REVAIL PROTOCOL

STUDY OF THE EFFICACY AND SAFETY OF FIRST LINE TREATMENT WITH CHOP AND LENALIDOMIDE (Rev-CHOP) IN PATIENTS AGED FROM 60 TO 80 YEARS WITH PREVIOUSLY UNTREATED ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL).

LYSARC

LYSARC : **LYmphoma Academic Research organisation**

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Version and date of Protocol: version 6.0 10/01/2017
EUDRACT Number: 2011-001356-10

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1 SYNOPSIS

Study ID Eudract N°	**REVAIL** 2011-001356-10
Title of the study	STUDY OF THE EFFICACY AND SAFETY OF FIRST LINE TREATMENT WITH CHOP AND LENALIDOMIDE (Rev-CHOP) IN PATIENTS AGED FROM 60 TO 80 YEARS WITH PREVIOUSLY UNTREATED ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA (AITL)
Protocol version	6.0 10/01/2017
Sponsor	LYSARC (Lymphoma Academic Research organization)
Coordinating investigator Co-coordinating investigator	**Pr Corinne Haioun** **Dr Violaine Safar**
Centers	LYSA centers in France and Belgium Approximately 40 centers
Study Objectives	To evaluate the Complete Metabolic Response (CMR) rate at the end of treatment defined according to Lugano Classification (Cheson et al, 2014, PET-CT Based response) To evaluate the efficacy and the safety of a front-line treatment combining CHOP regimen and lenalinomide (Rev-CHOP) in patients aged 60 to 80 years with previously untreated AITL. To evaluate the role of PET in defining an accurate staging To evaluate the tumor metabolic activity based on FDG avidity measured by SUV max at baseline and the decrease of SUV max at the end of treatment To analyse on blood samples and on tumour biopsies biological factors that could influence treatment response and prognosis. To favour the banking of tumor cell suspension in order to better understand the pathogenesis of AITL **Primary endpoint** Complete Metabolic Response (CMR) rate at the end of treatment defined according to Lugano Classification (Cheson et al, 2014, PET-CT-Based

response)

Secondary endpoints

- Complete response (CR) rate at the end of treatment according to the IWC (International Harmonization Project – Cheson 2007,) as assessed by site Investigator.
- Progression-free survival at 2 years (2y-PFS), events being relapse for complete responders, disease progression, death from any cause.
- Overall survival (OS) and event-free survival (EFS)
- To evaluate the tumor metabolic activity based on FDG avidity measured by SUV max at baseline and the decrease of SUV max at the end of treatment
- To correlate response rate, survival and biological factors (phenotype, EBV status, T/B clonality, circulating cytokine dosages).
- Biological studies at diagnosis:
  - Pathological and phenotypical description of the disease at presentation, with a detailed characterization of T-cells (T-cell antigens, CD10, CXCR5, PD1, CXCL13, ICOS, and Bcl6, Tbet, Gata3, RorγT transcription factors), FDC markers and EBV detection with B or T cells colocalization. Centralized pathological tissue banking and achievement of Tissue Micro Array within GELAP
  - TCR and IgH clonality analyses by PCR on tumor sample and blood
  - Phenotypic analysis of lymphoid cells in blood, including T antigens, CD10 CXCR5 CXCR3 CCR6 expression on CD4+ T-cells, CD19, CD20, CD27 and CD38 expression on B cell and NK cells numeration, using a 8- color flow cytometry device.
  - Cytokine profiles in serum samples (VEGF, IL4, IL5, IL10, IL13, IL21, IL17A, IL22, IL6, IFNγ, TNFα, CXCL13, EBI3) using luminex technology
  - EBV virus load in total blood, and in fractionated T and B cells.
- Biological studies at the end of induction including same diagnostic flow cytometry and EBV virus explorations.
- An additional objective is to favour the banking of tumor cells suspensions (from lymph node biopsies, Peripheral blood, effusions,…) with the aim to :
  - provide purified collection of neoplastic TFH cells for high throughput methods (GEP, mi-RNAs ..),
  - derive tumor cell lines and/or lymphoblastoid cell lines from the EBV^{pos} B cells of the microenvironment (to evaluate their capacity to induce T_{FH} commitment from autologous naïve normal $CD4^{pos}$ T cells). (in connection with the PAIR INCa program).
  - Define the molecular signature(s) (gene expression and mutations) of AITL entities and correlate these signatures with response to therapy;
  - Determine novel molecular predictive factors of response to Lenalidomide-CHOP treatment
  - Determine feasibility and clinical impact of cell free DNA sequencing in AITL
  - For all those purposes, the collection of fresh relapse samples will be encouraged through an oligocentric network.

Duration of the study	Patients will be recruited over 5 years and followed until 18 months after the last patient has completed the treatment. Study duration : 78 months
Number of patients.	Statistical analysis will be based on 70 evaluable subjects. Since subjects who are not evaluable for response will be replaced, it is anticipated that approximately 80 subjects will be enrolled in total.
Inclusion and exclusion criteria	**Inclusion criteria** • Patients with histologically proven T-cell angioimmunoblastic lymphoma (AITL) • Age from 60 to 80 years. • ECOG performance status 0 to 2. • No previous therapy (except corticosteroids providing they have been initiated less than 15 days before inclusion). • Spontaneous life expectancy > 1 month. • Written informed consent. The Lenalidomide Information Sheet (in appendix of the Patient Informed Consent Form) given to each patient receiving lenalidomide study therapy, must be read prior to starting treatment and at each new supply of study drug. • Male patients must: Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy. Agree to not give semen or sperm during study drug therapy and for a period after end of study drug therapy. • All patients must: Have an understanding that the study drug could have a potential teratogenicity. Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy. Agree not to share study medication with another person. Be counselled about pregnancy precautions and risks of foetal exposure. **Exclusion criteria** • Other categories of T-cell lymphoma. • Central nervous system involvement by lymphoma. • Any previous therapy for lymphoma except short-term corticosteroids (maximum 10 days) before inclusion. • Contra-indication to any drug included in the CHOP regimen. • Serious medical or psychiatric illness likely to interfere with participation in this clinical study (according to the investigator's decision). • Active bacterial, viral or fungal infection, in particular active hepatitis B or C and HIV positive serological test. • Impaired renal function (Creatinine clearance <50 ml/min),as calculated by the Cockcroft-Gault formula) or impaired liver function tests (total bilirubin level > 30 µmol/L, transaminases > 2.5 upper normal limits) unless they are related to the lymphoma. • Poor bone marrow reserve as defined by neutrophils < 1.0 x 109/L or platelets < 100 x 109/L, unless related to bone marrow infiltration.

<table>
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Any history of malignancy, other than that treated in this research, unless the patient has remained free of the disease for over 5 years.
Treatment with any investigational drug within 30 days before planned first cycle of chemotherapy and during the study.
Hypersensitivity to the active substance or to any of the excipients.
Pregnant and lactating woman
Females of Childbearing potential (FCBP*) according to the PPP (in appendix 18.13 of the protocol)

* A FCBP isa female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).
</td></tr>
<tr><td>Design of the trial</td><td>Phase II, multicentric, open-label, non-randomized study</td></tr>
<tr><td>Study Treatment</td><td>
CHOP (doxorubicine, vincristine, cyclophosphamide, prednisolone) plus Lenalidomide (Revlimid®) : Rev-CHOP

8 cycles of Rev-CHOP repeated every 3 weeks (Rev-CHOP 21)

<table>
<tr><th>Rev-CHOP</th><th>Doses</th><th>D1</th><th>D2</th><th>D3</th><th>D4</th><th>D5</th></tr>
<tr><td>Cyclophosphamide IV</td><td>750mg/m²</td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Doxorubicine IV</td><td>50mg/m²</td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Vincristine IV</td><td>1.4mg/m²</td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Prednisone PO</td><td>40m/m²</td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
<tr><td>Lenalidomide PO</td><td>25mg</td><td colspan="5">Day 1 to Day 14</td></tr>
</table>
Methotrexate (IT) 15 mg for the first 4 cycles

Treatment with sub-cutaneous G-CSF is mandatory at each cycle from day 6 to day 10 or until neutrophils>1.0 G/l or at D4 for delayed formulation

Details of prophylactic measures and permitted concomitant medications are in the protocol in section 8.2.3 and 8.2.4
</td></tr>
<tr><td>Registration in the study/ Randomization</td><td>Patients will be registered on the first day of treatment.

No randomization.</td></tr>
<tr><td>Statistical analysis</td><td>
The sample size calculation is based on a Simon’s phase II design which allows for assessment of efficacy for early termination if the treatment is not effective based on pre-specified hypotheses:
H0: $p < p0$ vs. H1: $p > p1$
where p0 and p1 are complete response rates at the end of treatment such that the test regimen does not or does merit further testing at given levels of statistical significance (α) and power (1-β). In this clinical study, p0 and p1 were chosen to be 45% (reference obtained with CHOP alone) and 60%, respectively. The significance level $\alpha = 0.05$ (one-sided) and type II error $\beta = 0.20$ were used.
In the first stage, 37 evaluable patients will be enrolled. At least 17 patients should achieve a CR to proceed with the second stage. The probability of early termination is 0.482.
If this condition is fulfilled, a total of 70 evaluable patients will be analyzed. At least 39 patients should respond to conclude that the treatment is effective.
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	Subjects not evaluable for response will be replaced. It is anticipated that approximately 80 subjects will be enrolled in total.
Planned start/end of Study	September 2011 / April 2018

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2 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
BSA	Body Surface Area
CD20	antigen expressed on the surface of normal and malignant B lymphocytes
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
EC	Ethic Committee
CR	Complete Response
CRF	Case Report Form
Cru	Complete Response unconfirmed
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLBCL	Diffuse Large cell B-Cell Lymphoma
IDMC	Independent Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
FFPE	Formalin-fixed, Paraffin-embedded (tissue)
LYSA	Lymphoma Study Association
LYSA-P	Lymphoma Study Association - Pathology
LYSARC	Lymphoma Academic Research organization
GCP	Good Clinical Practice

G-CSF	Granulocyte Colony-Stimulating Factor
INCa	Institut National du cancer
IMIDs®	Immunomodulatory drug (structural and functional analogues of thalidomide)
IV	IntraVenous
LDH	Lactic DeHydrogenase
MRD	Minimal residual disease
NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada - Clinical Trials Group
NGS	Next Generation Sequencing
NHL	Non-Hodgkin's Lymphoma
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PET	^{18}F-FDG Positon Emission Tomography
PFS	Progression Free Survival
PR	Partial Response
PS	Performance Status
RR	Response Rate
RT-MLPA	Reverse Transcriptase - Multiplex ligation-dependent probe amplification
SAE	Serious Adverse Event
SD	Stable Disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVmax	Maximum Standardized Uptake Value
ULN	Upper Limit of Normal
US	United States
WES	Whole Exome Sequencing
WHO	World Health Organization

3 RESPONSIBILITIES

3.1 Title of the trial

Study of the efficacy and safety of first line treatment with CHOP and lenalidomide (Rev-CHOP) in patients aged from 60 to 80 years with previously untreated angioimmunoblastic T-Cell lymphoma (AITL).

3.2 Sponsor and program coordination center

3.2.1 Sponsor

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3.2.3 Study management

Lymphoma Academic Research organization (LYSARC)

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Pharmacovigilance: Aude Fievet
Biology: Thibault Gelas
LYSA-P: Nadine Vailhen
LYSA-IM: Romain Ricci

✉ : Centre Hospitalier Lyon Sud

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3.3 Investigators

LYSA and LYSARC centers from France and Belgium may include patients in this study. Before any inclusion, each center must have been declared to the CPP / Ethical Committee and national authority according to each country procedures and have had the initiation visit/call. To be declared as a participating center, the principal investigator must have sent to the LYSARC his *curriculum vitae* with the local number affiliation medical association (Conseil de l'Ordre des Médecins for French centers).

3.4 Laboratory sites

Laboratories of each study center must provide their normal values and an updated accreditation for quality control.

4 RATIONALE

4.1 T-cell lymphomas

The incidence of non-Hodgkin's lymphoma (NHL) has been increasing worldwide during the last 40 years and accounts for 4% of all cancer diagnoses. An estimated 53,000 new cases are diagnosed annually in the United States (US) with a similar number estimated in the European Union. B-cell derived NHL accounts for approximately 80% of cases. Although localized NHL does occur, most patients present with disseminated disease. This is true in approximately 90% of follicular lymphomas, 70% of diffuse large B-cell lymphomas and 90% of T-cell lymphomas.

Peripheral T-cell lymphomas (PTCL) constitute an heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes (Swerdlow, 2008). These T-cell neoplasms account for approximately 15% of all lymphoid neoplasms. The most common PTCLs entity is PTCL, "not otherwise specified" (PTCL,NOS) which accounts for up to 40% of all PTCLs. Angioimmunoblastic T-cell Lymphoma (AITL) is the second most common PTCL worldwide, but appears more prevalent in Europe (representing 29% of the cases) than in North America or Asia where its estimated prevalence is below 20% (Armitage, 2008; Rudiger, 2002). Anaplastic large cell lymphoma (ALCL) accounts for about 17% of all PTCL. The other entities completing the classification of PTCL are extranodal natural killer (NK)/T-cell lymphoma (formerly called angiocentric), enteropathy-associated T-cell lymphoma and hepatosplenic T-cell lymphoma (8%, 7%, and 0.6%, respectively)(Swerdlow, 2008)

AITL normal cell counterpart

The recent identification of follicular helper T (TFH) cell as the cell of origin of AITL (Grogg, 2005; Krenacs, 2006; de Leval, 2007) represents a major step in the understanding of the clinicobiological characteristics of the disease (de Leval, 2010). Normal TFH cells constitute a minor subset of effector T cells with a specific microanatomic distribution and distinct gene signature and functions separable from

the other known Th1, Th2, Th17 effector subsets (Chtanova, 2004; Vinuesa, 2005; Fazilleau, 2009). Briefly, after naıve CD4+ T cells/ Dendritic cells (DC) cross talk within the T-cell zone, activated CD4+ T-cells upregulate CXCR5 and downregulate CCR7 allowing them to migrate to the follicle. At the T–B border T cells interact with activated B cells presenting cognate Ag. This results in the CD4+ T cells delivering help to the B cells via CD40L and IL-21, as well as T-cell co-stimulation via ICOS–ICOS-L interactions. Ongoing Ag stimulation provided by the B cells drives the development of TFH cells. Following interactions at the T–B border, B cells can differentiate into short-lived extrafollicular plasmablasts or enter into a germinal centre (GC). Within the GC, TFH cells continue to provide help to the B cells, supporting the GC reaction and allowing for the generation of long-lived plasma cells and memory B cells. Presumably, reciprocal signals provided by the B cells are also crucial for sustaining the TFH cells. Plasma cells can also present Ag to CD4+ T cells, however this presentation seems to inhibit – rather than promote – TFH cells. Interestingly, normal TFH cells can suppress T-cell responses by inhibiting the proliferation and function of conventional CD4 T cells, especially through transforming growth factor-b (TGF-β) and IL-10 production (Marinova, 2007). The life cycle of normal TFH is not well characterized. Recent data (Morita, 2011) show that blood CXCR5+CD4+ T cells comprise two subsets: T helper 2 (Th 2), and Th17 cells which can efficiently induced naive B cells to produce immunoglobulins via interleukin-21 (IL-21) and one Th1 substet which lacked the capacity to help B cells. Whether those populations represent recirculating memory TFH subset is under debate.

