Fondazione Italiana Linfomi ONLUS

Sede legale: piazza Turati 5, 15121 – Alessandria
P.IVA IT 02143940068 C.F. 96039680069
Uffici Studi FIL: c/o Uffici PACTO, Spalto Marengo 44, 15121, Alessandria
Tel. 0131– 033153, Fax 0131 - 263455; e-mail: startup@filinf.it; sito web: www.filinf.it

Study ID: FIL_GAEL
Eudract Number: 2014-005697-10
ClinicalTrials.gov Identifier: NCT02495454

Title: GA101-miniCHOP regimen for the treatment of elderly unfit patients with diffuse large B-cell non-Hodgkin's lymphoma. A phase II study of the Fondazione Italiana Linfomi (FIL).

Protocol: version 1, September 29th, 2014

Clinical Protocol

GA101-miniCHOP regimen for the treatment of elderly unfit patients with diffuse large B-cell non-Hodgkin's lymphoma. A phase II study of the Fondazione Italiana Linfomi (FIL).

Study ID: FIL_GAEL (GA101-miniCHOP elderly unfit)
Eudract Number: 2014-005697-10
Protocol version: version 1, 29 Sept 2014

Sponsor:	Fondazione Italiana Linfomi Onlus
Principal Investrigator	Francesco Merli (Reggio Emilia)
Writing Committee	Francesco Merli (Reggio Emilia) Annalisa Arcari (Piacenza) Guido Gini (Ancona) Alberto Santagostino (Vercelli) Vittorio Ruggero Zilioli (Milano Niguarda)
Statistical Analysis	Luigi Marcheselli (Modena)
Administrative Office	Francesca Massobrio (Alessandria) Marta Galliani (Alessandria)
Trial Office	Caterina Mammi (Reggio Emilia)

Contact information for the trial

Study Coordinator

dr. Francesco Merli
SC Ematologia
Arcispedale Santa Maria Nuova IRCCS
V.le Risorgimento 80
42123 Reggio Emilia
phone: + 39-0522-296618
fax: +39-0522-295654
email: merli.francesco@asmn.re.it

Writing Committee

dr. Annalisa Arcari
SC Ematologia e Centro Trapianti
Ospedale Civile
Piacenza
email: a.arcari@ausl.pc.it

dr Guido Gini
Clinica di Ematologia
A.O.Universitaria Ospedali Riuniti
Ancona
Ospedale
Piacenza
email: g.gini@ospedaliriuniti.marche.it

dr Alberto Santagostino
Onco-Ematologia
Ospedale S.Andrea
Vercelli
email: albemail@libero.it

dr Vittorio Ruggero Zilioli
SC Ematologia
A.O.Ospedale Niguarda Ca' Granda
Milano
email: vittorioruggero.zilioli@ospedaleniguarda.it

Statistical Analysis

dr. Luigi Marcheselli
Dipartimento di Oncologia, Ematologia
e Patologie dell'Apparato Respiratorio
Università di Modena e Reggio Emilia
COM Centro Oncologico Modenese
Via del Pozzo 71
41124 Modena
email: lmarcheselli@unimore.it

Administrative Office

Dr.ssa Francesca Massobrio
Dr.ssa Marta Galliani
Segreteria FIL
S.C. Ematologia, A.O.SS. Antonio e Biagio
Via Venezia 16
15121 Alessandria
phone: +39-0131-206288
fax: +39-0131-263455
email: segreteria@filinf.it

Trial Office

dr. ssa Caterina Mammì

SC Ematologia
Arcispedale Santa Maria Nuova IRCCS
V.le Risorgimento 80
42123 Reggio Emilia

phone: + 39-0522-295654
fax: +39-0522-295655
email: mammi.caterina@asmn.re.it

Pharmacovigilance Unit

Dr. Alessandro Levis
Segreteria FIL
S.C. Ematologia, A.O.SS. Antonio e Biagio
Via Venezia 16
15121 Alessandria

phone: +39-0131-206071-206066
fax: +39-0131-263455
email: segreteria@filinf.it

Independent Review Committee (Appendix K)

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug and the conduct of the study.

_____

Investigator's Signature Date

_____

Name of Investigator (Typed or Printed)

_____

_____

_____

Institution, Address*

_____

Phone Number*

_____

Investigator-Sponsor Signature* Date
(where required)

_____

Name of Coordinating Investigator (Typed or Printed)

_____

Institution

_____

* If the address or phone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and will not require protocol amendment(s)

TABLE OF CONTENTS

Synopsis

STUDY TITLE	**GA101-miniCHOP regimen for the treatment of elderly unfit patients with diffuse large B-cell non-Hodgkin's lymphoma. A phase II study of the Fondazione Italiana Linfomi (FIL).**
STUDY PHASE	II
OBJECTIVES	**Primary Objectives:** • To evaluate the activity of GA101-miniCHOP regimen in terms of complete response rate (CRR) **Secondary Objectives:** • To evaluate the safety and tolerability of GA101 miniCHOP regiment in terms of adverse events • Partial and Overall Response Rate: PR and ORR (CR+PR) • Overall Survival (OS) • Progression Free Survival (PFS) • Dynamics of Comprehensive Geriatric Assessment (CGA) • Dynamics of Quality of Life (QoL) questionnaires
ENDPOINTS	**Primary Endpoints:** • Complete Response Rate after 10 infusions of GA101 and 6 cycles of miniCHOP. The response rate to therapy will be based a central Independent Review Committee of response that will not consider the results of FDG-PET but will only use the conventional CT scan images (International Criteria, B. Cheson, JCO 1999) ***(Appendix K)*** **Secondary Endpoints:** • Rate of Adverse Events • Partial and Overall Response Rate (PRR, ORR) • Overall Survival (OS) • Progression Free Survival (PFS) • Change in ADL, IADL and CIRS • Change in QoL (EORTC QLQ C30)
STUDY DESIGN	Two stage phase 2, non-randomized, prospective, multicenter study.
STUDY DURATION	5 years: 30 months for patients enrolment plus 6 months of treatment and 24 months of follow up
INCLUSION CRITERIA	1) Histologically proven CD20 positive Diffuse Large B-cell Lymphoma

	and Follicular grade IIIB lymphoma, according to WHO classification (local pathologist) 2) Age ≥ 65 years 3) No previous treatment 4) CGA assessment performed before starting treatment 5) UNFIT patients defined as follows ***(see Appendices A-D)***: **Age ≥ 80 years with FIT profile**, i.e. ADL =6 residual functions IADL=8 residual functions CIRS: no comorbidity of grade 3-4 and <5 of grade 2 **or Age < 80 with UNFIT profile**, i.e ADL ≥ 5 residual functions IADL ≥ 6 residual functions CIRS: no comorbidity of grade 3-4 and 5-8 co-morbidities of grade 2 6) Ann Arbor Stage I with bulky, II-IV ***(Appendix E)*** 7) At least one bi-dimensionally measurable lesion defined as > 1.5 cm in its largest dimension on CT scan 8) ECOG performance status of 0, 1, or 2 ***(Appendix G)*** 9) Adequate hematologic function (unless caused by bone marrow infiltrate), defined as follows: Hemoglobin ≥ 10 g/dL Absolute neutrophil count ≥ 1.5 x 10^9/L Platelet count ≥ 100 x 10^9/L 10) LVEF ≥50% 11) Ability and willingness to comply with the study protocol procedure 12) Life expectancy > 6 months 13) Accessibility of patient for treatment and follow up 14) Written informed consent
EXCLUSION CRITERIA	1) History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products 2) Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines 3) History of other malignancies within 5 years prior to study entry except for adequately treated carcinoma in situ of the cervix or basal or squamous

	cell skin cancer 4) Stage I without bulky 5) Patients with transformed lymphoma 6) Prior therapy for DLBCL, with the exception of nodal biopsy or local irradiation 7) Previous exposure to cytotoxic agents 8) Suspect or clinical evidence of CNS involvement by lymphoma 9) HBsAg, HCV or HIV positivity; isolated HBcAb positivity is accepted only with concomitant treatment with Lamivudine 10) AST /ALT > twice upper the normal range; bilirubin > twice upper the normal range; serum creatinine > 2.5 mg /dl (unless these abnormalities were related to the lymphoma) 11) Evidence of any severe active acute or chronic infection 12) Concurrent co-morbid medical condition which might exclude administration of full dose chemotherapy
TREATMENT SCHEME ***(Appendix I)***	Patients will receive: **6 courses of GA101-miniCHOP regimen and 2 additional infusions of GA101, every 21 days *(for a total of 6 courses of miniCHOP and 10 infusions of GA101)*** **<u>GA101-miniCHOP regimen</u>** **Cycle 1** GA101: 1000 mg day 1, day 8 and day 15, iv Cyclophosphamide: 400 mg/mq, day 1, iv Doxorubicin: 25 mg/mq, day 1, iv Vincristine: 1 mg, day 1, iv Prednisone: 40 mg/mq, days 1-5, os **Cycles 2-6** GA101: 1000 mg day 1, iv Cyclophosphamide: 400 mg/mq, day 1, iv Doxorubicin: 25 mg/mq, day 1, iv Vincristine: 1 mg, day 1, iv Prednisone: 40 mg/mq, days 1-5, os **Two additional infusions of GA101: 1000 mg day 1, iv, every 21 days.** <u>Prophylactic granulocyte colony-stimulating factor (G-CSF) support is</u>

	mandatory starting within 24-72 hours from day 1 of each cycle for no less than 4 doses or until neutrophils count exceeds 1.00×10^9/L or more (*ASCO guidelines_JCO - 2006*). Alternatively a single dose of pegylated G-CSF or pegfilgrastim can be used. Use of erythropoietin is allowed according to clinical practice. A preliminary debulking or symptomatic phase of vincristine 1 mg or intermediate -- high dose steroid is allowed. In case of debulking with vincristine, this drug must be omitted from cycle1. **Involved Site Radiotherapy (ISRT) is allowed on previous bulky sites or on PET positive lesion at the end of treatment.** An interim check for response will be assessed after the completion of 4 courses of GA101-miniCHOP in order to identify non responding patients: patients achieving a CR, PR, or SD will continue to complete combined immunochemotherapy as planned, patients with progressive disease will stop treatment and will be considered as failure. All patients stopping study treatment due to early disease progression will be followed for survival until the end of the study. **Dosage Delays and Modifications: GA101 and CHOP chemotherapy** Dose reductions and delays are based on all laboratory values obtained within 72 hours prior to a study treatment infusion. A dose delay of 21 days is permitted for miniCHOP and GA101 to allow recovery of hematologic toxicities to Grade ≤ 2 (platelets must return to Grade ≤ 1) or non-hematologic toxicities to Grade ≤ 1 or baseline status for the first episode. **Dose Modifications of GA101-miniCHOP chemotherapy** No dose modifications of GA101 (1000 mg) are allowed. If administration of chemotherapy is delayed, there will be no dose modification of GA101, and the administration of GA101 and all

	chemotherapy drugs should be delayed for the same time frame, e.g., if miniCHOP therapy is delayed, administration of GA101 should also be delayed so that they are given on day 1 of the same cycles. **Hematologic and Non-Hematologic Toxicities** Dosing of miniCHOP and GA101 may be resumed upon the resolution of hematologic toxicity to Grade ≤2 (platelets must resolve to Grade ≤ 1) or baseline status for the first episode. For non-hematologic toxicities, dosing of GA101-miniCHOP-may only be resumed upon resolution to Grade ≤1 or baseline status. For Grade ≥ 2 non-hematologic toxicities (excluding alopecia, nausea, and vomiting), treatment with GA101-miniCHOP will be delayed until resolution to Grade ≤1 (or baseline status for all except hemorrhagic cystitis), for a maximum of 21 days. In addition, resumption of dosing without complete resolution of toxicity may only be considered after careful weighing of the risks and benefits with the patient and agreement between the investigator and the Sponsor. If treatment is delayed for more than 21 days (except for hepatitis B reactivation), the patient will be withdrawn from study treatment. (note that lymphopenia is not considered a cytopenic toxicity, as it is an expected outcome of therapy.) Patients who discontinue all study treatment for adverse events should remain on the study and continue to have disease assessments until progression and standard follow-up. In the event of grade 2 neurological vincristine-related toxicity (sensory or motor polyneuritis, constipation, or visual or auditory changes) vincristine can be discontinued. **Permitted concomitant therapies** Prevention of tumour lysis syndrome by alkalinisation or hypouricaemic drugs is allowed if necessary.

