LYMA101

Phase II study to evaluate the efficacy of upfront obinutuzumab in mantle cell lymphoma patients treated by DHAP followed by autologous transplantation plus obinutuzumab maintenance then MRD driven maintenance

A STUDY SPONSORED BY:

LYSARC

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Version and date of Protocol: 5.0 – 04/04/2018

EudraCT number: 2016-000548-33

CONFIDENTIALITY STATEMENT

PROTOCOL APPROVAL & SIGNATURE PAGE

LYMA101

Phase II study to evaluate the efficacy of upfront obinutuzumab in mantle cell lymphoma patients treated by DHAP followed by autologous transplantation plus obinutuzumab maintenance then MRD driven maintenance

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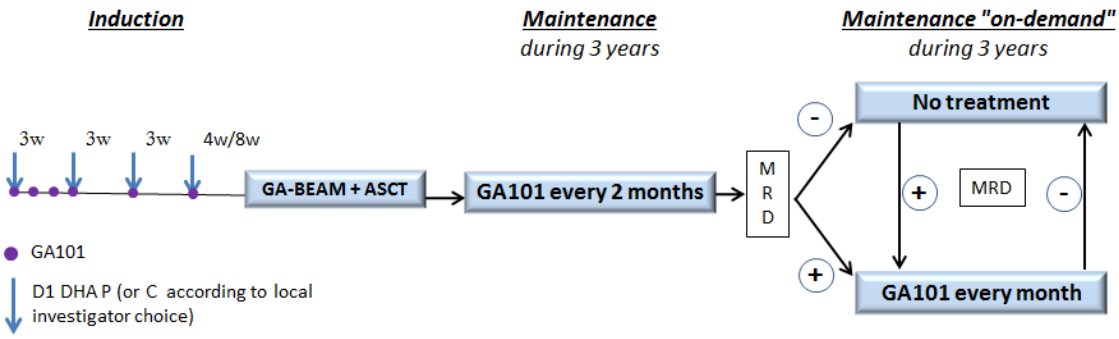
1 SYNOPSIS

Study Acronym	**LYMA101**
Title	Phase II study to evaluate the efficacy of upfront obinutuzumab in mantle cell lymphoma patients treated by DHAP followed by autologous transplantation plus obinutuzumab maintenance then MRD driven maintenance
Study Product	IMP: obinutuzumab
Protocol version	5.0 – 04/04/2018
EudraCT N°	2016-000548-33
Sponsor	LYSARC
Coordinator Investigators	Prof. S Le Gouill Prof. O. Hermine
Anticipated Countries	France
Objectives	The Primary objective is to evaluate the efficacy of upfront Obinutuzumab (GA101) at the molecular level (MRD) in bone marrow after induction, after the 4 cycles or at premature discontinuation, in patients with previously untreated MCL treated by DHAP. Secondary objectives are: • To evaluate the efficacy of the obinutuzumab in patients with MCL treated by DHAP before ASCT, after ASCT and every 6 months in terms of clinical response (Cheson 99) and MRD plus in terms of FDG-PET before and after ASCT • To evaluate PFS, Overall survival at study end • To evaluate the incidence of stem cell collection failure after obinutuzumab-DHAP = GA-DHAP • To evaluate MRD negativity after 3 years of maintenance and maintenance “on-demand” • To evaluate PET results after 3 years of maintenance • Duration of MRD negativity • To evaluate tolerability of obinutuzumab at induction and then “on-demand” Exploratory objective is : • To determine baseline prognostic factors on PFS and OS.

Inclusion Criteria	• Age ≥ 18 and age ≤ 65 • Histologically confirmed (according to the WHO classification) mantle cell lymphoma. The diagnosis has to be confirmed by phenotypic expression of CD5, CD20 and cyclin D1 or the t(11;14) translocation. • Bone marrow aspiration performed at inclusion for MRD analyses • Eligible for autologous stem cell transplant • Previously untreated MCL • Stage Ann Arbor II-IV in need of treatment • ECOG performance status of 0 – 2 • Life expectancy of more than 3 months • Written informed consent • Patient affiliated by any social security system
Exclusion Criteria	• Severe cardiac disease: NYHA grade 3-4 • Impaired liver (ALAT/ASAT ≥ 2.5ULN, bilirubin ≥ 1.5ULN), renal (calculated creatinine clearance < 50ml/min) or other organ function which will interfere with the treatment, if not related to lymphoma. • History of chronic liver disease • Hepatic veno-occlusive disease or sinusoidal obstruction syndrome • Any of the following laboratory abnormalities, if not result of a BM infiltration: - Absolute neutrophils count (ANC) <1,500 /mm^3 (1.5 x 10^9/L) - Platelet counts < 75,000/mm^3 (75 x 10^9/L) • Pregnancy/Nursing mothers • Fertile men or women of childbearing potential unless: - surgically sterile or ≥ 2 years after the onset of menopause - willing to use a highly effective contraceptive method (Pearl Index <1) such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly during study treatment and in female patients for 18 months after end of antibody treatment and in male for the duration of the treatment and after the last dose administered in accordance with the SmpC of the different products administered • Patients with a malignancy that has been treated but not with curative intent, unless the malignancy has been in remission without treatment for ≥ 5 years prior to enrollment. Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible. • Known seropositivity for HIV, HCV or other active infection uncontrolled by treatment.

	• Viral infection with hepatitis B virus (HBV) defined as hepatitis B surface antigen (HBsAg) positive and/or Hepatitis B core antibody (anti-HBc) positive *Note*: Patients who are immune due to hepatitis B vaccination or natural infection (HBs Ag and anti-HBc negative, anti-HBs positive) are eligible. But the patients who are immune due to hepatitis B natural infection should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation • Prior history of Progressive Multifocal Leukoencephalopathy (PML) • Vaccination with a live vaccine a minimum of 28 days prior to inclusion (Prolonged B cell depletion) • History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products • Psychiatric illness or condition which could interfere with their ability to understand the requirements of the study. • Person deprived of his/her liberty by a judicial or administrative decision • Person hospitalized without consent • Adult person under legal protection
Study design	
Study treatment	Patients will receive 4 cycles of GA-DHAP* every 21 days followed by ASCT using a GA-BEAM conditioning regimen plus a Obinutuzumab maintenance for 3 years then a Obinutuzumab maintenance on demand according to MRD status. Stem cells will be collected after cycle 3 and/or 4 of GA-DHAP*. Patients with high tumor load may receive a pre-phase treatment of COP. The pre-phase therapy should be started after inclusion and after samples for MRD analysis and cycle 1 of GA-DHAP has to be started 1 week after the end of the COP. In this trial, obinutuzumab is considered as investigational medical product (IMP). Cycle 1 : • Patients will receive their first obinutuzumab infusion (1000 mg) on Day 1 (Cycle 1 Day 1) along with standard premedication. During Cycle 1, obinutuzumab will also be administered on Days 8 and 15.

- Following obinutuzumab infusion, patients will receive DHAP chemotherapy as per standard administration procedures, along with standard premedications.
- Patients will be monitored for signs of acute TLS

Chemotherapy regimen	**Dose**	**D1**	**D2**	**D3**	**D4**	**D8**	**D15**
Dexamethasone	40mg	X	X	X	X		
GA-101 IV	1000mg	X				X	X
Aracytine IV	2 g/m^2/12h	X X					
Cisplatinum* IV	100 mg/m^2	X					

Cycle 2 to 4: one cycle every 21 days

Chemotherapy regimen	**Dose**	**D1**	**D2**	**D3**	**D4**
Dexamethasone	40mg	X	X	X	X
GA-101 IV	1000mg	X			
Aracytine IV	2 g/m^2/12h	X X			
Cisplatinum* IV	100 mg/m^2	X			

G-CSF administration is required during treatment cycles, stem cell collection and ASCT.

*In case of toxicities related to cisplatinum or according to the local investigator choice, Carboplatinum AUC = 5 could be used instead of cisplatinum

ASCT :

GA-BEAM: 4 to 8 weeks after D1 C4

Chemotherapy Regimen GA-BEAM	**Dose**	**D-8**	**D-7**	**D-6**	**D-5**	**D-4**	**D-3**	**D-2**	**D-1**	**D0**
GA-101 IV	1000mg	X								G
BCNU	300 mg/m^2		X							R
Etoposide	400 mg/m^2			X	X	X	X			A
Aracytine (CI)	400 mg/m^2			X	X	X	X			F
Melphalan	140 mg/m²							X		T

Maintenance:

Obinutuzumab maintenance: start between 2 to 3 months after D1 of ASCT. All patients in complete remission, complete remission unconfirmed, partial remission or stable disease (according to Cheson 99) will receive one injection of Obinutuzumab

	every 2 months for 3 years. **Treatment** / **Dose** / **D1 every 2 months** GA-101 IV / 1000mg / X When the MRD is informative at baseline in bone marrow and/or blood (prior to any treatment, before starting induction), this period will be followed by a maintenance "on-demand" for 3 years only for MRD positive patients at the end of the first 3 years of maintenance, MRD negative patients will stop obinutuzumab infusion. The therapeutic scheme will be one injection every month of Obinutuzumab (one injection at D1, 8 and 15 for the first month and then one time every month) until MRD negativity plus one additional injection after the last MRD negative control. MRD analyses will be continued for all patients with informative MRD and every patient once again with a positive MRD will restart Obinutuzumab maintenance. **treatment** / **Dose** / **1st month** (**D1**, **D8**, **D15**) / **Every month** (**D1**) GA-101 IV / 1000mg / X / X / X / X This scheme has to be used several times until clinical progression, toxicities or until end of the 3-years period, whichever comes first. Patients who withdraw from the study treatment or patients who progress will be followed until the end of the trial.
Tests performed at Study Commencement and follow-up	**Commencement:** • Clinical examination and complete medical history • Full blood count, biochemistry (creatinine, creatinine clearance according to Cockroft-Gault, bilirubin, ALAT, ASAT, albumin, LDH) • Surgical biopsy (avoid needle biopsies if possible to secure enough material) of tumour tissue for morphology and immunochemistry, frozen tissue if possible • Bone marrow biopsy/aspiration • CT-scan of neck, thorax and abdomen/pelvis • FDG-PET pre-treatment • gastroscopy/colonoscopy and other examinations if clinically indicated **Evaluation during treatment:** • Clinical exam and biochemistry: D-1 or D1 of each cycle of GA-DHAP, After induction (before ASCT), after ASCT and every two months during 3 years

	and then every 3 months for 3 years for MRD negative patients and every month for MRD positive patients • full blood count : before each Obinutuzumab injection (induction, conditioning regimen and maintenance) • CT-scan of thorax and abdomen/pelvis: After induction (before ASCT), after ASCT, every 6 months during the 3 years of obinutuzumab maintenance then every year during the maintenance "on-demand" • FDG-PET: After induction (before ASCT), after ASCT and after 3 years of maintenance • Bone marrow biopsy/aspiration: After induction (before ASCT), after ASCT (before maintenance) if clinically indicated **MRD monitoring:** • At baseline: blood and bone marrow (BM) aspiration • After induction: blood and BM aspiration • After ASCT: blood and BM aspiration • During 3 years of obinutuzumab maintenance: blood every 6 months and BM aspiration at the end of the 3 years • During 3 years of obinutuzumab maintenance "on-demand" (only for informative MRD at baseline) blood every 3 months • At the end of the "on-demand" maintenance or at premature discontinuation treatment: blood and BM aspiration
Statistical consideration	The primary endpoint of this phase II study is the MRD in bone marrow according to EU MCL network guidelines after the 4 cycles or at treatment discontinuation whatever reason, of GA-DHAP. **Analysis sets** The Efficacy set will include all patients having signed their informed consent, received at least one dose of the IMP and with an informative MRD (characterized tumoral clone) in bone marrow (BM) and/or blood at baseline. The Safety set will include all patients having signed their informed consent and received at least one dose of the IMP. The analysis of the primary criterion will be performed on the Efficacy set and also on modified Efficacy Set as sensitivity analysis. Secondary endpoints (including safety endpoints) will be performed on Efficacy and Safety sets.

Sample Size Calculation

Hypothesis:

We expect to have an increase of 15% of the MRD negativity in bone marrow for patients treated with GA-DHAP.

Based on the interim results of LYMA presented at ASH 2014, the MRD negativity rate was 65% (Legouill, ASH 2014). Nevertheless, in the LYMA study, the MRD has been assessed after 4 cycles of DHAP only for patient that completed the 4 cycles. Therefore this rate does not take into account the rate of patients who progressed on treatment or took R-CHOP because of insufficient response. If we take into account these patients considering them as non responder patients and based on the LYSA/LYSARC experience, then the MRD negativity rate of all patients in the LYMA may be around 55%. Considering that these patients will also be included in the LyMa101 we have to take into account a rate of 55% of MRD negativity instead of 65% in the sample size calculation.

The hypotheses are as follows:

- Experimental treatment will be considered ineffective if the MRD negativity in BM after the 4 cycles or at treatment discontinuation proportion is ≤ 55% (P0)
- Experimental treatment will be considered effective if the MRD negativity in BM after the 4 cycles or at treatment discontinuation proportion ≥ 70% (P1)
- α risk of 0.05 and β of 0.20
- one-sided test

Patients will be considered as MRD positive if the patient has no MRD assessment after the 4 cycles or at treatment discontinuation due to whatever reason.

Sample Size:

A total of 70 patients will be required for this study. Assuming that some included patients will not receive the treatment or will not be informative for MRD in bone marrow and/or blood at baseline, enrollment will be done until 70 patients are evaluable. For this purpose, about 83 patients should be enrolling (15% drop-out).

Among the 70 evaluable patients, if 46 patients or more have a MRD negativity in BM after the 4 cycles or at treatment discontinuation, the treatment will be considered as sufficiently effective and further investigations will have to be foreseen.

Sample size calculation was performed using an exact single-stage phase II design with East 5.4 (*A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med. 2001. 20(6):859-66*).

Analysis Plan

The primary endpoint of this phase II study is the MRD in bone marrow after the 4 cycles or at treatment discontinuation.

