Synopsis

SPONSOR	International Extranodal Lymphoma Study Group (IELSG)	
NAME PRODUCT / INTERVENTION	BENDAMUSTINE AND MABTHERA	
NAME OF ACTIVE PRINCIPLE	Bendamustine cloridrato and rituximab	
PROTOCOL CODE	IELSG36	
PROTOCOL TITLE	BRISMA Bendamustine and Rituximab for the treatment of Splenic Marginal Zone Lymphoma. The IELSG-36 phase II prospective study	
PRINCIPAL INVESTIGATORS	Dr. Andrés J. M. Ferreri	IRCC San Raffaele Scientific Institute Milan (IT)
	Prof. Francesco Passamonti	ASST Sette Laghi Ospedale di Circolo and Macchi Foudation Varese (IT)
	Prof. Marco Gobbi	IRCC Policlinico San Martino S.S.R.L.Genoa (IT)
	Prof. Bertrand Coiffier	Lyon Sud Hospital Pierre Benite (FR)
	Dr. Samantha Pozzi	Policlinico of Modena University Hospital Modena (IT)
	Dr. Francesco Merli	IRCCS - Arcispedale Santa Maria Nuova Reggio Emilia (IT)
	Dr. Nathalie Denizon	Le Mans Hospital Le Mans (FR)
	Dr. Manuela Zanni	SS. Antonio e Biagio e Cesare Arrigo Hospital Alessandria (IT)
	Dr Corinne Haiounne	Henri Mondor Hospital Cretiel (FR)
	Prof. Hervé Tilly	Centre Henri Becquerel Hospital Rouen (FR)
	Dr. Caterina Stelitano	Bianchi-Melacrino- Morelli Hospital Reggio Calabria (IT)
	Dr. Franck Morschhauser	Lille University Hospital Lille (FR)
	Dr. Daniele Vallisa	Guglielmo da Saliceto Hospital Piacenza (IT)
	Prof. Catherine Thieblemont	Saint-Louis Hospital Paris (FR)
	Dr. Giuseppina Cabras	Businco Oncological Hospital Cagliari (IT)
	Dr. Pierre Feugier	Brabois University Hospital Vandoeuvre-les-Nancy (FR)
	Dr. Salvatrice Mancuso	Policlinico Giaccone University Hospital Palermo (IT)
	Prof. Anna Marina Liberati	S. Maria Hospital Terni (IT)
	Prof. Steven Le Gouill	Hôtel Dieu Universitary Hospital Nantes (FR)
	Dr. Caroline Besson	Bicêtre Hospital Le Kremlin-Bicêtre Paris (FR)
	Dr. Olivier Casasnovas	D'Enfants University Hospital Dijon (FR)
	Dr. Guido Gini	A.O.U. Ospedali Riuniti – Università Politecnica delle Marche Ancona (IT)

	Dr. Barbara Castagnari	Santa Maria delle Croci Hosptial Ravenna (IT)
	Dr. Francesca Palombi	Regina Elena Institute – IFO Rome (IT)
	Dr. Caterina Patti	Villa Sofia-Cervello HospitalPalermo (IT)
	Dr. Francesca Re	Parma University Hospital Parma (IT)
	Dr. Rémy Gressin	Grenoble University Hospital Grenoble (FR)
	Dr. Kamal Boubdallah	François Magendie Hospital Pessac (FR)
	Dr. Pier Paolo Fattori	Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) Meldola (IT)
	Dr. Pellegrino Musto	IRCCS-Centro Riferimento Oncologico Rionero in Vulture (IT)
STUDY SITES	Two Countries involved – Italy and France - with a total of 30 enrolling sites.	
STUDY PERIOD	First Patient Enrolled 03.12.2012 Last Patient Enrolled 13.11.2014	
DEVELOPMENT PHASE	II	
OBJECTIVES	<u>Primary Objective</u> To evaluate the efficacy of bendamustine in combination with rituximab in previously untreated splenic marginal zone lymphoma (SMZL) measured by complete response rate <u>Secondary Objectives</u> To evaluate safety and tolerability measured by toxicities of Bendamustine - Rituximab To further evaluate efficacy measured by - Overall Response Rate (ORR) - 3-year Progression Free Survival (PFS) - Duration Of Response (DOR) - 3-year Event Free Survival (EFS) - Time To Next Treatment (TTNT) – 3-year Overall Survival (OS) – risk of histological transformation – 5 year PFS and OS	
STUDY DESIGN AND METHODOLOGY	Splenic Marginal Zone Lymphoma (SMZL) has been individualized as a specific entity among mature B-cell lymphoid neoplasms in the updated revision of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. The association of bendamustine and rituximab (B-R) has been shown to be highly effective for almost the entire spectrum of indolent B-cell lymphomas with manageable toxicity profile. B-R has never been tested in a prospective trial for SMZL. On this basis, the phase II IELSG36 study was designed to investigate the activity and safety of B-R as first-line systemic treatment in non-splenectomised SMZL patients or in those relapsing after splenectomy. This study investigated on the activity and safety of an immunochemotherapy with six cycles of bendamustine in combination with rituximab as first-line treatment in splenectomised and non-splenectomised patients with initial diagnosis of CD20+ SMZL confirmed by central diagnostic review. The B-R regimen consisted of	

