# SYNOPSIS

# MARSUM

## Phase III, Multicenter, Open label, Randomized, Controlled Study Investigating Mosunetuzumab-Lenalidomide versus investigator choices in Patients with Relapsed or Refractory Marginal Zone Lymphoma


**SPONSOR:**

**LYSARC**

LYSARC: THE LYMPHOMA ACADEMIC RESEARCH ORGANISATION

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| **Sponsor** | LYSARC |
| **Study name/code** | MARSUN |
| **Study title** | Phase III, Multicenter, Open label, Randomized, Controlled Study Investigating Mosunetuzumab-Lenalidomide versus investigator choices in Patients with Relapsed or Refractory Marginal Zone Lymphoma |
| **Identification #**<br>**(EUC)** | XXXX |
| **Protocol version** | 0.2 |
| **Development phase** | III |
| **Studied product** | Mosunetuzumab and Lenalidomide |
| **Coordinating investigator FR**<br>**Co-coordinating investigator**<br><br>**Coordinating investigator BE**<br>**Coordinating investigator other countries** | Pr THIEBLEMONT Catherine<br>Dr XXX XXX<br><br>Pr ANDRE Marc |
| **Sites** | 44 sites in France, Belgium, Portugal, Italy, and Germany |

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| **Rationale** | Marginal zone lymphomas (MZLs) account for approximately 5%–17% of all non-Hodgkin's lymphoma (NHLs) and are considered the second most common indolent NHL; MZL is the most frequent lymphoma for patients older than 80 y (Thieblemont 2008). The disease is complex and clinical presentation diverse because it arises from memory B lymphocytes, which are normally present in the marginal zone ofry lymphoid follicles within the spleen, lymph nodes, and mucosal lymphoid tissues (Thieblemont 2005, Kahl 2008, Thieblemont 2017). The World Health Organization (WHO) categorization for MZL recognizes three distinct subtypes: (i) extranodal MZL, mostly represented by mucosa-associated lymphoid tissue (MALT) lymphoma; (ii) nodal MZL (NMZL); and (iii) splenic MZL (SMZL) (Campo, et al 2017; Cook, et al 2017; Piris et al, 2017). Disease characteristics and clinical presentation of, and treatment for, MZL vary based on the subtype and site of involvement. MALT lymphoma is the most common subtype, occurring in approximately 50%–70% of all MZL; this is followed by splenic MZL (20% of all MZL), and then by nodal MZL (10% of all MZLs). Median age at diagnosis differs depending on MZL subtype, and ranges from 50 to 69 years. There is a greater incidence of MZL reported in men than women (Sriskandarajah and Dearden 2017).<br><br>MALT lymphomas can originate in any extranodal site, but they most commonly appear in the stomach, intestine, thyroid, lungs, and skin (Denlinger et al 2018; Nathwani et al 1999; Thieblemont et al 1997; Zucca et al 2003). MALT lymphomas are also subdivided into gastric, for those occurring in the stomach, and non-gastric that commonly affects the salivary glands, thyroid, lung, skin, and ocular tissues (Zucca 2016). Treatment for MALT lymphoma is dependent on the location and stage of disease with treatment for advanced-stage disease (stage III or IV) comprising regimens used for other indolent NHLs such as follicular lymphoma (FL), including systemic therapy with either single-agent or combination chemotherapy, anti-CD20 monoclonal antibody, and chemoimmunotherapy as first-line options.<br><br>SMZL is defined by involvement of the spleen, bone marrow, and sometimes peripheral blood without other nodal or extranodal sites of disease being implicated. Diagnosis relies on spleen histology and may be confirmed after a splenectomy, since immunophenotype and bone marrow morphologic features may be nonspecific. Patients with SMZL usually have a good prognosis, with median survival of approximately 10–15 years (Arcaini et al 2016; Thieblemont et al 2016), but there is a degree of heterogeneity in the condition, and 5%–10% of patients present with more aggressive disease and shorter survival (Thieblemont 2017).<br><br>NMZL is the least common of the subtypes and shares morphological and immunophenotypic similarities with other MZLs. Peripheral lymphadenopathy is present in nearly all cases of NMZL (>95%), and involvement of extranodal sites is common. Bone marrow involvement is seen in approximately 30%–40% of cases. Long-term outcome of NMZL tends to be less favorable than with MALT lymphomas (Nathwani et al 1999). Initiation of treatment may be deferred in NMZL considering tumor burden, and treatment will start based on the GELF criteria for follicular lymphoma (Thieblemont 2017). Treatment for patients with localized disease, radiotherapy may be one therapeutic option. For patients with high tumor burden based on GELF criteria, and patients with symptoms related to disease, the recommendation is rituximab in combination with chemotherapy. Bendamustine is |

actually the most used chemotherapy (Thieblemont 2017). Few data of the combined R-Bendamustine have been published, mostly in first line, not only in NMZL but also in EMZL and SMZL. In this setting of first line, a high response rate is usually observed, with ORR at 80-91% and a CRR at 73 -86%. Duration of response (DOR) have been reported of 18 months (Castelli 2017) and DOR, PFS and OS at 3 years at 93% (95CI 81-98), 90% (95CI 77-96) and 96% (95CI 84-98), respectively in the series published by Ianitto et al. However haematological toxicity rate is high, with neutropenia G≥3 recorded in 43% of patients, infections and febrile neutropenia in 5.4% and 3.6% (Ianitto 2018). In R/R MZL, Vannata et al. recently reported in a small series of 16 patients the association of **ofatumomab-bendamustine** with an ORR and a CRR at **92.9%** and 57.1%, respectively, and a median DOR at 30 mo and **2y-PFS at 77%** (95% CI: 43% - 92%) (Vannata et al 2020).

Improved understanding of the disease biology, including genetic, molecular characterization and microenvironment (Thieblemont 2014) has altered the therapeutic landscape of MZL, particularly in the relapsed/ refractory (R/R) setting. Targeted therapies focusing on intracellular signaling pathways such as the B-cell receptor-signaling pathway have resulted in improved efficacy and tolerable toxicity profiles over chemotherapy-based approaches (Denlinger et al 2018). For patients with relapsing disease after at least one CD20-based therapy, there are recently approved chemotherapy-free options available, including the Bruton tyrosine-kinase (BTK) inhibitor ibrutinib (received accelerated approval in the United States for MZL) and the combination of lenalidomide and rituximab (approved in the United States for MZL and FL). The phosphoinositide 3-kinase (PI3K) inhibitors, copanlisib and umbralisib, have also shown activity in MZL (Sindel et al 2019).

