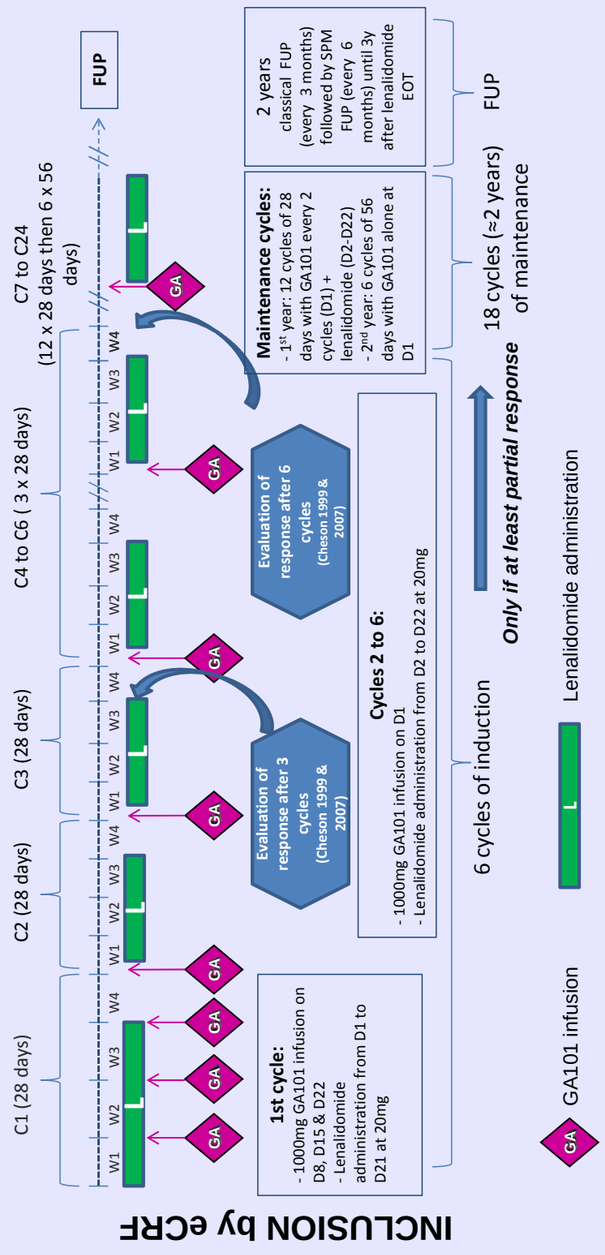
Main exclusion criteria

	Phase II cohort 1 (R /R aNHL)	Phase II cohort 2 (R/ R FL)	Phase II cohort 3 (1L FL)
Previous treatment with obinutuzumab or lenalidomide	X	X	X
Known CD20 negative status at last biopsy done. For patients of phase Ib and cohorts 1 and 2 of phase II, biopsy at relapse/progression is recommended but not mandatory. For patients of cohort 3 of phase II, an initial biopsy is mandatory.	X	X	X
Central nervous system or meningeal involvement by lymphoma	X	X	X
Contraindication to any drug contained in the study treatment regimen	X	X	X
Known HIV or HTLV-1 infection, positive serology to HB surface antigen [HBsAg] or total HB core antibody [anti-HB-c]) and Hepatitis C (Hepatitis C virus [HCV] antibody) Patients with positive HCV serology are eligible only if PCR is negative for known HCV RNA.	X	X	X
Any serious active disease or co-morbid medical condition (such as New York Heart Association Class II or IV cardiac disease, severe arrhythmia, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm or other according to investigator's decision)	X	X	X
Any of the following laboratory abnormalities unless secondary to underlying lymphoma: - neutrophils (ANC) < 1.5 x 10^9/L. - Platelets < 100 x 10^9/L unless due to lymphoma. - Serum SGOT/AST or SGPT/ALT 3.0 x ULN unless disease involvement. - Serum total bilirubin > 2.0 mg/dL (34 µmol/L), except if disease related or in case of Gilbert syndrome - Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) < 50 mL /min. Patients with calculated CrCl between 30 and 50ml/min can be included and lenalidomide dose will be adjusted as follows (10mg once daily)	X	X	X
Prior history of malignancies other than lymphoma unless the subject has been free of the disease for ≥ 5 years.	X	X	X
Any serious medical condition, laboratory abnormality (other than mentioned above), or psychiatric illness that would prevent the subject from signing the informed consent form	X	X	X
Pregnant or lactating females	X	X	X
Prior ≥ Grade 3 allergic reaction/hypersensitivity to thalidomide	X	X	X
Prior ≥ Grade 3 rash or any desquamating (blistering) rash while taking thalidomide.	X	X	X
Subjects with ≥ Grade 2 neuropathy	X	X	X
Use of any standard or experimental anti-cancer drug therapy within 28 days of the initiation (Day 1) of study drug therapy	X	X	X
Patients taking corticosteroids during 4 weeks before inclusion, unless administered at a dose equivalent to ≤ 10 mg/day prednisone (over these 4 weeks).	X	X	X
Prior history of Progressive Multifocal Leukoencephalopathy (PML)	X	X	X
LVEF ≤ 50%			X



GALEN phase II

New cohort !