	28-day cycle. Patients achieving a complete response (CR) after 3 cycles received only one more cycle of B-R, while those achieving a partial response (PR) received 3 additional cycles of B-R; if less than PR patients were withdrawn from the study.
SUBJECT POPULATION	Number of Subjects Planned 78 Number of Subjects Enrolled 78 <u>Brief description of demographic and baseline characteristics</u> The median age at diagnosis was 66 years, and 59% were males; significant anemia and thrombocytopenia were detected in 18% and 14%, respectively, while lymphocytosis was present in 56%. Two patients had undergone splenectomy and experienced disease progression within one year prior to registration; BM was involved in all patients. A huge splenomegaly, deep lateral lymphadenopathy and lung extranodal involvement were recorded in 75%, 54%, 5% of cases, respectively. No patient had received anti-hepatitis C virus therapy prior to the study entry. <u>Brief description of subjects excluded from primary analysis population</u> Twenty-two out 78 patients turned out ineligible for the following reasons: not confirmed SMZL diagnosis by central review (16 cases); age >80 years (3 cases); withdrawal of the Informed Consent (1 case); treatment not started (1 case); urgent treatment needed (1 case).
ELIGIBILITY CRITERIA	<u>Inclusion Criteria</u> 1. Initial diagnosis of CD20+ Splenic Marginal Zone Lymphoma morphology confirmed by histology, cytology, immunophenotype (chromosomal abnormalities by quantitative multiplex PCR of short fluorescent fragments (QMPSF) is optional) according to WHO 2008 classification of Lymphoma criteria or according to the recommendation of the Splenic Lymphoma Group (Matutes et al. Leukemia 2008) for non splenectomized patient. a) If patients not splenectomised: diagnosis on bone marrow biopsy (histology and immunohystochemistry), and blood (cytology, immunophenotype), chromosomal abnormalities by QMPSF optional. b) If patients splenectomised diagnosis on spleen, bone marrow biopsy (histology and immunohistochemistry), and blood (cytology, imunophenotype) chromosomal abnormalities by QMPSF optional. 2. No previous treatment with immunotherapy or chemotherapy or radiotherapy unless pretreatment by monocorticotherapy. 3 Patients requiring a treatment with at least one of the following following situation: a) Symptomatic SMZL in not splenectomized patients - Bulky (arbitrarily defined as ≥6 cm below left costal margin) or progressive or painful splenomegaly, without enlarged lymphoadenopathy, with or without cytopenia, not eligible for splenectomy or not willing splenectomy - One of the following symptomatic/progressive cytopenias: Hb <10 g/dL, or Platelets <80.000/mm^3, or ANC <1.000/mm^3, whatever the reason (autoimmune or hypersplenism or bone marrow infiltration) not eligible for splenectomy or not willing splenectomy - SMZL with enlarged lymphoadenopathy or involvement of extranodal sites with or without cytopenia b) Symptomatic disease in SMZL splenectomised patients with rapidly raising lymphocyte counts, development of lymphadenopaty or involvement of extranodal sites.

c) SMZL with concomitant hepatitis C infection who have not responded or are relapsed after Interferon and/or Ribavirin.