Despite the benefits of ibrutinib treatment in patients with MZL, there are some limitations. Specific adverse events (AEs) of interest most frequently related to ibrutinib treatment discontinuation or disruption include atrial fibrillation, hypertension, bleeding, diarrhea, and arthralgia. In a study of 63 patients with R/R MZL, AEs led to treatment discontinuation in 17% of patients, bleeding AEs occurred in 59% and atrial fibrillation in 6% of patients (Noy et al 2017). Zanubrutinib, another BTK inhibitor is currently reported the Phase 1/2 BGB-3111-AU-003 and the Phase 2 Magnolia study (BGB-3111-214) with high response rates and a favorable toxicity profile (Opat et al. ASH 2020; manuscript in preparation). Twenty patients with R/R MZL were enrolled in the BGB-3111-AU-003 study and sixty-eight patients enrolled in the BGB -3111-214 study. After a median follow-up of 27.1 months, the BGB-3111-AU-003 investigator-assessed overall response rate (**ORR) was 80%,** and the complete response **(CR) rate was 15%.** Median duration of response (DOR) and progression-free survival (PFS) were not reached. %]). Only two (2.9%) patients discontinued due to AEs. Most AEs were low grade. No hypertension or major hemorrhage were reported.

Lenalidomide was approved in the USA for R/R MZL based on data from patients with MZL in two studies, MAGNIFY (n=45 patients) and AUGMENT (n=63 patients) (FDA, 2019). In the single arm MAGNIFY study, patients received 12 induction cycles of lenalidomide and rituximab (Jacob Andorsky D 2019). **AUGMENT**

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| | evaluated lenalidomide in combination with rituximab (n=31 patients) versus placebo and rituximab (n=32 patients). **ORR and CR** for patients with R/R MZL **were** in MAGNIFY **63%** and **38%** (assessed by an independent review committee [IRC]), with a DOR at 38.6 (95% CI: NR-NR) and a median PFS at 41.2 months (95% CI: 26.5-38.4). In the AUGMENT study, best response was improved with $R^2$ (vs R-placebo) at **65%** vs 44% **ORR** and 2**9%** vs 13% **CR**, although neither were statistically significant (Thieblemont 2019; Leonard et al 2019). Improved response rates did not translate into a survival advantage for $R^2$. **Median PFS** for R/R MZL patients was **20.2 mo $R^2$ vs 25.2 mo R-placebo** (HR = 1.00; 95% CI, 0.47-2.13; *P* = 1.0) (Thieblemont 2019). The safety profile was consistent with known AEs associated with $R^2$ and rituximab monotherapy. The most common grade 3/4 AEs for MZL patients receiving $R^2$ vs R-placebo, respectively, were neutropenia (47% vs 16%), pneumonia (3% vs 13%), and leukopenia (10% vs 0).<br><br>PI3K inhibitors have shown encouraging activity in indolent lymphomas, including MZL, but they are limited by substantial toxicity including liver function abnormalities, hyperglycemia, and colitis. Copanlisib and umbralisib are currently being studied in R/R MZL**; ORR** of copanlisib was **78.3%** in a small cohort of 23 R/R MZL patients. **Median duration of response** was **17.4 months** with an estimated 45% in response after 2 years. **Median PFS** was **24.1 months**. Common drug related treatment emergent AE's were hyperglycemia (47.8%), hypertension (43.5%), diarrhea (26.1%) and neutropenia (26.1%) (Dreyling et al, 2019). An interim report of the UNITY Phase 2 trial of umbralisib including 42 patients with R/R MZL demonstrated **ORR of 55%,** and **PFS at 12 months** was **66%** (TG Therapeutics, 2019). Umbralisib appeared to have lower incidences of liver function test abnormalities and colitis than what have been reported for other PI3K inhibitors, but diarrhea was a common AE (grade 3 was reported in 10% of patients), and grade 3 transaminase elevation occurred in 9% of patients. At median follow-up of 12 months, 17% of patients had discontinued treatment due to AEs. These results suggest the tolerability challenges that exist with this therapeutic class.<br><br>While these new therapeutic agents are providing additional options for patients with R/R MZL, there remains an **unmet need for effective, tolerable therapies to improve long-term outcomes**.<br><br>Mosunetuzumab is a CD20xCD3 T-cell-engaging bispecific antibody designed to engage T cells and redirect their cytotoxic activity against B cells. Mosunetuzumab simultaneously binds to CD3epsilon (CD3ε), a component of the T-cell receptor (TCR) complex, and to CD20a B-cell surface protein expressed in a majority of B-cell malignancies. This results in crosslinking of the TCR, inducing downstream signaling events that lead to B-cell killing (Sun et al. 2015). Combination of mosunetuzumab and lenalidomide is currently under evaluation in follicular lymphoma (CELESTIMO, NCT04712097; Morschhauser F et al, ASH 2021). As suggested by MZL expert (Stathis 2018), there is a need to explore innovative treatments in disease – specific clinical trial and particularly MZL, often underrepresented in the so-called "indolent NHL". |

