FONDAZIONE ITALIANA LINFOMI

FIL Study Proposal Form

FOLL19 Trial

**Randomized study to assess if an early response adapted deintensified treatment
is as active as standard immunochemotherapy in patients
with untreated advanced stage high tumor burden follicular lymphoma.**

Background and Rationale	Follicular lymphomas are the most frequent indolent non Hodgkin lymphomas. Induction immunochemotherapy (ICT) is required for patients with advanced stage high tumor burden disease and allows to achieve an outstanding overall survival (OS) with median progression free survival that is 10 years or more. Regardless of very effective ICT regimens clinical hetereogeneity exists with 20-30% of patients who experience early treatment failure, shows more aggressive course of the disease and higher risk of dying from progressive disease. Conversely the 70-80% of patients with durable response have an excellent survival and their FL has limited, if none, effect on their estimated life expectancy. The presence of two distinct patients' population with different risk of dying from FL, identifies different unmet needs that should be used to support future clinical research in FL and to develop personalized treatment modalities. The main unmet clinical need for patients at high risk is represented by the lack of efficacy of currently available treatment options. The main unmet clinical need in patients with standard or low risk FL is represented by the identification of treatment modalities that are designed to reduce both early and late toxicity. As suggested by recently published randomized trials in FL (i.e. Foll05, Bright, Gallium), more active therapies were associated with an increased risk of developing second malignancies or severe adverse events and led national authorities to issue specific safety warnings on specific treatment combinations (i.e. Bendamustine base regimens). In this scenario the identification of new treatment modalities that are based on the use of predictive factors is warranted. Several prognostic factors have been identified to predict the clinical course of the disease in FL but so far none of them has been translated into a predictive decisional factor. Among available prognostic factors metabolic and molecular response at the end of induction therapy have been confirmed as clinically relevant prognostic factors and their role as decisional factors is currently being investigated in response adapted clinical trials (I.e. FOLL12 and Petrea). Both molecular and metabolic response have been associated with a different risk of progression or of death when used at the end of induction therapy but were also shown to be prognostic when used early during induction treatment (Dupuis et al JCO 2014; Pott et al. personal communication). The use of early assessment of metabolic and molecular response strongly support the design of clinical trials to test the hypothesis that deintensified therapy in patients with early response might be equally effective but less toxic than standard ICT.
Type of study	▫ **Experimental, phase_III**

Study objectives	**Principal** To assess if a response adapted strategy with shorter exposure to chemotherapy for patients who achieve early complete metabolic and molecular response is non inferior to a standard immunochemotherapy in patients with advanced stage high tumor burden Follicular Lymphoma **Secondary** To assess the safety profile of the deintensified strategy compared with the standard treatment To correlate early metabolic and molecular response with patient outcome (PFS, OS POD24) To identify biological, clinical and metabolic correlates that can be used to better profile patients with advanced stage Follicular lymphomas and to identify predictive factors for future studies. (i.e. MRD; cfDNA, TMTV, nanostring, etc)
Study endpoints	**Principal study end-points** (*description):* Metabolic response rate at the end of induction immunochemotherapy (That is defined as the rate of patients with centrally reviewed, confirmed Deauville score of 4 and 5 at end of induction PET) **Secondary study end-points** (*description):* Adverse event rate Progression free survival Rate of molecular response after 4 and 8 cycles of immunochemotherapy Overall survival **Ancillary biological end-points:** YES
Study design	This is an interventional randomized multicentre phase 3 Trial
Sample size/power calculation	588 patients are needed to grant for a non-inferiority randomized study design with a 8% non-inferiority margin; alfa 5%, power 80%

