Synopsis

SPONSOR	International Extranodal Lymphoma Study Group (IELSG)	
NAME PRODUCTS / INTERVENTION	Rituximab, doxorubicin, vincristine, prednisone, cyclophosphamide, depocyte® and methotrexate.	
NAME OF ACTIVE PRINCIPLE	Rituximab, doxorubicin, vincristine, prednisone, cyclophosphamide, depocyte® and methotrexate.	
PROTOCOL CODE	IELSG30	
PROTOCOL TITLE	A phase II study of R-CHOP with intensive CNS prophylaxis and scrotal irradiation in patients with primary testicular diffuse large B-cell lymphoma	
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STUDY SITES	Two countries involved, Italy and Switzerland, and a total of 18 enrolling sites.
STUDY PERIOD	First Patient Enrolled - 27 September 2009 Last Patient Enrolled - 13 July 2017
DEVELOPMENT PHASE	II
OBJECTIVES	Primary Objective To demonstrate safety and feasibility of the R-CHOP regimen in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional radiotherapy (RT) in untreated patient with stage I and II Primary Testicular Lymphoma (PTL) Secondary Objectives - To evaluate the efficacy of the R-CHOP regimen (a regimen consisting of cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine) in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional RT in prolonging 3-year Progression-Free Survival (PFS) and 3-year Event-Free-Survival (EFS) rate compared to historical standard treatment. - To evaluate 3-year overall survival (OS) of the patients treated with R-CHOP in combination with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate followed by loco-regional RT.
STUDY DESIGN AND METHODOLOGY	The study was divided in 4 phases: 1- Pre-treatment phase of 30 days. Patients were evaluated, according to the protocol, before to be enrolled in the study by means of the conventional procedures. 2- Open label nonrandomized multicenter treatment phase. The investigator assessed patient response to therapy using efficacy measurements and disease response criteria. Patients were evaluated through this phase for possible toxicities and delays in dosing. Dose modifications were made as required according to dose modification rules. Patients were treated with 6 cycles of R-CHOP chemotherapy with a twenty-one-day rest period between them. Cycles 2,3,4 and 5 were scheduled with the association of intrathecal (IT) chemotherapy with Depocyte®. 3- Consolidation phase. Three weeks after the 6th cycles of R-CHOP chemotherapy, patients will receive 2 cycles of intermediate-dose Methotrexate therapy every two weeks followed, 2 weeks later, by scrotal prophylactic RT or involved field RT (but can be planned concomitantly to R-CHOP in patients with bilateral disease). 4- Follow-up phase. Patients were followed for disease progression and survival until the end of the study which is expected to be 36 months after the last patients enrolled into the study completed the treatment. Patients with progressive disease at any time were withdrawn from the study. For OS determination information was required up to 5 years.
SUBJECT POPULATION	Number of Subjects Planned 54 Number of Subjects Enrolled 54

	Number of Subjects Randomized: NA Number of Subjects for Each Analysis Population: Overall, Intention to Treat Population, 54 subjects Brief description of demographic and baseline characteristics Patients aged between 18 and 80 years with untreated primary stage I and II testicular lymphoma at diagnosis were eligible for the study. A total of 54 consecutive patients were enrolled. The median age was 66 years (range: 37-79 years), with 50% of patients being over 65 years old. Of these patients, 32 had stage I disease, and 22 had stage II disease. All but three patients had a baseline PET/CT scan; the exceptions were one patient with stage I disease and two patients with stage II disease. Diffuse Large B-Cell Lymphoma (DLBCL) histology was confirmed by expert pathologist review in all patients. One patient with stage II disease had bilateral testicular involvement at diagnosis. Elevated lactate dehydrogenase levels were observed in 7 patients. Brief description of subjects excluded from primary analysis population. No patients were excluded from the primary analysis population: all 54 patients enrolled were treated and evaluated for response assessment.
ELIGIBILITY CRITERIA	**Inclusion Criteria** Patients must satisfy the following criteria to be enrolled in the study. 1. Patients with primary testicular lymphoma at diagnosis. Histological subtype included into the study is only DLBCL. 2. Orchiectomy is mandatory, before enrolment of the patient into the study. 3. Orchiectomy should be performed within 2 months before study entry. 4. Age 18-80 5. Untreated patients 6. Ann Arbor Stage IE and IIE. Bilateral testicular involvement at presentation will not be considered Stage IV. These patients may be included into the study and the final Ann Arbor stage (I or II) will be determined by the extent of nodal disease. 7. Bidimensionally measurable or evaluable disease. Patients who have had all disease removed by surgery are eligible. 8. Adequate haematological counts: ANC > 1.0 x 10^9/L and PLTs count > 75 x 10^9/L 9. Cardiac ejection fraction ≥ 45% by MUGA scan or echocardiography 10. Non peripheral neuropathy or any active non-neoplastic CNS disease. 11. No other major life-threatening illnesses that may preclude chemotherapy 12. Conjugated bilirubin ≤ 2 x ULN. 13. Alkaline phosphatase and transaminases ≤ 2 x ULN. 14. Creatinine clearance ≥ 45 ml/min. 15. HIV negativity 16. HBV negativity or patients with HBcAb +, HbsAg -, HBsAb+/- with HBV-DNA negative 17. HCV negativity except for patients with no signs of active chronic

