

Dear Friends,

Please find below the 52<sup>nd</sup> NEWSLETTER of the International Extranodal Lymphoma Study Group.

### IELSG further expands collaboration

The collaboration with China envisaged during the 2018 IELSG Annual Meeting in Stresa is about to be realized.

A draft protocol on Pembrolizumab and radiotherapy for previously untreated patients with limited stage NK/T cell lymphoma who are not eligible to chemotherapy has been already discussed among the IELSG representative and the Chinese investigators and a final version is being prepared. We can foresee the launch of this study in the second half of the year.

### Current status of the IELSG trials

More than 7'500 patients have been enrolled in IELSG prospective, retrospective and biological studies.

### Ongoing prospective clinical studies

#### IELSG47 – Phase II study of combination of ibrutinib and rituximab in untreated marginal zone lymphomas (MALILBU)

Aim of the study is to assess the safety and efficacy of the combination of rituximab and ibrutinib in EMZL patients and to explore its activity in SMZL and NMZL as exploratory subset.

Patients recruited	13	Currently open in:	 
			IT CH
Number of evaluable patients to recruit	160	More sites will be opened in	    
			IT CH FR BE PT

#### IELSG45 – Randomized phase II trial on fitness- and comorbidity- tailored treatment in elderly patients with newly diagnosed primary CNS lymphoma (FIORELLA)

This study involves patients aged  $\geq 70$  years. The more fit patients (Part “A”) will receive the standard chemotherapy combination (high-dose methotrexate, procarbazine and rituximab) as induction. Responding patients will receive either procarbazine or lenalidomide as maintenance therapy; the aim is to evaluate the efficacy of these two drugs. The more fragile patients (Part “B”) will receive a less aggressive therapy consisting of concomitant whole-brain radiotherapy, temozolomide and rituximab as induction therapy, followed by temozolomide as maintenance treatment; the aim is to evaluate the efficacy of this combination of treatment.

Patients recruited	16	Currently open in:	   
			IT CH DK FI
Number of evaluable patients to recruit	68	More sites will be opened in	    
			IT CH DK FI IL

### Biological IELSG trial

#### IELSG46 – Integrated Molecular and Clinical Profiling to Optimize Outcome Prediction in Splenic Marginal Zone Lymphoma

The aim of this study is to develop and validate an integrated clinic-molecular model for an accurate survival prognostication of newly diagnosed Splenic Marginal Zone Lymphoma (SMZL). Biological samples of about 400 subjects already collected

- The results of the first analysis have already been presented at EHA and ASH 2018 and at 15-ICML. The histologic review is nearly completed and the final results are planned before June 2020. The study has identified different molecular subtypes of SMZL characterized by distinct cytogenetic features, immunogenetic signature, mutational profile and clinical outcome. These results provide a basis for a provisional sub-classification in SMZL.

## Studies in their follow-up phase

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The following studies are now in their follow-up phase. Hereafter, we provide information on the current and planned activities. Since for several of them it is almost time to start the data analysis, it is of paramount importance to have **up-to-date data in the database**. Please check with your personnel or with the specific IELSG clinical project manager if the data of your site are complete for all the recruited patients.

### **IELSG30** (54 patients – enrolment completed – follow-up until July 2027)

Aim of this phase II trial is to assess the feasibility, activity and safety of a therapeutic program in which patients with testicular large cell lymphoma receive state-of-the-art chemo-immunotherapy (R-CHOP regimen) plus both intrathecal (with liposomal cytarabine) and systemic CNS prophylaxis (with intermediate-dose methotrexate), followed by loco-regional radiotherapy.

- The follow-up time is now mature for the analysis of this prospective study and the manuscript with the final results is in preparation (for submission in 2020).

### **IELSG32** (227 patients - enrolment completed – follow-up until April 2025)

This study compares the activity of three different chemotherapy combinations with high-dose methotrexate (HD-MTX) + high-dose cytarabine (HD-araC), HD-MTX + HD-araC + rituximab and HD-MTX + HD-araC + rituximab + thiotepa. Moreover, the trial will test in a randomised design the efficacy of two consolidation strategies: conventional whole-brain radiotherapy (WBRT) vs. high-dose chemotherapy supported by autologous stem cell transplantation (HDC + ASCT).

- The study, in addition to its primary clinical endpoint concerning the type of chemotherapy and the role of auto-transplantation, has gathered important data on the role of MRI imaging and on the quality of life in a large number of patients. These data analysis is ongoing. The manuscript reporting the results should be prepared in the next 12 months.