Overall, the cellular derivation of AITL from TFH cells provides a rational model to explain several of the peculiar pathological and biological features inherent to this disease, i.e. the expansion of B cells, the intimate association with germinal centres in early disease stages and the striking proliferation of FDCs. In AITL, non-neoplastic cells typically represent a quantitatively major component and clinically, it is generally assume that the manifestations of the disease reflect a deregulated immune and/or inflammatory response rather than direct complications of tumour growth (Mourad, 2008). Moreover, AITL patients have defective T-cell responses, linked to both quantitative and qualitative perturbations of T-cell subsets (Pizzolo, 1987). Among the mediators secreted by TFH cells, the chimiokine CXCL13, also expressed by AITL TFH cells, may contribute to the B-cell expansion observed in the disease through its its capacity to attract and activate B cells. Interleukin (IL)-21, a TFH cytokine with important roles in germinal centre development and B-cell differentiation to Ig-producing cells, as well as in TFH development through an autocrine mechanism, might also contribute to several features of AITL (Fazilleau, 2009).

Pathological diagnosis of AITL (review in de Leval 2011)

The diagnosis of AITL is often difficult, essentially relying on morphological features including a polymorphous infiltrate with eosinophils and plasma cells, expansion of follicular dendritic cells (FDC), scattered large B-cell immunoblasts (often infected by EBV) and abundant arborizing venules. Most of

these characteristics may individually be encountered in cases belonging to the heterogeneous group of PTCL,NOS. Some cases which do not display the whole array of morphological characteristics of AITL can be classified as borderline cases between the two entities. Inside AITL lesions, the neoplastic component is usually minor, as has been shown by analysis of the T-cell receptor repertoire on microdissected cells. Immunohistochemistry helps identifying the expansion of FDC, as well as the neoplastic component through expression of TFH markers such as CD10, CXCL13, ICOS, PD1, Bcl-6, SAP.. (Attygale, 2002; Dupuis, 2006; Grogg, 2006; Marafioti, 2010; Yuan, 2005; Roncador, 2007; Dorfman, 2006). In accordance with the known pathological features, the AITL molecular profile was dominated by a strong microenvironment imprint, including overexpression of B-cell- and FDC-related genes, chemokines and chemokine receptors, and genes related to extracellular matrix and vascular biology. Interestingly, the signature contributed by the neoplastic cells, albeit quantitatively minor, was enriched in genes normally expressed by TFH cells (de Leval 2007).

Oncogenesis

The molecular alterations underlying the neoplastic transformation of TFH cells remain unknown (reviewed in de Leval 2010). By cytogenetic analysis clonal aberrations – most commonly trisomies of chromosomes 3, 5 and 21, gain of X, and loss of 6q - are detected in up to 90% of the cases. Chromosomal breakpoints affecting the T-cell receptor (TCR) gene loci appear to be extremely rare. A role for the c-maf transcription factor has been suggested, because its overexpression in transgenic mice induces the development of T-cell lymphomas, and high levels of c-maf have been detected in human AITL tissues (Murakami, 2007). More recently, preliminary results of selected gene sequences have drawn our attention on recurrent mutations in AITL that need to be confirmed (personnal observations, Dr Ph. Gaulard & Dr C. Bastard).

EBV involvement

Although T cell deregulation could occur as the primary oncogenic event in AITL, one can speculate that the initiating event is antigen driven, as has been described in certain marginal zone lymphomas of the stomach and spleen (Parsonnet, 1994; Hermine 2002). This speculation is fuelled by the fact that EBV-positive B cells are almost universally present within AITL biopsies (Zhou, 2007). In this model, EBV might play a pivotal role in the early pathogenesis of AILT by activating TFH cells (Dunleavy, 2007). It is established that EBV-positive B cells can present EBV viral proteins (e.g EBNA-1 and LMP-1) to T cells in association with major histocompatibility complex class II molecules, upregulating the CD28 ligand (B7). This event could provide antigenic and costimulatory signals for TFH cell activation leading to CXCL13 production which in turn might stimulate B cell activation, thus creating an immune stimulatory loop. Within this loop an EBV-positive B cell might provide the stimulus leading to the emergence of an antigen independent TFH cell proliferation. This model has provided us a rational to evaluate Rituximab in association with CHOP in a previous phase II study.

EBV is a gamma-herpes virus that has succeeded in colonizing 95% of the human population. EBV infection commonly occurs in childhood and is asymptomatic; thereafter, the infected individual becomes a virus carrier for their lifetime. This harmless coexistence between the virus and its host is achieved through two mechanisms: a potent immunological reaction to the virally encoded latent proteins that eliminates the type III latent cells, and a viral strategy to down-regulate the expression of latent genes and reside in a silent state in the memory B cell pool (review in Niller 2008).The EBV genome has been detected in a variety of malignancies (Cohen, 2009).The latent gene expression seen in the EBV carrying tumors varies according to the tissue origin of the tumors and activation/differentiation stage of the malignant cells . EBV-positive B cells in AITL express EBNA-1, LMP-1, and LMP-2 (type II latency). EBNA-2 and EBNA-5 (-LP) regulate the expression of LMP-1 in type III latent lymphoblastoid cell lines (LCLs). The molecular mechanisms responsible for the expression of LMP-1 in type II latency (EBNA-2-independent LMP-1 expression) are only partially known.

TFH cells are the major producers of IL21 (King, 2008). Recent studies (Kis, 2010) suggest that IL21 could be involved in LMP-1 expression of type II normal GC B cells. Thus, IL-21 could be responsible for the EBNA-2-negative, LMP-1-positive viral gene expression seen in the EBV-positive B cells in AITL. Similarly to the CD40 activation, the IL-21-induced LMP-1 could be responsible for the induction of IRF4 expression and the down-regulation of BCL6 expression. The plasma cell differentiation leads to disruption of latency and initiation of virus replication (Sun, 2007). This could explain the EBV reactivation stigmata observed in some AITL patients with high tumor burden (RAIL study, *manuscript in preparation*).

In another model, EBV reactivation in AITL could be secondary to decreased immune surveillance. Against this hypothesis is the fact that EBV-positive B cells are found very early in the course of the disease (Weiss, Blood 1992) and is not associated with the degree of CD4 or CD8+ deficiencies (RAIL study, *manuscript in preparation)*. Moreover, in a previous study, we did not found any correlation between EBV reactivation (EBV genome in sera) and peripheral CD4+ or CD8+ T-cell depletion (RAIL study, *manuscript in preparation*).

Therefore, primary alteration or secondary activation of EBV and its role in the physiopathology of the disease remain to be established.

FDG PET in AITL

FDG avidity of T-cell lymphomas has been recently reported in several series, some of them including cutaneous lymphomas (Feeney, 2010; Cahu, 2011). In the larger published series based on 135 patients (Feeney, 2010), hypermetabolic tumoral sites were observed in 122 (90%) patients: 55 (45%) had cutaneous involvement, 95 (78%) had FDG-avid lymphadenopathy, and 54 (44%) had FDG-avid extranodal disease other than cutaneous involvement. Among them 18 patients only had AITL of whom 14 (78%) had hypermetabolic lesions, always nodal and in 50% of the cases associated with extranodal lesions. Mean maximum standardized Uptake value was 12.6 (4.8-29.2). Considering that the

characteristics of AITL on FDG PET are not yet clearly established, we propose to investigate prospectively the role of PET to define an accurate staging and to evaluate the Complete Metabolic Response (CMR) rate at the end of study treatment defined according to Lugano Classification (Cheson et al, 2014, PET-CT-Based response)(7).

Therapeutical approaches

Compared to B-cell NHL, PTCL is more resistant to conventional chemotherapy and is generally associated with an inferior outcome (Gisselbrecht, 1998). No specific treatment has been proposed specifically for AITL with the exception of the recent R-CHOP (see below). Numerous studies have reported poorer survival for patients with PTCL, with a median OS of less than 2 years and 5-year survival less than 30%. The 2-year failure-free survival for patients with high or intermediate-high risk disease is estimated at 10%. Even with ASCT, 5-year PFS and OS rates have been reported to be as low as 24% and 33%, respectively. These outcomes are inferior to those observed in the most aggressive B-cell lymphomas. While the precise biological reasons for the differences between B- and T-cell lymphomas is not clear, many explanations have been advanced, including: differences in intrinsic chemosensitivity, the fact that patients with PTCL have higher International Prognostic Index (IPI) at presentation, and the absence of drugs with unique activity in PTCL. Importantly, all regimens currently employed for PTCL are derived from B-cell lymphoma regimens. These data underscore the urgent need for new treatment options for patients with PTCL, especially those who typically have limited responses to salvage therapy and extremely poor overall survival.

Prognostic factors at first line are not well established in all PTCL; a separate prognostic model for patients with PTCL NOS called the prognostic index for PTCL-U (unspecified) PIT was proposed (Gallamini, 2004). In a retrospective analysis of 385 patients with PTCL-U, multivariate analysis showed that age, performance status, LDH level, and bone marrow involvement were predictive of survival, and these variables were used to develop a new prognostic model that could separate the patients into four distinct prognostic groups. Curiously, neither a high IPI nor PIT score predict for a poorer outcome in AITL (Tang T review, 2010; Mourad, 2008)

Most patients with aggressive disease are treated with anthracycline (doxorubicin)-containing regimens. These include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or CHOP-derived regimens (M BACOD, ProMACE-MOPP, ProMACE-cytaBOM, MACOP-B). The therapeutic regimens that use single alkylating agents (e.g., chlorambucil) or without anthracycline, especially use in elderly patients, had limited success, with very low response rates and short response duration. Compared to patients with aggressive B-cell lymphomas, patients with PTCL have quite similar response rates following therapy, but have a higher relapse rate.

The tendency of PTCL to relapse has prompted the initiation of several studies into high- dose chemotherapy followed by stem cell transplant at first line and for recurrent and refractory diseases. In

general, these studies have found that long-term survival remains in the range of 40% for first line-chemosensitive disease. However the prognosis for patients with T-cell lymphomas that are either ineligible for or have developed disease recurrence after high-dose chemotherapy remains poor.
Moreover, it should be emphasized that no randomized phase III trial has been yet reported in PTCL and that, by default, CHOP or CHOP-like chemotherapy, remains the most common regimens used despite their lack of efficacy.

During the past 10 years, to improve the outcomes of these patients, novel therapeutic approaches have explored the following concepts: Increase dose intensity regimens, high-dose consolidative chemotherapy with autologous stem cell rescue, graft versus lymphoma effect of allogenic transplantation (Corradini, 2004). These strategies cannot be applied to the majority of the patients because of age and potential toxicites but also early disease progression. Besides, in the same time the potential efficacy of novel agents used alone or in combination with chemotherapy, has been investigated, usually in a relapse/refractory setting. The main drugs (recently reviewed in Howman, 2011) were, as Alemuzumab (Gallamini, 2007; Kluins Nelemans, 2011), Pralatrexate (O' Connors, 2011), Gemcitabine (Zinzani, 2010), Denileukin Diftitox (Lansigan, 2010), Romidepsin (Piekarz, 2011) and Lenalinomide (Dueck, 2010) with encouraging results.

In 2005 within the GELA, we postulated that AITL - a disease often associated with a B cell hyperstimulation stigmates with autoimmune features, hypergammaglobulinemia and clonal immunoglobulin gene rearrangements, increased B cell population in the tumoral tissue -, might benefit from a treatment with anti-CD20 monoclonal antibody (Rituximab) in synergy with an anthracyclin containing chemotherapy (CHOP). The close relationship of tumoral T cells with follicular dentritic cells and the TFH origin of neoplastic cells strengthen this hypothesis. We prospectively evaluated the efficacy and the safety of a combination of rituximab and CHOP (R-CHOP) in patients aged 60 to 80 years with previously untreated AITL and led ancillary biological studies on the tumoral and peripheral blood samples of the enrolled patients. Twenty-five patients from 59 to 80 years received a combination of 8 cycles of R-CHOP21. The overall response rate appreciated based on Cheson 1999 (Cheson, 1999) criteria was 80%, 44% of the patients achieving a complete or uncertain complete response and 36% a partial response. Grade III-IV non-haematological toxicities were low. With a median follow up of 24 months, the 2y-progression free survival was only 42% and the 2y-overall survival was 62% leading to consider that R-CHOP21, although well tolerated in this elderly population, did not improve outcome from classical CHOP. Pathological examination of tumoral biopsies shows a high tumour load in only 36% patients. Circulating tumoral cells were detected in 12/21 pts (57%), a feature associated with poorer response to treatment (p=0.06). EBV was detected in 24/25 tumours by in situ hybridization and in 14/21 PBMC by PCR. The abundance of EBV DNA in PBMC correlated with EBV scoring in tissues (p<0.004). EBV viral load in PBMC > 100 copy/µg DNA tended to be associated with shorter PFS (p= 0.06) (manuscript in preparation)

Today, the challenge remains identifying an effective regimen. Lenalidomide, an immunomodulatory agent that has demonstrated clinical efficacy in several hematological malignancies including multiple myeloma (Dimopoulos, 2010), myelodysplastic syndrome (Ades L, 2009) and chronic lymphocytic leukaemia (Gentile M, 2011), has been evaluated in cutaneous T-cell lymphoma (Querfeld C, ASH 2005;106:3351) and in recurrent and refractory non-cutaneous T-cell lymphomas (Dueck G, 2010) with promising results. In the latter study at the time of interim analysis, 24 relapsed/refractory patients were enrolled (7 with AITL), and 23 were evaluable for response. The median age was 65 years. The overall response rate was 7 (30%) of 23; all were partial responses (2 patients with AITL). Two patients had stable disease for ≥5 cycles.. Median PFS was 96 days (range, 8-696+ days). Median OS was 241 days (range, 8-696+ days). The most common grade 4 adverse event was thrombocytopenia (33%). The most common grade 3 adverse events were neutropenia (21%), febrile neutropenia (17%), and pain not otherwise specified (17%).

Several hypothesized mechanisms of action have been characterized, including direct cytotoxicity to tumor cells, immunomodulatory effects such as cytokine modulation and enhanced natural killer and T-cell function. In addition, lenalidomide alters the tumor cell microenvironment to discourage the growth of tumor cells and inhibit the mitogenic signaling that supports tumor cells in the bone marrow, both by overcoming the protective role of bone marrow stromal cells and through antiangiogenic properties.

To the best of our knowledge, at least two other studies are ongoing in peripheral T-cell lymphoma: one Italian study (NCT01036399) in relapsed/ refractory patients, with Lenalinomide given alone from d1 to d21 for a total of 4 inductive cycles followed by 8 months of treatment in case of at least stable disease after induction; the other one, an Austrian study (NCT00972842) evaluate a combination of Lenalinomide with a dose escalation, Vorinostat and Dexamethasone in relapsed/refractory patients.

Rational for performing the combination of CHOP and lenalidomide

As CHOP or other combination chemotherapy are associated with low CR rates and short progression-free survival and overall survival, other combination therapies should be explored. Lenalinomide has a tolerable haematological toxicity profile and has been yet combined with R-CHOP (Rituximab + CHOP) in three prospective studies led in none previously treated patients with B-cell lymphoma. These studies are the following:

1) The LYSA, phase I study (NCT00901615), followed by a phase II - using the recommended dose of lenalinomide - in follicular lymphoma which is 25 mg delivered from d1 to d14,

2) The NCI phase I/II study, (NCT00670358) in diffuse large B cell and follicular lymphoma

3) The Italian phase I/II study, (NCT00907348) in elderly patients with diffuse large B-cell lymphoma

Until now, only preliminary results regarding toxicity are available: the adverse event profile on the 27 patients of the LYSA phase I study led in not previously treated patients with B-cell lymphoma is similar to that observed with CHOP alone. Twelve out of these 27 patients received CHOP combined to

lenalinomide 25mg d1-d14, of whom only four patients delayed their subsequent cycle. No major toxic event was observed. All the 12 patients received the 6 cycles planned.