	Antiemetic therapy with SHT3 antagonists can be given at each cycle. Patients will receive prophylactic treatment with Bactrim 2 cp/day twice a week during all the chemotherapy. CNS prophylaxis with intrathecal infusion of methotrexate and steriod is allowed according to local clinical practice (i.e. patients with testicular involvement or patients considered at high risk of CNS relapse). In patients HBcAb+, prophylaxis for hepatitis B reactivation with Lamivudine 100mg/die from the start of the treatment to one year after the end of the treatment is mandatory. Pre-medication for GA101 infusion with oral acetaminophen (e.g., 650−1000 mg) and an antihistamine such as diphenhydramine hydrochloride (50−100 mg) 30−60 minutes prior to starting each infusion (unless contraindicated). An additional glucocorticoid (e.g., 100 mg IV *prednisone or prednisolone* or equivalent) is allowed at the investigator's discretion. For patients who do not experience infusion-related symptoms with their previous infusion, pre-medication at subsequent infusions may be omitted at the investigator's discretion. Prophylaxis with levofloxacine or ciprofloxacine and fluconazole/itraconazole/posaconazole are allowed. Platelets and red blood cell transfusion are allowed, if needed.
STUDY PROCEDURES	**Baseline assessment** All the baseline tests and procedures must be completed within 28 days before chemotherapy starts. ▪ Medical history, physical examination and concomitant medications ▪ Histological diagnosis on lymph node biopsy or other pathologic tissue with immunoistochemistry ▪ ECG, cardiac assessment ▪ Cardiac ultrasound to assess LVEF

	▪ Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count) ▪ Blood chemistry (glucose, serum creatinine, total serum bilirubin, AST, ALT, γ-GT, urea/BUN, electrolytes/ alkaline phosphatase, LDH, beta2-microglobulin, electrolytes/ Na, K, Cl, Ca, P, erythrocyte sedimentation rate, uric acid, total protein, serum albumin, protein electrophoresis) ▪ Viral markers (HIV Ab, HBsAg,antiHBsAb, HBcAb, HCV Ab) ▪ Neck, chest, abdomen and pelvis CT scan. Cerebral CT scan is recommended but not mandatory ▪ Bone marrow biopsy mandatory for patient in CT scan stage I-II, optional for patient in CT scan stage III-IV. ▪ Lung function (spirometry with DLCO) ▪ ADL, IADL, and CIRS assessments ***(Appendix B,C,D)*** ▪ Quality of Life evaluation according to EORTC QLC-C30 version 3.0 questionnaire ***(Appendix H)*** ▪ Written informed consent **All the following are optional:** ▪ PET/CT (<u>strongly recommended</u>) ▪ MRI (CNS, spinal cord), endoscopy and any other diagnostic imaging only if clinically relevant under medical judgment ▪ Chest X-ray **Investigation before each course** ▪ Physical examination, concomitant medications ▪ Collection of adverse events according to CTCAE v 4.0 ▪ Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count) ▪ Blood chemistry (glucose, serum creatinine, alkaline phosphathase, total serum bilirubin, AST, ALT, LDH, urea/BUN, uric acid) ▪ Any test or instrumental assessment considered relevant under medical judgement in case of clinical suspect of progression or toxicity **Investigations during each course (day 10 +/- 2)**

	▪ Physical examination, concomitant medications ▪ Collection of adverse events according to CTCAE v 4.0 ▪ Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count) ▪ Blood chemistry (glucose, serum creatinine, alkaline phosphathase, total serum bilirubin, AST, ALT, LDH, urea/BUN, uric acid) **Check for response after 4 courses of GA101-miniCHOP** Check for response will be assessed after the completion of 4 courses of GA101-miniCHOP in order to identify non responding patients: ▪ ECOG performance status, physical examination ▪ Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count) ▪ Blood chemistry (glucose, serum creatinine, alkaline phosphathase, total serum bilirubin, AST, ALT, LDH, urea/BUN, uric acid) ▪ Clinical/radiological assessment of target lesion to check for tumor response (CT-SCAN and/or echography and/or chest radiogram) **Investigations at the end of treatment** **(28 days after the last study medication administration)** ▪ Physical examination, concomitant medications ▪ Collection of adverse events during the month after the last dose of study drug administration according to CTCAE v 4.0 ▪ ECG, cardiac assessment ▪ Cardiac ultrasound with LVEF ▪ Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count) ▪ Blood chemistry (glucose, serum creatinine, total serum bilirubin, AST, ALT, γ-GT, urea/BUN, electrolytes/ Na, K, Cl, Ca, P, alkaline phosphatase, LDH, beta2-microglobulin, erythrocyte sedimentation rate, uric acid, total protein, serum albumin, protein electrophoresis) ▪ Chest, abdomen and pelvis CT scan (mandatory) ▪ PET Total body (mandatory) ▪ ADL, IADL, and CIRS assessments ▪ Quality of Life evaluation according to EORTC QLC-C30 version

	3.0 questionnaire ***(Appendix H)*** ▪ Bone marrow biopsy is recommended if positive at diagnosis ▪ Lung function (spirometry with DLCO) **All the following are optional:** ▪ MRI (CNS, spinal cord), endoscopy and any other diagnostic imaging only if positive at the diagnosis or if useful according to clinical judgement **Investigation during follow-up** **At month + 3, then every 6 months for two years** ▪ Physical examination, concomitant medications ▪ Late adverse event assessment: late organ toxicity; second tumours ▪ Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count) ▪ Blood chemistry (glucose, serum creatinine, total serum bilirubin, AST, ALT, LDH) ▪ Chest, abdomen and pelvis CT scan (only at month + 3, then every 6 months) ▪ ECG, cardiac assessment if clinically indicated ▪ ADL, IADL, and CIRS ▪ Quality of Life evaluation according to EORTC QLC-C30 version 3.0 questionnaire **At any time** ▪ Any test or instrumental assessment considered relevant under medical judgement in case of clinical suspected disease progression or toxicity.
PLANNED SAMPLE SIZE	The primary objective of the study is to demonstrate a clinical benefit in Complete Remission Rate (CRR) with GA101-miniCHOP association in elderly unfit patients diagnosed with diffuse large B-cell lymphoma. For the purposes of this study, as the reference CR rate *(Peyrade et al, Lancet Oncol – 2011)* was defined with 1999 International Criteria for response *(Cheson, JCO 1999)*, the response rate to therapy will be based on

	a Central Independent Review of response that will not consider the results of FDG-PET but will only use the conventional CT scan images. Response defined according to Cheson 2007 criteria will also be provided as study result. The sample size has been estimated according to a optimal Simon two-stages design. The null hypothesis (p0) has been set equal **0.60** on the basis of what reported by F. Peyrade et al. *(Lancet Oncol - 2011)*. With a type I (alfa) error of **0.10 (10%)** and a type II (beta) error of **0.10** (power=90%) the alternative hypotesis (p1) is **0.75**, i.e. a CR rate of 75% with the combination GA101-miniCHOP expected. A schema of the design is below reported. R1 = 21 N1 = 34 R2 = 47 Ntot = 71 EN(p0) = 47 PET(p0) = 64.6% According to the two-stage design patients enrolment will proceed as follows: - the enrolment of **34** patients (stage 1) is planned: if at least **22** patients will achieve CR the study will continue; - additional **37** patients are entered (stage II): if at least **48** patients out of **71** will achieve a CR the study will be considered of possible evaluation for the efficacy of the treatment. Considering a withdrawal rate of 10%, the enrollment may continue until **78** patients are accrued in order to have at least 71 eligible patients. If GA101-miniCHOP will be active, the probability to declare inactivity is 0.0964 and the probability to stop the study at first stage is 0.0610.

1. BACKGROUND AND INTRODUCTION

1.1 Diffuse large B-cell lymphoma

Diffuse large B-cell Lymphoma (DLBCL) is the most frequent Lymphoma subtype and represents around 35-40% of all lymphomas. The incidence of DLBCL increases with age more than one third of cases involves patients older than 70 years [1]. With the synergistic effect of the increase in lymphoma incidence and the ageing population, a large increase in the number or DLBCL cases can be anticipated in elderly patients in the near future.

The vast majority of patients with localized disease are curable with combined chemoimmunotherapy or combination chemotherapy alone [2]. Among patients with advanced-stage disease, 50% of patients are cured with doxorubicin-based combination chemotherapy and rituximab [3] [4] [5]. The addition of rituximab to CHOP-based chemotherapy improves patient outcomes, as demonstrated in three randomized, prospective studies, consisting of approximately 2000 older (< 60 or ≥ 60 years old, depending on the study), previously untreated patients with advanced DLBCL [6].

1.2 Diffuse large B-cell lymphoma in the elderly

More than half of patients with DLBCL are older than 60 years and age is an adverse prognostic factor for them. When a cut of at 60 years is used, elderly patients have a reduced chance of responding to their therapy and show a shorter disease and overall survival compared with the younger subjects [7]. The reason why age is a prognostic indicator is not fully understood but it can be assumed this is the combined result of the different biology of the elderly compared to young subjects, of the progressive accumulation of co-morbidities and of a reduced tolerability to cytotoxic therapies of the old subject; in addition, elderly patients have a natural reduction of their life expectation that might become relevant when the disease is diagnosed at a later age.

Notwithstanding the complexity of the elderly subject, when DLBCL is diagnosed the only treatment that is currently considered as standard is the R-CHOP combination. The scientific evidence to support this choice is based on the results of large phase III trials that showed that the addition of anti-CD20 monoclonal antibody rituximab to CHOP chemotherapy is safe and increases treatment efficacy [3-6]. Before rituximab was available activity and efficacy of chemotherapy in elderly patients with DLBCL was very low; complete response rates ranged from 36% to 59% but median survival was usually shorter than 18 months [8] [9-11]. With the addition of rituximab it was shown that complete response rate could be increased to more than 70% and median survival prolonged to more than 8 years [12], without an increase in the rate of toxic events. Due to the adoption of strict inclusion criteria however,

transferability of study results to daily clinical practice is very difficult. In the randomized studies very few patients older than 80 years were included and patients with poor performance status or not able to tolerate full dose chemotherapy were not included. In the real life most elderly patients with DLBCL show one or more comorbid conditions that might limit the adoption of full dose therapy with curative intent and make treatment choice a real challenge. Though immunotherapy is generally safe the chemotherapeutic regimens used in the adult population can cause unpredictable, severe and possibly lethal toxicities in the elderly. Cardiac toxicity caused by anthracyclines, pulmonary toxicity caused by bleomycin, neurological toxicity caused by vinca alkaloids can be more severe in elderly than in young patients. Moreover the chances of recover can be jeopardized by the frequent coexistence of co-morbidities and multiple drug regimens which raise the risk of toxicity [13, 14].

As a consequence the standard R-CHOP therapy is not used in all patients and personalized approaches are usually prescribed to elderly subjects using empirical dose reductions of the toxic drugs or substituting standard drugs with less toxic formulations of the same substance (i.e. epidoxorubicin or liposomal doxorubicin instead of conventional doxorubicin). Currently results from clinical research specifically dedicated to the elderly unfit patient or to the very old subjects is lacking. Among published studies specifically designed for the treatment of elderly or very old patient with DLBCL interesting data come form the use of modified, light versions of the three-weekly CHOP chemotherapy [15-18], or from the adoption of weekly dosing of cytotoxic drugs [19]. Among available studies Peyrade et al. recently published the results of a large phase II trial on elderly patients with DLBCL investigating activity and toxicity of a R-mini-CHOP regimen. R-miniCHOP was an attenuated version of the standard R-CHOP in which rituximab was used at full doses while cytotoxic drugs (doxorubicin, vincristine and cyclophosphamide) and steroids were administered at half dose. In this study patients older than 80 years were included with ECOG PS of 2 or less and with a life expectancy of at least 3 months. One hundred and fifty patients were treated and treatment could be completed in 72% of cases. Grade 3-4 neutropenia was the most frequent adverse event and occurred in 40% of cases; febrile neutropenia was reported in 8%. The 29 month median overall survival and the 62% complete and unconfirmed response rates observed prompted the authors to suggest that immunochemotherapy with R-mini-CHOP offers a good compromise between efficacy and safety for the initial treatment of selected patients older than 80 years with DLBCL and good performance status. This regimen can be considered as a platform for the introduction of new targeted drugs in the first line of this population.

In addition to achieving higher efficacy with modification of study regimens additional improvement in the treatment of elderly patients with DLBCL should come from a better selection of patient. In the Peyrade study as well as in most studies on elderly patients the initial selection of patient was based on subjective assessment of patient performance status and ability to receive full dose chemotherapy done

by the local investigator. This approach is questionable as it has very low reproducibility and lacks standardization.

1.3 Comprehensive Geriatric Assessment (CGA)

There are currently several tools that can be used to provide an accurate description of the elderly subject; they range from a very simple assessment of performance status (ECOG or Karnofsky scales) [20] to more complex scales that use a multidimensional approach. Among available multidimensional test Comprehensive Geriatric Assessment (CGA) has been proposed as useful and reproducible tool. CGA includes the evaluation of physical disability, nutrition conditions, psychological status and co-morbidities, relying on scales profiling different aspects of the patient status. [21, 22] ***(Appendix A)***. Particularly:

- **ADL** (Activities of Daily Living) scale, includes the assessment of six basic self-care skills needed to maintain independence in the home; particularly, the ability of bathing, dressing, toileting, feeding oneself, maintain continence, and transferring from a bed or chair without assistance [23, 24]; **(Appendix B)**
- **IADL** (Instrumental Activities of Daily Living) scale includes the assessment of eight skills to maintain independence in the community: using the phone, shopping, cooking meals, housekeeping, doing laundry, using public transport, taking medications and managing money [25] ***(Appendix C)*;**
- **CIRS** (Cumulative Illness Rating Scale) plans a global assessment of severity of possible co-morbidities [26, 27] ***(Appendix D)***

Some studies have showed that ADL and IADL are more appropriate to define functional deficits in elderly than Performance Status. By the use of the above mentioned scales and the age of the patient CGA allows the qualification of subject status. Patients are considered as FIT if young and without impairment of ADL or IADL and with only mild co-morbidities, or frail if old (80 years as cutoff), and/or with severe impairment or functional status and/or with severe co-morbidities. The qualification of patient fitness status has relevant clinical implication as it might be used to define therapeutic goals in patients with potentially curable disease such as DLBCL.

Since 1996 the FIL has adopted the use of CGA to initially identify patients that are able to undergo treatment with curative intent and to distinguish them from those who are frail and should be addressed to palliative therapy [17] [28].

This approach has been used by the FIL for the design of trials investigating treatment options of elderly patients with malignant lymphoma either of Hodgkin or of Non Hodgkin subtype. In all recent FIL prospective trials for elderly patients with lymphoma CGA was considered among the screening procedures and patients were required to qualify as FIT to be included in the study and receive the study treatment. Frail patients were excluded as they were not considered able to tolerate treatment with curative intent.