### **IELSG37** (547 patients – enrolment completed – follow-up until August 2024)

Aim of this randomized trial is to evaluate the possibility to spare the radiotherapy in PMBCL patients, who have become “PET-negative” after a chemotherapy containing rituximab.

- Since both the randomization rate (driven by the number of metabolic complete responses) and the event rates were lower than envisaged when the protocol was written, an unplanned interim analysis was required in 2019 year by the Independent Data Monitoring Committee (IDMC). The IDMC suggested to complete the planned accrual (during the summer 2019) and to perform the data analysis for the primary endpoint when at least 80% of the patients will reach a minimum follow-up of 30 months from randomization. In addition to the estimation of the relative effect in terms of hazard ratio, the absolute difference between the two arms will also be analysed to calculate the number of PET-negative patients status that needed to receive radiotherapy to prevent a relapse. The collection of all the follow-up data is ongoing. The study collected PET/CT scans at diagnosis, during and after treatment in more than 500 patients. This number of exams will allow to perform a validation analysis on the hypothesis generated by the IELSG26 study. Moreover, this study may provide very important data for the awaited standardization of PET-metrics in lymphoma.

### **IELSG38** (112 patients - enrolment completed – follow-up until September 2028)

Aim of this phase study II is to assess the safety and therapeutic activity of the combination of chlorambucil and rituximab given for 6 months, followed by 2-year maintenance treatment with subcutaneous rituximab alone in MALT lymphomas.

- The data analysis is ongoing and the submission of an abstract on the first results to ASH 2020 is planned.

### **IELSG39** (44 patients - enrolment completed – follow-up until July 2021)

Aim of this phase II study is to establish in a prospective, multicentre phase II trial, the efficacy of an upfront targeted therapy consisting of *Chlamydomphila psittaci* -eradicating therapy with prolonged administration of

doxycycline followed by eradication monitoring and antibiotic re-treatment at infection re-occurrence in patients with newly diagnosed Ocular Adnexal Marginal Zone Lymphoma (OAMZL).

➤ The data analysis is ongoing and the first results should be published in an abstract during 2020.

**IELSG40** (44 patients - enrolment discontinued per protocol, after the interim analysis)

To assess the overall response rate (complete and partial responses) of the combination treatment of clarithromycin and lenalidomide in patients with MALT lymphoma, refractory or relapsing after radiotherapy and/or chemotherapy and/or immunotherapy.

➤ Since a planned interim analysis showed a lower percentage of that expected (i.e., 42% versus 63%), it was decided to stop the enrolment. It was agreed that only the patients with clinical response may continue the treatment. The follow-up will continue according to the protocol, unless treatment and assessment data revision would require a different follow-up duration.

**IELSG42** (76 patients - enrolment completed – follow-up until September 2023)

Aim of this phase II study is to evaluate the efficacy, safety and feasibility of a new sequential combination of Methotrexate-Aracytin-based chemoimmunotherapy, followed by R-ICE regimen, and autologous transplantation (MARIETTA regimen).

➤ The results of the first analysis are described in an abstract, which was selected for presentation in an oral session at ASH 2019. A manuscript will be subsequently prepared.

**IELSG43** (342 patients - enrolment completed – follow-up until August 2021)

Aim of this phase III randomized study (MATRix) is to compare the efficacy (in terms of progression-free survival) of two consolidation policies: high-dose chemotherapy followed by autologous stem-cell transplantation and chemotherapy at conventional doses (with a regimen specifically developed for CNS lymphoma).

➤ Enrolment completed in August 2019. Data analysis will be performed during 2020. Submission of an abstract to ASH 2020 (or to ICML in 2021) is planned.

### Prospective trials in the pipeline

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➔ **IELSG49** - Phase II trial of acalabrutinib in combination with MOR208 in patients with previously treated marginal zone lymphomas (MZL)

➔ **IELSG50** - Pembrolizumab and radiotherapy for previously untreated patients with limited stage NK/T cell lymphoma who are not eligible to chemotherapy

The pharmaceutical companies involved in these studies are reviewing both protocols.



Save the date and  
Mark your presence @ IELSG Annual Meeting 2020  
March 27-28, 2020 Stresa (Italy)  
Register now on [www.ielsg.org](http://www.ielsg.org)