On these bases, CHOP being the most frequently used regimen to treat newly diagnosed PTCL, it seems to us logical to evaluate the potential efficacy of the addition of lenalidomide to CHOP in order to improve the efficacy of CHOP alone

5 STUDY OBJECTIVES:

- To evaluate the Complete Metabolic Response (CMR) rate at the end of treatment defined according to Lugano Classification (Cheson et al, 2014, PET-CT-Based response)
- To evaluate the efficacy and the safety of a front-line treatment combining CHOP regimen and lenalinomide (Rev-CHOP) in patients aged 60 to 80 years with previously untreated AITL.
- To evaluate the role of PET in defining an accurate staging
- To evaluate the tumor metabolic activity based on FDG avidity measured by SUV max at baseline and the decrease of SUV max at the end of treatment
- To analyse on blood samples and on tumour biopsies biological factors that could influence treatment response and prognosis.
- To favour the banking of tumor cells suspensions with the aim to better understand the pathogenesis of the disease

5.1 Primary Objective

Complete Metabolic Response (CMR) rate at the end of treatment defined according to Lugano Classification (PET-CT-Based response)(Cheson et al, 2014))

5.2 Secondary objectives

- Complete response (CR) rate at the end of treatment according to the IWC (International Harmonization Project – Cheson 2007,) as assessed by site Investigator.

- Progression-free survival at 2 years (2y-PFS), events being relapse for complete responders, disease progression, and death from any cause.

- Overall survival (OS) and event-free survival (EFS)
- To evaluate the role of PET in defining an accurate staging

- To evaluate the tumor metabolic activity based on FDG avidity measured by SUV max at baseline and the decrease of SUV max at the end of treatment- To correlate response rate, survival and biological factors (phenotype, EBV status, T/B clonality, circulating cytokine dosages).
- Biological studies at diagnosis:

➢ Pathological and phenotypical description of the disease at presentation, with a detailed characterization of T-cells (T-cell antigens, CD10, CXCR5, PD1, CXCL13, ICOS, and Bcl6, Tbet, Gata3, RorγT transcription factors), FDC markers and EBV detection with B or T cells colocalization (by combined immunohistochemistry and in situ hybridization). A centralized pathological tissue

banking, pathological review by a panel of expert hematopathologists, achievement of Tissue Micro Array and collection of frozen tumour samples (and/or DNA and RNA) will be achieved within the LYSA-P institute.

- TCR and IgH clonality analyses by PCR on tumor sample and blood
- Phenotypic analysis of lymphoid cells in blood, including T antigens, CD10 CXCR5 CXCR3 CCR6 expression on CD4+ T-cells, CD19, CD20, CD27 and CD38 expression on B cell and NK cells numeration, using a 8- color flow cytometry device.
- Cytokine profiles in serum samples (VEGF, IL4, IL5, IL10, IL13, IL21, IL17A, IL22, IL6, IFNγ TNFα, CXCL13, EBI3) using luminex technology
- EBV virus load in total blood, in fractionated T and B cells and their impact on treatment response.

- Biological studies at the end of induction including same diagnostic flow cytometry and EBV virus explorations.

- An additional objective is to favour the banking of tumor cells suspensions (from lymph node biopsies, PB, effusions,…) with the aim to :

- provide purified collection of neoplastic TFH cells for high throughput methods (GEP, mi-RNAs, deep sequencing ..). For deep sequencing interpretaion, a blood sample will be collected for autologous allelic polymorphism analyses.
- derive tumor cell lines and/or lymphoblastoid cell lines from the EBVpos B cells of the microenvironment (to evaluate their capacity to induce TFH commitment from autologous naïve normal CD4pos T cells). (in connection with the PAIR INCa program).
- Define the molecular signature(s) (gene expression and mutations) of AITL entities and correlate these signatures with response to therapy;
- Determine novel molecular predictive factors of response to Lenalidomide-CHOP treatment
- Determine feasibility and clinical impact of cell free DNA sequencing in AITL
- For all those purposes, the collection of fresh relapse samples will be encouraged through an oligocentric network integrated to the National TENOMIC PHRC-PAIR program.

6 STUDY DESIGN

This study is a multicentric, phase II trial, open-label, non-randomized trial.

Patients will be recruited over 2 years and followed until 18 months after the last patient included.

The anticipated study dates (start / end) are:

1st patient included: Sept 2011

Last patient included: Sept 2016

Last patient followed for principal analysis: April 2018

Patients will be followed until death if possible.

Statistical analysis will be based on 70 evaluable subjects.

Since subjects who are not evaluable for response will be replaced, it is anticipated that approximately 80 subjects will be enrolled in total.

In the first stage, 37 evaluable patients will be enrolled. At least 17 patients should achieve a CR to proceed with the second stage.

The duration of the treatment period is approximately 26 weeks for 8 cycles of chemotherapy.

7 STUDY POPULATION

Adult patients aged between 60 and 80 years with T-cell angioimmunoblastic lymphoma (AITL) previously untreated.

7.1 Inclusion criteria

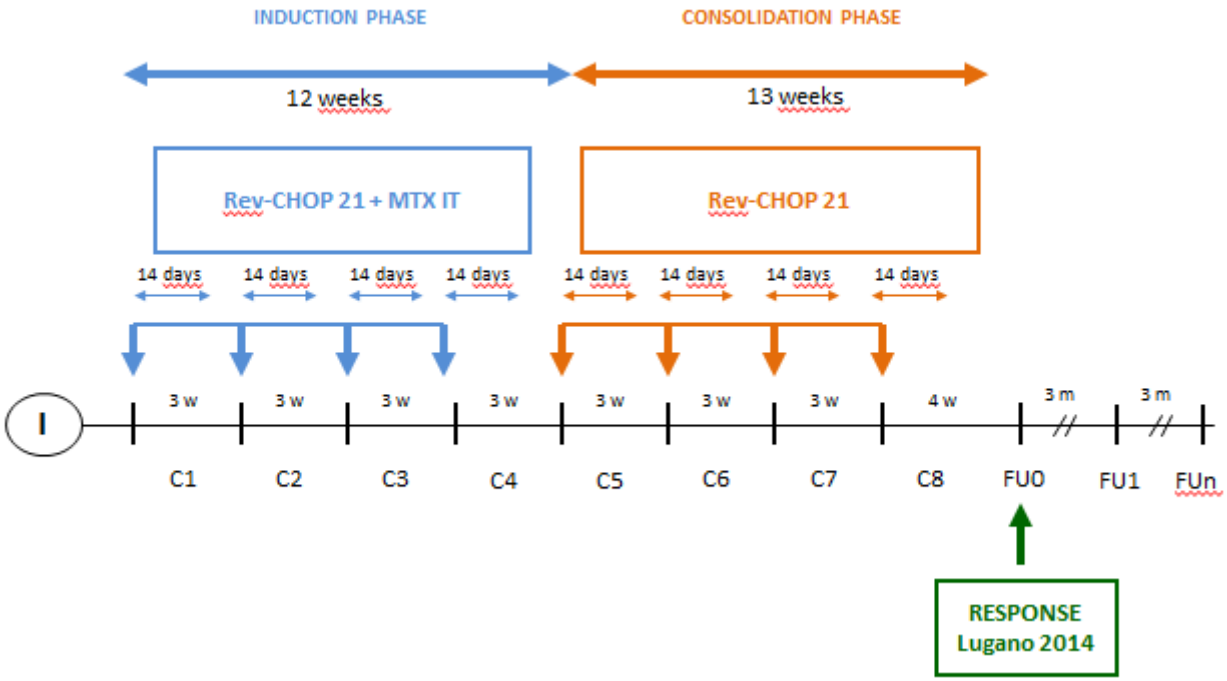
- Patients with histologically proven T-cell angioimmunoblastic lymphoma (AITL)
- Age from 60 to 80 years.
- ECOG performance status 0 to 2.
- No previous therapy (except corticosteroids providing they have been initiated less than 15 days before inclusion).Spontaneous life expectancy > 1 month.
- Written informed consent. The Lenalidomide Information Sheet (in appendix of the Patient Informed Consent Form see appendix 18.13 of the protocol) will be given to each patient receiving lenalidomide study therapy. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.
- Male patients must:
  Agree to use a condom during sexual contact with a FCBP, even if they have had a vasectomy, throughout study drug therapy, during any dose interruption and after cessation of study therapy.
  Agree to not give semen or sperm during study drug therapy and for a period after end of study drug therapy.
- All patients must:
  Have an understanding that the study drug could have a potential teratogenicity.
  Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy.
  Agree not to share study medication with another person.
  Be counselled about pregnancy precautions and risks of foetal exposure.

7.2 **Exclusion criteria**

- Others categories of T-cell lymphoma.
- Central nervous system involvement by lymphoma.
- Any previous therapy for lymphoma except short-term corticosteroids (maximum 10 days) before inclusion.
- Contra-indication to any drug included in the CHOP regimen.
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study (according to the investigator's decision).
- Active bacterial, viral or fungal infection, in particular active hepatitis B or C and HIV positive serological test.
- Impaired renal function (Creatinine clearance <50 ml/min (as calculated by the Cockcroft-Gault formula)) or impaired liver function tests (total bilirubin level > 30 µmol/L, transaminases > 2.5 upper normal limits) unless they are related to the lymphoma.
- Poor bone marrow reserve as defined by neutrophils < 1.0 x 10^9/L or platelets < 100 x 10^9/L, unless related to bone marrow infiltration.
- Any history of malignancy, other than that treated in this research, unless the patient has remained free of the disease for over 5 years.
- Treatment with any investigational drug within 30 days before planned first cycle of chemotherapy and during the study.
- Hypersensitivity to the active substance or to any of the excipients.
- Pregnant and lactating woman
- Females of Childbearing potential (FCBP*) according to the PPP (in appendix 18.13 of the protocol)

* A FCBP isa female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

8 TREATMENTS



8.1 Drugs description, storage and handling

Drugs composing the CHOP regimen are registered and are available at the hospital pharmacy.

Chemotherapy products are to be used according to summary of product characteristics or document of reference such as Brochure Investigator.

8.1.1 Description

Each capsules contains 10mg and 5mg of lenalidomide.

8.1.2 Storage conditions

Capsules of Revlimid do not store above 25°C.

8.1.3 Handlings

Revlimid® capsules should be taken at about the same time each day. The capsules should not be broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

8.2 Treatment schedule and design

8.2.1 Dose regimen

8 cycles of Rev-CHOP repeated every 3 weeks (Rev-CHOP 21)

CHOP will be administered at hospital the first day of each cycle repeated at D21 for 8 cycles.

Subjects will be treated with lenalidomide on an outpatient basis during. Oral lenalidomide is initiated on Day 1 of cycle 1 at a dose of 25mg daily and continued for in each 14 day cycle, and repeated at D21. Treatment is to be continued as tolerated for 8 cycles.

Rev- CHOP		**Dose (mg/m²)**	**Days**
CYCLOPHOSPHAMIDE	**IV**	**750**	**1**
DOXORUBICINE	**IV**	**50**	**1**
VINCRISTINE	**IV**	**1,4 (max 2 mg)**	**1**
PREDNISONE	**PO**	**40**	**1 to 5**
LENALIDOMIDE	**PO**	**25 mg**	**1 to 14**
METHOTREXATE ***For the first 4 cycles***	**IT**	**15 mg**	**1**

Treatment with sub-cutaneous G-CSF is mandatory at each cycle from day 6 to day 10 or until neutrophils >1.0G/l or at D4 for delayed formulation.

8.2.2 Dose adjustments

CHOP regimen

There is no adjustement of CHOP components related to hematological toxicity. However, in the case where cytopenia (absolute neutrophil count < 1,000 cells/mm^3 ($1.0x10^9$ /L) or platelet count < 75,000/mm^3 ($750x10^9$ /L) is observed at day 21, the next cycle will be postponed for 3 days. In the case of cytopenia persists on day 24, the next cycle will be postponed for 3-4 additional days (until day 28).

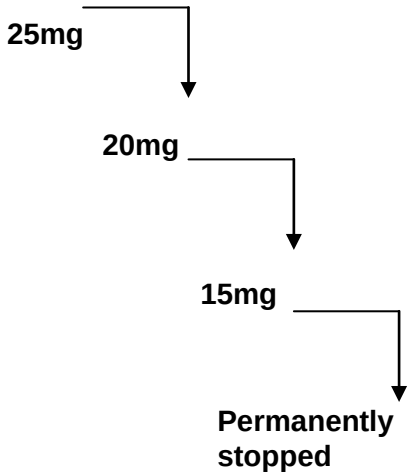
In case of grade 1 neurological toxicity to vincristine (sensory or motor neuropathy, constipation, visual or auditory changes), the dose will be reduced to 1mg by cycle. If the neurological toxicity increased despite of dose reduced, vincristine will be definitively stopped.

Lenalidomide

The lenalidomide dosing should be reduced in case of related toxicities, defined as follow:

- Grade 3 hematological toxicity (neutrophils and/or platelets) lasting more than 7 days,
- Grade 4 hematological toxicity (neutrophils and/or platelets) lasting more than 3 days,
- Creatinine clearance between 30 and 50 mL/min,
- Neurological toxicity > grade 2,
- Any other toxicity ≥ grade 3 except for alopecia and for ALT and Bilirubin (see below specific guidelines),
- Cycle of Rev-CHOP postponed because of toxicity for 7 days (corresponding to D28 of cycle) or more, and until D35 of cycle maximum.

Lenalidomide will be temporarily stopped for the current cycle (if toxicity is observed during the 14 days of the lenalidomide treatment), and dose of lenalidomide will be reduced as follow:



If a patient has had dose reduction, then dose re-escalation of lenalidomide is not permitted at any time.

If ALT > 5 x ULN or Total bilirubin > 3 x ULN, lenalidomide will be temporarily stopped for the current cycle. Then, at next cycle:

- if recovery from the event: dose of lenalidomide will be the same,
- if no, lenalidomide dose should be decreased by one dose level, and weekly testing of liver functions should occur during that cycle. If the values do not return to baseline within the two next cycles, lenalidomide dose should be discontinued.

Important: If creatinine clearance <30 mL/min, lenalidomide must be definitely stopped,

If next cycle has to be postponed for related toxicity or other reason beyond the D35, a premature withdrawal should be registered for the patient.

In case of DVT occurrence, antithrombotic treatment (heparin or coumadin [INR 2-3] must be started (and kept during the whole treatment duration with lenalidomide) and lenalidomide can be resumed without dose reduction.

8.2.3 Prophylactic measures

All subjects will be required to take a low molecular weight heparin as thromboembolic event prophylaxis during study period.

8.2.4 Concomitant medications

All patient treatments 8 days prior to study treatment, at any time during the study, and up to 30 days after the end of the study treatment will be considered as concomitant treatments. Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the investigational products, they may be given at the discretion of the investigator and recorded in the case report form.

The following concomitant treatments <u>are permitted</u> during this study treatment:

- All supportive measures (including blood transfusions) consistent with optimal patient care will be given throughout the study and should be documented in the CRF.
    - Treatment of anemia with recombinant erythropoietin (ESA) according to drug approval recommendations. ESA can be used for the treatment of anaemia in symptomatic patients with non-myeloid tumours receiving chemotherapy according to the EMEA guidance from June 2008. For patients receiving ESA, DVT prophylaxis must be either LMW heparin or warfarin.
    - In case of AIHA, treatment with Corticosteroids should be associated. The scheme of the de-escalation is at the discretion of the treating physician. The persistence of an AIHA at the end of the treatment is a non-response criteria.

- Medications for chronic pain management, including narcotic analgesics, are permitted as clinically indicated.

The following concomitant treatments are not permitted during this study treatment:

- Systemic anticancer agents other than study drugs.
- Other investigational therapies or devices.
- Concomitant radiotherapy.

If a patient's clinical status requires administration of a prohibited concomitant medication or treatment, then administration of study drugs should be stopped, and the patient will be entered in the study follow up period. The change in clinical status mandating the use of the medication in question must be reported as the reason for study drug discontinuation.