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| | We propose to investigate the efficacy and the safety of Mosun + Len, a chemo-free regimen, compared with investigator choices, in patients with R/R MZL in need of systemic treatment and not eligible for local therapy such as radiotherapy or surgery, due to lack of standard second line treatments.<br><br>L1, L2, L3: previous line must include at least one systemic line with a drug targeting CD20 (monoclonal antibody or T-cell engager, at least 2 cycles) with or without chemotherapy (R-CHOP, R-bendamustine, R-CVP, at least 2 cycles) or targeted treatment such as ibrutinib (at least 1 month). Patients should not have received Lenalidomide before.<br><br>Two stratification factors are implemented at time of registration and will be used for the randomization in order to balance the treatment allocation<br><br>- MZL subtypes: EMZL, SMZL and NMZL (with probable incidence will be respectively 40%, 30%, 30%), but disseminated disease (DMZL) will be accepted if the origin subtype is not clearly defined and included in NMZL as a subtype<br><br>Relapse < 2 years or ≥ 2 years (since C1D1 of previous treatment line before consent form signature) |
| **Study objectives and endpoints** | **Principal objective**:<br><br>The primary objective of the study is to evaluate the efficacy of mosunetuzumab-lenalidomide compared with investigator choices. The primary efficacy endpoint for comparison is the Progression–free survival (PFS) as determined by investigator (Lugano criteria 2014).<br><br>**Secondary objectives**:<br><br>● CR24 as determined by investigator (at 24 months from the C1D1 (+/- 15 days)) according to Lugano criteria 2014<br><br>● CR24 as determined by central review based on PET result (at 24 months from the C1D1 (+/- 15 days)) according to Lugano Criteria 2014<br><br>● Overall response rate (ORR) and CR other than CR24 as determined by investigator according to Lugano criteria 2014<br><br>● ORR and CR other than CR24 as determined by central review based on PET result according to Lugano Criteria 2014<br><br>Time frame:<br><br>○ Primary response:<br><br>● at C6 D22-D28 for Mosunetuzumab -Lenalidomide<br><br>● at C6 D22-D28 for Rituximab-Lenalidomide,<br><br>● at C3 D22-D28 for Rituximab-Bendamustine. In this cohort, patients may stop after C4 (if already in CR) or after C6. Those patients who stop after C4 will not have a repeat imaging before |

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| | beginning the consolidation phase. Patient who will receive 6 cycles of R-Benda will have to repeat evaluation at C6 D22-D28.<br>● at C6 D56-D63 for R-CHOP treatment<br>○ End of treatment (EOT) i.e 12 months after C1D1 administration<br>○ M24, M36, M48 and M60 after C1D1<br><br>● Duration of response (DOR)<br>● Event-free survival (EFS)<br>● Time to next anti-lymphoma treatment (TTNLT)<br>Histological transformation rate<br>● Safety: incidence and severity of AE, incidence and severity of SAE, incidence and severity of CRS, Incidence and severity of AE grade 3 or 4 of study-drug related events, Death, Secondary Primary Malignancies, vital sign and clinical laboratory<br>● Tolerability, as assessed by dose interruptions, dose reductions, and dose intensity, and study treatment discontinuation because of adverse events<br>● Health related quality of life as measured by the EQ-5D-5L (Appendix 11)<br><br>**Exploratory objectives**:<br>● Assessment of the prognostic role of the quantitative measures of FDG-PET/CT scan (quantitative measures to be defined Deauville score, and delta SUV at each assessment; TMTV and distance at baseline)<br>● Biomarker with ancillary studies for:<br>○ Histological review<br>○ Tumor microenvironment on biopsy<br>○ MRD in blood (baseline, C2J1, primary response, EOT, M24, and relapse)<br>○ Radiomics at FDG-PET (baseline, primary response, EOT, M24, and relapse)<br>○ Cell-free DNA and ctDNA (baseline, C2D1, primary response, EOT, M24, and relapse) |
| **Study design** | This study is a phase III, multicenter, open label, randomized, controlled study. Patients are randomized at a 1:1 ratio to receive either (arm A) mosunetuzumab and lenalidomide or (arm B) investigator choice.<br><br>The number of patients will be 10 patients with MZL (including at least 3 with blood involvement) in the safety run in and 125 patients by arm. The total number of patients will be 260. |

**Arm A - Experimental arm**

- Mosunetuzumab and lenalidomide
  - ○Mosunetuzumab will be administered SC (21 days first cycle, then 28 days next cycles)
    - C1 (21-days cycle): step-up dosing schedule 5 mg Day 1, 45 mg on Day 8 and 45 mg Day 15
    - C2 to C12: 45 mg D1 28-days cycles
  - ○Lenalidomide PO 20 mg/day, D1-21/28 C2 to C6

**Arm B – Comparator arm**

**I**nvestigator choice that had to be decided before randomization between rituximab-lenalidomide and rituximab-chemotherapy, and for each patient. Rituximab-chemotherapy should represent 60% of the patients allocated in the arm B and Rituximab-Len 40% of the patients allocated in Arm B.

- Rituximab-lenalidomide (28 days cycles)
  - ○Lenalidomide PO 20 mg/day, D1-21/28 X 6 cycles
  - ○Rituximab 375 mg/m2 intravenously at Day 1 cycle 1, and then subcutaneous (1400 mg, flat dose) at D1 of cycles 2-12

- Rituximab-Bendamustine (28 days cycles)
  - ○Bendamustine, IV 70 or 90 mg/m² (according to the investigator's judgment) D1 and D2/28 days x 6 cycles. For patients in complete response (CR) at 3 cycles, Bendamustine could be stopped after 4 cycles at investigator discretion
  - ○Rituximab 375 mg/m² intravenously at cycle 1 Day 1, and then subcutaneous (1400 mg, flat dose) at D1 of cycles 2 to 6, C7, C9 and C11