4 Clinically and/or radiologically confirmed measurable disease before treatment start.
5 Aged ≥ 18 yo at time of initial diagnosis and ≤ 80 yo.
6 Eastern Cooperative Oncology Group [ECOG] performance status 0-2.
7 Minimum life expectancy of >6 months.
8 Voluntary signed informed consent before performance of any study related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
9 The following laboratory values at screening:
- Absolute neutrophil count (ANC) ≥1.000/mm3 and Platelets ≥100.000/mm3, unless these abnormalities are related to bone marrow infiltration or to hypersplenism.
- Aspartate transaminase (AST) ≤2 x ULN; Alanine transaminase (ALT) ≤2 x ULN; total bilirubin ≤1.5 x ULN.
- Creatinine clearance ≥ 10 ml/min (as calculated by the Cockcroft-Gault formula).

All patients must:
1. Agree to abstain from donating blood while taking study drug therapy and following discontinuation of study drug therapy.
2. Agree not to share study medication with another person.
3. Agree to use an adequate method of contraception for women of childbearing potential during the study treatment and until 12 months after the end of the study treatment.
4. Agree to use an adequate method of contraception for men during the study treatment and until 6 months after the end of the study treatment

Exclusion Criteria

1. Any type of lymphoma other than SMZL.
2. Patients with proven biopsy of histological transformation.
3. Contraindication to any drug contained in the chemotherapy regimen.
4. Myocardial infarction during last 3 months or unstable coronary disease or uncontrolled chronic symptomatic congestive heart insufficiency NYHA III – IV.
5. Uncontrolled hypertension.
6. Uncontrolled diabetes mellitus as defined by the investigator.
7. Active systemic infection requiring treatment.
8. Previously known HIV positive serology.
9. Active hepatitis B virus infection (presence of antigen HBS+; in case of presence of antibody anti HBC+ and anti HBS+, controls should be organized according to guidelines of AASLD and l'EASL).
10. Active and previously untreated HCV infection.
11. Prior history of malignancies other than lymphoma within 3 years (except for complete resection of basal cell carcinoma, squamous cell carcinoma of the skin, or in situ malignancy). Patients previously diagnosed with prostate cancer are eligible if (1) their disease was T1-T2a, N0, M0, with a Gleason score ≤7, and a prostate specific antigen (PSA) ≤10 ng/mL prior to initial therapy, (2) they had definitive curative therapy (ie, prostatectomy or radiotherapy) ≥2 years before Day 1 of Cycle 1, and (3) at a minimum 2 years following therapy they had no clinical evidence of prostate cancer, and their PSA was undetectable if they underwent prostatectomy or <1 ng/mL if they did not undergo prostatectomy.
12. Major surgery within 30 days before the inclusion in the study
13. A positive Coombs test without haemolysis or an autoimmune