	hepatitis histologically confirmed 18. Life expectancy > 6 months. 19. Performance status < 2 according to ECOG scale. 20. No psychiatric illness that precludes understanding concepts of the trial or signing informed consent 21. Written Informed Consent **Exclusion Criteria** Potential patients who meet any of the following criteria were excluded from participating in the study. 1. Has known or suspected hypersensitivity or intolerance to rituximab. 2. History of clinically relevant liver or renal insufficiency; significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, rheumatologic, hematologic, psychiatric, or metabolic disturbances 3. Uncontrolled diabetes (if receiving antidiabetic agents, subjects must be on a stable dose for at least 3 months before first dose of study drug) 4. Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment, New York Heart Association (NYHA) Class III or IV heart failure (Attachment 5, NYHA Classification of Cardiac Disease), uncontrolled angina, clinically significant pericardial disease, or cardiac amyloidosis. 5. History of clinically relevant hypotension 6. Central Nervous System (CNS) involvement (meningeal and/or brain involvement by lymphoma) 7. Evolving malignancy within 3 years except for localized non-melanomatous skin cancer. 8. HIV positivity 9. HBV positivity except for patients with HBcAb +, HbsAg -, HBs Ab+/- with HBV-DNA negative 10. HCV positivity except for patients with no signs of active chronic hepatitis histologically confirmed. 11. Active opportunistic infection 12. Receipt of extensive radiation therapy, systemic chemotherapy, or other antineoplastic therapy 13. Exposure to Rituximab prior study entry 14. Have received an experimental drug or used an experimental medical device within 4 weeks before the planned start of treatment. Concurrent participation in non-treatment studies is allowed if it not interfere with participation in this study. 15. Any other co-existing medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent
STUDY PRODUCTS / DOSE AND MODE OF ADMINISTRATION/ INTERVENTIONS	**Treatment program and treatment phase** *WEEKS 1-15* 6 cycles of R-CHOP on days 0/1 to 5, to be repeated q21 days. **R-CHOP** Rituximab 375 mg/m2 day 0 or day 1 Cyclophosphamide 750 mg/m2 day 1 Doxorubicin 50 mg/m2 day 1

	Vincristine 1.4 mg/m2 (2 mg dose max) day 1 Prednisone 40 mg/m2 day 1-5 **IT CHEMOTHERAPY** Depocyte® 50 mg on day 0 of cycles 2, 3, 4 and 5 of R-CHOP The prophylactic IT Depocyte was administered a total of 4 times, during R-CHOP cycles. **CONSOLIDATION PHASE** Begins three weeks after the R-CHOP/IT therapy completion. **DOSE MTX** *WEEKS 18-22* Methotrexate 1.5 g/m^2 q 14 days x 2 cycles. It was administrated diluted in 500 ml of normal saline solution (NaCl 0.9%). A urine flow ≥ 125 ml/hour should have been recorded in the 12 hours prior to MTX administration. *FROM WEEKS 25* - Scrotal prophylactic RT or involved field RT (could be planned concomitantly to R-CHOP in patients with bilateral disease) All patients underwent intermediate restaging procedures after the third (and before the fourth) cycle of R-CHOP. The clinical response was reassessed at the end of the planned treatment, one to two months after completion of the entire therapy, including RT. Patients with progressive disease at any time were withdrawn from the study.
DURATION OF TREATMENT	195 days
STUDY PRIMARY ENDPOINT	**Adverse Events** Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. **Clinical Laboratory Tests** All laboratory tests should be performed at the laboratory of the investigational site: laboratory certificates or accreditation and normal ranges must be submitted before the patient's enrollment. **Electrocardiogram** Vital Signs (pulse, temperature, blood pressure, respiration rate) **Physical Examination** Any clinically significant abnormalities persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint. **Safety and feasibility of treatment** Severe hematological toxicities (grade 3-4) expected. Grading of toxicity will be defined according to the International Common Toxicity Criteria, version 3.0
STATISTICAL METHODS	Time-related endpoints were defined according to the revised National Cancer Institute (NCI) criteria; PFS was calculated from the date of diagnosis (date of orchiectomy) to relapse/progression or death as a result of any cause or to the date of last follow-up visit for event-free patients; OS was calculated from the date of diagnosis to death as a result of any cause or to the date of last follow-up visit.[13] The median follow-up was computed by the reverse Kaplan-Meier method. Survival probabilities were calculated using the life-table method,

