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**WEEKLY VERSUS TWICE WEEKLY BORTEZOMIB GIVEN IN
CONJUNCTION WITH RITUXIMAB IN PATIENTS WITH
RECURRENT FOLLICULAR LYMPHOMA, MANTLE CELL
LYMPHOMA AND WALDENSTRÖM
MACROGLOBULINAEMIA**

Athos Agathocleous, Ama Z Rohatiner, Simon Rule, Hannah Hunter, Jonathan Paul Kerr, Sally Neeson, Janet Matthews, Sandra Strauss, Silvia Montoto, P W M Johnson, et al.

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LYMPHOMA AND WALDENSTRÖM MACROGLOBULINAEMIA**

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Key Words:	Bortezomib, Rituximab, B-cell malignancies

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11 Agathoclis, Agathocleous¹, Ama Rohatiner¹, Simon Rule², Hannah Hunter²,

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14 Johnson³, John Radford⁴, Andrew Lister¹.

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44 *Running Short Title: bortezomib + rituximab in B-cell malignancies*

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SUMMARY

The combination of bortezomib and rituximab was evaluated in mantle cell lymphoma (MCL), follicular lymphoma (FL) and Waldenström macroglobulinaemia (WM), in a Phase I and later, a randomised Phase II study. In the latter, 42 patients with recurrent/refractory disease received either: bortezomib 1.3mg/m² on days 1,4,8 and 11 of a 3-week cycle with rituximab 375mg/m² on day 1,(21 patients) or: bortezomib 1.6mg/m² and rituximab on days 1, 8,15 and 22 of a 5-week cycle (with rituximab being given only in cycles 1 and 4).Twenty-eight patients were withdrawn (toxicity 16, progression7, and 'patient choice' 5). The main toxicities were neurological, gastro-intestinal and haematological. The overall response rate was 28/42(67%) and by histology: MCL 11/19, FL 8/15, and WM 9/10. Ten of 28 responding patients remain progression-free at 1-3.5 years. Toxicity and efficacy were equivalent between the two groups. The combination has significant toxicity but is effective, particularly in patients with WM.

Keywords: bortezomib, rituximab, B-cell malignancies



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- Comment [A1]:** Suggest supplying the number of patients with each
- Comment [A2]:** It might be more clear to say days 1, 4, 8, 11 of a 21-day cycle
- Comment [A3]:** Same as previous comment: suggest providing the day# and total cycle length in days
- Comment [A4]:** Do you mean more than one third of patients? Consider using a percentage rather than a fraction.
- Comment [A5]:** This is a bit hard to follow: since the study is comparing arms, consider presenting results by arm instead of , or as well as, overall.
- Comment [A6]:** This sentence should be clarified and split. Would clarify that the subsequent ratios just refer to response (not CR), and that the ratios by histology represent both groups combined.
- Comment [A7]:** There's been no mention of the common or significant toxicities-suggest adding a sentence about them.
- Deleted:** The proteasome inhibitor, Bortezomib, is active in follicular lymphoma (FL), mantle cell lymphoma (MCL) and Waldenström macroglobulinaemia (WM). Standard treatment for FL and MCL now includes rituximab. The combination was evaluated in a Phase I and subsequently a , randomised Phase II study. In the latter, 42 fForty-two patients with recurrent/refractory FL, MCL(19),FL(13), or WM (r10) received either: Bortezomib 1.3mg/m² on days 1,4,8 and 11 of a 21-day cyclex2/week, for two consecut[... [1]
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INTRODUCTION

The concept of 'targeted' therapy, first proposed by Ehrlich (1890) came to fruition in the management of malignant lymphoma with the demonstration of single-agent efficacy for the monoclonal antibody, anti-CD20 (rituximab) in B-cell malignancy. Most effective, and licensed originally for use alone, in follicular lymphoma (FL) (McLaughlin *et al*, 1998; Hainsworth *et al*, 2000 Hainsworth *et al*, 2002; & Witzig *et al*, 2005), it also induces responses in mantle cell lymphoma (MCL) (Foran *et al*, 2000; Ghielmini *et al*, 2005 & Tobinai, 2002), and Waldenström macroglobulinaemia (WM) (Treon *et al*, 2001; Dimopoulos, *et al* 2002; Gertz *et al*, 2004 & Treon *et al*, 2005). The limited toxicity profile makes it an ideal partner for cytotoxic chemotherapy and 'chemo-immunotherapy' has now been shown to prolong not only freedom from recurrence but also survival in FL (Marcus *et al*, 2005; Hiddeman *et al*, 2005; Kropff *et al*, 2005; van Oers *et al*, 2007; Herold *et al*, 2007). Several studies in MCL have likewise shown a significant advantage for the addition of rituximab in terms of response rate, complete response rate and 'time to treatment failure' (Howard *et al*, 2002 & Lenz *et al*, 2005), but only one has thus far shown a survival advantage (Forstpointner *et al*, 2004).

