed within this document and agrees to supervise and conduct the trial in accordance with the protocol, Guideline for Good Clinical Practice ICH E6 (R2), Declaration of Helsinki, and all applicable regulatory requirements.

Authorized Sponsor Fabio Ciceri	**Signature**	**Affiliation**	**Date**

Principal Investigator Andrés J.M. Ferreri	**Signature**	**Affiliation**	**Date**

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KEY TRIAL CONTACTS

Sponsor	IRCCS Ospedale San Raffaele Via Olgettina, 60 20132 – Milano, Italy
Authorized Sponsor Representative	Fabio Ciceri, Prof/MD Head of Onco-Hematology and Bone Marrow Transplant Unit IRCCS Ospedale San Raffaele, Milan, Italy Via Olgettina 60 20132 – Milan, Italy Email: ciceri.clinicaltrials@hsr.it
Principal Investigator	Andrés J.M. Ferreri, MD Lymphoma Unit, Dept. of Onco-Hematology IRCCS Ospedale San Raffaele, Milan, Italy Via Olgettina 60 20132 – Milan, Italy Telephone: 0039-02-2643 7649 E-mail: ferreri.andres@hsr.it
Co-Investigators	Maurilio Ponzoni, Prof Pathology Unit IRCCS San Raffaele Scientific Institute, Milan, Italy Via Olgettina 60 20132 – Milan, Italy Telephone: 0039-02-2643 2544 E-mail: ponzoni.maurilio@hsr.it Lorenza Pecciarini, MS Pathology Unit IRCCS San Raffaele Scientific Institute, Milan, Italy Via Olgettina 60 20132 – Milan, Italy Telephone: 0039-02-2643 2512 E-mail: pecciarini.lorenza@hsr.it
Trial Office	Ufficio Ricerche Cliniche – Stem Cell Program Coordinamento Stefania Trinca Regolatorio Dott. Vincenzo Mercurio
Funding source(s)	Roche S.p.A.

SYNOPSIS (English)

Study Title	Single-center, retrospective study aimed to perform a molecular characterization of aggressive b-cell lymphomas (diffuse large b-cell lymphoma, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations, high-grade B-cell lymphoma not otherwise specified) and to observe the clinical patients' outcomes according to the 2017 WHO classification	
Protocol Acronym/Number	CHARTHER	
Protocol Version and Date	1.0 - 21 March 2022	
Sponsor	IRCCS Ospedale San Raffaele Via Olgettina 60 – 20132, Milan, Italy	
Principal Investigator	Andrés J.M. Ferreri, MD Lymphoma Unit, Dept. of Onco-Hematology IRCCS Ospedale San Raffaele Via Olgettina 60 20132 – Milan, Italy Telephone: 0039-02-2643 7649 E-mail: ferreri.andres@hsr.it	
Study Description	This is a retrospective analysis of the presence of chromosomal rearrangements involving MYC, BCL2 and BCL6 genes by FISH in a retrospective, single-center series of large B-cell lymphomas, in order to allow a better classifications of these cases according to the current WHO 2017 classification. If this evaluation will be confirmed as a reliable method to reclassify in different groups the evaluated tumors, it can be subsequently routinely apply to indicate the best treatment approaches in this high-risk setting of patients with a significant impact on patients' morbidity and mortality, and also on the health system and related costs.	
	Primary	**Secondary**
Objectives	1. To re-classify retrospective series of large B-cell lymphomas (LBCL) according to the current WHO 2017 classification by using FISH for the detection of MYC, BCL2 and BCL6 rearrangements. 2. To establish the association between re-classification of LBCL using FISH for the detection of MYC, BCL2 and	1. To establish the association between re-classification of LBCL using FISH for the detection of MYC, BCL2 and BCL6 rearrangements and patients' outcomes. 2. To establish the association between re-classification of LBCL and risk of relapse. 3. To demonstrate that re-classification of LBCL exploiting FISH for the detection of MYC,