8.3 Drug Dispensation and accountability

8.3.1 Packaging and labeling

Celgene Corporation will supply lenalidomide capsules in 10 mg, and 5 mg strengths. The packaging containing capsules will be labelled according to the Good Manufacturing Practice guidelines and the local requirements. Wallets will be labelled as follows:

- Sponsor's name, address,
- Protocol/Study number, Eudract number,
- Lenalidomide: dosage, number of capsules, pharmaceutical form
- Method and route of administration
- Batch number, expiry date,
- Subject identification,
- Date of dispensed,
- Investigator name and phone number,
- Storage conditions, directions for use and regulatory mentions.

8.3.2 Responsibilities

All drug packages are to be inspected upon receipt at the study site prior to being drawn up. If any particulate matter is detected, the packaging is not to be used. Damaged packagings are to be reported to the sponsor and stored until instructions have been given.

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense Investigational Product (Revlimid) will be responsible for ensuring that the Investigational Product used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements. All Investigational Product must be stored in accordance with

labelling and shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained. Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labelling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure. Under no circumstances will the Investigator supply Investigational Product to a third party, allows the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

8.3.3 Retrieval or destruction

All partially used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned Investigational Product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team. The Investigator will not destroy the unused Investigational Product unless the Sponsor provides written authorization. A potential defect in the quality of Investigational Product may be subject to initiation by the Sponsor of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Investigational Product and eliminate potential hazards.

8.3.4 Accountability and compliance

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the investigational product. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed and used for each patient. The study monitor will periodically check the supplies of investigational products held by the investigator or pharmacist to verify accountability of all investigational products used. All unused investigational products and all medication containers will be returned to the Sponsor unless other arrangements have been approved by the Sponsor. The Sponsor will verify that a final report of drug accountability to the unit dose level is prepared and maintained in the investigator study file. Administration of the study treatment will be supervised by the investigator or subinvestigator.

9 STUDY FLOW CHART (APPENDIX 18.1) AND SCHEDULE OF ASSESSMENTS (APPENDIX 18.2)

9.1 Study flow chart

See on **Appendix 18.1.**

9.2 Baseline examination

The patients will be required to give written informed consent to participate in this study before any non routine baseline evaluations are conducted.

The subject's eligibility has to be evaluated during the baseline period prior to administration of the first cycle of chemotherapy. The assessments are to be conducted up to 14 days before administration of the study treatment:

- Age, gender, weight, height and vital signs
- Staging **(see Appendix 18.3)**, IPI and aaIPI **(see Appendix 18.5)**
- ECOG Performance Status **(see Appendix 18.4)**
- Relevant medical history and concomitant treatments
- History of the NHL
- Physical examination
- Complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit
- Biochemical tests: calcium, sodium, potassium, urea, β2 microglobuline, LDH, ALT, AST, total bilirubin, alkaline phosphatase, albumin, creatinine, creatinine clearance as calculated by the Cockroft-Gault formula **(see Appendix 18.6)**.
- Serum electrophoresis
- HIV, HBV and HCV serologies
- Thoracic and abdominal and pelvis CT scan (within 28 days before administration of the study treatment)
- Cerebral CT scan if clinically indicated (within 28 days before administration of the study treatment)
- Baseline PET scan (PET0) performed before inclusion in the trial (within 28 days before administration of the study treatment)
- Bone marrow biopsy (mandatory) (within 56 days before administration of the study treatment)
- ECG
- Echocardiography or isotopic method to determine resting ejection fraction
- Confirmation of non childbearing potential. A female NOT of chilbearing potential is a woman who has a natural menopause for at least 24 consecutive months, a hysterectomy or bilateral oophorectomy.
- All conditions of the Lenalidomide Pregnancy Prevention Risk Management Plan (in appendix 18.13 of the protocol) must be checked and fulfilled by all the patients enrolled in the study.
- Samples for biological studies **(cf Appendix 18.12)** after informed biological consent **:**
    - Phenotyping analysis in blood, by flow cytometry of lymphoid cells
    - TCR and IgH clonality analyses by PCR on tumor sample, and blood.
    - Cytokines profiles in serum samples.

- EBV status in B and T lymphocytes on tumoral sample.
- EBV virus load in total blood
- Genetic polymorphism analyses
- Storage of serum and plasma samples, DNA samples and Formalin-fixed Paraffin-Embed tumor samples for molecular characterization of AITL

9.3 **Evaluation during treatment**

	When
Weight and body surface area	D1 of each induction and consolidation cycle prior administration
Pulse, blood pressure, body temperature	D1 of each induction and consolidation cycle prior administration
Physical examination and PS	D1 of each induction and consolidation cycle prior administration
Biochemical tests: calcium, sodium, potassium, urea, creatinine, LDH, ALT, AST, total bilirubin, alkaline phosphatase, creatinine clearance	Day 1 of each cycle induction and consolidation cycle prior administration
Complete blood cell counts including white blood cell count with differential count, platelet count,, haemoglobin, and haematocrit	D-2 or D-1 of each induction and consolidation cycle prior administration, D10
Adverse events	See section 12

Lenalidomide Education and Counseling Guidance Document (in appendix M of the protocol) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of lenalidomide study treatment. A copy of this document must be maintained in the patient records.

The Lenalidomide Information Sheet (Appendix N of the protocol) will be given to each patient receiving lenalidomide study therapy. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.

9.4 End of treatment evaluation

The following assessments must be conducted 30 days (maximum 60 days) after the last intake of lenalidomide treatment of cycle 8 (see **Appendix 18.2**):

- Physical examination
- Vital signs (Weight and body surface area, pulse, blood pressure, body temperature).
- ECOG PS.
- Biochemical tests: calcium, sodium, potassium, urea, creatinine, LDH, ALT, AST, total bilirubin, alkaline phosphatase.
- Complete blood cell counts.
- Bone marrow biopsy to confirm an initial documentation of CR in subjects with a positive bone marrow result at baseline (assessment not required for patients with already cleared bone marrow at previous evaluation).
- Cervical, Chest, abdomen and pelvis CT scan with oral and IV contrast.
- PET scan
- Evaluation of the disease response (Lugano Classification (PET-CT-Based response), **see Appendix 18.7** and for Cheson 2007, **see Appendix 18.8**).
- Any other evaluations or procedures performed at baseline for evaluation of the disease response.
- Adverse events
- Biological studies **(**see **Appendix 18.12):**
    - Phenotyping of lymphoid cells by flow cytometry
    - EBV virus load in Total blood
    - Storage of serum and plasma samples, DNA samples and Formalin-fixed Paraffin-Embed tumor samples for molecular characterization of AITL

In case of premature withdrawal during the study treatment period, the evaluation should be performed 30 days after the last drug administration or before any new treatment start date.

9.5 Follow-up assessments

The patients will be followed 18 months after the last patient has completed the treatment. Thereafter, the long term follow-up of patients will be organized for further analysis.

Every 3 months during the first 2 years, then every 6 months during the next 5 years and every year thereafter. Patients will be followed until death if possible.

- Physical examination
- Vital signs (Weight, pulse, blood pressure, body temperature).

- Complete Blood cell counts
- ECOG Performance Status **(see Appendix 18.4)**
- Bone marrow aspirate and biopsy if clinically indicated
- Evaluation of the treatment response (Cheson et al., 1999) **(see Appendix 18.9)**.
- Thoracic and abdominal CT scan for evaluation of progression every 6 months during the 1st 24 months after completion of treatment, and every year thereafter.
- Any other evaluations or procedures for evaluation of the treatment response every 6 months during the 1st 24 months after completion of treatment, and every year thereafter.
- Adverse event
- Follow-up for any second malignancies which must be reported as serious adverse event regardless of when they occur and regardless of their relationship to study treatments/procedures

Patients who withdraw from the study treatment or patients who progress / receive new treatment after treatment period should be followed according to the local requirements until death.

9.6 **Progression/relapse**

Relapse/progression will be determined as per Cheson 1999 criteria **(see Appendix 18.9).**

Progressive disease should be based on CT scan or relevant clinical data, exams (e.g., PET-Scan).

A pathological confirmation by biopsy of the lesion should be done if possible.

10 STUDY PROCEDURES

10.1 **Informed consent**

Written informed consent in compliance with local regulatory authority will be obtained from each subject prior to entering the trial or prior to performing any unusual or non-routine procedure that involves any risk to the subject in the purpose of evaluating the subject of the study. The informed consent for biological studies should be signed before sampling for proteomic and genetics analysis.

The patient and the investigator will date and sign the informed consent form, and the LYSARC will be notified of the investigator's request to register the patient for the study.

The investigator shall provide a copy of the signed consent to the study patient, a copy shall be maintained in the investigator's study file.

10.2 Registration procedure

A patient will be registered after verification of eligibility directly on the data capture system by the investigators through the internet network with the address below. To access the interactive registration program, the investigator needs to record the study name (Revail), a username and a password.

Internet: http://study.lysarc.info

Registration should be done before the start of the protocol treatment. The study site will receive back the registration number and arm for the registered patient.

The investigator should fax **(+33 4 72 66 38 57**) at the same time the following documents whatever the registration way used: a copy of the pathology report, copy of PET0 report or enough information for organizing PET review (see concerned chapters). Information on the samples storage location at -80°C for proteomic (plasma) and for genetic (dry pellets) will be asked. **The LYSARC coordination center (Tel: +33 4 72 66 93 33)** will be the contact for any request.

10.3 Pathological diagnosis

The pathological diagnosis of AITL should have been performed locally before the inclusion.

The process of tissue review will be organized by the LYSA-Pathology Institute according to procedures commonly used in the clinical trials of the LYSA. For details, **see Appendix 18.11.**

Centralized collection of the tumour material in the LYSA Pathology Institute (LYSA-P), located at Hôpital Henri Mondor, 94010 Créteil. The request of the tumour tissue (paraffin-embedded and whenever possible frozen sample, or if not possible the DNA and/or RNA extracted after histological control) will be done by the LYSA-P project manager after randomization of the patient and receipt of a copy of the pathology report (by Fax) indicating the reference number of the report.

Tissue microarray (TMA) construction: For tissue microarray construction, a slide stained with hematoxylin and eosin will be prepared from each formalin-fixed paraffin donor block, and three tissue cylinders representative of tumor regions with a diameter of 0.6 mm will be punched and transferred into a recipient paraffin block. Reactive lymphoid tissues will be also included in the TMA blocks, as controls. As far as possible, two twins TMA blocks will be prepared, according to procedures used in LYSA-P.

The review process will be coordinated by P. Gaulard and done by a defined panel of expert pathologists. For this process, routinely stained (hematoxylin-eosin,) sections will be obtained and an appropriate panel of antibodies (comprising CD20, CD3, other T-cell antigens, CD4, CD8, CD10, CXCR5, PD1, CXCL13, ICOS, and Bcl6, Tbet, Gata3, RorγT transcription factors), FDC markers (CD21 or CD23) and EBV detection by in situ hybridization with EBERs probes and with B or T cells

colocalization (assessed by combined immunohistochemistry and in situ hybridization) according to morphological aspects will be applied. As far as possible, for clonality analysis and further molecular investigation, DNA will be extracted for each case either from the frozen material or, when not available from paraffin-embedded samples through a method established in LYSA-P.

For the need of further ancillary study, blocks will be kept temporarily to avoid a second request. Meanwhile, the block will be at the entire disposition of the initial anatomopathology laboratory under request if they need it.

When the review process is achieved, the LYSA reviewers will establish a report sent to the initial pathologist and the investigator of the inclusion centre.

10.4 Peripheral blood samples

Sampling of blood will be required for biological studies (lymphocyte phenotyping, TcR and IgH clonality, cytokines profiles, EBV virus load) and to future ancillary studies. A specific informed consent for biological collection and for genetic analyzes should be signed by the patient before any sample procedure.

The samples processing is described on **the Appendix 18.12.**

10.5 CT scan Review

NA

10.6 PET scan Review

A central review of the PET scan is mandatory and organized.

For each patient when applicable, the data and images of:

- baseline
- at the end of treatment (after cycle 8)

Will be reviewed by a panel of PET experts.

The review processing is described on **the Appendix 18.10.**

10.7 Independent Data Monitoring Committee

The Independent Committee, including at least three independent members will be established. The IDMC will meet regularly throughout the research, at least every six months in case of occurrence of second malignancies. Each report of the independent committee will be forwarded to ANSM electronically. The committee provides general advice on the progress of research, it decides on whether

to continue the trial in light of such prolonged and exhaustive collection of cases of secondary cancers that may occur in the study.

11 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

11.1 Premature withdrawal from trial intervention

Circumstances that lead to premature withdrawal of a patient from the trial must be reported by the investigator on the appropriate CRF page.

Criteria for subject withdrawal include (but are not limited to):

- death,
- disease progression
- major protocol violation (including initiation of alternate anti-neoplastic therapy),
- toxicity,
- intercurrent illness,
- non compliance (including loss of subject to follow-up),
- voluntary withdrawal,
- failure to meet the eligibility criteria.

Patients should however remain in the trial for the purposes of follow-up and data analysis.

11.2 Withdrawal of Consent

Patients are free to withdraw from the study at any time without prejudice to their treatment. When a patient decides to withdraw from the study, she/he should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When possible, the patient should return for a study visit at the time of, or soon after withdrawal, and the relevant assessments should be performed.

If the patient explicitly states their wish not to contribute further data to the study, the relevant LYSARC contact should be informed and the withdrawal of consent should be documented by the investigator in the patient's case report form. However, data up to the time of consent withdrawal will be included in the data reported for the study.

11.3 Patients Lost to Follow up

Every effort will be made to contact patients who fail to return for scheduled visits. A patient is considered lost to follow-up if no information has been obtained when the last patient has completed the clinical phase of the study. During this time there must be documented attempts to contact the patient either by phone or letter.

Subjects who are withdrawn from the study will not been replaced. Furthermore, those subjects may not re-enter the study at any time.

11.4 Premature discontinuation of the study

The sponsor reserves the right to stop the trial at any time. The investigators will be informed of this decision in writing.

The same applies to any investigator wanting to discontinue his/her participation to the trial. The investigator must immediately inform the sponsor in writing of this decision.

12 SAFETY PARAMETERS

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence occurring at any dose that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any medical condition that was present prior to study treatment and that remains unchanged or improved should not be recorded as an AE. If there is a worsening of that medical condition, this should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the Case Report Form rather than the individual signs or symptoms of the diagnosis or syndrome.

12.1 Serious adverse event

A serious adverse event (SAE) is any AE which:

- Results in death
- Is life-threatening (i.e., in the opinion of the Investigator(s) the subject is at immediate risk of death from the AE)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Constitutes an important medical event

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur

on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator(s) will provide information on severity, start and stop dates, relationship to study drug, action taken regarding study drug, and outcome.

12.2 Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The severity of adverse events (AEs) will be graded on a scale of 1 to 5 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0. This can be viewed online at the following NCI web site: http://ctep.cancer.gov/reporting/ctc.html

If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event

Grade	Definition
1	Mild Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities
2	Moderate Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres
3	Severe Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required
4	Life-threatening Immediate risk of death; requires hospitalization and clinical intervention.
5	Death

Classification of Relationship/Causality of adverse events (SAE/AE) to study drug

Below is a recommendation for classification of AE/SAE, however the sponsor may want to use other classifications

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event

Suspected: The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

12.3 Adverse Events reporting

All adverse events of intensity grade ≥ 2 (see paragraph 12.1) regardless of relationship to Revlimid that occurred after the informed consent up to 30 days after the last study drug administration will be recorded in the AE pages of the Case Report Form (CRF).

All events that meet one or more criteria of seriousness (see paragraph 12.1) will be reported as **Serious Adverse Event** in the SAE form.

Any episode of any grade of toxicities, related to a Serious Adverse Event must be reported as “Adverse Event” on the appropriate CRF page.

Exemption rules*:*

- Adverse events will not be recorded after the start of a new chemotherapy treatment or after lymphoma progression, except if considered related to the study treatment.
- Sign, symptoms and physical findings indicative of lymphoma or lymphoma progression, including death of lymphoma, are not to be reported as “Adverse Event” nor “Serious Adverse Event".
- “Alopecia” toxicity (any grade) will never be reported as “Adverse event”.

Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding trial medication, corrective therapy given, outcome of all adverse events and his opinion as to whether the adverse event can be related to the study drug Revlimid.

Special monitoring is required for adverse events referring to the drug hypersensitivity (ex. skin rash), and thromboembolic events.

12.4 Serious Adverse Event reporting

All defined **Serious Adverse Events (SAEs)**, whether or not ascribed to the study, occurred after **the date of informed consent signature up to 30 days after the last drug administration,** will be recorded in the Serious Adverse Event Form.

In addition, a serious adverse event that occurs after this time, including during the follow-up period, **should be reported if considered related to the study medication.**

Exemption rules*:*

- Serious Adverse event will not be recorded after new treatment administration or after lymphoma progression, except if considered related to the study treatment
- Sign, symptoms and physical findings indicative of lymphoma or lymphoma progression including death of lymphoma, are not to be reported as “Serious Adverse Event”.
- Hospitalisation that lasted less than 8 days for haematological toxicity (anemia, neutropenia, lymphopenia, leukocytopenia, thrombocytopenia), febrile neutropenia, vomiting are not to be reported as “Serious Adverse Event”, unless the event is life-threatening or fatal.
- Planned hospital admissions or surgical procedures for an illness or disease which existed before the subject was enrolled in the study or before study drug was given are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the study (eg surgery was performed earlier than planned).
- Second malignancies must be reported as serious adverse event regardless of when they occur and regardless of their relationship to study treatments/procedures

Investigator’s responsibilities

All Serious Adverse Events (SAE) must be reported to the LYSARC by fax **within 24 hours of the awareness of the event**. All details should be documented on the specified **Serious Adverse Event form**.

PLEASE SEND THE REPORTS TO LYSARC SAFETY DESK:

FAX NUMBER +33(0) 3 59 11 01 86.

ALL SAE Forms must be dated and signed by the investigator or one of his/her authorized staff Members.

For serious adverse events, the following must be assessed: relationship to study drug, action taken regarding trial medication, and outcome to date. Whenever possible, symptoms should be grouped as a single syndrome or diagnosis.

The Relationship to the study drug (Revlimid) is assessed by the investigator. For adverse events, causality can be one of two possibilities:

Unrelated:	The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Related:	The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Feel free to join any anonymous copy of pertinent results, exams or reports related to the serious event.

All serious adverse events must also be reported on the Adverse Event page of the CRF.

Initial reports must be followed-up by a complete report within further 10 calendar days and sent to LYSARC. The investigator should answer to the safety desk requests for complementary information regarding the SAE.

LYSARC will supply Celgene with a copy of all SAEs within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (IB).

LYSARC will provide Celgene with a copy of the annual safety report at the time of the submission to the regulatory authority and the Ethics Committee.

12.5 Pregnancies

Female of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study drug, or within 28 days of the subject's last dose of study drug, are considered events to be reported immediately to LYSARC Pharmacovigilance on the appropriate Pregnancy Form. If the subject is on study drug, the study drug is to be discontinued immediately and the subject instructed to return any unused portion of the study drug to the Investigator.

The female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify LYSARC of the outcome of the pregnancy (including notification of false-positive tests) within 24 hours of having knowledge of the event. The outcome of the pregnancy will be reported as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator(s) should follow the procedures for reporting SAEs.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator(s) suspects is related to the *in uterus* exposure to the study drug should also be reported to LYSARC within 24 hours of the Investigator's knowledge of the event.

If the female is found not to be pregnant, any determination regarding the subject's continued participation in the study will be determined by the Investigator(s).

Male Subject:

Female partners of males taking investigational product should be advised to call their healthcare provider immediately if they get pregnant. The male subject should notify the Investigator of his partner's pregnancy and her healthcare provider information. The Investigator will then provide this information to the Sponsor for follow-up as necessary.

12.6 Revlimid Adverse event updates

Celgene shall notify the principle investigator/sponsor of the following information:

- Any AE associated with the use of study drug or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The principle investigator/sponsor will forward this information to other investigators involved in the trial.

The sponsor shall only forward this information to Ethic Committees or Competent Authorities when explicitly asked to do so by the Company (and following the Company's detailed instructions)

Sponsors responsibilities

The LYSARC pharmacovigilance desk will decide of the expected or unexpected nature of this event. An unexpected adverse event is one of which the nature or severity is not consistent with the applicable product information (Investigator Brochure). Suspected Unexpected Serious Adverse Events (SUSARs) will be reported to the EMA, Health Authorities and Ethics Committees of concerned countries within 7 days for fatal or life-threatening events and within 15 days for other serious adverse events.

The LYSARC pharmacovigilance desk will be responsible for expedited reporting (SUSAR, New Safety Issues, Annual safety Reports) to the relevant Health Authorities and to the Ethics Committee according to the local regulation.

12.7 Follow up of Adverse Events and Serious Adverse events

Any SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or underlying condition. Any additional information known after the event has been initially reported should be sent to the LYSARC as soon as information becomes available.

All adverse events must be documented and the outcome must be followed up until the return to normal or consolidation of the patient's condition.

13 STATISTICAL CONSIDERATIONS

13.1 Study design

This study is designed as a multicenter, open-label, single-arm phase II trial to evaluate the efficacy and the safety of first line treatment with CHOP and lenalidomide (Rev-CHOP) in patients aged from 60 to 80 years with previously untreated T-Cell angioimmunoblastic lymphoma (AITL).

A two-stage Simon's design for phase II trials is used for statistical data analysis. Statistical analysis will be based on Complete Metabolic Response (CMR) (according to Lugano Classificaction (PET-CT-Based

response)"rate in order to determine if Rev-CHOP treatment has sufficient efficacy to warrant further clinical study.

13.2 Primary endpoint

The primary endpoint is the Complete Metabolic Response (CMR) rate at the end of treatment defined according to Lugano Classification (PET-CT-Based response).

Response will be assessed after complete treatment if patient received all planned cycles or at withdrawal. Patient without response assessment (due to whatever reason) will be considered as non-responder.

A descriptive analysis will also be performed considering as non-responders all patients who relapsed or died during treatment phase even if they were prematurely withdrawn as responder.

The categorization of the patients according to response results at the end of study treatment or at premature treatment discontinuation will be performed as follows:

- CMR : Complete metabolic response (responder)
- PMR : Partial metabolic response
- NMR : No metabolic response
- PMD: Progressive metabolic disease
- Not Evaluated / Missing (for any reason): non responder

Complete Response (CR) rate based on investigator evaluation of PET scan will be used as secondary endpoint.

13.3 Secondary endpoints

13.3.1 Efficacy endpoints

Secondary efficacy endpoints will include:

Complete Response Rate at the end of treatment according to Cheson 2007 criteria (based on Investigator site PET scan)

Disease response evaluation after 8 cycles will be used to determine the Complete Response Rate. Response will be assessed if patient received all planned cycles or at withdrawal. Assessment of

response will be based on the International Workshop to Standardize Response criteria for NHL (Criteria for evaluation of response in Non-Hodgkin's lymphoma (Cheson, 2007)).

Patient without response assessment (due to whatever reason) will be considered as non-responder.

PROGRESSION-FREE SURVIVAL (PFS)

Progression-Free Survival will be measured from the date of inclusion to the date of first documented disease progression, relapse or death from any cause, whichever occurs first.

Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

OVERALL SURVIVAL (OS)

Overall survival will be measured from the date of inclusion to the date of death from any cause. Patients alive will be censored at their last follow-up date. Patients who are alive or lost to follow-up at the time of analysis will be censored at the date of the last contact.

EVENT-FREE SURVIVAL (EFS)

Event-Free Survival will be measured from the date of inclusion to the date of first documented disease progression, relapse, initiation of new anti-lymphoma therapy or death from any cause. Responding patients and patients who are lost to follow up will be censored at their last tumor assessment date.

13.3.2 Safety endpoints

All subjects who received at least one dose of Revlimid will be considered evaluable and analyzed for safety.

Analysis of safety will be performed by summarizing adverse events, laboratory data, physical examination findings and vital signs. When applicable, summary of safety data will also be performed by cycle.

13.3.3 Exploratory analyses

All other analyses (like subgroup analyses, role of PET scan, biological studies, prognostic factors) will be considered as exploratory analyses.

13.4 Statistical and analytical methods

13.4.1 Statistical methods

A 2-stage statistical analysis following Simon's two-stage design will be conducted to assist with making decisions about the utility of continuing the study. The analysis will be based on complete metabolic response (CMR) rate (according to Lugano classification (PET-CT-Based response).

Continuous variables will be summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles will also be presented when considered relevant. Categorical data will be described in counts and percentages (of non-missing data).

Censored data will be presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points, with 95% CIs. The median time to event will be calculated (if reached) with 95% confidence intervals.

The number and percent of subjects falling into each category of response according to the Lugano Classification will be provided. Deaths will also be included as a category, if patients died during the corresponding period. Response rates will be expressed with 95% confidence limits according to Pearson-Clopper method.

13.4.2 Sample size calculation

The sample size calculation is based on Simon's phase II design. This two-stage design allows for assessment of efficacy for early termination if the treatment is not effective based on pre-specified null and alternative hypotheses.

Based on the two-stage design, the hypotheses are:

H0: p < p0 ***versus*** **H1: p > p1**

where p0 and p1 are complete response rates such that the test regimen does not or does merit further testing at given levels of statistical significance (α) and power (1-β). Rejection of H1 is possible at stage 1, but acceptance can only occur at stage 2. Rejection of H0 (or H1) means that further (or no further) study should be carried out.

In this clinical study, **p0 and p1** were chosen to be **45%** (reference obtained with CHOP alone) and **60%**, respectively. The significance level α **= 0.05** and type II error β **= 0.20** were used.

In the first stage, 37 evaluable patients will be enrolled. At least 17 patients should achieve a CR to proceed with the second stage. The probability of early termination is 0.482.

If this condition is fulfilled, a total of 70 evaluable patients will be analyzed. At least 39 patients should respond to conclude that the treatment is effective. Subjects not evaluable for response, as defined in section 13.4.3, will be replaced. It is anticipated that up to 80 subjects (approximately) will be enrolled in total.

13.4.3 Populations for analysis

Efficacy population

Evaluable patients are defined as all patients who received at least one cycle of Rev-CHOP

- with complete treatment and with central review of PET scans at baseline and at the end of treatment
- prematurely withdrawn before C8

This population will be used for all efficacy analyses.

Safety population

The safety population includes all subjects who received at least one dose of Revlimid. This population will be used for all safety analyses.

13.4.4 Interim analysis

A two-stage analysis will be conducted.

The first stage analysis will be performed after 37 evaluable patients (as defined) have been included. The trial will be terminated if 16 or fewer patients respond to treatment and treatment will be considered as ineffective. The probability of early termination is 0.482. All data available at the scheduled time of interim analysis will be used for these patients. Otherwise, the trial will proceed to second stage and include 33 additional evaluable patients. Thus, a total of 70 evaluable patients (as defined) will be

studied. At the end of the second stage, if the total number of responder patients is less than or equal to 38, treatment will be considered as inefficient.

14 STUDY MONITORING

14.1 Responsibilities of investigators

The investigator(s) undertake(s) to perform the study in accordance with Good Clinical Practice and specifically either good clinical practice for trials on medicinal products in the European Community (ISBN 92 - 825-9563-3) or 21 CFR - Part 312 subpart D and guidelines for the monitoring of clinical investigations.

The investigators are required to ensure compliance with respect to the investigational drug schedule, visit schedule and procedures required by the study. The investigators agree to provide all information requested in the case report form in an accurate and legible manner according to instructions provided.

Subject compliance to the study treatment is the investigator's responsibility and will be checked during site monitoring visits by a representative of the LYSARC.

14.2 Responsibilities of the sponsor

The sponsor (LYSARC) of this study has responsibilities to health authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, study adherence, integrity and validity of the data recorded on the case report forms. Thus, the main duty of the project leader and of his clinical research support team (LYSARC) is to help the investigator maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the center will be contacted, through site visits, letters or telephone calls, by a representative of the monitoring team (LYSARC) to review study progress, investigator and subject adherence to study requirements and any emergent problems.

During monitoring visits, the following points will be scrutinized with the investigator: subject informed consent, inclusion and exclusion criteria, subject recruitment and follow-up, subject compliance to the study treatment, study treatment accountability, concomitant therapy use, evaluations of response, serious/non serious adverse event documentation and reporting, and quality of data. Sections of Case Report Forms may be collected on a visit per visit basis.

14.3 Source document requirements

According to the guidelines on Good Clinical Practice, the study monitor has to check the case report form entries against the source documents. The consent form will include a statement by which the patients allow the sponsor's duly authorized personnel (trial monitoring team) to have direct access to source data which supports data on the case report forms (e.g. patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

14.4 Use and completion of the electronic case report forms (e-CRF)

An electronic Case Report Form (e-CRF) will be completed for each study subject. It is the investigator's responsibility to ensure the accuracy, completeness, legibility and timeliness of the data reported in the subject's e-CRF. Source documentation supporting the e-CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events and subject status.

The investigator, or designated representative, should complete the e-CRF pages as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action.

14.5 Study drug monitoring

Accountability for the study drug at the clinical site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each subject, or disposal of the drug will be maintained by the clinical site. These records will adequately document that the subjects were provided the doses as specified in the protocol. The sponsor or its designee will review drug accountability at the site on an ongoing basis during monitoring visits.

All unused study drug will be retained at the site until they are inventoried by the monitor. All used, unused or expired study drug and all material containing Revlimid™ will be treated and disposed of as hazardous waste in accordance with governing regulations.

15 ETHICAL AND REGULATORY STANDARDS

15.1 Ethical principles

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983) and the 41st (Hong Kong, 1989), the 48th (Somerset West, 1996), the 52nd (Edinburg, 2000) World Medical Assemblies, notes for clarification added by the WMA General Assembly on paragraph 29 (Washington 2002) and on Paragraph 30 (Tokyo 2004) and amendment laid down by the 59th (Seoul, October 2008) World Medical Assemblies.

15.2 Laws and regulations

This study is also in accordance with laws and regulations of the country(ies) in which the trial is performed, as well as any applicable guidelines.

15.3 Informed consent

It is the responsibility of the investigator to obtain informed consent in compliance with national requirements from each subject prior to entering the trial or, where relevant, prior to evaluating the patient's suitability for the study.

The informed consent document used by the investigator for obtaining subject's informed consent must be reviewed and approved by LYSARC prior to Ethics Review Committee submission.

The investigator must explain to potential patient the aims, methods, reasonable anticipated benefits and potential hazards of the trial and any discomfort it may entail. Patients will be informed that they are free not to participate in the trial and that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The patient should receive a signed and dated copy of the informed consent form and patient information leaflet. The inclusion process will be documented in each patient’s medical records.

For ancillary studies, a specific informed consent form will be signed and dated by patients.

15.4 Ethics Review Committee and competent authorities submission

The sponsor must submit this study to country central ethics review committee, and to competent authorities and it is required to forward a copy of written approvals / advices signed to the investigators.

16 ADMINISTRATIVE PROCEDURES

16.1 Curriculum vitae

An updated copy of the *curriculum vitae* of each investigator and sub-investigator will be provided the LYSARC prior to the beginning of the study.

16.2 Secrecy agreement

All goods, materials, information (oral or written) and unpublished documentation provided to the investigators (or any company acting on their behalf), inclusive of this study, the patient case report forms are the exclusive property of LYSARC.

They may not be given or disclosed by the investigator or by any person within his authority either in part or in totality to any unauthorized person without the prior written formal consent of LYSARC.

It is specified that the submission of this study and other necessary documentation to the Ethics Review Committee or a like body is expressly permitted, the Ethics Committee members having the same obligation of confidentiality.

The investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced in the course of the trial, other than that information to be disclosed by law.

16.3 Record retention in investigating center(s)

The investigator must maintain all study records, patient files and other source data for the maximum period of time permitted by the hospital, institution or private practice.

However national regulations should be taken into account, the longest time having to be considered.

For trials performed in the European Community, the investigator is required to arrange for the retention of the patient identification codes for at least 15 years after the completion or discontinuation of the trial.

Any center will notify the sponsor before destroying any data or records.

16.4 Ownership of data and use of the study results

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 any country.

16.5 Publication

The results of the trial will be published after complete data collection and evaluation. Partial or preliminary results can be published beforehand. Publication is to be initiated by the two chairmen in charge of the study with approval of coordinators.

Any publication in the form of a lecture, poster or article must be basically approved by the Scientific Committee of the LYSARC.

The authors will be proposed (according to the updated LYSARC publication rules) by the chairmen in charge of the study, approved by coordinators and finally decided by the Steering Committee of the LYSARC.

All study data and publications are the property of the LYSARC.

16.6 Insurance compensation

The sponsor certifies having taken out a liability insurance policy which covers the investigator and his co-workers and which is in accordance with the local laws and requirements. Specific statements will be contained in appendix where is needed.

A certificate of insurance will be provided to the investigator in countries in which this document is required.

16.7 Company audits and inspections by regulatory agencies

For the purpose of ensuring compliance with good clinical practice and regulatory agency guidelines it may be necessary to conduct a site audit or an inspection.

By signing this study, the investigator agrees to allow LYSARC and its representative, and drug regulatory agencies to have direct access to his study records for review. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

These audits involve review of source documents supporting the adequacy and accuracy of data gathered in CRF, review of documentation required to be maintained, and checks on drug accountability.

LYSA will in all cases help the investigator prepare for an inspection by any regulatory agency.

16.8 **Clinical study report**

The sponsor will inform of the end of the trial the Competent Authorities and Ethics Committees during the 3 months following the end of the study. A publication, as a study report will be prepared under the responsibility of the sponsor, less than one year after the end of the study and forwarded to the Competent Authorities and Ethics Committees

16.9 **Study amendments**

It is specified that the appendices attached to this study and referred to in the main text of this study, form an integral part of the study.

No changes or amendments to this study may be made by the investigator or by the sponsor after the study has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by the investigator and the LYSARC.

Any change agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by the sponsor and the signed amendment will be appended to this study.

Approval / advice of amendments by Ethics Review Committee and Competent Authorities are required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The investigator must receive approval / advice of the revised consent form prior to implementation of the change. In addition, changes to the case report forms, if required, will be incorporated in the amendment.

Prior to initiating the changes, study amendment must be submitted to regulatory agencies, where applicable, except under emerging conditions.

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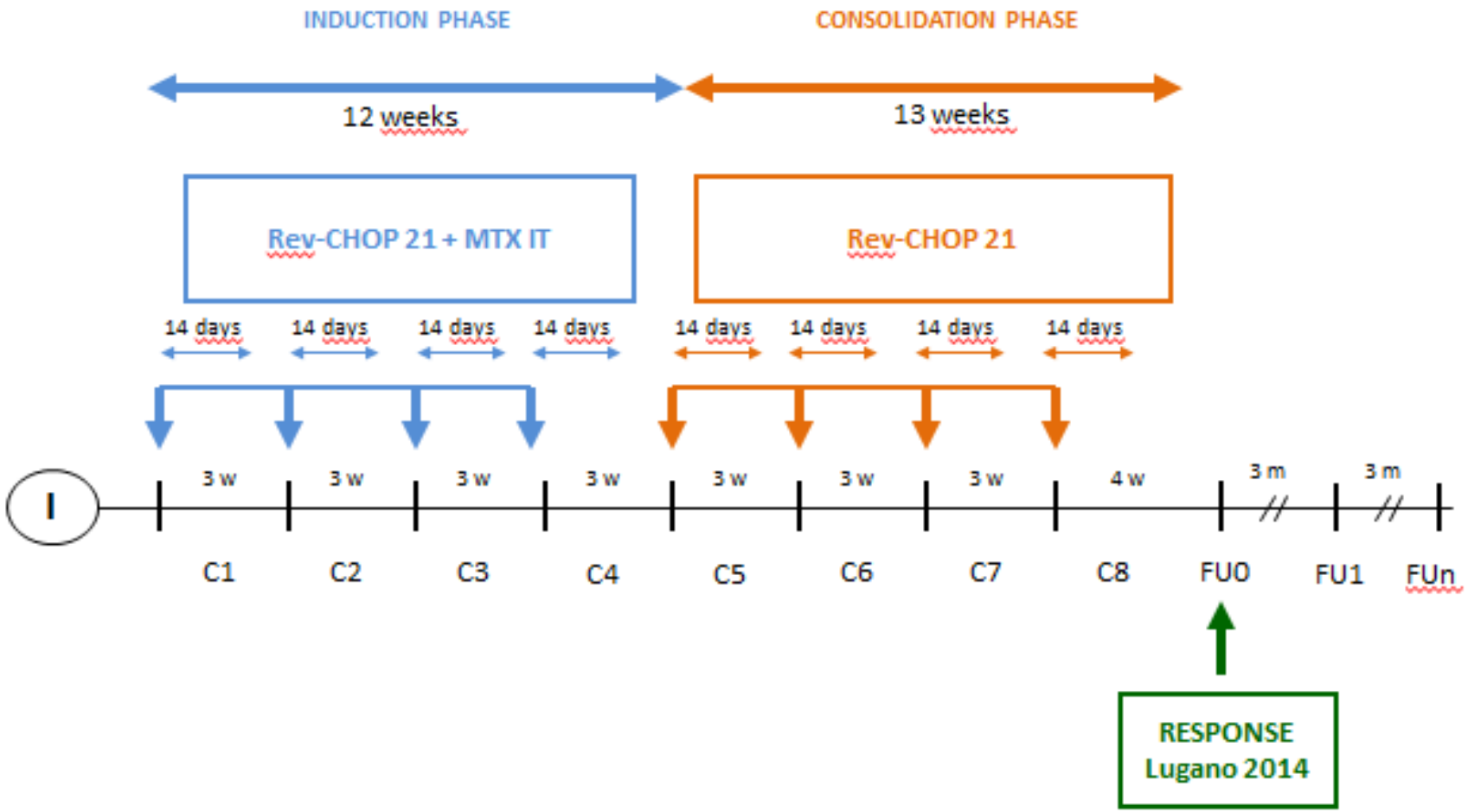
18 APPENDIXES

18.1 Study Flow Chart



18.2 **Schedule of Evaluations**

Events	**Screening**	**Cycle 1 to Cycle 8**		**End of treatment evaluation**	**Follow-up period**	
Date	within 14 days before first dose	D1	D10	30 days after the last drug administration	every 3 months during 2 years	every 6 months, the next 5 years
Informed consent	X					
Inclusion/Non inclusion criteria	X					
Patient characteristics [(a)]	X	X[(f)]		X[(f)]	X[(f)]	X[(f)]
Physical examination and vital signs[(b)]	X	X		X		
Complete relevant medical history	X					
ECOG PS	X	X		X	X	X
Staging, IPI and aaIPI	X					
Serologies HIV, HCV, HBV	X					
Serum electrophoresis	X					
Cardiac exams	X					
Chest, abdomen, pelvis CT with oral and IV contrast (cerebral if indicated)	X[(c)]			X	X[(h)]	X[(j)]
PET scan	X[(c)]			X		
Bone marrow aspirate and biopsy	X[(d)]			X[(g)]	X[(i)]	X[(i)]
Complete Blood cell counts	X	X	X	X	X	X
Clinical biochemistry [(e)]	X	X		X		
Sample for constitutional genetic analysis	X					
Samples for TcR and IgH clonality	X					
Samples for phenotyping, Samples for EBV virus in blood	X			X		
Concomitant medications	X					
Adverse events (AE)	X					
Evaluation of the disease response				X	X	X

(a) Weight, height, body surface area, demographics, non childbearing potential confirmation
(b) Pulse, Blood pressure and Body temperature
(c) May be performed up to 28 days before first dose of study drug.
(d) May be performed up to 56 days before first dose of study drug.
(e) calcium, sodium, potassium, urea, β2 microglobuline (only at baseline), LDH, ALT, AST, total bilirubin, alkaline phosphatase, albumin (only at baseline), creatinine
(f) Weight and body surface area during treatment period and at last treatment evaluation (30 days after last drug administration).
(g) Bone marrow aspirate and biopsy to be performed to assess CR in subjects with a positive bone marrow result at screening (not required for patients with already cleared bone marrow at previous evaluation)
(h) Every 6 months
(i) Bone marrow aspirate and biopsy to be performed if clinically indicated.
(j) Every 12 months unless clinically indicated.

18.3 Ann Arbor staging

- **Stage I:**
  - I: Involvement of a single lymph node region
  - IE: Localized involvement of a single extralymphatic organ or site.
- **Stage II:**
  - II: Involvement of 2 or more lymph node regions on the same side of the diaphragm
  - IIE: Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm
- **Stage III:**
  - III: Involvement of lymph node regions on both sides of the diaphragm
  - IIIE: Involvement of lymph node regions on both sides of the diaphragm accompanied by localized involvement of an extralymphatic organ or site
  - IIIS: Involvement of lymph node regions on both sides of the diaphragm accompanied by involvement of the spleen
  - IIIS+E: Both IIIS+IIIE
- **Stage IV:**
  - IV: Disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (non regional) nodal involvement

    IVE: Extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

Source: American Joint Committee on Cancer. Non Hodgkin's lymphoma. In: AJCC Staging Manual. 5th ed. Philadelphia, PA: Lippincott-Raven;1997:289-294.

18.4 **Performance Status Criteria**

The following table presents the ECOG performance status scale:

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

18.5 Age-adjusted International Prognostic Index (aa-IPI)

The international Non Hodgkin Lymphoma prognostic factor project. A predictive model for aggressive non Hodgkin lymphoma. New England Journal of Medicine. 1993, 329:987-994.

PRONOSTIC FACTORS :

- Lactate deshydrogenase (LDH) level — Normal seric level *versus* elevated seric level
- Ann Arbor stage — I-II *versus* III-IV
- Performance status (PS) — 0-1 *versus* 2-4

All are independent prognostic factors.

18.6 Cockcroft-Gault formula

Cockcroft-Gault Equation:

[(140-age *(years)*) * weight *(kg)* * A] / Serum Creatinin *(µmol/L)*

For male: A= 1.23

For female: A= 1.04

It is the responsibility of the investigator to make sure that creatinine clearance will be calculated according to Cockcroft- Gault formula

18.7 Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2013; 53:5229

Revised Criteria for Response Assessment		
Response and Site	**PET-CT–Based Response**	**CT-Based Response**
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3_ with or without a residual mass on 5 Point Scale† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LD No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Not applicable
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, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 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 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured 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 chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not Applicable

No Response or stable disease	**No metabolic response**	**Stable Disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesion	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive Metabolic Response**	**Progressive disease requires at least 1 of the following:**
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	PPD progression 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 ≤ 2 cm 1.0 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 (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesion	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if < 1.0 cm 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

18.8 **Response criteria for lymphoma: Cheson 2007**

Cheson BD et al. J Clin Oncol 2007; 25:579-586

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative b) Variable FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, IHC should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET b) Variable FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Complete response = CR

The designation of CR requires the following (Table 2):

- 1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
- 2a. Typically FDG-avid lymphoma: in patients with no pre-treatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
- 2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (< 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than

1.0 cm in their short axis before treatment must have decreased to < 1.0 cm in their short axis after treatment.

- 3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not al-ways reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma

- 4. If the bone marrow was involved by lymphoma before treat-ment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

CRu

The use of the above definition for CR and that below for PR eliminates the category of CRu.

Partial response = PR

The designation of PR requires all of the following:

- 1- At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

- 2- No increase should be observed in the size of other nodes, liver, or spleen.

- 3- Splenic and hepatic nodules must regress by > 50% in their SPD or, for single nodules, in the greatest transverse diameter.

- 4- With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

- 5- Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

  When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

- 6- No new sites of disease should be observed.

- 7- Typically FDG-avid lymphoma: for patients with no pre-treatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

- 8- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan, or if a pre-treatment PET scan was negative, CT criteria should be used.

  In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease

Stable disease (SD) is defined as the following:

- 1- A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

- 2- Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

- 3- Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pre-treatment PET scan or if the pre-treatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes < 1.0X< 1.0cmwillnotbe considered as abnormal for relapse or progressive disease.

- 1- Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

- 2- At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by > 50% and to a size of 1.5 X 1.5 cm or more than 1.5 cm in the long axis.

- 3- At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

- 4- Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

  Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

  In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in patients with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

18.9 **Response Criteria for Lymphoma *Cheson 1999***

Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 1999; 17:1244–53.

Complete Response (CR)

A complete response requires the following:

- Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities [e.g., lactate dehydrogenase (LDH)] definitely assignable to NHL
- All lymph nodes and nodal masses must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes ≥1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to < 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
- The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
- Bone marrow, if positive at baseline, must be histologically negative for lymphoma.

Complete Response, unconfirmed (CRu)

CRu includes those patients who fulfil criteria 1 and 3 above, but with one or more of the following features:

- A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
- Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

Partial Response (PR)

A partial response requires the following:

- ≥50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase in the size of the other nodes, liver, or spleen
- Splenic and hepatic nodules must regress by at least 50% in the SPD.

- With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
- No new sites of disease

Stable Disease (SD)

Stable disease is defined as less than a PR (as described above) but not progressive disease (see below).

Relapsed disease (CR, Cru)

- Appearance of any new lesion or increase by ≥50% in the size of previously involved sites.
- ≥50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in SPD of more than one node.

Progressive Disease (PD)

Progressive Disease is defined as follows:

- ≥50% increase from nadir in the SPD of any previously identified abnormal node.
- Appearance of any new lesion during or at the end of therapy

18.10 PET SCANs

18.10.1 Patient preparation

- Patient should be fasting for at least 6 hours prior to scanning. Free access to water and normal medication are allowed. Intravenously administered fluids should not contain glucose.
- The height of the patient will be recorded at baseline, and the weight checked on each scan days.
- Venous access could be either a vein catheter of the forearm, or a central venous catheter

18.10.2 PET scanner technical requirements

- FDG-PET scanning must be performed with a modern full-ring dedicated PET camera. Coincidence PET cameras are not allowed, because of lower sensitivity. Combined PET in which the images are fused, are recommended for an improved data interpretation.
- Each patient is preferably scanned on the same camera for baseline, intermediate and final study.

18.10.3 PET acquisition and reconstruction

- The 18F-FDG injected activity will be defined according to on site rules but should be >3.5 MBq/kg
- Patients are kept well hydrated (oral or intravenous fluid intake of 500 ml water during FDG uptake phase) to minimize image artifacts due to urinary stasis, and are asked to lie still to avoid muscular FDG uptake. A whole body acquisition with attenuation correction (either with a high energy photons source or non contrast-enhanced CT) and with emission scans of at least 4 minutes per bed position is started 60-90 minutes after FDG injection, starting from groin up to the head.
- Scan data will be recorded and reconstructed using an iterative algorithm. For each patient, the same FDG dose, acquisition protocol and reconstruction algorithm must be used for baseline and further PET scans.
- It is especially important to ensure that the time between tracer administration and starting of PET acquisition will be the same (± 5 min) at each of the 3 PET

18.10.4 PET Review LOGISTICS

18.10.4.1 Local FDG-PET reports

As soon as the inclusion of the patient is effective, the local nuclear medicine physician will receive from the ***PET review board:***

- A copy of the randomization form
- A request :
    1. For sending the images of the sequential PET scans (PETxxx)
    2. For a copy of xxx reports accompanied by a transmittal form

All these requirements will be sent on LYSARC web-platform (https://lysarc.imagys.com).

