MORNINGLYTE

A Phase III randomized, open-label, international, multicenter study evaluating the efficacy and safety of mosunetuzumab plus lenalidomide in comparison to anti-CD20 mAb plus chemotherapy in subjects with previously untreated high-tumor burden follicular lymphoma

A STUDY PERFORMED BY THE LYSA AND THE GLA, AND SPONSORED BY LYSARC

THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION
Centre Hospitalier Lyon Sud - Bâtiment 2D - CENS-ELI
69495 PIERRE BÉNITE Cedex – France

COORDINATING INVESTIGATORS **NATIONAL COORDINATORS:** **CO-COORDINATING INVESTIGATOR – FR** **COORDINATING INVESTIGATOR - BE** **COORDINATING INVESTIGATOR - PO** **COORDINATING INVESTIGATOR - DE/AT** **COORDINATING INVESTIGATOR - ES** **COORDINATING INVESTIGATOR – CH** **COORDINATING INVESTIGATOR - JP**	Pr Franck MORSCHHAUSER (LYSA) Pr Christian BUSKE (GLA) NN Pr Gilles CROCHET Pr Maria GOMES SILVA Pr Christian BUSKE Pr Armando LOPEZ Pr Francesco BERTONI NN
PROTOCOL WRITING COMMITTEE	Pr Franck MORSCHHAUSER Pr Christian BUSKE Pr Emmanuel BACHY Dr Benoît TESSOULIN Dr Sylvain CARRAS Dr Pascale CONY-MAKHOUL
BIOLOGIST COORDINATORS	Pr Marie-Hélène DELFAU-LARUE (LYSA) Pr Christiane POTT (GLA)
PATHOLOGIST COORDINATORS	Pr Camille LAURENT (LYSA) Pr Luc XERRI (LYSA) Pr Wolfgang KLAPPER (GLA)
IMAGING COORDINATOR	Dr Anne-Ségolène COTTEREAU
COORDINATION SITE	LYSARC

REGISTRATION (SEE SECTION 11-1)	https://lysarc.ennov.com/
SAE REPORTING (SEE SECTION 14)	Send to pharmacovigilance@lysarc.org or Fax to +33 (0)3 59 11 01 86

Version and date of Protocol: 0.2 – 28/07/2023

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CONFIDENTIALITY STATEMENT

1. SYNOPSIS

Sponsor	LYSARC
Study name	MO4482 - MorningLyte
Study title	Phase III randomized, open-label, international, multicenter study evaluating the efficacy and safety of mosunetuzumab plus lenalidomide in comparison to anti-CD20 mAb plus chemotherapy in subjects with previously untreated high-tumor burden follicular lymphoma
Identification # (EuCT Number)	2023-505436-35-00
Protocol version	0.2
Development phase	III
Study treatment	Investigational Medicinal Product (IMP): - Mosunetuzumab - Lenalidomide - Rituximab - Obinutuzumab - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) - Bendamustine - Tocilizumab
Coordinating investigators	Pr Franck MORSCHHAUSER (LYSA) Pr Christian BUSKE (GLA)
Countries and number of sites	France : 36 sites Belgium : 8 sites Portugal : 1 site Germany/Austria: 45 sites Spain:12 sites Switzerland: 12 sites Japan: 10 sites
Enrollment of patients	Randomization of 790 patients This study is being conducted by LYSA and GLA with Austria in collaboration with SAKK and GELTAMO. Japan will be involved, the sponsor will be Chugaï, in co-sponsorship with LYSARC.t To enhance enrollment, LYSARC will use a digital tool (Klineo).
Rationale	For patients with follicular lymphoma (FL), frontline treatment approaches typically entail a combination of an anti-CD20 monoclonal antibody (mAb) with alkylator-based chemotherapy, often followed by maintenance with an anti-CD20 mAb therapy for an additional two years. Despite encouraging response rates and remission durations, most patients will eventually relapse, and, therefore, there is a need for novel therapies to increase the anti-tumor activity and to prolong remission in patients with previously untreated FL. Also, these chemotherapy-containing regimen come with substantial short- and long-term toxicities, stressing the need for new therapies with a potentially improved safety profile. FL has been shown to be one of the most responsive lymphoid malignancies to immunotherapy. Synergistic activity between lenalidomide and anti-CD20 antibodies is well established[1,2]. Efficacy and safety of chemotherapy-free immunomodulatory

regimens combining lenalidomide plus anti-CD20 antibodies has been reported first in relapsed and/or refractory (R/R) FL[3,4] and more recently confirmed in the first line setting.

In the SAKK 35/10 Phase II study, 154 patients with untreated FL in need of systemic therapy were randomized either to rituximab monotherapy (8 infusions of 375 mg/m^2 at Day 1 of Weeks 1, 2, 3, 4, and repeated on Day 1 of Weeks 12, 13, 14 and 15) or to rituximab (given at the same schedule) in combination with lenalidomide (lenalidomide given orally, 15 mg daily, starting 14 days before the first rituximab administration and continuously until 14 days after the last). Complete Response (CR)/unconfirmed CR (CRu) rate assessed at Week 23 were significantly higher (predefined 1-sided type 1 error of 0.10) in patients treated with rituximab plus lenalidomide (R2) in the intent to treat population (CR/CRu rate, 36% vs. 25%, respectively; p=0.056) and the per-protocol population (CR/CRu rate, 40% vs. 27%, respectively; p=0.055[5].

The Phase 2 GALEN study enrolled 100 patients with previously untreated advanced FL; Patients received oral lenalidomide (20 mg) plus IV infused obinutuzumab as induction therapy (1000 mg; six 28-day cycles), 1-year maintenance with lenalidomide (10 mg; twelve 28-day cycles; Days 2-22) plus obinutuzumab (1000 mg; alternate cycles), and 1-year maintenance with obinutuzumab (1000 mg; six 56-day cycles;). The combination of obinutuzumab and lenalidomide revealed 94% ORR, 80% of CR (Lugano 2014). At the median follow-up of 3.7 years, 3-year PFS and overall survival were 82% and 94% respectively. The most common adverse event was neutropenia (48% any grade; 47% grade ≥3) with 2% of febrile neutropenia[6].

Similarly, the phase III RELEVANCE study showed that a chemo-free immunomodulatory regimen combining lenalidomide plus rituximab (R2) provided similar efficacy to rituximab plus chemotherapy (R-chemo) in 1030 patients with advanced-stage, previously untreated, FL. At a median follow-up of 72 months, 6-year PFS was 60% and 59% for R2 and R-chemo, respectively (HR=1.03 [95% CI, 0.84-1.27]). Six-year OS was estimated to be 89% in both groups. Median PFS and OS were not reached in either group. Overall response after progression was 61% and 59%; 5-year estimated survival rate after progression was 69% and 74% in the R2 and R-chemo groups, respectively. The safety profile of R2 is distinct from that of R-chemo and manageable. The most common Grade 3 or 4 adverse events were neutropenia (50% for rituximab chemotherapy vs. 32% for rituximab-lenalidomide), febrile neutropenia (7% vs. 2%), and leukopenia (6% vs. 2%), and were less common with rituximab plus lenalidomide. Hence, R2 provides an acceptable chemo-free alternative in previously untreated patients with FL[7,8].

