SYNOPSIS OF CLINICAL STUDY RESULTS

Name of Sponsor: Niguarda Ca' Granda Hospital **Name of Finished Product:** NA **Name of Active Ingredient:** Pentostatin, Cyclophosphamide, Ofatumumab **Therapeutic Area:** Oncology	*(For National Authority Use only)*
Title of Study: A single-arm multi-center trial of Pentostatin plus Cyclophosphamide with Ofatumumab (PCO) in older patients with previously untreated chronic lymphocytic leukemia	
Protocol Number: PCO	
EudraCT Number: 2010-022332-37	
ClinicalTrials.Gov Number: NCT01681563	
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Study Centers: Presidi Ospedalieri Spedali Civili – Brescia; Città della Salute e della Scienza Ospedale Molinette – Torino; IRCCS Istituto clinico Humanitas – Rozzano; Azienda Ospedaliera San Gerardo – Monza; Ospedale Maggiore Policlinico – Milano; Ospedale Valduce – Como; Policlinico San Matteo – Pavia; A.O. Papa Giovanni XXIII – Bergamo; Azienda ospedaliera-universitaria Maggiore della Carità – Novara; IRCCS Fondazione Centro S. Raffaele del Monte Tabor – Milano; A.O.U. Azienda Ospedaliera Ospedale Civile – Legnano; IRCCS Ospedale Cà Granda - Niguarda – Milano.	
Publication Reference: • M. Montillo, D. Rossi, M. Motta, G. Quaresmini, M. Rossi, M. Coscia, A. Anastasia, F. Rossini, A. Cortellezzi, G. Nador, L. Scarfò, R. Cairoli, D. Dal Ceggio, L. De Paoli, E. Morra, A. Rambaldi, E. Orlandi, M. Massaia, A. Tedeschi. A Phase II Multi-center Trial of Pentostatin plus Cyclophosphamide with Ofatumumab (PCO) in Older Previously Untreated Chronic Lymphocytic Leukemia (CLL) Patients. Blood 122: 4177, 2013 (ASH 2013, December 7-13, 2013, New Orleans, USA) • M. Montillo, D. Rossi, M. Motta, G. Quaresmini, M. Rossi, M. Coscia, A. Anastasia, F. Rossini, A. Cortellezzi, G. Nador, L. Scarfò, R. Cairoli, A.M. Frustaci, D. Dal Ceggio, P. Picardi, L. De Paoli, E. Orlandi, A. Rambaldi, E. Morra, M. Massaia, A. Tedeschi. A Phase II Multi-center Trial of Pentostatin plus Cyclophosphamide with Ofatumumab (PCO) in Older Previously Untreated Chronic Lymphocytic Leukemia (CLL) Patients. Hematologica 99(s1): 61-62, 2014 (19th Congress of the European Hematology Association, June 12-15, 2014, Milano, Italy) • Tedeschi, D. Rossi, M. Motta, G. Quaresmini, M. Rossi, M. Coscia, A. Anastasia, F. Rossini, A. Cortellezzi, G. Nador, L. Scarfò, R. Cairoli, A.M. Frustaci, D. Dal Ceggio, P. Picardi, L. De Paoli, E. Orlandi, A. Rambaldi, M. Massaia, G. Gaidano, M. Montillo. A Phase II Multi-center Trial of Pentostatin plus Cyclophosphamide with Ofatumumab in Older Previously Untreated Chronic Lymphocytic Leukemia Patients. Hematologica 100 (12): e501-e504, 2015; doi:10.3324/haematol.2015.132035	
Studied Period (Years): 2011-2015 **Date of first patient enrolled:** 05 September 2011	**Phase of Development:** 2

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Date of last patient completed/last follow-up: 18 November 2015	

Objectives:

Primary objective:

- To determine whether the PCO combination is effective as first line treatment of older CLL patients as defined by Overall Response Rate (ORR).

Secondary objectives:

- To monitor and assess toxicity of pentostatin, cyclophosphamide, and ofatumumab in patients with previously untreated CLL.
- To determine the progression-free survival in CLL patients treated with pentostatin, cyclophosphamide, and ofatumumab.
- To determine the proportion of patients who achieve a minimal residual disease (MRD) negative state as assessed by flow cytometry.
- To assess the complete response of CLL patients treated with pentostatin, cyclophosphamide, and ofatumumab.
- To determine if molecular prognostic parameters (ZAP-70, CD38, cytogenetic abnormalities identified by FISH, IgVH mutation status) relate to response to PCO therapy.
- To evaluate ofatumumab plasma pharmacokinetics.

