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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).

Final Study Report: version 1, April 30th, 2020

FINAL STUDY REPORT

Name of Sponsor/Company:	Fondazione Italiana Linfomi ONLUS (FIL)
Study type:	Interventional/clinical study
Study phase:	II
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).
EudraCT:	2014-005697-10
ID study:	FIL_GAEL
Version:	1
Date:	September 29th, 2014
Name of Active Ingredient:	GA101 (Obinutuzumab) Cyclophosphamide Doxorubicin Vincristine Prednisone
Conditions (diagnosis):	Elderly unfit patients with CD20 positive Diffuse Large B-cell Lymphoma and Follicular grade IIIB, according to WHO classification
Studied period (years):	
CA authorization:	24/04/2015
lead EC opinion date:	25/03/2015
date of first enrolment:	25/08/2015
date of last completed:	19/02/2020
date of Interim Analysis (If applicable):	22/03/2017
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Date of last database download:	27/04/2020
Report date:	30/04/2020
	List of abbreviations
	ADL Activity of Daily Living
	AE Adverse Events
	ALC Absolute Lymphocyte Count
	ALT Alanine Aminotransferase
	AST Aspartate Aminotransferase
	ASCO American Society of Clinical Oncology
	B2M Beta2-microglobuline
	BM Bone Marrow
	CGA Comprehensive Geriatric Assessment
	CHOP Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
	CI Confidence interval
	CIRS Cumulative Illness Rating Scale

	CNS	Central Nervous System
	CR	Complete Remission
	CRR	Complete Remission Rate
	CT scan	Computed Tomography Scan
	CTCAE	Common Terminology Criteria for Adverse Events
	DLBCL	Diffuse Large B Cell Lymphoma
	ECOG	Eastern Cooperative Oncology Group
	EORTC	European Platform of Cancer Research
	FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
	FIL	Fondazione Italiana Linfomi
	FU	Follow Up
	GA101	Obinutuzumab
	G-CSF	Granulocyte Colony-Stimulating Factor
	Hb	Hemoglobin
	HBcAb	Hepatitis B Core Antibody
	HBsAg	Hepatitis B surface antigen
	HCV	Hepatitis C Virus
	HIV	Human Immunodeficiency Virus
	I	Initial
	IADL	Instrumental Activity of Daily Living
	ISRT	Involved Site Radiation Therapy
	IPI	International Prognostic Index
	LVEF	Left Ventricular Ejection Fraction
	MEDdra	Medical Dictionary for Regulatory Activities
	ORR	Overall Response Rate
	OS	Overall Survival
	PET	Positron Emission Tomography
	PFS	Progression Free Survival
	PR	Partial Remission
	PRR	Partial Response Rate
	QoL	Quality of Life
	SAE	Serious Adverse Event
	SD	Stable Disease
	SUSAR	Suspected Unexpected Serious Adverse Reaction
	TLBCL	T-cell/histiocyte LBCL
	ULN	Upper Limit of Normality
	WBC	White Blood Cell
	WHO	World Health Organization
Study description (Aim of the study)		
Primary objectives	The primary objective is to assess whether the regimen GA101-miniCHOP achieves an absolute increase of the CR proportion of at least 15% (from 60% to 75% respect to R-miniCHOP regimen. 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
Primary end-points:	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)
Secondary end-points:	- 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)
Eligibility criteria	
Inclusion	1) Histologically proven CD20 positive Diffuse Large B-cell Lymphomaand 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 - 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 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 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	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
Treatments description	
	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.** 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 (*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 nonresponding 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.

