THE LUPIAE STUDY

Towards personalized medicine for refractory/relapsed Follicular Lymphoma patients: the Cantera/Lupiae registry

VERSION: 1.0

DATE: DECEMBER 13, 2018

INVESTIGATOR AGREEMENT

I have read the attached protocol entitled "Towards personalized medicine for refractory/relapsed Follicular Lymphoma patients – The LUPIAE study" and agree to abide by all provisions set forth therein. I agree to comply with the International Conference on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (GCP) as well as all applicable regulatory requirements.

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Principal Investigator Signature Date

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Principal Investigator Name and Title (printed)

SPONSOR

EHA Lymphoma Group

DATE AND VERSION:

Version 1.0 – December 13, 2018

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SUMMARY

1. INTRODUCTION

Non-Hodgkin's lymphoma (NHL) comprises a heterogeneous group of lymphoproliferative diseases, resulting from a malignant transformation of mature B cells. Follicular Lymphoma (FL) is the second most frequent NHL in the US and Western Countries, accounting for about 10- 20% of all newly diagnosed NHLs and 70% of all indolent Lymphomas.[1, 2] The incidence of FL, as of other non-Hodgkin lymphoma, is rising, but varies between geographical regions and racial groups, being higher in developed countries and lower in Asian and sub-Saharan African countries.[3] In the US the frequency is about one case for every 20.000 or 250000 people per year, whereas in Italy the incidence is approximately 11% and the standardized annual incidence rate is 2 per 100000 people.[3, 4] Generally, the incidence increases with the age and the disease is typically diagnosed during the 5th to 7th decade. Nearly 10% of patients are diagnosed as young adults (age 18-40). Moreover FL is slightly more prevalent in the female population with a male to female ration of 1:1,7.[2–5]

The pathogenesis of FL is best explained by a model that takes into account genetic alterations harbored by the neoplastic B cells and an immunological hypothesis that suggests prominent crosstalk between the tumor cells and non-neoplastic immune cells in the tumor microenvironment, which include T cells, macrophages, follicular dendritic cells and stromal elements.[6] It is well known that the translocation t(14;18), present in about 80-90% of FL, is assumed to represent the first oncogenic hit of lymphomagenesis. This somatic rearrangement juxtaposes the B cell Lymphoma 2 (BCL2 gene) (located on chromosome 18) under the influence of transcriptional enhancers of immunoglobulin variable heavy chains (IgH), thus leading to constitutive BCL2 protein expression; the cells then slowly proliferate, but do not die by apoptosis, and hence proliferate uncontrolled and acquire genetic alterations.[7, 8] The presence of the t(14;18) translocation alone is most likely insufficient for complete neoplastic transformation. Other rearrangements and mutations provide the malignant cells with a growth advantage.[9]

The diagnosis is based on examination of excisional biopsy samples, including immunohistochemistry. According to the 2016 WHO classification of Tumours of Haematopoietic and Lymphoid Tissues, currently 4 variants of FL are recognized: in situ FL, duodenal-type FL, testicular FL and the diffuse variant of FL.[2] FL is graded by counting or estimating the absolute number of centroblasts in 10 neoplastic follicles per high power microscopic field (***Appendix A – Grading of Follicular Lymphoma***).[10]

The clinical course of FL is typically indolent, with impressive responses to initial treatment. Nevertheless, frequent relapses occur, that need additional therapeutic interventions resulting in shorter remission duration and increased risk of drug resistance, and most of the patients will eventually die of their disease. As a consequence, currently the median progression free survival

(PFS) is between 6-7 years and the overall survival (OS) ranges from 10 to 15 years. Despite the observed improvement in survival over time, the outcome is not favorable for all patients affected by the disease, and FL is therefore considered incurable. Indeed, some patients, about 20% of newly diagnosed FL, will undergo early progression after treatment (<24 months) or will present with chemoresistance disease.[11, 12] In addition, from 20 to 40% of patients will experience transformation into aggressive lymphoma, mostly diffuse large B cell lymphoma.[13]

Multiple parameters were shown to have prognostic significance, either related to the patient (age, sex, vitamin D), the lymphoma (stage, bone marrow involvement, LDH, β2M, and early progression of disease), or to the effect of the disease on the patient (B symptoms, performance status); several scoring systems have been proposed to enable more accurate prognostication (FLIPI, FLIPI-2, PRIMA-PI) ***(Appendix B – Prognostic scores)***.[14–19] Techniques such as GEP have increased our understanding of the biology of FL, and novel prognostic scores like the m7-FLIPI now incorporate biologic markers such as mutational status of specific genes.[20]

However, current knowledge is insufficient to guide treatment decisions in patients with high risk disease. Especially for patients who relapse early after immuno-chemotherapy, the optimal therapeutic strategy is not known.