- **FIT** patients, without any co-morbidity and potentially able to receive standard treatment;
- **UNFIT** patients, with mild co-morbidities and possibly able to receive reduce-dose of a standard treatment;
- **FRAIL** patients, with severe co-morbidities and able to receive only palliative treatment

1.4 Treatment of unfit patients

Currently there is no doubt that R-CHOP is the standard therapy for elderly FIT patients with DLBLCL. Also, it is reasonable to adopt a palliative approach in FRAIL patients for whom the costs of treatment in terms of toxicity is not acceptable. Regarding the intermediate UNFIT category the choice of treatment is more problematic as for these patients the risk to benefit ratio of therapy is crucial. So far no or very few studies have tried to identify a specific therapy tailored for unfit patient as currently available standard option apply to fit patients. Based on available data R-miniCHOP regimen represents a good platform for further improvement [18]. What is questionable from the Peyrade study however is the adoption of age and of performance status as selection criteria for study enrolment. As observed by the same authors among treated patients impaired IADL score was associated with poor survival and was independent of ECOG. This observation clearly demonstrates that the use of more complete assessment of patients status is useful to better identify those subjects that may benefit from therapy. As previously described CGA represents a good tool to improve the definition of patients status and to define treatment objectives for elderly patients with DLBCL. In particular as used by the FIL CGA can be added to anagraphic criteria and improves the ability to define which patient can tolerate a full treatment course, an intermediate therapy or palliation.

1.5 Obinutuzumab (GA101)

1.5.1 Structure and Mechanism of Action

RO5072759 (GA101) is a humanized and glyco-engineered monoclonal antibody, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glyco-engineering leading to the following characteristics [29] [30].

- High-affinity binding to CD20
- Type II binding to the CD20 epitope, leading to low complement-dependent cytotoxicity (CDC) activity related to the recognition of the CD20 epitope and the lack of CD20 localization into lipid rafts after binding of the monoclonal antibody to CD20
- Compared with the chimeric Type I anti-CD20 antibody rituximab, increased antibody-dependent cellular cytotoxicity (ADCC) related to an improved binding of GA101 to the different allotypes of FcγRIIIa expressed by natural killer cells and monocytes
- Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino acid exchange of the Fab region and Type II binding of the CD20 epitope

Given the significantly greater ADCC and direct cell-death induction, it is possible that GA101 may have greater efficacy than rituximab, particularly in the 80%−85% of patients who are carriers of the FcγRIIIa low-affinity receptor polymorphism.

1.5.2 Pre-clinical efficacy with GA101

GA101 has demonstrated in vivo efficacy superior to that of rituximab in various human lymphoma xenograft models. Both antibodies have been compared in human SUDHL-4 cells (a DLBCL model) that were subcutaneously injected into severely immunodeficient beige mice.

Therapy began when tumors were established and were rapidly growing. It was shown that, at 10 mg/kg, rituximab inhibited tumor growth more than rituximab at 1 mg/kg; however, increasing the dose to 30 mg/kg did not result in increased efficacy of rituximab. In contrast, GA101 showed a dose-dependent increase in efficacy in the range of 1 –30 mg/kg and resulted in complete tumor regression in all animals and in lasting tumor eradication in 9 of 10 animals at the highest dose of 30 mg/kg and in 1 of 10 animals at a dose of 10 mg/kg.

Additional studies have also shown similar results, in which GA101 treatment was able to control tumor growth when vehicle- and rituximab-treated tumors were not controlled [29]

1.5.3 Clinical experience with GA101

For more detailed clinical information on GA101, please refer to the current version of the Investigator's Brochure .

As of June 2013, clinical data on GA101 regarding efficacy and safety are available from four Phase I/II studies (BO20999, BO21003, BO21000, and JO21900) and two Phase III studies (GAO4753g and BO21004/CLL-11). As of 2 July 2013, an estimated 503 CLL patients and 1476 NHL patients from the 12 studies have been exposed to obinutuzumab, either as monotherapy or in combination therapy.

Phase II results from the aggressive and indolent NHL cohorts of patients in ongoing studies are described below. For information about chronic lymphocytic leukemia (CLL) and all Phase I studies, please refer to the GA101 Investigator's Brochure .

Study BO20999 (Phase I/II): GA101 Monotherapy

The results from the Phase II part of the study are presented as follows.

Patients with Indolent NHL. Forty patients with relapsed or refractory indolent NHL were randomized to receive GA101 in a low-dose (LD) cohort (n=18) or a high-dose (HD) cohort (n=22).Patients were pre-treated with a median of four prior regimens (range: 1–13), and the majority (39 of 40 patients) had received prior rituximab treatment. More than half of these patients (24 of 40) were considered to be rituximab refractory, and 25% (10 of 40) of all patients had previously received an autologous stem-cell transplant. The treatment regimen in the LD cohort was 400 mg for Cycles 1–8 (21-day cycles), with an additional 400-mg dose on Day 8 of Cycle 1. The treatment regimen in the HD cohort was 1600 mg on Days 1 and 8 of Cycle 1 and 800 mg for Cycles 2–8 (21-day cycles). The end-of-treatment response rate (response evaluation 4 weeks after the end of treatment) was 17% in the LD cohort (3 patients with partial response [PR], 6 with stable disease [SD], 7 with progressive disease [PD], and 2 unevaluable) and 55% in the HD cohort (2 patients with CR, 10 with PR, 6 with SD, and 4 with PD).

GA101 was well tolerated in both cohorts. During the treatment period, 9 patients experienced a total of 12 serious adverse events, with four events (herpes zoster, neutropenia, febrile neutropenia, and pancreatitis; all in the HD cohort) assessed by the investigator as related to GA101. During the additional follow-up period, 2 patients experienced serious adverse events of pyrexia (LD cohort) and bacteremia (HD cohort). The most common adverse events (all grades), occurring with an incidence of ≥ 10%, were infusion-related reaction (IRR; 73%), asthenia (33%), nasopharyngitis (13%), peripheral edema (10%), pyrexia (10%), abdominal pain (10%), bronchitis (10%), and nausea (10%). Thirty-three percent of patients had Grade 3 or 4 adverse events, the three most common being lymphopenia (8%), neutropenia (8%), and infections (10%).

Patients with Aggressive NHL. Forty patients with aggressive NHL were enrolled in the Phase II part of the study. Of these patients with aggressive NHL (25 with DLBCL and 15 with mantle-cell lymphoma [MCL]), 19 were treated in the HD cohort (15 with DLBCL and 4 with MCL) and 21 in the LD cohort (10 with DLBCL and 11 with MCL). Preliminary safety and efficacy data are available (data on file). The primary endpoint was end-of-treatment response, assessed 4 weeks after the last infusion (25 weeks after treatment start). Patients were heavily pre-treated (median of three prior therapies), with 63% of patients having not responded to or relapsed within 6 months after a previous rituximab-containing regimen (rituximab refractory), and 45% of patients completed all nine infusions.

The end-of-treatment response rate was 24% (DLBCL: 2 patients with PR, 1 with CR unconfirmed; MCL: 2 with CR) in the LD cohort and 32% (DLBCL: 4 with PR; MCL: 2 with PR) in the HD cohort. The five most common adverse events were IRR (75%), infection (25%), asthenia (18%), anemia (15%), and lymphopenia (15%). Fifty percent of patients had Grade 3 or 4 adverse events, with the five most common being lymphopenia (15%), anemia (10%), thrombocytopenia (8%), IRR (8%), and tumor lysis syndrome (5%). Serious adverse events occurring in 2 or more patients included cardiac failure (n=2), IRR (n=3), tumor lysis syndrome (n=2), and anemia (n=2). There was one Grade 5 adverse event, cardiorespiratory arrest, which was thought to be secondary to ventricular arrhythmia.

Study BO21003 (Phase II): GA101 Monotherapy plus Maintenance

This is an ongoing, open-label, multicenter, randomized, Phase I/II study to investigate the efficacy and safety of GA101 monotherapy compared with rituximab monotherapy in patients with relapsed indolent NHL. The Phase II portion of the study began in July 2009, and approximately 176 patients have been enrolled. An interim analysis for safety and a futility analysis for efficacy was performed in July 2010 using data from 78 patients. According to the protocol, futility stopping rules recommended a halt to the trial if the rituximab arm had 2 or more patients with a response at the end of treatment than the GA101 arm ($\Delta < -3.14\%$). The internal monitoring committee's recommendation was to continue the study as planned. No new safety issues were identified.

Study BO21000 (Phase Ib): GA101 in Combination with Chemotherapy

Study BO21000 is an ongoing trial, investigating two doses of GA101 (400 mg and 1600/800 mg) in combination with chemotherapy given every 4 weeks for a maximum of six cycles (GA101 plus fludarabine and cyclophosphamide [G-FC]), or a maximum of eight cycles (GA101 plus CHOP [G-CHOP]) in patients with relapsed follicular lymphoma. In the 1600/800-mg G-CHOP arm, patients receive a cumulative dose of 7200–8000 mg, depending on the standard number of cyclesdelivered. In addition, the protocol has recently been amended to include GA101 at a flat dose of 1000 mg plus bendamustine (G-bendamustine) or CHOP (G-CHOP) in previously untreated patients with follicular lymphoma. Patients with a PR or CR who complete a minimum of four cycles of G-FC, six cycles of G-CHOP, or four cycles of G-bendamustine have the option of receiving maintenance therapy with GA101 alone every 3 months for up to 2 years.

Fifty-six patients with relapsed or refractory follicular lymphoma have been enrolled in the study to receive either 6 or 8 cycles of G-CHOP every 21 days (n =28) or 4 or 6 cycles of G-FC every 28 days (n=28), with an additional GA101 dose administered to patients on Day 8 of Cycle 1. All 28 patients treated with G-CHOP have completed induction treatment, whereas 6 of the 28 patients who started G-FC withdrew early from induction treatment. Reasons for discontinuation of study treatment for the 6

patients who withdrew from the G-FC arm were PD for 1 patient and adverse events in 5 patients: neutropenia (3 patients), and rash and infection (1 patient each).

Overall, between the LD and HD arms, the rate of adverse events by system organ class did not differ greatly, and given the small numbers of patients, definitive conclusions cannot be drawn about differences between GA101 adverse events rates in these arms. All 56 patients experienced at least one adverse event. The most commonly reported events were classified under the system organ class "general disorders and administration-site conditions," with the highest rate for IRR events regardless of the chemotherapy backbone and dose level group considered.

The percentage of patients with IRRs was 68% in the G-CHOP arm and 82% in the G-FC arm, with 7% of events being Grade 3 or 4 events in both chemotherapy arms. Events in the gastrointestinal disorders system organ class were the second most common reported adverse events and were reported in 86% and 71% of patients in the G-CHOP and G-FC arms, respectively. Infections and infestations events were experienced by 79% (93% HD; 64% LD) of patients in the G-CHOP arm and 57% (57% HD; 57% LD) of patients in the G-FC arm. Grade 3 and 4 infections and infestations events were reported in 21% of patients in the G-CHOP arm and 29% of patients in the G-FC arm.

Blood and lymphatic system events, with neutropenia being the most common event, were observed for 57% and 64% of the patients in the G-CHOP and G-FC arms, respectively. Of these events, 46% and 61% were considered Grade 3 or 4 events.

Neutropenic events (i.e., neutropenia, febrile neutropenia, neutropenic sepsis, and neutropenic infections) were reported in 14 patients (50%) and 17 patients (61%) in the G-CHOP and G-FC arms, respectively.

Serious adverse events were reported in 8 (29%) and 7 (25%) patients receiving G-CHOP and G-FC induction, respectively. Infections were the most commonly reported events.

No deaths have been reported during the induction treatment period.

Study GAO4753g (Phase III): GA101 in Combination with Chemotherapy

This is an ongoing, open-label, multicenter, randomized, Phase III study to investigate the efficacy and safety of bendamustine compared with G-bendamustine in patients with rituximab-refractory indolent NHL. Approximately 360 patients will be enrolled. The first patient was enrolled in April 2010. The study is ongoing, and the results remain blinded. All these data demonstrate that the new anti-CD20 antibody is safe either in untreated patients or in pre-treated patients. Therefore at now no more data on safety are needed in particular as a primary objective in a study evaluation.

1.5.4 Pharmacokinetic and Pharmacodynamic results for GA101

A population pharmacokinetic *(PK)* model has been developed for StudiesBO20999 and BO21003 to characterize the pharmacokinetics of GA101 and its variability. A two-compartment model, comprising both a linear clearance pathway and a non-linear time-varying clearance pathway, was fitted to the data. Data are available for 134 patients following intravenous (IV) administration of GA101 in Studies BO20999 (114 patients) and BO21003 (20 patients). Following infusion of GA101, the elimination appears to be characterized by clearance that is dependent on time, i.e., starting at a typical value of 594 mL/day and then gradually declining to an asymptote of 112 mL/day at steady state. Tumor burden potentially contributes significantly to the clearance of GA101, especially at the beginning of treatment when there is an excess of CD20-expressing cells. As tumor burden decreases, clearance reaches an asymptote, which was thought to be primarily a function of the proteolytic metabolic clearance. Consequently, some patients with a high tumor burden appear to clear the drug from the plasma faster than patients with a low tumor burden as GA101 binds to the CD20-positive tumor cells and is effectively removed from the plasma. Therefore, the clearance of the drug will vary with time since repeated treatment with GA101 is expected to reduce the number of CD20-positive tumor cells. Treatment with GA101 resulted in extensive B-cell depletion, with all patients showing a reduction in cell count to absolute zero and most reductions occurring after the first infusion. Overall, no notable increase has been observed in complement levels pre- and post-infusion, but changes have been observed in the levels of interleukin-6 and interleukin-8 before and after infusion.