Mosunetuzumab is a T-cell recruiting bispecific antibody targeting CD20-expressing B-cells. As a single agent, mosunetuzumab provides a high CR Rate (CRR) of 60% and median progression-free survival (mPFS) of 17.9 months in patients with relapsed/refractory (R/R) FL who have received at least two prior systemic therapies[9]. Mosunetuzumab received conditional marketing authorization on 3 June 2022 in the EU as monotherapy for the treatment of adult patients with FL who have received at least two prior systemic therapies. The available data from mosunetuzumab in combination with lenalidomide in the R/R FL cohort in Study CO41942 demonstrate an manageable safety profile and encouraging efficacy with Overall Response Rate (ORR) of 92% and CRR of 77%[10].

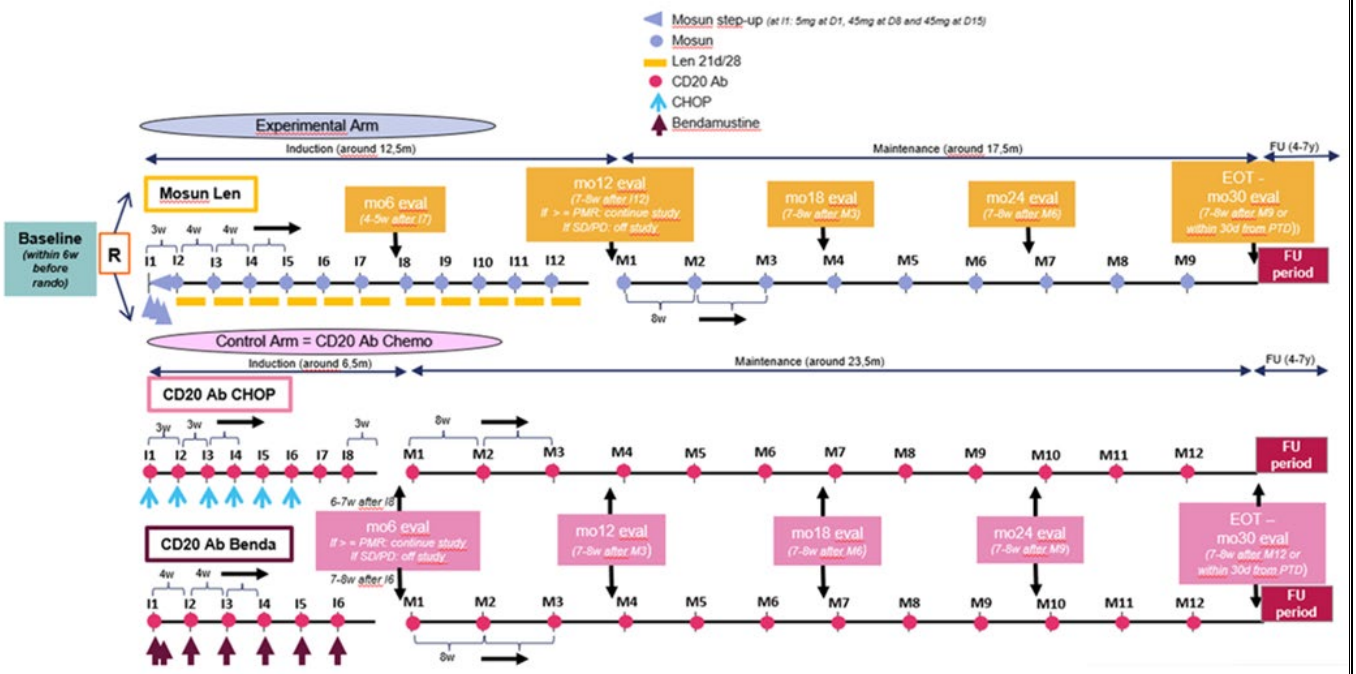
Mosunetuzumab in combination with lenalidomide is predicted to be more active when administered in chemotherapy naïve patients due to the deleterious effects of commonly used agents on T cells[11]. This strategy in front-line FL would allow avoidance of the intrinsic detrimental consequences of aging on the T-cell pool in older patients with subsequent relapsed FL.

SC mosunetuzumab monotherapy or combined with lenalidomide was currently evaluated in previously untreated patients FL patients in the phase 2 BrUOG-401/ML43251 trial (NCT04792502; Olszewski ASH 2022 #2890) and in the CO41942 study (NCT04246086). Based on available data from study CO41942 R/R FL cohort, there is no evidence to

	suggest that lenalidomide modifies mosunetuzumab target exposure. Preliminary results indicated that IV mosunetuzumab PK is similar when administered in combination with lenalidomide as compared to monotherapy. Additionally, based on its mechanism of action, mosunetuzumab in combination with lenalidomide would be expected to have fewer late effects than most first-line therapies for FL. Taken together, there is a strong rationale to evaluate a novel, chemotherapy-free regimen in a randomized study to offer improved treatment outcomes in patients with newly diagnosed FL.
Study objectives and endpoints	**Primary objective**: To demonstrate the superiority of mosunetuzumab + lenalidomide combination *versus* CD20 Ab plus chemotherapy with regards to Progression Free Survival (PFS) assessed by Independent Review Committee (IRC), blind of treatment arms in previously untreated patients with high-tumor burden (International Prognostic Index (FLIPI) 2-5) Follicular Lymphoma. PFS is defined as the time from randomization to the date of first documented disease progression/relapse or death from any cause, according to the Lugano 2014 criteria. **Secondary objectives**: o To compare the efficacy between arms using the following secondary efficacy endpoints: - Overall Response (OR) and CMR rate at 6 months and 12 months by Lugano 2014 and by Deauville criteria, assessed by investigator and IRC - Overall Response (OR) and CMR rate at EOT (i.e., end of maintenance or at permanent treatment discontinuation), by Lugano 2014 and by Deauville criteria, assessed by investigator and IRC - Best Overall Response (CMR or PMR) rate by Lugano 2014 and by Deauville criteria, assessed by investigator and IRC - POD24, defined as rate of progression of disease (POD) within 2 years of first line therapy - Progression Free Survival assessed by investigator - Event Free Survival (EFS) by Lugano 2014, defined as time between randomization and date of first documented disease progression/relapse, initiation of a new anti-lymphoma treatment or death from any cause - Time to Next Anti-Lymphoma Treatment (TTNLT), defined as time between randomization and date of first documented administration of any new anti-lymphoma treatment - Duration of response, defined for patients with a best overall response of CMR or PMR determined by Lugano 2014, defined as the time of 1st occurrence of CMR or PMR to disease progression/relapse or death from any cause - Duration of complete response, defined for patients with a best overall response of CMR determined by Lugano 2014, define as the time of first occurrence of CMR to disease progression/relapse or death from any cause - Overall Survival (OS) defined as time from randomization to death from any cause o To describe mosunetuzumab PK in combination with Len in a subset of mosunetuzumab-treated patients (n~125) o To describe anti-drug antibodies (ADA) in a subset of mosunetuzumab-treated patients (n~125) o To evaluate PROMs via a digital tool o To compare health related quality of life: - Time to deterioration in physical functioning, as measured by the EORTC QLQ-C30

