Clinical trial results:
Phase II study with Ga101-DHAP as induction therapy in relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) patients before High-Dose chemotherapy BEAM with autologous stem cell transplantation (ASCT).

Summary

EudraCT number	2013-004014-17
Trial protocol	IT
Global end of trial date	23 June 2020

Results information

Result version number	v1 (current)
This version publication date	01 April 2022
First version publication date	01 April 2022

Trial information

Trial identification

Sponsor protocol code	FIL_GA101_DHAP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02374424
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione Italiana Linfomi (FIL) ONLUS
Sponsor organisation address	Piazza Turati 5, Alessandria, Italy,
Public contact	Segreteria FIL ONLUS, Fondazione Italiana Linfomi (FIL) ONLUS, 0039 0131/033151, segreteriadirezione@filinf.it
Scientific contact	Segreteria FIL ONLUS, Fondazione Italiana Linfomi (FIL) ONLUS, 0039 0131/033151, segreteriadirezione@filinf.it

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	06 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2018
Global end of trial reached?	Yes
Global end of trial date	23 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Aim of this trial is to assess the efficacy of new anti-CD20 antibody (GA101) in association with DHAP as induction therapy before high dose chemotherapy BEAM with ASCT in patients with relapsed/refractory DLBCL.
Primary objective is to assess whether the treatment achieves an absolute increase of the CR proportion of at least 20% (from 30% to 50%) with respect to the standard treatment with an acceptable extra-hematological toxicity grade 3-4 of 0.25 (unacceptable extra-hematological toxicity=0.40).

Protection of trial subjects:

The GA101 dose will be delayed or adjusted in case of:
- febrile neutropenia or neutropenia with infection;
- severe thrombocytopenia (platelets < 10,000/µL) and/or symptomatic bleeding in patients who are not receiving concomitant anticoagulants or platelet ihibitors;
- thrombocytopenia with platelets < 20,000/µL and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet ihibitors

Patients must discontinue study drug if they experience any of the following:
- Pregnancy
- PML
- Grade 4 IRR
Patient should be withdrawn immediately and treatment must be discontinued permanently.

- Grade 3 IRR at re-challenge despite adequate premedication: patient must be withdrawn immediately and treatment must be discontinued permanently
- Grade 3 or 4 hematological toxicity that has not resolved to Grade ≤ 2 and requires to delay treatment by more that 14 days (Thrombocytopenia needs to resolve to Grade ≤1)
- Grade ≥ 2 non-hematological toxicity that does not resolve to Grade ≤ 1/baseline and requires to delay treatment by more that 14 days
- Hepatitis B reactivation

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	05 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty-nine young patients recruited in Italy from 05 November 2014, with date of last completed at 25 January 2017.

Pre-assignment

Screening details:

Patients with DLBCL who failed or relapsed after one previous chemotherapy regimen will be enrolled. All patients must satisfy all the inclusion criteria and none of exclusion criteria.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

GA101-DHAP x 2 cycles (28 days), restaging, mobilization and harvest of peripheral stem cell + GA101-DHAP x 2, restaging with PET evaluation and consolidation with BEAM/FEAM and ASCT in responsive patients (CR + PR).
GA101-DHAP scheme could be performed as in-patient or out-patient due to different organizational needs. No differences are reported in literature in term of efficacy of the two schemes.

Arm type	Single arm study
Investigational medicinal product name	Obinutuzumab (GA101)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

GA101 will be administered by IV infusion as an absolute (flat) dose of 1000 mg on Day 1 of each 28-day cycle for 4 cycles. GA101 will be administered prior to DHAP, and patients should be observed 30 minutes prior to starting DHAP. If DHAP is not started or completed on Day 1 because of the long duration of GA101 therapy, DHAP chemotherapy may be administered on Day 2. During Cycle 1, GA101 will also be infused on Days 8 and 15.
GA101 1000 mg iv 24 hours before apheresis as purging in vivo during second courses of therapy.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In-patient version:
- 100 mg/sqm iv day 1 of every cycles in 24-hours infusion

Out-patient version:
- 100 mg/sqm iv day 1 of every cycles in 3-hours infusion

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

In-patient version:
• 2000 mg/sqm in 3-hours infusion every 12 hours iv day 2 of every cycles

Out-patient version:
• 2000 mg/sqm in 3-hours infusion iv day 2 and day 3 of every cycles

Investigational medicinal product name	Dexametasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In-patient version:
• 40 mg day 1-4 of every cycles

Out-patient version:
• 40 mg day 1-4 of every cycles

Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In-patient version:
• 6 mg sc single dose 24 hours after the end of chemotherapy or G-CSF from day 4 till stem cell harvest during mobilization’s course (II o III cycle GA101-DHAP)

Out-patient version:
• 6 mg sc single dose 24 hours after the end of chemotherapy or G-CSF from day 5 till stem cell harvest during mobilization’s course (II or III cycle GA101-DHAP)

Number of subjects in period 1	Single arm
Started	29
Completed	8
Not completed	21
Physician decision	1
Adverse Event	3
Patient Refusal	1
Other Reason	1
Progression Disease	15