The proteasome and in particular, the NFκB pathway is also a potentially attractive target in malignant lymphoma (de Martino *et al*, 1999 & Adams *et al*, 1999). A phase I study of the proteasome inhibitor, bortezomib in patients with refractory haematological malignancy identified a feasible dosing schedule, the most debilitating clinical toxicities being fatigue and

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3 mostly reversible, but sometimes painful, peripheral neuropathy;
4 thrombocytopenia was also observed (Orlowski *et al*, 2002) . Evidence of
5 efficacy was most impressive in multiple myeloma but responses were
6 also seen in FL, MCL and WM (Orlowski, *et al*, 2002).
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12 In subsequent phase II studies, bortezomib was generally given twice
13 weekly, at doses ranging from 1-1.6mg/m². Activity was observed in
14 patients with FL who had received multiple previous therapies (Di Bella *et*
15 *al*, 2008; O'Connor *et al*, 2005 & Strauss *et al*, 2006) and in MCL,
16 (O'Connor *et al*, 2005; Goy *et al*, 2005 & Strauss *et al*, 2006). However, a
17 subsequent multi-centre trial (in MCL) suggested a rather lower response
18 rate (31%), with a median duration of response of 9 months in a heavily
19 pre-treated population (Fisher *et al*, 2006). Again, the principal toxicities
20 were gastro-intestinal tract symptoms, peripheral neuropathy and
21 thrombocytopenia (O'Connor *et al*, 2005; Strauss *et al*, 2006; O'Connor
22 *et al*, 2007; Goy *et al*, 2005; Fisher *et al*, 2006; Gerecitano *et al*, 2009 &
23 de Vos *et al* 2009).
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40 Bortezomib has also been shown to be highly active in WM. On the
41 basis of *in vitro* data, using cell lines and cells from patients with WM
42 (Mitsiades *et al*, 2003; Roccaro *et al*, 2007; Leleu *et al*, 2007), the drug
43 was first used alone, in patients with recurrent or refractory disease.
44 Unusually for such a patient population, 'major response' rates (Kimby *et*
45 *al*, 2006) of >50% were observed (Treon *et al*, 2007; Chen *et al*, 2007;
46 Dimopoulos *et al*, 2005 & Goy *et al*, 2005).
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On the basis of these preliminary results, a phase I/II randomised study of bortezomib given in conjunction with rituximab was initiated at four hospitals in the United Kingdom. The objective was to compare two different doses and schedules of administration of bortezomib in patients with recurrent and/or refractory FL, MCL and WM.

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DESIGN AND METHODS

Study design

The protocol was approved by the Ethics Committees of the four participating hospitals; all patients gave informed consent. The study was carried out under the auspices of the NCRI Lymphoma Clinical Studies Group.

This was originally conceived as a phase I/II study, the objective of the phase I component being to determine the optimal weekly or twice-weekly dose of bortezomib when given in conjunction with rituximab. However, after the first 7 patients had been treated (in the Phase I component), in the light of data from a phase II study conducted in the United States, (Leonard *et al*, 2005) the protocol was amended to proceed directly to the randomised phase II component. The primary end points were: toxicity, which was monitored at each visit (using WHO criteria) and overall response rate. Secondary end points were freedom from progression and survival.

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The total number of patients in the Phase II part of the study was based on the following considerations: assuming a 50% response rate to rituximab alone (from historical, control data), in order to demonstrate that the combination of bortezomib + rituximab was more effective than antibody alone, 20 patients were to be treated initially. If 16 responses were seen, a further 20 patients would be recruited. If between 7 and 15 responses were seen, a further 30 would be required. The planned interim analysis was duly conducted after 20 patients had been entered. On the basis of the safety and efficacy data, the decision was made to continue.

Response was assessed at the end of 4 cycles in arm A and after 3 cycles in arm B (please see below) and one month after completion of therapy. Patients deemed to have 'stable disease' completed planned therapy (unless withdrawn because of subsequent progression, toxicity or 'patient choice'). For patients withdrawn from the study for any reason, formal assessment of response was undertaken at the time of that decision.