Due to the indolent nature of the lymphoma, most patients are diagnosed with advanced disease, including bone marrow involvement, in the absence of B symptoms.[2] The disease is staged according to the criteria of the Lugano classification (***Appendix C – Lugano modification***).[21] Currently, the treatment of patients is still guided by staging. Radiotherapy with curative intent is proposed for patients with stage I or II disease. For patients with contraindications for radiotherapy, clinical observation or treatment with rituximab, alone or in combination with chemotherapy, may be considered.[22, 23] For patients with advanced disease, no curative therapy is established, and treatment should only be initiated in case of symptomatic disease according to the GELF criteria (***Appendix D – GELF criteria***).

The choice of treatment in patients with advanced disease varies according to patient's performance status, age, comorbidities and purpose of therapy, but usually comprises of rituximab in combination with chemotherapy such as CHOP, CVP, FM, bendamustine, or novel agents such as lenalidomide for patients enrolled in clinical trials.[24–26]

Response evaluation should be performed midterm and after completion of chemotherapy. Patients who achieve a complete or partial remission can be treated with rituximab maintenance for 2 years as this results in an improvement of PFS (59% versus 43% after 6 years, p <0.0001).[27] On the other hand, patients with an inadequate response should be evaluated for early salvage regimens. The use

of FDG_PET-CT after completion of chemotherapy induction has been recommended for prognostic reasons since persistent PET positivity identifies a worse prognosis group.[28]

FL follows a chronic relapsing course and a new course of treatment is indicated based on GELF criteria. Histologic documentation of progressive disease and exclusion of transformation[2] are highly recommended before the start of new lines of therapy.[2] For patients requiring a second line of treatment, the chemotherapy regimen used in first line may be employed again if relapse occurs after an interval of at least 24 months. Otherwise, a non-cross-resistant scheme should be preferred. Obinutuzumab is an option for patients with rituximab refractory disease[22, 23, 29] as well as the PI3K inhibitor idelalisib.[30] Autologous transplantation is an option to be considered as consolidation in first relapse, especially in young patients with short remission.[31]

The optimal treatment strategy in patients with early progressive disease is not well known. In recent years, novel insights into the biology of FL, and especially the role of the microenvironment, have resulted in the development of multiple novel treatment modalities. These new agents may ultimately improve the outlook for patients with FL with an unfavorable course, but for the development of the optimal therapeutic strategy, knowledge on the clinical and biological determinants of early refractory FL is needed.

2. OBJECTIVES

The purpose of the present study is (1) to define the prognosis of refractory/relapsed FL after second line therapy; (2) to report current treatment strategies; (3) to provide rationale for the design of novel treatments strategies.

3. ENDPOINTS

Primary Endpoints

- Rate of Progression of disease within 24 months from start of second line treatment (second POD24)

Secondary Endpoints

- Overall Survival (OS)
- Progression-free survival after second line therapy (second PFS)
- Complete response rate at 30 months (CR30) from start of second line treatment (second CR30)

4. STUDY DESIGN

This is an international, prospective, longitudinal, observational study of patients with histological diagnosis of follicular lymphoma refractory/relapsed after first line therapy.

4.1 Subject selection

Inclusion criteria

- Patients with initial diagnosis of follicular lymphoma, refractory/relapsed/transformed after first line therapy;
- All stages at the time of relapse;
- Histological grade 1-3a at the time of initial diagnosis;
- Age over 18 years;
- Availability of clinical data, including baseline information, comorbidities, data on disease localization, laboratory parameters at staging, features of treatment adopted and assurance of follow-up updating as requested - Data collection list (***Appendix E_Data collection list***)
- Diagnostic material available for review;
- Written informed consent.