18.10.4.2 PET review Board

Local and the central analysis of the PETs should be done according to Juweid criteria for PET at the end of treatment.

The reviewer panel is composed by 3 nuclear physicians for review the PETs according to the following rules:

- 2 reviewers will analyze the PET scans independently.
- The local analysis will be taken into account if the 2 reviewers do not agree.
- A third reviewer is needed when the local reviewer belong to the reviewer panel.

18.10.5 Recommendations

Sally F. Barrington, N. George Mikhaeel, Lale Kostakoglu, Michel Meignan, Martin Hutchings, Stefan P. Mueller, Lawrence H. Schwartz, Emanuele Zucca, Richard I. Fisher, Judith Trotman, Otto S. Hoekstra, Rodney J. Hicks, Michael J. O'Doherty, Roland Hustinx, Alberto Biggi, and Bruce D. Cheson. Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2013; 54:8800

Section 1: Interpretation of PET-CT scans

1. Staging of FDG-avid lymphomas is recommended using visual assessment, with PET-CT images scaled to fixed SUV display and color table; focal uptake in HL and aggressive NHL is sensitive for bone marrow involvement and may obviate need for biopsy; MRI is modality of choice for suspected CNS lymphoma (type 1)
2. Five-point scale is recommended for reporting PET-CT; results should be interpreted in context of anticipated prognosis, clinical findings, and other markers of response; scores 1 and 2 represent CMR; score 3 also probably represents CMR in patients receiving standard treatment (type 1)
3. Score 4 or 5 with reduced uptake from baseline likely represents partial metabolic response, but at end of treatment represents residual metabolic disease; increase in FDG uptake to score 5, score 5 with no decrease in uptake, and new FDG-avid foci consistent with lymphoma represent treatment failure and/or progression (type 2)

Section 2: Role of PET-CT for staging

1. PET-CT should be used for staging in clinical practice and clinical trials but is not routinely recommended in lymphomas with low FDG avidity; PET-CT may be used to select best site to biopsy (type 1)
2. Contrast-enhanced CT when used at staging or restaging should ideally occur during single visit combined with PET-CT, if not already performed; baseline findings will determine whether contrast-enhanced PET-CT or lower-dose unenhanced PET-CT will suffice for additional imaging examinations (type 2)
3. Bulk remains an important prognostic factor in some lymphomas; volumetric measurement of tumor bulk and total tumor burden, including methods combining metabolic activity and anatomical size or volume, should be explored as potential prognosticators (type 3)

Section 3: Role of interim PET

1. If midtherapy imaging is performed, PET-CT is superior to CT alone to assess early response; trials are evaluating role of PET response–adapted therapy; currently, it is not recommended to change treatment solely on basis of interim PET-CT unless there is clear evidence of progression (type 1)
2. Standardization of PET methods is mandatory for use of quantitative approaches and desirable for routine clinical practice (type 1)
3. Data suggest that quantitative measures (eg, δSUVmax) could be used to improve on visual analysis for response assessment in DLBCL, but this requires further validation in clinical trials (type 2)

Section 4: Role of PET at end of treatment

1. PET-CT is standard of care for remission assessment in FDG-avid lymphoma; in presence of residual metabolically active tissue, where salvage treatment is being considered, biopsy is recommended (type 1)
2. Investigation of significance of PET-negative residual masses should be collected prospectively in clinical trials; residual mass size and location should be recorded on end-of-treatment PET-CT reports where possible (type 3)
3. Emerging data support use of PET-CT after rituximab-containing chemotherapy in high–tumor burden FL; studies are warranted to confirm this finding in patients receiving maintenance therapy (type 2)
4. Assessment with PET-CT could be used to guide decisions before high-dose chemotherapy and ASCT, but additional studies are warranted (type 3)

The 5-PS scores the most intense uptake in a site of initial disease, if present, as follows:

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions

X. New areas of uptake unlikely to be related to lymphoma.

18.11 Review of Pathological Samples

General principles and organization of the pathological review:

The Revail study requires a histological review of all cases included in the trial at diagnosis. Histological criteria of inclusion and exclusion have been detailed in the current protocol. Histological review requires both morphology and immuno-histochemistry. In addition, a tissue collection will be organized to allow production of tissue-arrays and to optimize collection and conservation of frozen tissue and when not available of DNA extracted from the paraffin-embedded tumor sample.

The review process will be organized by the Institute of Pathology of LYSA (LYSA-P). Each centre should send the material (paraffin blocks and/ or slides) of their cases directly to the LYSA-P in Créteil (Hôpital Henri-Mondor)

Practical aspects of the LYSA review:

At patient enrolment, the investigator is requested to fax to LYSARC registration centre a pathological form with a copy of the histopathological report on which the name and address of the pathologist having diagnosed the angioimmunoblastic T-cell lymphoma will be easily identified. In the case where no histopathological report is available, the pathological form with the name and address of the pathologist can be faxed. This procedure is set up to optimize tracing of the samples.

The LYSARC registration centre will fax to the LYSA-P and to the correspondent panel pathologist, the pathological form or the histo-pathological report. As soon as the registration of the patient is effective, the primary pathologist will receive from LYSA-P:

- a copy of the pathological form or the histo-pathological report
- an explanatory letter describing the importance of the ancillary genomic and tissue micro-arrays projects
- a request:

1. for sending the paraffin embedded block of the tumour. In cases where the block no longer contains tumour material, stained slides could be sent to the Institut and will be returned as soon as the review is completed. In order to save material, the initial pathologist will be encouraged to send the original immunostained slides that will be returned to him as soon as the review is achieved.
2. for a copy of the pathological report if it was not obtained before
3. for one H&E and 5 unstained slides of the bone marrow biopsy with pathological report.
4. to notify the Institut of the presence of frozen tissue from this tumour, to be collected soon after.

All these requirements (excluding frozen tissue) will be sent in a prepaid envelope to the following address:

LYSA-P, LYSA-REVAIL study
Hôpital Henri Mondor
51, avenue de Lattre de Tassigny
94 010 CRETEIL
Email: lysa-p@lysarc.org

Tissue microarray (TMA) construction: For tissue microarray construction, a slide stained with hematoxylin and eosin will be prepared from each formalin-fixed paraffin donor block, and three tissue cylinders representative of tumor regions with a diameter of 0.6 mm will be punched and transferred into a recipient paraffin block. Reactive lymphoid tissues will be also included in the TMA blocks, as controls. Therefore, two twins TMA blocks will be prepared, according to procedures used in the LYSA-P.

Review process: For the review process, routinely stained (hematoxylin-eosin) sections will be obtained and an appropriate panel of antibodies (comprising CD20, CD3, other T-cell antigens, CD4, CD8, CD10, CXCR5, PD1, CXCL13, ICOS, and Bcl6, Tbet, Gata3, RorγT transcription factors), FDC markers (CD21 or CD23) and EBV detection by in situ hybridization with EBERs probes and with B or T cells colocalization (assessed by combined immunohistochemistry and in situ hybridization) will be applied according to morphological aspects. A review of the case will be organized by a defined Pathology Panel. Discordant cases will be review by the whole panel to reach a consensus diagnosis.

As far as possible, for clonality analysis and further molecular investigation, DNA will be extracted for each case either from the frozen material or, when not available from paraffin-embedded samples through a method established in the LYSA-P.

The review pathologists for Revail Study will send to the study site pathologist and pathology centre that submitted the case for review, its review conclusions, based on the consensus diagnosis established according to the WHO classification (2008). For the need of further ancillary study, blocks will be kept temporarily to avoid a second request. Meanwhile, the block will be at the entire disposition of the initial anatomopathology laboratory under request if they need it.

18.12 : Biological samples for further ancillary studies

A) RATIONALE

The Revail study represents a unique opportunity to collect biological samples from patients with AITL lymphoma at diagnosis that can be used to improve comprehension of the disease, better define the prognostic criteria in diffuse large B cell lymphoma and identify new factors that influence treatments results and outcome. These scientific studies will be performed as ancillary studies based on the Revail protocol.

Angioimmunoblastic T-cell lymphomas (AITL) is the most frequent entity in France. AITL have a dismal prognosis. Indeed, when treated by conventional chemotherapies, AITL have a 5 year overall survival at 30%. Therefore, AITL constitutes an unmet medical need.

We and others have described recurrent mutations in epigenetic modifiers TET2, DNMT3A and IDH2 in AITL and other TFH-derived lymphomas. Interestingly, epigenetic anomalies are not restricted to TFH-derived lymphomas (AITL and a part of PTCL-NOS), but large mutational studies revealed that alterations in genes involved as epigenetic regulators are found in various entities [Sézary syndrome, EATL and HSTL (unpublished)], and our preliminary data indicate epigenetic changes (5 hydroxymethylcytosine loss) in a large majority of PTCL. Targeting these epigenetic anomalies could be a promising approach to improve PTCL treatment.

Mutational landscape analysis in PTCL, especially in AITL,revealed that epigenetic alterations are not isolated, but are associated with other anomalies, especially those involving TCR signalling-associated molecules, with description of PLCG1 or CD28 mutations, and CD28-CTLA4 fusion. Immune escape and neoangiogenesis are also important mechanisms of oncogenesis. Lenalidomide is a drug with antiproliferative, anti neoangiogenesis and Immunomodulation effects, and is currently under investigation in association with CHOP in the present study.

However, little is known with respect to the biological consequences of Lenalidomide in PTCL, and important information is missing to determine which patient could benefit of this drug, in association to CHOP chemotherapy. The major aim of this project is to identify biomarkers predictive of response after lenalidomide treatment, and, in using these well annotated cohorts of patient, to improve our knowledge of AITL oncogenesis.

For this, sampling of blood will be encouraged at inclusion.

B) TUMOR BIOPSY

Paraffin embedded tissue will be collected in LYSA-P, Hôpital Henri Mondor (Créteil) - France *under the responsibility of Pascal Deschaseaux.*

Frozen samples will be collected by LYSA-P and stored in *Département de pathologie (INSERM U617 / EA 2348) - l'Hôpital Henri Mondor (Créteil) – France under Karen Leroy responsibility.*

Those samples will be placed at the LYSA tumor library's network disposal. It will be useful for ancillary studies on gene expression (transcriptoma) and protein expression analysis (proteoma) (see section D – Experimental work):

- NGS sequencing will be performed on DNA extracted from FFPE tumor biopsies, in collaboration with L de Leval, CHU Lausanne, Switzerland

- RT-MLPA analysis of molecular signature from RNA extracted from tumor biopsies, in collaboration with Ph Ruminy & F Jardin, Rouen

C) **PERIPHERAL BLOOD SAMPLE**

A specific informed consents must be signed before any sample taken in order to allow storage of its derivate like plasma, serum, cells or DNA samples and the genomic DNA analysis of markers known to influence disease outcome and response to therapy. (Patients with circulating lymphoma cells, detected by cytology in peripheral blood, will be excluded because of possible modifications of polymorphism analysis by genetic alterations present in tumor cells)

1/ Sample processing for BELGIUM CENTERS only:

A special isolation tubes (PAXgene tubes) and a label will be provided by LYSARC. Sample will consist of 8,5 mL of blood at registration in all patients participating in the study. This tube will be.frozen on site on the day of collection at -80°C.

🕭 *Please, complete the information sheet "REVAIL – Genomic Study – Biological Samples Storage" and fax it to LYSARC at +33 (0)4 72 66 93 71.*

2/ Sample processing for FRENCH CENTERS only:

The following sample will be collected at baseline before treatment and at the end of treatment:

❖ Blood samples for biological studies at inclusion :

- 7ml on EDTA for flow cytometry analysis (1 EDTA tube of 7 ml)
- 21 ml on EDTA for TCR and IgH clonality analyses by PCR, B and T cell separation and EBV quantification (3 EDTA tubes of 7 mL)
- 7 ml on EDTA for genomic DNA storage
- 14ml on dry tube for serological analyses (Cytokines profile) and storage (2 tubes of 7 mL)
- 7 ml on EDTA for plasma storage (1 EDTA tube of 7 mL)

❖ Blood sample for biological studies at the end of treatment:

- 7ml on EDTA for flow cytometry analysis (1 EDTA tube of 7 mL)
- 7ml on EDTA for EBV quantification in total blood (1 EDTA tube of 7 mL).
- 14ml on dry tube for serological analyses (Cytokines profile) and storage (2 tubes of 7 mL)

All these tubes will be sent and their derivate stored at Hôpital Henri Mondor – Créteil by DHL:

Hôpital Henri-Mondor

Service d'Immunologie Biologique

A l'attention du Pr Marie-Hélène DELFAU-LARUE

Protocole REVAIL

51 av du maréchal de Lattre de Tassigny – 94010 CRETEIL – France

🔔 *Please, complete the information sheet "REVAIL – LYSARC study – Sending of blood sample by DHL to Henri Mondor Hospital" and send this card with blood tubes at Henri Mondor.*

All known samples will be gathered in Lyon-Sud hospital following a collect organized at the end of inclusions (special carrier respecting cold storage). They will be stored at –80°C until DNA extraction at:

Laboratoire de biologie moléculaire et Hématologie – JP Magaud

Centre de Biologie Sud – Espace Jacques Monot – Etage 1

HOPITAL LYON SUD

165 chemin du Grand Revoyet

69310 PIERRE BENITE

After extraction, the DNA will be stored at –20°C and will be then delivered to the other laboratories participating to the project. After the end of the study, all the remaining samples will be destroyed.

- Frozen samples will be placed at the LYSA biological library's network disposal. It will be useful for ancillary studies on serological biomarkers and development of genetic analysis from liquid biopsies (see section D – Experimental work):2HGA dosage from frozen samples
- Sequencing of cell free (circulating) tumoral DNA from frozen samples

D) EXPERIMENTAL WORK Part 1: Define the molecular signature(s) (gene expression and mutations) of AITL and correlate these molecular signatures with treatment response

We will use 2 novel panels that have recently been developed through collaborations within teams belonging to the LYSA-CALYM network (Créteil, Lausanne and Rouen).

1-a - The first one use **Reverse Transcriptase Multiplex Ligation Probe Amplification (RT MLPA)** technique to assess gene expression of a selected set of 20 genes involved in T cell differentiation and lymphomagenesis, using low amount of FFPE extracted RNA. This panel will be applied to all tumor blocks of the AITL collected at the LYSA-Pathology plateform for the REVAIL clinical trial. Results will be compared with pathological (histopathology and phenotype) data, and preliminary results show that this approach can classify accurately main entities and can also define discrete subsets within pathological entities. Finally response to treatment and outcome will be evaluated in various entities or molecularly defined sub entities.

1-b - The second one use **Next Generation Sequencing** (PGM, Life-ThermoFisher) to assess the mutational status of a selected panel of genes recurrently mutated in different entities comprising those involved in DNA methylation (TET2, IDH2, DNMT3A), TCR-signalling (CD28, PLCG1), JAK-STAT pathway (STAT3, STAT5, JAK3), the GTPase associated gene RHOA etc… High coverage analysis (1000X) will be realized and will be necessary to detect subclonal events, especially in AITL where tumor cells usually represent only a minor component of the tumor tissue. Among these genes, IDH2 has a special interest because it can be specifically targeted by IDH2 inhibitor. We will compare the results of sequencing with results of anti IDH2R172K immunohistochemistry and serum D-2 hydroxyglutarate level (2HGA), the oncometabolite produced by the mutant enzyme. We will confirm the distribution of these mutations in the AITL entity, and assess prognostic impact of these mutations in this well annotated series of patient.

Finally RT-MLPA and mutational data will be compared and correlation between the mutational profile and gene expression signatures, pathological, phenotypic, clinical features and response to treatment will be evaluated.