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	29	29	
Age categorical Units: Subjects			
Adults (18-64 years)	29	29	
Age continuous Units: years			
median	56.33		
inter-quartile range (Q1-Q3)	48.01 to 61.36	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	17	17	
Systemic Symptoms Units: Subjects			
Systemic Symptoms A	24	24	
Systemic Symptoms B	5	5	
Stage AA Units: Subjects			
Stage I	1	1	
Stage II	5	5	
Stage III	10	10	
Stage IV	13	13	
ECOG PS Units: Subjects			
ECOG 0	15	15	
ECOG 1	12	12	
ECOG 3	2	2	
Abnormal LDH Units: Subjects			
No	9	9	
Yes	20	20	
Bone Marrow Involved Units: Subjects			
No	25	25	
Yes	3	3	
NA	1	1	
IPI Units: Subjects			
Score 0	1	1	
Score 1	6	6	
Score 2	12	12	

Score 3	7	7	
Score 4	3	3	
Patient status Units: Subjects			
Refractory	17	17	
Relapsed	12	12	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

GA101-DHAP x 2 cycles (28 days), restaging, mobilization and harvest of peripheral stem cell + GA101-DHAP x 2, restaging with PET evaluation and consolidation with BEAM/FEAM and ASCT in responsive patients (CR + PR).
GA101-DHAP scheme could be performed as in-patient or out-patient due to different organizational needs. No differences are reported in literature in term of efficacy of the two schemes.

Primary: Complete response rate (CR)

End point title	Complete response rate (CR)[1]

End point description:

The complete response rate (CR) evaluated by PET scan after four cycles of GA101-DHAP before ASCT according to Cheson criteria. Historical data with which we will compare the results of our study were obtained in the same study population but with different response evaluation criteria (Cheson criteria 1999).

End point type	Primary

End point timeframe:

After four cycles of GA101-DHAP before ASCT

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study is single-arm without comparator.
Historical data with which we will compare the results of our study were obtained in the same study population but with different response evaluation criteria (Cheson criteria 1999).

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Complete Response (CR)				
number (confidence interval 95%)	20.69 (7.99 to 39.7)			

Statistical analyses

No statistical analyses for this end point

Primary: Safety Evaluation

End point title	Safety Evaluation[2]

End point description:

Severe, life-threatening, fatal (grade 3, 4 and 5) extra-hematological toxicity till one month after the last obinutuzumab administration (cycle 4), according to "Common Terminology Criteria for Adverse Events" CTCAE), version 4.0, are defined for primary toxicity evaluation.
Proportion of patients with non-hematologic toxicity (of grade 3 or greater).

End point type	Primary

End point timeframe:

Till one month after the last obinutuzumab administration

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study is single-arm without comparator.
The number of patients with non-haematological toxicities with grade> = 3 during experimental therapy should be less than 19 out of 29 patients.

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Pts extra-hematological toxicity grade≥3				
number (confidence interval 95%)	31.03 (15.28 to 50.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

Overall response rate (ORR): a patient is defined as a responder if she/he has a complete or partial response, evaluated by PET/TC, after four cycles of GA101-DHAP.

End point type	Secondary

End point timeframe:

Evaluated by PET/TC after four cycles of GA101-DHAP, prior to consolidation with BEAM and ASCT

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Proportion				
number (confidence interval 95%)	34.48 (17.94 to 54.33)			

Statistical analyses

No statistical analyses for this end point

Secondary: The hematopoietic cell mobilization

End point title	The hematopoietic cell mobilization

End point description:

Mobilizing potential: amount of CD34 + stem cell collected /Kg

End point type	Secondary

End point timeframe:

2 years

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: CD34 Mobilized				
median (inter-quartile range (Q1-Q3))	5.525 (5 to 6.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: ASCT feasibility

End point title	ASCT feasibility

End point description:

ASCT feasibility will be evaluated as the proportion of patients successfully completing ASCT.

End point type	Secondary

End point timeframe:

2 years

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Percent				
number (confidence interval 95%)	31.03 (15.28 to 50.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Progression free survival (PFS) is measured from the date of starting salvage therapy to the date of disease progression, relapse or death from any cause. Responding patients and patients who are lost to follow up will be surveyed at their last assessment date.

End point type	Secondary

End point timeframe:

In the protocol at 6 month after the end of treatment (EOT); analyzed to 24 months from enrollment

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Kaplan Meier probability				
number (confidence interval 95%)	37.93 (20.87 to 54.90)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Measured from the date of starting salvage therapy to the date of death from any cause. Patients alive at the time of the final analysis will be surveyed at the date of the last contact.