	- Time to deterioration in lymphoma symptoms, as measured by FACTLym o To compare the safety between both arms - Incidence and severity of AEs including SAEs and AESIs - Tolerability, as assessed by incidence of dose interruptions, delays, dose reductions, and study treatment discontinuation - Incidence of Secondary Primary Malignancies (SPM) **Exploratory objectives**: o To compare efficacy in subgroups such as, but not limited to, age ≤60 vs >60, FLIPI 2 vs 3-5, FLIPI2, longest diameter of the longest node ≤6 vs >6cm, sex, disease stage I-II vs III-IV, control arm received o To describe PFS2 assessed locally by investigator, defined as time from 1st progression/relapse to the date of second documented disease progression/relapse or death from any cause, according to the Lugano 2014 criteria o To describe subsequent line treatments o To evaluate histological transformation rate assessed by central review at first progression o To describe the OS since POD24, defined as time from 1st progression for patients who progressed within 2 years of first line therapy and time from 2 years after the initiation of the first line therapy for other patients to death from any cause o Biomarkers: ▪ Monitor kinetics of molecular residual disease (MRD), including rate and duration of MRD negativity ▪ Investigation of biological markers with predictive/ prognostic value (i.e., analysis of tumor microenvironment, mutation profile) ▪ Pharmacodynamic (PD) biomarkers to investigate activity of Mosun + Lenalidomide combination in untreated FL o PET metrics (TMTV, dissemination features/radiomics/machine learning) o Change from baseline in health status, as measured by the EQ-5D-5L
Study design	This study is a phase III, randomized, open-label, international, multicenter, interventional trial, designed to compare the efficacy and safety of mosunetuzumab in combination with lenalidomide versus anti-CD20 mAb + chemotherapy in patients with previously untreated high-tumor burden follicular lymphoma. This study is composed of a screening period (up to 6 weeks before randomization, i.e., 42 days), a treatment period (30 months i.e., 125w), a safety follow-up period (3 months), and a survival follow-up period (up to 7 years after the last randomized patient). The enrollment will last approximately 34 months. The total duration of the study will be therefore approximately 10 years. Once a patient provides written consent, they may enter the screening phase, which duration is up to 6 weeks prior to randomization and initiation of treatment. Upon completion of the required assessments in the screening phase, and fulfillment of the eligibility criteria, patients will be randomized. Investigators will be requested to indicate their treatment choice among permitted immuno-chemotherapy regimens just before randomization.

	The treatment period for each patient starts with the first intake. The patients will receive protocol-specified treatments until: - inability to achieve a response at the end of induction phase (at mo12 evaluation for experimental arm, and at mo6 evaluation for control arms), - relapse or progression of the disease, - withdrawal of consent, - or unacceptable toxicity In the experimental arm, patients will be treated for 1 cycle of 3 weeks and then 11 cycles of 4 weeks (47 weeks, around 11 months) during the induction phase, and for a maximum of 9 additional cycles of 8 weeks during the maintenance phase (72 weeks, around 17 months), up to around 125 weeks (30 months). Patients should start the maintenance phase 7 to 8 weeks after the start of last induction cycle (I12). In the control arm, patients will be treated for 8 or 6 cycles of 3 or 4 weeks for CD20 Ab + CHOP or Benda, respectively, depending on the assigned arm (24 weeks, around 5 months) during the induction phase, and for a maximum of 12 additional cycles of 8 weeks during the maintenance phase (96 weeks, around 22 months), up to around 125 weeks (30 months). Patients should start the maintenance phase, 6 to 7 or 7 to 8 weeks after the start of last induction cycle (I8 or I6). The option to cross-over from the control arm to the experimental arm is not allowed. All randomized patients will be followed for progression-free survival and overall survival using the same schedule. Patients will be followed up from End of treatment evaluation every 3 months during the first two years, then every 6 months during the next 3 years, then yearly until the end of study. The end of study will occur when the last randomized patient has been followed-up for survival for at least 7 years after his end of treatment evaluation, has died, has withdrawn his consent, or is lost to follow up (whatever event occurs first).
Study design: The following flow chart presents the study treatment duration for the experimental and the control arms, which are balanced.	



Mosun=Mosunetuzumab; Len=Lenalidomide; CD20 Ab=anti-CD20 antibody (either branded rituximab or branded Obinutuzumab); CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; Benda=bendamustine;
R=randomization (1:1 ratio; Mosun-Len *vs* Investigator's choice); w=weeks; mo=months; I=induction; M=maintenance; mo6 eval=evaluation after 6months of treatment; mo12/18/24 eval=evaluation after 12/18/24months of treatment; EOT=end of treatment evaluation; FU=Follow-up

Experimental arm:

***Mosun-Len**

The experimental arm will include mosunetuzumab administered subcutaneously (SC) using a step-up dosing method in combination with lenalidomide given orally (PO) and divided into two parts as follows:

Induction

- Induction 1, i.e., I1 will be a 3-week cycle of mosunetuzumab alone (step up dosing: 5 mg on Day 1; 45 mg on Day 8; and 45 mg on Day 15 via SC injection).
- I2 to I12 will be 4-week cycles of mosunetuzumab (45 mg on Day 1 via SC injection) in combination with lenalidomide (20 mg PO daily on D1-21).

Patients must achieve the threshold clinical activity of at least partial metabolic response (PMR) at mo6 evaluation (PET assessment) to continue the induction treatment (i.e., I8 to I12).

Maintenance

Patients exhibiting a PMR or CMR at mo12 evaluation, i.e., after I12 (PET assessment) will then receive mosunetuzumab maintenance every 8 weeks for a total of 9 cycles (72 weeks; Maintenance 1 to 9, i.e., M1 to M9).

If one cycle of maintenance is delayed for 2 weeks (i.e., cycle lasting more than 10 weeks) or more, then the patient must have a new step-up dosage with mosunetuzumab 5mg SC at Day 1 and 45mg SC at Day 8 of the involved maintenance cycle.

In this arm, patients who do not achieve the threshold clinical activity of at least PMR (compared to baseline) at mo12 evaluation (PET assessment) will be withdrawn from the study treatment and followed for PFS and survival. Patients who withdraw from the study treatment for toxicity or any other reason than not achieving a PMR will be followed for PFS and survival.

Control arms:

CD20 antibodies can be either branded Rituximab or branded Obinutuzumab (GA101), depending on investigators' choice on a patient's basis before randomization. Biosimilar products are not permitted in the study.

***G-CHOP**
Induction

I1 will be a 3-week cycle of:

- Branded Obinutuzumab administered intravenously at Day 1, Day 8 and Day 15,
- CHOP administered intravenously at Day 1 (prednisone until Day 5) (doses may be adjusted according to the site's practice)

I2 to I6 will be a 3-week cycle of:

- Branded Obinutuzumab administered intravenously at each Day 1,
- CHOP administered intravenously at each Day 1 (prednisone until Day 5) at standard dose (doses may be adjusted according to the site's practice)

I7 to I8 will be a 3-week cycle of:

- Branded Obinutuzumab administered alone at I7 and I8

Maintenance

· Patients exhibiting a PMR or CMR at mo6 evaluation i.e., after I8 will then receive branded Obinutuzumab every 8 weeks for a total of 12 cycles, i.e., 96 weeks, from M1 to M12.
M1 must be performed 7 +/-1w after I8.

***R-CHOP**
Induction

· I1 will be a 3-week cycle of:

- Branded Rituximab administered intravenously at Day 1
- CHOP administered intravenously at Day 1 (prednisone until Day 5) at standard dose (doses may be adjusted according to the site's practice)

· I2 to I6 will be a 3-week cycle of:

- Branded Rituximab administered subcutaneously in the absence of grade 3 or 4 infusion-related reaction (IRR) during I1; otherwise an additional branded IV Rituximab should be performed. In the absence of grade 3 or 4 IRR, branded SC Rituximab should be used for subsequent injections.
- CHOP administered intravenously at each Day 1 at standard dose (doses may be adjusted according to the site's practice)

· I7 to I8 will be a 3-week cycle of:

- Branded Rituximab administered alone at I7 and I8

Maintenance

· Patients exhibiting a PMR or CMR at mo6 evaluation after I8 will then receive Branded Rituximab SC every 8 weeks for a total of 12 cycles, i.e., 96 weeks, from M1 to M12.
M1 must be performed 7 +/-1w after I8.