	BCL6 rearrangements and response to therapy.	BCL2 and BCL6 rearrangements is a reliable tool to support treatment decision plan. 4. To complete IHC analysis for further and/or novel pattern of antigen expression in HGBL. 5. To estimate the prevalence of MYC, BCL2 and BCL6 rearrangements/ amplifications detected by FISH in LBCL
Study Population	Adult subjects (> 18 years old) of any age and gender affected by large B-cell lymphoma. We expect to enroll around 555 subjects.	
Inclusion Criteria	• Histologically-confirmed diagnosis of LBCL (i.e., DLBCL, HGBCL, unclassifiable B-cell lymphoma with features intermediate between DLBCL and BL), or aggressive B-cell lymphomas with blastoid morphology (excluding blastoid variant of mantle cell lymphoma and lymphoblastic lymphoma) • Histopathological diagnosis performed between 2000 and 2019. • HIV sero-negativity • Age ≥18 • Treatment with R-CHOP or other intensified polychemotherapy regimen • Availability of adequate histopathological samples at diagnosis for FISH analysis • Availability of clinical records and outcomes data	
Exclusion Criteria	• Histologic diagnosis other than DLBCL or unclassifiable B-cell lymphoma with features intermediate between DLBCL and BL	
Statistical Design	Subjects who fulfil selection criteria for enrolment into the study will undergo local histopathological revision and analysis of chromosomal rearrangements involving MYC, BCL2 and BCL6 genes by FISH. Moreover, completion of IHC analysis for further and/or novel pattern of antigen expression in HGBL will be performed. *Histopathology and Immunohistochemistry* Nodal and extra nodal tissues with a diagnosis of DLBCL, lymphomas with intermediate features between Burkitt lymphoma and DLBCL, Burkitt-like lymphomas, and atypical Burkitt lymphomas will be searched within the files of Pathology Unit at San Raffaele Scientific Institute. The selection process will rely on sequential steps. First, we will retrieve archival cases from our tissue repository placed in a remote place outside our Institution. Second, we will carefully consider only tissue blocks showing enough material to allow completion of immunohistochemistry and FISH analyses.	

	Third, original slides will be reviewed and re-classified according to present WHO (2017) classification of lymphomas. Given that it is expected that a brand-new Classification will be shortly released in the forthcoming months by WHO, it is likely that additional diagnostic criteria will be further included within the central pathology review. Each DLBCL case will be stained, whenever not previously evaluated, with CD10, bcl-6 and MUM-1 antibodies and their respective secondary antibodies using an automated immunostainer. Staining data will be interpreted semiquantitatively. According to immunohistochemical results, each case will be further classified following to Hans' algorithm criteria. Each case will be also evaluated for c-MYC immunoreactivity and will be considered positive whenever more than 40% of cells will be stained for this marker. The correlation with FISH results will enable to select the actual high grade B cell lymphomas, which will be matched with clinical parameters and therapeutic responses. *FISH* Interphase Fluorescence In Situ Hybridization (I-FISH) for detection of MYC, BCL2 and BCL6 rearrangements will be performed on the previously histologically reviewed large B-cell lymphoma cases. A "split-apart" FISH approach will be used: the chosen probes for each gene of interest consist of two direct labelled gene locus regions (green and orange), hybridizing distal and proximal to the gene breakpoint and separation/fusion of the two signals will indicate presence/absence of the rearrangements. Three 4 μm tissue sections will prepared for each sample, they will be pretreated according to the ZytoLight FISH-Tissue Implementation Kit protocol (Zytovision, GmbH). Hybridization will be then carried out overnight on a Thermobrite hybridizer (Euroclone), using the ZytoLight SPEC MYC Dual Color Break Apart Probe, ZytoLight SPEC BCL2 Dual Color Break Apart Probe, ZytoLight SPEC BCL6 Dual Color Break Apart Probe, following the manufacturer protocol; the next day, after unbound probes are removed by stringency washing steps, the slides will be counterstained with DAPI. Hybridized probes will be visualized using a fluorescence microscope (AxioImager Z2, Zeiss) equipped with excitation and emission filters specific for the fluorochromes by which the FISH probes are directly labeled. FISH semiautomatic analysis will be performed using the Metafer4 software (Metasystems): FISH signals will be counted in 200 interphase nuclei from at least 4 to 8 areas selected for well-preserved cellular and nuclear morphology to ensure representative sampling and to avoid nuclear truncation artifacts; a signal split, which indicates gene rearrangement, will be counted when the distance between splitted green and orange signals is ≥2 of the estimated signal diameter. The already defined laboratory cutoff for gene rearrangements will be used (2% for all the used probes).