Methodology:

This is a phase II multicenter, non-comparative, open label study in older previously untreated CLL patients, requiring therapy, aimed at defining the efficacy profile (ORR, Complete Response Rate [CRR] and Time-To-Progression [TTP]) of pentostatin and cyclophosphamide given in combination with the fully-human anti-CD20 monoclonal antibody ofatumumab specifically designed for untreated CLL patients aged ≥65 years.
Patients with a confirmed untreated B-cell CLL showing an active disease in need of treatment had to received up to 6 cycles pentostatin 2 mg/m^2 IV and cyclophosphamide 600 mg/m^2 IV over 30 minutes on Day 1 and ofatumumab 300 mg IV on Day 1 and 1000 mg IV on Day 8 (Cycle 1) or 1000 mg IV on Day 1 (Cycles 2-6) every 21 days.
The primary endpoint was the overall response rate (ORR) after treatment with pentostatin, cyclophosphamide and ofatumumab, i.e. the number of patients that achieved Complete Remission (CR), CRi (complete remission with incomplete marrow recovery) or Partial Remission (PR) out of the total number of patients evaluable.
Safety assessments (vital signs, hematology, blood chemistry, ECG monitoring and Chest X-ray assessments) were to be performed at baseline (if provided) and repeated at different time points during the treatment period, and at the end of treatment, depending on the parameter. Patients were to be followed for AE from the signing of the 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. Adverse effects were graded with the use of the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
Efficacy assessments were to be based on careful physical examination and evaluation of the peripheral blood and bone marrow as well as, for patients with documented nodal/extramedullary disease, CT scans and abdominal ultrasonography (USG) scans. The evaluation of the treatment outcome and disease progression were to be performed according to the updated criteria of the NCI Sponsored Working Group on CLL and assessed as: CR, CRi , PR, stable disease (SD) and progressive disease. CR required that all criteria were to be assessed at least 2 months after completion of therapy and PR that all parameters were to be documented for a minimal duration of 2 months. In patients achieving a CR, Molecular assessment of Minimal Residual Disease (MRD) was quantified by four-color flow cytometry on peripheral blood samples collected 3 months after the

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last course of treatment with a sensitivity of at least 10^{-4}.
Genetic analyses by FISH and molecular analysis for mutation in IgVH genes by flow cytometry to describe in vivo purging effect of treatment were to be performed at baseline, at the end of treatment and during follow-up at 12 and 24 months.
Plasma samples for evaluation of the pharmacokinetic profile of ofatumumab were to be collected during Cycles 1-6 at different time points, only from patients who signed the specific informed consent for the participation in the ofatumumab PK study.

Number of Subjects (Planned and Analyzed):

It was planned to enroll up to 45 patients with active B-CLL requiring treatment, who didn't received previous therapy. Overall 49 patients were enrolled in the study. Two patients were never treated and went off study for Investigator's decision and consent withdrawal.

Diagnosis and Main Criteria for Inclusion:

Subject Inclusion Criteria

Subjects had to meet all of the following inclusion criteria to be eligible for enrolment into the study:
1. Diagnosis of B-CLL defined by:
   a) Circulating lymphocytes of more than or equal to 5 $x10^9$/L B lymphocytes/L (5000/μL) in the peripheral blood for the duration of at least 3 months.
   AND
   b) Flow cytometry confirmation of immunophenotype: CD5, CD19, CD20, CD23, CD79b, and surface Ig
2. Active disease and indication for treatment based on modified NCI-WG guidelines (Hallek M et al., Blood.; 111 (12):5446-56: Erratum in: Blood. 2008 Dec 15;112(13):5259) defined by presenting at least any one of the following conditions:
- Evidence of progressive marrow failure as manifested by development of, or worsening of anemia and/or thrombocytopenia;
- Massive (i.e. > 6 cm below the left costal margin) or progressive or symptomatic splenomegaly;
- Massive nodes (i.e. > 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy;- Progressive lymphocytosis with an increase of > 50% over a two month period or an lymphocyte doubling time < 6 months;
- A minimum of any one of the following disease-related symptoms must be present:
  a) Unintentional Weight loss ≥ 10% within the previous six months
  b) Fevers > 38.0 °C for ≥ 2 weeks without evidence of infection
  c) Night sweats for more than 1 month without evidence of infection
3. Not been previously treated for B-CLL (prior autoimmune hemolytic anemia treatment permitted)
4. ECOG Performance Status of 0-2
5. Age ≥ 65 years
6. Signed written informed consent prior to performing any study-specific procedures