***G-Benda**
Induction

· I1 will be a 4-week cycle of:

- Branded Obinutuzumab administered intravenously at Day 1, Day 8 and Day 15,
- Bendamustine administered intravenously at each Day 1 and Day 2 at standard dose (doses may be adjusted if medically indicated, according to the site's practice).

· I2 to I6 will be a 4-week cycle of:

- Branded Obinutuzumab administered intravenously at each Day 1,

- Bendamustine administered intravenously at each Day 1 and Day 2 at standard dose (doses may be adjusted according to the site's practice).

Maintenance

· Patients exhibiting a PMR or CMR at mo6 evaluation after I6 will then receive Obinutuzumab every 8 weeks for a total of 12 cycles, i.e., 96 weeks, from M1 to M12.
M1 must be performed 8 +/-1w after I6.

***R-Benda**
Induction

· I1 will be a 4-week cycle of:

- Branded Rituximab administered intravenously at Day 1,
- Bendamustine administered intravenously at each Day 1 and Day 2 at standard dose (doses may be adjusted if medically indicated, according to the site's practice).

· I2 to I6 will be a 6-week cycle of:

- Branded Rituximab administered subcutaneously in the absence of grade 3 or 4 infusion-related reaction (IRR) during I1; otherwise an additional branded IV Rituximab should be performed. In the absence of grade 3 or 4 IRR, branded SC Rituximab should be used for subsequent injections.
- Bendamustine administered intravenously at each Day 1 and Day 2 at standard dose (doses may be adjusted according to the site's practice).

Maintenance

· Patients exhibiting a PMR or CMR at mo6 evaluation after I6 will then receive branded Rituximab SC every 8 weeks for a total of 12 cycles, i.e., 96 weeks, from M1 to M12.
M1 must be performed 8 +/-1w after I6.

In these 4 arms, patients who do not achieve the threshold clinical activity of at least PMR (PET assessment) at mo6 evaluation and at mo12 evaluation (compared to baseline) will be withdrawn from the study treatment and followed for PFS and survival. Patients who withdraw from the study treatment for toxicity or any other reason than not achieving a PMR will be followed for PFS and survival.

Treatments

Investigational Medicinal Product (IMP):

***Experimental arm**:

Mosun-Len	Route	Dose	Days
Mosunetuzumab	SC	5 mg (step-up dosing) 45 mg 45 mg 45 mg	Day 1 of I1 Day 8 and Day 15 of I1, Day 1 from I2 to I12, Day 1 from M1 to M9

Lenalidomide	PO	20 mg/day	Day 1 to Day 21 from I2 to I12

In case of treatment interruption lasting beyond 4 weeks, please contact the Sponsor.

***Control arm**: Patients randomized to the control arm will receive ONE of the following, as per investigator choice:

-CD20 Ab-CHOP:

CD20 Ab-CHOP	Route	Dose	Days
CD20 Ab: - either Branded Obinutuzumab	IV	1000 mg*	Day 1, Day 8, Day 15 of I1 Day 1 from I2 to I8 Day 1 from M1 to M12
- or Branded Rituximab	IV SC	375mg/m² 1400 mg allowed from I2	Day 1 of I1 Day 1 from I2 to I8 Day 1 from M1 to M12
Cyclophosphamide#	IV	750 mg/m²	Day 1 from I1 to I6
Doxorubicin#	IV	50 mg/m²	Day 1 from I1 to I6
Vincristine	IV	1.4 mg/m² (cap cf. below)$	Day 1 from I1 to I6
Prednisone	PO	100 mg/day	Day 1 to Day 5 from I1 to I6

IV=intravenous; PO=orally; SC=subcutaneous
Administration according to local institutional guidelines.

Refer to the specific package inserts for preparation, administration, and storage guidelines:
*For Obinutuzumab, rituximab and prednisone, no dosage adjustments should be performed.
#For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (10%) that lead to changes in BSA
$The vincristine dose will be capped at 2 mg. At the discretion of the investigator, for patients >= 70 years old, the vincristine dose will be capped at 1 mg.

-CD20 Ab-Bendamustine:

CD20 Ab-Bendamustine	Route	Dose	Days
CD20 Ab: - either branded Obinutuzumab	IV	1000 mg*	Day 1, Day 8, Day 15 of I1 Day 1 from I2 to I6 Day 1 from M1 to M12
- or branded Rituximab	IV SC	375mg/m² 1400 mg allowed from I2	Day 1 of I1 Day 1 from I2 to I6 Day 1 from M1 to M12
Bendamustine#	IV	90 mg/m²	Day 1 and D2 from I1 to I6

IV=intravenous; PO=orally; SC=subcutaneous

Administration according to local institutional guidelines.

Refer to the specific package inserts for preparation, administration, and storage guidelines:
*For CD20 Ab, no dosage adjustments should be performed.
#For chemotherapy, dosages may be adjusted in case of large changes in body weight compared to baseline (10%) that lead to changes in BSA.

In case of treatment interruption lasting beyond 4 weeks, please contact the Sponsor.

***Tocilizumab**:
Tocilizumab, IV route. For patients requiring treatment of CRS, tocilizumab should be administered at a dose of 8 mg/kg IV (not exceeding 800 mg per infusion). If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, a second dose may be administered at least 8 hours apart (maximum 2 doses per CRS event). Within each time-period of 6 weeks of mosunetuzumab treatment, the total number of tocilizumab doses should not exceed 3 doses.

Relevant prophylactic measures:
Anti-infectious prophylaxis
Anti-infective prophylaxis for viral, fungal, bacterial or Pneumocystitis infections is permitted should be instituted per institutional practice or investigator preference based on individual patient risk factors. Patients in countries where prophylactic anti-viral medications for hepatitis B reactivation are the standard of care may be treated prophylactically. All anti-infective prophylaxis used should be recorded appropriately in the eCRF.
G-CSF
Granulocyte colony stimulating factors (G-CSF) are recommended in case of in Grade 4 neutropenia (< 0.5 x 10^9/L) if clinically appropriate according to local practice.
Other prophylaxis measures
Platelet and red blood cell transfusions are permitted, as necessary.

Mosunetuzumab will be administered in a setting with immediate access to trained critical care personnel and facilities equipped to respond to and manage medical emergencies.
Patients who receive the **Mosunetuzumab-Lenalidomide** combination do not require hospitalization. Although hospitalization is not mandated, the investigator should actively assess the need for hospitalization, and patients should be hospitalized whenever clinically indicated. Neurology consultation services should be readily available to address any neurologic adverse events that may arise as a result of mosunetuzumab treatment, and nephrology consultation with acute dialysis capabilities should be readily available to address any renal toxicity that might accompany Tumor Lysis Syndrome (TLS).

Premedication with acetaminophen/paracetamol (650-1000 mg orally), diphenhydramine (50 to 100 mg IV or orally) and corticosteroids, at least 30 minutes before starting each **CD20 Ab or Mosunetuzumab injection**, may attenuate infusion reactions.