	Results will be summarized for each case and reported to the pathologist.
Planned Study Periods	Duration of the Enrollment period: 1 year Duration of the retrospective Follow-up: NA Duration of total study period: 1 year

ABBREVIATIONS AND DEFINITIONS

Abbreviations

BL	Burkitt lymphoma
CR	complete remission
DLBCL	diffuse large B-cell lymphoma
DOR	Duration of response
FISH	fluorescent in situ hybridization
HGBL	High-grade B-cell Lymphoma
IC	Informed Consent
I-FISH	Interphase Fluorescence In Situ Hybridization
IHC	immunohistochemistry
OS	Overall Survival
PFS	Progression-free Survival
PR	partial response

BACKGROUND

The 2017 WHO classification introduced the new clinical entity “High-grade B-cell Lymphoma” (HGBL), including large B-cell lymphomas with chromosomal rearrangements involving MYC gene (region 8q24) and BCL2 gene (region 18q21) (so called “double hit lymphoma”, representing 60% of HGBL) and/or BCL6 (region 3q27) (also called “triple hit lymphoma”, representing 20% of HGBL), identified by means of fluorescent in situ hybridization (FISH) and/or conventional cytogenetic analysis. HGBL replaced the old WHO 2008 category of ‘unclassifiable B-cell lymphoma with features intermediate between diffuse large B-cell lymphoma and BL’ and encompasses also diffuse large B-cell lymphoma (DLBCL) by morphology harboring MYC and BCL-2 and/or BCL-6 rearrangements.

Clinically, HGBL are characterized by adverse prognosis and poor response to standard treatments, such as R-CHOP regimen, with a median OS of 12 months or less. The role of

intensified chemo-immunotherapy approaches has been investigated. Promising results emerged when treating patients with R-DA-EPOCH regimen, together with adequate CNS prophylaxis. [Petrich AM, Blood 2014]. Excellent efficacy and safety results were also reported in a multicenter phase II trial addressing a dose-dense, short-term therapy in HIV-positive patients diagnosed with high-risk BL or HGBL with MYC rearrangements [Ferreri et al. BJH 2021]. In the last decades, the “CARMEN” regimen was adopted at out institution and at several Italian Centers also for the treatment of HIV-negative patients diagnosed with high-risk DLBCL as well as B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL with alterations of c-MYC. A retrospective series of 63 HIV-negative and –positive patients (22 HGBL) confirmed good tolerability and efficacy: after induction, 18 (82%) HGBL patients achieved a response, which was CR in 10 (45%) patients. At a median follow-up of 54 (2-131) months, the 5-year PFS and OS among HGBL were 67% and 66%, respectively. HIV seropositivity did not modify outcome.

Although FISH represents the gold standard for detection of MYC, BCL2 and BCL6 rearrangements, it is not routinely recommended in all cases at diagnosis. Indeed, a consensus has not yet been reached to provide specific guidelines as to which LBCL should be evaluated. Some believe that all DLBCL should have genetic studies for the detection of the three genes rearrangements, whereas others would limit them, for example, to cases with a GCB phenotype and/or high-grade morphology or to cases with >40% MYC+ cells in immunohistochemistry (IHC). In particular, at our institution, FISH for MYC is considered when MYC expression by IHC is >40%, and FISH for BCL-2 and BCL-6 are performed only when FISH for MYC is positive. However, since the presence MYC and BCL2 and/or BCL6 rearrangements is not invariably associated with IHC overexpression, the current diagnostic approach could have underestimated the real incidence of HGBL leading to the undertreatment of these patients.

