Clinical trial results:
A SINGLE-ARM MULTI-CENTER TRIAL OF PENTOSTATIN PLUS CYCLOPHOSPHAMIDE WITH OFATUMUMAB (PCO) IN OLDER PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA

Summary

EudraCT number	2010-022332-37
Trial protocol	IT
Global end of trial date	18 November 2015

Results information

Result version number	v1 (current)
This version publication date	17 December 2017
First version publication date	17 December 2017
Summary attachment (see zip file)	PCO Synopsis (PCO Synopsis Clinical Study Results_final_28Jun17.pdf)

Trial information

Trial identification

Sponsor protocol code	PCO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01681563
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AZIENDA OSPEDALIERA OSPEDALE NIGUARDA CA' GRANDA
Sponsor organisation address	P.zza Ospedale Maggiore, 3 , Milano, Italy, 20162
Public contact	Dipartimento Oncologia/Ematologia, Ospedale Niguarda Ca' Granda, +39 0264444074, marco.montillo@ospedaleniguarda.it
Scientific contact	Dipartimento Oncologia/Ematologia, Ospedale Niguarda Ca' Granda, +39 0264444074, marco.montillo@ospedaleniguarda.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	Final
Date of interim/final analysis	06 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2015
Global end of trial reached?	Yes
Global end of trial date	18 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to determine whether the PCO combination is effective as first line treatment of older CLL patients as defined by Overall Response Rate (ORR)

Protection of trial subjects:

According to study protocol all patients should receive prophylaxis against pneumocystis carinii pneumonia, antiemetic medications, allopurinol for tumor lysis and acyclovir. Antifungal agents may be used as per institutional practice. Use of granulocyte colony stimulating factors (G-CSF) and erythropoietin (EPO) to treat for neutropenia and anaemia respectively is permitted while on study. Subjects received full supportive care, including antibiotics and hydration when appropriate and according to the most appropriate manner determined by the treating physician.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2011
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: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	0
From 65 to 84 years	49

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From 02 August 2011 to 24 June 2013

Pre-assignment

Screening details:

49 patients, aged>/= 65, with untreated B-Cell CLL showing progressive disease were enrolled.

Period 1

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

Arms

Arm title	PCO combination

Arm description:

The regimen consisted of intravenous pentostatin 2mg/m2 and cyclophsphamide 600 mg/m2 on day 1 every 3 weeks for a total of 6 cycles. On the first cycle, intravenous ofatumumab was administered at 300 mg on day 1 and 1000 mg on day 8. For the subsequent cycles, patients received ofaumumab on day 1 at the dose of 1000 mg.

Arm type	Experimental
Investigational medicinal product name	Ofatumumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ofatumumab was infused intravenously on day 1 (300 mg) and day 8 (1000 mg) in the first cycle, followed by infusions of 1000 mg at the first day from cycle 2 to cycle 6. Each cycle lasted 21 days.

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

Dosage and administration details:

Pentostatin was administered at the dose of 2 mg/m2 over a 30 minutes infusion on Day 1 from cycle 1 to cycle 6. Each cycles lasted 21 days.

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

Dosage and administration details:

Cyclofosphamide was administered at the dose of 600 mg/m2 over a 30 minutes infusion on day 1 of each cycle for a total of 6 cycles of 21 days.

Number of subjects in period 1	PCO combination
Started	49
Completed	34
Not completed	15
Adverse event, serious fatal	2
Physician decision	1
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Progression	9
Start a new therapy	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	49	49	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	49	49	
85 years and over	0	0	
Age continuous Units: years			
median	72		
full range (min-max)	65 to 83	-	
Gender categorical Units: Subjects			
Female	17	17	
Male	32	32	
ECOG PS Units: Subjects			
Zero	38	38	
One	10	10	
Two	1	1	
Binet Staging System Units: Subjects			
Binet A	2	2	
Binet B	38	38	
Binet C	9	9	
Not recorded	0	0	
RAI Classification Stage Units: Subjects			
RAI 0	1	1	
RAI I	15	15	
RAI II	20	20	
RAI III	7	7	
RAI IV	6	6	
Active Disease Conditions - Marrow Failure Units: Subjects			