	Continuous data: will be summarized in tables displaying number of patients, 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) Response and MRD rates (according to Cheson 1999 or at a molecular level): will be expressed with 90% confidence limits (to be consistent with one sided 5% level of significance) according to Pearson-Clopper method. The number and percent of patients falling into each category of response will be provided. Time to event: will be performed using Kaplan-Meier method. Survival probabilities, median survival and quartiles will be estimated with their 95% CI. Survival curves will be provided. **Time of Analysis** Given the fact that primary endpoint is prematurely determined in study treatment period, 2 types of analysis will be performed: • Primary criterion analysis • Final analysis Primary criterion analysis: Primary criterion analysis will be performed once all patients included in efficacy set (70 evaluable patients) have completed 4 cycles of treatment or treatment discontinued prior to cycle 4 of the study and will consist of analyzing: • Primary criterion : MRD rate in bone marrow after the 4 cycles or at treatment discontinuation of GA-DHAP • Treatment exposure • Stem cell collection failure • Secondary safety endpoints Final analysis: All analyses will be performed when all included patients will have performed the end of treatment visit (end of maintenance “on demand” period or treatment discontinuated from the study).
Safety consideration	• AE of grade 3-5 (CTCAE – v 4.03) regardless the relationship to IMP occurring from the date of informed consent signature, and up to 28 days after last treatment administration, will be recorded on the AE pages of eCRF. • Some adverse events which are attributable to the ASCT procedure only and not to the study drug are not to be entered in the eCRF (listed in section 14.2). • Any grade for AESI will be collected from ICF signature and until 28 days after last treatment administration regardless the relationship to IMP • All events that meet one or more criteria of seriousness, regardless the relationship to IMP, occurring from the date of the informed consent signature, during treatment administration period and up to 28 days after last drug administration, will be reported as SAE.

	A SAE that occurs after this time, including follow up period, will be reported if considered related to IMP. In a case of SAE the Investigator must immediately (within 24 hours): **SEND the SAE pages to LYSARC Pharmacovigilance department:** **FAX: +33 (0) 3 59 11 01 86 OR EMAIL TO pharmacovigilance@lysarc.org** Pregnancy and suspected pregnancy will be reported on Pregnancy Form to LYSARC PV from the date of informed consent signature and up to 28 days after the last study drug administration.
Independent Data Monitoring Committee	This trial is designed to allow premature termination or modification of the protocol for safety concerns based on an Independent Data Monitoring Committee (IDMC). Safety variables based on NCI-CTCAE v4.0 and described below will be followed by the LYSARC and a IDMC review will be planed when the rate of these AE is greater than expected. Safety variables assessed and planning of a IDMC meeting when: - during the induction : IRR grade 4, identified as AESI, ≥ 10% or infections grade 3-4 ≥ 25% or opportunistic infections ≥ 5% - during the ASCT : toxic deaths ≥ 5% - during the maintenance : infections grade 3-4 ≥ 10% - throughout the study : SAE ≥ 60%, all death not related to the disease will be analyzed by LYSARC pharmacovigilance department that could induced a safety review
Planned Timelines	Date first patient included: November2016 Duration of enrollment: about 2 years Planned date last patient included: September 2018 Planned date last patient last visit: Q1 2025 Primary criterion analysis: Q1 2019. Final analysis: Q1 2025

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3 LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT (SGPT)	ALanine Transaminase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplant
AST (SGOT)	ASpartate Transaminase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area Under the Curve
BSA	Body Surface Area
CA	Competent Authorities
CBC	Complete Blood Cell
CD20	antigen expressed on the surface of normal and malignant B lymphocytes
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednison
CLL	Chronic lymphocytic leukaemia
CR	Complete Response
Cru	Complete Response unconfirmed
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSUR	Development Safety Update Report
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event Free Survival
EOR	End of treatment Response
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
FCBP	Female of Childbearing Potential
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medical Product
IRB	Institutional Review Board
IRR	Infusion Related Reaction
IV	IntraVenous
LDH	Lactic DeHydrogenase
LYSA	The Lymphoma Study Association
LYSARC	The Lymphoma Academic Research Organisation
MCL	Mantle Cell Lymphoma
MRD	Minimal Residual Disease

NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada - Clinical Trials Group
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	18F-FDG Positon Emission Tomography
PFS	Progression Free Survival
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Response
PS	Performance Status
RPPS	Répertoire Partagé des Professionnels de Santé *(Health Professionals Shared Directory)*
RR	Response Rate
SAE	Serious Adverse Event
SD	Stable Disease
SPM	Second Primary Malignancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUVmax	Maximum Standardized Uptake Value
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

4 RESPONSIBILITIES

4.1 Sponsor and program coordination site

4.1.1 *Sponsor*

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4.2 Investigators

All participating LYSA sites from France may include patients in this study. Before any inclusion, each site must be declared to the Ethical Committee and national competent authority according to each country regulations and have a study training delivered by the sponsor or is delegate (ie initiation visit/call). To be declared as a participating site, the principal investigator must send to LYSARC all administrative documents required for regulatory submission (e.g. Curriculum vitae, for France the RPPS number, etc ...).

4.3 Laboratory sites

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

5 BACKGROUND AND STUDY RATIONALE

5.1 Use of DHAP followed by ASCT in front line in MCL

The experts of The EBMT/EMCL consensus for treatment of young untreated patients with MCL concluded that Autologous Stem Cell Transplant (ASCT) is the standard first-line consolidation therapy and that induction therapy should include high-dose cytarabine and Rituximab (Robinson et al. Leukemia. 2015 Feb). The LyMa101 trial follows this recommendation.

A front to front comparison between induction with R-CHOP alone versus alternating R-CHOP/R-DHAP demonstrated the benefice of cytarabine-containing regimen before ASCT (Hermine abstract ASH 2012; Delarue et al. Blood. 2013 Jan). Indeed, the use of cytarabine increases both complete remission rate (CR) and response duration. More recently, the first interim analyses of the LYSA trial for young untreated MCL patients, so-called LyMa, have been presented at the American society of Hematology (ASH) (le Gouill et al, ASH 2012, 2014). The LyMa trial was a phase III international trial that addressed the question of a Rituximab maintenance after ASCT. The induction chemotherapy regimen before ASCT in the LyMa trial consisted of only 4 courses of rituximab, cytarabine plus cisplatinum (R-DHAP regimen) instead of 3 courses of R-CHOP plus 3 courses of R-DHAP in the previous trial (Hermine abstract ASH 2012). Interim analyses demonstrate that CR rate including at the molecular level and progression-free survival (PFS) for all patients are similar after 4xR-DHAP than after 6 courses of alternating R-CHOP/R-DHAP. Therefore, the design of the present LyMa101 trial is similar to the previous LyMa trial with 4 courses of DHAP. Rituximab will be replaced by the new generation of anti-CD20 antibody Obinutuzumab (See below).

A debulking by COP could be recommended before administration of chemotherapy for high-risk tumor lysis syndrome patients (Jabbour et al. Rev. Med. 2005; Ribrag et al. The Lancet. 2016 Jun 11). This decision will be led by investigator's judgment.

Regarding conditioning regimen of ASCT, there is no evidence that total body irradiation (TBI) is superior to non-TBI containing chemotherapy conditioning regimen like BEAM (BCNU, Etoposide, cytarabine, melphalan) (Touzeau et al. Ann Hematol. 2014 Feb). BEAM is easier to use in clinical practice than TBI and risk of myelodysplasia is lower. Therefore, BEAM is the more frequently used conditioning regimen in MCL.

5.2 Maintenance after ASCT

Rituximab maintenance prolongs PFS and overall survival (OS) after R-CHOP in elderly patients and PFS after ASCT (Kluin-Nelemans NEJM, Le Gouill et al. ASH 2014).

The EMCL study reported by Kluin-Nelemans et al. demonstrated the benefice of OS of a Rituximab maintenance for patients in response after R-CHOP. Maintenance consisted of one injection of Rituximab every 2 months until progression (Kluin-Nelemans NEJM). This study included only elderly patients that were not eligible for ASCT. The impact of a Rituximab maintenance has not been demonstrated after ASCT. However, the planned interim analysis of the LyMa trial showed that Rituximab maintenance (one injection every 2 months for 3 years) prolongs PFS (Le Gouill et al. ASH 2014). The final analysis will be performed in 2016 and results are expected for ASH 2016. The present study anticipates this result and all patients will receive a 3 years maintenance after ASCT as in the LyMa trial. After 3 years of maintenance, only MRD positive patients will receive Obinutuzumab injections until MRD negativity. As shown by Ladetto et al. and the Nordic group, a pre-emptive treatment with an anti-CD20 monoclonal antibody for molecular positive patient can protect patient from clinical relapse and may prolongs PFS. A similar approach using a maintenance "on-demand" according to MRD status will be used after the first 3 years of maintenance.

5.3 Use of Obinutuzumab in MCL

Obinutuzumab is the new generation of anti-CD20 monoclonal antibody and is highly active against CD20 positive B-cell malignancies including MCL.

Obinutuzumab (GA101) is a type II glycoengineered, humanized anti-CD20 monoclonal antibody that has increased antibody-dependent cellular cytotoxicity and direct cell death activity but lower complement-dependent cytotoxicity compared with type I anti-CD20 antibodies such as rituximab and ofatumumab. Phase III trials are ongoing in diffuse large B-cell lymphoma and follicular lymphoma. In a phase I/II study of GA101 monotherapy in patients with relapsed/refractory aggressive non-Hodgkin's lymphoma, 15 patients with MCL were included, all previously exposed to rituximab. (Morschhauser et al. JCO 2013) The overall response rate was 4/15 (27%). Two MCL patients had an ongoing response for ≥ 20 months (20.0 and 20.4 months). GA101 was well tolerated, with infusion-related reactions as the most common adverse event (AE). This finding has been confirmed in the GAUSS study (Sehn et al JCO 2015) Obinutuzumab has also been combined with various chemotherapy regimen like CHOP, Fludarabine/Endoxan, Bendamustine, Chlorambucil … The safety of Obinutuzumab in combination has been confirmed in the published trial (Brown et al. Blood. 2015 Apr 30) and Obinutuzumab plus chlorambucil has been approved for treatment of relapse/refractory CLL (Goede et al. N Engl J Med. 2014 Mar 20).

5.4 Molecular CR as a primary endpoint

Molecular response predicts patients' outcome.

Response assessment using standard evaluation criteria (Cheson 99) in MCL is not a powerful tool to predict PFS or OS in particular for patients in PR, CR or CRu. In contrast, molecular response assessed by PCR techniques from bone marrow (BM) or peripheral blood (PB) samples is an independent prognostic marker and MRD negativity is strongly associated with duration of response (Pott et al Blood 2010). The best time point to assessed MRD is not fully established and today molecular response is not recommended outside of clinical trials (Dreyling et al; Leuk Lymphoma. 2015 Apr;56(4)). However, the predictive value of MRD response is no longer questionable and all experts agree that MRD should be monitored if possible (Dreyling et al; Leuk Lymphoma. 2015 Apr;56(4)).

Patients' outcome according to MRD status has also been investigated for patients included in the previous LyMa trial and results have been presented in an oral session at ASH 2015 (Callanan et al.). The predictive value of MRD status is confirmed and results show that MRD status in the BM assessed before ASCT is probably the best time point. Taken together, MRD appears to be a strong surrogate marker for PFS and maybe OS. MRD before ASCT could therefore be used as a primary endpoint to assess efficacy of an induction therapy. The results of the LyMa101 trial will be compared to results of the previous LyMa trial that shares the same design with exception of Obinutuzumab that replaces Rituximab. Indeed, LyMa101 will help to establish the role of Obinutuzumab in MCL.

6 STUDY OBJECTIVES

6.1 Primary Objective

The Primary objective is to evaluate the efficacy of upfront Obinutuzumab (GA101) at the molecular level (MRD) in bone marrow after induction, after the 4 cycles or at premature discontinuation, in patients with previously untreated MCL treated by DHAP.

6.2 Secondary objectives

Secondary objectives are:

- To evaluate the efficacy of the Obinutuzumab in patients with MCL treated by DHAP before ASCT, after ASCT and every 6 months in terms of clinical response (Cheson 99) and MRD plus in terms of FDG-PET before and after ASCT

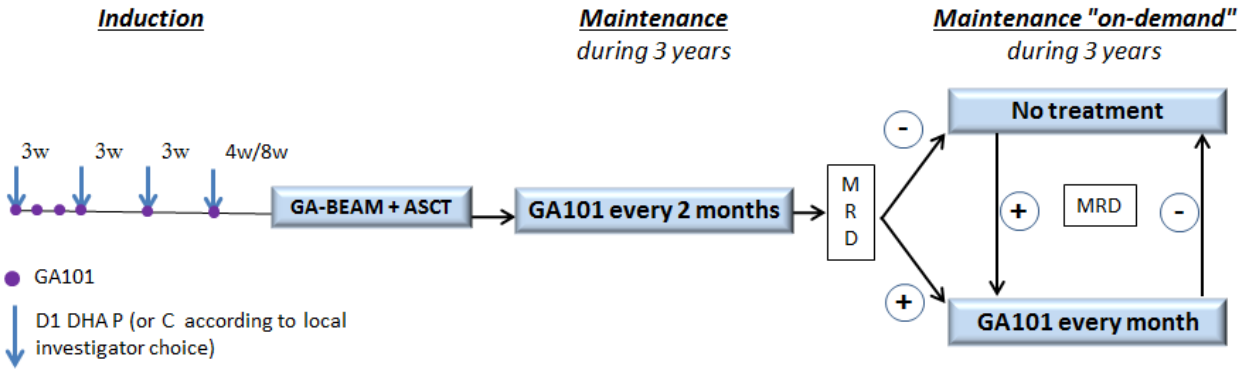
- To evaluate PFS, Overall survival at study end
- To evaluate the incidence of stem cell collection failure after obinutuzumab-DHAP = GA-DHAP
- To evaluate MRD negativity after 3 years of maintenance and after maintenance “on-demand”
- To evaluate PET result after 3 years of maintenance
- To evaluate duration of MRD negativity
- To evaluate tolerability of Obinutuzumab at induction and then “on-demand” (safety analyses)

Exploratory objective is :

- To determine baseline prognostic factors on PFS and OS.

7 STUDY DESIGN

This study is a multicentric, single arm phase II trial to evaluate the efficacy of upfront obinutuzumab in mantle cell lymphoma patients treated by DHAP followed by autologous transplantation plus obinutuzumab maintenance then MRD driven maintenance.



Patients will be recruited over about 2 years and followed until 6.5 years after the last patient included.
The theoretical study dates (start / end) are:

- 1st patient included (FPFV): Q4 2016
- Last patient included (LPFV): Q3 2018
- Last patient followed for principal analysis: Q1 2025

It is expected about 83 patients to had 70 evaluable patients included in the study.
The duration of the treatment period is approximately:

- induction: 12 weeks for 4 cycles of chemotherapy
- conditioning regimen: 8 days
- maintenance : 3 years
- maintenance “on-demand” : 3 years

End of study is defined as the last visit of the last patient in follow-up planned by the protocol.