RATIONALE

We propose to retrospectively analyze the presence of chromosomal rearrangements involving MYC, BCL2 and BCL6 genes by FISH in a retrospective, single-center series of large B-cell lymphomas, in order to allow a better classifications of these cases according to the current WHO 2017 classification. If this evaluation will be confirmed as a reliable method to reclassify in different groups the evaluated tumors, it can be subsequently

routinely apply to indicate the best treatment approaches in this high-risk setting of patients with a significant impact on patients' morbidity and mortality, and also on the health system and related costs. Moreover, this study could give important information about the real incidence and predictive value of MYC, BCL2 and BCL6 rearrangements.

OBJECTIVES

Primary objectives:

1. To re-classify retrospective series of large B-cell lymphomas (LBCL) according to the current WHO 2017 classification by using FISH for the detection of MYC, BCL2 and BCL6 rearrangements.
2. To establish the association between re-classification of LBCL using FISH for the detection of MYC, BCL2 and BCL6 rearrangements and survival.

Secondary objectives:

1. To establish the association between re-classification of LBCL using FISH for the detection of MYC, BCL2 and BCL6 rearrangements and patients' response to treatments.
2. To establish the association between re-classification of LBCL and risk of relapse.
3. To demonstrate that re-classification of LBCL exploiting FISH for the detection of MYC, BCL2 and BCL6 rearrangements is a reliable tool to support treatment decision plan.
4. To complete IHC analysis for further and/or novel pattern of antigen expression in HGBL.
5. To estimate the prevalence of MYC, BCL2 and BCL6 rearrangements/ amplifications detected by FISH in LBCL
6. To describe the main treatment patterns according to disease characteristics.

THERAPEUTIC OUTCOME

Primary outcome:

1. Overall Survival (OS)

Secondary outcome:

1. Progression-free Survival (PFS)
2. Overall Response Rate (ORR; partial response [PR] + complete remission [CR])
3. Duration of response (DOR; partial response [PR] + complete remission [CR])
4. Relapse rates and patterns
5. Incidence of MYC, BCL2 and BCL6 rearrangements in LBCL

STUDY DESIGN

Single center, retrospective observational, pharmacological and of molecular characterization study.

Study duration 1 year

STUDY POPULATION

Adult subjects (> 18 years old) of any age and gender affected by large B-cell lymphomas.

Inclusion Criteria:

- Histologically-confirmed diagnosis of LBCL (i.e., DLBCL, HGBCL, unclassifiable B-cell lymphoma with features intermediate between DLBCL and BL), or aggressive B-cell lymphomas with blastoid morphology (excluding blastoid variant of mantle cell lymphoma and lymphoblastic lymphoma)
- Histopathological diagnosis performed between 2000 and 2019.
- HIV sero-negativity
- Age ≥18
- Treatment with R-CHOP or other intensified polychemotherapy regimen
- Availability of adequate histopathological samples at diagnosis for FISH analysis
- Availability of clinical records and outcomes data

Exclusion criteria

- Histologic diagnosis other than DLBCL or unclassifiable B-cell lymphoma with features intermediate between DLBCL and BL

METHODS

Diagnostic tissue samples of patients who fulfil selection criteria for enrolment into the study will undergo local histopathological revision and analysis of chromosomal rearrangements involving MYC, BCL2 and BCL6 genes by FISH. Moreover, completion of IHC analysis for further and/or novel pattern of antigen expression in HGBL will be performed.

Treatments: anthracycline-based combinations followed or not by involved-field radiotherapy

Assignment of Subject Identification

The participants will be assigned a unique trial specific number and will henceforth be identified by that number in the database.

Data Collection

The data of all patients enrolled in the study will be collected from clinical folders and source documents (e.g., hospital records; clinical and office charts; laboratory notes etc.) and registered in the database as described in the following paragraphs.