Marrow failure	13	13	
No Marrow failure	36	36	
Active Disease Conditions - Splenomegaly Units: Subjects			
Splenomegaly	8	8	
No Splenomegaly	41	41	
Active Disease Conditions - Lymphadenopathy Units: Subjects			
Lymphdenopathy	21	21	
No Lymphadenopaty	28	28	
Active Disease Conditions - Lymphocytosis Units: Subjects			
Lymphocytosis	17	17	
No Lymphocytosis	32	32	
Disease evaluation by physical examination - Abnormal liver Units: Subjects			
Abnormal liver	46	46	
No abnormal liver	3	3	
Disease evaluation by physical examination - Abnormal spleen Units: Subjects			
Abnormal spleen	27	27	
No abnormal spleen	22	22	
Disease evaluation by physical examination - Abnormal Nuchal LN Units: Subjects			
Abnormal nuchal LN	45	45	
No abnormal nuchal LN	4	4	
Disease evaluation by physical examination - Abnormal Cervical LN Units: Subjects			
Abnormal cervical LN	19	19	
No abnormal cervical LN	30	30	
Disease evaluation by physical examination - Abnormal axillary LN Units: Subjects			
Abnormal axillary LN	17	17	
No abnormal axillary LN	32	32	
Disease evaluation by physical examination - Abnormal sipraclavicular LN Units: Subjects			
Abnormal sipraclavicular LN	35	35	
No abnormal sipraclavicular LN	14	14	
Disease evaluation by physical examination - Abnormal inguinal LN Units: Subjects			
Abnormal inguinal LN	25	25	
No abnormal inguinal LN	24	24	
Beta-2 microglobulin Units: Subjects			

>/= 4 mg/ml	9	9	
< 4mg/ml	26	26	
Not recorded	14	14	
IgHV (peripheral blood) Units: Subjects			
Mutated	9	9	
Unmutated	15	15	
Not recorded	25	25	
IgHV (bone marrow) Units: Subjects			
Mutated	9	9	
Unmutated	6	6	
Not recorded	34	34	
FISH (peripheral blood) Units: Subjects			
Del11q22+	4	4	
Del13q14+	9	9	
Trisomy 12+	6	6	
No mutations	1	1	
Not recorded	29	29	
FISH (Bone marrow) Units: Subjects			
Del17p13+	3	3	
Del13q14+	9	9	
Trisomy 12+	3	3	
No mutations	2	2	
Not recorded	32	32	
CD Markers - CD5+ (peripheral blood) Units: Subjects			
Positive	34	34	
Negative or Not Recorded	15	15	
CD Markers - CD19+ (peripheral blood) Units: Subjects			
Positive	35	35	
Negative or Not Recorded	14	14	
CD Markers - CD20+ (peripheral blood) Units: Subjects			
Positive	28	28	
Negative or Not Recorded	21	21	
CD Markers - CD23+ (peripheral blood) Units: Subjects			
Positive	31	31	
Negative or Not Recorded	18	18	
CD Markers - CD79b+ (peripheral blood) Units: Subjects			
Positive	8	8	
Negative or Not Recorded	41	41	
CD Markers - ZAP70+ (peripheral blood) Units: Subjects			
Positive	7	7	

Negative or Not Recorded	42	42	
CD Markers - CD5+ (bone marrow) Units: Subjects			
Positive	36	36	
Negative or Not Recorded	13	13	
CD Markers - CD19+ (bone marrow) Units: Subjects			
Positive	37	37	
Negative or Not Recorded	12	12	
CD Markers - CD20+ (bone marrow) Units: Subjects			
Positive	31	31	
Negative or Not Recorded	18	18	
CD Markers - CD23+ (bone marrow) Units: Subjects			
Positive	38	38	
Negative or Not Recorded	11	11	
CD Markers - CD79b+ (bone marrow) Units: Subjects			
Positive	5	5	
Negative or Not Recorded	44	44	
CD Markers - ZAP70+ (bone marrow) Units: Subjects			
Positive	8	8	
Negative or Not Recorded	41	41	

Subject analysis sets

Subject analysis set title	Evaluable Patients
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population included all patients who received at least one dose of study medication

Reporting group values	Evaluable Patients		
Number of subjects	47		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	47		
85 years and over	0		
Age continuous Units: years			
median	72		
full range (min-max)	65 to 83		

