SYNOPSIS

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Name of Sponsor/Company	Janssen-Cilag Germany GmbH
Name of Finished Product	Velcade®
Name of Active Ingredient(s)	Bortezomib

Protocol No.: 26866138LYM2021

Title of Study: Pilot study with bortezomib in combination with rituximab standard therapy in patients with relapsed or refractory follicular lymphoma and at least 2 previous therapies

EudraCT Number: 2005-003949-14

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Publication (Reference): No publication due to premature termination.

Study Period: FPI 27-02-2006
LPO 27-08-2007
Study closed 02-12-2008
Database locked 02-02-2009

Phase of Development: 2

Objectives: To investigate tolerability and efficacy of bortezomib in combination with rituximab standard therapy in patients with relapsed or refractory follicular lymphoma.

The primary efficacy criterion was time to progression or relapse.

Secondary efficacy criteria were

- tolerability of bortezomib in combination with rituximab standard therapy
- remission status
- disease-free survival
- overall survival

Methods: prospective, open label, multicenter, non-randomized single-arm phase II study. It was planned to enroll 30 patients in about 7 centers. Centers belong to the German Low grade Lymphoma Study Group (GLSG).
Patients with relapsed or, refractory CD-20+ follicular Grad I/II lymphoma stage III/IV with at least 2 previous lines of therapy were to be enrolled.
Each patient could receive a maximum of 3 cycles. Cycle 3 was only to be given in case of stable disease (SD) or partial response (PR) according to remission criteria by Cheson et al1 after cycle 2. The planned duration of a cycle was 35 days. In each cycle the planned dose of bortezomib was 1.6 mg/m² to be given as intravenous bolus injection on days 1, 8, 15 and 22 of the respective cycle, i.e., on days 1, 8, 15 and 22 during cycle 1, on days 36, 43, 50 and 57 during cycle 2, and (if applicable) on days 71, 78, 85 and 92 during cycle 3.
In cycles 2 and (if applicable) 3, injection of bortezomib was to be followed by administration of rituximab in a dose of 375 mg/m² as intravenous infusion.

Number of Subjects (planned and analyzed): 30 patients were to be enrolled. After enrolment of 8 patients the study was closed due to poor recruitment.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

1. Male and female patients with an age from 18 to 70 years
2. Histologically confirmed relapsed/refractory follicular $CD20^+$ lymphoma (grade 1 and 2) of stages III/IV (WHO) that requires therapy
3. Patients in whom treatment with rituximab is planned after ≥ 2 cytostatic previous therapies
4. Written informed consent signed by the patient
5. Women must be either postmenopausal or sterilized; women of childbearing potential had to fulfill the following criteria:
   - consistent and correct use of a safe contraceptive method during and 12 months after completion of treatment (effective contraceptive methods include oral combined contraceptives, depot injections, implants, intrauterine device (“hormone spiral” as combination of mechanical and hormonal contraception), sexual abstinence, partner with vasectomy)
   - negative pregnancy test at screening
6. Men must use a safe contraceptive method during and 12 months after completion of treatment (Cryoconservation of sperms was to be offered to men who want to have children)
7. Karnofsky status ≥ 60%
8. AST (S-GOT) or ALT (S-GPT) below 2.5-fold upper limit of normal
9. Total bilirubin below 1.5-fold upper limit of normal
10. Sufficient hematological function:
    - Leukocytes ≥ 3.0×10^9/l
    - Neutrophil granulocytes ≥ 1.5×10^9/l
    - Thrombocytes ≥ 75×10^9/l
11. Creatinine below 2-fold upper limit of normal

Exclusion criteria:

1. Use of prohibited concomitant medication as specified in the summary of product characteristics
2. Previous treatment with bortezomib within 6 months prior to enrollment
3. Previous treatment with a combination of rituximab and bortezomib
4. Known allergic reaction to bortezomib, boron or mannitol
5. Life-expectancy of less than 3 months
6. Malignant neoplasm (except basalioma) within previous 5 years
7. Patients with peripheral neuropathy CTC-grade ≥ 2
8. Other severe concomitant diseases that do not allow participation in the clinical study according to the investigator’s assessment:
   a) hepatic or renal insufficiency; clinically relevant pulmonary or gastrointestinal diseases
   b) cardiac insufficiency > NYHA II; myocardial infarction in the previous 6 months prior to screening; angina pectoris; cardiac arrhythmias (≥ Lown IVb); electrocardiographic signs of acute ischemia
   c) patients with systemic infection requiring therapy
   d) not adequately controlled hypertension or other clinically relevant vascular disease
   e) not adequately controlled diabetes mellitus or other clinically relevant endocrine disease

9. Patients with hypotension (RR_{sys} sitting ≤ 100 mmHg and/or RR_{dia} sitting ≤ 60 mmHg)
10. HIV-positive patients
11. Patients with active hepatitis B and/or hepatitis C
12. Pregnant or lactating women
13. Not willing or unable to cooperate; predictable problems with follow-up; psychiatric diseases; currently known abuse of alcohol, legal or illegal drugs; legal incapacity