8 STUDY POPULATION

Patients must have a histologically proven diagnosis of mantle cell lymphoma with at least one measurable mass, splenomegaly not included, be aged from 18 to 65 years at the time of registration. Patients must be eligible for autologous transplant and not previously treated for their lymphoma at inclusion.

8.1 Inclusion criteria

Patients meeting all of the following criteria will be considered for enrollment into the study:

- Age ≥ 18 and age ≤ 65
- Histologically confirmed (according to the WHO classification) mantle cell lymphoma. The diagnosis has to be confirmed by phenotypic expression of CD5, CD20 and cyclin D1 or the t(11;14) translocation
- Bone marrow aspiration performed at inclusion for MRD analyses
- Eligible for autologous stem cell transplant
- Previously untreated MCL
- Stage Ann Arbor II-IV in need of treatment
- ECOG performance status of 0 – 2
- Life expectancy of more than 3 months
- Written informed consent.
- Patient affiliated by any social security system

8.2 Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- Severe cardiac disease: NYHA grade 3-4
- Impaired liver (ALAT/ASAT ≥ 2.5ULN, bilirubin ≥ 1.5ULN), renal (calculated creatinine clearance < 50ml/min) or other organ function which will interfere with the treatment, if not related to lymphoma.
- History of chronic liver disease
- Hepatic veno-occlusive disease or sinusoidal obstruction syndrome
- Any of the following laboratory abnormalities, if not result of a BM infiltration:
    - Absolute neutrophils count (ANC) <1,500 /mm^3 (1.5 x 10^9/L)
    - Platelet counts < 75,000/mm^3 (75 x 10^9/L)
- Pregnancy/Nursing mothers
- Fertile men or women of childbearing potential unless:
    - surgically sterile or ≥ 2 years after the onset of menopause
    - willing to use a highly effective contraceptive method (Pearl Index <1) such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly during study treatment and in female patients for 18 months after end of antibody treatment and in male for the duration of the treatment and after the last dose administered in accordance with the SmpC of the different products administered
- Patients with a malignancy that has been treated but not with curative intent, unless the malignancy has been in remission without treatment for ≥ 5 years prior to enrollment. Patients with a history of curatively treated basal or squamous cell carcinoma or melanoma of the skin or in situ carcinoma of the cervix are eligible.
- Known seropositivity for HIV, HCV or other active infection uncontrolled by treatment
- Viral infection with hepatitis B virus (HBV) defined as hepatitis B surface antigen (HBsAg) positive and/or Hepatitis B core antibody (anti-HBc) positive

  Note: Patients who are immune due to hepatitis B vaccination or natural infection (HBs Ag and anti-HBc negative, anti-HBs positive) are eligible but the patients who are immune due to hepatitis B natural infection should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation
- Prior history of Progressive Multifocal Leukoencephalopathy (PML)
- Vaccination with a live vaccine a minimum of 28 days prior to inclusion (Prolonged B cell depletion)
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products
- Psychiatric illness or condition which could interfere with their ability to understand the requirements of the study

- Person deprived of his/her liberty by a judicial or administrative decision
- Person hospitalized without consent
- Adult person under legal protection

9 STUDY FLOW CHART AND SCHEDULE OF ASSESSMENTS

9.1 Study design

See on Appendix 2.

9.2 Schedule of evaluations

These exams have to be included, but are not limited to, the following.

See on Appendix 3.

9.3 Informed consent

To participate in this study and before any baseline or screening evaluation (except biopsies, imaging and any exam done in routine), each patient must be informed and have signed a written consent. This consent is signed after the investigator has given all required information to the patient and the patient has asked all his/her questions. The patient and the investigator will date and sign the informed consent form.

Two original copies of the signed consent will be completed. A copy will be provided to the patient; a copy will be maintained in the investigator's study file.

The investigator will attest on eCRF that the patient has signed and dated the informed consent. The participation to the clinical trial will be tracked in patient medical dossier.

9.4 Baseline examination

The subject's eligibility has to be evaluated during the baseline period prior to the first administration of the study drug. The assessments are to be conducted **within 28 days** (or within 14 days for biology tests) before administration of the study treatment:

- Age, gender, weight, height, BSA
- Surgical biopsy (avoid needle biopsies if possible to secure enough material) of tumour tissue for morphology and immunochemistry. A tumor biopsy must be made available during the trial for confirmation of the disease (see section 11.2)
- CT scan with IV contrast of neck, thorax and abdomen/pelvis
- Baseline PET scan (PET0)
- Bone marrow biopsy and bone marrow aspiration for local diagnosis
- Gastroscopy/colonoscopy and other examinations if clinically indicated
- Exploratory lumbar puncture if clinically indicated
- Staging **(**see Appendix 4 "Ann Arbor staging")
- Clinical examination (including tumor assessment)
- ECOG Performance Status (see Appendix 6 "Performance Status Criteria")
- Relevant medical history
  Any abnormal medical condition, already present before ICF signature, not due to lymphoma will be reported on medical history pages and for laboratory abnormal value: on haematology/biochemistry pages.
- Blood cell count : Hemoglobin, leukocyte count, neutrophils, lymphocytes, platelets and lymphoma cells
- Biochemical tests: serum creatinin, calculated creatinine clearance according to Cockroft-Gault, total bilirubin, ALAT, ASAT, albumin, LDH
- HIV, HBV (Ag HBs, Ac anti-HBs and Ac anti-HBc) and HCV serologies
- Pregnancy test
- ECG

- **Samples for MRD study**, (cf. Paragraph 11.3 MRD analysis and Appendix 13 **"**Biological studies") after informed consent: blood sampling and bone marrow aspiration.

9.5 Evaluation during induction

	When
Weight and body surface area (see Appendix 5 "Body surface area")	D-1 or D1 of each cycle
Clinical examination	D-1 or D1 of each cycle
ECOG PS	D-1 or D1 of each cycle
Biochemical tests: serum creatinin, creatinin clearance according to Cockroft-Gault formula, ASAT, ALAT, total bilirubin and LDH	D-1 or D1 of each cycle
Blood cell counts: Hemoglobin, leukocyte count, neutrophils, lymphocytes, platelets and lymphoma cells	D-1 or D1 of each cycle + D7 or D8 and D14 or D15 at cycle 1
The adverse events reporting	Continuous

9.6 Evaluation after induction and before Autologous Stem Cell Transplant

The pre-transplant assessment and the autologous transplantation have to be performed according to local practices.

	When
Weight and body surface area (see Appendix 5 "Body surface area")	1 day before GA101-BEAM or at D1
Clinical examination	1 day before GA101-BEAM or at D1
ECOG PS	1 day before GA101-BEAM or at D1
Biochemical tests: serum creatinin, creatinin clearance according to Cockroft-Gault formula, ASAT, ALAT, total bilirubin	1 day before GA101-BEAM or at D1
Complete blood cell counts : Hemoglobin, leukocyte count, neutrophils, lymphocytes, platelets and lymphoma cells	1 day before GA101-BEAM or at D1
Bone marrow aspirate and biopsy if previously positive according to local diagnosis	Between 4 weeks after D1 of cycle 4 and before GA101-BEAM
Thorax, abdomen and pelvis CT with IV contrast (Disease response assessment results must be available and reviewed by the investigator before the first dose of study drug in the next planned cycle)	Between 4 weeks after D1 of cycle 4 and before GA101-BEAM
FDG-PET	Between 4 weeks after D1 of cycle 4 and before GA101-BEAM
Evaluation of the disease response (Cheson 1999 / the Lugano classification 2014)	Between 4 weeks after D1 of cycle 4 and before GA101-BEAM
Any other evaluations or procedures performed at baseline for evaluation of the disease response	Between 4 weeks after D1 of cycle 4 and before GA101-BEAM
Samples for MRD study: blood sampling and bone marrow (BM) aspiration	Between 4 weeks after D1 of cycle 4 and before GA101-BEAM
The adverse events reporting	Continuous

9.7 Evaluation after Autologous Stem Cell Transplant

	When
Clinical examination	After aplasia and before maintenance
ECOG PS	After aplasia and before maintenance
Biochemical tests: serum creatinin, creatinin clearance according to Cockroft-Gault formula, ASAT, ALAT, total bilirubin	After aplasia and before maintenance
Blood cell counts: Hemoglobin, leukocyte count, neutrophils, lymphocytes, platelets and lymphoma cells	After aplasia and before maintenance
Bone marrow aspirate and biopsy if positive before ASCT according to local diagnosis	After aplasia and before maintenance
Thorax, abdomen and pelvis CT with IV contrast (Disease response assessment results must be available and reviewed by the investigator before the first dose of study drug in the next planned cycle)	After aplasia and before maintenance
FDG-PET	After aplasia and before maintenance
Evaluation of the disease response (Cheson 1999 / the Lugano classification 2014)	After aplasia and before maintenance
Any other evaluations or procedures performed at baseline for evaluation of the disease response	After aplasia and before maintenance
Samples for MRD study : blood sampling and BM aspiration	After aplasia and before maintenance
The adverse events reporting	Continuous

9.8 Evaluation during maintenance

	When
Clinical examination	Before each GA101 injection*
ECOG PS	Before each GA101 injection*
Blood cell counts: Hemoglobin, leukocyte count, neutrophils, lymphocytes, platelets and lymphoma cells	Before each GA101 injection*
Thorax, abdomen and pelvis CT with IV contrast (Disease response assessment results must be available and reviewed by the investigator before the first dose of study drug in the next planned cycle)	Every 6 months during 3 years then once a year
FDG-PET (Evaluation of the disease response : the Lugano classification 2014)	At the end of the first 3 years of maintenance
Evaluation of the disease response (Cheson 1999)	Every 6 months during 3 years then once a year
Any other evaluations or procedures performed at baseline for evaluation of the disease response	Every 6 months during 3 years then once a year
Samples for MRD study : - BM aspiration - Blood sampling	- At the end of the first 3 years of maintenance - Every 6 months during the 1st 3 years then every 3 months during the 3 following years
The adverse events reporting	Continuous

*__MRD negative patients__ after 3 years of maintenance will be evaluated every 3 months during the 3 following years. Samples for MRD study will be performed as indicated above.

The following parameters will be assessed:

- Physical examination
- Blood cell counts as described above
- Thorax, abdomen and pelvis CT with IV contrast every year
- Any other evaluations or procedures for evaluation of the treatment response.
- Evaluation of the treatment response (Cheson 1999)

9.9 End of treatment and premature treatment discontinuation evaluations

Patients will be evaluated within 28 days of end of last injection or following premature treatment discontinuation

- Physical examination
- ECOG PS
- Blood cell counts: Hemoglobin, leukocyte count, neutrophils, lymphocytes, platelets and lymphoma cells
- Bone marrow aspiration and biopsy if positive at previous evaluation according to local diagnosis
- Cervical, Chest, abdomen and pelvis CT scan IV contrast
- Evaluation of the disease response (Cheson 1999)
- Any other evaluations or procedures performed at baseline for evaluation of the disease response
- Adverse events
- **Samples for MRD study** : blood sampling and BM aspiration

9.10 Follow-up assessments

The patients mentioned below will be in follow-up, if possible until death up to the end of the study:

- the patients who complete the first 3 years of maintenance and whose MRD was not informative at baseline
- the patients who discontinue the study treatment
- the first patients who complete the 6 years of maintenance

Thereafter, the long term follow-up of patients will be organized for further analysis.
The following assessments must be conducted every 3 months during the first 2 years, then every 6 months until the last visit of the last patient.

9.10.1 *Patients who have discontinued treatment due to reasons other than progressive disease or relapse (meaning patients who did not experienced progression or relapse)*

The following parameters will be assessed:

- Physical examination
- ECOG PS
- Blood cell counts: Hemoglobin, leukocyte count, neutrophils, lymphocytes, platelets and lymphoma cells
- Thorax, abdomen and pelvis CT with IV contrast every year
- Any other evaluations or procedures for evaluation of the treatment response.
- Evaluation of the treatment response (Cheson 1999: **see Appendix 8** “Response criteria for lymphoma”)

Patients included in the study who withdraw before study treatment start will not be followed.

9.10.2 *Patients who experienced progressive disease or relapse*

Only survival status and other malignancies will be recorded at every evaluation period.

9.11 Progression/relapse

Relapse/progression will be determined as per Cheson 1999 criteria **(see Appendix 8** "Response criteria for lymphoma")

Progressive disease should be based on CT scan and not PET or MRD.

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

10 TREATMENTS

10.1 Drugs description, storage, handling and administration

Drugs composing the DHAP and conditioning regimen for transplant are registered and are available at the hospital pharmacy.

Chemotherapy products are to be used according to summary of product characteristics.

Obinutuzumab is considered as investigational medicinal product (IMP) and will be supplied by Roche from induction to maintenance.

10.1.1 ***Obinutuzumab: Description***

Obinutuzumab as know as GA101 is a humanized glycoengineered type II anti-CD20 monoclonal antibody that recognizes the CD20 antigen present on normal and malignant B cells and is being developed for the treatment of hematological malignancies including NHL and CLL.

10.1.2 ***Obinutuzumab: Packaging***

Obinutuzumab is provided as a single-dose, sterile liquid formulation in a 50mL pharmaceutical grade glass vial containing a nominal 1000 mg of Obinutuzumab (G3 material). The formulated drug product consists of 25 mg/mL drug substance (G3) formulated in histidine, trehalose, and poloxamer 188. The vial–contains 41 mL (with 2.5% overfill).

10.1.3 ***Obinutuzumab: Storage conditions***

The recommended storage conditions for the Obinutuzumab drug product are between 2°C to 8°C protected from light. Chemical and physical in-use stability for Obinutuzumab dilutions in 0.9% sodium chloride in the concentration range from 0.2 to 20mg/mL have been demonstrated for 24 hours at 2°C to 8°C and at ambient temperature and ambient room lighting. The prepared diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C. Obinutuzumab should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use an additional in-line filter due to potential adsorption.

10.1.4 ***Obinutuzumab: Handlings***

Obinutuzumab should be given as a slow IV infusion. It should not be administered as an IV push or bolus. Obinutuzumab infusions should be made through a dedicated line. Isotonic 0.9% sodium chloride solution should be used as the infusion vehicle. Obinutuzumab will be administered at the flat dose of 1000mg.