Deep vein thrombosis (DVT) prophylaxis for patients treated with lenalidomide:

	DVT prophylaxis is mandatory for experimental arm and will be performed according to local practices (aspirin, low weight molecular heparin or direct oral anticoagulants). **Premedication and Cytokine Release Syndrome (CRS) prophylaxis:** Premedication with antihistamines, and antipyretics is mandatory for each dose. For each dose of mosunetuzumab in Cycle 1, corticosteroids are mandatory to prevent/reduce severity of symptoms from potential CRS. For administration of mosunetuzumab beyond the second dose (first full dose), CRS prophylaxis with corticosteroids is optional, except if CRS occurred with prior dose, then it is fully recommended. Corticosteroid prophylaxis consisting of 20 mg dexamethasone (preferred) or 80 mg methylprednisolone should be administered orally or intravenously prior to each mosunetuzumab dose during Cycle 1. The administration of corticosteroid prophylaxis may be optional for Cycle 2 and beyond at the investigator's discretion. However, if the patient experiences CRS with prior administration of mosunetuzumab, premedication with corticosteroids must be administered for subsequent doses until no additional CRS events are observed. The use of an alternative corticosteroid compound (e.g., due to unavailability of dexamethasone or methylprednisolone), or alternative dose of dexamethasone, should be confirmed with the Sponsor at the time of enrollment. **Prohibited agents:** The following concomitant medications are specifically excluded during the course of the study: 1. Anti-cancer therapies other than the study drugs, including chemotherapy, concomitant radiotherapy or other investigational therapy, including targeted small molecule agents. 2. Live, attenuated vaccines~~, except for acute pandemic situation such COVID19.~~ 3. Other investigational therapies or devices. **Concomitant treatments/procedures**: Concomitant treatment/procedures have to be recorded into the eCRF from 8 days prior to study treatment, at any time during the study and up to 30 days after the last study drug administration (or after, if treatment taken for related SAE/AE management).
Inclusion criteria	Patient must meet all of the following criteria to be enrolled in the study: 1. Patient with histologically proven previously untreated CD20+ follicular lymphoma grade 1, 2, or 3a (including patient watched during up to 10 years after initial diagnosis) as assessed by the investigators according to the WHO 2016 classification[12], or classical follicular lymphoma according to the WHO 2022 classification[13]. Diagnostic tissue must be available for central pathology review, exploratory endpoints and secondary data use. 2. FLIPI 2-5. 3. All Ann Arbor stages (including stage I if FLIPI ≥ 2). 4. Must need treatment as evidenced by at least one of the following criteria: • Bulky disease defined as: • a nodal or extranodal mass/lesion > 7 cm in its largest diameter or, • 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: • fever (> 38°C) of unclear etiology

- night sweats
- weight loss greater than 10% within the prior 6 months

- Symptomatic splenomegaly
- Any compressive syndrome (for example, but not restricted to- ureteral, orbital, gastrointestinal)
- Any one of the following cytopenias due to lymphoma:
  - hemoglobin < 10g/dL (6.25 mmol/L)
  - platelets <100 x 10^9/L, or
  - absolute neutrophil count (ANC) < 1.5 x 10^9/L
- Pleural or peritoneal serous effusion (irrespective of cell content)
- β2microglobulin > ULN or LDH > ULN

5. Bi-dimensionally measurable disease with at least one FDG-avid lesion > 1.5 cm.
6. Patient who understood and voluntarily signed and dated an informed consent prior to any study-specific assessments/procedures.
7. Must be ≥ 18 years at the time of signing the informed consent form (ICF).
8. ECOG performance status 0 to 2.
9. Estimated minimum life expectancy of 3 months.
10. Adequate hematological function within 28 days prior to signing informed consent, including:
    - Absolute neutrophil count (ANC) ≥ 1 x 10^9/L
    - Platelet count ≥ 75 x 10^9/L, or ≥ 30 x 10^9/L if bone marrow infiltration or splenomegaly
    - Hemoglobin ≥ 8.0 g/dL (5 mmol/L) unless related to bone marrow infiltration or splenomegaly. Transfusion is allowed before starting treatment (no required window)
11. Normal laboratory values:
    - Measured or estimated creatinine clearance ≥ 40mL/min calculated by institutional standard method (MDRD or Cockcroft-Gault)
    - AST or ALT ≤ 2.5 x the upper limit of normal (ULN), except in patients with documented liver or pancreatic involvement by lymphoma
    - Serum total bilirubin ≤ 1.5 x ULN (or ≤ 3 x ULN for patients with Gilbert syndrome), except in patients with documented liver or pancreatic involvement by lymphoma
12. LVEF within normal range.
13. Patients should be able to receive adequate prophylaxis and/or therapy for thromboembolic events (aspirin,low molecular weight heparin or direct oral anticoagulants).
    Patients with a curative anticoagulation therapy can be enrolled. A patient with deep vein thrombosis due to compressive syndrome is eligible if a curative anticoagulation therapy has been started at least 1 week before initiating study treatment: low molecular weight heparin possible at treatment onset, then direct oral anticoagulants according to local practices.
14. Must be able to adhere to the study visit schedule and other protocol requirements.
15. Negative SARS-CoV-2 test within 7 days prior to enrolment. Rapid antigen test is also acceptable.
16. Negative HIV test at screening, with the following exception:

	Individuals with a positive HIV test at screening are eligible provided they are stable on antiretroviral therapy for at least 4 weeks, have a CD4 count ≥ 200/uL, have an undetectable viral load, and have not had a history of opportunistic infection attributable to AIDS within the last 12 months. 17. For women of childbearing potential (WOCBP) (refer to section 14.1.10.1.1**):** must have a negative result for pregnancy test (highly sensitive serum), prior to study treatment start, at screening and within 7 days before first dose, and agree to abstain from breastfeeding during study participation, and for at least 28 days after the final dose of lenalidomide (if applicable), 3 months after the final dose of mosunetuzumab and tocilizumab (if applicable), 6 months after the final dose of chemotherapies (if applicable), 12 months after the final dose of rituximab (if applicable), and 18 months after the final dose of obinutuzumab (if applicable). 16. For men (refer to section 14.1.10.2**)**: Agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below: with a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period (including periods of treatment interruption), and for at least 28 days after the final dose of lenalidomide (if applicable), 3 months after the final dose of ~~Mosunetuzumab and~~ tocilizumab (if applicable), 6 months after the final dose of chemotherapies (if applicable), 12 months after the final dose of rituximab (if applicable), and 18 months after the final dose of obinutuzumab (if applicable). 17. Patient covered by any social security system (France). 18. Patient who understands and speaks one of the country official languages, unless local regulation authorizes independent translators.
Exclusion criteria	Patient who meets any of the following criteria should be excluded from enrollment in the study: 1. Grade 3b follicular lymphoma according to the WHO 2016 classification[12], or follicular large B-cell lymphoma according to the WHO 2022 classification[13] 2. Suspicion or clinical evidence of transformed lymphoma at enrollment by investigator assessment (e.g., very high SUV in at least one lesion that was not biopsied, and discordant with SUV of biopsied lesion, LDH > 2.5 ULN in a context of rapidly progressive disease, etc. *Please contact the Sponsor to discuss any possible inclusion in borderline cases or any doubt*) 3. Prior localized radiotherapy for the FL 4. Prior history of another lymphoma 5. Use of any standard or experimental anti-cancer drug therapy within 42 days of the start (Day 1) of study treatment. 6. Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) or corticosteroid > 1mg/kg/day prednisone or equivalent within 10 days prior to first dose of study treatment. Systemic corticosteroid treatment < 20 mg/day of prednisone or equivalent, inhaled corticosteroids and mineralocorticoids for management of orthostatic hypotension is permitted. A single dose of dexamethasone for nausea or B symptoms is permitted. 7. Received a live, attenuated vaccine within 4 weeks before the first dose of study treatment, or in whom it is anticipated that such a live attenuated vaccine will be required during the study period or within 5 months after the final dose of study treatment.