Principal statistical analysis	**Phase III two arms randomized study of non-inferiority.** Principal end-point: EFS from registration (events: treatment interruption, response <PR, relapse, death for any cause) Reference value 3-yr EFS = 80% Low marginal level, 3yr-EFS = 72% Delta -8% (margin HR 1.47) The low 90%CI of experimental arm must be inferior of the HR margin 1.47. FIL potential accrual: about 150-160 patients/years (FOLL5 and FOLL12) Alpha error = 0.05 one-sided Beta error = 0.20 Sample Size N = **588**, expected total number of events n= 166. Considering 5% of not eligibility n=618 (by arm **309**) One interim analysis at 33% information (after about 3 years from first registration and 55 events), considering Lan deMets method with O'Brien-Fleming boundary (z=3.218). [Software: R version 3.3.2; package gsDesign v3.0-1]
Study duration (enrolment + FU) **Please specify if long term FU is needed**	Accrual 48 months, plus additional 30 months (total duration 78 months, 4+2.5=6.5 years)
Number of Centers (if predefined)	Around 70 FIL centers are planned
Patients Selection criteria	Main inclusion criteria: - Histologically proven grade 1-3a Follicular lymphoma - Stage II-IV with high tumor burden according to GELF criteria - ECOG 0-2 - Any FLIPI2 - Baseline PET available - Age 18 or more - Signed informed consent Main exclusion criteria: - Transformed FL or grade 3b FL - HIV positivity - Stage I - Low tumor burden disease

If interventional, treatment plan	Once eligibility criteria are verified patients will be randomized in 1:1 ratio to receive: **<u>A) Standard therapy:</u>** - 6 courses of immunochemotherapy followed by two doses of anti-CD20 monoclonal antibody - non decisional PET will be performed after cycle 4 - non decisional early MRD assessment will be performed on PB sample collected after cycle 4 **<u>B) Experimental therapy:</u>** - 4 courses of immunochemotherapy, then - 4 additional cycles of anti-CD20 monoclonal antibody in case of complete metabolic response after cycle 4 and negative MRD analysis on PB sample collected after cycle, or - 2 additional courses of immunochemotherapy followed by 2 doses of antCD20 monoclonal antibody in case of incomplete metabolic response at cycle 4 or lack of molecular response on PB sample after cycle 3. In both arms response assessment at the end of induction therapy will be performed with PET and central review of metabolic response. The choice of immunochemotherapy is left to treating physician. Bendamustine, and CHOP are allowed chemotherapy regimens. Branded or biosimilar rituximab, subcutaneous rituximab and obinutuzumab are allowed anti CD20 monoclonal antibodies and will be used according to labelled and approved indications. Post induction maintenance is allowed and left to phisician discretion. Randomization will be stratified acording to - FLIPI2 0-2 vs 3-5 - Chemotherapy: CHOP vs Benda - Monoclonal antibody: rituximab vs obinutuzumab

Biological studies	**MRD analysis** The MRD analysis will be performed with the support of the FIL MRD network using standardized procedure to monitor molecular response in FL: The following timepoints are identified: - Baseline: search for molecular marker on peripheral and marrow sample - Interim (Day + 20 to +28 of cycle 3): MRD assessment on peripheral blood sample - End of induction (day + 28 to + 56 of cycle 8) - Follow up (month + 6 +12 +18 + 24 after the end of induction) **Circulating free DNA** Samples for cfDNA analysis will be collected and centralized at different study timepoints: - Baseline (day – 28 to -1 of cycle 1) - Interim assessment (day 20 to 28 of cycle 3) - End of induction (day + 28 to + 56 of cycle 8) - Follow up (month + 6 +12 +18 + 24 after the end of induction) **Gene expression studies** Nanostring analysis of diagnostic pathology samples will be performed in a central lab: To realize this secondary objective unstained slides of paraffin embedded material will be sent to central lab after patient enrolment.
External pathology review	**YES**
PET/CT review	**YES** Metabolic response will be assessed after cycle 4 (PET4) and at the endo of induction treatment (PET8): PET 4 will be decisional for patients randomized to the experimental arm PET8 will be used as primary study endpoint Baseline PET, PET4 and PET 8 will be centralized using the Widen web platform and revised by a maximum of 5 nuclear medicine expert.

Study IMP (please specify if the IMP has an AIC in Italy)	All drugs will be used according to their approved indications
Study costs	See FOLL19 Budget