- R-CHOP (21 days cycles)
  - ○CHOP, IV standard dose x 6 cycles

| CHOP | | Dose (mg/m²) | Days |
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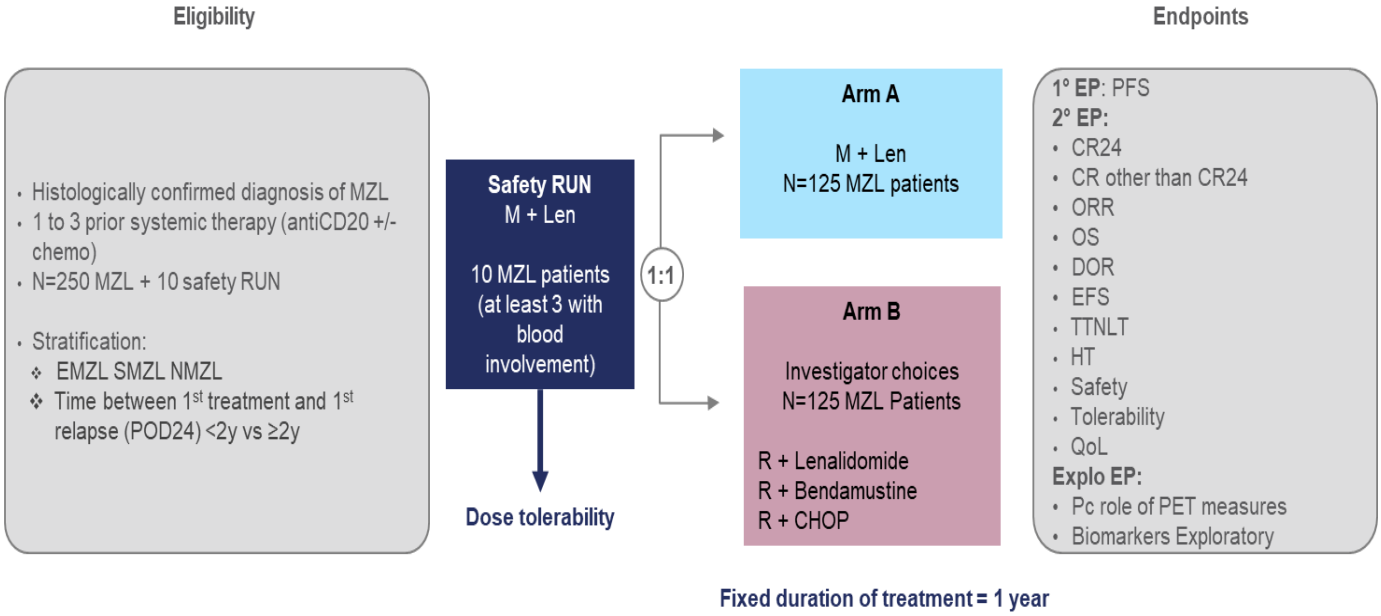
| CYCLOPHOSPHAMIDE | IV | 750 | 1 |
| DOXORUBICINE | IV | 50 | 1 |
| VINCRISTINE | IV | 1,4 (max 2 mg) | 1 |
| PREDNISONE | PO | 40 | 1 to 5 |

  - ○Rituximab 375 mg/m² intravenously at Day 1 cycle 1, and then subcutaneous (1400 mg, flat dose) at D1 of cycles 2-6, C7, C9 and C11

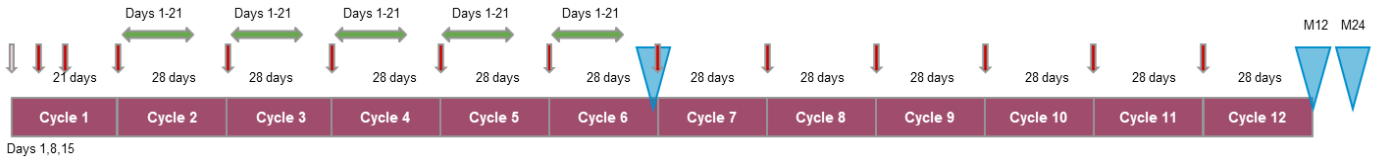
The Rituximab will be administered every 3 weeks from C1 to C6 and every 8 weeks from C7 to C11.

# Study design /Overview




Patients with complete response (CR), partial response (PR), stable disease (SD) will continue the treatment after primary response evaluation. Only patient with PD will be discontinued from the treatment

# Arm A: Mosunetuzumab + Lenalidomide




Mosunetuzumab SC 5 mg on Day 1 of Cycle 1

Mosunetuzumab SC 45 mg on Day 8 and 15 of Cycle 1 and then on D1 of each cycles for up to 12 total cycles

Lenalidomide PO 20 mg/d on D1-21 of C2-C6

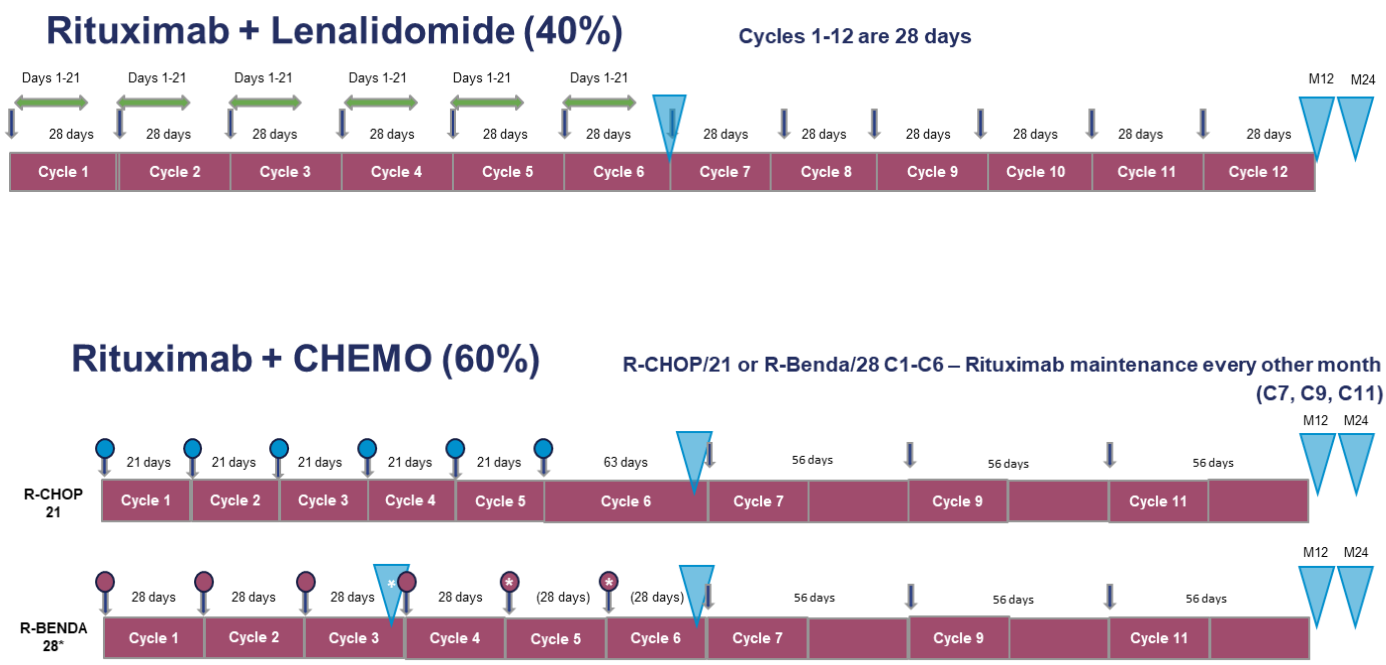
Cycle 1 is 21 days
Cycles 2-12 are 28 days