Histopathology and Immunohistochemistry

Nodal and extra nodal tissues with a diagnosis of DLBCL, lymphomas with intermediate features between Burkitt lymphoma and DLBCL, Burkitt-like lymphomas, and atypical Burkitt lymphomas will be searched within the files of Pathology Unit at San Raffaele Scientific Institute. The selection process will rely on sequential steps. First, we will retrieve archival cases from our tissue repository placed in the Pathology unit of the OSR. Second, we will carefully consider only tissue blocks showing enough material to allow completion of immunohistochemistry and FISH analyses. Third, original slides will be reviewed and re-classified according to present WHO (2017) classification of lymphomas. Given that it is expected that a brand-new Classification will be shortly released in the forthcoming months by WHO, it is likely that additional diagnostic criteria will be further included within the central pathology review.

Each DLBCL case will be stained, whenever not previously evaluated, with CD10, bcl-6 and MUM-1 antibodies and their respective secondary antibodies using an automated immunostainer. Staining data will be interpreted semiquantitatively. According to immunohistochemical results, each case will be further classified following to Hans' algorithm criteria. Each case will be also evaluated for c-MYC immunoreactivity and will be considered positive whenever more than 40% of cells will be stained for this marker. The correlation with FISH results will enable to select the actual high grade B cell lymphomas, which will be matched with clinical parameters and therapeutic responses.

FISH

Interphase Fluorescence In Situ Hybridization (I-FISH) for detection of MYC, BCL2 and BCL6 rearrangements will be performed on the previously histologically reviewed large B-cell lymphoma cases. A "split-apart" FISH approach will be used: the chosen probes for each gene of interest consist of two direct labelled gene locus regions (green and orange), hybridizing distal and proximal to the gene breakpoint and separation/fusion of the two signals will indicate presence/absence of the rearrangements. Three 4 μm tissue sections will prepared for each sample, they will be pretreated according to the ZytoLight FISH-Tissue Implementation Kit protocol (Zytovision, GmbH). Hybridization will be then carried out overnight on a Thermobrite hybridizer (Euroclone), using the ZytoLight SPEC MYC Dual Color Break Apart Probe, ZytoLight SPEC BCL2 Dual Color Break Apart Probe, ZytoLight SPEC BCL6 Dual Color Break Apart Probe, following the manufacturer protocol; the next day, after unbound probes are removed by stringency washing steps, the slides will be counterstained with DAPI. Hybridized probes will be visualized using a fluorescence microscope (AxioImager Z2, Zeiss) equipped with excitation and emission filters specific for the fluorochromes by which the FISH probes are directly labeled. FISH semiautomatic analysis will be performed using the Metafer4 software (Metasystems): FISH signals will be counted in 200 interphase nuclei from at least 4 to 8 areas selected for well-preserved cellular and nuclear morphology to ensure representative sampling and to avoid nuclear truncation artifacts; a signal split, which indicates gene rearrangement, will be counted when the distance between splitted green and orange signals is ≥2 of the estimated signal diameter. The already defined laboratory cutoff for gene rearrangements will be used (2%

for all the used probes). Results will be summarized for each case and reported to the pathologist.

STUDY VARIABLES

Conventional anagraphic variables, findings of histopathological diagnosis, results of IHC and FISH analyses, staging, therapeutic management and outcome will be considered.

DATA MANAGEMENT

Data Recording and Record-Keeping

All relevant data collected during the study for all of the patients enrolled in the study shall be entered in a database (password protected excel) from source documents (e.g., hospital records; clinical and office charts; laboratory notes etc.) by the responsible investigator or someone authorized by the investigator in a timely manner (as soon as possible after the information is collected) to ensure that they are clear, complete and correct.

On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

The investigator shall arrange for the retention of patient files, other source data, and the Trial Master File for at least 7 years after the completion or discontinuation of the study.

Data Protection

The confidentiality of participant data, including, but not limited to forms, records and samples and participant privacy will be maintained according to the GDPR (UE) 2016/679. The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a Patient ID number on the ICF and the electronic database. All documents will be stored securely and only accessible by trial staff and authorized personnel.

