Synopsis

SPONSOR	International Extranodal Lymphoma Study Group (IELSG)	
NAME PRODUCT / INTERVENTION	Positron Emission Tomography, conventional immunochemotherapy regimens and radiotherapy	
NAME OF ACTIVE PRINCIPLE	Rituximab, Cyclophosphamide, Doxorubicin, Methotrexate, Vincristine, Bleomycin, Prednisolone, Etoposide, Cytarabine, Ifosfamide, Vindesine	
PROTOCOL CODE	IELSG26	
PROTOCOL TITLE	A clinico-pathologic study of Primary Mediastinal B-cell lymphoma	
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STUDY SITES	Five Countries involved – Switzerland, Italy, United Kingdom, Spain and Chile – and a total of 21 sites.	

STUDY PERIOD	**First Patient Enrolled** 22/06/2007 **Last Patient Enrolled** 17/06/2009
OBJECTIVES	Primary Objective 1) To systematically analyse the phenotype and molecular characteristics of Primary Mediastinal B-Cell Lymphoma (PMBCL) 2) To determine the PET response rate following immunochemotherapy. Secondary Objectives 1) To obtain data, on a non-randomised basis, regarding the outcomes of treatment using different chemotherapy regimens, and using or omitting mediastinal radiotherapy depending upon the practice of the participating institutions 2) Progression Free Survival (PFS) and Overall Survival (OS).
STUDY DESIGN AND METHODOLOGY	The IELSG26 represents a prospective multi-centre cohort study designed to determine the PET response rate following immunochemotherapy in PMBCL. Each treating centre could choose among one of the standard immunochemotherapy regimens in use for PMBCL. Following is reported the list of the standard immunochemotherapy regimens: R-CHOP-21, R-CHOP-14, R-MACOP-B, R-VACOP-B and R- ACVBP. The centre was also allowed to complete the front-line treatment with a consolidation radiotherapy to the mediastinum, according to the local guidelines. Follow up was at monthly intervals for the first 3 months and then every 2 months until 1 year post treatment. In the second year the patient was assessed every 3 months, in the third year every 4 months, in the fourth year every 6 months and then annually.
SUBJECT POPULATION	Number of Subjects Planned: A minimum of 100 patients Number of Subjects Enrolled: 125 Number of Subjects for Each Analysis Population: Overall (intention-to-treat) population:125 Primary analysis [(Complete Metabolic Response (CMR) after immunochemotherapy]: 115 Population receiving consolidation radiotherapy: 88 Quantitative baseline parameters and metabolic heterogeneity: 103 Combination of quantitative parameters:100 Safety-Evaluable Population: 125 Brief description of demographic and baseline characteristics - Patients older than age 18 years with a histological confirmation of PMBCL, CD20 positive, and a dominant mass within the anterior mediastinum. - Patients with diseases newly diagnosed, any stage, eligible for intensive immunochemotherapy with curative intent. Brief description of subjects excluded from primary analysis population After front line immunochemotherapy, response assessment and risk stratification by PET was possible only in 115 out of the enrolled 125 patients. In particular, the 10 subjects were excluded due to the following

	reasons:
	- Early withdrawals (a total of 6 patients):
	  - 4 deaths (patients No. 20, 68, 78, 116)
	  - 2 lost to follow up (patients No.105 and 118)
	- Not evaluable PET images (a total of 4 patients, i.e. patients No. 7, 31, 47,101).

ELIGIBILITY CRITERIA	Inclusion Criteria 1. Primary mediastinal diffuse large B-cell lymphoma, CD20 positive. Patients must have histological confirmation of the diagnosis, and in addition have a dominant mass within the anterior mediastinum. 2. No prior treatment of lymphoma. Patients may have received corticosteroids for up to 1 week for the relief of local compressive symptoms. 3. Any stage of disease. 4. Age at least 18 years. 5. Fit to receive chemotherapy with curative intent. 6. Able and willing to give informed consent, and to undergo staging including PET scanning 7 Willingness to comply with an appropriate contraceptive method in women of childbearing potential or men. Exclusion Criteria 1. Evidence of clinically significant cardiac disease, as defined by history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within 12 months before study entry. Cardiac compromise due to local extension of lymphoma will not be an exclusion criterion in the absence of other cardiac disease. 2. Impairment of bone marrow function (WBC $<3.0x10^9$/L, ANC $<1.5x10^9$/L, PLT $<100x10^9$/L), unless due to involvement by lymphoma. 3. Major impairment of renal function (serum creatinine >2x upper normal) or liver function (ASAT/ALAT >2,5 upper normal, total bilirubin >2,5x upper normal), unless due to lymphoma involvement. 4. Known HIV infection. Patients will not be tested routinely. 5. Pregnant or lactating women. 6. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.
STUDY PRODUCTS / DOSE AND MODE OF ADMINISTRATION/ INTERVENTIONS	Immunochemotherapy Patients received one of the following standard immunochemotherapy regimens in use for DLBCL; the choice of regimens was defined by each centre for each patient.