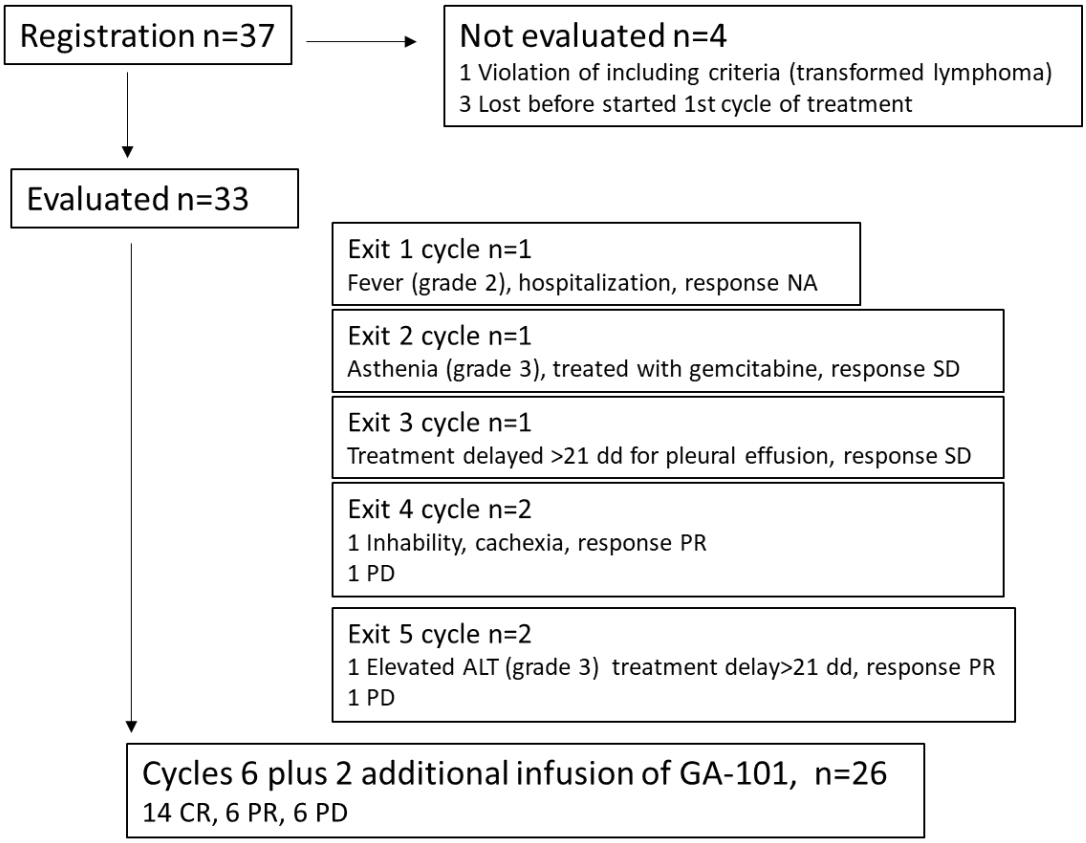
	All patients stopping study treatment due to early disease progression will be followed for survival until the end of the study. **Dosage Delays and Modifications: GA101 and CHOP chemotherapy** Dose reductions and delays are based on all laboratory values obtained within 72 hours prior to a study treatment 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 dosemodification 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 steroid 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.
Treatment duration	6 months
Statistical methods:	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) 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 International Criteria will also be provided as study result.
Sample size:	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. 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.

Study Flow Chart

Number of patients planned	**34** patients
Number of patients analysed	**33**
Number of excluded patients	4



Overall Study

Table 1: Overall Study and Treatment Administration

	Therapy: **GA101-miniCHOP**
Started	N. Patients enrolled 33
Completed	N. Patients that have completed therapy 26
Not Completed	7
Lack of Efficacy	19

Table 2: Demographic characteristic of enrolled patients (n=33)

Variable	**Median (2.5-97.5 percentile)**
Age, years	82 (68-89)
Hb, g/dL	12.9 (8.9-15.7)
WBC 10^9/l	7.7 (3.6-20.5)
ALC 10^9/l	1.2 (0.2-3.5)

Variable	**Status**	**N (%)**
Gender	M	18 (55)
	F	15 (45)
Stage	II	6 (18)
	III	11 (33)
	IV	16 (48)
BM	-	27 (82)
	+	6 (18)
ECOG PS	0	12 (35)
	1	19 (58)
	2	1 (3)
	3	1 (3)
B-symptoms	A	27 (82)
	B	6 (18)
Histology	DLBCL	32 (97)
	T LBCL	1 (3)
LDH	≤ULN	10 (30)
	>ULN	23 (70)
B2M	≤ULN	2 (7)
	>ULN	25 (93)
IPI	0-1	4 (12)
	2	8 (24)
	3-5	21 (64)
CGA	UNFIT	28 (85)
	FRAIL	5 (15)

Missing: ALC n=1, B2M n=6
DLBCL: diffuse large B-cell lymphoma, TLBCL: T-cell/histiocyte LBCL
WBC: white blood cell; ALC: absolute lymphocyte count; ULN: upper limit of normality; B2M: beta2-microglobuline; LDH lactate dehydrogenase; BM bone marrow involvement

Efficacy evaluation:

Table 3. Complete remission (CR) rate according to Cheson 1999.