Subject Exclusion Criteria

The presence of any of the following excluded a subject from study enrolment:
1. Prior therapy for B-CLL with any agent except corticosteroids used to treat autoimmune hemolytic anemia
2. Active autoimmune hemolytic anemia (AIHA) requiring corticosteroid therapy >100 mg equivalent to hydrocortisone, or chemotherapy
3. Known Richter transformation

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4. Known CNS involvement of B-CLL
5. Any radiation therapy ≤ 4 weeks prior to registration;
6. Any major surgery ≤ 4 weeks prior to registration;
7. Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active Hepatitis C
8. Past or current malignancy with the exception of successfully treated basal cell carcinoma of the skin and in situ carcinoma of the cervix or the breast, unless the tumor was successfully treated with curative intent at least 2 years prior to trial entry.
9. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within 6 months prior to Visit 1, congestive heart failure, and arrhythmia requiring therapy, with the exception of extra systoles or minor conduction abnormalities
10. History of significant cerebrovascular disease
11. Glucocorticoid unless given in doses ≤ 100 mg/day hydrocortisone (or equivalent dose of other glucocorticoid) if for exacerbations other than B-CLL (e.g. asthma)
12. Known HIV positive
13. Positive serology for Hepatitis B (HB), defined as a positive test for HBsAg. In addition if negative for HBsAg but HBcAb positive and HBsAb negative a HB DNA test will be performed and if positive the subject will be excluded. Note: if HBcAb positive and HBsAb positive, which is indicative of a past infection, the subject can be included.
14. Screening laboratory values:
    - Creatinine Clearance < 60 mL/min;
    - Total bilirubin > 2.0 times upper normal limit (unless due to liver involvement of BCLL);
    - ALT > 3.0 times upper normal limit (unless due to liver involvement of B-CLL).
15. Treatment with any non-marketed drug substance or experimental therapy within 4 weeks prior to Visit 1 or currently participating in any other interventional clinical study.
16. Known or suspected inability to comply with the study protocol.

Test Product, Dose and Mode of Administration, Batch Number: Ofatumumab, Pentostatin

Ofatumumab is commercially available as a 100 mg and 1000 mg liquid concentrate for solution for IV infusion.

Pentostatin is commercially available as 10 mg powder for IV infusion.

Cyclophosphamide is commercially available as 200 mg, 500 mg and 1000 mg powder for IV infusion.

Patients had to be treated with the following schedule (21-day cycle):

Cycles 1-6
• Pentostatin 2 mg/m2 IV over 30 minutes on Day 1
• Cyclophosphamide 600 mg/m2 IV over 30 minutes on Day 1
• Ofatumumab

Cycle 1: ⇒ 300 mg IV on Day 1
⇒ 1000 mg IV on Day 8
Cycles 2-6: ⇒ 1000 mg IV on Day 1

The ofatumumab infusion required pre-medication, given within 30 minutes to 2 hours prior to the treatment, with acetaminophen, an anthihistamine and a glucocorticoid and a rate of infusion adequate to avoid adverse drug reactions.

Before pentostatin administration patients had to received hydratation.

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Reference Therapy, Dose and Mode of Administration, Batch Number:
NA

Duration of Treatment:
Patients remained on treatment up to 6 cycles of pentostatin, cyclophosphamide, and ofatumumab or until disease progression, patient refusal, consent withdrawal or medical decision.

Endpoints and Criteria for Evaluation:

Primary Endpoint: To assess the ORR using pentostatin, cyclophosphamide, and ofatumumab in patients with previously untreated CLL requiring therapy.