Drug/administration route	Dose	Days
R-MACOP-B (a total of 71 patients)		
Rituximab i.v.	375 mg/m^2	1,22,43,64,85,106
Cyclophosphamide i.v.	350 mg/m^2	1,15,29,43,57,71
Doxorubicin i.v.	50 mg/m^2	1,15,29,43,57,71
Methotrexate i.v.	400 mg/m^2	8,36,64
Vincristine i.v.	1.4 mg/m^2	8,22,36,50,64,78
Bleomycin i.v.	10 mg/m^2	22,50,78
Prednisolone p.o	40 mg/m^2	1 to 84 then tail off
R-VACOP-B (a total of 34 patients)		
Rituximab i.v.	375 mg/m^2	1,22,43,64,85,106
Cyclophosphamide i.v.	350 mg/m^2	1,29,57
Doxorubicin i.v.	50 mg/m^2	1,15,29,43,57,71
Etoposide i.v.	75 mg/m^2	15,16,43,44,71,72
Vincristine i.v.	1.4 mg/m^2	8,22,36,50,64,78

	Bleomycin i.v.	10 mg/m^2	8,22,36,50,64,78
	Prednisolone p.o.	40 mg/m^2	1 to 84 then tail off
	R-CHOP-21 (a total of 7 patients), cycle of 21 Days		
	Rituximab i.v.	375 mg/m^2	1
	Cyclophosphamide i.v.	750 mg/m^2	1
	Doxorubicin i.v.	50 mg/m^2	1
	Vincristine i.v.	1.4 mg/m^2	1
	Prednisolone p.o.	100 mg	1 to 5
	R-CHOP-14 (a total of 7 patients), cycle of 14 Days		
	Rituximab i.v.	375 mg/m^2	1
	Cyclophosphamide i.v.	750 mg/m^2	1
	Doxorubicin i.v.	50 mg/m^2	1
	Vincristine i.v.	1.4 mg/m^2	1
	Prednisolone p.o.	100 mg	1 to 5
	R-ACVBP (0 patient)		
	Rituximab i.v.	375 mg/m2	1
	Doxorubicin i.v.	75 mg/m2	1
	Cyclophosphamide i.v.	1200 mg/m2	1
	Vindesine i.v.	2 mg/m2	1,5
	Bleomycine i.v.	10 mg	1,5
	Prednisone p.o.	60 mg/m2	1,2,3,4,5
	Methotrexate i.t.	15 mg	2
	After 4 cycles: of **R-ACVBP**, a consolidation with HD-Methotrexate i.v. Rituximab i.v. Ifosfamide i.v. Etoposide i.v. Cytarabine i.v.	 3 g/m2 375 mg/m2 1500 mg/m2 300 mg/m2 100 mg/m2	
	Intensified R-CHOP14 (a total of 6 patients), cycle of 14 Days		
	Rituximab i.v.	375 mg/m2	1
	Cyclophosphamide i.v.	1750 mg/m2	1
	Doxorubicin i.v.	75 mg/m2	1
	Vincristine i.v.	1.4 mg/m2	1
	Prednisolone p.o.	100 mg	1 to 5
	G-CSF s.c.	300mg	6 to 12

Consolidation radiotherapy

Consolidation radiotherapy was given to 102 of the 115 evaluable patients receiving immunochemotherapy.

Radiotherapy involved the original mediastinal tumour volume (involved field radiotherapy, IFRT) with a delivered dose of at least 30 Gy and commenced within 8 weeks of the last dose of chemo-immunotherapy.