Reconstituted Obinutuzumab drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% sodium chloride, to the final drug concentration of 4 mg/mL.

Dilution preparation:

Using a 250-mL infusion bag containing 0.9% sodium chloride, withdraw and discard 40 ml of the sodium chloride.

Withdraw 40 ml of Obinutuzumab from a single glass vial and inject into the infusion bag (discard any unused portion of Obinutuzumab left in the vial). Gently invert the infusion bag to mix the solution; do not shake.

10.1.5 ***Obinutuzumab: Administration***

See also section *10.5.1. Infusion-Related Reactions related to Obinutuzumab* and section *10.5.2 Tumor Lysis Syndrom*

Infusion rates of Obinutuzumab will be managed as follows:

Administration of First and Subsequent Infusions of GA101

First Infusion (Day 1 of Cycle 1)	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hour. • If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, *use full premedication including 100 mg prednisone/prednisolone (until no further IRR occurs),* begin infusion at an initial rate of 50 mg/hour and follow instructions for first infusion. • If the patient tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of ≥ 100 mg/hour), begin infusion at a rate of 100 mg/hour. • If no reaction occurs, increase the infusion rate in 100-mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. • If a reaction develops, stop or slow the infusion. Administer medications and supportive care in accordance with institutional guidelines. If reaction has resolved, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

In all parts of the study, Obinutuzumab must be administered in a clinical (inpatient or outpatient) setting. Full emergency resuscitation facilities should be immediately available and patients should be under close supervision of the investigator at all times.

Obinutuzumab should be administered as a slow IV infusion through a dedicated line. For patients who are considered to be at risk of tumor lysis syndrome (TLS) with a high lymphocyte count or bulky lymphoadenopathy, the infusion have to be given extremely slowly (25 mg/hour) over a long period of time or the dose may be split and given over more than one day. The first recommended dosage is 100 mg followed by 900mg administered on day 1 or day 2. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values.

IV infusion pumps should be used to control the infusion rate of Obinutuzumab. Do not administer as an IV push or bolus. Administration sets with PVC, PUR, or PE as a product contact surface and IV bags with PO, PP, PVC, or

PE as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption.

After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 2 hours to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, the IV line or central venous catheter should remain in place for at least 1 hour after the end of the infusion. If no adverse events occur after 1 hour, the IV line may be removed or the central venous catheter may be de-accessed.

For further information on description, storage, handling and administration please consult the Investigators Brochure (IB).

10.2 Treatment schedule and design

Upon completion of the required assessments in the screening phase and fulfillment of the eligibility criteria, eligible patients will be included and will enter in the treatment phase.

Patients with high tumor load may receive a pre-phase treatment of COP described below. The pre-phase therapy should be started after inclusion and after samples for MRD analysis.

Chemotherapy regimen	Dose	D1	D2	D3	D4	D5
Prednisolone	80 mg/m²	X	X	X	X	X
Cyclophosphamide	750 mg/m²	X				
Vincristine	1.4 mg/m²	X				

10.2.1 ***Induction treatment: GA-DHAP***

Patients will receive 4 cycles of GA-DHAP every 21 days.

*In case of toxicities related to cisplatinum or according to the local investigator choice, carboplatinum AUC = 5 could be used instead of cisplatinum.

G-CSF administration is required during treatment cycles and stem cell collections.

10.2.1.1 **Cycle 1**

- Patients will receive their first Obinutuzumab infusion (1000 mg) on Day 1 (Cycle 1 Day 1) along with standard premedication. During Cycle 1, Obinutuzumab will also be administered on Days 8 and 15.
- Patients will be monitored for signs of acute tumor lysis syndrome (TLS)
- For patients treated with pre-phase, Cycle 1 has to be started 1 week after the end of the COP
- The products doses should be capped at 2m²

Chemotherapy regimen	Dose	D1	D2	D3	D4	D8	D15
Dexamethasone	40mg	X	X	X	X		
GA-101 IV	1000mg	X				X	X
Aracytine IV (every 12 hours)	2 g/m^2	X X					
Cisplatinum* IV	100 mg/m^2	X					

10.2.1.2 **Cycle 2 to 4 one cycle every 21 days**

Chemotherapy regimen	**Dose**	**D1**	**D2**	**D3**	**D4**
Dexamethasone	40mg	X	X	X	X
GA-101 IV	1000mg	X			
Aracytine IV (every 12 hours)	2 g/m^2	X X			
Cisplatinum* IV	100 mg/m^2	X			

10.2.1.3 **Peripheral stem cell collection**

Collection of peripheral blood stem cell progenitors will be organized after cycle 3 at the time of hematological recovery with G-CSF support. In case of failure to collect a sufficient number of CD34+ cells at this phase, a second attempt will be performed after the fourth cycle. CD34+ cells will be quantified to evaluate the graft and methods of determination will be performed according to each center policy and reported.
The target dose of collected CD34+ cells is 3x10^6 cells/kg.
Leukapheresis will be performed according to current recommended practice. Procedures of harvest, freezing and storage will be performed according to each center policy.
In case of failure to harvest a sufficient number of CD34+ after these two attempts, the patient will be treated according to physician decision.

10.2.2 ***Conditioning regimen and ASCT: GA-BEAM***

All patients in complete remission, complete remission unconfirmed, partial remission or stable disease (according to Cheson 99) after induction treatment will be transplant.
Autologous transplantation will be performed in hematopoietic stem cell transplantation authorized centers.
The conditioning regimen has to start 4 to 8 weeks after D1 C4.

Chemotherapy regimen GA-BEAM	**Dose**	**D-8**	**D-7**	**D-6**	**D-5**	**D-4**	**D-3**	**D-2**	**D-1**	**D0**
GA101	1000mg	X								G
BCNU	300 mg/m²		X							R
Etoposide	400 mg/m^2			X	X	X	X			A
Aracytine (CI)	400 mg/m^2			X	X	X	X			F
Melphalan	140 mg/m²							X		T

G-CSF administration is required from day 7 of ASCT.

10.2.3 ***Maintenance: Obinutuzumab***

All the patients in complete remission, unconfirmed complete remission, partial remission or stable disease (according to the Cheson 99 criteria) after ASCT and whatever the result of the MRD analysis (negative or positive) will receive a maintenance treatment for 3 years.

The maintenance treatment will start between 2 to 3 months after D1 of ASCT.
The patient will be treated with one injection of Obinutuzumab every 2 months for 3 years.

Treatment	**Dose**	**D1 every 2 months**
GA-101 IV	1000mg	X

The patients with an informative MRD at baseline on bone marrow and/or blood (MRD done before starting induction, with characterized tumoral clone) will continue with 3 additional years of maintenance in wich the patients will receive Obinutuzumab according to their MRD status, the so-called “on-demand” maintenance.
During the “on-demand” maintenance, the patients with a negative MRD status will not receive Obinutuzumab while the patients with a positive MRD status will be treated with Obinutuzumab as followed: the therapeutic scheme will be one Obinutuzumab injection at D1, 8 and 15 for cycle 1 and then every month. The Obinutuzumab injections will be continued until the patients reach MRD negativity plus one additional injection after the last MRD negative control. The patients, whom the MRD becomes positive, will restart the obinutuzumab injections.

Treatment	**Dose**	**1st month**			**Every month**
		D1	**D8**	**D15**	**D1**
GA-101 IV	1000mg	X	X	X	X

This scheme has to be used several times until clinical progression, in case of unacceptable toxicity or until of the 3-years period ends, whichever comes first.
The patients who prematurely stop the study treatment or the patients with disease progression will be followed until the end of the trial.

10.3 Dose adjustments

10.3.1 ***Hematological toxicity***

10.3.1.1 **Management of hematological toxicity in patients receiving DHAP**

If neutrophils <1x10^9/l or thrombocytes <20x10^9/l postpone 1 week.

Based on the potential toxicity, a sufficient hydration (2-3 l/m^2 and day) and regular ENR examinations during the course of Cisplatinum containing induction therapy is mandatory.

10.3.1.2 **Management of hematological toxicity in patients receiving GA101**

10.3.1.2.1 ***Neutropenia***

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with GA101 administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of granulocyte colony-stimulating factors (G-CSF) has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), EORTC, and European

Society for Medical Oncology (ESMO) guidelines, namely for patients who are ≥ 60 years old and/or with co-morbidities (Lyman et al. 2004). The use of G-CSF is mandatory in Cycle 1 for all patients.

10.3.1.2.2 ***Thrombocytopenia***

Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with GA101. Fatal haemorrhagic events have also been reported in patients treated with GA101. It seems that the first cycle is the greatest risk of haemorrhage in GA101-treated patients. A clear relationship between thrombocytopenia and haemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician.

10.3.1.2.3 ***GA101 dose adjustments***

There will be no dose reductions for GA101 (1000 mg). During Cycle 1, the Day 8 and D15 doses of GA101 may be administered whatever the neutrophil count if there is no evidence of infection or bleeding and if platelet count is $>50\times10^9$/L.

If the platelet count is $<50x10^9$/L, GA101 will not be administered and the platelet count will be closely monitored and platelet transfusion will be performed to maintain a platelet count $>20x10^9$/L

If the patient presents an active infection of any grade at day 8 or at day 15 of the first cycle of induction treatment, GA101 will not be administered.

10.3.2 ***Renal toxicity***

If >50% decrease of creatinin clearance, cisplatinum will be stopped or replaced by carboplatinum AUC = 5

10.3.3 ***Neurotoxicity***

In case of neurotoxicity such as peripheral neuropathy, severe constipation/paralytic ileus, ototoxicity: cisplatinum should be reduced by 50% or stopped according to the discretion of the treating physician.

Carboplatinum AUC = 5 could be used instead of cisplatinum

10.3.4 ***Potentiel risk of Progressive Multifocal Leukoencephalopathy (PML)***

The therapy with anti-CD 20 antibodies (obinutuzumab) should be discontinued during the investigations of a potential PML and permanently stopped if the diagnosis of PML is confirmed. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the adequate monitoring and treatment of PML.

10.3.5 ***Other toxicities***

Other toxicities will be managed according to local practice and guidelines of chemotherapy induced toxicities

10.4 Concomitant treatment

Any patient treatments taken 8 days prior to study treatment, at any time during the study and up to 28 days after the end of the study treatment will be considered as concomitant treatments.

10.4.1 ***Prohibited therapies***

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 withdrawn from the study treatment.
The change in clinical status mandating the use of the medication in question must be reported as the reason for study drug discontinuation.

10.4.2 ***Restricted/allowed therapies***

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.
All therapies necessary for the patient management are permitted besides other antineoplasic agents for lymphoma. The use of antibiotics and other supportive therapies is in the discretion of the treating physician.
Administration of Granulocyte colony-stimulating factor is mandatory after each GA101-DHAP cycle and recommended after autologous stem cell transplant (see section 10.2).
Platelet and red blood cell transfusions are permitted, as necessary.

10.5 Prophylactic measures

10.5.1 ***Infusion-Related Reactions related to Obinutuzumab***

The most frequently observed adverse drug reactions (ADR) in patients receiving Obinuzumab were IRR; these occurred predominantly during the first infusion. The incidence and severity of infusion related symptoms decreased substantially with subsequent infusion.
See also section *10.1.5. Administration* for the management of IRR
During induction treatment, dexamethasone should be administrated before the infusion of Obinutuzumab
If a patient experiences an IRR during the prior infusion, he should receive 100mg prednisolone or equivalent.

If a patient does not experience an IRR (grade ≥ 1) during the first infusion, the premedication for the infusions of maintenance can be omitted.

The first Obinutuzumab infusion should be administered to patient after premedication with oral analgesic/anti pyretic (e.g. 1000mg) and anti-histaminic drug (e.g. 50 mg diphenhydramine)

Grade 4 (life-threatening)	**Stop infusion and discontinue therapy.**
Grade 3 (severe)	Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose
Grade 1-2 (mild and moderate)	Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose

10.5.2 *Tumor Lysis Syndrome*

Patients who are considered to be a risk of TLS (e.g. patients with a high tumor burden or a high circulating lymphocyte count) should receive adequate tumor lysis prophylaxis with allopurinol (or adequate alternative) and hydration starting 12-24 hours prior to the infusion of Obinutuzumab.

10.5.3 *Infection*

Obinutuzumab should not be administrated in the presence of an active infection.

Prophylaxis of infections is required for all patients during all the study treatment, in the discretion of the treating physician.

Physicians should exercise caution when considering the use of GA101 in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Advice should be given to patients to minimize the risks of acquiring infections from endogenous sources e.g. oral hygiene, avoidance of constipation etc. Signs and/or symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment by the treating physician.

10.6 Drug Dispensation and accountability

10.6.1 *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 packaging is 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 (Obinutuzumab) are responsible for ensuring that the Investigational Products used in the clinical trial are securely maintained as specified by the Sponsor and in accordance with the applicable regulatory requirements. All Investigational Medical Products are stored in accordance with labeling and must be dispensed in accordance with the investigator's prescription. The investigator and the pharmacist are responsible of maintening an accurate record of Investigational Product issued and returned. **The product traceability at site must be available as it could be asked by the sponsor at any moment during the study.** Any quality issue noticed with the receipt or use of an Investigational Product (deficient IP in condition, appearance, pertaining documentation, labeling, 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, allow the Investigational Product to be used other than as directed by this Clinical Trial Protocol, or dispose of Investigational Product in any other manner.

10.6.2 ***Retrieval or destruction***

All unused and undelivered treatments will be destroyed by the Investigator or the pharmacist after the Sponsor provides a written authorization. All partially used disposable treatments will be immediately destroyed by the investigator (or the pharmacist). All destroyed treatments have to be documented by the pharmacist on a Certificate

In case of a potential defect in the quality of Investigational Product, the Sponsor may initiate 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.

10.6.3 ***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, to assess the patient treatment compliance. The sponsor representative 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 destroyed by the study sites. The Sponsor will verify that a final report of drug accountability at the unit dose level is maintained and archived in the investigator study file. Administration of the study treatment will be supervised by the investigator or sub-investigator.

11 STUDY PROCEDURES

11.1 Registration and inclusion procedure

A patient will be registered after verification of eligibility directly on the data capture system by the investigators or designated representative through the internet network with the address below. To access the interactive registration program, the investigator needs to record the study name (LYMA101), 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 for the registered patient.

The investigator should fax **(+33 (0) 4 26 07 40 13**) **or email (lyma101@lysarc.org)** at the same time the following documents whatever the registration way used:

- anonym copy of the initial pathology report where the name and address of the pathologist having diagnosed the lymphoma will be easily identified as well as a copy of the bone marrow report.
- copy of PET0 report or enough information for organizing PET review (see concerned chapters).

LYSARC coordination site (Tel: +33 (0) 4 72 66 93 33) will be the contact for any request.

11.2 Pathological diagnosis

The pathological diagnosis of mantle cell lymphoma should have been performed locally before the inclusion for each patient.

In the last years, histopathology central review process has become a common and prerequisite procedure for clinical trials in the field of lymphomas. A mandatory pathological review will therefore be organized for all patients included in the trial at diagnosis. The goal of this central review will be to confirm the diagnosis and to precise its classification according to the WHO classification 2008.

The central pathological review will be performed at LYSA-Pathology institute (LYSA-P), Hôpital Henri Mondor, Créteil.

The tumor paraffin embedded blocks from the formalin fixed sample that have been used for diagnosis (or 10 unstained slides if block is not available) will be sent to the LYSA-P according to the process described in Appendix 12. At reception, routinely stained sections will be performed and an appropriate panel of antibodies according to morphological aspects will be applied.

The central pathological review will be performed by at least two expert hematopathologists and will be organized at LYSA-P. A consensus diagnosis will be established and communicated to the clinical coordinator and to the initial pathologist.

Initial tumor block will also be used to make tissue microarray (TMA), to study the expression of markers known to influence the prognosis of mantle cell lymphoma.

For the need of the 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.

At the end of the inclusions, frozen tumor tissue will be requested for all included patients. The collection of the frozen tumor specimen will be organized and centralized at the LYSA-P. On frozen tissue, gene and protein expression analysis will be performed to assess the level of expression of genes/proteins known to influence the outcome of mantle celllymphoma patients.

11.3 MRD Analysis

11.3.1 ***Study rationale***

Achievement and preservation of minimal residual disease (MRD) response is the strongest independent predictor of prognosis in MCL patients. By using MRD status as tool for treatment selection, treatment should be focused to achieve and maintain a maximum MRD response to improve outcome. (Pott Blood 2010, Abstract ASH 2014).

Because of the economic constraints of maintenance therapy, preemptive treatment using rituximab based on MRD relapse should be evaluated and might be effective at preventing clinical relapse. Indeed, it has been shown in 32 MCL patients that MRD-based preemptive rituximab therapy restored a PCR-negative state in 81% of cases, of whom 38% subsequently relapsed clinically at a median time of 3.9 years (Andersen JCO 2009, Geisler BJH 2012). Pre-emptive treatment may thus prevent relapse in at least some patients and may prove to be a more cost effective strategy. Use of pre-emptive treatment requires definition of molecular relapse, which is classically based on a progressive rise in MRD levels in three consecutive samples, which can be increasingly closely spaced.

The gold standard for monitoring MRD in MCL is real-time quantitative polymerase chain reaction (RQ-PCR) amplification of clonal immunoglobulin heavy chain (IgH) VDJ or IgH-BCL1 rearrangements, which are informative in 90% and 40% of patients respectively (Pott Blood 2006, Andersen JCO 2009). RQ-PCR strategies are sufficiently sensitive (minimum 0.01%) and specific for MRD quantification in around 85% of MCL patients. These strategies are, however, long, complex and associated with a significant grey zone of non-quantifiable positivity, Below the Quantitative Range (BQR). The quantifiable range (QR) should ideally be at least 0.01% (10E-4), but this is not achieved in 20-25% of samples (Cheminant et al. submitted). For these reasons, RQ-PCR is increasingly challenged by multicolor Flow cytometry (MFC) or droplet digital PCR (ddPCR).

Approximately 10% of MCL patients are not accessible to RQ-PCR MRD with acceptable sensitivity and QR. A proportion of these cases become accessible to MRD assessment by MFC (Cheminant, submitted) or by PCR quantification relative to patient specific plasmid calibrators (Gimenez et al. BJH 2012). The use of MRD results for patient stratification obviously requires maximal informativity. Therefore, the present project will also investigate complementary techniques, including MFC, ddPCR and/or plasmid calibrators.

During follow-up, the percentage of MRD positive samples was approximately 20-25% during the first 3 years, and less than 20% at later time points (Pott ASH 2014 abstract 147). Among patients with clinical relapses, it has been shown that clinical relapse is strongly associated with MRD positivity. In an analysis of the EU-MCL network, only

13% of MCL patients were peripheral blood (PB)-negative (Pott ASH 2014 abstract 147), whereas this will be the predominant source of material for MRD analysis in the proposed study, for ease of sampling, patient comfort and because informativity is comparable to bone marrow analysis, particularly at later time points.

To the present trial will determine what proportion of patients' clinical relapse is preceded by molecular relapse and with what delay. In the EU-MCL studies, the latency between the first positive MRD and the clinical relapse varies greatly between patients. The median latency for prediction by RQ-PCR when any increase to at least 2 positive triplicates was considered as MRD relapse was 22.5 months [range 1-48m] and 5 months [range 2-11m] when only results above 0.01% were considered positive, with no difference between RQ-PCR and MFC quantification (Cheminant et al. submitted).

11.3.2 ***MRD analysis***

11.3.2.1 **MRD follow-up**

Cf appendix 13

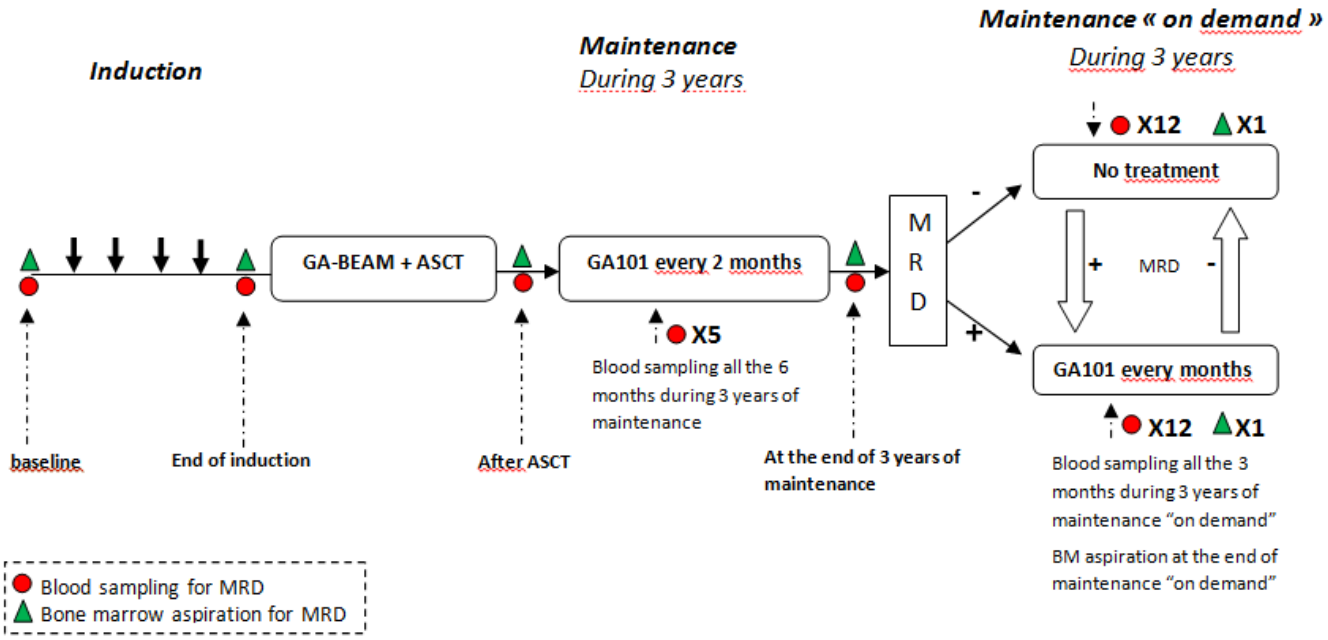
Only the patients with informative MRD in bone marrow and/or in blood at baseline will be sampled for the MRD.

15mL of peripheral blood (PB) samples on EDTA tubes and 2 to 5mL of bone marrow (BM) samples on EDTA tube will be collected at diagnosis, after completion of induction therapy (before the ASCT) and after ASCT (before maintenance).

Then, 15mL of PB samples on EDTA tubes will be collected every 6 months during the first 3 years of maintenance and 2 to 5mL of BM sample will be collected at the end of the first 3 years of maintenance.

During the on-demand maintenance period, the therapeutic strategy with an MRD-based pre-emptive treatment will be restricted to PB MRD values, since regular monitoring makes this a more appropriate source of material. 15mL of blood on EDTA tubes will be performed at 3-monthly intervals, until progression or the end of the 3-years "maintenance-on-demand" surveillance phase. 2 to 5mL of BM sample will be collected at the end of maintenance "on demand".

In case of premature treatment discontinuation, BM and blood will be collected. After premature treatment discontinuation, STOP the MRD sampling.



11.3.2.2 **Therapeutic strategy after molecular relapse**

The time between the first positive MRD and the clinical relapse vary greatly between patients. The median latency for prediction by RQ-PCR when any increase to at least 2 positive triplicates was considered as MRD relapse was 22.5 months [range 1-48m] and 5 months [range 2-11m] when only results above 0.01% were considered positive (Cheminant et al. submitted).

In this study, patients with a high kinetic of relapse (with a clinical relapse < 3 months after the first positive MRD, 1/10 patients) will not benefit from GA101 treatment.

The optimal MRD values for treatment intervention are thus proposed in the algorithm for an MRD based therapeutic strategy.

MRD results	RQ-PCR < 0.01%	Pos RQ-PCR ≥0.01
Suggested therapeutic intervention	3 months MRD surveillance	GA101 treatment

BQR : below the quantitative range.

11.4 PET scan interpretation

Local analysis of the PETs should be done according to Lugano recommandations for baseline PET. Additional quantitative datas (listed in the CRF) will be registered.

Local analysis of the PETs should be done according to Lugano recommandations using Deauville criteria (appendix 9-10) for PET realized before and after ASCT. Additional quantitative datas (listed in the eCRF) will be registered.

A central review of the 3 FDG-PET scan should be organized for this study with sending CD.

For each patient when applicable, the following data and images will be reviewed by a panel of PET experts:

- Baseline FDG-PET (PET0)
- FDG-PET realised after Induction (before ASCT)
- FDG-PET realised after ASCT (before maintenance)

12 STUDY COMMITTEE

This trial is designed to allow premature termination or modification of the protocol for safety concerns based on an Independent Data Monitoring Committee (IDMC), including at least three independent members (2 experts in NHL and one statistician).

Safety variables based on NCI-CTCAE v4.0 and described below will be followed by the LYSARC and an IDMC review will be planed when the rate of these AE is greater than expected.

Safety variable assessed and planning of an IDMC meeting when:

- during the induction : IRR grade 4, identified as AESI, ≥ 10% or infections grade 3-4 ≥ 25% or opportunistic infections ≥ 5%
- during the ASCT : toxic deaths ≥ 5%
- during the maintenance : infections grade 3-4 ≥ 10%
- throughout the study : SAE ≥ 60%, all death not related to the disease will be analyzed by LYSARC pharmacovigilance department that could induced a safety review

13 CRITERIA FOR PREMATURE DISCONTINUATION OF THE STUDY

13.1 Premature treatment discontinuation

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

Criteria for subject premature treatment discontinuation include (but are not limited to):

- death,
- toxicity of study treatment, that would be, in the investigator's opinion, detrimental to the patient's well-being
- progression,
- concurrent illness,
- noncompliance (including loss of subject to follow-up),
- refusal to continue treatment,
- major protocol violation, including initiation of alternate anti-neoplasic therapy.

Patients who prematurely discontinue study treatment should however remain in the trial for the purpose of follow-up and data analysis, with the exception of patients who withdrew their consent. Patients who don't want to receive anymore study treatment can remain in the trial for the purpose of follow-up and data analysis.

Any patient who discontinues before completing the study will be encouraged to return to the study centre within 28 weeks for an evaluation.

13.2 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, he/she should always be contacted in order to obtain information about the reason for withdrawal and to record any adverse events. When patient agrees, he/she 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 his/her 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.

13.3 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 site investigator must document at least 3 attempts to contact the patient either by phone or letter.

13.4 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. Study discontinuation will also be declared to CA and EC according to local regulation.

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.

14 SAFETY PARAMETERS

14.1 Definitions

14.1.1 *Adverse Events*

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

14.1.2 *Serious Adverse Events*

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event ; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (the term “persistent or significant disability or incapacity” means that there is a substantial disruption of person’s ability to carry out normal life functions.)
- Is a congenital anomaly/birth defect
- Is a medically significant event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriated in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above.

The term “severe” is a measure of intensity, thus a severe AE is not necessarily serious. For example, “nausea of several hours duration” may be severe but may not be clinically serious.

14.1.3 *Intensity*

The intensity of the AE or SAE will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system v4.0 in the toxicity categories that have recommended grading (see investigator’s file or online at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

AEs not listed on this grading system will be graded according to the five-point system below:

- Mild (grade 1): Discomfort noticed but no disruption of normal daily activity
- Moderate (grade 2): Discomfort sufficient to reduce or affect normal daily activity
- Severe (grade 3): Incapacitating with inability to work or perform normal daily activity
- Life-threatening (grade 4): Substantial risk of dying at time of event
- Death (grade 5)

14.2 Adverse Events reporting rules

Due to expected toxicity of study treatment, all AEs of grade 3-5 for toxicities (hematological or non-hematological) (CTCAE – version 4.0) regardless relationship to investigational product occurring **from the date of informed consent signature to 28 days after the last study drug administration of the study will be recorded in the AE pages of the eCRF**. When associated to a SAE and regardless the time of occurrence and the grade, the AE must be reported as “Adverse Event” in the appropriate eCRF pages.

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 AEs and his opinion as to whether the AE can be related to the study drugs.

All events that meet one or more criteria of seriousness (see Section 13.1.2.) will be reported as SAE (see Section 13.3).