2. RATIONALE OF THE STUDY

Considering that the treatment of elderly unfit patients with DLBCL cannot be based on a full course of R-CHOP, and that using a less intense R-miniCHOP combination an acceptable cure rate can be achieved this study is designed to try to improve the cure rate in unfit patients with DLBCL by adopting the R-miniCHOP scheme substituting Rituximab with the more active GA101 monoclonal antibody. The study hypothesis is that a higher activity of the treatment can be achieved without modifying the cytotoxic part of the treatment but using a more active immunotherapy. Differently from the previous experience with R-miniCHOP eligible patient are not only identified using anagraphic criteria but adopting CGA as part of initial assessment and considering as eligible unfit patients (i.e. those older than 80 year without significant inabilities or co-morbidities and patients younger than 80 years with mild inabilities or non severe co-morbidities).

3. OBJECTIVES OF THE STUDY

3.1 General Objectives

The purpose of the study is to evaluate feasibility and activity of GA101-miniCHOP combination in elderly unfit patients with diffuse large B-cell lymphoma (DLBCL). Addition of a new and more active monoclonal antibody to the same chemotherapy should consist in an increase of response for elderly unfit patients with DLBCL newly diagnosed.

Primary Objectives

- Primary objectives is to asses whether the regimen GA101-miniCHOP achieves an absolute increase of the CR proportion of al least 15% (from 60% to 75% respect to R-miniCHOP regimen [18]). To evaluate the activity of GA101-miniCHOP regimen in terms of complete response rate (CRR)

Secondary Objectives:

- To evaluate the safety and tolerability of GA101-miniCHOP regimen in terms of rate of adverse events
- Partial and Overall Response Rate: PR and ORR (CR+PR)
- Overall Survival (OS)
- Progression Free Survival (PFS)
- Dynamics of Comprehensive Geriatric Assessment (CGA)
- Dynamics of Quality of Life (QoL) questionnaire

3.2 Endpoints

3.2.1 Primary Endpoints:

- Complete Response Rate (CRR) after 10 infusions of GA101 and 6 cycles of miniCHOP. The response rate to therapy will be based a central Independent Review Committee of response that will not consider the results of FDG-PET *(according to the revised Cheson criteria [31]*) **but will only use the conventional CT scan images** *(according to Cheson criteria, 1999)* [32]. ***(Appendix K)***

3.2.2 Secondary Endpoints:

- Rate of Adverse Events
- Partial and Overall Response Rate (PRR, ORR)
    - ORR: defined as the sum of complete or partial response evaluated by CT scan, after 6 GA101-miniCHOP courses plus 2 GA101 infusions
- Overall Survival (OS)
    - OS is defined as the time from entry onto the study until death as a results of any cause

- Progression Free Survival (PFS)
    - PFS is defined as the time from entry onto the study until lymphoma progression or death as a results of any cause
- Change in ADL, IADL and CIRS
    - Change in ADL, IADL and CIRS from study entry to end of treatment/follow up
- Change in QoL (EORTC QLQ C30)
    - Change in QoL from study entry to end of treatment/follow up

4. STUDY DESIGN

4.1 Description of the study

This is a prospective, multicenter, single arm, phase II trial in elderly patients (≥ 65 years) affected by DLBCL defined as unfit according to CGA and previously untreated.

After providing written informed consent, patients will be evaluated for eligibility during a 28-day screening period. If they continue to meet eligibility criteria they will receive the fist dose of GA101-miniCHOP.

Duration of treatment will be approximately 6 months (6 courses of GA101-miniCHOP + 2 GA101, every 21 days); during the study disease status will be evaluated for tumor response after the 4 th cycle by clinical/radiological assessment of target lesion (CT/SCAN and/or echography). Final response will be evaluated within 28 days after the last study medication administration. All patients will be monitored during follow up, every 3-6 months for 2 years.

4.2 Study duration

Five years: 30 months for patients enrolment plus 6 months of treatment and 24 months of follow up

4.3 Study time table

This study is expected to start in May 2015. The last patient is expected to be enrolled at November 2017. This trial is due to be completed by the end of April 2020.

5. PATIENT SELECTION CRITERIA

Elderly patients, aged ≥ 65 years, classified as "unfit" according to CGA ***(Appendix A)***, with histologically proven diagnosis of CD20+ Diffuse Large B-Cell non-Hodgkin's Lymphoma (DLBCL) at diagnosis (not previously treated) will be candidate for the study.

Eligible patients who are in conformance with the following inclusion and exclusion criteria may enrolled in this study.

5.1 Inclusion Criteria

1) Histologically proven CD20 positive Diffuse Large B-cell Lymphoma and Follicular grade IIIB lymphoma, according to WHO classification (local pathologist)

2) Age ≥ 65 years

3) No previous treatment

4) CGA assessment performed before starting treatment

5) UNFIT patients defined as follows (see *Appendices A-D*):

Age ≥ 80 years with FIT profile, i.e.

ADL =6 residual functions

IADL=8 residual functions

CIRS: no comorbidity of grade 3-4 and <5 of grade 2

or Age < 80 with UNFIT profile, i.e

ADL ≥ 5 residual functions

IADL ≥ 6 residual functions

CIRS: no comorbidity of grade 3-4 and 5-8 co-morbidities of grade 2

6) Ann Arbor Stage I with bulky, II-IV ***(Appendix E)***

7) At least one bi-dimensionally measurable lesion defined as > 1.5 cm in its largest dimension on CT scan

8) ECOG performance status of 0, 1, or 2 ***(Appendix G)***

9) Adequate hematologic function (unless caused by bone marrow infiltrate), defined as follows:

Hemoglobin ≥ 10 g/dL

Absolute neutrophil count ≥ 1.5 x 10^9/L

Platelet count ≥ 100 x 10^9/L

10) LVEF ≥50%

11) Ability and willingness to comply with the study protocol procedure

12) Life expectancy > 6 months

13) Accessibility of patient for treatment and follow up

14) Written informed consent

5.2 Exclusion Criteria

1) History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products

2) Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines

3) History of other malignancies within 5 years prior to study entry except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer

4) Stage I without bulky

5) Patients with transformed lymphoma

6) Prior therapy for DLBCL, with the exception of nodal biopsy or local irradiation

7) Previous exposure to cytotoxic agents

8) Suspect or clinical evidence of CNS involvement by lymphoma

9) HBsAg, HCV or HIV positivity; isolated HBcAb positivity is accepted only with concomitant treatment with Lamivudine

10) AST /ALT > twice upper the normal range; bilirubin > twice upper the normal range; serum creatinine > 2.5 mg /dl (unless these abnormalities were related to the lymphoma)

11) Evidence of any severe active acute or chronic infection

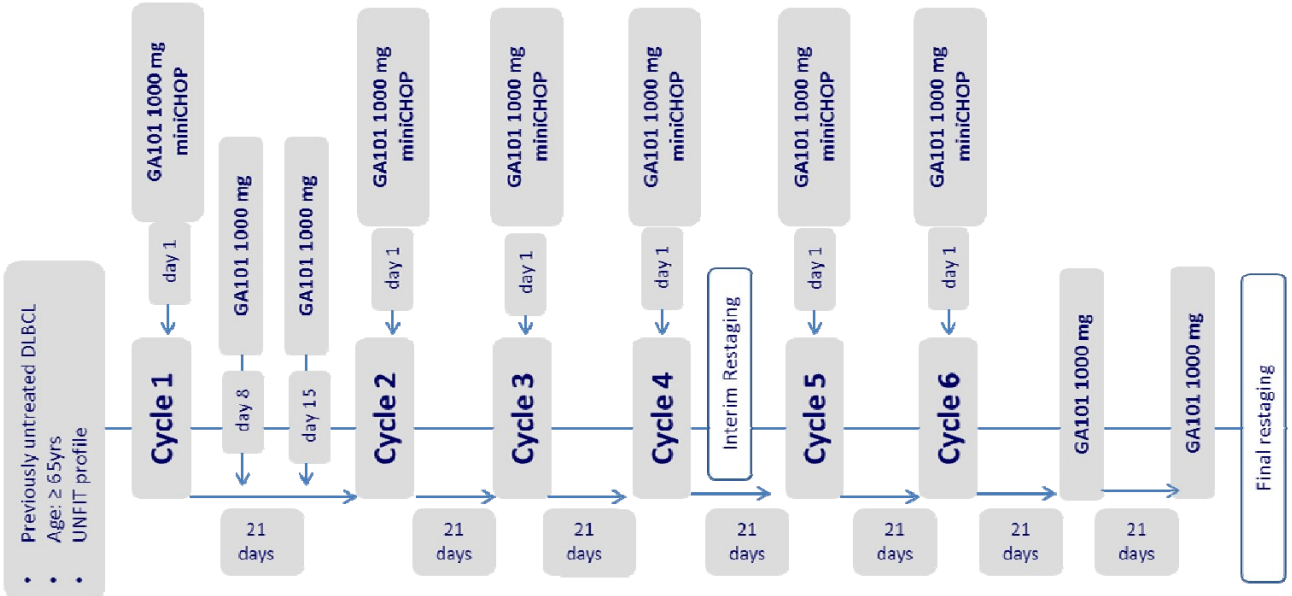
12) Concurrent co-morbid medical condition which might exclude administration of full dose chemotherapy

6. STUDY TREATMENT

6.1 Treatment Plan

Patients will receive:

6 courses of GA101-miniCHOP regimen and 2 additional infusions of GA101, every 21 days ***(for a total of 6 courses of miniCHOP and 10 infusions of GA101)***



GA101-miniCHOP regimen

Cycle 1

GA101: 1000 mg day 1, day 8 and day 15, iv

Cyclophosphamide: 400 mg/mq, day 1, iv

Doxorubicin: 25 mg/mq, day 1, iv

Vincristine: 1 mg, day 1, iv

Prednisone: 40 mg/mq, days 1-5, os

Cycles 2-6

GA101: 1000 mg day 1, iv

Cyclophosphamide: 400 mg/mq, day 1, iv

Doxorubicin: 25 mg/mq, day 1, iv

Vincristine: 1 mg, day 1, iv

Prednisone: 40 mg/mq, days 1-5, os

Two additional infusions of GA101: 1000 mg day 1, iv, every 21 days.

An interim check for response will be assessed after the completion of 4 courses of GA101-miniCHOP in order to identify non responding patients: patients achieving a CR, PR, or SD will continue to complete combined immunochemotherapy as planned, patients with progressive disease will stop treatment and will be considered as failure.

All patients stopping study treatment due to early disease progression will be followed for survival until the end of the study.

Prophylactic granulocyte colony-stimulating factor (G-CSF) support is mandatory starting within 24-72 hours from day 1 of each cycle for no less than 4 doses or until neutrophils count exceeds 1.00×10^{9}/L or more [33]. Alternatively a single dose of pegylated G-CSF or pegfilgrastim can be used.

Use of erythropoietin is allowed according to clinical practice; other supportive measures care will be administered according to medical judgement.
A preliminary debulking or symptomatic phase of vincristine 1 mg or intermediate - high dose steroid is allowed. In case of debulking with vincristine, this drug must be omitted from cycle 1.

Involved Site Radiotherapy (ISRT) is allowed on previous bulky sites or on PET positive lesion at the end of treatment.

6.2 Dosage Delays and Modifications: GA101 and CHOP chemotherapy

Dose reductions and delays are based on all laboratory values obtained within 72 hours prior to a study treatment infusion.

A dose delay of 21 days is permitted for miniCHOP and GA101 to allow recovery of hematologic toxicities to Grade ≤ 2 (platelets must return to Grade ≤ 1) or non-hematologic toxicities to Grade ≤ 1 or baseline status for the first episode.

Dose Modifications of GA101-miniCHOP chemotherapy

No dose modifications of GA101 (1000 mg) are allowed.
If administration of chemotherapy is delayed, there will be no dose modification of GA101, and the administration of GA101 and all chemotherapy drugs should be delayed for the same time frame, e.g., if miniCHOP therapy is delayed, administration of GA101 should also be delayed so that they are given on day 1 of the same cycles.

Hematologic and Non-Hematologic Toxicities

Dosing of miniCHOP and GA101 may be resumed upon the resolution of hematologic toxicity to Grade ≤2 (platelets must resolve to Grade ≤ 1) or baseline status for the first episode.

For non-hematologic toxicities, dosing of GA101-miniCHOP-may only be resumed upon resolution to Grade ≤1 or baseline status.
For Grade ≥ 2 non-hematologic toxicities (excluding alopecia, nausea, and vomiting), treatment with GA101-miniCHOP will be delayed until resolution to Grade ≤1 (or baseline status for all except hemorrhagic cystitis), for a maximum of 21 days.

In addition, resumption of dosing without complete resolution of toxicity may only be considered after careful weighing of the risks and benefits with the patient and agreement between the investigator and the Sponsor.

If treatment is delayed for more than 21 days (except for hepatitis B reactivation), the patient will be withdrawn from study treatment. (note that lymphopenia is not considered a cytopenic toxicity, as it is an expected outcome of therapy.)

Patients who discontinue all study treatment for adverse events should remain on the study and continue to have disease assessments until progression and standard follow-up.

In the event of grade 2 neurological vincristine-related toxicity (sensory or motor polyneuritis, constipation, or visual or auditory changes) vincristine can be discontinued.

6.3 Permitted concomitant therapies and medications

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 7 days preceding the baseline evaluations and the end of last study visit.
All concomitant medications should be reported to the investigator and recorded on the appropriate CRF.

- Prevention of tumour lysis syndrome by alkalinisation or hypouricaemic drugs is allowed if necessary.
- Antiemetic therapy with SHT3 antagonists can be given at each cycle.
- Patients will receive prophylactic treatment with Bactrim 2 cp/day twice a week during all the chemotherapy.
- CNS prophylaxis with intrathecal infusion of methotrexate and steriod is allowed according to local clinical practice (i.e. patients with testicular involvement or patients considered at high risk of CNS relapse).
- In patients HBcAb+, prophylaxis for hepatitis B reactivation with Lamivudine 100mg/die from the start of the treatment to one year after the end of the treatment is mandatory.
- Pre-medication for GA101 infusion with oral acetaminophen (e.g., 650−1000 mg) and an antihistamine such as diphenhydramine hydrochloride (50−100 mg) 30−60 minutes prior to starting each infusion (unless contraindicated). An additional glucocorticoid (e.g., 100 mg IV *prednisone or prednisolone* or equivalent) is allowed at the investigator's discretion. For

patients who do not experience infusion-related symptoms with their previous infusion, pre-medication at subsequent infusions may be omitted at the investigator's discretion.