	8. Major surgery (excluding surgical documentation of FL) within 28 days prior to signing informed consent. 9. Seropositive for or active viral infection with hepatitis B virus (HBV): - HBsAg positive - HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA *(Patients who are HBsAg negative, anti-HBs positive and/or anti-HBc positive but viral DNA negative are eligible; Patients who are seropositive due to a history of hepatitis B vaccine (anti-HBs positive) are eligible).* 10. Known seropositive for, or active infection hepatitis C virus (HCV) (*Patients who are positive for HCV antibody with a negative viral RNA are eligible).* 11. Known or suspected hypersensitivity to biopharmaceuticals produced in CHO cells or any component of the mosunetuzumab, CD20 Ab, tocilizumab, lenalidomide formulation, including mannitol; or to any of the excipients. 12. History of solid organ transplantation or allogeneic stem cell transplant (SCT). 13. Active autoimmune disease requiring treatment. 15. History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis ▪ Participants with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible. ▪ Participants with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study. ▪ Participants with a history of disease-related immune thrombocytopenic purpura or autoimmune hemolytic anemia may be eligible. ▪ Participants with a remote history of, or well-controlled autoimmune disease, with a treatment-free interval from immunosuppressive therapy for 12 months may be eligible after review and discussion with the Primary investigator. 16. Participants with any active infection such as known active bacterial, viral (including SARS-CoV-2), fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds), known or suspected chronic active Epstein-Barr virus (EBV) infection, are excluded. 17. Evidence of any significant, concomitant disease that could affect compliance with the protocol or interpretation of results, including, but not limited to: ▪ significant cardiovascular disease [e.g., Objective Class C or D heart diseases (cf. Classes of Heart Failure | American Heart Association), myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) ▪ significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm) ▪ clinically significant history of liver disease, including viral or other hepatitis, or cirrhosis ▪ current or past history of central nervous system (CNS) disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease. Participants with a history of stroke who have not experienced a stroke or transient ischemic attack in the past 1 year and have no residual neurologic deficits as judged by the investigator are allowed. Participants with a history of epilepsy who have had no seizures in the past 2 years with or without anti-epileptic medications can be eligible.

	18. History of confirmed progressive multifocal leukoencephalopathy (PML). 19. Known or suspected history of hemophagocytic lymphohistiocytosis. 20. History of erythema multiforme, Grade ≥3 rash, or blistering rash following prior treatment with immunomodulatory derivatives. 21. History of interstitial lung disease (ILD), drug-induced pneumonitis, and autoimmune pneumonitis. 22. Active malignancy other than the one treated in this research. Prior history of malignancies unless the patient has been free of the disease for ≥ 3 years. However, patients with the following history/concurrent conditions are eligible: - Localized non-melanoma skin cancer. - Carcinoma in situ of the cervix. - Carcinoma in situ of the breast. - Incidental histologic finding of prostate cancer (T1a or T1b as per Tumor Node Metastasis [TNM] staging system) or prostate cancer that has been treated with curative intent. 23. Presence or history of CNS or meningeal involvement by lymphoma. 24. Pregnant, planning to become pregnant or lactating WOCBP. 25. Any significant medical conditions, including the presence of laboratory abnormality or psychiatric illness which places the patient at unacceptable risk if he/she were to participate in the study, and likely to interfere with participation in this clinical study (according to the investigator's decision) or which confounds the ability to interpret data from the study. 26. Person deprived of his/her liberty by a judicial or administrative decision 27. Person hospitalized without consent 28. Adult person under legal protection *NB: for 26., if there is an individual benefit for such patients, an Ethics Committee will have to be informed case by case.*
Assessment schedule	**At baseline (within 6 weeks before randomization, except for biopsy within 6 or 12 months and pregnancy test within 7 days):** ✔ **SCREENING assessments:** ✔ Patient characteristics (Age, gender, weight, height, BSA) ✔ Clinical examination (including tumor assessment) ✔ Relevant medical history ✔ Registration of concomitant medication taken within 8 days before treatment start ✔ History of the NHL ✔ Staging: Ann Arbor stage and FLIPI1 and FLIPI2 scores ✔ Vital signs (heart rate, blood pressure, body temperature) ✔ B symptoms ✔ ECOG Performance Status ✔ Complete blood cell count: hemoglobin, platelets, white blood cell (WBC) count with monocytes, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), abnormal lymphoma cells ✔ Biochemistry: potassium, magnesium, creatinine, measured creatinine clearance according to MDRD/Cockcroft-Gault formula, total and direct bilirubin, ALT, AST, alkaline phosphatases ✔ Lactate Dehydrogenase (LDH) ✔ Beta-2-microglobulin ✔ Thyroid Stimulating Hormone (TSH) ✔ Serum pregnancy test (within 7 days before initiation of study treatment) for WOCBP

- ✔ Serum electrophoresis
- ✔ HIV, HBV (Ag HBs, Ab anti-HBs, Ab anti-HBc and viral DNA) and HCV (with viral RNA) serologies
- ✔ SARS-CoV-2 testing by antigen or PCR is required within 7 days prior to randomization.
- ✔ Epstein-Barr (EBV) and Cytomegalovirus (CMV) by PCRECG
- ✔ Transthoracic echocardiography to determine left ventricular ejection fraction (LVEF); isotopic method (MUGA scan) can only be used for patients whose LVEF cannot be assessed by echocardiography
- ✔ CT-scan of neck, chest and abdomen/pelvis (CT-NCAP) with IV contract (in absence of contraindication)
- ✔ ^{18}FDG-PET scan
- ✔ Surgical biopsy of tumor tissue (paraffin block from the formalin fixed sample) and standard histology and immunohistochemistry slides for morphology and immunochemistry within 6 months prior to initiation of treatment is **mandatory** (strongly recommended for patients watched for at least 12 months), for central review to confirm the diagnosis of lymphoma (see section 11.2) and secondary data use of the disease:
  - If the paraffin block is not available, 10 to 15 unstained Superfrost slides will be requested.
  - In the case of a needle biopsy, send 15 chips of 10-micron.
  - In the case of a 1 cm x 1 cm lymph node removal, send 6 chips of 10-micron.
- ✓ Highly recommended:
  - Frozen Tumor: 1 cryotube
  - Cryostor:
    - ✓ with at least 2 cryotubes if surgical biopsy of tumor tissue

or 4 cryotubes in the case of a core needle biopsy

- ✔ Bone marrow biopsy within 6 months prior to initiation of treatment is **mandatory** (even for patients watched for at least 12 months). Bone marrow aspirate will not be acceptable.