Gender categorical Units: Subjects			
Female	16		
Male	31		
ECOG PS Units: Subjects			
Zero	38		
One	9		
Two	0		
Binet Staging System Units: Subjects			
Binet A	1		
Binet B	37		
Binet C	9		
Not recorded	0		
RAI Classification Stage Units: Subjects			
RAI 0	0		
RAI I	14		
RAI II	20		
RAI III	7		
RAI IV	6		
Active Disease Conditions - Marrow Failure Units: Subjects			
Marrow failure	13		
No Marrow failure	34		
Active Disease Conditions - Splenomegaly Units: Subjects			
Splenomegaly	7		
No Splenomegaly	40		
Active Disease Conditions - Lymphadenopathy Units: Subjects			
Lymphdenopathy	20		
No Lymphadenopaty	27		
Active Disease Conditions - Lymphocytosis Units: Subjects			
Lymphocytosis	16		
No Lymphocytosis	31		
Disease evaluation by physical examination - Abnormal liver Units: Subjects			
Abnormal liver	44		
No abnormal liver	3		
Disease evaluation by physical examination - Abnormal spleen Units: Subjects			
Abnormal spleen	26		
No abnormal spleen	21		
Disease evaluation by physical			

examination - Abnormal Nuchal LN Units: Subjects			
Abnormal nuchal LN	43		
No abnormal nuchal LN	4		
Disease evaluation by physical examination - Abnormal Cervical LN Units: Subjects			
Abnormal cervical LN	18		
No abnormal cervical LN	29		
Disease evaluation by physical examination - Abnormal axillary LN Units: Subjects			
Abnormal axillary LN	16		
No abnormal axillary LN	31		
Disease evaluation by physical examination - Abnormal sipraclavicular LN Units: Subjects			
Abnormal sipraclavicular LN	33		
No abnormal sipraclavicular LN	14		
Disease evaluation by physical examination - Abnormal inguinal LN Units: Subjects			
Abnormal inguinal LN	24		
No abnormal inguinal LN	23		
Beta-2 microglobulin Units: Subjects			
>/= 4 mg/ml	9		
< 4mg/ml	25		
Not recorded	13		
IgHV (peripheral blood) Units: Subjects			
Mutated	9		
Unmutated	14		
Not recorded	24		
IgHV (bone marrow) Units: Subjects			
Mutated	9		
Unmutated	6		
Not recorded	32		
FISH (peripheral blood) Units: Subjects			
Del11q22+	4		
Del13q14+	9		
Trisomy 12+	6		
No mutations	1		
Not recorded	27		
FISH (Bone marrow) Units: Subjects			
Del17p13+	3		
Del13q14+	8		
Trisomy 12+	2		
No mutations	2		

Not recorded	32		
CD Markers - CD5+ (peripheral blood) Units: Subjects			
Positive	33		
Negative or Not Recorded	14		
CD Markers - CD19+ (peripheral blood) Units: Subjects			
Positive	34		
Negative or Not Recorded	13		
CD Markers - CD20+ (peripheral blood) Units: Subjects			
Positive	27		
Negative or Not Recorded	20		
CD Markers - CD23+ (peripheral blood) Units: Subjects			
Positive	31		
Negative or Not Recorded	16		
CD Markers - CD79b+ (peripheral blood) Units: Subjects			
Positive	8		
Negative or Not Recorded	39		
CD Markers - ZAP70+ (peripheral blood) Units: Subjects			
Positive	7		
Negative or Not Recorded	40		
CD Markers - CD5+ (bone marrow) Units: Subjects			
Positive	35		
Negative or Not Recorded	12		
CD Markers - CD19+ (bone marrow) Units: Subjects			
Positive	36		
Negative or Not Recorded	11		
CD Markers - CD20+ (bone marrow) Units: Subjects			
Positive	30		
Negative or Not Recorded	17		
CD Markers - CD23+ (bone marrow) Units: Subjects			
Positive	37		
Negative or Not Recorded	10		
CD Markers - CD79b+ (bone marrow) Units: Subjects			
Positive	5		
Negative or Not Recorded	42		
CD Markers - ZAP70+ (bone marrow) Units: Subjects			
Positive	8		
Negative or Not Recorded	39		

End points

End points reporting groups

Reporting group title	PCO combination
Reporting group description:	
The regimen consisted of intravenous pentostatin 2mg/m2 and cyclophsphamide 600 mg/m2 on day 1 every 3 weeks for a total of 6 cycles. On the first cycle, intravenous ofatumumab was administered at 300 mg on day 1 and 1000 mg on day 8. For the subsequent cycles, patients received ofaumumab on day 1 at the dose of 1000 mg.	
Subject analysis set title	Evaluable Patients
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all patients who received at least one dose of study medication	

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]
End point description:	
Overall response rate (ORR) is defined as the proportion of patients who have a partial or complete response to therapy.	
End point type	Primary
End point timeframe:	
All trial period.	
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: An ORR of 87.2% was obtained. The one-sided p-value obtained by the binomial test (<. 05) lead the rejection of the null hypothesis (p=.75) in favor of the alternative one (p=.90). The drug association is to be considered effective enough to worth further clinical studies.	