	Final response	
Response	N	% (95CI)
CR	**14**	**42.4 (25.5-60.8)**
PR	8	24.2 (11.1-42.3)
SD	2	6.1 (0.7-20.2)
PD	8	24.2 (11.1-42.3)
NA	1	3.0 (0.1-15.8)
Total	33	

CR: complete remission, PR: partial remission, SD: stable disease, PD: progression disease, NA: not assessed.
95CI: 95% confidence interval (Clopper-Pearson)
NA: one patents withdrawal after 1 cycle due fever hospitalization.

 # CR 14: it does not exceed the threshold of 21 CR as expected from the optimal Simon two stage. Interim analysis failed for efficacy.

Table 4. Dose Intensity (mean, 95%CI) according to Hryniuk.

Cycles	GA101	Doxorubicin	Cyclophosphamide	Vincristine
1-4	0.94 (0.92-0.96)	0.93 (0.90-0.95)	0.93 (0.90-0.95)	0.94 (0.91-0.96)
5-8 (6)	0.99 (0.95-1.04)	0.98 (0.95-1.01)	0.97 (0.94-1.00)	0.98 (0.93-1.03)

Safety Evaluation:

Table 5. Hematological and extra-hematological adverse events (AE). Maximum adverse event collected during induction treatment (n=33).

Adverse Event - Haematological	Grade 1-2		Grade 3-4	
	n	%	n	%
Anemia	6	18,2	0	0,0
Leukopenia	2	6,1	2	6,1
Neutropenia	2	6,1	13	39,4
Piastrinopenia	10	30,3	1	3,0
Febrile neutropenia	0	0,0	0	0,0
Adverse Event - Non-heamatological	**Grade 1-2**		**Grade 3-4**	
	n	%	n	%
Cardiac disorders	3	9,1	2	6,1
Congenital/familial/genetic disorders	0	0,0	0	0,0
Ear and labyrinth disorders	0	0,0	0	0,0
Endocrine disorders	0	0,0	0	0,0
Eye disorders	0	0,0	0	0,0
Gastrointestinal disorders	11	33,3	1	3,0
General disorders and administration site conditions	4	12,1	2	6,1
Hepatobiliary disorders	0	0,0	2	6,1
Immune system disorders	0	0,0	0	0,0
Infections	6	18,2	1	3,0
Injury/poisoning/procedural complications	0	0,0	2	6,1
Investigations	2	6,1	1	3,0
Metabolism and nutrition disorders	5	15,2	3	9,1
Musculoskeletal and connective tissue disorders	5	15,2	3	9,1
Neoplasms benign/malignant/unspecified	0	0,0	2	6,1
Nervous system disorders/Psychiatric disorders	6	18,2	1	3,0
Pregnancy/puerperium and perinatal conditions	0	0,0	0	0,0
Renal and urinary disorders	2	6,1	0	0,0
Reproductive system and breast disorders	0	0,0	0	0,0
Respiratory/thoracic and mediastinal disorders	5	15,2	0	0,0
Skin and subcutaneous tissue disorders	0	0,0	0	0,0
Social circumstances	0	0,0	0	0,0
Surgical and medical procedures	0	0,0	0	0,0
Vascular disorders	1	3,0	0	0,0
Other (specify)	8	24,2	0	0,0

One patient was dead after with heart failure grade 4

Collected ad Other toxicities (n=8) - description	grade
Epigastric pain	2
Dysgeusia	1
Fever	2
Infusion reaction	2
Asthenia; bone pain	2
Infiammatory edema	1
Fever	2
Pain	2

Table 6. List of serious advent events (SAE)