Exclusion Criteria

- Age < 18 years

5. STUDY PROCEDURES

5.1 Patient enrollment and registration

Patients with histologically confirmed follicular lymphoma are registered in the study at the time of the first event after first line treatment. An event is defined as refractory/relapsed disease documented by biopsy, imaging, or clinical evaluation. Registration is based on the locally established histological diagnosis, with exclusion of cases diagnosed on fine needle aspiration cytology, while tru-cut core-needle biopsies are permitted in the study. Registration will be done on-line on a key restricted accessible web-database: the Investigator must complete the on-line registration form after obtaining informed consent dated and signed by the patient.

Investigators are requested to register consecutive cases diagnosed at each participating Institution (all patients satisfying Inclusion criteria without any further selection). Inclusion criteria will be checked at the Trial Office. A patient number (Patient ID) will be assigned strictly sequentially in ascending order as patient's eligibility is verified. In case a patient's eligibility is not confirmed by the Trial office and the patient is withdrawn from the study, the patient number will not be reused.

The assigned number will be used as the identification code for the subject. A space will be provided for the Clinician to enter a local alphanumeric code to better identify the patient.

5.2 Pathology review

Every registered case has to undergo histopathology review by a panel of experts. The reference pathologist will collect and review the pathology material sent by the participating centers, without knowledge of the clinical outcome of the patient. Both material obtained at diagnosis, and at relapse will be reviewed. Classification will be performed according to the World Health Organization recently published.[2]

5.3 Data collection list

The list of data that will be collected is shown in ***Appendix E_Data collection list***.

5.4 Data collection modalities

Registration of patients and data collection will be performed on-line in an Electronic Case Report Forms (eCRFs). eCRFs must be reviewed and verified for accuracy by the local Investigator. Patients registered into the study will not be identified by name on any study documents to be collected, but will be identified by a Subject Identification Number (Patient ID).

The adoption of SSL03 technology will assure protection of subject's clinical data in web communications. Data access and management will be regulated by the use of passwords with different levels of admittance, providing that subject confidentiality be respected. Once the patient has been registered, an email is sent to the local Investigator, the local Data Manager and to the Trial Office. Data will be stored into different electronic forms. After completion of a single form, data will be locked and it will not be possible to modify, unless a specific and documented written query is submitted to the Trial Office. To guarantee the data quality, the eCRF must be completed in real time.

6. STATISTICAL CONSIDERATIONS

6.1 Sample size

Sample size calculation is based on the aim of defining the prognosis of refractory/relapsed FL after second line therapy. To evaluate number of recordable events, we hypothesize that PFS after refractory/relapse has a risk function which follows Weibull distribution with time parameter (in months) $\lambda = 0.008$ and form parameter $p = 0.97$. After 10,000 Monte Carlo simulations we calculated that with **500** prospective cases enrolled, we would observe **145** events at the end of the study. If, for

epidemiological reasons, it will be difficult to record 500 cases, we plan to enroll all cases in two years from the study start.

6.2 Statistical analysis plan (SAP)

Descriptive variables: continuous variables will be expressed as median and inter-quartile distance, while categorical variables will be reported as absolute frequencies and percentages. Continuous variables will be compared with the use of the Mann-Whitney test (2 groups) or the Kruskal-Wallis test (three or more groups), while categorical variables will be compared through the use of Fisher's exact test or Chi-square test as appropriate.

Survival analyses: survival functions will be calculated utilizing Kaplan-Meier method and survival rate at specific time-points will be expressed with the correspondent 95% confidence interval (95CI). The effect related to potential variables with prognostic value will be estimated through Cox proportional risk regression and will be expressed as hazard ratio (HR) with 95CI. Risk proportionality will be verified through Schoenfeld partial residual analysis, both graphically and through cubic-spline smooth linear regression. The influence of residues will be evaluated through likelihood displacement as a function of the residues martingala analysis.

6.3 Study duration

Patients will be followed for at least two years after enrollment. However, a five year follow-up period is desirable (an update is requested at least every 6 months).