Of note, radiotherapy was to carry out if declared at patient's registration, irrespectively of the PET findings obtained after immunochemotherapy.

18FDG PET-CT imaging

PET scans were scheduled as follows:

- At baseline, within 14 days before commencing treatment
- After the end of the immunochemotherapy (after 3 to 4 weeks)
- After radiotherapy (at least after 2 months; scheduled for patients receiving mediastinal irradiation and mandatory if not in CMR after immunochemotherapy)

Interim PET-CT imaging was permitted according to local protocols, but the results were not used to alter the planned therapy.

DURATION OF TREATMENT	Patients could continue study treatment until disease progression,

	unacceptable toxicity dictating cessation of treatment, patient refusal or withdrawal of consent. Follow up was at monthly intervals for the first 3 months and then every 2 months until 1 year post treatment. In the second year the patient was assessed every 3 months, in the third year every 4 months, in the fourth year every 6 months and then annually. The IELSG26 study ended on 27 February 2017, with a sufficient and adequate number of events for the definition of primary and secondary outcomes and with all alive patients on a follow up of at least 60 months.
STUDY ENDPOINTS	The primary endpoint was response rate on PET scanning at the completion of chemo-immunotherapy. No secondary endpoints were established for this study.
STATISTICAL METHODS	The sample size was based on the primary endpoint, namely the complete response rate on PET (PET-CRR) scanning at the completion of chemotherapy. The PET-CRR was expected to be approximately 50% for patients in the group of the planned chemotherapy and with a sample size of a minimum of 100 patients; the PET CRR would be estimated with a standard error of <5% (and hence the 95% CI would extend from approximately 40%-60%). *Interim Analysis and Data Monitoring* The protocol established annual interim analyses of the accumulating data, that should had been reviewed by an Independent Data Monitoring Committee (IDMC). During the conduct of the study it became evident that IDMC and annual interim analysis were a surplus considering the nature of the study that not evaluated new drugs, nor concerned serious safety, nor unknown risks or vulnerable populations. Therefore, no interim analysis were conducted nor an IDMC was established.
SUMMARY OF RESULTS	<u>Efficacy Results</u> At the completion of chemotherapy, 54 patients (47%) achieved a PET CRR, that was defined by the CMR on PET-CT scanning. The results of treatment with rituximab and anthracycline-containing chemotherapy in this study, in which the majority of patients received consolidation radiotherapy, are favorable, with more than 90% projected to be alive and progression-free at 5 years. The IELSG26 study demonstrated that visual assessment of post-treatment PET/CT scans, using a 5-point scale (Deauville score) can identify the patients who will be likely cured and showed that functional ^{18}FDG PET parameters, namely SUVmax, MTV and TLG, as well as metabolic heterogeneity, can be powerful predictors of PMBCL outcomes. One of the objectives of this study was to analyse the phenotype and molecular characteristics of PMBCL. However, due to the lack of commitment of the local pathologists, most of the required information could not been collected and the planned analysis were not performed. During the conduct of the study, a central pathological revision was anyway performed, all diagnosis were confirmed and no cases were excluded on the basis of histology. The results of pathological revision were not disclosed to the Sponsor but were kept by the referral pathologist.

	Safety Results Safety was not an objective of this study. Neverthless, as per protocol, Adverse Events (AEs) of Grade ≥3 with a suspected relationship to the study drugs and Serious Adverse Events (SAEs) were collected. Their incidence was consistent with the expected AE profile of the products. During the whole study period, no unexpected side effects were recorded and no safety findings were observed that necessitated any action to be taken with regard to the conduct of the study. The benefit-risk assessment of the use of the involved medicinal products in the indication under investigation proved to be favourable.
CONCLUSIONS	The IELSG26 results showed that PET-CT imaging has an essential role in the development of PET-guided therapeutic strategies. In fact, ^{18}FDG PET-CT is an accurate tool for response assessment and prognostic stratification of patients with PMBCL and can play a significant role in their clinical management. In particular, thanks to PET imaging, it is possible: - To identify patients potentially cured by immunochemotherapy alone. - To early identify patients with residual disease after immunochemotherapy who are not cured with consolidation radiotherapy and are at significantly higher risk of progression and death after the end of radiotherapy. - To predict the risk of the PMBCL patients before treatment.
VERSION AND DATE OF THE REPORT	Version 1.0 – 22/02/2018