End point values	Evaluable Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: percent				
number (confidence interval 95%)				
CR + CRi + PR	87.2 (74.0 to 95.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
Measured as the time from inclusion in the trial to disease progression, or death.	
End point type	Secondary
End point timeframe:	
All study period.	

End point values	Evaluable Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: Months				
median (confidence interval 95%)	30.42 (27.27 to 9999999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate (CRR)

End point title	Complete Response Rate (CRR)

End point description:

Complete response rate (CRR) is defined as the proportion of patients who have complete response to therapy.

End point type	Secondary

End point timeframe:

All study period

End point values	Evaluable Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	47			
Units: percent				
number (confidence interval 95%)				
CR+CRi	44.7 (30.0 to 60.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimal Residual Disease (MRD)

End point title	Minimal Residual Disease (MRD)

End point description:

Complete Response Rate according to minimal residual disease

End point type	Secondary

End point timeframe:

From 3 months after end of treatment within 2 years of follow-up

End point values	Evaluable Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	21[2]			
Units: percent				
number (not applicable)				
MDR negative	76.2			
MDR positive	19.0			
Missing	4.8			

Notes:

[2] - CR + CRi

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate according to beta-2 microglobulin

End point title	Complete Response Rate according to beta-2 microglobulin

End point description:

End point type	Secondary

End point timeframe:

All study period

End point values	Evaluable Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	21[3]			
Units: percent				
number (not applicable)				
Beta-2 microglobulin >=4 mg/L	4.8			
Beta-2 microglobulin <4 mg/L	76.2			
Beta-2 microglobulin missing	19.0			

Notes:

[3] - CR + CRi

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All study period: from the signing informed consent up to 28 days after the last dose of study treatment or until all drug-related toxicities had resolved or a new anticancer therapy was started.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5.1

Reporting groups

Reporting group title	PCO combination

Reporting group description:

All patients who receive at least one dose of study medication.

Serious adverse events	PCO combination		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 47 (17.02%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural mesothelioma malignant advanced			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Squamous cell carcinoma			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 47 (4.26%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anaphylactoid reaction			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			

subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 47 (2.13%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	PCO combination		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 47 (100.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 47 (6.38%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	40 / 47 (85.11%)		
occurrences (all)	143		
Anaemia			
subjects affected / exposed	16 / 47 (34.04%)		
occurrences (all)	60		
Thrombocytopenia			
subjects affected / exposed	6 / 47 (12.77%)		
occurrences (all)	11		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Rigors subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all)	16 / 47 (34.04%) 26 8 / 47 (17.02%) 16 7 / 47 (14.89%) 16 6 / 47 (12.77%) 8 3 / 47 (6.38%) 4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all)	 23 / 47 (48.94%) 42 13 / 47 (27.66%) 25 4 / 47 (8.51%) 4 3 / 47 (6.38%) 4		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 8 / 47 (17.02%) 18 6 / 47 (12.77%) 6		
Skin and subcutaneous tissue disorders			

Rash subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	39 / 47 (82.98%) 89 8 / 47 (17.02%) 14 3 / 47 (6.38%) 5		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	5 / 47 (10.64%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2012	The purposes of the protocol amendment are: • To re-define processes related to SAEs management and evaluation of MRD (Minimal Residual Disease), as a result of the delegation of these activities to Nerviano Medical Sciences S.r.l. (NMS). • To remove the list of clinical centers participating in the trial reported in the original protocol since it became out of date; the updated list of participating investigators and relevant clinical centers will be provided as a separate document. • To add the signature of principal investigator and the signature of the relevant investigator by clinical site. • To modify exclusion criterion n. 14, from 'Creatinine Clearance < 70 mL/min' into 'Creatinine Clearance < 60 mL/min'; this better represents the normal condition of renal efficiency in elderly patients. • To add the ofatumumab pharmacokinetic assessment among the secondary study objectives/endpoints, as well as overall survival (OS) and time-to-progression (TTP) for consistency purpose.
07 June 2013	The purpose of the present protocol amendment is: • To modify Ofatumumab Pharmacokinetic Profile Assessment. In order to improve patient compliance and optimize study organization, from April 2013 the number of blood samples collected for pharmacokinetic assessment has been reduced (21 samples required, instead of 33 at all) and timepoints scheduled only during patient's cycles monitoring visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported