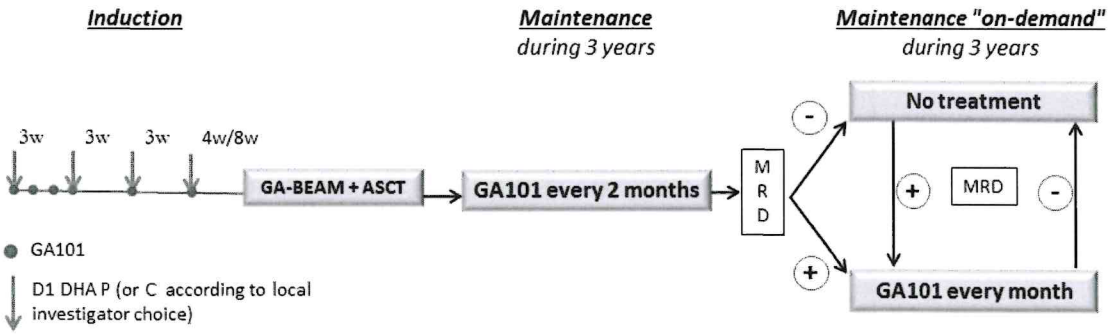
1 SYNOPSIS

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/m^2							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			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, 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