Patients

Fifty patients were originally recruited, one withdrew before starting treatment and has therefore been excluded from the analysis. Thus a total of 49 patients, 7 in the phase I component and 42 in the phase II

form the basis of this report. Clinical characteristics at the time of study entry are shown in Table 1. Histological sub-types comprised: MCL: 21, FL: 17 and WM: 11. The median number of prior treatments was 2, range 1-7. Thirty-six of the 49 patients had bone marrow infiltration at the time of study entry; nine had previously received high-dose treatment supported by autologous peripheral blood progenitor cells.

Treatment

Phase I component: the first 7 patients were randomly allocated to receive bortezomib intra-venously (i/v), at the following doses: in Arm A:

0.7mg/m² (3 patients) and 1mg/m² (2 patients), twice weekly, or in arm B: 1.3mg/m² (2 patients), weekly.

Phase II component: Forty-two patients were randomised to receive one of two different doses and schedules of administration as shown in Figure I. Arm A comprised: bortezomib given at a dose of 1.3mg/m² i/v, on days 1,4,8 and 11, of a 21-day cycle, to a maximum of 8 cycles, rituximab :375mg/m² being given on day 1. In arm B, bortezomib was given at a dose of 1.6mg/m² on days 1, 8, 15 and 22 of a 35-day cycle, to a maximum of 6 cycles. In order for the total dose of rituximab to be equivalent, the antibody was given on the same days as bortezomib but only in cycles 1 and 4 (i.e. a total of 8 infusions in both arms of the study)

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Definitions

Standard response criteria were applied for patients with FL and MCL (Cheson *et al*,1999). Response in patients with WM was assessed using the Fourth International Workshop Criteria (Kimby *et al*, 2006). Progression-free survival is the interval between the date of assessment of response and evidence of progression. Overall survival is the interval from the time of commencing trial therapy until death or date of last follow-up.

RESULTS

Phase I Component:

In general, toxicity was minimal, **however**, one patient with bone marrow infiltration at the time of starting treatment was withdrawn after the first cycle due to prolonged thrombocytopenia and concurrent progression. There was no evidence of response in the 6 other patients at the designated time of evaluation, although one patient with WM subsequently had a continuing decline in paraprotein from 26 to 10 g/L over a three year period, only having evidence of progression after a period of 4 years. Four of the 7 patients are alive, 2 having had further treatment.

Phase II Component:

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ARM A (total - 8 cycles)¶

Bortezomib: 1.3mg/m² i.v. on days

1, 4, 8 & 11 of a 21-day cycle.¶

Rituximab : 375mg/m² i.v. infusion

on day 1 of each cycle¶

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ARM B (total - 6 cycles)¶

Cycles 1 and 4¶

. Bortezomib:1.6mg/m² i.v. on days 1,

8, 15 and 22 of a 35-day cycle¶

. . Rituximab : 375mg/m² i.v. infusion

. (on same days as above)¶

Cycles 2, + 3,5 and 6 . ¶

Bortezomib:1.6mg/m² i.v. on days 1,

8, 15 and 22, as aboveas above¶

Cycle 4 . Bortezomib:1.6mg/m² i.v. as

above . . ¶

Rituximab: 375mg/m²

i.v. inf. on same days as above¶

Cycles 5 + 6 . Bortezomib:1.6mg/m²

i.v. as abovabove¶

Definitions¶

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Following a satisfactory interim analysis of the results for the first 19 patients (one having been withdrawn prior to starting treatment), a further 23 were recruited.

Clinical Toxicity (Table 2)

There were no deaths directly related to the therapy, although two patients died of infection after the blood count had recovered. Planned therapy was however completed in only 14/42 patients. Twenty-eight were withdrawn for the following reasons: toxicity:16, progressive lymphoma: 7 and 'patient choice': 5. Four of the patients in the latter group asked to be withdrawn because they found the side effects unacceptable.

Comment [A10]: Should clarify what this means- Where there were intolerable AE's, were the unsatisfied with the responses, etc?

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The number of patients withdrawn from each arm of the study because of toxicity and the specific reasons for cessation of treatment according to arm are shown in Table III; they were approximately equivalent. Overall, grade 1 or 2 neurotoxicity was observed in 43% of patients treated twice weekly and 48% of those receiving treatment weekly. Grade 3 or 4 neurotoxicity (in most cases, painful neuropathy) developed in 14% and 19% of patients in the 2 groups respectively. In all cases it was reversible. Three patients were withdrawn from the trial because of gastro-intestinal (g/i) tract toxicity. Overall, grade I or 2 g/i toxicity was observed in 48%(nausea) and 52% (diarrhoea) patients receiving twice weekly treatment and 62% and 62% of patients receiving bortezomib weekly.