ID	Date of Onset	SAE/SUSAR	Report (I or FU)	Event Short Description	Gravity of the event	Outcome of the event at report time	Relationship	Suspected Drug
0002GAEL	20/12/2015	SAE	I	nausea	Caused/Prolonged Hospitalisation	Not Recovered/Not Resolved	Unrelated	none
0002GAEL	19/02/2016	SAE	I	femure fracture	Caused/Prolonged Hospitalisation	Not Recovered/Not Resolved	Unrelated	none
0002GAEL	19/02/2016	SAE	FU	femure fracture	Caused/Prolonged Hospitalisation	Recovered/Resolved	Unrelated	none
0002GAEL	31/03/2016	SUSAR	I	congestive heart failure	Caused/Prolonged Hospitalisation	Not Recovered/Not Resolved	Unrelated	none
0002GAEL	22/06/2016	SAE	I/FU	congestive heart failure	Death	Fatal	Possible	GA101
0004GAEL	08/12/2015	SAE	I	lumbar pain, vertebral collapse	Caused/Prolonged Hospitalisation	Not Recovered/Not Resolved	Unrelated	obinutuzumab miniCHOP
0005GAEL	08/02/2016	SAE	I	fever	Caused/Prolonged Hospitalisation	Not Recovered/Not Resolved	Unrelated	obinutuzumab miniCHOP
0005GAEL	08/02/2016	SAE	FU	sepsis	Caused/Prolonged Hospitalisation	Recovered/Resolved	Unrelated	none
0005GAEL	07/08/2016	SAE	I/FU	sepsis	Death	Fatal	Unrelated	
0015GAEL	15/04/2016	SAE	I	BPCO - Heart Failure	Caused/Prolonged Hospitalisation	Not Recovered/Not Resolved	Probable	obinutuzumab miniCHOP
0026GAEL	09/05/2017	SUSAR	I	breast cancer	Other medically important condition	Not Recovered/Not Resolved	Unrelated	GA101
0026GAEL	09/05/2017	SUSAR	FU	breast cancer	Other medically important condition	Not Recovered/Not Resolved	Unrelated	doxorubicina, vincristina, ciclofosfamide
0026GAEL	09/05/2017	SUSAR	FU	breast cancer	Other medically important condition	Not Recovered/Not Resolved	Unrelated	prednisone
0026GAEL	19/07/2017	SUSAR	I	non small cell lung cancer	Other medically important condition	Unknown	Unrelated	obinutuzumab
0026GAEL	19/07/2017	SUSAR	FU	non small cell lung cancer	Other medically important condition	Unknown	Unrelated	obinutuzumab/vincristina/doxorubicina/ciclofosfamide
0026GAEL	19/07/2017	SUSAR	FU	non small cell lung cancer	Other medically important condition	Unknown	Unrelated	prednisone
0032GAEL	16/06/2016	SAE	I	Fever	Caused/Prolonged Hospitalisation	Not Recovered/Not Resolved	Possible	GA101
0036GAEL	16/06/2016	SAE	I	Atrial fibrillation	Caused/Prolonged Hospitalisation	Unknown	Unrelated	not started
0036GAEL	18/06/2016	SAE	FU	Atrial fibrillation - sepsi due to Klebsiella Pneumoniae	Caused/Prolonged Hospitalisation	Fatal	Possible	not started

I: Initial; FU: adverse event follow-up
ID 0036: SAE recorded before starting 1st cycle of treatment. Not included in the 33 evaluable patients.
ID 0026: SUSAR during follow-up post induction.
SAE/SUSAR reported in 7 patients (Six evaluated and one exit before treatment).

Secondary End-Point

Overall Response Rate (ORR: CR+PR): 67% (95%CI 48-82%)

Overall survival (OS): After a median of 32 months (95%CI 15-38 months), from the date of registration in the study, were observed 11 death: 7 for progression of disease, 1 for probable progression of lymphoma, 1 for heart failure, 1 for sepsis and one due unknown cause.

The 24-months OS% was 69% (95%CI 50-82%).

Progression Free Survival (PFS): Were observed 17 events, with a 24-months PFS of 53% (34-68%).

Summary – Conclusions:

In conclusion, our phase II study confirmed the activity and safety of Ga101-miniCHOP for the treatment of older, unfit patients with DLBCL, but was not able to show it as a promising regimen to challenge the current standard R-miniCHOP. To improve treatment efficacy in this hard to-treat patient population, different strategies should be adopted that include better patient and/or lymphoma profiling and the use of new drugs with a novel non-cross-resistant mechanism of action.

We attest the accuracy and truthfulness of the information contained in this Report.

Date of report: April 30th, 2020

Dr. Francesco Merli

Principal Investigator and

President of Fondazione Italiana Linfomi