Eudract n°: 2011-005150-62

A Phase Ib/II study of OBINUTUZUMAB (GA101) combined with LENALIDOMIDE for the treatment of follicular and relapsed/ refractory aggressive (DLBCL and MCL) B-cell Lymphoma

Cohort 1: R/R aNHL (DLBCL, MCL) —> Completed!

Cohort 2: R/R FL —> almost completed

Cohort 3: 1st line FL —> open now!

Sponsor

LYSARC — Centre Hospitalier Lyon Sud
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Primary objective

To assess the efficacy of the association of the RD of lenalidomide in combination with obinutuzumab, as measured by the overall response rate (ORR) by IWG criteria (Cheson 1999) at the end of 6 cycles in 2 different populations of patients with relapsed/refractory disease: follicular lymphoma and aggressive lymphoma [aNHL] (DLBCL and MCL)

V2 July 2015

Inclusion criteria

	Phase II cohort 1 (R /R aNHL)	Phase II cohort 2 (R/ R FL)	Phase II cohort 3 (1L FL)
Patients with either histologically documented CD20-positive Diffuse large-cell lymphoma (including transformations of low-grade lymphoma into DLBCL) or Mantle cell lymphoma (cohort 1) or follicular lymphoma, WHO grade 1, 2 or 3a	X	X	X
Relapsed/refractory NHL after =1 prior R-containing regimen with no curative option	X	X	
No prior systemic treatment for lymphoma			X
Must be in need of treatment as evidenced by at least one of the following criteria: • Bulky disease defined as: o A nodal or extranodal (except spleen) mass > 7 cm in its greater diameter or, o Involvement of at least 3 nodal or extranodal sites (each with a diameter greater than = 3 cm) • Presence of at least one of the following B symptoms: o Fever (> 38°C) of unclear etiology o Night sweats o Weight loss greater than 10% within the prior 6 months • Symptomatic splenomegaly • Compression syndrome • Any of the following cytopenias due to lymphoma: o Hemoglobin < 10g/dL (6.25mmol/L) o Platelets < 100 x 10^9/L o Absolute neutrophil count (ANC) < 1.5 10^9/L • Pleural or peritoneal serous effusion • LDH > ULN or β2 microglobulin > ULN			X
Aged 18 years or more	X	X	X
ECOG performance status 0, 1 or 2	X	X	X
At least one bi-dimensionally measurable nodal or tumor lesion defined by CT scan as: greatest transverse diameter > 1.5 cm and a short axis = 10mm	X	X	X
Signed inform consent	X	X	X
Life expectancy = 3 months	X	X	X
All subjects must be able to understand and fulfil the lenalidomide Pregnancy Prevention Plan requirements	X	X	X
FCBP must agree to use 2 reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 18 months after discontinuation of all study treatments	X	X	X

Inclusion process: by eCRF (CS-online)

Inclusion must be done by eCRF before patient treatment

Login to eCRF of GALEN2 study on the following website:
http://study.lysarc.info

Inclusion is automatic after baseline data entry into eCRF:

- P1: demography
- P15: CNS involvement
- P17: hematology
- P18: biochemistry
- P19: serology, pregnancy tests
- P20: clinical examination
- P22&23: inclusion & exclusion criteria

Inclusion fax to be sent to LYSARC: +33(0)4 72 66 38 57 **with anonymized anatomopathology report**

Pharmacovigilance: SAEs and AESI

SAE declaration within 24h:

- From ICF signature up to 28 days after the last study drug administration
- After that, only if SAE is related to study drug(s) or SPM.

AESI to be reported with specific form within 24H:

- tumor lysis syndrom
- tumor flare reactions
- infusions related reactions

Study SAE and AESI form sto be faxed to LYSARC pharmacovigilance department within 24 hours of the Investigator's knowledge

+33 (3) 59 11 01 86 / pharmacovigilance@lysarc.org

Prohibited concomitant treatment

* Systemic anticancer agents other than study drugs
* Radiotherapy
* Other investigational therapies or devices

Dose adaptations rules (lenalidomide)

Please refer to tables 1&2 of study protocol.