	survival curves were estimated by the Kaplan-Meier method. Binomial exact 95% confidence intervals (CIs) were calculated for percentages. The sample size was calculated using the STATA/SE 11.2 statistical software. At the time the IELSG30 study was designed, the previous IELSG10 trial was still ongoing, and no reliable information on long-term PFS was available for sample size estimation. Hence, the study began with a planned inclusion of 35 patients over 4 years, followed by a calculation of a final sample size that could identify a clinically relevant PFS improvement of 15% (the primary endpoint). Once mature results of the IELSG10 study were available, showing a PFS of 67% at 7 years, the final sample size of 54 patients was subsequently defined. This was to allow the detection, in a single-arm study, of a 15% PFS increase (from 67% to 82%), with 80% power and an alpha of .05 (1-sided).
SUMMARY OF RESULTS	<u>Efficacy Results</u> The IELSG30 prospective trial demonstrated that the administration of IV HD-MTX in combination with IT liposomal cytarabine and the R-CHOP21 program is feasible and effective in a patient population with very high risk of CNS relapse and advanced age at diagnosis in many cases. Ninety-six percent of the enrolled patients received all the planned IT treatment, and 83% of them completed the program of systemic prophylaxis; >90% are alive and/or progression-free at 5 years. The 5-year survival rates in the IELSG30 trial appear more favourable. Moreover, the intensified CNS prophylaxis apparently abrogates the risk of CNS relapse. Nevertheless, the IELSG30 study also indicates potential benefit of IV HD-MTX in a patient population at very high risk of CNS recurrence. However, the experience gained in this study suggests that the administration of IV HD-MTX at the dose of ≥1.5 g/m^2 per 2 cycles, in combination with IT chemotherapy, may reduce the risk of CNS relapse, or that the addition of IV HD-MTX may have contributed to an overall improved outcome with a more effective systemic treatment. This trial provided further evidence of the efficacy of RT to prevent the risk of contralateral relapse; moreover, the lack of isolated retroperitoneal relapses in patients with stage II disease suggests that irradiation of retroperitoneal lymph nodes may be omitted in stage II disease without impairing the outcome. At the end of the treatment, 53 patients (98%) were in CR (confirmed by a PET/CT scan in all but 3 cases), and only 1 experienced progressive disease at nodal and extranodal sites and died 9 months later. Seven relapses occurred and 4 of them after 6 years from diagnosis. No CNS relapse was reported. Four of these patients died of lymphoma after 0.2 to 9 months after disease relapse, and 3 were alive after 2.5 to 20 months. Upon closure of the study, a total of 12 deaths were registered. The causes of death were lymphoma (n= 6), second primary malignancy (n= 1), cerebral vasculopathy (n= 1), bone marrow transplant complication (n= 1) unknown (n= 3).
	<u>Safety Results</u> All patients who entered in the study were included in the safety analysis. Forty-seven out of 54 patients, corresponding to 87% of the population, presented at least an AE related to the study drug and for 31 patients, corresponding to 57% of the total patients enrolled, was

	observed at least one severe AE (Grade ≥3). The 35% of the total patients experienced at least one SAE. The R-CHOP21 treatment was well tolerated with no unexpected adverse events. The administration IV HD-MTX was planned at the end of chemoimmunotherapy to prevent an adverse impact of MTX toxicity on the regular and complete delivery of the R-CHOP program. Two patients discontinued treatment after 4 and 5 cycles, respectively, because of toxicity (in both cases febrile neutropenia complicated by pneumonia). The adverse events induced by IT prophylaxis were mild and occurred at low frequency, only 1 patient discontinued treatment after 3 doses because of systemic toxicity related to R-CHOP21. High-dose MTX was feasible, with only 3 patients discontinuing treatment after the first dose because of adverse events (i.e., intracranial hemorrhage, acute kidney failure, and Grade 3 mucositis, in 1 patient each).
CONCLUSIONS	The IELSG30 prospective trial demonstrated the feasibility and effectiveness of administering IV HD-MTX in combination with IT liposomal cytarabine and the R-CHOP program in a patient population with a high risk of CNS relapse and advanced age at diagnosis in many cases. Ninety-six percent of the enrolled patients received all the planned IT treatment and 83% of them completed the systemic prophylaxis program, with over 90% alive and/or progression-free at 5 years. Moreover, in the present study the intensified CNS prophylaxis apparently abrogates the risk of CNS relapse. The IELSG30 study also indicates potential benefit of IV HD-MTX in a patient population at very high risk of CNS relapse. The data suggest that the administration of IV HD-MTX at the dose of 1.5 gr/m^2 or higher, in combination with IT chemotherapy, may reduce the risk of CNS relapse or that the addition of IV HD-MTX may have contributed to an overall improved outcome with a more effective systemic treatment. In addition, the present trial provides further evidence of the efficacy of RT to prevent the risk of contralateral recurrence. Late relapses, mainly involving extranodal sites, still represent a clinical challenge in the management of PTL.
VERSION AND DATE OF THE REPORT	Version 1.0 – 30.08.2024