Test Product, Dose and Mode of Administration, Batch No.:

Bortezomib 1,6 mg/m2 i.v. d1+8+15+22 and d36+43+50+57 and if SD/PR:

d70+77+83+90

Rituximab 375 mg/m2 d36+43+50+57 and if SD /PR: d70+77+83+90

Reference Therapy, Dose and Mode of Administration, Batch No.: n/a

Duration of Treatment: Treatment consisted of 2 cycles of 5 weeks. After the second cycle a response evaluation was to be performed. If the patient achieved a complete response (CR) a follow-up period of 1 year began. In the case of progressive disease (PD) the patient was excluded from the study. If the patient achieved SD or PR an additional cycle of 5 weeks was to be applied and a follow-up of 1 year was to be performed.

Exit criteria were:

The study could be terminated for an individual subject if

- an SAE occured.
- the investigator believed that for safety reasons it was in the best interest of the subject to stop treatment.

The study had to be discontinued for an individual subject if
- the subject withdrew his/her consent.
- the subject became pregnant
- progressive disease occurred during treatment phase (cycle 1-3)
- more than 2 weeks delay in start of next cycle

Criteria for Evaluation:

Evaluations had to be performed according to the following flow-chart:

Study period	Enroll-ment[a]	Treatment day per cycle (cycles 1+2: all patients, cycle 3: if PR/SD at staging I)[b]				Staging I cycle 2	Staging II cycle 3	Follow-up period in case of CR/PR/SD		
Study day (d)/ Study week (w)		d1/36 (d71)	d8/43 (d78)	d15/50 (d85)	d22/57 (d92)	final ex. w10 terminat.	final ex. w15 terminat.	6-month FU[o]	9-month FU[o]	12-month FU[o]
Informed consent	X									
Demogr. data / med. history	X									
Check in-/exclusion criteria	X									
Karnofsky performance status	X					X	X	X	X	X
Vital parameters[c]	X	X*	X*	X*	X*	X*	X*			
Physical examination[d]	X	X*				X*	X*			
Previous treatm. of foll. lymphoma	X									
Planned measures/operations	X									
ECG	X									
CT neck, chest, abdomen	X					X	X	X	X[e]	X
CT skull[f]	X									
Bone marrow biopsy / aspirate	X					X[g]	X[g]			
Lumbar puncture[f]	X									
Hematology	X[h]	X[h]	X[i]	X[i]	X[i]	X[h]	X[h]	X[h]	X[h]	X[h]
Blood chemistry	X	X				X	X	X	X	X
Immunoglobulins in serum (quant.)	X					X	X	X		X
Pregnancy test[k]	X									
Weight (plus height at d1 of cycle 1)		X								
BSA		X								
Admin. of bortezomib		X	X	X	X					
Admin. of rituximab (from cycle 2 on)		X	X	X	X					
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Adverse events[m]		X	X	X	X	X	X	X	X	X

Study period	Enroll-ment[a]	Treatment day per cycle (cycles 1+2: all patients, cycle 3: if PR/SD at staging I)[b]				Staging I cycle 2	Staging II cycle 3	Follow-up period in case of CR/PR/SD		
Remission status						X[n]	X	X	X	X

a within 14 days prior to start of therapy; laboratory within 7 days prior to start of therapy
b treatment is repeated in every cycle; deviations by ± 1 day are allowed
c blood pressure, pulse, temperature
d including neurological, peripheral neurological and urine examination
e CT after 9 months only if required to confirm CR
f if clinically indicated
g in case of initial involvement
h hemoglobin, hematocrit, erythrocytes, leukocytes, thrombocytes, with differential white blood count
i hemoglobin, hematocrit, erythrocytes, leukocytes, thrombocytes
j urea in serum, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), CRP, LDH, ß2-microglobulin, glucose, calcium, potassium; if clinically indicated weekly controls are recommended but not documented
k women of childbearing age
l administration of rituximab (in cycles 2 and 3) immediately after administration of bortezomib
m in case of premature study termination documentation for up to 30 days after last administration of bortezomib
n In case of CR the final examination is performed and the 1-year follow-up is started (1 year = 1 year after enrollment); in case of PR or SD cycle 3 is started; thereafter the final examination is performed and the 1-year follow-up is started; in case of PD the final examination is performed and the study is over.
o 6, 9 and 12 months after enrollment; deviations by ± 1 week are allowed
* adverse clinically relevant changes are documented as “adverse events” in the CRF

Response was evaluated according to response criteria published by Cheson et al.[1].

Statistical Methods: It was planned to enroll 30 patients which is a common sample size in oncological phase II studies. With such a sample size the probability to observe events with a true incidence of 5% at least once is almost 80% (78.5%). Events with a true incidence of 10% are observed at least once with a probability of more than 95% (95.8%). With such a sample size, proportions (e.g., for CR/PR or relevant toxicities) can be estimated with a precision of ± 20%-points (95% confidence intervals according to Pearson and Clopper).