Secondary Endpoints:

- To monitor and assess toxicity of pentostatin, cyclophosphamide, and ofatumumab in patients with previously untreated CLL.
- To assess the complete response rate (CRR) as well as overall survival (OS) and time-to-progression (TTP) of CLL patients treated with pentostatin, cyclophosphamide, and ofatumumab.
- To determine the proportion of patients who achieve a minimal residual disease (MRD) negative state as assessed by flow cytometry.
- To determine the progression-free survival in CLL patients treated with pentostatin, cyclophosphamide, and ofatumumab.
- To determine if molecular prognostic parameters (ZAP-70, CD38, cytogenetic abnormalities identified by FISH, IgVH mutation status) relate to response to PCO therapy.
- To assess ofatumumab pharmacokinetic parameters.

Statistical Methods:

The single stage Phase II protocol was designed to test the null hypothesis that $P \leq 75\%$ versus the alternative that $P \geq 0.90\%$. In other words, it was assumed that if responding patients were 75% or less ($ORR \leq 0.75$), then the tested drug association would not be effective and must be rejected, while, if the proportion responding was 90% or more ($ORR \geq 0.90$), then the tested drug association would be considered effective.

Required sample size was 45 subjects. If the tested drug association was actually not effective, there would be a 4.5% probability of concluding that it was (the target for this value was $\alpha = 5\%$). If the drug was actually effective, there would be a 15.9% probability of concluding that it was not (the target for this value was $\beta = 20\%$), thus the actual power was 84.1%. After testing the drug association on 45 patients in the single stage, if 38 or fewer showed OR, then the tested association would be rejected, whereas, if 39 or more showed OR, then the drug association would be considered effective enough to worth further clinical studies.

All data analyses were performed by the sponsor after the study was completed and the database was released. Statistical programming and analyses were performed using validated statistical software as required.

The statistical analyses were performed as outlined in the Statistical Analysis Plan, which was finalized prior to database lock and was included in the clinical study report for this protocol. The final statistical analysis plan took into account any amendment to the protocol.

Descriptive statistics and graphical evaluation were used for age, Creatinine Clearance (CrCl, to investigate the impact of renal function on toxicity in elderly population), performance status, plus all the demographic variables in all the patients. Distributions of these data were described by median, minimum and maximum, mean and standard deviation. CRR among the cohort was evaluated by percentage and 95% CI. For the whole cohort, progression free survival (PFS), overall survival (OS) and time to response were analyzed by product limit estimation according to Kaplan-Meier; event incidence and incidence rate (with 95% CIs) were also

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calculated. Incidence and incidence rate of infections, and of adverse events of any grade were also calculated with their 95% CI; myelosuppression were evaluated by means of percentage and CI 95%. All prognostic markers correlating with clinical response (OR and CR) were evaluated by Fisher's exact test and by generalized linear model with logit link and Wald's test. Patients were dichotomized on the basis of having a B2M level < 4.0 mg/L or ≥ 4.0 mg/L (since this cutpoint predicts early discontinuation of FCR therapy), and the Fisher's exact test was used to verify the presence/absence of an association with therapy discontinuation in this cohort. In case of absence of association, a ROC analysis would have been carried out with the actual B2M values to evaluate the presence of an alternative cutoff value. As a further evaluation, all the collected variables were compared in the responders and non-responders (for both OR and CR), to look for any possible association or predictive capability of the above variables. Continuous ones were checked by Mann-Whitney U test, while discrete ones were checked by Fisher's exact test.

SUMMARY OF RESULTS:

Disposition of Subjects and Baseline Characteristics:
Between 05 September 2011 and 06 July 2013, 49 patients with a confirmed B-cell CLL showing progressive disease were enrolled and 47 treated at 12 Italian investigational sites. The majority of patients were defined at the study entry as belonging to Binet stage B (37 patients, 78.7%) and RAI classification stage I or II (34 patients, 72.4%); the patients had evidence of progressive marrow failure (13 patients, 27.7%), lymphadenopathy (20 patients, 42.6%), splenomegaly (7 patients, 14.9%) and lymphocytosis (16 patients, 34.0%). The reasons for treatment discontinuation were treatment completed as per protocol (44 patients, 93.6%), adverse event (2 patients, 4.3%; one patient experienced Grade3 nausea, grade 2 vomiting and Grade 1 pyrexia at Cycle 2 and another one Grade 2 hives-urticaria at Cycle 5) and reason not reported (1 patient, 2.1%), while the off-study reasons were completion of study as per protocol (34 patients, 72.3%), disease progression (9 patients, 19.1%), death (2 patients, 4.3%), adverse event and start of a new therapy (1 patient each, 2.1%). The median age was 72 years (min 65- max 83), 66% male, all white race and ECOG PS score of 0 in 38 patients (80.9%), and 1 in 9 patients (19.1%). The median value of creatinine clearance in the treated patients was 75.3 mL/min (min 42.6 – max 112.6). Further biological characteristics of treated patients are reported in Table 1 below.

Table 1. Other disease characteristics

Biological Characteristics		Treated patients (N=47)	
β-2 microglobulin	≥ 4 mg/L	9	19.1
	< 4 mg/L	25	53.2
	Missing	13	27.7
IgHV (peripheral blood)	Mutated	9	19.1
	Unmutated	14	29.8
	Missing	24	51.1
IgHV (bone marrow)	Mutated	9	19.1
	Unmutated	6	12.8
	Missing	32	68.1
FISH (peripheral blood)	Del 11q22+	4	8.5
	Del 13q14+	9	19.1
	Trisomy 12+	6	12.8
	No Mutations	1	2.1
FISH (bone marrow)	Del 17p13+	3	6.4
	Del 13q14+	8	17.0
	Trisomy 12+	2	4.3

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	No Mutations	2	4.3
CD Markers (peripheral blood)	CD5+	33	70.2
	CD19+	34	72.3
	CD20+	27	57.4
	CD23+	31	66.0
	CD79b+	8	17.0
	ZAP70+	7	14.9
CD Markers (bone marrow)	CD5+	35	74.5
	CD19+	36	76.6
	CD20+	30	63.8
	CD23+	37	78.7
	CD79b+	5	10.6
	ZAP70+	8	17.0

%=(n/N)*100

Treatment Exposure:

The 47 treated patients received a total of 273 cycles; the median number of cycles per patient was 6 (min 2- max 6) and the median of treatment duration was 18.9 weeks (min 6 – max 26.9). Treatment was reduced in 4 patients and in one of them for hematological toxicity (2.1%). Treatment delay, reported in 27 patients, was due to hematological toxicity in 16 patients (34.0%) and to liver toxicity in one (2.1%). Ofatumumab administration was omitted in 6 patients (12.8%).

Efficacy Results:

All 47 treated patients were evaluable for efficacy analysis.
The Overall Response Rate and the Complete Response Rate resulted 87.2% (95% CI 74.0%-95.0%) and 44.7% (95% CI 30.00%-60.00%), respectively, with 18 completed responses (CRs), 3 CRs with incomplete recovery (CRi) and 20 partial responses (PRs) observed. The Overall Tumor Response was reported in Table 2.
Overall Survival (OS), Progression Free Survival (PFS) and Time to Progression are reported in Table 3.
Three death were observed with a 2-year OS rate of 95.5% (95% CI 83.1% - 98.9%), as estimate by Kaplan-Meier method. The median of duration of response, evaluated in 41 patients showing CR, Cri and PR, was 25.63 months (min 5.85 – max 30.62+).
Progression Free Survival (PFS) ranged from 1.61 to 32.43+ months, with a median value of 30.42 months (95% CI. 27.27 - -) as estimate by Kaplan-Meier method. Table 3 summarizes the estimate PFS of 47 evaluable patients. The median Time to Progression was 27.27 months (min 1.61+ - max 32.43+).
Twenty–one patients who achieved a CR and a CRi were investigated by four-color flow cytometry on peripheral blood samples for Minimal Residual Disease: 16 resulted negative (76.2%), 4 positive (19.0%) and, for one patient (4.8%), the result was not available (Table 4).
Tumor responses and treatment failure according to baseline clinical characteristics and tumor responses related to dichotomic or continuous prognostic markers are shown in Table 5, Table 6 and Table 7, respectively. None of the prognostic and clinical features considered significantly impacted on tumor response, except the level of β-2 microglobulin below 4 mg/L at baseline that is the only pre-treatment characteristic significantly associated with CR and CRi (P= 0.01). On the base of this result no multifactorial generalized linear model was performed.