6.4 Endpoint definition

The endpoints of interest in the present study have been adapted from the Standardize Response Criteria for Non-Hodgkin's Lymphoma and from Recommendations for Revised Response Criteria for Malignant Lymphoma (***Appendix C2_Revised Response Criteria for malignant lymphoma***). In particular:

- Second POD24 is defined as the rate of progression of disease at 24 months after the second line treatment;
- OS is measured from the date of diagnosis until death from any cause;
- Second PFS is measured from the date of study entry until the date of disease progression or death from any cause;
- Second CR30 is defined as the rate of complete remissions at 30 months from start of second line treatment.

7. WITHDRAWAL OF PATIENTS

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment.

All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient. If the last assessment was more than three months prior to withdrawal from study and patient status has not been documented, if possible a final assessment of treatment status should be reported.

Moreover, patients can be withdrawn in case of:

- Lack of eligibility criteria;
- Histological revision reveals a diagnosis other than those in the inclusion criteria;
- Missing data; warnings will be periodically sent to the Investigators. In case of persistent missing data, the patient can be excluded from the study.

8. ETHICAL CONSIDERATIONS

8.1 Subject Informed Consent

An informed consent form (ICF) must be signed by the patient (or the patient's legally authorized representative) before his or her participation in the study. The medical file for each patient should document the informed consent process and that written informed consent was obtained prior to participation in the study. A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate. For any updated or revised ICFs, the medical file for each patient should document the informed consent process and that written informed consent was obtained for the updated/revised ICF for continued participation in the study.

Every participating center will develop its own Subject Information Sheet/Informed Consent form according to directories of its own country regulations. Once the patient has signed the consent, the local investigator is required to send to the Trial Office the ***Appendix F_Informed Consent – Substitute Sheet***.

8.2 Subject Confidentiality

In order to maintain patient confidentiality, each patient will be assigned a unique patient identifier (Patient ID) upon study enrolment. This patient identifier will be used in place of patient name and

date of birth for the purpose of data analysis and reporting. Medical record number or other local reference identifiers are not collected as part of the database, with exception of the year of birth. All parties will ensure protection of patient personal data and will not include patient names or date of birth on any study forms, reports, publications, or in any other disclosures, except where required by law. In accordance with local regulations in each of the included countries, patients will be informed about data handling procedures and asked for their consent.

8.3 Ethical Conduct of the Study

This protocol was developed following the SPIRIT 2013 guidelines, where appropriate.[32] Consistent with local regulations and prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., ICF) to the responsible IEC for review. Patient enrolment will not start at any site before the Sponsor has obtained written confirmation of a favorable opinion/approval from the relevant central or local IEC. The IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given that clearly identify the study, the protocol version, and the ICF version reviewed.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations. It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, if applicable, from their local IEC and provide documentation of approval to the Sponsor. All correspondence with the IEC should be retained in the Investigator File.

Should the study be terminated early for any unanticipated reason, the investigator will be responsible for informing the IEC of the early termination.

9. PUBLICATION RULES

It is responsibility of the Study Coordinators (the LUPIAE team) to publish the study results after the completion of the study. It will be ensured that the data from one center are not published before the publication of the whole study. All publications regarding the results of the study will be marked with the sentence “on behalf of the EHA-LyG/Cantera-Lupiae study group". Participating centers and sites will be mentioned according to their overall contribution to the study, while all members of the study group will be included as authors of the manuscripts for their active contribution on the study design and procedures. No publication can occur without agreement of the study sponsor. Study results will be submitted for publication in peer-reviewed journals and for presentation at appropriate scientific meetings and conferences.

The sponsor has the ownership of all data and results collected during this study. In consequence, the sponsor reserves the right to use the data of the present study, either in the form of case report forms (or copies of these), or in the form of a report, with or without comments and with or without analysis, in order to submit them to the health authorities of each country.

10. DATA HANDLING AND RECORD KEEPING

10.1 Data/Documents

The Investigator(s) must ensure that the records and documents pertaining to the conduct of the study, that is copies of CRFs and source documents original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; evaluation checklists; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; patient files) and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study are complete, accurate, filed and retained.