This was regarded as sufficient for a preliminary assessment of tolerability and efficacy of bortezomib in combination with rituximab.

RESULTS:

The present trial was terminated prematurely with only 8 patients having been enrolled.

5 patients have been withdrawn from study treatment: one subject withdrew consent, one due to progressive disease, in one subject a transformation to high grade NHL was observed before receiving study medication, one patient showed secondary malignoma and one for protocol violation. 3 patients completed treatment phase and entered follow-up period.

Study Completion/Withdrawal Information
(All Randomized Subjects Analysis Set)

	Total (N= 8) n (%)
Completed	3 (37.5%)
Withdrawn	5 (62.5%)
Subject choice (subject withdrew consent)	1 (12.5%)
Lost to follow-up	0
Adverse event	0
Progressive disease	1 (12.5%)
Protocol deviation	1 (12.5%)
Other	2 (25%)

Demographic And Baseline Characteristics (Intent-to-Treat Analysis Set)

	(N=8)
Sex, n (%)	
N	8
Male	5 (62.5)
Female	3 (37.5)
KPS	
N	8
Mean (SD)	91.3 (9.9)
Median	90
Range	(70;100)
Weight, kg	
N	7
Mean (SD)	79.4 (16.4)
Median	83.0
Range	(60;99)

EFFICACY RESULTS: Regarding tumor response at final examination 3 out of 8 patients had a PR, 1 had a SD and 1 had a PD. For 3 patients tumor response was not evaluable. 1 patient has never received study medication due to transformation into secondary high-grade NHL.

SAFETY RESULTS:

Subjects With Adverse Events/Reactions

	(N= 8) n (%)
One or more adverse events	8 (100)
One or more serious adverse events	4 (50)
Deaths	1 (12.5)
Treatment stopped due to adverse events	2 (25)

Most Frequent Adverse Events That Occurred in at least 2 Patients

Adverse Event	All AEs	
	N	%
Diarrhoea	5	62.50
Constipation	4	50.00
Nausea	4	50.00
Abdominal pain	3	37.50
Asthenia	3	37.50
C-reactive protein increased	3	37.50
Dyspnoea	3	37.50
Fatigue	3	37.50
Oedema peripheral	3	37.50
Chills	2	25.00
Herpes zoster	2	25.00

Neoplasm progression	2	25.00
Paraesthesia	2	25.00
Pyrexia	2	25.00
Thrombocytopenia	2	25.00
Vomiting	2	25.00

The present trial was terminated prematurely at 12/01/2008 because of poor recruitment with only 8 patients having been enrolled.
Overall, 13 SAEs were documented in 4 patients (50%). In one patient with a fatal outcome (12,5%) 5 SAEs occurred (38.46%). Other 5 out of 13 SAEs (38.46%) were recovered with sequelae in 4 patients , two SAEs (9.09%) were recovered without sequelae and one SAE was still persisting. 5 out of 13 SAEs (38.46%) were considered at least possibly related to bortezomib in 3 out of 4 patients and only one SAE was considered at least possibly related to Rituximab. Within those 8 patients no previously unknown (unexpected) SAEs related to bortezomib were documented. The fatal outcome in one patient was due to progression of the underlying disease and acute renal failure, both unrelated to study medication .

STUDY LIMITATIONS: Due to early termination of this study for poor recruitment no valid scientific evaluation of the combination therapy with bortezomib and rituximab in advanced follicular lymphoma can be made.

CONCLUSION: 5 patients were evaluable for disease staging. In 1 patient progressive disease was diagnosed at staging I. In 3 patients partial response was documented at staging 2 and for one patient stable disease as final response was reported. This corresponds with a response rate (CR+PR) of 60%.

With respect to safety a rather high rate of infections was documented although most of them were mild or moderate. Rate of polyneuropathy was consistent with previous data. 2 out of 3 patients with hematotoxic events had signs of decreased hematopoesis already at screening.

Since only 8 patients were included in this trial and only 5 patients were evaluable for staging, it seems to be too early to draw final conclusions. Further investigations are needed.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations

abbreviation	description of abbreviated term
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
B-CLL	B cell chronic lymphocytic leukaemia
BMI	Body Mass Index
CD	Cluster Designation
CHOP	Cyclophosphamide + doxorubicine + vincristine + prednisolone
COP	Cyclophosphamide + vincristine + prednisolone
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogramme
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
IB	Investigators Brochure
Ig	Immunoglobuline
IPI	International Prognostic Index
ITT	Intention to treat
KPS	Karnofski Performance Score
LAF	Local Administrative File
LDH	Lactate Dehydrogenase
MAX	Maximum
MED	Median
MIN	Minimum
MV	Arithmetric mean
NHL	Non Hodgkin Lymphoma
NYHA	New York Heart Association
OTC	Over the counter
PD	Progressive Disease
PR	Partial Response
SD	Stable Disease

Definitions of Terms

Term	definition of term