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Table 2. Overall Tumor Response

Overall Tumor Response	Evaluable/Treated Patients (N=47	
	n	%
Complete Response	18	38.3
Complete Response with Incomplete Recovery	3	6.4
Partial Response	20	42.6
Stable Disease	3	6.4
Progressive Disease	1	2.1
Missing	2	4.3

%=(n/N)*100

Table 3. Progression Free Survival, Overall Survival and Time to Progression

		Evaluable/Treated Patients
Progression Free Survival (months)	No. of Patients	47
	No. of Events	19
	Death	3
	Progression Disease	16
	Median	30.42
	Median 95% CI - LL	27.27
	Median 95% CI - UL	
	Min	1.61
	Max	32.43+
Overall Survival (Months)	No. of Patients	47
	No. of Events	3
	Median	
	Median 95% CI - LL	30.42
	Median 95% CI - UL	
	Min	1.61
	Max	42.48+
Time To Progression (Months)	No. of Patients	47
	No. of Events	17
	Median	
	Median 95% CI - LL	27.27
	Median 95% CI - UL	
	Min	1.61+
	Max	32.43+

No. of Events: the number of failure patients for the given endpoint.
Median and 95% CI: calculated by the Kaplan-Meier method.

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Table 4. Complete Response Rate according to Minimal Residual Disease (MRD) - Evaluable/Treated Patients

	MDR					
	Negative		Positive		Missing	
	n	%	n	%	n	%
CR + CRi Patients (N=21)	16	76.2	4	19.0	1	4.8

Table 5. Tumor Response and Treatment Failure according to baseline clinical characteristics

			CR + CRi + PR Patients			CR + CRi Patients			Treatment Failure		
			n	%	p-value	n	%	p-value	n	%	p-value
		No of Treated Pts									
Age	<= 70 years	20	18	90.0	1.00	9	45.0	1.00	2	10.0	
	> 70 years	27	23	85.2		12	44.4		4	14.8	
Beta-2 microglobulin	>=4 mg/L	9	6	66.7	0.16	1	11.1	0.01	3	33.3	
	< 4 mg/L	25	23	92.0		16	64.0		2	8.0	
	Missing	13	12	92.3		4	30.8		1	7.7	
Binet Stage	A	1	1	100.0	0.41			0.58			
	B	37	31	83.8		18	48.6		6	16.2	
	C	9	9	100.0		3	33.3				

%=(n/N)*100

Table 6. Tumor Response related to dichotomic prognostic markers

			CR + CRi + PR Patients			CR + CRi Patients		
			n	%	p-value	n	%	p-value
Prognotic markers		Treated Patients (n)						
ZAP70 (peripheral blood)	Positive	7	3	42.9	0.08	1	14.3	0.22
	Negative	5	5	100.0		3	60.0	
ZAP70 (bone marrow)	Positive	8	4	50.0	0.08	2	25.0	0.28
	Negative	6	6	100.0		4	66.7	
IgHV (peripheral blood)	Mutated	9	9	100.0	1.00	6	66.7	0.40
	Unmutated	14	13	92.9		6	42.9	
IgHV (bone marrow)	Mutated	9	7	77.8	0.49	3	33.3	0.62
	Unmutated	6	6	100.0		3	50.0	
FISH - Del17p13 (peripheral blood)	Negative	20	18	90.0		10	50.0	
FISH - Del11q22 (peripheral blood)	Positive	4	3	75.0	0.37	1	25.0	0.58
	Negative	16	15	93.8		9	56.3	

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FISH - Del13q14 (peripheral blood)	Positive	9	9	100.0	0.48	6	66.7	0.37
	Negative	11	9	81.8		4	36.4	
FISH - Del6q (peripheral blood)	Negative	6	5	83.3		3	50.0	
FISH - Trisomy12 (peripheral blood)	Positive	6	5	83.3	0.52	3	50.0	1.00
	Negative	14	13	92.9		7	50.0	
FISH - Del17p13 (bone marrow)	Positive	3	3	100.0	1.00	1	33.3	1.00
	Negative	13	10	76.9		6	46.2	
FISH - Del11q22 (bone marrow)	Negative	16	13	81.3		7	43.8	
FISH - Del13q14 (bone marrow)	Positive	8	6	75.0	1.00	3	37.5	1.00
	Negative	7	6	85.7		3	42.9	
FISH - Del6q (bone marrow)	Negative	12	9	75.0		6	50.0	
FISH - Trisomy12 (bone marrow)	Positive	2	1	50.0	0.37	1	50.0	1.00
	Negative	13	11	84.6		5	38.5	