**Evaluations** — **After 6 cycles : primary response** → **Patients en PD will be discontinued from the treatment**

**M12**
**M24 (=CR24)**
**And relapse**

**cT DNA, scanner, FDG-TEPscanner, MRD**

# Arm B: Investigator choices

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| **Duration of the study** | Patients will be enrolled for 3.7 months for safety run and 3.6 years for randomization (including temporary stop of the recruitment during safety run), treated for 1 year (47 or 48 weeks depending on the arm) and followed up to 4 years after the last dose of study treatment for the last randomized patient. The total duration of the study is therefore 8 years<br><br>Theoretical dates of study:<br><br>- 1st patient included (FPFV): Q2 2023<br><br>- Last patient included (LPFV): Q2 2027<br><br>- Last patient treated: Q2 2028<br><br>- End of study: Q2 2032<br><br>The end of study is defined as the last visit of the last patient who performed his/her visit 60 months after the beginning of the treatment. |

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| **Number of patients** | 260 (10 patients with MZL (including at least 3 with blood involvement) in the safety run in and 125 patients by arm) |
| **Inclusion criteria** | Participants are eligible to be included in the study only if all the following criteria apply:<br>1. Have a diagnosis of MZL, of extranodal (EMZL) or splenic (SMZL) or nodals (NMZL subtypes. In case of large dissemination, disseminated MZL will be included as DMZL and included in NMZL subtype.<br>2. Have been treated with at least one prior systemic treatment and not more than three prior lines. Previous line must include at least one systemic line with a drug targeting CD20 (monoclonal antibody at least 2 cycles) with or without chemotherapy (R-CHOP, R-bendamustine, R-CVP, at least 2 cycles) or targeted treatment such as ibrutinib (at least 1 month). Patients should not have received Lenalidomide before. Prior local therapy (including surgery, radiotherapyn antibiotics for *H. pylori*-positive gastric lymphoma, and antiviral for hepatitis C virus) is not considered as one line of treatment<br>3. Signed Informed Consent Form<br>4. Age ≥ 18 years at the time of signing the informed consent form<br>5. Ability to comply with the study protocol and procedures and required hospitalizations, in the investigator's judgement<br>6. Eastern Cooperative Oncology Group (ECOG) performance score (PS) of ≤ 2<br>7. Have a symptomatic disease requiring a systemic treatment<br>8. Not eligible for a local treatment including radiotherapy or surgery<br>9. Stage I disease of EMZL, SMZL or NMZL may be eligible only if not candidate to local therapy (surgery or radiotherapy).<br>10. Measurable disease in at least two perpendicular dimensions on an imaging scan is defined as: lymph node or nodal mass bi-dimensional measurement with > 15 mm in longest transverse diameter or the short diameter must measure > 10 mm regardless of the longest transverse diameter.<br>Spleen is considered as a measurable disease if vertical axis is higher than 13 cm.<br>11. Adequate hematopoietic function at screening as follows unless cytopenia is clearly due to marrow involvement of MZL or hypersplenism or autoimmune thrombocytopenia:<br>11.1. Platelet count ≥ 75 G/L; in cases of thrombocytopenia clearly due to marrow involvement of MZL or hypersplenism or auto-immune thrombocytopenia, platelet count should be ≥ 30,000/µL. Washout platelet transfusion is 7 days between transfusion and D1 of starting treatment |

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| | 11.2. ANC ≥ 1 G/L unless neutropenia is clearly due to marrow involvement of MZL or hypersplenism. G-CSF is not allowed within 7 days before screening<br>11.3. Total hemoglobin > 8 g/dL unless anemia is clearly due to marrow involvement of MZL or hypersplenism or autoimmune hemolytic anemia. Washout erythrocyte transfusion is 7 days between transfusion and D1 of starting treatment<br>12. Serum total bilirubin ≤ 1.5 x the upper limit of normal (ULN) (or ≤3 x ULN for patients with Gilbert syndrome),<br>13. AST or ALT ≤ 2.5 x ULN, unless directly attributable to the patient's MZL<br>14. Measured or estimated creatinine clearance ≥ 40 mL/min by institutional standard method<br>15. Contraception:<br>15.1. **For women of childbearing potential** (refer to section 14.6.1 and 14.6.1.1**):** Serum at screening and Day 1 before first dose. Monthly in WOCBP with regular menstrual cycles or every 2 weeks in WOCBP with irregular menstrual cycles until EOT.<br>15.2. **For men:** 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 tocilizumab (if applicable), 6 months after the final dose of chemotherapies (if applicable) and 12 months after the final dose of rituximab) (if applicable).<br>16. Patient covered by any social security system (France)<br>17. Patient who understands and speaks one of the country official languages |
| **Exclusion criteria** | Participants are excluded from the study if any of the following criteria apply:<br>1. MZL with histologic transformation to high-grade lymphoma<br>2. Pregnant or breastfeeding or intending to become pregnant during the study or within 28 days after the final dose of lenalidomide, 3 months after the final dose of mosunetuzumab and tocilizumab (if applicable), 6 months after the final dose of chemotherapies and 12 months after the final dose of rituximab (if applicable). Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study treatment.<br>3. Participants who have received any of the following treatments prior to study entry: |

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| | - Treatment with mosunetuzumab or other CD20/CD3-directed bispecific antibodies<br><br>- Allogeneic stem cell transplant<br><br>4. Participants who have received any of the following treatments, whether investigational or approved, within the respective time periods prior to initiation of study treatment:<br><br>- Radiotherapy within 2 weeks prior to the first dose of study treatment<br><br>- Autologous stem cell transplant within 100 days prior to first study treatment<br><br>- Use of monoclonal antibodies within 4 weeks prior to first study treatment<br><br>- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within 2 weeks prior to first dose of study treatment (C1D1); Systemic corticosteroid treatment <20 mg/day prednisone or equivalent and inhaled corticosteroids are permitted. Last dose of corticosteroid >20 mg/day prednisone or equivalent will not be permitted during the last 15 days before inclusion.<br><br>Administration of acute, low-dose, systemic immunosuppressant medications (e.g., single dose of dexamethasone for nausea or B-symptoms) is permitted during 4 days without washout.<br><br>- Any other anti-cancer investigational therapywithin 4 weeks prior to initiation of study treatment.<br><br>5. Received a live, attenuated vaccine within 4 weeks before 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, except for acute pandemic situation such COVID19<br><br>6. Active or history of CNS lymphoma or leptomeningeal infiltration<br><br>7. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibody therapy (or recombinant antibody-related fusion proteins) – grade 3 and 4<br><br>8. Known hypersensitivity to biopharmaceuticals produced in CHO cells or any component of the mosunetuzumab, rituximab, tocilizumab, lenalidomide, or thalidomide formulation, including mannitol<br><br>9. Patients should be able to receive adequate prophylaxis and/or therapy for thromboembolic events (aspirin or low molecular weight heparin)<br><br>10. History of prior malignancy, except for conditions as listed below if patients have recovered from the acute side effects incurred as a result of previous therapy:<br><br>- Malignancies treated with curative intent and with no known active disease present for ≥2 years before enrollment<br><br>- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease |

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| | - Adequately treated cervical carcinoma in situ without evidence of disease<br>- Surgically/adequately treated low grade, early stage I, localized prostate in situ<br>11. Participants with infections requiring IV treatment with antibiotics or hospitalization (Grade 3 or 4) within the last 4 weeks prior to inclusion or known active bacterial, viral (including SARS-CoV-2), fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds),<br>12. Evidence of any significant, concomitant disease that could affect compliance with the protocol or interpretation of results, including, but not limited to:<br>- 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)<br>- Significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)<br>- Clinically significant history of liver disease, including viral or other hepatitis, or cirrhosis<br>- Current or past history of 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.<br>13. History of confirmed progressive multifocal leukoencephalopathy (PML)<br>14. Known Positive serologic HIV test at screening<br>15. Patients who are hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (HBcAb) positive, must be negative for hepatitis B virus (HBV) polymerase chain reaction (PCR) to be eligible for study participation<br>16. Acute or chronic hepatitis C virus (HCV) infection<br>Participants who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation.<br>17. Known or suspected history of hemophagocytic lymphohistiocytosis<br>18. Known or suspected chronic active Epstein-Barr virus (EBV) infection within the last 4 weeks prior to inclusion<br>19. History of erythema multiforme, Grade ≥3 rash, or blistering following prior treatment with immunomodulatory derivatives<br>20. History of interstitial lung disease (ILD), drug-induced pneumonitis, and autoimmune pneumonitis<br>21. Active autoimmune disease requiring treatment<br>22. History of autoimmune disease, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis |

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| | associated with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis; except :<br>- Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.<br>- Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.<br>- Patients with a history of disease-related immune thrombocytopenic purpura or autoimmune hemolytic anemia may be eligible.<br>- Partients 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 Medical Monitor.<br>23. Recent major surgery with risk of bleeding within 4 weeks prior to first study treatment administration (C1D1)<br>24. History of solid organ transplantation<br>25. Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes an individual's safe participation in and completion of the study<br>26. Person deprived of his/her liberty by a judicial or administrative decision<br>27. Person hospitalized without consent<br>28. Adult person under legal protection<br>29. Adult person unable to provide informed consent because of intellectual impairment, any serious medical condition, laboratory abnormality or psychiatric illness |
| **Study treatment** | Mosunetuzumab-Lenalidomide<br>○Mosunetuzumab will be administered SC (21 days first cycle, then 28 days next cycles)<br>• C1 (21-day cycle): step-up dosing schedule 5 mg Day 1, 45 mg on Day 8 and 45 mg Day 15<br>• C2 to C12 (28-day cycles): 45 mg on Day 1<br>○Lenalidomide PO 20 mg/day, D1-21/28 C2 to C6 |
| **Assessment schedule** | **At Baseline:**<br>· Relevant medical history<br>· Concomitant medication<br>· Vital signs<br>· Physical examination (including tumor assessment) and ECOG |

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| | · TTE (transthoracic echography) or MUGA are mandatory at baseline for all patients<br>· ECG<br>· Hematological test: haemoglobin, platelets, leukocytes, , and differential count (neutrophils, lymphocytes, monocytes, abnormal lymphoma cells),<br>· Biochemical tests: LDH, serum creatinine, creatinine clearance, ASL, ALT, total bilirubin, alkaline phosphatase,<br>· Beta-2-microglobulin<br>· Coombs test<br>· CRP<br>· Coagulation test: aPTT, PT, INR, fibrinogen<br>· TSH<br>· For EMZL and NMZL patients, tumor biopsy collection for central pathology. For each enrolled patient, tumor FFPE tissue blocks or 10 unstained slides, as well as stained slides that were used for diagnosis confirmation at relapse (at time of inclusion) will be requested. In case of NMZL, biopsy strongly recommended at baseline to exclude transformation. If biopsy material at inclusion is not available, archived material will be requested (cf. 11.2)<br>· For SMZL patients, cytology review of blood smears and flow cytometry results of peripheral blood will be requested for central review. The flow cytometry panel in the blood must include the Matutes panel and CD200, CD180, CD20, CD43, CD11c.If the whole panel is not used in a center, a blood sample will have to be sent for a centralized cytometry (cf. 11.3)<br>· Local Flow cytometry of peripheral blood only for SMZL<br>· Bone Marrow aspirate + local Marrow Flow cytometry for all subtypes<br>· For SMZL, Bone Marrow Biopsy mandatory only in case of absence of lymphoma cells in blood or marrow aspirate (no central review)<br>· HIV, HBV, and HCV serologies.<br>· Serum IgG, IgM, IgA (serum immunofixation if a monoclonal component is suspected)<br>· CT scan of cervical, chest, abdomen, and pelvis with IV contrast<br>· FDG-PET/CT scan<br>· Quality of life as measured by the EQ-5D-5L<br>· Endoscopic investigations with biopsies and MRI which will be performed if clinically appropriate (orbital MRI or scanner, gastric endoscopy….)<br>· Samples for centralized biological banking for ancillary studies (for patients who have signed the biological and samples collection consent forms only). For sampling details please refer to the part 11.4 Biological Banking and ancillary studies: |