	hemolytic anemia is not an exclusion criterion. 14. Impaired renal function with creatinine clearance <10 ml/min. 15. Severe chronic obstructive pulmonary disease with hypoxemia. 16. Medical condition requiring long-term use (>1 months) of systemic corticosteroids. 17. Serious medical or psychiatric illness likely to interfere with participation in this clinical study. 18. Prior participation in another study with experimental drug during the last 4 months. 19. Pregnant or currently breast-feeding woman.
STUDY PRODUCTS / DOSE AND MODE OF ADMINISTRATION/ INTERVENTIONS	**Induction Phase** ***Bendamustine - Rituximab(B-R)***: cycles 1 to 3: (week 0, 4, 8) Rituximab: 375 mg/sqm i.v. day 1* Bendamustine: 90 mg/sqm iv days 1-2 or days 2-3 according to institutional/patient/physician choice Treatment will be administered on a 28-day cycle basis. * Administration of rituximab during cycle 1 and 2 can be postponed to day 8 or day 14 in case of risk of tumor lysis syndrome: i.e. marked splenomegaly or lymphocytosis above 10.000 lymphocytes/µl. **Extended Phase** ***Bendamustine - Rituximab(B-R):*** cycles 4 to 6: (week 12, 16, 20) Rituximab: 375 mg/sqm i.v. day 1 Bendamustine: 90 mg/sqm iv days 1-2 or days 2-3 according to institutional/patient/physician choice. Treatment will be administered on a 28-day cycle basis. Prophylaxis with valaciclovir 500 mg once a day and trimethoprim/cotrimoxazole 800 mg twice a day, twice a week, was recommended for all patients during all treatment cycles. Patients will be treated with 3 cycles of Bendamustine - Rituximab and then restaged. If in PR patients will proceed to the next extended phase with 3 more R-B cycles. If in CR only one more Bendamustine - Rituximab course will be delivered. Patients with clinical response less than PR will go off the study. Patients in CR or PR at the end of the third course of Bendamustine - Rituximab and who proceeded to the extended phase will be considered to have completed the chemio-immunotherapy program and will undergo final restaging after 4 cycles or after 6 cycles (24 weeks) of Bendamustine - Rituximab treatment respectively.
DURATION OF TREATMENT	Patients will be treated for up to a total of 4-6 cycles R-B, unless removed from study for failure to respond after 3 cycles or toxicity. All responding patients will be followed-up until disease progression or death for a maximum of 60 months.
STUDY ENDPOINTS	**Primary endpoints** Efficacy of Bendamustine - Rituximabstine measured by **Complete Response rate.** Complete response rate will be assessed by means of CT-scan, Immunophenotype in blood and bone marrow (PET-scan optional). The recently published recommendations of an International experts panel will be applied. Response criteria will be determined as follows: **Complete response (CR)** requires the disappearance of all evidence of disease a. Regression to normal size on CT of organomegaly (splenomegaly, hepatomegaly and lymphoadenopathies) b. Normalization of the blood counts (Hb >12 g/dl; platelets >100.000/mm^3; neutrophils >1.500/mm^3 and no evidence of circulating clonal B-cells) c. No evidence or minor (<5%) BM infiltration detected by

	immunohistochemistry. **Partial response (PR)** requires regression of 50% or greater in the measurable disease manifestations and no new sites of disease. This should include: resolution or decrease in spleen size, improvement on cytopenias and resolution or decrease in lymphadenopathy if present. Bone Marrow should show a decrease in the level of lymphoid infiltration and improvement of the haemopoietic reserve. **No response (NR) and progressive disease (PD)** less than 10% improvement on the disease manifestations or deterioration, by increase >50%, of measurable signs of the disease from nadir- **Relapsed disease**: Reappearance of any measurable sign of the disease. A patient is defined as a *responder* if she/he has a complete or partial response. Patients without response assessment (due to whatever reason) will be considered as *non-responders*. **Secondary endpoints** **Overall Response Rate (ORR)** (Complete response + Partial response) **Safety and tolerability measured by toxicities of Bendamustine - Rituximab** evaluated by assessment of laboratory parameters and adverse events coded with NCI Common Toxicity Criteria, version 4.0. **3-year Progression Free Survival (PFS)**, defined as the time from entry into the study until reappearance of cytopenia or lymphoma relapse/ progression with enlarged lymph node(s) or spleen if present, histologic transformation or death as a result of any cause. Responding patients, patients who are lost to follow up, who withdrawal the consent or drop-out due to adverse event will be censored at their last assessment date. Patients died due to tumor will be considered in progression. Patients died for any other cause will be censored to the death date. **Duration of Response (DR)**, is defined for all patients who achieved a response (CR and PR) and is measured from the time of response until the date of first documentation of progression or relapse. Patients without relapse or progression will be censored at their last assessment date. Patients died due to tumor will be considered in progression. Patients died for any other cause will be censored to the death date. **3-year Event Free Survival (EFS)**, will be measured from the day of treatment start to the date of documentation of one of the following events: any treatment failure including disease progression, or discontinuation of treatment for any reason (eg, disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death). Responding patients, patients who are lost to follow up, who withdrawal the consent or drop-out due to adverse event will be censored at their last assessment date. **Time To Next Treatment (TTNT)**, defined as the time from the end of the chemo-immunotherapy course to the day of next treatment commencement irrespective of cause **3-year Overall Survival (OS),** defined as the time from the date of treatment start into the study until the date of death irrespective of cause. Patients who have not died at the time of end of the whole study, and patients who are lost to follow up, will be censored at the date of the last contact **Risk of histological transformation** **5-year PFS and OS**
STATISTICAL METHODS	This phase II study has been designed according to Simon's two-stage Optimal Design. The primary objective of the study is to demonstrate a clinical benefit in Complete Response Rate (CRR) with Bendamustine - Rituximab association in patients with splenic