%=(n/N)*100

Table 7. CRR/ORR related to continuous prognostic marker CD-38

		CD-38		P-value
Prognostic Marker at baseline	n	Mean	SD	
CR + CRi + PR Patients	27	13.2	19.8	0.3734
No CR + CRi + PR Patients	3	24.7	31.4	
CR + CRi Patients	17	16.4	23.3	0.5428
No CR + CRi Patients	13	11.7	17.5	

%=(n/N)*100

Safety Results:

Overall 47 patients were treated and were evaluable for safety. Forty-four patients (93.6%) completed the 6 planned treatment cycles.
All 47 treated patients experienced at least 1 treatment emergent AE in the first or subsequent cycles and 43 patients (91.5%) had at least one drug-related AE.
Overall the most frequent drug related AEs (frequency of ≥ 5%) were rash (34 patients, 72.3%), nausea (21 patients, 44.7%), vomiting (13 patients, 27.7%), neutropenia and pyrexia (10 patients each, 21.3%), rigors (7 patients, 14.9%), fatigue and pruritus (6 patients each, 12.8%) and dyspnea (5 patients, 10.6%).
Treatment emergent drug related Grade 3-4 events occurred in 15 patients (31.9%). They are: neutropenia (5 patients, 10.7%), rash (4 patients, 8.5%), dyspnea (2 patients, 4.3%), nausea, pruritus, diarrhea, febrile neutropenia, laryngeal oedema, liver function test abnormal, lung infection and renal failure acute (1 patient each, 2.1%). Two treatment emergent drug related Grade 5 events were reported: pleural mesothelioma malignant advanced and septic shock.

Eight patients experienced 15 on treatment serious adverse events. Among them 7 patients had 13 serious

Name of Sponsor: Niguarda Ca' Granda Hospital **Name of Finished Product:** NA **Name of Active Ingredient:** Pentostatin, Cyclophosphamide, Ofatumumab **Therapeutic Area:** Oncology	*(For National Authority Use only)*

adverse events drug related: pyrexia (2 patients), anaphylactoid reaction, rash, diarrhea, hypotension, lung infection, myelodysplastic syndrome, pleural mesothelioma malignant advanced, renal failure acute, septic shock and vomiting (one patient each). Three patients died on study, two due to adverse event (pleural mesotelioma malignant advanced and septic shock) and one due to progression disease.

Hematological abnormalities included: leucopenia (39 patients, 83.0%, 29.8% Grade 3-4), neutropenia (37 patients, 78.7%, 55.3% Grade 3-4), lymphocytopenia (33 patients, 63.8%, 27.6% Grade 3-4), anemia (21 patients, 44.6%, 2.1% Grade 3), thrombocytopenia (9 patients, 19.1%, all Grade 1-2). No CTC Grade on treatment was reported for 3 patients each regarding lymphocytopenia and neutropenia.

Blood chemistry laboratory abnormalities were mainly mild to moderate with the exception of two cases of Grade 3 hyperkalemia, one case of Grade 3 hyperglycemia and one case of Grade 4 hyponatremia.

Pharmacokinetic Results:
Since the collected samples were considered not adequate from the qualitative and quantitative point of view, no analyses were conducted.

CONCLUSIONS:

In this study it is confirmed the good tolerability and efficacy of pentostatin and cyclophosphamide in combination with ofatumumab even in an elderly CLL population. Treatment was completed in the majority of patients (93.6%) with no difference when patients were categorized according to age. The Overall Response Rate and the Complete Response Rate resulted 87.2% and 44.7%, respectively, with 18 completed responses (CRs), 3 CRs with incomplete recovery (CRi) and 20 partial responses (PRs) observed. None of the prognostic and clinical features considered significantly impacted on tumor response, except the level of β-2 microglobulin below 4 mg/L at baseline that is the only pre-treatment characteristic significantly associated with CR and CRi (P= 0.01).

Date of the report:

28 June 2017