10.2 Data management

Data will be entered into the clinical database as per SOPs. These data will be electronically verified through use of on-line checks during data entry, and through programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary, in the form of a Data Clarification Form (DCF). Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

10.3 Retention of records

The Investigator(s) must maintain records of all study documents and supporting information relating to the conduct of the study. This documentation includes, but is not limited to, protocols, case report forms, advertising for patient participation, patient source data, correspondence with health authorities and IRBs/IECs, informed consent forms, Investigator(s) curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice specified below. The study monitor must be consulted if the Investigator(s) wishes to assign the study files to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator(s) must retain study records for the time period according to local laws or requirements, whichever is longer. The monitor will inform the Investigator(s) of the dates for retention. All study documents should be made

available if required by relevant health authorities. These documents should be retained for a longer period if required by other applicable regulatory requirements.

11. PRIVACY OF PERSONAL DATA

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The Investigator-sponsor ensures that the personal data will be

1. processed fairly and lawfully
2. collected for specified, explicit, and legitimate purposes and not further processed in a way incompatible with these purposes
3. adequate, relevant, and not excessive in relation to said purposes
4. accurate and, where necessary, kept current

Explicit consent for the processing of personal data will be obtained from the participating subject (or his/her legally acceptable representative) before collection of data. Such consent should also address the transfer of the data to other entities and to other countries. The subject has the right to request through the Investigator access to his/her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps should be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Patients will be registered in the study via web site, before beginning any study procedure. The name of the patient will not be asked for, nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify and must be included on all case report form.

12. REFERENCES

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APPENDIX A – GRADING OF FOLLICULAR LYMPHOMA

Grading of follicular lymphoma

Grade	Description
1	≤ 5 blasts/high power field
2	6-15 blasts/high power field
3A	> 15 blasts/high power field, centroblasts with centrocytes
3B	>15 blasts/high power field, only blasts

APPENIDX B – PROGNOSTIC SCORES

FLIPI. Risk Groups according to the FLIPI (age ≥ 60, advanced stage, elevated LDH, >4 nodal areas, Hemoglobin level less than 12g/dl).

Risk Groups	*Number of adverse variables*	*% -yrs OS*
Low	0-1	91
Intermediate	2	78
High	≥ 3	52

FLIPI2. Risk Groups according to the FLIPI2 (age >60, bone marrow infiltration, Hemoglobin level < 12 g/dl, elevated beta2-microglobulin, longest diameter of largest lymph node > 6 cm).

Risk Groups	*Number of adverse variables*	*3-yrs PFS*	*5-yrs PFS*
Low	0-1	91	79
Intermediate	2	69	51
High	≥ 3	51	20

PRIMA-PI. Risk Groups according to the PRIMA-PI (bone marrow involvement and beta2-microglobulin).

Risk Groups	*Adverse variables*	*5-yrs PFS*
Low	β2m ≤3mg/L without bone marrow involvement	69
Intermediate	β2m ≤3mg/L with bone marrow involvement	55
High	β2m >3mg/L	37

APPENDIX C1 - LUGANO MODIFICATION OF ANN ARBOR STAGING SYSTEM

A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response.

Lugano Modification of Ann Arbor Staging System

Stage	Involvement	Extranodal (E) Status
Stage I	One node or a group of adjacent Nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky*	II as above with "bulky" disease	Not applicable
Stage III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional noncontiguous extralymphatic involvement	Not applicable

NOTE. Extent of disease is determined by positron emission tomography–computed tomography for avid lymphomas and computed tomography for nonavid histologies. Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

*Whether stage II bulky disease is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

APPENDIX C2 – REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA

A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response.

Response Assessment

Response	Site	PET-CT (Metabolic Response)	CT (Radiologic response)
Complete response	Lymph nodes and extralymphatic sites	Score 1, 2 or 3 with or without a residual mass on 5-point scale (5-PS).	All of the following: Target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of a lesion (LDI); No extralymphatic sites of disease.
	Non-measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, and flow cytometry IHC negative.
Partial Response	Lymph nodes and extralymphatic sites	Score 4 or 5 with reduced uptake compared with baseline. No new or progressive lesions. At interim these findings suggest responding disease. At end of treatment these findings may indicate residual disease.	All of the following: ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites ; When a lesion is too small to measure on CT, assign 5mm x 5mm as the default value; When no longer visible, 0x0mm, For a node > 5mm x 5mm, but smaller than normal, use actual measurement for calculation.
	Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal.
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from	Not applicale

		chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consider further evaluation with biopsy, or an interval scan.	
No response or stable disease	Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG-uptake from baseline at interim or end of treatment. No new or progressive lesions.	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
	Non-measured lesions	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicale	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease	Individual target nodes/nodal masses, extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end of treatment assessment.	Requires at least one of the following PPD progession. An individual node/lesion must be abnormal with: LDI > 1.5 cm and increase by ≥50% from PPD nadir and an increase in LDI or SDI from nadir 0.5 cm for lesions ≤ 2cm 1 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly.
	Non-measured lesions	None	New or clear progression of preexisting non-measured lesions.
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be consider.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1cm in any axis; if < 1cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma.
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

PET 5-PS

1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Uptake markedly higher than liver and/or new lesions
x	New areas of uptake unlikely to be related to lymphoma

SPD = sum of the product of the perpendicular diameters for multiple lesions

LDI = longest transverse diameter of a lesion

SDI = shortest axis perpendicular to the LDI

PPD = cross product of the LDI and perpendicular diameter

APPENDIX D – GELF CRITERIA

GELF criteria

Parameter	Description
Lymph nodes	Bulky (>7 cm) or 3 lymph nodes in distinct areas > 3 cm
Spleen	Symptomatic splenic enlargement
Complication	Organ compression by tumor, pleural or peritoneal effusion
Serum markers	Cytopenias (leukocytes <1.0 x 10 9/L and/or platelets 9</sup>/L) or Leukemia (>5.0 x 10 9/L malignant cells)
Clinical presentation	B symptoms

APPENDIX E – DATA COLLECTION LIST

Patients characteristics (dated)
Gender
Year of birth
Comorbidities
ECOG Performance Status
B symptoms
FLIPI
FLIPI2
PRIMA-PI

Laboratory
Haemoglobin
Total white blood count & differential (absolute values)
Platelets
LDH serum level
β2-microglobulin serum level

Disease characteristics (at diagnosis and start of each treatment; dated)
Date of histologic diagnosis
Site of biopsy
Histological grade
BCL-2 translocation status (if available)
Ann Arbor Stage
Nodal sites of involvement in detail, with indication of major lesion (TAC and PET)
Presence of bulky disease
Presence of extra nodal disease
Sites of extra nodal involvement
Bone marrow involvement (percentage and pattern of involvement)
Presence/absence of systemic symptoms

About course of disease
Reason for first (second, third…) treatment
Time to first (second, third…) treatment
First (second, third…) line of treatment
Start/end dates treatment
Toxicity
Response (Lugano criteria)
Maintenance therapy

The following variables will be recorded during follow-up (alive patients)
Date of last contact
Disease status at last contact
Evidence of second malignancy or late toxicities
Date of diagnosis of second malignancy/late toxicity
Treatment for second malignancy/late toxicity

The following variables will be recorded in case of disease progression or relapse
Date of progression or relapse
Histological transformation indication, if present

BCL2 rearrangement status (if available)
Salvage treatment modalities
Response after salvage treatment
Subsequent treatments received

The following variables will be collected in case of death:
Date of death
Cause of death
Disease status at time of death

APPENDIX F – INFORMED CONSENT SUBSTITUTE SHEET

Study protocol:

Towards personalized medicine for refractory/relapsed Follicular Lymphoma patients

Protocol ID: LUPIAE study

DECLARATION OF ELEGIBILITY
(form replacing the informed consent)

Patient code: ..... Sex M F Date of birth: ...../...../.....

I, the undersigned Dr/Prof …….., declare:

1) That the patient has signed the informed consent (version: ..... Date: .....) to participate in the study on ...../...../.....
2) That the patient received the complete information on the study and treatment of personal data in compliance with Legislations, and that the patient has signed the informed consent to process his/her personal data.
3) That the patient complies with the inclusion criteria defined in the protocol.

Date: ...../...../.....

First and last name of the Investigator Signature

....

This document is to be sent by fax to +390594223707 or via email to marmanni@unimore.it at the time of patient enrollment.