- ✔ **Randomization**

<u>During Study treatment</u>

- ✔ **Assessments performed during cycles of Induction and maintenance**
- ✔ Clinical examination
- ✔ Weight
- ✔ Vital signs (pulse, blood pressure, temperature)
- ✔ B symptoms
- ✔ ECOG Performance Status
- ✔ Complete blood cell count
- ✔ Biochemical tests
- ✔ LDH
- ✔ TSH (if clinically indicated)
- ✔ Serum pregnancy test for WOCBP
- ✔ ECG at I3D1 in experimental arm
- ✔ QoL questionnaires only at I1D1
- ✔ Serum PK/ADA samples
- ✔ Samples for banking and biological studies (after patient's signature of specific consent)
- ✔ Registration of concomitant medication taken
- ✔ Registration of AE/AESI/SAE

<u>During evaluations</u>

- ✔ **Assessments performed at mo6 and mo12 evaluations**
- ✔ Clinical examination

	✔ ECOG PS ✔ Complete blood cell count ✔ Biochemical tests ✔ LDH ✔ Serum pregnancy test for WOCBP ✔ Chest, Abdomen and Pelvis CT with IV contrast (in absence of contraindication) ✔ ^{18}FDG-PET scan ✔ Evaluation of the disease response (Lugano Response Criteria) ✔ Bone marrow Biopsy: ✔ at mo6 evaluation: mandatory only for patients with involved bone marrow at screening, to confirm CMR within 28 days of first achieving radiological, clinical and biological CMR. ✔ at mo12 evaluation: mandatory only for patients with involved bone marrow at screening **and** with still abnormal bone marrow biopsy obtained at mo6 evaluation, and in CMR at this assessment ✔ QoL questionnaires ✔ Samples for banking and biological studies ✔ Registration of concomitant medication taken ✔ Registration of AE/AESI/SAE ✔ **Assessments performed at mo18 and mo24 evaluations** ✔ Serum pregnancy test for WOCBP ✔ Chest, Abdomen and Pelvis CT with IV contrast (in absence of contraindication) ✔ ^{18}FDG-PET scan ✔ Evaluation of the disease response (Lugano Response Criteria) ✔ Bone marrow Biopsy: mandatory only for patients with positive bone marrow at screening and still involved at mo12 evaluation and in CMR at this assessment ✔ QoL questionnaires ✔ Samples for banking and biological studies (after patient's signature of specific consent) ✔ Registration of concomitant medication taken ✔ Registration of AE/AESI/SAE ✔ **Assessments performed at End of treatment evaluation (mo30) or at premature treatment discontinuation** ✔ Clinical examination ✔ Weight ✔ Vital signs ✔ B symptoms ✔ ECOG PS ✔ Complete blood cell count ✔ Biochemical tests ✔ LDH ✔ TSH (if clinically indicated) ✔ Serum pregnancy test for WOCBP ✔ ECG ✔ Chest, Abdomen and Pelvis CT with IV contrast (in absence of contraindication) ✔ ^{18}FDG-PET scan ✔ Evaluation of the disease response (Lugano Response Criteria) ✔ Bone marrow Biopsy: mandatory only for patients with involved bone marrow at screening and still involved at previous evaluation and in CMR at this assessment ✔ QoL questionnaires

- ✔ Serum PK/ADA samples
- ✔ Samples for banking and biological studies (after patient's signature of specific consent)
- ✔ Registration of concomitant medication taken
- ✔ Registration of AE/AESI/SAE up to 30 days post last study treatment dose, unless a new lymphoma treatment is administered; all related SAE occurring after 30 days post last study treatment dose

After treatment

- ✔ **Assessments performed at Follow-up visits**
- ✔ Clinical examination
- ✔ Weight
- ✔ B symptoms
- ✔ ECOG PS
- ✔ Complete blood cell count
- ✔ LDH
- ✔ TSH (if clinically indicated)
- ✔ Chest, Abdomen and Pelvis CT with IV contrast (in absence of contraindication)
- ✔ QoL questionnaires
- ✔ Samples for banking and biological studies (after patient's signature of specific consent)
- ✔ Registration of AE/AESI/SAE up to 90 days post last study treatment dose, unless a new lymphoma treatment is administered; all related SAE occurring after 30 days post last study treatment dose

- ✔ **Assessment in case of progression:**
- ✔ Clinical examination
- ✔ Complete blood cell count
- ✔ LDH
- ✔ ^{18}FDG-PET scan
- ✔ Evaluation of the disease response (Lugano Response Criteria)
- ✔ Progression will be based on the first exam which shows the progression but a Chest, abdomen and pelvis CT with IV contrast (in absence of contraindication) must be performed
- ✔ A pathological confirmation by surgical biopsy of tumor tissue for morphology and immunochemistry is strongly recommended, especially in case of suspicion of transformation:
  - If the paraffin block is not available, 10 to 15 unstained Superfrost slides will be requested.
  - In the case of a needle biopsy, send 15 chips of 10-micron.
  - In the case of a 1 cm x 1 cm lymph node removal, send 6 chips of 10-micron.
- ✓ Highly recommended:
  - Cryostor:
    - ✓ with at least 2 cryotubes if surgical biopsy of tumor tissue
    - ✓ or 4 cryotubes in the case of a core needle biopsy
- ✔ Samples for biological studies at relapse/progression (after patient's signature of specific consent)

- ✔ **Assessment after progression (follow-up survival):**
- ✔ Survival status
- ✔ Type of subsequent treatment after first progression and response according to Lugano Response Criteria (with date)
- ✔ Second progression (with date) at least, and clinical factors
- ✔ Second Primary Malignancy (SPM)

	✔ AE/AESI/SAE (related and not related) recorded up to 30 days after the last study drugs administration, unless a new lymphoma treatment is administered ✔ From 30 days, related SAE only, even if a new lymphoma treatment is administered
Duration of the study	Patients will be enrolled for approximately 34 months. Treatment will associate an induction phase followed by a maintenance phase, according to their assigned arms. Patients will be followed up to 7 years after the last randomized patient. The total duration of the study is therefore approximately 10 years. Anticipated milestones: - 1st patient randomized (FPFV): Q1 2024 or 1y after the Roche Formal Agreement at the latest - Last patient randomized (LPFV): approximatively 34 months after FPFV - Last patient treated (end of maintenance): 30 months after LPFV - End of study (LPLV): 7 years after LPFV The end of study will occur when the last randomized patient has been followed-up for survival for at least 7 years.
Safety considerations - Pharmacovigilance	**AESI, infections of grade ≥ 2 and all other AE of grade ≥ 3** (CTCAE – version 5.0) (regardless of relationship to any investigational product, i.e., Mosunetuzumab, Lenalidomide, Rituximab or Obinutuzumab, CHOP or Bendamustine) occurring from first administration of study drug up to 90 days after last definitive study drugs administration will be recorded in the AE pages of the eCRF. The following AEs are considered as of special interest and require attention from investigator if occurring. In addition, they have to be reported in the eCRF, irrespective of the seriousness criteria, and whatever the grade, **from the date of first administration of study drug to 90 days after the last definitive administration of study drug(s) (i.e Mosunetuzumab, Lenalidomide, Rituximab or Obinutuzumab, CHOP or Bendamustine)**. They have to be signaled to Sponsor using the dedicated form: - Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law - Cytokine release syndrome (CRS) ≥ Grade 2 graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) grading for CRS - Other infusion related reactions ≥ Grade 2 CTCAE - Immune Effector Cell-Associated Neurotoxicity (ICANS) ≥ Grade 2 graded according to ASTCT grading for ICANS and other neurotoxicity ≥ Grade 2 graded according to CTCAE scale (v5.0), except peripheral neuropathy - Tumor lysis syndrome (TLS) grade ≥ 3 CTCAE (by definition) - Any suspected hemophagocytic lymphohistiocytosis - Tumor inflammation or tumor flare grade ≥ 2 CTCAE - Febrile neutropenia grade ≥3 CTCAE (by definition) - AST, ALT or total bilirubin elevation Grade ≥ 3 CTCAE - Disseminated intravascular coagulation grade ≥ 2 CTCAE (by definition)