* If lenalidomide intake at the beginning of a cycle is delayed for toxicity reason, GA101 should be delayed in parallel.
* In case of disease progression ⇒ premature withdrawal
  - If toxicity occurs on or after D16: stop treatment until end of cycle and ↓ dose for next cycles
  - If toxicity occurs before D16: stop ttt until recovery and re-start at the same dose for the rest of the cycle and ↓ dose for next cycles

Resumption of treatment only at following conditions:

- neutrophils ≥ 1G/L
- platelets ≥ 50G/L
- lenalidomide related allergic reaction or hypersensitivity not requiring discontinuation has resolved to ≤ Grade 1
- any other lenalidomide-related AE not requiring discontinuation has resolved to ≤ Grade 2

If a new cycle is delayed > 28 days → notification to sponsor

Never increase the dose after dose reduction due to toxicity

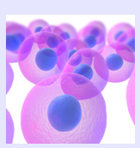
Never modify the dose during an ongoing cycle

Flow Chart

	Treatment															EOT
	Baseline	**Induction period** (visits +/- 1 day—28 days cycles)								**Maintenance period** (visits +/-3 days)						
Duration		Cycle 1		Cycles 2 + 3		Interme-diate assess-ment	Cycles 4 to 6		End of induction evaluation	Cycles 7 to 12 (cycles of **28** days)	Evalua-tion	Cycles 13 to 18 (cycles of **28** days)	Evalua-tion	Cycles 19 to 21 (cycles of **56** days)	Evalua-tion	Cycles 22 to 24 (cycles of **56** days)	End of Treatment evaluation
Date	Within 28 days from D1 C1	D1	D8 D15 D22	D1	D15	Between C3D21 and C3D28	D1	D15	Between C6D22 and C6D28	D1	28 days after C12D1 *(=C13D1)*	D1	28 days after C18D1 *(=C19D1)*	D1	28 days after C18D1 *(=C22D1)*	D1	28 days after C24D1 or PWD
GA101 infusion			X	X			X			X every 2 cycles (C7, C9, C11)		X every 2 cycles (C13, C15, C17)		X		X	
Lenalidomide administration		X (D1 to D21)		X (D2 to D22)			X (D2 to D22)			X (D2 to D22)		X (D2 to D22)					
ICF Inclusion/Exclusion criteria Serologies Dipstick urinalysis (blood, protein) Electrocardiogram	X																
Weight +/- BSA	X					X			X		X		X		X		X
Clinical and neurological examination	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X
B-symptoms	X					X			X		X		X		X		X
Vital signs (b)	X	X	X	X		X	X		X	X every 2 cycles (C7, C9, C11)	X	X every 2 cycles (C7, C9, C11)	X	X	X	X	X
ECOG performance status	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X
Pregnancy test (FCBP only)	X (c)	X	X	X (d)	X (d)		X (d)	X (d)	X	X (d)		X (d)	X (d)				X
Blood cell counts with differential	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X
Biochemical tests (m)	X	X		X		X	X		X	X every 2 cycles (C7, C9, C11)	X	X every 2 cycles (C7, C9, C11)	X	X	X	X	X
Optional blood sample for genomic	X																
Biological samples (optional)		X	X (f)	X (g)					X								
CT-scan	X					X			X		X		X		X		X
PET Scan	X					X			X		X (i)		X (i)		X (i)		X
Bone marrow biopsy	X					X (k)			X (k)		X (k)		X (k)		X (k)		X(k)
Evaluation of disease response						X			X		X		X		X		X
AEs	Continuous reporting of AEs																
SAEs	X (l)	Continuous reporting of SAES															

Anatomopathology

Biopsies central review is managed by LYSA-P study team.



Please remind to send anonymized copy of the most recent anatomopathology biopsy report at inclusion

galen2@lysarc.org / +33(4) 72 66 38 57

Biology & genomics

For BioGALEN study , please refer to BioGALEN booklet

For all patients, **if specific ICF for genetics + blood samples collection are signed ⇒ proceed to genomics sample at baseline**

At baseline: 1 Paxgene tube → CENTRE HOSPITALIER LYON-SUD Genomics

LA POSTE

Shipment kit provided by LYSARC

Contact details :
Thibault GELAS
Biological Project Officer- LYSARC
Tel : +33 (0)4 72 66 93 33
Email : thibault.gelas@lysarc.org

V2 July 2015

(b) Heart rate, blood pressure and body temperature
(c) 1st test 10 to 14 days before C1D1 and 2nd test <24h before 1st lenalidomide administration
(d) If regular cycles or no cycle: every 28 days; otherwise every 14 days
(f) On C1D8 at T0h (predose)
(g) On C2D1 before GA101 infusion
(i) only if clinically indicated
(k) only to confirm an initial documentation of CR / CRu in subjects with a positive bone marrow result at baseline or previous evaluation
(l) only if related to study procedures