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| | ○Blood on streck for cfDNA and ctDNA analysis and banking for all patients<br>○Blood on EDTA for MRD analysis and banking for SMZL patients<br>○Blood on Lithium Heparin for CyTOF analysis and banking for all patients included in France, Belgium and Italy<br>○Bone marrow on Lithium Heparin tube for MRD and CyTOF analysis, and banking for all patients included in France, Belgium and Italy<br><br>**Within 3 days before C1D8 and C1D15 (only for arm A):**<br>· Vital signs<br>· Hematological tests<br>· Biochemical tests<br><br>**At day 1 of Cycle 2 before starting treatment (C2D1):**<br>Samples for biological studies **(for sampling details please refer to part 11.4 Biological Banking and ancillary studies):**<br>· Blood on streck for cfDNA and ctDNA analysis and banking for all patients included in France, Belgium and Italy<br>· Blood on EDTA for MRD analysis and banking for SMZL patients<br>· Blood on Lithium Heparin for CyTOF analysis and banking for all patients included in France, Belgium and Italy<br>Please look below for all other required actes/items that are common with all other cycles.<br>**Evaluation during treatment (cf. 9.6):**<br>***Before C4 (only for patients treated with R-Benda):**<br>· Cervical, chest, abdomen, and pelvis CT with IV contrast<br>· FDG-PET/CT scan<br>· Endoscopic investigations with biopsies and MRI: if clinically appropriate<br>***Before C7** = primary response evaluation (for patients who stopped R-Benda after C4, do not repeat exams already done after C3):<br>· Clinical examination including ECOG PS and tumor assessment<br>· Vital signs<br>· Hematological tests<br>· Abnormal lymphoma cells by flow cytometry<br>· Biochemical tests<br>· Cervical, chest, abdomen, and pelvis CT with IV contrast<br>· FDG-PET/CT scan |

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| | · Endoscopic investigations with biopsies and MRI: if clinically appropriate<br>· Bone marrow aspirate with local flow cytometry of marrow<br>· Evaluation of the disease response Lugano 2014 criteria<br>· Registration of concomitant medication taken<br>· Adverse events (AEs) / SAEs / AESI<br>· Quality of life as measured by the EQ-5D-5L<br>· Samples for ancillary biological studies (either blood or marrow aspirate).<br>· For sampling details please refer to part 11.4 Biological Banking and ancillary studies:<br>o Blood on EDTA for MRD analysis and banking for SMZL patients<br>o Blood on Lithium Heparin for CyTOF analysis and banking for all patients included in France, Belgium and Italy<br>o Bone marrow aspirate samples (only for patients with marrow involvement at baseline<br><br>**At 12 months from treatment start, i.e. 12 months from C1D1 (end of treatment= EOT) or within 30 days following permanent treatment discontinuation:**<br>· Vital signs<br>· Clinical examination including ECOG PS and tumor assessment<br>· Endoscopic investigations as appropriate<br>· Hematological tests<br>· Abnormal lymphoma cells<br>· Biochemical tests<br>· Serum IgG, IgM, IgA, and serum Immunofixation if a monoclonal component is known<br>· Abnormal lymphoma cells by flow cytometry, only if SMZL and in abnormal lymphoma cells present at baseline. Not centralized<br>· Bone marrow aspirate with local flow cytometry of marrow: for confirmation of CR for patients with initial marrow involvement (that persists at the evaluation of primary response). No centralization<br>· CT scan of cervical, chest, abdomen, pelvis<br>· FDG-PET/CT scan<br>· Endoscopic investigations with biopsies and MRI: if clinically appropriate<br>· Evaluation of the disease response Lugano 2014 criteria<br>· Samples for biological studies. Refer to the part 11.4 Biological Banking and ancillary studies<br>o Blood on streck for cfDNA and ctDNA analysis and banking for all patients included in France, Belgium and Italy |

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| | ○ Blood on EDTA for MRD analysis and banking for SMZL patients<br>○ Blood on Lithium Heparin for CyTOF analysis and banking for all patients included in France, Belgium and Italy<br>○ Bone marrow aspirate on Lithium Heparin tube for MRD and CyTOF analysis and banking for all SMZL patients, and only if the bone marrow is involved at baseline for EMZL and for NMZL patients included in France, Belgium and Italy<br>· Adverse events (AEs) / SAEs / AESI: until 90 days after the last study drug administration.<br>· Quality of life as measured by the EQ-5D-5L<br><br>**Follow-up assessments:**<br>**At 24 months from treatment start, i.e. 24 months from C1D1**<br>· Vital signs<br>· Clinical examination including ECOG PS and tumor assessment<br>· Endoscopic investigations as appropriate<br>· Serum IgG, IgM, IgA, and serum Immunofixation if a monoclonal component is known<br>· Hematological tests<br>· Abnormal lymphoma cells<br>· Biochemical tests<br>· Abnormal lymphoma cells by flow cytometry, only if SMZL and in abnormal lymphoma cells present at baseline. Not centralized<br>· Bone marrow aspirate with local flow cytometry of marrow: for confirmation of CR for patients with initial marrow involvement (that persists at the evaluation of EOT response). No centralization<br>· CT scan of cervical, chest, abdomen, pelvis<br>· FDG-PET/CT scan: mandatory<br>· Endoscopic investigations with biopsies and MRI: if clinically appropriate<br>· Evaluation of the disease response Lugano 2014 criteria<br>· Samples for biological studies. Refer to the part 11.4 Biological Banking and ancillary studies for sampling détails:<br>○ Blood on streck for cfDNA and ctDNA analysis and banking for all patients<br>○ Blood on EDTA for MRD analysis and banking for SMZL patients<br>○ Blood on Lithium Heparin for CyTOF analysis and banking for all patients<br>○ Bone marrow on Lithium Heparin tube for MRD and CyTOF analysis and banking for all SMZL patients and only if the bone marrow is involved at baseline for EMZL and for NMZL patients |

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| | · Adverse events (AEs) / SAEs / AESI related to treatment<br>· Quality of life as measured by the EQ-5D-5L<br><br>**At 36, 48 and 60 months +/- 1 month from treatment start, i.e. from C1D1**<br>· Vital signs<br>· Clinical examination including ECOG PS and tumor assessment Endoscopic investigations as appropriate<br>· Hematological test<br>· Biochemistry: only LDH<br>· Serum IgG, IgM, IgA, and serum Immunofixation if a monoclonal component is known<br>**At the time of progression / relapse:**<br>· Vital signs<br>· Clinical examination including ECOG PS and tumor assessment Endoscopic investigations as appropriate<br>· Hematological test<br>· Biochemical tests<br>· Local Flow cytometry of peripheral blood mandatory in case of SMZL or if hyperlymphocytosis > 5 G/L for all subtypes. No centralization<br>· Biopsy of a lesion for pathological confirmation should be done if possible<br>· CT scan of cervical, chest, abdomen, pelvis<br>· FDG-PET/CT scan<br>· Endoscopic investigations with biopsies and MRI: if clinically appropriate<br>· Samples for biological studies. Refer to the part **11.4 Biological Banking and ancillary studies for sampling** details:<br>o Blood on streck for cfDNA and ctDNA analysis and banking for all patients<br>o Blood on EDTA for MRD analysis and banking for SMZL patients<br>o Blood on Lithium Heparin for CyTOF analysis and banking for all patients<br>o Bone marrow on Lithium Heparin tube for MRD and CyTOF analysis and banking for all SMZL patients and only if the bone marrow is involved at baseline for EMZL and for NMZL patients<br>• Adverse events (AEs) / SAEs / AESI related to treatment<br>**Survival follow-up, after progression**<br>· Subsequent Treatment line |