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Comment [A11]: What were the common manifestations of the G3-4 PN events?

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Comment [A12]: Did this result in dose reductions or delays?

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7 *Haematological toxicity (Table 2),*

8 Grade 1 or 2 toxicity occurred in more than one third of patients, being
9 observed equally in the two arms of the study. There was a trend for
10 Grade 3 or 4 haematological toxicity to be more severe in arm A, in which
11 bortezomib was given twice weekly, but no significant difference.
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13 Treatment was delayed in 14 patients, by 1-21 days, for various reasons
14
15 but only in 2 cases because of neutropenia or thrombocytopenia.

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19 **Comment [A14]:** As above-what
about neuropathy?

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23 *Response (Table 3)*

24 The overall response rate was 28/42 (67%) with seven complete
25 responses (CR) and 21 partial responses (PR) being observed. **The**
26 **response rate (CR + PR) was identical in the two treatment groups,**
27 **namely, 14/21 (67%) in each arm. There was no significant**
28 **difference in CR rate.**

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38 In terms of histological subtype, the response rates were, as follows,
39 MCL: 11/19 (58%), FL: 8/15 (53%) and WM: 9/10 (90%). Twelve of the
40 14 patients who completed the planned therapy responded (3 CR, 9 PR),
41 as did 16 (4 CR, 12 PR) of the 28 patients who did not complete
42 treatment (7 because of disease progression). Sixteen of the latter 28
43 had been withdrawn because of toxicity, but 12/16 responded. (including
44 6/8 withdrawn specifically because of neuropathy) . In addition, four out
45 of five patients withdrawn because of 'patient choice' had a PR.
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Progression-free survival

Ten of the 28 patients who responded remain well without progression between 1 and 3.5 years. Four patients with WM remain asymptomatic without further treatment for between 2 and 2.5 years, five have progressed, (progression being defined as a >25% increase in the M band).

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Overall Survival (Fig. 2)

Twenty-two of the original 42 patients remain alive, between 1.4 and 4 years, 10 without progression. Twelve patients have developed recurrent lymphoma but 10 of them remain well, (8 without further treatment and 2 having gone on to receive a reduced intensity allograft). Twenty patients have died, 16 following progression of lymphoma (8 having had further treatment. Four patients died without evidence of progression, 2 of pneumonia (one with a history of COPD), one of secondary acute myeloblastic leukaemia and one as a consequence of previous therapy.

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this (patient not at Barts).

Survival curves according to treatment arm are shown in Fig.2

DISCUSSION

These results, evaluating the combination of bortezomib and rituximab in B-cell malignancies show that the weekly and twice-weekly schedules,

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designed to deliver the same total amount of both drugs yield the same results in terms of both ~~toxicity and efficacy~~. **Although outcome assessment was performed at somewhat different timepoints (the total duration of treatment being longer in Arm B), this is unlikely to confound the response rates since the discrepancy is only 6 weeks.**

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The results are in keeping with data from most other studies in which bortezomib has been combined with conventional chemotherapy in other settings (Barr *et al*, 2009, Ribrag *et al*, 2009; Sehn *et al*, 2009 & Leonard *et al*, 2005). One report has however suggested that when combined with rituximab, bortezomib is better tolerated and has greater efficacy when given weekly, to patients with recurrent or refractory follicular or marginal-zone lymphoma, (de Vos *et al*, 2009). Conversely, it was concluded in a phase II study of bortezomib given alone, weekly, (Gerecitano *et al*, 2009) that whilst the latter schedule was less toxic than twice-weekly bortezomib, (O'Connor *et al*, 2005) the overall response rate was inferior, with no complete remissions in patients with recurrent FL and MCL.

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Nonetheless, despite this, ~~the considerably greater ease of giving treatment on a weekly basis~~, provides a compelling argument for adopting this schedule in the future, certainly when the drug is being given in conjunction with rituximab.

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Two recent Phase II studies using bortezomib in combination with bendamustine and rituximab, in patients with recurrent/refractory 'indolent' and mantle cell lymphoma (Friedberg *et al*, 2009), and

specifically, recurrent follicular lymphoma (Fowler *et al*, 2009) have reported high response rates (79% and 86% respectively), with complete responses being observed in >50% of patients. Bortezomib has also recently been combined with 'CVAD' (Kahl *et al*, 2009) and 'R-CHOP' (Ruan *et al*, 2009) in newly-diagnosed patients with mantle cell lymphoma with very high response rates and CR rates of >70%.