	- Any pulmonary toxicity (e.g any grade pneumonitis, interstitial lung disease, pulmonary fibrosis, organizing pneumonia…) - Embryo-fetal toxicity - Grade ≥ 3 severe skin reactions - Grade ≥ 3 renal impairment - Grade ≥ 3 thyroid disorder - Grade ≥ 3 peripheral neuropathy - Suspected transmission of an infectious agent by the study drug, as defined below: o Any organism, virus, or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected. Signs, symptoms and physical findings indicative of lymphoma or progression of lymphoma are not to be reported as "Adverse Event". AE with onset date after new lymphoma treatment administration are not to be reported. **Serious adverse events** (SAEs) occurring from ICF signature to 90 days after last definitive study drugs administration (Mosunetuzumab, Lenalidomide, Rituximab or Obinutuzumab, CHOP or Bendamustine), regardless of relationship to study drugs, will be reported. A SAE that occurs after this time, including during the follow-up period, will be reported only if considered related to study treatments administration, i.e., Mosunetuzumab, Lenaomide, Rituximab or Obinutuzumab, CHOP or Bendamustine. An **Independent Data Monitoring Committee (IDMC)** will be commissioned to assess the safety of Mosunetuzumab in combination with Lenalidomide versus CD20 Ab + chemotherapy and make recommendations to the sponsor for any safety concern. The IDMC will be held every year, starting 6 months after the first randomization and until the last patient is on treatment including maintenance. This Committee will also evaluate the interim results of the primary endpoint. The IDMC will be composed of at least three independent members, including 2 experts in NHL/HL and one statistician. Details of the IDMC activities and meetings will be described in a separate IDMC charter.
Registration in the study and Randomization	Once a patient gives written consent, the patient may enter the Screening Period, which is permitted to last up to 6 weeks. Before randomization the investigator will be requested to indicate his/her choice among the list of the permitted standard-of-care immune-chemotherapy regimens in case of control arm allocation. In addition, during the Screening Period, the patient will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm versus control arm. Patients will be randomized into treatment arms in a 1:1 ratio by means of a permuted block randomization scheme through the use of an IWRS system. Randomization will be stratified on FLIPI (2 vs 3-5) and size of largest lesion (≤6 vs >6cm) as follows: 1. FLIPI 2 and size of largest lesion ≤6

	2. FLIPI 2 and size of largest lesion >6 3. FLIPI 3-5 and size of largest lesion ≤6 4. FLIPI 3-5 and size of largest lesion >6
Statistical consideration	**ANALYSIS SET** The **Intent To Treat (ITT) Set** will include all patients having signed their informed consent and who have been randomized, regardless of study drug being received or not. Patients will be analyzed based on assigned treatment group per randomization. This set will be used for demographic/baseline characteristics and analyses of efficacy endpoints. The **Per Protocol (PP) Set** will include patients in the ITT set without major protocol violation. Patients will be analyzed according to the treatment actually received. This set will be used for supportive analysis of primary efficacy endpoint.. Major protocol deviations will be defined in SAP. The **Safety Set** will include all patients in the ITT set who received at least one dose of either one investigational drug (Lenalidomide or Mosunetuzumab) or the investigator's choice therapy. This set will be used for safety analysis. Patients will be analyzed according to the treatment actually received. The **QOL set** will be the ITT set but it may vary depending on the subscale analyzed and the number of patients with available scores for that subscale. The minimum QoL set wil be defined as patients included in the ITT set with at least one questionnaire evaluable at baseline and with >=1 post-baseline assessment. The **PK/ADA set** will include a subset of mosunetuzumab-treated patients in the ITT set who are evaluable at baseline and for ≥1 post-baseline PK/ADA assessment(s). Patients may be excluded from the PK/ADA-evaluable population where dose delays/ interruptions or other factors/ protocol deviations are deemed to compromise interpretation of results. **SAMPLE SIZE CALCULATION** Sample size calculation was performed with EAST software version. 6.5. The hypotheses are the followings: - superiority test - 3-years PFS in the control arm = 78.2% (based on subset of GALLIUM patients, 73.6% in R-Chemo arm and 82.8% in G-chemo arm) - 3-years PFS in the experimental arm = 85.23% - HR=0.65 - H0: PFS in the control arm = PFS in the experimental arm - H1:PFS in the experimental arm > PFS in the control arm - two-sided alpha = 5% - power = 80% - drop-out: 5% per 12 months - randomization ratio 1:1 - one interim analysis of early efficacy at 75% (130 events) of events with efficacy boundary based on Lan-DeMets spending function with Lan DeMets O'Brien-Fleming approximation Based on these assumptions, 173 PFS events assessed by IRC would have to be observed on the ITT set for the primary effiacy endpoint analysis. Assuming the randomization of 790 patients based on an increasing accrual rate (up to 30 patients per month with a ramp-up phase), enrollment period will be 34 months.

ANALYSIS PLAN

Time-to-event endpoints will be analyzed on ITT set. The Kaplan-Meier estimate will be provided. The Brookmeyer-Crowley method will be used to construct the 95% CI for the median of the endpoints. The Kaplan-Meier method will be used to estimate the time-to-event probabilities at fixed time points (e.g. at 1 year, at 2 year, etc), along with the standard error and the corresponding 95% Cis using Greenwood's formula. Stratified Cox proportional hazard regression model will be used to estimate the hazard ratios (HR) and associated 95% CIs. Stratification will be performed on the randomization stratification factors.

For the primary endpoint PFS, superiority will be established based on the stratified log-rank test based on ITT population. To control the overall Type I error rate at a two-sided 5% level of significance, the α risk will be adjusted for early efficacy analysis.

Boundaries and p-values for primary efficacy endpoint analyses

Analysis	PFS events	Cumulative alpha spent	Estimate time event since FPI in months (in years) *	Boundary		
				HR		Two-sided p-value
				Lower	Upper	
Interim analysis of PFS	130	0.0194	55 (4.6 y)	0.664	1.507	0.01944
Primary analysis of PFS	173	0.05	70 (5.8 y)	0.736	1.358	0.0442

* Based on 1000 simulations

TIME OF ANALYSIS

Three analyses of efficacy are planned:

Early efficacy analysis (Interim analysis of PFS)

The analysis will be conducted when approximately 130 PFS events assessed by IRC have occurred and at least 55 months after the last patient is randomized. At the time of occurrence of approximately 130th PFS event, it is estimated that the median follow-up duration from randomization will be more than 2.5 years.

Primary efficacy and safety endpoints will be analyzed. In addition, if statistical significance is reached on the primary endpoint, analysis of secondary efficacy criteria and exploratory criteria (depending on data availability) will be conducted.

Primary analysis of PFS

If the early efficacy were demonstrated, this analysis will be exploratory.

The analysis will be conducted after approximately 173 PFS events assessed by IRC have occurred or based on a minimal follow-up from the randomization of the last patient assessed as clinically relevant. At the time of occurrence of the 173th PFS event, it is estimated that the median follow-up duration will be approximately 4 years.

Primary efficacy endpoints, secondary efficacy endpoints and safety endpoints will be analyzed. Depending on data availability, exploratory criteria will be analyzed.

Final analysis / End of study analysis

Update of the efficacy and safety criteria will be performed at the end of study.