- Prophylaxis with levofloxacine or ciprofloxacine and fluconazole/itraconazole/posaconazole are allowed.
- Platelets and red blood cell transfusion are allowed, if needed.
- CNS Prophylaxis: CNS prophylaxis with intrathecal chemotherapy only should be given according to institutional practice and its use documented on the CRF.
- Prophylaxis for Hemorrhagic Cystitis: Patients should be adequately hydrated prior to and after cyclophosphamide administration and should be instructed to void frequently. Mesna may be used as prophylaxis according to institutional practice.

6.4 GA101

6.4.1 Rationale for GA101 Dose

PK analyses of the GA101 Phase I studies, together with published data on rituximab [34], demonstrate that patients with higher disease burden have a faster antibody clearance. Although dosing according to target volume is difficult, these data suggest that patients with high tumor burden may require higher doses to saturate the target. This finding was further substantiated by modeling and simulation experiments, which showed a higher degree of clearance variability observed at lower GA101 doses.

To further understand a potential dose effect, in the Phase II part of Study BO20999, patients were randomized to two different GA101 dose cohorts. In the LD cohort, patients received 8 cycles of 400 mg of GA101, with an additional 400-mg dose given on Day 8 of the first cycle. In the HD cohort, GA101 was given at 1600 mg on Days 1 and 8 of the first cycle, followed by 800 mg at Cycles 2–8. Cumulative doses were 3600 mg and 8800 mg in the LD and HD cohorts, respectively. In comparison, a typical dose for the reference antibody rituximab is approximately 5000–6000 mg ($3 \times 375 mg/m^2$), which would be in between the low and high doses tested for GA101. PK simulations show that the 95% confidence limits for exposure are between the low and high doses and are not overlapping. No dose-limiting toxicities were observed across the two doses and, although there was a slight increase of IRRs and neutropenia rates in the HD cohort, GA101 was generally very well tolerated. As expected, PK variability was lower at the higher dose. Importantly, increased overall response rate have been observed in the HD cohort compared with those in the LD cohort (55% vs. 13%, respectively) in the subset of patients with indolent lymphoma. Findings in the aggressive lymphoma cohort did not show a marked difference in response rates between patients receiving the high and low doses (32% and 24%, respectively), yet this cohort was further subdivided by the inclusion of patients with relapsed

DLBCL and relapsed MCL and small numbers (25 patients with DLBCL and 15 patients with MCL) might have prevented a more compelling result.

In summary, it was concluded that a higher dose—1000 mg—of GA101 can be delivered intravenously and that the available evidence from nonclinical studies, PK studies, modeling and simulation, and clinical trials (Phase I and Phase II) in patients with NHL are suggestive of a higher dose being more appropriate to saturate the target in the majority of patients with NHL irrespective of their tumor load and, thus, more efficacious than a lower dose.

6.4.2 Rationale for Administration of Additional Loading Doses on Days 1 and 8

In the Phase II part of Study BO20999, the first two doses of GA101 in the HD cohort were set at 1600 mg. Although well tolerated by patients, the dosing scheme resulted in administration times of up to and exceeded 5 hours. With the goal in mind to maintain the loading dose concept, and to provide a significant amount of antibody early on during the treatment course, it was decided to split GA101 administration and to change the schedule and dose during the first 2 weeks of any future studies from 1600 mg on Days 1 and 8 to 1000 mg on Days 1, 8, and 15, providing comparably fast rising PK exposure and early target saturation, while avoiding the practical challenges of delivering 1600 mg of drug in a single day together with chemotherapy. The dose for subsequent cycles is also set at 1000 mg. This dose and schedule result in a GA101 exposure of 3000 mg during the first 2 weeks for a cumulative exposure of 10,000 mg and is therefore very close to the regimen that has delivered the best results thus far for GA101 in both indolent and aggressive lymphoma. There is no indication that the additional GA101 doses on Days 8 and 15 in the first cycle would negatively affect the safety of patients. In this study, GA101 will be given for a total of 10 infusions, regardless of the number of miniCHOP cycles, with additional doses of GA101 to be administered to patients on Days 8 and 15 of Cycle 1

6.4.3 GA101 Formulation

GA101 is provided as a single-dose, sterile liquid formulation in a 50-mL pharmaceutical grade glass vial containing a nominal 1000 mg of GA101. The formulated drug product consists of 25 mg/mL drug substance (G3) formulated in histidine, trehalose, and poloxamer 188. The vial contains 41 mL (with 2.5% overfill). For further details, see the GA101 Investigator's Brochure.

6.4.4 GA101 Handling and Storage

The recommended storage conditions for the GA101 drug product are between 2 °C and 8 °C protected from light. Chemical and physical in-use stability for GA101 dilutions in 0.9% sodium chloride (NaCl)

have been demonstrated for 24 hours at 2°C–8°C and at ambient temperature and ambient room lighting. The prepared diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2C–8°C. GA101 should not be frozen or shaken. Mix gently. All transfer procedures require strict adherence to aseptic techniques. Do not use an additional in-line filter because of potential adsorption. For further details, see the GA101 Investigator's Brochure.

6.4.5 GA101 Dose and Schedule

GA101 will be administered by IV infusion as an absolute (flat) dose of 1000 mg on Day 1 of each 28-day cycle for 8 cycles.

GA101 will be administered prior to miniCHOP, and patients should be observed 30 minutes prior to starting miniCHOP. If miniCHOP is not started because of the long duration of GA101 therapy, miniCHOP chemotherapy may be administered on Day 2.

During Cycle 1, GA101 will also be infused on Days 8 and 15.

6.4.6 GA101 Preparation

GA101 drug product intended for IV infusion is prepared by dilution of the drug product into an infusion bag containing 0.9% NaCl to the final drug concentration of 4 mg/mL. Using a 250-mL infusion bag containing 0.9% NaCl, withdraw and discard 40 mL of the sodium chloride. Withdraw 40 mL of GA101 from a single glass vial and inject into the infusion bag (discard any unused portion of GA101 left in the vial). Gently invert the infusion bag to mix the solution; do not shake.

Administration sets with polyvinyl chloride (PVC), polyurethane (PUR), or polyethylene as product contact surface and IV bags with polyolefine, polypropylene (PP), PVC, or polyethylene, as product contact surface are compatible and may be used.

Do not use GA101 beyond the expiration date stamped on the carton.

6.4.7 GA101 Administration

GA101 should be administered to patients in a clinical setting (inpatient or outpatient), where full emergency resuscitation facilities are immediately available and patients should be under close supervision of the investigator at all times. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line or central venous catheter should remain in place for ≥ 2 hours in order to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed or the central venous catheter may be de-accessed. For subsequent infusions, access (either

through an IV line or central venous catheter) should remain in place for at least 1 hour from the end of infusion, and if no adverse events occur after 1 hour, the IV access may be removed.
Instructions for the first and subsequent infusions of GA101 are presented in Table 1.

Table 1

Administration of First and Subsequent Infusions of GA101

First Infusion (Day 1)	Subsequent Infusions
Begin infusion at and initial rate of 50 mg/hr. If no infusion reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved.	If a patient experienced an infusion reaction during the prior infusion, start at the same rate as the first infusion (50 mg/hr) and follow directions as noted. If the patient tolerated the prior infusion well *(defined as an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hr)*, begin the infusion at a rate of 100 mg/hr. If no infusion reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional protocol. Resume the infusion at a 50% reduction in rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred) if the reaction has resolved.

GA101 should be given as a slow IV infusion through a dedicated line. IV infusion pumps should be used to control the infusion rate of GA101. Do not administer as an IV push or bolus.

On days when both GA101 and miniCHOP are given, GA101 will be administered prior to miniCHOP and patients should be observed 30 minutes prior to starting miniCHOP.
MiniCHOP chemotherapy may be administered the next day if it cannot be given on the same day as GA101 administration.

Prior to each GA101 infusion that is given in combination with miniCHOP (Day 1 of Cycles 1–6) patients should take the Day 1 dose of oral prednisone (40 mg/mq) specified for each cycle of the miniCHOP regimen.

The prophylactic use of corticosteroids (e.g., 100 mg of IV prednisolone or equivalent) may also be considered for patients thought to be at high risk for IRRs, if deemed appropriate by the investigator, and should be also administered prior to the GA101 infusion.)

Table 2 Premedication to be administered before Obinutuzumab infusion to reduce the risk of Infusion Related Reactions (recommended for ALL patients).

Day of Treatment Cycle	Patients requirement premedication	Premedication	Administration
Cycle 1: Day 1	All patients	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion
		Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
		Anti-histaminic drug[3]	
Cycle 1: Day 8, Day15 **Cycle 2-6: Day 1**	Patients with a Grade 3 IRR with the previous infusion OR Patients with the lymphocyte counts > 25 x 10^9/L prior the next treatment	Intravenous corticosteroid[1]	Completed at least 1 hour prior to obinutuzumab infusion
	All patients	Oral analgesic/anti-pyretic[2]	At least 30 minutes before obinutuzumab infusion
	Patients with an IRR (Grade 1 or more) with the previuos infusion	Anti-histaminic drug[3]	

[1] *100 mg di prednisone/prednisolone or 20 mg di dexamethasone or 80 mg di methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.*
[2] e.g. *1.000 mg acetaminophen/paracetamol*
[3] e.g. *50 mg di diphenhydramine*

6.4.8 GA101 Pre-Medication

All GA101 infusions should be administered to patients after pre-medication with oral acetaminophen (e.g., 650-1000 mg) and an antihistamine such as diphenhydramine hydrochloride (50-100 mg) 30-60 minutes prior to starting each infusion (unless contraindicated).

An additional glucocorticoid (e.g., 100 mg IV *prednisone or prednisolone* or equivalent) is allowed at the investigator's discretion.

For patients who do not experience infusion-related symptoms with their previous infusion, pre-medication at subsequent infusions may be omitted at the investigator's discretion.

Patients with high tumor burden and who are considered by the investigator to be at risk for tumor lysis should also receive tumor lysis prophylaxis prior to the initiation of treatment. Patients should be well hydrated. Starting 1 or 2 days before the first dose of GA101, it is desirable to maintain a fluid intake of approximately 3 L/day. In addition, all patients with high tumor burden and who are considered to be at risk for tumor lysis should be treated with 300 mg/day of allopurinol PO or a suitable alternative treatment starting 48–72 hours prior to Cycle 1, Day 1 of treatment and hydration. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator.
Patients who have preexisting cardiac or pulmonary conditions should be monitored carefully throughout the GA101 infusion and the post-infusion period.

6.4.9 GA101: Management of Toxicities

a. Life-Threatening Infusion-Related Reactions and Anaphylaxis

Medications (including epinephrine for subcutaneous injections, corticosteroids, diphenhydramine hydrochloride for IV injection) and resuscitation equipment should be available for immediate use. Management of infusion-related symptoms for GA101 are summarized in Table 3 according to the administration rates.. In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, GA101 should be discontinued and no additional drug should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment. Patients who experience GA101-associated infusion-related temperature elevations of > 38.5 C or other minor infusion-related symptoms may be treated symptomatically with acetaminophen (≥ 500 mg) and/or H1- and H2-histamine–receptor antagonists (e.g., diphenhydramine hydrochloride, ranitidine). Serious infusion-related events, manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress, should be managed with additional supportive therapies (e.g., supplemental oxygen, β2-agonists, epinephrine, and/or corticosteroids) as clinically indicated according to standard clinical practice. For the management of IRRs and anaphylaxis, see Table 3.

Table 3
Management of Infusion-Related Symptoms

Infusion-Related Symptoms [a]	Guidance
Grades 1 and 2	Slow or hold infusion. Give supportive treatment. [b] Upon symptom resolution, may resume infusion-rate escalation at the investigator's discretion [c]
Grade 3	Discontinue infusion. Give supportive treatment. [b] Upon symptom resolution, may resume infusion rate escalation, at investigator discretion. [c] Note: If the same adverse event recurs with same severity, treatment must be permanently discontinued.
Grade 4	Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug.

[a] Refer to National Cancer Institute Common Terminology Criteria for Adverse Events, v.4.0, for the grading of symptoms.

[b] Supportive treatment: Patients should be treated with acetaminophen/paracetamol and an antihistamine such as diphenhydramine hydrochloride if they have not been received in the last 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg of IV prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors. See text for additional medications.

[c] Escalation of the infusion rate after re-initiation: Upon complete resolution of symptoms, the infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

b. Tumor Lysis Syndrome

Patients should be closely monitored for the development of tumor lysis syndrome. For patients with evidence of tumor lysis syndrome, all study treatment (GA101-miniCHOP) should be discontinued and the patient should be treated as clinically indicated. Following the complete resolution of tumor lysis syndrome complications, treatment with GA101-miniCHOP may be resumed at the full dose at the next scheduled infusion in conjunction with prophylactic therapy.

6.4.10 Excluded Therapy

Treatment with other concomitant anti-tumor agents not defined in this protocol as study treatment, radiotherapy, or other concurrent investigational agents of any type will result in withdrawal of patients from study treatment.

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy (other than miniCHOP)
- Experimental agent
- Immunotherapy
- Hormone therapy (other than hormone-replacement therapy, or megestrol acetate)

- Any therapies (other than intrathecal CNS prophylaxis) intended for the treatment of lymphoma whether European Medicines Agencies (EMA) or FDA approved or experimental (outside of this study)

Patients who require the use of any of these agents will be discontinued from study treatment.

Patients who are discontinued from study treatment for reasons other than PD will complete an early study treatment termination visit, including a tumor response assessment.

7. STUDY PROCEDURES: CLINICAL EVALUATION, LABORATORY TEST AND FOLLOW UP

7.1 Baseline assessment

All the baseline tests and procedures must be completed within 28 days before chemotherapy start.

- Medical history, physical examination and concomitant medications
- Histological diagnosis on lymph node biopsy or other pathologic tissue with immunoistochemistry
- ECG, cardiac assessment
- Cardiac ultrasound to assess LVEF
- Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count)
- Blood chemistry (glucose, serum creatinine, total serum bilirubin, AST, ALT, γ-GT, urea/BUN, electrolytes/ alkaline phosphatase, LDH, beta2-microglobulin, electrolytes/ Na, K, Cl, Ca, P, erythrocyte sedimentation rate, uric acid, total protein, serum albumin, protein electrophoresis)
- Viral markers (HIV Ab, HBsAg, antiHBsAb, HBcAb, HCV Ab)
- Neck, chest, abdomen and pelvis CT scan. Cerebral CT scan is recommended but not mandatory
- Bone marrow biopsy mandatory for patient in CT scan stage I-II, optional for patient in CT scan stage III-IV.
- Lung function (spirometry with DLCO)
- ADL, IADL, and CIRS assessments ***(Appendix B,C,D)***
- Quality of Life evaluation according to EORTC QLC-C30 version 3.0 questionnaire ***(Appendix H)***
- Written informed consent

All the following are optional:

- PET/CT (<u>strongly recommended</u>)

- MRI (CNS, spinal cord), endoscopy and any other diagnostic imaging only if clinically relevant under medical judgment
- Chest X-ray

7.2 Investigation before each course

- Physical examination, concomitant medications
- Collection of adverse events according to CTCAE v 4.0
- Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count)
- Blood chemistry (glucose, serum creatinine, alkaline phosphathase, total serum bilirubin, AST, ALT, LDH, urea/BUN, uric acid)
- Any test or instrumental assessment considered relevant under medical judgement in case of clinical suspect of progression or toxicity

7.3 Investigations during each course (day 10 +/- 2)

- Physical examination, concomitant medications
- Collection of adverse events according to CTCAE v 4.0
- Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count)
- Blood chemistry (glucose, serum creatinine, alkaline phosphathase, total serum bilirubin, AST, ALT, LDH, urea/BUN, uric acid)

7.4 Check for response after 4 courses of GA101-miniCHOP

Check for response will be assessed after the completion of 4 courses of GA101-miniCHOP in order to identify non responding patients:

- ECOG performance status, physical examination
- Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count)
- Blood chemistry (glucose, serum creatinine, alkaline phosphathase, total serum bilirubin, AST, ALT, LDH, urea/BUN, uric acid)
- Clinical/radiological assessment of target lesion to check for tumor response (CT/SCAN and/or echography and/or chest radiogram)

7.5 Investigations at the end of treatment

(28 days after the last study medication administration)

- Physical examination, concomitant medications
- Collection of adverse events during the month after the last dose of study drug administration according to CTCAE v 4.0
- ECG, cardiac assessment
- Cardiac ultrasound with LVEF
- Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count)
- Blood chemistry (glucose, serum creatinine, total serum bilirubin, AST, ALT, γ-GT, urea/BUN, electrolytes/ Na, K, Cl, Ca, P, alkaline phosphatase, LDH, beta2-microglobulin, erythrocyte sedimentation rate, uric acid, total protein, serum albumin, protein electrophoresis)
- Chest, abdomen and pelvis CT scan (mandatory)
- PET/CT (mandatory)
- ADL, IADL, and CIRS assessments
- Quality of Life evaluation according to EORTC QLC-C30 version 3.0 questionnaire
- Bone marrow biopsy is recommended if positive at diagnosis
- Lung function (spirometry with DLCO)

All the following are optional:

- MRI (CNS, spinal cord), endoscopy and any other diagnostic imaging only if positive at the diagnosis or if useful according to clinical judgement

7.6 Investigation during follow-up

At month + 3, then every 6 months for two years

- Physical examination, concomitant medications
- Late adverse event assessment: late organ toxicity; second tumours
- Haematology (haemoglobin, haematocrit, platelet count, RBC, WBC with differential leucocyte count)
- Blood chemistry (glucose, serum creatinine, total serum bilirubin, AST, ALT, LDH)
- Chest, abdomen and pelvis CT scan (only at month + 3, then every 6 months)
- ECG, cardiac assessment (if clinically indicated)
- ADL, IADL, and CIRS
- Quality of Life evaluation according to EORTC QLC-C30 version 3.0 questionnaire

At any time

- Any test or instrumental assessment considered relevant under medical judgement in case of clinical suspected disease progression or toxicity.

8. REMOVAL OF SUBJECTS FROM TREATMENT AND/OR STUDY

8.1 Discontinuation of Treatment

A subject must be discontinued from study treatment in case of:

- personal reason
- the investigator believes that for safety reasons it is in the best interest of the subject to discontinue the treatment
- disease progression at any time
- occurrence of an unacceptable adverse event (> grade 3 toxicity for > 2 weeks)
- If the treatment is discontinued for more than 3 weeks patient is withdrawn from study.

8.2 Withdrawal of subjects from the study

A subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

A subject must be withdrawn from study treatment if:

- The investigator believes that for safety reasons it is in the best interest of the subject to discontinue the treatment
- the subject starts taking any concomitant lymphoma therapy
- disease progression at any time

If the patient withdraws the consent or doesn't fulfil the inclusion criteria he must be considered off protocol and cannot be calculated for study endpoints.

At the time of withdrawal all study procedures outlined for the end of treatment should be completed.

The primary reason for a patient's withdrawal from the study is to be recorded in the source document and documented on the case report forms (CRF).

8.3 Completion of treatment

A subject will be considered as having completed the study if all assessments of the treatment phase and follow-up have been completed.

Subjects who discontinue study treatment due to lack of efficacy are also considered to have completed the study.

9. STATISTICAL METHODS

9.1 Sample Size

The primary objective of the study is to demonstrate a clinical benefit in Complete Remission Rate (CRR) and safety with GA101-miniCHOP association in elderly unfit patients newly diagnosed with diffuse large B-cell lymphoma.

For the purposes of this study, as the reference CR rate *(Peyrade et al, Lancet Oncol – 2011)* [18] was defined with 1999 International Criteria for response *(Cheson, JCO 1999) [32]*, the response rate to therapy will be based on a Central Independent Review of response that will not consider the results of FDG-PET but will only use the conventional CT scan images.
Response defined according to Cheson 2007 International Criteria [31] will also be provided as study result.

The sample size has been estimated according to a optimal Simon two-stages design. The null hypothesis (p0) has been set equal **0.60** on the basis of what reported by F. Peyrade et al. [18]..

With a type I (alfa) error of **0.10 (10%)** and a type II (beta) error of **0.10** (power=90%) the alternative hypothesis (p1) is **0.75**, i.e. a CR rate of 75% with the combination GA101-miniCHOP expected.
A schema of the design is below reported.

R1 = 21 N1 = 34 R2 = 47 Ntot = 71

EN(p0) = 47
PET(p0) = 64.6%

According to the two-stage design patients enrolment will proceed as follows:
- the enrolment of **34** patients (stage 1) is planned: if at least **22** patients will achieve CR the study will continue;
- additional **37** patients are entered (stage II): if at least **48** patients out of **71** will achieve a CR the study will be considered of possible evaluation for the efficacy of the treatment.

Considering a withdrawal rate of 10%, the enrollment may continue until **78** patients are accrued in order to have at least 71 eligible patients.

If GA101-miniCHOP will be active, the probability to declare inactivity is 0.0964 and the probability to stop the study at first stage is 0.0610.

10. EFFICACY AND SAFETY ASSESSMENT

10.1 Efficacy Measurement

Patients receiving at least 1 course of GA101-miniCHOP will be considered for the Efficacy Population (EP).

10.1.1 Efficacy parameters

Primary variable

Efficacy of GA101-miniCHOP will be measured by Complete Response Rate (CRR) calculated for the EP.

Complete Response Rate will be evaluated according to 1999 Cheson criteria [32].

A patient is defined as a responder if she/he has a complete (confirmed or not) response. Patients in the EP without response assessment (due to whatever reason) will be considered as non-responders.

The analysis of efficacy parameter will be performed according to the Intent to Treat principle for the EP.

Secondary variables

- **Progression free survival (PFS)**: defined as the time from entry into the study until lymphoma relapse/ progression 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.
- **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

The complete response rate will be estimated with the 95% confidence interval.

Time to event data (PFS, OS) will be estimated using the Kaplan-Meier method.

The curves will be plotted and the 95% confidence interval for median time will be calculated.

10.2 Safety Measurements

All patients who have received at least one dose of study medication will be considered for the **Safety Population (SP)** and will be evaluated for toxicity from the time of their first drug administration.

When toxicity occurs, it should be graded according to the NCI Common Toxicity Criteria, version 4.0 ***(Appendix F).***

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.

The study will include the evaluations of safety and tolerability using adverse events, clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs) as described in the following sections.

Adverse events, including toxicities, will be analyzed calculating the number and percentage of patients and cycles with event.

10.2.1 Safety parameters

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects and are mandated by regulatory agencies worldwide.

10.2.2 Adverse Event Definitions

Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product (Definition per International Conference on Harmonization [ICH]).

This includes:

- Any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

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.

The Investigator must collect adverse events starting from the time of signing the informed consent through the end of the designated FU period.

Abnormal laboratory values defined as adverse events

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

-results in discontinuation from the study

-requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention

-is judged by the Investigator to be significant clinical importance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

Serious Adverse Event

A Serious Adverse Event (SAE) as defined by ICH is any untoward medical occurrence that at any dose:

- results in death
- is life threatening (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization
- results in persistent or significant disability/ incapacity, or
- is a congenital anomaly/birth defect

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in situations other than those listed above. For example, important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Events not considered to be SAEs are hospitalizations which: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria above); are part of the normal treatment or monitoring of the studied indication and are not associated with any deterioration in condition.

If an AE is considered serious, both the AE pages of the CRF and the SAE Report form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to (investigational product) study drug, action taken regarding (investigational product) study drug and outcome.

Adverse Events of Special Interest (AESI)

The following types of events are considered to be AESIs due to their observed frequency and/or clinical relevance:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice,as defined below :

The finding of an elevated ALT or AST (> 3 × ULN) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN

Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- SAE associated with obinutuzumab infusion (defined as any treatment-related AEs occurring during or within 24 hours of an obinutuzumab infusion and related to obinutuzumab)
- Serious infections
- Serious neutropenia
  - Tumor lysis syndrome (TLS)
  - Progressive multifocal leukoencephalopathy (PML)
  - Hepatitis B reactivation

Unexpected Adverse Event

An adverse event, the nature or severity of which is not consistent with the applicable product information (for an investigational medicinal product, the Investigator's Brochure).

10.2.3 Adverse Event Classifications

Classification of severity

For both AEs and SAEs, the investigator(s) must assess the severity of the event. The severity of adverse events (AEs) will be graded on a scale of 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE). The NCI CTCAE V 4.0 can be viewed on-line at the following NCI web site: http://ctep.cancer.gov/reporting/ctc.html. If a specific event is not included in the NCI CTCAE toxicity scale, the following scale should be used to grade the event.

Grade	Definition
1	**Mild** Awareness of sign, symptom, or event, usually transient, requiring no special treatment and generally not interfering with usual daily activities
2	**Moderate** Discomfort that causes interference with usual activities; usually ameliorated by basic therapeutic manoeuvres
3	**Severe** Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention. Hospitalization may or may not be required
4	**Life-threatening** Immediate risk of death; requires hospitalization and clinical intervention.
5	**Death**

Association With the Use of the Investigational Medicinal Product (IMP)

An adverse event is considered associated with the use of the investigational product if the attribution is possible, probable, or very likely by the definitions listed above.

Attribution Definitions

- *Not related*.

An adverse event that is not related to the use of the investigational product.

- *Doubtful.*

An AE for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

- *Possible.*

An AE that might be due to the use of the investigational product. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

- *Probable.*

An AE that might be due to the use of the investigational product. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

- *Very likely.*

An AE that is listed as a possible adverse event reaction, and cannot be reasonably explained by an alternative explanation, e.g., concomitant investigational drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge).

Classification of Relationship/Causality of adverse events (AE/SAE) to study drug

The Investigator(s) must determine the relationship between the administration of study drug and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	The temporal relationship of the adverse event to study drug administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event
Suspected:	The temporal relationship of the adverse event to study drug administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

Treatment-related mortality

If an adverse event considered associated with the study medication results in a patient's death, then the event will be listed as a "treatment-related mortality".

10.2.4 Adverse Event Procedures

All Adverse Events

All AEs that occur between the fist study-related procedures and for 30 days following the last dose of investigational product will be reported. Resolution information after 30 days should also be provided for grade 3 to 4 drug related events. This subset should be followed up until resolution to a grade 1 or better.

Adverse events occurring after 30 days should also be reported if considered related to investigational product.

Clinically relevant changes in laboratory values must be recorded in the adverse event section of the CRF.

All AEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded in the source document and the CRF. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to the study therapy. All measures required for adverse event management must be recorded in the source document.

Immediate reporting by Investigator to the Trial Office (SAE)

The investigator will inform the Trial Office of any serious adverse event and/or non serious AESIs. This applies to all SAEs, regardless of relationship to the study medication, that occur during the study, those made known to the Investigator(s) within 30 days after a subject's last dose of study drug, and those made known to the investigator(s) at any time that are suspected of being related to the study medication. This must be documented on an SAE form ***(Appendix J).*** This form must be completed and supplied to Trial Office within 24 hours/1 business day or at the latest on the following working day.