<u>Part 2: Determine novel molecular predictive factors of response to treatment</u>

We will select 7 patients with persistent complete remission after treatment, and 7 refractory/early relapse patients with matched genomic DNA available. We will perform Whole Exome Sequencing (WES) of tumor and matched normal DNA, and RNAseq of the tumor (to validate the genetic events, correlate the alterations with the gene expression level and to identify potential translocations as primary or secondary events. We will search for mutations and gene deregulation associated with good and poor prognosis after treatment. We will analyse these results at the single gene level and on biologically relevant pathways as well. The candidate genes identified in this exploratory cohort will be validated through targeted resequencing on the well-annotated cohort of AITL patients from the REVAIL trial (estimated n=80).

Part 3: Determine feasibility and clinical relevance of cell free DNA sequencing in AITL

Because tumor tissue is not easily accessible, and makes sequential samples impossible to perform excepted in refractory patients, cell free DNA sequencing is an attractive idea, as shown in patients with solid tumors. However, the feasibility and the reliability of this approach have not been evaluated within the context of AITL patients. In parallel to tumor sequencing with our customized AITL panel, we will sequence cell free DNA in serum of patients when available at a high depth, and compare results of the 2 approaches. In addition, for hotspot mutations (*RHOA, IDH2*), NGS and droplet PCR approaches could be compared. When sequential samples are available, and if a mutation is present at diagnosis, post treatment samples will be sequenced to investigate an interest of this method as minimal residual disease (MRD) biomarker.

E) CONTROL AND IDENTIFICATION OF THE BIOLOGICAL SAMPLES FROM THE BLOOD

At patient inclusion in the study, the information about the place of storage for proteomic and/or genomic samples will be provided by the center on inclusion/randomisation fax.

In order to organize the tracking of biological samples, the LYSARC asks the centres to complete a document "*Revail – Fiche accompagnatrice des prélèvements pour études protéomique et génomique"* (in investigator file). This document must accompany the blood sample for genomic and/or proteomic study. The personnel on site or the laboratory must complete this document and fax him to LYSARC (+33 4 72 66 93 71).

All the samples will be immediately coded if they are not yet, or identification will be controlled at reception (first 3 letters of last name, number of inclusion in the study). The complete procedure will remain anonymous all along the biological analysis. Observations will be linked with the LYSA clinical database (registered to the CNIL) only after the end of the study. This database contains the main information about patients participating to the study including demographic data, baseline clinical evaluation, treatment, response to treatment and follow-up (relapse, death). Beyond the period of study monitoring, the database will be actualized every year.

18.13 Lenalidomide Pregnancy Prevention Plan

This Pregnancy Prevention Plan (PPP)applies to all subjects receiving lenalidomide within a clinical trial. The following PPP documents are included:

1) The Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (section 1) provides the following information:

- Potential risks to the fetus associated with lenalidomide exposure
- Definition of female childbearing potential (FCBP) / female not of childbearing potential (FNCBP)
- Requirements for counselling of all subjects receiving lenalidomide about pregnancy precautions and the potential risks of fetal exposure to lenalidomide
- Acceptable birth control methods for both female subjects of childbearing potential and male subjects receiving lenalidomide in the study
- Pregnancy testing requirements for subjects receiving lenalidomide who are FCBP

2) Lenalidomide Education and Counseling Guidance Document for each gender (female and male; Section 2 and Section 3 respectively) must be completed and signed by a trained counselor at the participating clinical center prior to each dispensing of lenalidomide. A copy of this document must be maintained in the subject's records for each dispense.;

3) The Lenalidomide Information Sheet (Section 4)) will be given to each subject receiving lenalidomide. The subject must read this document prior to starting lenalidomide and each time the subject receives a new supply of lenalidomide.

•

Section 1: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. A teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

1.1.1 Definition of Females of Childbearing Potential

A FCBP isa female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Definition of Females Not of Childbearing Potential

Females who do not meet the above definition of FCBP should be classified as FNCBP.

Counseling

Females of Childbearing Potential

For a FCBP,, lenalidomide is contraindicated unless all of the following are met (i.e, all FCBP must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 daysbefore starting lenalidomide,, throughout the entire duration of lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She mustbe capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence lenalidomideas soon as it is dispensed following a negative pregnancy test
- She understands and accepts the need to undergo pregnancy testing based on this plan (Section 1.1.1.2) and in the Informed Consent
- She acknowledges that she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of thepregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements

Females Not of Childbearing Potential

For a FNCBP,, lenalidomide is contraindicated unless all of the following are met (ie, all FNCBPmust be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges she understands the hazards lenalidomide can cause to an unborn fetus and the necessary precautions associated with the use of lenalidomide.

Males

Traces of lenalidomide have been found in semen. Male subjectstaking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a FCBP.
- Understand the potential teratogenic risk if the subject donates semen or sperm.

Contraception

Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e g calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) while taking lenalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of lenalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)

- Hormonal (birth control pills, injections, implants), levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel]
- Tubal ligation
- Partner's vasectomy

• Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjectswith neutropenia.

Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.

Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP. Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide. The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at Day 28 following the last dose of lenalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.

Pregnancy Precautions for Lenalidomide Use

Before Starting Lenalidomide

Female Subjects of Childbearing Potential:

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting lenalidomide.. The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomideand the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide.. The subjectmay not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting lenalidomide.

Male Subjects:

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide , even if he has undergone a successful vasectomy.

During and After study Participation

Female Subjects:

- Females of childbearing potentialwith regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while taking lenalidomide, at study discontinuation, and at day 28 following the last dose of lenalidomide..
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy test weekly for the first 28 days and then every 14 days while taking lenalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of lenalidomide.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.

- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study subject, lenalidomide , must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subjectmisses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking lenalidomide and for at least 28 days after the last dose of lenalidomide..

Male Subjects:

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [e g calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving lenalidomide, during dose interruptions or for at least 28 days after the last dose of lenalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking lenalidomide , the Investigator must be notified immediately.

Additional precautions

- Subjects should be instructed to never give this lenalidomide. to another person and
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide..
- No more than a 28-day lenalidomide supply may be dispensed with each cycle of lenalidomide..

Section 2: Lenalidomide Education and Counseling Guidance Document for Female Subjects

To be completed prior to each dispensing of Lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: ¬¬¬¬¬¬¬_____/_____/_____ (mm/dd/yyyy)

Check one risk category

□ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)

□ NOT FCBP

Female of Childbearing Potential:

1. I have verified and:counseled the subjectregarding the following:

☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. Females of childbearing potential must agree not to become pregnant while taking lenalidomide.

☐ That the required pregnancy tests performed are negative.

☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact [at least 28 days prior to receiving lenalidomide, while receiving lenalidomide, during dose interruption and for at least 28 days after the last dose of lenalidomide).

- One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of lenalidomide and at the last dose of lenalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

- Two pregnancy tests will be performed prior to receiving lenalidomide, one within 10 to 14 days and the second within 24 hours of the start of lenalidomide.
- Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking lenalidomide if menstrual cycles are regular.
- Every week during the first 28 days of this study and a pregnancy test or every 14 days while the subject is taking lenalidomide if menstrual cycles cycles are irregular.
- If the subject missed a period or has unusual menstrual bleeding.
- When the subject is discontinued from the study and at Day 28 after the last dose of lenalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after the last dose of lenalidomide.

- ☐ The subject confirmed that she will stop taking lenalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.
- ☐ The subject confirmed that she has not and will not breastfeed a baby while taking lenalidomide and for at least 28 days after the last dose of lenalidomide.The subject has not and will NEVER share lenalidomide with anyone else.
- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will not break, chew, or open lenalidomide capsules capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject..

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to lenalidomide: A teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
- ☐ The subject has not and will NEVER share lenalidomide with anyone else.
- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will not break, chew, or open study drug capsules at any point.
- ☐ The subject confirmed that she will return unused lenalidomide capsules to the study doctor.

2. I have provided the Lenalidomide Information Sheet to the subject..

Do Not Dispense Lenalidomide if:

- The subject is pregnant.
- No pregnancy tests were conducted for a FCBP.

- The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving lenalidomide, while receiving lenalidomide and during dose interruptions.
- The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this PPP.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

Section 3 Lenalidomide Education and Counseling Guidance Document for Male Subjects

To be completed prior to each dispensing of lenalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:

   ☐ Potential risks of fetal exposure to lenalidomide: a teratogenic potential of lenalidomide in humans cannot be ruled out. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.

   ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a FCBP, while taking lenalidomide,, during dose interruptions and for at least 28 days after the last dose of lenalidomide..

   ☐ The subject confirmed that he has not impregnated his female partner while in the study

   ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and female partners of male subject taking lenalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.

   ☐ The subject has not and will NEVER share lenalidomide with anyone else.

- ☐ The subject confirmed that he hasnot donated and will not donate semen or sperm while taking lenalidomideor during dose interruptions and.and for at least 28 days after the last dose of lenalidomide.
- ☐ The subject has not and will not donate blood while taking lenalidomide, during dose interruptions and for at least 28 days after the last dose of lenalidomide
- ☐ The subject has not and will not break, chew, or open study drug capsules at any point.
- ☐ The subject confirmed that he will return unused lenalidomide capsules to the study doctor.

2. I have provided Lenalidomide Information Sheet to the subject..

Do Not Dispense Lenalidomide if:

The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

Maintain a copy of the Education and Counseling Guidance Document in the patient records.

Section 4 French Lenalidomide Information Sheet

Fiche d'information sur le lénalidomide

POUR LES SUJETS INCLUS DANS LES ETUDES CLINIQUES

Veuillez lire la fiche d'information sur le lénalidomide avant le début du traitement par le lénalidomide et chaque fois que l'on vous délivre ce médicament. La fiche d'information sur le lénalidomide ne remplace pas le consentement éclairé pour participer à l'étude clinique ou la discussion avec le médecin de l'étude ou le professionnel de santé concernant votre affection médicale ou votre traitement.

Quelles est l'information la plus importante à connaître à propos dulénalidomide ?

1. Le lénalidomide peut provoquer des malformations congénitales (**malformations chez le nouveau-né) ou le décès d'un enfant à naître.** Le lénalidomide est semblable à un autre médicament, le thalidomide. On sait que le thalidomide provoque des malformations congénitales potentiellement fatales .

Si vous êtes une femme qui n'est pas susceptible de procréer:

Pour s'assurer de l'absence d'exposition au lénalidomide d'un enfant à naître, le médecin de l'étude confirmera que vous n'êtes pas en mesure de devenir enceinte. Si vous avez un début de saignement menstruel vous devez en informer immédiatement le personnel du site de l'étude.

Si vous êtes un homme :

Une faible quantité de lénalidomide est présente en quantités infimes dans le sperme humain. Les risques pour un enfant à naître chez une femme dont le partenaire masculin reçoit le lénalidomide ne sont pas connus à ce jour..

- Les sujets masculins (y compris ceux ayant subi une vasectomie) doivent pratiquer l'abstinence totale ou doivent utiliser un préservatif pendant les relations sexuelles avec une femme enceinte ou une femme susceptible de devenir enceinte :
    - Pendant la période de traitement par le lénalidomide
    - Pendant les pauses thérapeutiques (interruptions du traitement) du lénalidomide
    - Pendant au moins les 28 jours qui suivent l'administration de la dernière dose de lénalidomide après
- Les hommes ne doivent pas donner de spermatozoïdes ni de sperme pendant la période de traitement par lelénalidomide, les pauses thérapeutiques (interruptions du traitement) et au moins les 28 jours suivant l'administration de la dernière dose de lénalidomide..

- **Vous devez prévenir immédiatement le médecin de l'étude en cas de grossesse suspectée de votre partenaire à n'importe quel moment au cours de l'étude. Le médecin de l'étude signalera tous les cas de grossesse à Celgene Corporation. Votre partenaire doit immédiatement contacter son professionnel de santé en cas de grossesse.**

2. Tous les sujets :

- Ne **pas** partager le **lénalidomide** avec une autre personne. Il doit **toujours** être tenu hors de portée des enfants et ne doit pas être donné à une autre personne.
- Ne pas donner de sang pendant la période d'administration du lénalidomide, les pauses thérapeutiques (interruptions du traitement) et au moins les 28 jours suivant l'administration de la dernière dose de lénalidomide.
- Ne pas casser, **mâcher**, ni ouvrir les gélules de **lénalidomide à aucun moment**.
- Il ne vous sera pas délivréplus d'un cycle de 28 jours de traitement par le lénalidomide à la fois.
- Rapporter les gélules de lénalidomide non utilisées au médecin de l'étude.

Des informations supplémentaires sont fournies dans le formulaire de consentement éclairé et vous pouvez demander de plus amples informations au médecin de l'étude.

Section 4 Dutch Lenalidomide Information Sheet

Lenalidomide – informatieblad

VOOR PATIËNTEN DIE DEELNEMEN AAN KLINISCH ONDERZOEK

Lees dit informatieblad over lenalidomide voordat u het onderzoeksgeneesmiddel gaat gebruiken en ook telkens als u een nieuwe voorraad krijgt. Dit informatieblad over lenalidomide dient niet ter vervanging van het toestemmingsformulier voor deelname aan klinisch onderzoek en ook niet ter vervanging van het gesprek met uw onderzoeksarts of zorgverlener over uw ziekte of uw behandeling.

Wat is de belangrijkste informatie die ik over lenalidomide moet weten?

1. **Lenalidomide kan geboorteafwijkingen (misvormde baby's) of het overlijden van een ongeboren baby veroorzaken.** Lenalidomide lijkt op het geneesmiddel thalidomide. Van thalidomide is bekend dat het levensbedreigende geboorteafwijkingen veroorzaakt.

   Als u een vrouw bent die niet zwanger kan worden:

Om zeker te zijn dat een ongeboren baby niet wordt blootgesteld aan lenalidomide zal uw onderzoeksarts bevestigen dat u niet zwanger kunt worden.

Als u een man bent:

Lenalidomide wordt in zeer kleine hoeveelheden in de zaadcellen (sperma) bij de mens waargenomen. Het is op dit moment onbekend, wat het risico is voor het ongeboren kind van vrouwen op vruchtbare leeftijd van wie de mannelijke partner lenalidomide krijgt.

- Mannelijke patiënten (ook mannen die een sterilisatie hebben ondergaan) dienen géén geslachtsgemeenschap te hebben óf moeten een condoom gebruiken wanneer ze geslachtsgemeenschap hebben met een zwangere vrouw of een vrouw die zwanger kan worden:
  - tijdens de behandeling met lenalidomide;
  - tijdens onderbrekingen in het gebruik van lenalidomide;
  - gedurende ten minste 28 dagen na inname van de laatste dosis lenalidomide.

- **Mannelijke patiënten mogen geen sperma of zaadcellen doneren** tijdens het gebruik van lenalidomide, tijdens dosisonderbrekingen en gedurende ten minste 28 dagen ná het stoppen met lenalidomide.
- **Als u op enig moment tijdens het onderzoek vermoedt dat uw partner zwanger is, dient u onmiddellijk uw onderzoeksarts hierover te informeren. De onderzoeksarts zal alle gevallen van zwangerschap aan Celgene melden. Uw partner dient meteen een arts te bellen als zij zwanger wordt.**

2. Voor alle patiënten geldt:

- Laat uw onderzoeksgeneesmiddel nooit door iemand anders gebruiken. Bewaar het onderzoeksgeneesmiddel buiten het bereik van kinderen en geef het nooit aan iemand anders.
- U mag geen bloed doneren tijdens het gebruik van lenalidomide, tijdens dosisonderbrekingen en gedurende ten minste 28 dagen na het stoppen met lenalidomide.
- U mag de capsules niet breken of openen. U mag niet kauwen op de capsules.
- Per keer krijgt u een voorraad lenalidomide voor maximaal 28 dagen.
- Geef niet-gebruikte capsules van het onderzoeksgeneesmiddel altijd terug aan uw onderzoeksarts.

Meer informatie vindt u in het toestemmingsformulier en u kunt ook uw onderzoeksarts raadplegen voor verdere informatie.