Data anonymization

Since this is a retrospective study without ad hoc informed consent, in order to ensure anonymity, the following procedure will be followed for all data of all subjects:

the assigned patient ID will not be related to the identification code present in the patient's clinical material; this will be guaranteed with the following procedures:

- A patient code will be associated with the clinical material (nominal);

- The code will be transcribed in a second document and associated with a second code obtained by randomization (called "Patient ID");
- The patient ID will then be reported in the CRF and the intermediate document will be destroyed at termination of data collection.

At the end of this process and in the continuation of the study, patient data will be treated completely anonymously.

STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Clinical characteristics and response rates of the therapeutic subgroups will be compared using the α2 test or Fisher exact test for categorical variables, according to the sample size. Factors potentially conditioning outcome will be assessed by α2 test and logistic regression. Survival curves will be generated by the Kaplan-Meier method. Overall survival (OS) will be calculated from the date of pathologic diagnosis to death or to the last date of follow-up, while progression-free survival (PFS) will be calculated from the first day of treatment to relapse, progression or death, or to the last date of follow-up. Survival rates will be reported as 2-year OS and 95% CI. Impact on survival of clinical and therapeutic variables will be evaluated by comparing the entire OS curves by means of the log-rank test.

The independent prognostic value of variables will be analyzed using the Cox model. The year of diagnosis will be included as a continuous variable in the multivariate analyses to exclude the possibility that modern medical management could influence outcome more than the treatment itself. Backward stepwise regression will be performed to identify the most powerful predictors of survival. All the probability values will be two-sided. Statistical analysis will be performed with Statistical software (Statistica 10.0, Tuxon, AZ, USA) on a unique database including clinical and pathological data on an estimated sample size of 555 patients.

ETHICAL CONSIDERATIONS AND INFORMED CONSENT

The Investigator and all study staff will ensure that the clinical study is conducted in accordance with good clinical practice and institutional requirements, including those for subject privacy, Ethics Committee approval and record retention, and with the Declaration of Helsinki (revised October 2008) and in compliance with principles defined in the Determinazione of the Agenzia Italiana del Farmaco, dated 20 March 2008. The protocol, being retrospective, will be notified to the IEC of the IRCCS San Raffaele Scientific Institute

of Milan. In the context of clinical practice, patients already provided consent to use of health data for research purposes.

PATIENT SAFETY

Given the observational retrospective nature of the study, for the patients enrolled in this study, there are no additional physical, psychological, or social adverse effects compared to the standard of care clinical practice.

FINANCE AND INSURANCE

The study is non-profit in nature.

Funding for the study has been received from Roche S.p.A.

This funding will cover the whole costs of the study.

Given the observational retrospective nature of this study, no insurance policy is needed.

OWNERSHIP OF DATA AND PUBLICATIONS

The Sponsor has the ownership of all data and results collected during the study. The results of this study will be presented anonymously to national and international scientific meetings and reported in scientific publication focused on translational research.

Each publication of protocol results will occur in mutual agreement between the principal investigator and any other investigators involved. All data will be treated in confidence by the principal investigator and all others involved in the protocol until publication. Final results may only be published (orally or in writing) with agreement from the principal investigator. This is essential for a thorough exchange of information between theaforementioned parties and will ensure that the opinions of all parties involved have been heard before publication. This agreement, which does not include any veto right or right of censorship for any of the parties involved, may not be refused without good reason.

The Principal Investigator/Sponsor is responsible for the preparation of an annual report on the clinical study to be sent to the Ethics Committee and for the preparation of the final report of the clinical study.

REFERENCES

1. Ferreri AJM, Cattaneo C, Lleshi A, et al. A dose-dense short-term therapy for human immunodeficiency virus/acquired immunodeficiency syndrome patients with high-risk

Burkitt lymphoma or high-grade B-cell lymphoma: safety and efficacy results of the "CARMEN" phase II trial. Br J Haematol. 2021;192(1):119-128.

2. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014;124(15):2354-2361.