The initial report must be as complete as possible, including details of the current illness and serious adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up SAE form.

SAE reporting to Regulatory Authorities and Ethic Committees

The pharmacovigilance team will inform relevant Regulatory Authorities and the Ethics Committee:

(a)- of all relevant information about serious unexpected adverse events suspected to be related to the study medication that are fatal or life threatening as soon as possible, and in any case no later than seven days after knowledge of such a case. Relevant follow-up information for these cases will subsequently be submitted within an additional eight days.

(b)- of all other serious unexpected events suspected to be related to the study medication as soon as possible, but within a maximum of fifteen days of first knowledge by the investigator(s).

Post-Study Adverse Events

The Sponsor should be notified if the investigator becomes aware of any serious adverse event/AESI that occurs after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment. During this period, the investigator is required to report such events to the Sponsor although he/she is not required to actively monitor patients for adverse events.

10.2.5 Safety contact information

PHARMACOVIGILANCE

SC Ematologia, AO SS Antonio e Biagio
Via Venezia, 16-15121 Alessandria, Italy

	Safety phone number	**Safety Fax/e-mail**
Dr Alessandro Levis (responsible)	+39 0131 206066-6071	+39 0131 263455 alevis.sandro@gmail.com

11. FORMS AND PROCEDURES FOR COLLECTING DATA AND DATA MANAGEMENT

The web study area, with a dedicated database, the electronic Case Report Form (CRF) and all the required functions, will be developed through the FIL website (http://www.filinf.it). All participating centers will receive a password to access the internet-based database. Electronic CRFs will be realized with OpenClinica [Open Source Software versione 3.1.2 (Isovera INC, USA) and maintained by Data River srl, Modena, Italy]. A confirmation email will be sent to the investigator, to the trial office and to the study coordinator(s). If electronic CRFs are not available at study opening, paper CRFs will be distributed to be used by Investigators only until the electronic version is finalized.

Several systematic quality controls will be active during data entry; periodic statistical checks and personalized queries will be performed during the study.

Frequency of on-site monitoring will be planned according to the results of the statistical quality controls.

12. ETHICAL CONSIDERATIONS

12.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice

The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) (“IEC”).

12.2 Subject identification – Personal Data protection

All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient initials and date of birth will also be reported on the case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. Breach of such regulations may result in administrative or even criminal sanctions.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must therefore accompany the informed consent administered to the patient (see paragraph 12.3 below). Such information must (i) identify the roles of the holder ("titolare") and processor ("responsabile", appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient's prior and specific consent to such processing.

Patient information or documentation may be considered "anonymous", and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer available.

Particular attention should therefore be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed, or biological samples/materials are taken and kept for future research purposes, associated or not with the pathology considered in the study.

12.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

12.4 Conflict of Interest

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

12.5 Data ownership

According to the ICH Guidelines on Good Clinical Practice the Sponsor of a study is the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Sponsor's prior express consent.

12.6. Publication Policy

After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator for coordination and homogeneity purposes: specific advance periods for submission and review are specified in the FIL's Procedure.

The results of this study will be submitted for publication in peer reviewed journals and for presentation at appropriate scientific meetings according to the rules of FIL publication policy.

No publication of any results will occur without the agreement of the study chairs

12.7 Study insurance

The sponsor of the Study must ensure that adequate insurance coverage is available to the patients, in accordance with Section 5.8 of the ICH Guidelines of Good Clinical Practice. Such coverage must extend to all damages deriving from the study, to the exclusion of those attributable to willful misconduct or negligence of the institution or investigator. A copy, or excerpt, or insurer's certificate, attesting the existence and amount of such coverage at least for the duration of the study must be supplied as part of the study documentation to the review and approval of the IEC.

A specific insurance with company HDI - GERLING Versicherung AG INDUSTRIES was concluded for patients enrolled in this study.
No extra expenses, neither for therapies nor for clinical or laboratory procedures can be asked or expected to be paid by SSN or patients.

REFERENCES

1. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood* 2011,**117**:5019-5032.
2. Miller TP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM*, et al.* Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1998,**339**:21-26.
3. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R*, et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002,**346**:235-242.
4. Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C*, et al.* Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 2005,**23**:4117-4126.
5. Habermann TM, Weller EA, Morrison VA, Gascoyne RD, Cassileth PA, Cohn JB*, et al.* Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol* 2006,**24**:3121-3127.
6. Pfreundschuh M, Trumper L, Osterborg A, Pettengell R, Trneny M, Imrie K*, et al.* CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. *Lancet Oncol* 2006,**7**:379-391.
7. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med* 1993,**329**:987-994.
8. Hoerni B, Sotto JJ, Eghbali H, Sotto MF, Hoerni-Simon G, Pegourie B. Non-Hodgkin's malignant lymphomas in patients older than 80. 70 cases. *Cancer* 1988,**61**:2057-2059.
9. Bairey O, Benjamini O, Blickstein D, Elis A, Ruchlemer R. Non-Hodgkin's lymphoma in patients 80 years of age or older. *Ann Oncol* 2006,**17**:928-934.
10. Thieblemont C, Grossoeuvre A, Houot R, Broussais-Guillaumont F, Salles G, Traulle C*, et al.* Non-Hodgkin's lymphoma in very elderly patients over 80 years. A descriptive analysis of clinical presentation and outcome. *Ann Oncol* 2008,**19**:774-779.
11. Bastion Y, Blay JY, Divine M, Brice P, Bordessoule D, Sebban C*, et al.* Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival--a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. *J Clin Oncol* 1997,**15**:2945-2953.
12. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S*, et al.* Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood* 2010,**116**:2040-2045.
13. Tirelli U, Zagonel V, Errante D, Fratino L, Monfardini S. Treatment of non-Hodgkin's lymphoma in the elderly: an update. *Hematol Oncol* 1998,**16**:1-13.
14. Vose JM, Armitage JO, Weisenburger DD, Bierman PJ, Sorensen S, Hutchins M*, et al.* The importance of age in survival of patients treated with chemotherapy for aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 1988,**6**:1838-1844.
15. Luminari S, Montanini A, Caballero D, Bologna S, Notter M, Dyer MJ*, et al.* Nonpegylated liposomal doxorubicin (MyocetTM) combination (R-COMP) chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL): results from the phase II EUR018 trial. *Ann Oncol* 2010,**21**:1492-1499.
16. Merli F, Bertini M, Luminari S, Mozzana R, Botto B, Liberati AM*, et al.* Long term results of a randomized study performed by Intergruppo Italiano Linfomi comparing Mini-CEOP vs P-

VEBEC in elderly patients with diffuse large B-cell lymphoma. *Leuk Lymphoma* 2007,**48**:367-373.
17. Merli F, Luminari S, Rossi G, Mammi C, Marcheselli L, Tucci A*, et al.* Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi. *Leuk Lymphoma* 2012,**53**:581-588.
18. Peyrade F, Jardin F, Thieblemont C, Thyss A, Emile JF, Castaigne S*, et al.* Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2011,**12**:460-468.
19. Bertini M, Freilone R, Vitolo U, Botto B, Pizzuti M, Gavarotti P*, et al.* P-VEBEC: a new 8-weekly schedule with or without rG-CSF for elderly patients with aggressive non-Hodgkin's lymphoma (NHL). *Ann Oncol* 1994,**5**:895-900.
20. Verger E, Salamero M, Conill C. Can Karnofsky performance status be transformed to the Eastern Cooperative Oncology Group scoring scale and vice versa? *Eur J Cancer* 1992,**28A**:1328-1330.
21. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007,**25**:1824-1831.
22. Wedding U, Honecker F, Bokemeyer C, Pientka L, Hoffken K. Tolerance to chemotherapy in elderly patients with cancer. *Cancer Control* 2007,**14**:44-56.
23. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged. The Index of Adl: A Standardized Measure of Biological and Psychosocial Function. *JAMA* 1963,**185**:914-919.
24. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970,**10**:20-30.
25. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969,**9**:179-186.
26. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. *J Am Geriatr Soc* 1968,**16**:622-626.
27. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. *J Am Geriatr Soc* 1995,**43**:130-137.
28. Merli F, Luminari S, Rossi G, Mammi C, Marcheselli L, Ferrari A*, et al.* Outcome of frail elderly patients with diffuse large B-cell lymphoma prospectively identified by Comprehensive Geriatric Assessment: results from a study of the Fondazione Italiana Linfomi. *Leuk Lymphoma* 2014,**55**:38-43.
29. Mossner E, Brunker P, Moser S, Puntener U, Schmidt C, Herter S*, et al.* Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood* 2010,**115**:4393-4402.
30. Beers SA, French RR, Chan HT, Lim SH, Jarrett TC, Vidal RM*, et al.* Antigenic modulation limits the efficacy of anti-CD20 antibodies: implications for antibody selection. *Blood* 2010,**115**:5191-5201.
31. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ*, et al.* Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007,**25**:579-586.
32. Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM*, et al.* Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol* 1999,**17**:1244.
33. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L*, et al.* 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006,**24**:3187-3205.

34. Dayde D, Ternant D, Ohresser M, Lerondel S, Pesnel S, Watier H*, et al.* Tumor burden influences exposure and response to rituximab: pharmacokinetic-pharmacodynamic modeling using a syngeneic bioluminescent murine model expressing human CD20. *Blood* 2009,**113**:3765-3772.
35. Liu H, Gao JB, Hild KE, 2nd, Principe JC, Chris Sackellares J. Epileptic seizure detection from ECoG using recurrence time statistics. *Conf Proc IEEE Eng Med Biol Soc* 2004,**1**:29-32.

APPENDIX A: Comprehensive Geriatric Assessment (GCA) in onco-hematology

Definition of FIT, UNFIT and FRAIL elderly patients [21, 22]

FIT:

non UNFIT, non FRAIL

UNFIT:

CHRONOLOGIC CRITERIA: age≥ 80 years and FIT

CLINICAL FUNCTIONAL CRITERIA: according to ADL, IADL and CIRS scores

FRAIL:

CHRONOLOGIC CRITERIA: age≥ 80 years and UNFIT

CLINICAL FUNCTIONAL CRITERIA: according to ADL, IADL and CIRS scores

scale	FIT	UNFIT	FRAIL
ADL	6	5*	≤ 4
IADL	8	7-6*	≤ 5
CIRS	0 score=3-4 ≤ 5 score=2	0 score=3-4 5-8 score=2	1 score=3-4 > 8 score=2
Age		≥ 80 fit	≥ 80 unfit

*number of residual functions

APPENDIX B: Activity of Daily Living (ADL)

Valutazione delle attività di base della vita quotidiana (ADL) [23, 24]

A Fare il bagno (vasca, doccia, spugnature)

[1] Fa il bagno da solo (entra ed esce dalla vasca da solo) 1

[2] Ha bisogno di assistenza soltanto nella pulizia di una parte del corpo (es. schiena) 1

[3] Ha bisogno di assistenza per più di una parte del corpo 0

B Vestirsi (prendere i vestiti dall'armadio e/o cassetti), inclusa biancheria intima, vestiti, uso delle allacciature o delle bretelle, se utilizzate)

[1] Prende i vestiti e si veste completamente da solo senza bisogno di assistenza 1

[2] Prende i vestiti e si veste senza bisogno di assistenza eccetto che per allacciare le scarpe 1

[3] Ha bisogno di assistenza per prendere i vestiti o nel vestirsi oppure rimane parzialmente o completamente svestito 0

C Toilette (andare nella stanza da bagno per la minzione e l'evacuazione, pulirsi, rivestirsi)

[1] Va in bagno, si pulisce e si riveste senza bisogno di assistenza (può utilizzare mezzi di supporto, come bastone, deambulatore o seggiola a rotelle, può usare vaso da notte o comoda svuotandoli al mattino) 1

[2] Ha bisogno di assistenza nell'andare in bagno o nel pulirsi o nel rivestirsi o nell'uso del vaso da notte o della comoda. 0

[3] Non si reca in bagno per l'evacuazione 0

D Spostarsi

[1] Si sposta dentro e fuori dal letto ed in poltrona senza assistenza eventualmente con canadesi o deambulatore) 1

[2] Compie questi trasferimenti se aiutato 0

[3] Allettato, non esce dal letto 0

E Continenza di feci e urine

[1] Controlla completamente feci e urine 1

[2] "Incidenti" occasionali 0

[3] Necessita di supervisione per il controllo di feci e urine, usa il catetere, è Incontinente 0

F Alimentazione

[1] Senza assistenza	1
[2] Assistenza solo per tagliare la carne o imburrare il pane	1
[3] Richiede assistenza per portare il cibo alla bocca o viene nutrito parzialmente o completamente per via parenterale	0

PUNTEGGIO TOTALE (numero totale funzioni residue):_____

APPENDIX C: Instrumental Activity of Daily Living (IADL)

Valutazione delle attività strumentali della vita quotidiana (IADL) [25]

A Capacità di usare il telefono

[1] Usa il telefono di propria iniziativa	1
[2] Compone solo alcuni numeri ben conosciuti	1
[3] Risponde ma non è capace di comporre il numero	1
[4] Non risponde al telefono	0
Non applicabile	NA

B Fare acquisti

[1] Fa tutte le proprie spese senza aiuto	1
[2] Fa piccoli acquisti senza aiuto	0
[3] Ha bisogno di essere accompagnato	0
[4] Completamente incapace di fare acquisti	0
Non applicabile	NA

C Preparazione del cibo

[1] Organizza, prepara e serve pasti adeguatamente preparati	1
[2] Prepara pasti adeguati solo se sono procurati gli ingredienti	0
[3] Scalda o serve pasti preparati oppure prepara cibi ma non mantiene una dieta adeguata	0
[4] Ha bisogno di avere cibi preparati e serviti	0
Non applicabile	NA