General AE reporting rules:

- Non-serious AE will be reported through eCRF
- Any episode of any grade of toxicity, related to a SAE must be reported as “Adverse Event” in the appropriate eCRF pages regardless the time of occurrence
- Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as “Adverse Event”
- “Alopecia” toxicity (any grade) will never be reported as “Adverse event”
- AEs will be considered ended (recovered without sequelae) when recovered to a grade 0 or baseline
- In case of screening failure, at least AEs corresponding to SAEs will be reported in the AEs pages of eCRF.
- When a medical history resolves or decreases at a grade lower than baseline, the new grade will be the new reference grade for following AEs
- For laboratory abnormalities, the laboratory test to be taken as reference will be the one performed nearest to the Cycle 1 Day 1.

Abnormal laboratory values reporting rules:

If a laboratory abnormality is one component of a diagnosis or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (e.g., cholecystitis) or syndrome should be recorded on the AE page/screen of the eCRF. If the laboratory abnormality was not a part of diagnosis or syndrome, the laboratory abnormality should be recorded as an AE.

An abnormal laboratory value which is not a component of a diagnosis or syndrome is considered as an AE if the abnormality:

- results in discontinuation from the study; or
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

The investigator has to notify in the patient medical file all abnormal laboratory values considered as clinically significant (write next to each abnormal laboratory value assessed as clinically significant “CS” or precise it in the medical report).

Regardless of severity grade, only laboratory abnormalities that fulfill the seriousness criterion need to be documented as a serious adverse event.

During the transplant period (that is to say the period from the first day of hospitalization to the day before C1 Obinutuzumab maintenance), neutropenia and thrombocytopenia resulting from bone marrow aplasia will not be recorded as AEs in the eCRF. Only the following have to be recorded in the eCRF:

- any evolution of ongoing AE
- any new AE related, or that appears to be related, to Obinutuzumab
- any new infection from at least grade 3
- any new oral mucositis from at least grade 3
- any AE fulfilling seriousness criteria

A special attention is required for the following AEs:

- ICU admission whatever the cause
- Clinically Significant Neurological disorders
- Creatinin increased> 1.5 baseline

- Documented germ infection
- Prolongation of hospitalization beyond J 25 after stem cell reinfusion whatever the cause
- AE deemed unusual by the investigator

Please note that AEs of at least grade 3 associated with Stem Cell mobilization should be recorded in the eCRF

14.3 Serious Adverse Events reporting rules

All events that meet one or more criteria of seriousness (see Section 13.1.2.) will be reported **continuously** from the date of informed consent signature to 28 days after the last study drug administration of the maintenance period. During maintenance on-demand, if GA101 is discontinued (temporarily or permanently), SAEs will be reported until 28 days after last study drug administration. If GA101 is reintroduced (according to MRD results), SAEs will further be reported according to the same reporting rules.

SAE will be reported regardless:

- the relationship to the study treatment
- the administration of new lymphoma therapy,
- disease progression.

Nevertheless, the following SAEs that occur during maintenance on-demand beyond 28 days after the last administration of GA101 will be reported as SAEs regardless relationship to study treatment:

- Death
- Life-threatening events
- Severe infections, hepatitis, progressive multi-focal encephalopathy
- Cardiac events
- Neutropenia

To note that all SAEs **considered related to the study medication** will **always** be reported even if occur beyond 28 days after the last administration of GA101 including during the follow-up period.
Whenever possible, symptoms should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, intensity, action taken regarding the study medication, corrective therapy given, outcome of all SAEs and his/her opinion as to whether the SAE can be related to the IMP.

General SAE reporting rules:

- Any episode of any grade of toxicities, which meets one of the seriousness criteria must be reported as “Serious Adverse Event” in the appropriate SAE form
- Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as “Serious Adverse Event”
- Hospitalizations **not to be considered** as SAE are:
    - Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the study or before the 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).
    - A procedure for protocol therapy administration or protocol/disease-related investigations. Hospitalization or prolonged hospitalization for a complication will be reported as an SAE
    - Routine treatment (e.g. administration of blood or platelet transfusion) or monitoring of the studied indication (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling) not associated with any deterioration in condition. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE

- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE
- Emergency outpatient treatment or observation that does not result in admission (unless considered as an important medical or life-threatening event)

14.3.1 *Obligations of the investigator*

In a case of SAE the investigator must immediately (within 24 hours):

- **Complete SAE form with all relevant information regarding SAE**
- **SEND the SAE pages to**

LYSARC Pharmacovigilance department
FAX: +33 (0) 3 59 11 01 86
Email: pharmacovigilance@lysarc.org

All SAE forms must be dated and signed by the responsible Investigator or one of his/her authorized staff Members.

- May attach the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical study are properly mentioned on any copy of source document. For laboratory results, include the laboratory normal ranges.
- Follow up of any SAE that is fatal or life-threatening should be provided within one calendar week.

For SAEs, the following must be assessed: relationship to each study drug, action taken, and outcome to date. The assessment of whether there is a reasonable possibility of a causal relationship is usually made by the investigator; it can be one of two possibilities:

- Unrelated (no reasonable possibility)
- Related. (reasonable possibility)

Items to be considered when assessing the relationship of a SAE to the study drug are:

- Temporal relationship of the onset of the event to the initiation of the study drug
- The course of the event, considering especially the effect of discontinuation of study drug or reintroduction of study drug, as applicable
- Whether the event is known to be associated with the study drug or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of non-study drug-related factors which are known to be associated with the occurrence of the event.

14.3.2 *Obligations of the Sponsor*

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to study drugs, to the EMA, Health Authorities, Ethic Committees in each country in accordance with international and local regulations, and to the Investigators. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

The expectedness of a serious adverse reaction will be determined by the Sponsor according to the reference safety information (Investigator's Brochure) of the study drugs.

LYSARC Pharmacovigilance department will report all safety information from the trial in the Development Safety Update Reports and will notify the reports to the Health Authorities and Ethics Committees in accordance with international and local regulations.

14.4 Follow up of AEs and SAEs

Any SAE should be monitored until it is resolved or is 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 LYSARC as soon as information becomes available.

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

Subjects who prematurely discontinued study treatment due to any AE will be followed at least until the outcome is determined even if it implies that the follow-up continues after the patient has left the trial.

14.5 Adverse Events of Special Interest

The following AE is considered as of special interest and require attention from investigator if occurring. In addition, they have to be reported immediately in the eCRF, irrespective of the seriousness criteria, and whatever the grade:

- **TLS (**tumor lysis syndrom)
- **IRR** grade 4 occuring during or within 24 hours after the GA101 infusion

They have to be signaled to sponsor using the dedicated form:

LYSARC fax number +33 (3) 59 11 01 86
Email: Pharmacovigilance@lysarc.org

14.6 Pregnancy

14.6.1 *Females 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.

LYSARC fax number +33 (3) 59 11 01 86
Email: Pharmacovigilance@lysarc.org

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 exposure of any pregnant female (e.g. caregiver or pharmacist) to study drug is also an immediately reportable event.

The female should be referred to an obstetrician/gynecologist preferably one 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 immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy is abnormal (i.e., spontaneous or therapeutic abortion) the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, regardless of causality, as SAEs. In addition, any infant death after 28 days that the Investigator(s) suspects to be related to the in utero exposure to the study drug should also be reported to LYSARC within 24 hours of the Investigator's knowledge of the event using SAE form.

14.6.2 ***Male patients***

If a female partner of a male patient taking the study drug becomes pregnant, the male patient taking the study drug should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.
If a pregnancy related event is reported in a female partner of a male subject, the investigator should determine whether the female partner is willing to release her medical information to LYSARC Pharmacovigilance and allow the pregnancy related event to be followed-up to completion.

14.7 Potential risk of Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML occurred in patients treated with anti-CD 20 including obinutuzumab. PML is a destructive infection of oligodendrocytes of the Central Nervous System (CNS) white matter, leading to neurologic deficits associated with demyelination. Death of oligodendrocytes leads to focal loss of myelin and dysfunction of associated myelinated tracts involving the cerebral hemispheres, cerebellum, or brainstem.
The symptoms of PML are unspecific, appear gradually, and can vary depending on the location of brain lesions. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) occur because the pathology of PML is typically immediately subcortical in the white matter, undermining the cortex referable to the clinical syndrome.
In this context, a clinical neurological examination must be performed at each clinical examination planned in the study protocol during treatment and follow up periods. The LYSARC would like to focus on the importance of investigating further any unexplained neurological symptoms identified during the study.
The diagnosis of PML should be considered in any patient presenting with new-onset neurological manifestations or symptoms like weakness or paralysis, vision loss, impaired speech and cognitive deterioration, and not only to the possible cerebral relapse of patient lymphoma. Exploration of PML includes, but is not limited to, consultation with a neurologist, brain MRI and a lumbar puncture for JC virus detection by PCR in Cerebrospinal Fluid (CSF). PCR analysis of CSF for JC virus is the best test to confirm PML (the other parameters of spinal fluid are typically normal).
The therapy with obinutuzumab should be discontinued during the investigations of a potential PML and permanently stopped if the diagnosis of PML is confirmed. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient should be referred to a neurologist for the adequate monitoring and treatment of PML.

15 GENERAL STATISTICAL CONSIDERATIONS

15.1 Endpoints

15.1.1 ***Primary endpoint***

The primary endpoint is the Molecular residual disease (MRD) negativity after induction. Assessment of MRD will be based on molecular level in BM according to EU MCL network guidelines. Patient without MRD assessment (due to whatever reason) will be considered as MRD positive.
This endpoint will be analyzed on efficacy set (ES) and also on modified efficacy set (mES) as sensitivity analysis.

15.1.2 ***Secondary endpoints***

15.1.2.1 **Efficacy endpoints**

Response according to Cheson 99 and overall response rate after 3 years of maintenance

Response after 3 years of maintenance will be evaluated. 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, 1999) See Appendix 8). Patient without response assessment (due to whatever reason) will be considered as non-responder. Overall (CR/PR) response rate will be also presented.

An additional analysis will be performed considering as non-responders all patients who relapsed or died during treatment phase even if they were prematurely treatment discontinued as responder during treatment phase.
This endpoint will be analyzed on efficacy set (ES) and on safety set (SS).

PET result after 3 years of maintenance

PET result after 3 years of maintenance will be evaluated. Assessment of PET will be based on Lugano 2014 criteria (according to Cheson & Al. J. Clinic Oncol 2015). See Appendix 9 (Reponse criteria for lymphoma – Lugano classification).

This endpoint will be analyzed on efficacy set (ES) and on safety set (SS).

MRD after 3 years of maintenance and after maintenance "on demand"

Molecular residual disease (MRD) after 3 years of maintenance and after maintenance "on demand" will be evaluated. Assessment of MRD will be based on molecular level in BM according to EU MCL network guidelines. Patient without MRD assessment (due to whatever reason) will be considered as MRD positive.

This endpoint will be analyzed on efficacy set (ES).

PFS

PFS is defined as the time from inclusion into the study to the first observation of documented disease progression or death due to any cause. If a subject has not progressed or died, PFS will be censored at the time of last visit with adequate assessment.

This endpoint will be analyzed on efficacy set (ES) and on safety set (SS).

OS

Overall survival will be measured from the date of inclusion to the date of death from any cause. Alive patients will be censored at their last contact date.

This endpoint will be analyzed on efficacy set (ES) and on safety set (SS).

Stem cell collection failure

Stem cell collection failure will be evaluated after induction.

This endpoint will be analyzed on efficacy set (ES) and on safety set (SS).

Duration of MRD negativity

Duration of MRD negativity is defined as the time from the date of attainment the first negative MRD to the date of positive MRD. Duration or MRD negativity would be assessed for patients with at least one MRD negativity and as survival endpoint. For patients achieving a negative MRD but who have not positive MRD or not MRD assessment at the time of analysis, duration of MRD negativity will be censored on the date of last MRD assessment.

This endpoint will be analyzed on efficacy set (ES).

15.1.2.2 **Safety endpoints**

Summary of study drug administration including treatment duration and average dose will be displayed.

Number, frequency, reasons for premature treatment discontinuation and study discontinuation will be summarized.

Adverse events, clinical laboratory measurements will be described.

AEs will be classified using the latest version of Medical Dictionary for Drug Regulatory Activities (MedDRA) coding system at the time of database lock. The severity of the toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) whenever possible. Subsets of AEs to be summarized include serious, NCI CTCAE grade severities, suspected treatment-related, and events that resulted in withdrawal of investigational product. The most severe grade of each preferred term for a patient will be utilized for summaries of adverse events by NCI CTCAE grade.

All AEs and SAEs will be described by system organ class and preferred term (a patient having the same event more than once will be counted only once) by period. Focus on AEs leading to death, Aes leading to discontinuation from treatment and AEs of special interest (i.e Tumor Lysis Syndrom) will also be displayed in a separate table and listing.

All deaths will be listed and summarized by cause of death and narratives of death will be also presented.

This endpoint will be performed on safety set (SS)

15.1.3 ***Exploratory endpoints***

Baseline prognostic factors on PFS and OS

A dedicated analysis on survival (PFS/OS) will be performed in order to determined baseline prognostic factors. The implemented method will take into account the specificities of on-demand treatment during the second maintenance period.

15.2 Sample size calculation and tested hypothesis

Hypothesis:

We expect to have an increase of 15% of the MRD negativity in bone marrow (BM) rate for patients treated with GA-DHAP.

Based on the interim results of LYMA presented at ASH 2014, the MRD negativity rate were 65% (Legouill, ASH 2014). Nevertheless, in the LYMA study, the MRD has been assessed after 4 cycles of DHAP only for patient that completed the 4 cycles. Therefore this rate does not take into account the rate of patients who progressed on treatment or took R-CHOP because of insufficient response. If we take into account these patients considering them as non responder patients and based on the LYSA/LYSARC experience, then the MRD negativity rate of all patients in the LYMA may be around 55%. Considering that these patients will also be included in the LyMa101 we have to take into account a rate of 55% of MRD negativity instead of 65% in the sample size calculation.

The hypotheses are as follows:

- Experimental treatment will be considered ineffective if the MRD negativity in BM after the 4 cycles or at treatment discontinuation (at a molecular level) proportion is ≤ 55% (P_0)
- Experimental treatment will be considered effective if the MRD negativity in BM after the 4 cycles or at treatment discontinuation (at a molecular level) proportion ≥ 70% (P_1)
- α risk of 0.05 and β of 0.20
- one-sided test

Patients will be considered as MRD positive if the patient has no MRD assessment due to whatever the reason.

Sample Size:

A total of 70 evaluable patients will be required for this study. Assuming that some included patients will not receive the treatment or will not be informative for MRD in bone marrow and/or blood at baseline, enrollement will be done until 70 patients are evaluable. For this purpose, about 83 patients should be enrolling (15% drop-out).