End point type	Secondary

End point timeframe:

In the protocol 2 years after the EOT; analyzed 48 months after enrollment

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Kaplan Meier probability				
number (confidence interval 95%)	36.85 (16.23 to 57.80)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 5 November 2014 to 23 June 2020 (LPLV)

Adverse event reporting additional description:

Grade>=3 toxicities

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Single arm

Reporting group description: -

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 29 (65.52%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	1		
Vascular disorders			
Fever, hypotension, thrombocytropenia, vomit and low potassium and sodium serum levels			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fever, Neutropenia e Trombocitopenia, emottisi dovuta a infezione?			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Suspected epileptic seizure, cardiac arrest, hypokaliemia, trasfer to intensive care			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dizziness and confabulation. MRI			

subscript for Wernicke's encephalopathy				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia, trombocytopenia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	2 / 29 (6.90%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
pancytopenia: anemia Gr4, neutropenia Gr4, thrombocytopenia Gr4				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia and thrombocytopenia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia and cough				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Subdoral hematoma with concomitant seizures an pneumonia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting and diarrhea grade III Ipotension, fever			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain - PD			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	2 / 29 (6.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
suspected pneumonitis (granulomatous reaction)			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chronic renal failure			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Aspergillus pneumonia				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious disaese				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection by Klebsiella KPC				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis carinii (pneumonia)				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fever for klebsiella pneumoniae infection. Isolated from BAL				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Septick shock (acute renal failure, dysionemia, hypotension)				
subjects affected / exposed	1 / 29 (3.45%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 29 (48.28%)		
Vascular disorders			
Thrombotic event			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Subdural haematoma			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Nervous system disorders			
Suspect Epilectic seizure			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	2		
Hallucinations, confabulation			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Encephalopathy			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
General disorders and administration site conditions			
Hemoptysis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Tongue oedema			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Severe neutropeny and thrombocitopenie			

subjects affected / exposed	2 / 29 (6.90%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	5 / 29 (17.24%)		
occurrences (all)	14		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Mucositis			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Vomiting and diarrhea			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Pneumonia (Aspergillus)			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
pneumocystis carinii pneumonia			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Renal and urinary disorders			
Kidney failure			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Renal insufficiency			
subjects affected / exposed	1 / 29 (3.45%)		
occurrences (all)	1		
Infections and infestations			

Klebsiella infection subjects affected / exposed occurrences (all) Septic Shock (Gram- infection) subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1		
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypokalemia, Hyponatremia subjects affected / exposed occurrences (all) NA subjects affected / exposed occurrences (all)	 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2016	1) Change of the reference laboratory responsible for the histological review (Referent: Stefano Pileri, MD, Unità di Emolinfopatologia, Istituto Europeo di Oncologia IEO - Milano). 2) Clarification regarding the biopsy specimen for histological review (Inclusion criteria). The relapse biopsy was particularly recommended if the relapse occurred more than a year before complete remission. If harmful to the patient, it was possible to enroll if the tumor specimen or block from the first diagnosis was available. 3) Correction of typos concerning ancillary biological studies. All the references to the conduct of biological studies, which are not included in the protocol, have been removed. 4) Patient information sheet / Informed consent form / Privacy protection / Letter for the treating physician were modified with non-substantial corrections, modifications, additions and clarifications as requested by the local Ethics Committees in order to standardize the documentation for all sites.
09 September 2016	5) Modifications to statistical considerations. The definition of toxicity considered unacceptable has been completed, in all the points in which it occurs, with the specification "grade 3-4 extra-haematological toxicity", forgotten in the initial version. The correction is related, as obvious, to the fact that standard DHAP chemotherapy is almost always associated with pancytopenia that defines a grade 3 or 4 haematological toxicity which does not constitute an unexpected event that could compromise the costeffectiveness ratio of the therapeutic scheme. As already understood, but not specified in the initial text, all possible organ toxicities will be evaluated as unacceptable toxicities, including infectious complications following the expected pancytopenia. It has also been added a grade 3 or 4 toxicity level that identifies the unacceptability, since the lower grades are not relevant to imply a real clinical risk and also affect the stopping rule. The preliminary stopping rule evaluation remains calculated on the percentages related to the first 29 patients. Taking into account the limited knowledge of the obinutuzumab-DHAP association, toxicity assessments at the end of chemotherapy with Ga101-DHAP of each patient have been specified (up to 1 month after the last cycle). Late assessments up to 6 months after the autotransplant were also planned, although these do not appear relevant to the stopping rule. 6) Increased study duration, extended to 88 months (52 months for enrollment and 36 months of follow up). 7) Withdrawal. It has been specified that it is possible to collect information on patient status for patients prematurely withdrawn from study participation. 8) Risks associated with GA101 Therapy. There have been added the guidelines to be followed in case a delayed administration of GA101 during the first cycle of therapy (day 8 and 15), in case toxicities occur.
09 September 2016	9) Investigator's Brochure Update. The risk/benefit profile was confirmed, therefore no modifications has been reported on the study documents. 10) Update of the participating centers. Five sites were closed and 4 sites were involved in the study. 11) Typos correction and other not substantial modification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 February 2018	According to the results of the interim analysis study enrolment was stopped. According to Briant & Day design, in the first stage the number of complete response pre-ASCT (6 on 29 patients, 21%) was lower than the level set for continuing the study (10 on 29 patients). The number of patients with non-haematological toxicities with grade>=3 during experimental therapy (9 on 29, 31%) was within the limits of acceptability (no more than 19 of 29 patients). According of the results of the interim analysis, enrollment in this study was not reopened and the experimental induction therapy was not considered worthy for further investigation.	-

Notes:

Limitations and caveats

None reported