D Governo della casa

[1] Mantiene la casa da solo o con occasionale assistenza (per es. aiuto per i lavori pesanti)	1
[2] Esegue compiti quotidiani leggeri ma non mantiene un accettabile livello di pulizia della casa	1
[3] Ha bisogno di aiuto in ogni operazione di governo della casa	1
[4] Non partecipa a nessuna operazione di governo della casa	0
Non applicabile	NA

E Biancheria

[1] Fa il bucato personalmente e completamente	1
[2] Lava le piccole cose (calze, fazzoletti)	1
[3] Tutta la biancheria deve essere lavata da altri	0
Non applicabile	NA

F Mezzi di trasporto

[1] Si sposta da solo sui mezzi pubblici o guida la propria auto	1

[2] Si sposta in taxi ma non usa mezzi di trasporto pubblici	1
[3] Usa i mezzi di trasporto se assistito o accompagnato	1
[4] Può spostarsi solo con taxi o auto e con assistenza	0
[5] Non si sposta per niente	0
Non applicabile	NA
G Responsabilità nell'uso dei farmaci	
[1] Prende le medicine che gli sono state prescritte	1
[2] Prende le medicine se sono preparate in anticipo e in dosi separate	0
[3] Non è in grado di prendere le medicine da solo	0
Non applicabile	NA
H Capacità di maneggiare il denaro	
[1] Maneggia le proprie finanze in modo indipendente	1
[2] E' in grado di fare piccoli acquisti	1
[3] E' incapace di maneggiare i soldi	0
Non applicabile	NA

PUNTEGGIO TOTALE (numero totale funzioni residue):_____

APPENDIX D: Cumulative Illness Rating Scale (CIRS)

Valutazione dell'indice di comorbidità (CIRS) [26, 27]

1) Patologie cardiache (solo cuore)	0	1	2	3	4
2) Ipertensione si valuta la severità, gli organi coinvolti sono considerati separatamente	0	1	2	3	4
3) Patologie vascolari sangue, vasi, midollo, milza, sistema linfatico	0	1	2	3	4
4) Patologie respiratorie polmoni, bronchi, trachea sotto la laringe	0	1	2	3	4
5) O.O.N.G.L. occhio, orecchio, naso, gola, laringe	0	1	2	3	4
6) Apparato GI superiore esofago, stomaco, duodeno, albero biliare, pancreas	0	1	2	3	4
7) Apparato GI inferiore intestino, ernie	0	1	2	3	4
8) Patologie epatiche solo fegato	0	1	2	3	4
9) Patologie renali solo rene	0	1	2	3	4
10) Altre patologie genito-urinarie ureteri, vescica, uretra, prostata, genitali	0	1	2	3	4
11) Sistema muscolo-scheletro-cute	0	1	2	3	4

muscoli, scheletro, tegumenti

12) Patologie sistema nervoso sistema nervoso centrale e periferico; non include la demenza	0	1	2	3	4
13) Patologie endocrine-metaboliche include diabete, infezioni, sepsi, stati tossici	0	1	2	3	4
14) Patologie psichiatriche-comportamentali include demenza, depressione, ansia, agitazione, psicosi	0	1	2	3	4

0: assente; 1: lieve; 2: moderato; 3: grave; 4: molto grave

Indice di severità:_____ indice di comorbidità: _____

APPENDIX E: Ann Arbor staging* - Cotswolds recommendations**

(Sources: * Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. Cancer. Res. 31:1860-1861, 1971. ** Lister TA, Crowther D, Sutcliffe SB, et al. Staging for Hodgkin's disease. Report of a committee convened todiscuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. J. Clin. Oncol. 7:1630-1636,1989 [Erratum J. Clin. Oncol. 8:1602,1990])

Stage I: involvement of a single lymphatic region (I), or localized involvement of a single extralymphatic organ or site (IE).
Stage II: involvement of two or more lymphatic regions on the same side of diaphragm (II) or localized involvement of an extralymphatic organ or site and one ore more lymph node regions the same side of diaphragm (IIE).
Stage III: involvement of two or more lymphatic regions on both sides of diaphragm (III) which may also be accompanied either by localized involvement of an extralymphatic organ or site (IIIE), or by involvement of the spleen (IIIS).
Stage IV: Diffuse or disseminated involvement of one or more extralymphatic organs or tissue, with or without associated lymph node involvement.
Bone marrow or liver involvement will always be considered as stage IV.
Lymphatic structures include lymph nodes, spleen, thymus, Waldeyer's ring including tonsils. The lymphatic regions are defined according to Ann Arbor as (a) clinical enlargement of a node when alternative pathology may reasonably be ruled out (suspicious nodes should always be biopsied if treatment decisions are based on their involvement) ; and (b) enlargement on plain radiograph, CT scan, or lymphography.

Localized involvement of an extralymphatic site (extranodal site or E-lesion) is diagnosed when the involvement is small enough to be in principle accessible for curative radiotherapy (thereby excluding diffuse organ involvement corresponding to stage IV).

Criteria for "B" symptoms
The presence of (a) unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation and/or (b) unexplained, persistent, or recurrent fever with temperatures above 38 C during the previous month and/or (c) recurrent drenching night sweats during the previous months is denoted by the suffix letter 'B'. 'A' indicates the absence of these symptoms.

Criteria for Bulky disease

Bulky disease is present if:

− there is massive lymphoma development in a lymph node with a greatest diameter of ≥7.5 cm or a conglomerate tumour with a greatest diameter ≥7.5 cm

− there is a mediastinal tumour with a diameter ≥7.5 cm, whereby the hili and the pericardium should not be included in the measurement.

APPENDIX F: National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 4.0

In the present study, adverse events and/or adverse drug reactions will be recorded according to the: **Common Terminology Criteria for Adverse Events (CTCAE), version 4.0**.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

APPENDIX G WHO performance status scale

Grade Performance scale

0 Able to carry out all normal activity without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work

2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4 Completely disabled; cannot carry on any self-care; totally confined to bed or chair

APPENDIX H: Quality of Life evaluation according to EORTC QLC-C30 version 3.0 questionnaire

EORTC QLQ-C30 (version 3.0)

Con questo questionario vorremmo sapere alcune cose su di Lei e sulla Sua salute. La preghiamo di rispondere a tutte le domande ponendo un cerchio attorno al numero che meglio corrisponde alla Sua risposta. Non esiste una risposta "giusta" o "sbagliata". Le Sue informazioni verranno tenute strettamente riservate.

Per favore scriva solo le iniziali del Suo nome e cognome:
Data di nascita (g, m, a):
La data di oggi (g, m, a): 31

	No	Un po'	Parec-chio	Moltis-simo
1. Ha difficoltà nel fare lavori faticosi, come sollevare una borsa della spesa pesante o una valigia?	1	2	3	4
2. Ha difficoltà nel fare una lunga passeggiata?	1	2	3	4
3. Ha difficoltà nel fare una breve passeggiata fuori casa?	1	2	3	4
4. Ha bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4

Durante gli ultimi sette giorni:	No	Un po'	Parec-chio	Moltis-simo
6. Ha avuto limitazioni nel fare il Suo lavoro o i lavori di casa?	1	2	3	4
7. Ha avuto limitazioni nel praticare i Suoi passatempi-hobby o altre attività di divertimento o svago?	1	2	3	4
8. Le è mancato il fiato?	1	2	3	4
9. Ha avuto dolore?	1	2	3	4
10. Ha avuto bisogno di riposo?	1	2	3	4
11. Ha avuto difficoltà a dormire?	1	2	3	4
12. Ha sentito debolezza?	1	2	3	4
13. Le è mancato l'appetito?	1	2	3	4
14. Ha avuto un senso di nausea?	1	2	3	4
15. Ha vomitato?	1	2	3	4

Durante gli ultimi sette giorni:	**No**	**Un po'**	**Parec-chio**	**Moltis-simo**
16. Ha avuto problemi di stitichezza?	1	2	3	4
17. Ha avuto problemi di diarrea?	1	2	3	4
18. Ha sentito stanchezza?	1	2	3	4
19. Il dolore ha interferito con le Sue attività quotidiane?	1	2	3	4
20. Ha avuto difficoltà a concentrarsi su cose come leggere un giornale o guardare la televisione?	1	2	3	4
21. Si è sentito(a) teso(a)?	1	2	3	4
22. Ha avuto preoccupazioni?	1	2	3	4
23. Ha avuto manifestazioni di irritabilità?	1	2	3	4
24. Ha avvertito uno stato di depressione?	1	2	3	4
25. Ha avuto difficoltà a ricordare le cose?	1	2	3	4
26. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con la Sua vita familiare?	1	2	3	4
27. Le Sue condizioni fisiche o il Suo trattamento medico hanno interferito con le Sue attività sociali?	1	2	3	4
28. Le Sue condizioni fisiche o il Suo trattamento medico Le hanno causato difficoltà finanziarie?	1	2	3	4

Per le seguenti domande ponga un cerchio intorno al numero da 1 a 7 che meglio corrisponde alla Sua risposta

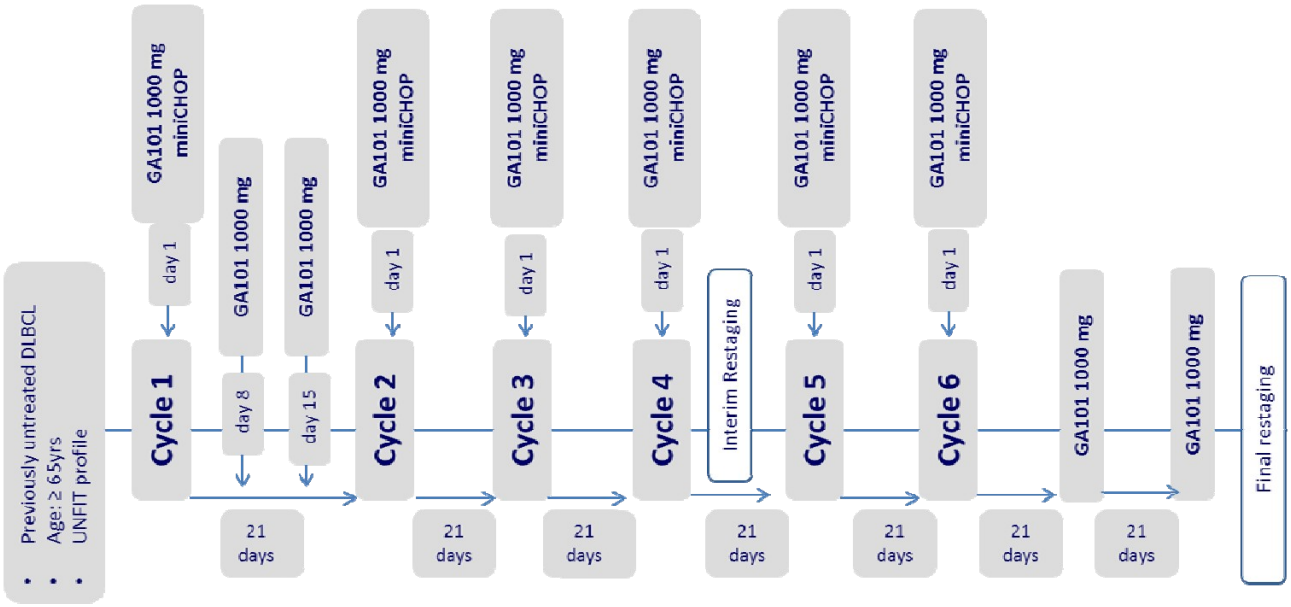
29. Come valuterebbe in generale la Sua salute durante gli ultimi sette giorni?

1	2	3	4	5	6	7
Pessima						Ottima

30. Come valuterebbe in generale la Sua qualità di vita durante gli ultimi sette giorni?

1	2	3	4	5	6	7
Pessima						Ottima

APPENDIX I: Study Flow Chart



GA101-miniCHOP regimen

Patients will receive 6 courses of GA101-miniCHOP regimen and 2 additional infusions of GA101, every 21 days (for a total of 6 courses of miniCHOP and 10 infusions of GA101)

Cycle 1

- GA101: 1000 mg day 1, day 8 and day 15, iv
- Cyclophosphamide: 400 mg/mq, day 1, iv
- Doxorubicin: 25 mg/mq, day 1, iv
- Vincristine: 1 mg, day 1, iv
- Prednisone: 40 mg/mq, days 1-5, os

Cycles 2-6

- GA101: 1000 mg day 1, iv
- Cyclophosphamide: 400 mg/mq, day 1, iv
- Doxorubicin: 25 mg/mq, day 1, iv
- Vincristine: 1 mg, day 1, iv
- Prednisone: 40 mg/mq, days 1-5, os

APPENDIX J: SAE FORM

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	Eudract Number:

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)	
	☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING ☐ CONGENITAL ANOMALY ☐ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-
17. INDICATION(S) FOR USE		DUCTION? ☐ YES ☐ NO ☐ NA
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last menstrual period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		26-26a. NAME AND ADRESS OF REPORTER (INCLUDE ZIP CODE)
ORIGINAL REPORT NO.	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL ☐ REGULATORY AUTHORITY ☐ OTHER	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOW-UP	

APPENDIX K: INDEPENDENT REVIEW COMMITTEE

For the purposes of this study, as the reference CR rate *(Peyrade et al, Lancet Oncol – 2011)* after 10 infusions of GA101 and 6 cycles of miniCHOP, was defined with 1999 International Criteria for response *(Cheson, JCO 1999)*, the response rate to therapy will be based on a Central Independent Review of response that will not consider the results of FDG-PET but will only use the conventional CT scan images.

Response defined according to Cheson 2007 criteria will also be provided as study result.

CT scan images will be sent by Centers to the Independent Review Committee, coordinated by Dr. Francesco Merli.

All details (timing, shipment information, etc.) concerning CT review are available in the specific operating procedure.