Sample size calculation was performed using an exact single-stage phase II design with East 5.4 (A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med. 2001. 20(6):859-66).

15.3 Analysis sets

Included set (IS)

The enrolled set will include all patients having signed the informed consent.

Efficacy set (ES)

The Efficacy set will include all patients having signed the informed consent, received at least one dose of the IMP study drug (Obinutuzumab) and with an informative MRD in BM and/or blood at baseline.

Modified Efficacy set (mES)

The modified Efficacy Set will include all patients having signed the informed consent, received at least one dose of the IMP study drug (Obinutuzumab), with an informative MRD in BM and/or blood at baseline and an informative MRD in BM after the 4 cycles of GA-DHAP or at treatment discontinuation.

Safety set (SS)

The Safety set will include all patients having signed the informed consent and received at least one dose of the IMP study drug (Obinutuzumab).

15.4 Statistical methods

Continuous data: 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)

Response rates (according to Cheson 1999 or MRD): will be expressed with 90% confidence limits (to be consistent with one sided 5% level of significance) according to Pearson-Clopper method. The number and percent of patients falling into each category of response will be provided.

Time to event: will be performed using Kaplan-Meier method. Survival probabilities, median survival and quartiles will be estimated with their 95% CI. Survival curves will be provided. A dedicated analysis on survival (PFS/OS) will be performed in order to determined baseline prognostic factors. The implemented method will take into account the specificities of on-demand treatment during the second maintenance period.

15.5 Time of analyses

Given the fact that primary endpoint is prematurely determined in study treatment period, 2 types of analysis will be performed:

- Primary criterion analysis

- Final analysis

Primary criterion analysis:

This analysis will be performed once all patients included in efficacy set (70 patients) have completed the 4 cycles of treatment or treatment discontinued prior to cycle 4 and will consist of analyzing:

- Primary criterion : MRD negativity in BM rate after the 4 cycles or at treatment discontinuation of GA-DHAP
- Treatment exposure
- Stem cell collection failure
- Secondary safety endpoints

Among the 70 evaluable patients, if 46 patients or more have a MRD negativity after the 4 cycles or at treatment discontinuation the treatment will be considered as sufficiently effective and further investigations (another trial) will have to be foreseen.

Final analysis:

This analysis will be performed when all included patients will undergo the end of treatment visit (at end of maintenance “on demand” period or at treatment discontinuation) and will consist of the whole statistical analyses.

At this time all secondary and exploratory endpoints will be analyzed.

16 STUDY MONITORING

16.1 Responsibilities of investigators

The investigator(s) undertake(s) to perform the study in accordance with Good Clinical Practice and specifically either European 2001/20/CE and 2005/28/CE directives and ICH **E**6 and guidelines for the monitoring of clinical investigations.

The investigators 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.

As may be required by the local legislation, the investigators will check that the patients are directly or indirectly affiliated to the national health insurance or coverage system if there is any.

16.2 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 sponsor project leader and of the Sponsor clinical research support team (LYSARC) is to help the investigator maintaining a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

At regular intervals during the study, the site 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.

The frequency of site contact/visits, and data monitored are defined in the monitoring plan developed specifically for the study.Source document requirements

According to the guidelines on Good Clinical Practice, the sponsor representative will check the case report form entries against the source documents following the study monitoring plan. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

16.3 Use and completion of electronic case report form (eCRF)

An electronic Case Report Form (eCRF) 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 eCRF available at the following website:

http://study.lysarc.info.

Source documentation supporting the eCRF 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 and study site staff will receive system documentation, training and support for the use of the eCRF.

Use and completion of eCRF will be carried out according to the instructions provided in the data entry and monitoring guidelines.

The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement of a user ID and password to enter or change data. These user ID and password transmitted by LYSARC to study sites staff are personal and confidential. The investigator has to maintain a list of individuals who are authorized to enter or correct data. All data entry and corrections are recorded in the audit trail (date of data entry/correction, name of person, type of action).

17 ETHICAL AND REGULATORY STANDARDS

17.1 Ethical principles

This study is in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and subsequent amendments and will be conducted according to ICH/GCP guidelines.

17.2 Laws and regulations

This study is performed also in accordance with applicable laws and regulations of each country involved in the trial, as well as any applicable guidelines.

All data of the patients collected by the sponsor will be anonymized.

17.3 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.

As LYSARC participates to the "Plan Cancer", the informed consent document will be reviewed by a patient committee (*Ligue contre le cancer*).

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 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.).

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.

17.4 Ethics Review Committee and Competent Authorities submission

The Sponsor must submit this study to country Ethics Review Committee(s), and Competent Authorities. It is required to forward a copy of written signed opinions / approvals to investigators.

18 ADMINISTRATIVE PROCEDURES

18.1 Curriculum vitae

An updated signed copy of the curriculum vitae of each investigator and sub-investigator will be provided to LYSARC prior to their involvement in the study.

18.2 Confidentiality 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.

18.3 Record retention in investigating site(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. The investigators will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

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 site will notify the sponsor before destroying any data or records.

18.4 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 or any third Party either appointed by the Sponsor or having concluded a specific agreement with 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.

The Investigator is committed to give his support to any requests for a patent or any property title based on, or illustrated with the results of the present Study for any country.

18.5 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 coordinating investigators in charge of the study with approval of partner if applicable.

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

The authors will be proposed (according to the updated LYSA publication rules) by the coordinating investigators in charge of the study, and finally endorsed by the Steering Committee of LYSA.

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

18.6 Insurance compensation

The sponsor certifies having taken out appropriate liability insurance policy which covers the Sponsor, 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 needed.

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

The Investigator(s) will remain responsible towards the Sponsor of any fault or misconduct regarding the performance of the Study.

18.7 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.

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

18.8 Clinical study report

The sponsor will declare the trial end to Competent Authorities and Ethics Committees according to local regulations.

A summary of the study results will be prepared under the responsibility of the sponsor, within one year after the end of the study and will be forwarded to Competent Authorities and Ethics Committees and posted on Authorities' website if required by local regulations.

A suitable study report will be also prepared under the responsibility of the sponsor, within one year after the end of the study if required by local regulations.

18.9 Protocol 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 coordinating investigator and LYSARC.

Approval / opinion of amendments by Ethics Review Committee(s) 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.

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 in the Investigator Study File.

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.

19 REFERENCES

Andersen NS, Pedersen LB, Laurell A, et al. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2009;27(26):4365–4370
Pre-emptive treatment with rituximab of molecular relapse after autologous stem cell transplantation in mantle cell lymphoma.

Brown JR, O'Brien S, Kingsley CD, Eradat H, Pagel JM, Lymp J, Hirata J, Kipps TJ. Blood. 2015 Apr 30;125(18):2779-85.
Obinutuzumab plus fludarabine/cyclophosphamide or bendamustine in the initial therapy of CLL patients: the phase 1b GALTON trial.

Callanan M, Delfau MH, Macintyre E, Thieblemont C, Oberic L, Gyan E, Bouabdallah K, Gressin R, Damaj G, Casasnovas O, Ribrag V, Gimenez E, Hermine O and Le Gouill S. ASH 2015 Abstract #79544.
Predictive Power of Early, Sequential MRD Monitoring in Peripheral Blood and Bone Marrow in Patients with Mantle Cell Lymphoma Following Autologous Stem Cell Transplantation with or without Rituximab Maintenance; Interim Results from the LyMa-MRD Project, Conducted on Behalf of the Lysa Group

Dreyling M, Amador V, Callanan M, Jerkeman M, Le Gouill S, Pott C, Rule S, Zaja F; European Mantle Cell Lymphoma Network. Leuk Lymphoma. 2015 Apr;56(4):866-76.
Update on the molecular pathogenesis and targeted approaches of mantle cell lymphoma: summary of the 12th annual conference of the European Mantle Cell Lymphoma Network.

Delarue R, Haioun C, Ribrag V, Brice P, Delmer A, Tilly H, Salles G, Van Hoof A, Casasnovas O, Brousse N, Lefrere F, Hermine O; Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood. 2013 Jan 3;121(1):48-53
CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte.

Gimenez E, Chauvet M, Rabin L, et al. Cloned IGH VDJ. Br. J. Haematol. 2012;158(2):186–197
Targets as tools for personalized minimal residual disease monitoring in mature lymphoid malignancies; a feasibility study in mantle cell lymphoma by the Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang.

Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, Chagorova T, de la Serna J, Dilhuydy MS, Illmer T, Opat S, Owen CJ, Samoylova O, Kreuzer KA, Stilgenbauer S, Döhner H, Langerak AW, Ritgen M, Kneba M, Asikanius E, Humphrey K, Wenger M, Hallek M. N Engl J Med. 2014 Mar 20;370(12):1101-10.
Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions

Hermine O, Hoster E, Walewski J, Ribrag V, Klapper W, Brousse N, Thieblemont C, Bouabdallah R, Feugier P, Forspointner R, Haioun C, Kneba M, Hänel M, Casasnovas O, Mertelsmann RH, Hallek M, Bosly A, Nowacki M, Klapper W, Gisselbrecht C, Coiffier B, Unterhalt M, Hiddemann W, Dreyling MH. ASH 2012 Abstract #151.
Alternating Courses of 3x CHOP and 3x DHAP Plus Rituximab Followed by a High Dose ARA-C Containing Myeloablative Regimen and Autologous Stem Cell Transplantation (ASCT) Increases Overall Survival When Compared to 6 Courses of CHOP Plus Rituximab Followed by Myeloablative Radiochemotherapy and ASCT in Mantle Cell Lymphoma: Final Analysis of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net).

Jabbour E, Ribrag V. Rev. Med. 26 (2005) 27–32
Acute tumor lysis syndrome: update on therapy

Kluin-Nelemans HC, Hoster E, Hermine O, Walewski J, Trneny M, Geisler CH, Stilgenbauer S, Thieblemont C, Vehling-Kaiser U, Doorduijn JK, Coiffier B, Forstpointner R, Tilly H, Kanz L, Feugier P, Szymczyk M, Hallek M, Kremers S, Lepeu G, Sanhes L, Zijlstra JM, Bouabdallah R, Lugtenburg PJ, Macro M, Pfreundschuh M, Procházka V, Di Raimondo F, Ribrag V, Uppenkamp M, André M, Klapper W, Hiddemann W, Unterhalt M, Dreyling MH.
N Engl J Med. 2012 Aug 9;367(6):520-31.
Treatment of older patients with mantle-cell lymphoma.

Le Gouill S, Callanan M, Macintyre E, delfau-Larue MH, bodet-Milin C, Meignan M, Moreau A, Traverse-Glehen A, Béné MC, Haouin C, Gressin R, Casasnovas O, Ribrag V, Damaj G, Gyan E, Oberic L, Bouabdallah K, Thieblemont C, Hermine O. ASH 2012 Abstract #152
Clinical, Metabolic and Molecular Responses After 4 Courses of R-DHAP and After Autologous Stem Cell Transplantation for Untreated Mantle Cell Lymphoma Patients Included in the LyMa Trial, a Lysa Study.

Le Gouill S, Thieblemont C, Oberic L, Bouabdallah K, Gyan E, Damaj G, Ribrag V, Bologna S, Gressin R, Casasnovas C, Haioun C, Solal-Celigny P, Maisonneuve H, Van Den Neste E, Moreau A, Bene MC, Gilles Salles G, Tilly H, Lamy T, Hermine O. ASH 2014 Abstract #146
Rituximab Maintenance Versus Wait and Watch after Four Courses of R-DHAP Followed By Autologous Stem Cell transplantation in Previously Untreated Young Patients with Mantle Cell Lymphoma: First Interim Analysis of the Phase III Prospective Lyma Trial, a Lysa Study.

Morschhauser FA, Cartron G, Thieblemont C, Solal-Céligny P, Haioun C, Bouabdallah R, Feugier P, Bouabdallah K, Asikanius E, Lei G, Wenger M, Wassner-Fritsch E, Salles GA.
J Clin Oncol. 2013 Aug 10;31(23):2912-9.
Obinutuzumab (GA101) monotherapy in relapsed/refractory diffuse large b-cell lymphoma or mantle-cell lymphoma: results from the phase II GAUGUIN study.

Pott C, Schrader C, Gesk S, et al. Blood. 2006;107(6):2271–2278
Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma.

Pott C, Hoster E, Delfau-Larue MH, Beldjord K, Böttcher S, Asnafi V, Plonquet A, Siebert R, Callet-Bauchu E, Andersen N, van Dongen JJ, Klapper W, Berger F, Ribrag V, van Hoof AL, Trneny M, Walewski J, Dreger P, Unterhalt M, Hiddemann W, Kneba M, Kluin-Nelemans HC, Hermine O, Macintyre E, Dreyling M. Blood. 2010 Apr 22;115(16):3215-23.
Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study.

Pott C, Macintyre E, Delfau-Larue M-H, et al. Network. Abstract 2977. Presented at: ASH Annual Meeting, Atlanta, GA, USA, 6-9 December 2014
MRD Eradication Should be the Therapeutic Goal in Mantle Cell Lymphoma and May Enable Tailored Treatment Approaches: Results of the Intergroup Trials of the European MCL

Ribrag V, Koscielny S, Bosq J, Leguay T, Casasnovas O, Fornecker LM, Recher C, Ghesquieres H, Morschhauser F, Girault S, Le Gouill S, Ojeda-Uribe M, Mariette C, Cornillon J, Cartron G, Verge V, Chassagne-Clément C, Dombret H, Coiffier B, Lamy T, Tilly H, Salles G. Lancet 2016; 387: 2402–11
Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial

Robinson S, Dreger P, Caballero D, Corradini P, Geisler C, Ghielmini M, Le Gouill S, Kimby E, Rule S, Vitolo U, Dreyling M, Hermine O. European MCL Network and the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation
The EBMT/EMCL consensus project on the role of autologous and allogeneic stem cell transplantation in mantle cell lymphoma

Sehn LH, Goy A, Offner FC, Martinelli G, Caballero MD, Gadeberg O, Baetz T, Zelenetz AD, Gaidano G, Fayad LE, Buckstein R, Friedberg JW, Crump M, Jaksic B, Zinzani PL, Padmanabhan Iyer S, Sahin D, Chai A, Fingerle-Rowson G, Press OW. J Clin Oncol. 2015 Oct 20;33(30):3467-74.
Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study

Touzeau C, Leux C, Bouabdallah R, Roussel M, Delarue R, Bouabdallah K, Thieblemont C, Cacheux V, Cartron G, Compain L, Gyan E, Morschhauser F, Casasnovas O, Moles MP, Michallet AS, Gressin R, Damaj G, Rose C, Sirvent A, Hermine O, Mohty M, Milpied N, Le Gouill S. Ann Hematol. 2014 Feb;93(2):233-42.
Autologous stem cell transplantation in mantle cell lymphoma: a report from the SFGM-TC.