	marginal zone lymphoma. Complete Remission (CR) was used to determine the sample size of the study. There are no established data in splenic marginal zone lymphoma patients in first line treatment. The CR rate with rituximab and different chemotherapy regimens in previous studies ranged from 40 to 80%. Comparison data for the study design and sample size calculations come from a median of those reported from different studies. The median expected CR rate for splenic marginal zone with the same characteristics indicated into the study and treated with standard rituximab + chemotherapy may be estimated to be approximately 60%. We would consider a positive result to increase CR rate from 60% to 80%.
SUMMARY OF RESULTS	<u>Efficacy Results</u> As per protocol, the study included an interim analysis and a final analysis. The interim analysis was performed on the first 19 evaluable patients and CR was reported in 14 patients (74%). The response assessment of the final analysis was performed by local clinicians after 3 B-R cycles: at this time point, response was complete in 7 patients (13%) and partial in 39 patients (70%), with an overall response rate of 82%. Importantly, a centralized review of final response was performed, according to the intention to treat principle. Forty-one patients were classified as CRs (34 CR and 7 CRu) (73%); residual abnormalities of seven CRu patients remained stable or even decreased on imaging studies after 6 months of follow-up, so their response was reclassified as CR. PR were assessed in 10 patients (18%). Four patients were classified as stable disease (7%)
	<u>Safety Results</u> Adverse events of any grade were reported in 50 (89%) patients, including treatment related grade ≥3 toxicity reported in 38 (68%) patients. Five patients discontinued treatment due to toxicity. The most frequent grade ≥3 adverse events were neutropenia (24, 42.8%), thrombocytopenia (9, 16.1%) and anaemia (5, 8.9%). Non-haematological toxicity was almost exclusively of grade 1–2, with nausea/vomiting, maculo-papular rash and infusion-related reactions being the most frequent adverse events; only 5 patients experienced grade ≥3 toxicities: infections in 2 patients (3.6%) and febrile neutropenia in 3 patients (5.3%). Serious adverse events occurred in 14 patients (25%). Seven second tumours were observed. In particular, thyroid cancer (1 case), kidney cancer (1 case), myelodysplasia (1 case), malignant peripheral nerve (1 case), prostate cancer (1 case), Hodgkin lymphoma (1 case) and basalioma (1 case).
CONCLUSIONS	This international multicentre study is a first attempt to study the B-R combination focusing on SMZL. The results of the study show that B-R is a safe and active first-line treatment compared to other rituximab-chemotherapy combinations previously reported for SMZL. In fact, B-R is associated with a better toxicity profile than R-COMP, with lower rates of severe infections (36% vs. 8%) and lethal toxicity. Of the patients enrolled in the study, 13% achieved CR after only three cycles. Furthermore, disease failures were uncommon, with four deaths in a median follow-up of 60 months, and therefore this combination can be recommended as the first choice for non-splenectomized patients with symptomatic, progressive SMZL. Although any direct comparison is not appropriate, the different time-dependent outcomes (DOR, PFS, EFS and OS) and safety profile of the B-R combination addressed in this study compare favourably with those reported using regimens including anthracyclines or cladribine, leading us to recommend B-R over other rituximab-chemotherapy

	combinations for patients with symptomatic SMZL.
VERSION AND DATE OF THE REPORT	Version 1.0 – 22.11.2021