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| | · Vital status<br>· Other malignancies |
| **Safety considerations - Pharmacovigilance** | SAE (see section 14.3), AESI (see section 14.5), neurotoxicities and infections from grade ≥ 2, and all other AEs from grade ≥ 3, regardless of the relationship to investigational products, occurring **from the date of informed consent signature to 90 days after last study treatments administration (i.e. mosunetuzumab and lenalidomide, rituximab, CHOP, bendamustine)** will be recorded in the AE pages of the eCRF.<br><br>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 and lenalidomide, rituximab, CHOP, bendamustine)**<br><br>All patients who received at least one dose of study treatments will be included for all safety analyses. Safety will be assessed by monitoring and recording of CRS by ASTCT (Lee, 2019) and by NCI-CTCAE v5.0 for other AEs. Laboratory values (e.g., hematology, clinical chemistry), vital signs, electrocardiograms, ECOG performance status, and physical examinations will also be used in determining safety. Drug exposure will be summarized by duration, dosage, and dose intensity.<br><br>**Safety Monitoring Committee**<br><br>A Safety Monitoring Committee (SMC) will review data throughout the study to fully evaluate the safety of Mosunetuzumab + lenalidomide. The SMC will include an independent member.<br><br>The SMC will review the data of safety with a safety run, with a stop of the enrollment after inclusion of the first 10 MZL patients, including at least 3 patients with blood involvement. These patients will not be randomized, and all will be treated in the experimental arm. All data collected before the beginning of C3 of the 10th patient will be analyzed.<br><br>Following meetings of SMC will take place at least once a year during the treatment period. The SMC, in accordance with the charter, may recommend study modification including termination of the study due to safety concerns.<br><br>Following SMC recommendations, the sponsor will make all final decisions regarding any change in study conduct. |
| **Registration in the study and Randomization** | Patients will be included and randomized after verification of their eligibility directly in the data entry system by investigators, via Internet at the following address: http://study.lysarc<br>To access the interactive registration program, the investigator must enter the name of the study (MARSUN), his username and password. |
| **Statistical consideration** | **Analysis set**<br><br>The **Enrolled Set** will include all patients having signed the informed consent whether they have been randomized or not.<br><br>The **ITT Set (ITT)** will include all patients having signed their informed consent and who are 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 **Patient-reported-outcome-evaluable Set (PRO)** will include patients in the ITT set who have a baseline and at least 1 post-baseline assessment.

The **Per Protocol Set (PP)** 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 main criterion.

The **Safety Set** will include all patients having signed their informed consent and who received at least one dose of either one investigational drug or the investigator's choice therapy. Patients will be analyzed according to the treatment actually received.

**Sample size calculation**

Sample size calculation was performed with EAST software version. 6.5.

**Primary endpoint: PFS**

The hypotheses are the following:

- superiority test
- median PFS in the control arm = 20.2 months
- median PFS in the experimental arm = 30 months (HR = 0.673)
- one-sided alpha = 5%
- power = 80%
- one interim early efficacy analysis (75% of events)
- efficacy boundary based on Lan-DeMets spending function with O'Brien-Fleming approximation
- drop-out: 10% per year
- randomization ratio 1:1

Based on these assumptions and including an efficacy interim analysis, 163 PFS events would have to be observed on the ITT set.

Assuming an accrual rate of 2.67 patients per months the first 6 months of inclusion, 4 patients per month from month 6 to month 12, and 6.67 patients per month after 12 months, 260 (10+250) patients will be included over an approximately 4-year accrual period.

Ten patients will be included in the experimental arm A for the safety-run (and inclusions will be stopped during safety-run analysis) and then 250 supplemental patients will be randomized:

- 125 in the experimental arm A Mosun-Len,

- 125 in the control arm B: 40% Ritux-Len (i.e. n=50) and 60% Ritux-Chemo (i.e. n=75).

**Analysis plan**

Survival endpoints will be analyzed using Kaplan-Meier method. Survival probabilities at fixed time points, median survival and quartiles will be estimated (if reached) with their 95% CI. Survival curves will be provided. 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 main criterion, superiority will be established based on the one-sided stratified log-rank test. The main analysis of primary criterion will be performed on the ITT set and a supportive analysis will be conducted on PP set.

In order to ensure an overall one-sided 0.05 study-wise Type I error rate for PFS, a fixed-sequence gate-keeping procedure with an O'Brien-Fleming alpha spending function is used to interpret the analysis results.

Response rates will be expressed with 95% confidence limits according to Pearson-Clopper method. Missing response will be considered as not evaluated. Patients without response assessment at one evaluation will be considered as non-responder at the evaluation. The number and percent of patients falling into each category of response (CR, PR, SD, PD, Not evaluated) will be provided.

Descriptive analysis of safety endpoints will be conducted on Safety Set.

**Time of Analysis**

Three analyses are planned:

*Interim analysis of primary endpoint*

Analysis will be performed after 122 PFS events will have been observed in the ITT set. It is estimated that cut-off for analysis will occur approximately 4.1-4.5 years after the first patient has been randomized.

Main criterion, secondary efficacy criteria (when relevant) and safety endpoints will be analyzed.

*Final analysis of primary endpoint*

Final analysis of primary endpoint will be conducted (except if early efficacy was demonstrated) once 163 PFS events will have been observed in the ITT set or at the latest at the time of end of study analysis.

It is estimated that cut-off for analysis will occur approximately 5.5-6.5 years after the first patient has been randomized.

*End of study analysis*

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