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20 APPENDICES

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20.1 Appendix 1: Declaration of Helsinki

Special Communication

World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

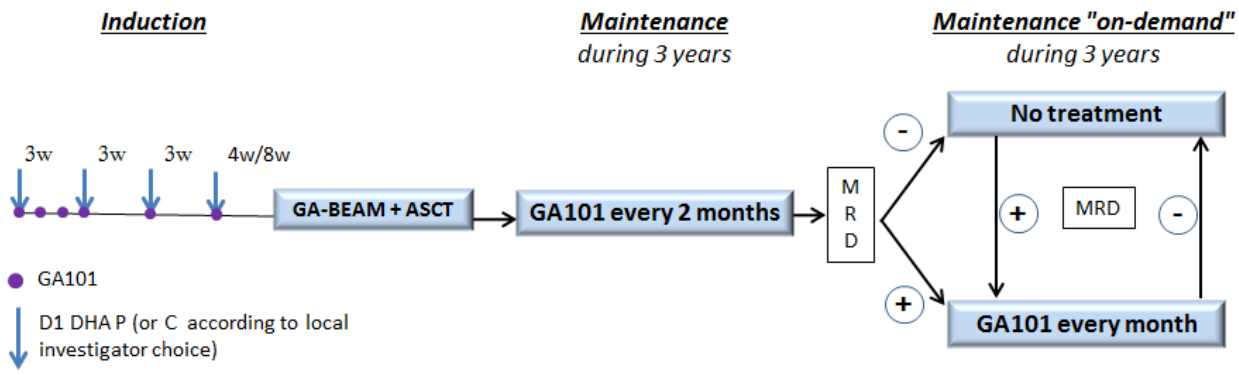
Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it

20.2 Appendix 2: Study Design



20.3 Appendix 3: Schedule of Evaluations

		Baseline	During Induction	Autologous Stem Cell Transplant		During Maintenance	At the end treatment	Follow-up
Date: days (D), weeks (W) , months (M) or years (Y)		Within 28 days before D1 C1 and 14 days for biology tests (b)	D-1 or D1 of each cycle	D-1/D1 of GA-BeEAM and within 4W for imageries, BOM, MRD	After ASCT-induced aplasia and before maintenance	Before each GA101 and every 6 months during 3 years then every year for imageries	28 days after last cycle Or at premature treatment discontinuation	Every 3 months during the first 2 years then every 6 months until the end of study
Written informed consent		X						
Patient characteristics (a)		X						
Clinical examination		X	X	X	X	X	X	X
Surgical biopsy		X						
Samples for MRD analyses	Blood	X		X	X	Each 6M during 3Y then 3M	X	
	Bone marrow	X		X	X	At midterm	X	
Bone marrow biopsy/ aspirate		X		(f): If previously involved			(f)	
HIV, HBV and HCV serologies		X						
Complete Blood cell counts (c)		X	Before each GA101 injection	X	X	X	X	X
Biochemical tests	creatinin, creatinin clearance, ASAT/ALAT, Bilirubin	X	X	X	X			
	LDH	X	X					
	Albumin	X						
Pregnancy test		X						
CT: neck, thorax, abdomen and pelvis (d)		X		X	X	X	X	Every year
PET Scan		X		X	X	At the end of the 1st 3Y		
ECG		X						
Other examinations if clinically indicated (e)		X		X	X	X	X	X
Adverse Events		Safety reporting according to protocol section 13						

(a): Age, gender, weight, height, relevant medical history, history of the NHL

(b): biology tests = Blood cell counts and biochemical tests

(c): Blood cell counts: Hemoglobin, leukocyte count, neutrophils, lymphocytes platelets and lymphoma cells

(d): if no neck involvement: neck CT only at baseline and EOT

(e): Exploratory lumbar puncture, endoscopy and other investigations for extranodal localisations

20.4 Appendix 4: 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.*

20.5 Appendix 5: Body Surface Area calculation

The algorithm to be used in this study is Mosteller formula (1987):

BSA = √ [(Height (cm) x Weight (kg))/3600]

20.6 Appendix 6: 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.*

20.7 Appendix 7: MCL International Prognostic Index (MIPI) and combined biological Index ($MIPI_b$)

Source: Hoster E et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008; 111:558-565. Erratum in: Blood 2008;111(12):5761.

MIPI Score = 0.03535 x age (years)

+ 0.6978 (if ECOG PS > 1, otherwise 0)

+ 1.367 x $\log_{10}$(LDH/ULN)

+ 0.9393 x $\log_{10}$(WBC count per 10^{-6} L)

$MIPI_b$ Score = 0.03535 x age (years)

+ 0.6978 (if ECOG PS > 1, otherwise 0)

+ 1.367 x $\log_{10}$(LDH/ULN)

+ 0.9393 x $\log_{10}$(WBC count per 10^{-6} L)

+ 0.02142 x Ki67 (%)

ECOG: ECOG performance status (see Appendix E), LDH: lactate dehydrogenase, $\log_{10}$: logarithm with respect to base 10, ULN: upper limit of the normal range, LDH/ULN: LDH divided by ULN, WBC: white blood cell, Ki67: cell proliferation.

Risk groups are defined by:

MIPI risk group	**MIPI score**	**$MIPI_b$ score**
Low risk	< 5.7	< 5.7
Intermediate risk	≥ 5.7 and < 6.2	≥ 5.7 and < 6.5
High risk	≥ 6.2	≥ 6.5

20.8 Appendix 8: 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

20.9 Appendix 9: Response Criteria for Lymphoma – Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister. J Clin Oncol 2014;32(27):3059-68.

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 progressionNo increase consistent with progression
Organ enlargement	Not applicable	
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	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	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

20.10 Appendix 10: Deauville criteria for PET analysis

Deauville criteria is a scoring system and it will be used for intermediate evaluation of PET realized before and after ASCT.

We will use a 5 points scale (adapted from the Deauville workshop in Leukemia & Lymphoma, August 2009; 50(8): 1257–1260), with new modifications (mainly 4 and 5 scales).

It includes visual and quantitative analysis.

1. No uptake.
2. Uptake < mediastinum.
3. Uptake > mediastinum but < liver.
4. Uptake moderately more than liver uptake, at any site.
5. Markedly increased uptake at any site and/or new sites of disease.

20.11 Appendix 11: PET SCAN

FDG PET/CT imaging should follow the standardized protocol elaborated by EANM organization (*).

In particular, careful attention should be paid to the scheduled protocol (1 hour between FDG administration and PET acquisition), the glycemic status and, for each patient, unchanged technical parameters of acquisition.

FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0, Ronald Boellaard & Mike J. O'Doherty &Wolfgang A. Weber & Felix M. Mottaghy., November 2009 Eur J Nucl Med Mol Imaging DOI 10.1007/s00259-009-1297-4 (available on ***http://www.eanm.org/publications/guidelines/index.php?navId=37***)

20.11.1 *Timing of FDG PET scans*

20.11.2 *Patient preparation*

- Patients are not allowed to consume any food or sugar for at least 6 h prior to the start of the PET study (i.e. with respect to time of injection of FDG).
- Adequate pre-hydration is important to ensure a sufficiently low FDG concentration of FDG in urine (fewer artifacts) and for radiation safety reasons (for example, 1 l of water in the 2 h prior to injection).
- Parental nutrition and intravenous fluids containing glucose should be discontinued at least 4 h before the PET/CT examination. In addition, the infusion used to administer intravenous pre-hydration must not contain any glucose.
- During the injection of FDG and the subsequent uptake phase the patient should remain seated or recumbent and silent to minimize FDG uptake in muscles.
- Blood glucose level must be measured prior to administering FDG:
- If plasma glucose level is <7 mmol/l (or <120 mg/dl) the FDG PET study can be performed
- If plasma glucose level is ≥7 mmol/l (or >120 mg/dl) the FDG PET study must be rescheduled or the patient excluded depending on the patient circumstances.
- The following recommendations apply to patients with diabetes mellitus:
- type II diabetes mellitus (controlled by oral medication)
    - the PET study should preferably be performed in the late morning
    - patients must comply with the fasting rules indicated above
    - patients continue to take oral medication to control their blood sugar.
- type I diabetes mellitus and insulin-dependent type II diabetes mellitus
    - ideally, an attempt should be made to achieve normal glycemic values prior to the PET study, in consultation with the patient and his/her attending medical doctor
    - the PET study should be scheduled for late morning
    - the patient should eat a normal breakfast at 7.00 a.m. and inject the normal amount of insulin.
- Height and body weight must be determined at first scan and weight must be measured directly prior to each PET study because body weight often changes during course of disease.

20.11.3 *PET scanner technical requirements*

- FDG-PET scanning should be performed with a combined PET/CT for an improved data interpretation. Unless specifically excluded for particular protocols.
- Each patient is preferably scanned on the same camera for each PET (baseline, before and after ASCT).

20.11.4 ***PET acquisition and reconstruction***

- The 18F-FDG injected activity will be defined according to on-site rules but should be >3.5 MBq/kg (or recommended activity for more recent PET-CT technology (TOF).

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 scans

- The patient should be positioned with the same positions of arms for each exam (elevated over the head or along the body) and PET acquisition should cover at least from the mid-femora to the external auditory meatus.
- A whole body acquisition with attenuation correction (non contrast-enhanced CT) and with emission scans of at least 2 minutes per bed position (or less for more recent PET-CT technology (TOF) is started 60+/-10 minutes after FDG injection, starting from groin up to the head.
- FDG PET/CT imaging should follow the standardized protocol elaborated by EANM organization. In particular, a careful attention should be paid to maintain unchanged technical parameters of reconstruction within patient.
- A standard diagnostic CT scan with (i.v.) contrast agent may, if appropriate, be carried out according to standard radiological methods **after** the low-dose CT without contrast agent and PET acquisition.

20.12 Appendix 12: Pathological Samples Review

General principles and organization of the pathological review:

The LyMa101 study requires a histological review of all cases included in the trial at diagnosis. The aims of the centralized histopathological review will be to **confirm the diagnosis of mantle cell lymphoma,** according to the criteria of the updated WHO classification 2008 (S. Swerdlow et al.) for each patient in the LyMa101 study. Histological criteria of inclusion and exclusion have been detailed in the current protocol.

The review process will be organized by the LYSA-Pathology institute, Hopital Henri Mondor, Créteil (LYSA-P).

Therefore for each included patient, tumor tissue blocks - or only when not possible - unstained slides will have to be sent for analysis and confirmation of diagnosis to LYSA-P.

Practical aspects of the LYSA review:

1. Information on patient inclusion

At patient /inclusion, the investigator will be requested to fax to LYSARC registration centre with the inclusion form a copy of the initial histopathological report on which the name and address of the pathologist having diagnosed the mantle cell lymphoma will be easily identified as well as the bone marrow report when possible.

LYSARC registration centre will then fax/mail these documents to LYSA-P.

2. Sample request

At reception of the pathological report and inclusion form, LYSA-P will send to the initial pathologist a letter requesting:

- The paraffin block from the formalin fixed sample that was used to set the diagnosis and/ or 10 unstained Superfrost+ slides
- A copy of the bone marrow pathological report if not sent previously
- To notify LYSA-P of the presence of frozen tissue

3. Sample centralisation at LYSA-P

All these requirements (excluding frozen tissue) will be sent in prepaid envelope and centralized by LYSA-P at the following address:

LYSA-P, LYSA – LYMA101 study,
Hôpital Henri Mondor
51, avenue de Lattre de Tassigny, 94010 Créteil France

4. Sample review

At sample reception, routinely stained sections will be performed and an appropriate panel of antibodies according to morphological aspects will be applied. When sufficient slides are available, a pathological review will be organized at LYSA-P with the designated panel of pathologists for this study. All the cases will be reviewed by at least 2 experts hematopathologists and a consensus diagnosis will be set and registered in LYSA-P data base. This consensus diagnosis will then be sent to the clinical investigator and to the initial pathologist. For the need of the 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.

20.13 Appendix 13: Biological studies

MRD Monitoring and sample processing:

Blood sampling at baseline, at the end of induction treatment, after ASCT, all the 6 months during the first 3 years of maintenance (5 blood samplings), at the end of first maintenance, all the 3 months during the 3 years of maintenance "on demand" (12 blood samplings), at the end of treatment or at premature discontinuation.

⇨ **collect 12mL of blood on EDTA tubes (3 tubes) for DNA collection and MRD analyses**

Bone marrow aspiration at baseline, at the end of induction treatment, after ASCT, at the end of first 3 years of maintenance, at the end of maintenance "on-demand", at the end of treatment or at premature discontinuation.

⇨ **collect 3 to 5mL of bone marrow (aspiration) on EDTA tube (1 tube)**

Identifie the tubes with labels provided by LYSARC.
The traceability form "LyMa101_ Traceability form of biological samples molecular residual disease study (MRD)" will be completed the day of blood sampling.
The day of blood sampling, send the tubes to laboratory according to distribution center by carrier, at room temperature.

LYSARC will provide to the centres kits for biological studies, containing the consumables required to perform these studies (tubes + labels), as well as biological studies handbook and traceability forms.

The first kit is present in the investigator study file. LYSARC will send you a new kit after each new inclusion and before each theoretical date of sampling.

2 laboratories support the MRD analysis. According to the distribution centres specified in the biological studies handbook, you will work only with one of these laboratories:

Pr Marie-Hélène Delfau-Larue - hôpital Henri Mondor - laboratoire d'immunologie - 51 avenue du Maréchal de Lattre de Tassigny - 94010 Créteil

Pr Elisabeth MacIntyre - hôpital Necker enfants malades et Université Paris Descartes - Hématologie Biologique - Tour Pasteur, 2ème étage - 149 rue de Sèvres - Paris 75743 Cedex 15

The traceability form must be completed the day of blood sampling / bone marrow aspiration **and faxed to laboratory the day of sampling**.

Fax Créteil: 01 49 81 28 97

Fax: Necker: 01 44 49 49 99

The day of sampling (blood and marrow), send the tubes and filled in traceability form to the laboratory by carrier, at room temperature, according to the procedures required in biological studies handbook.