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It is heartening for all three subtypes of lymphoma, that the results appear better than those reported in almost all studies for either drug given alone, in similar circumstances. Certainly, the combination warrants further evaluation. Particularly encouraging are the findings in the small number of patients with WM. Whilst no complete remissions were observed, partial responses were observed in 9/10 patients and 4 of the patients who responded continue well, transfusion-free without progression, between 2 and 2.5 years following completion of therapy.

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Similar results have recently been reported in two studies from the Dana Farber Cancer Institute (Ghobrial, in press, 2010, & Treon *et al*, 2009).

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In the first of these, in newly diagnosed patients, dexamethasone was included and in an illness where previously, complete responses were virtually never seen, a small number of patients entered CR and the 'major response' rate was 83%. A phenomenon specific to WM is reflected in the most recent classification of response in this illness (Kimby *et al*, 2006). It is now recognised that responses to Bortezomib when given in conjunction with rituximab may occur late and may

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3 continue for several years, as was the case in one patient with WM
4 treated in the Phase I component of the study.
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9 Against this background, the toxicity of the treatment is of paramount
10 importance. Whilst meaningful responses were observed in the majority
11 of patients withdrawn from the study, for whatever reason, it is disturbing
12 that only 14/42 patients were able to complete the planned therapy. A
13 quarter developed 'intolerable' side effects, the most serious being
14
15 painful peripheral neuropathy, and treatment was therefore stopped
16 without prior dose reduction. **The incidence and severity of**
17 **neuropathy were similar in the two groups of patients. Equivalent**
18 **degrees of neurotoxicity have likewise been observed in other**
19 **reports where bortezomib has been given once or twice weekly**
20 **(O'Connor et al, 2005; Strauss et al, 2006; O'Connor et al, 2007; Goy**
21 **et al, 2005; Fisher et al. 2006; Gerecitano et al, 2009 & de Vos et al**
22 **2009).**
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Comment [A18]: Did patients receive dose reductions first, and then proceed to discontinuation, or were they just discontinued? Also, what were the manifestations (i.e., pain, others) leading to d/c?

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37 Even though largely reversible, as in myeloma (San Miguel *et al*, 2006),
38 the neuropathy was distressing and debilitating for a significant
39 proportion of patients, as was the case for similarly pre-treated patients
40 with lymphoma in another report (de Vos *et al*, 2009). Very close
41 monitoring and asking patients specifically about symptoms of 'early'
42 neurotoxicity, with appropriate treatment modification is mandatory and
43 may reduce the severity of the problem (Richardson *et al*, 2006).
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It may be concluded that overall, these results give strong support to further investigation of bortezomib and rituximab in malignant lymphoma, particularly in patients with WM.

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Authors' Contributions

TAL, AR, SR, PJ, and JR are the principal physicians, and take primary responsibility for the paper. AR and TAL wrote the paper. TAL, AR, SR, PJ, JR, AA, HH, SN, SS, and SM were involved in the care of the patients. AA and TAL compiled and analysed the data. All authors reviewed the manuscript.

Conflicts of interest

JR has participated in Advisory Boards for Millenium Pharmaceuticals and for Roche and is a stockholder of Glaxo-Smith-Kline (GSK).

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PJ has participated in Advisory Boards for GSK and for Roche, and receives research funding from Janssen Cilag and from Johnson and Johnson.

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SR has participated in Advisory Boards for Roche and GSK and receives research funding from Johnson and Johnson.

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Table 1. Clinical characteristics¶

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Patient Characteristics	Phase I	Phase II	Phase II	
	(7 pts.)	(42 pts.)	Arm A	Arm B
			(21 pts.)	(21 pts.)
Age, median (range)	54 (45-67)	60 (46-79)	60 (46-79)	61 (51-77)
Gender				
Male : Female	3 : 4	30 : 12	15 : 6	15 : 6
Histological Subtype				
Mantle Cell lymphoma	2	19	9	10
Follicular Lymphoma	4	13	6	7
Waldenström Macroglobulinaemia	1	10	6	4
WHO Performance Status				
0	3	22	11	11
1	4	14	6	8
2	0	6	4	2
Serum LDH				
Normal : Elevated	4 : 3	21 : 21	9 : 12	12 : 9
Stage				
I	1	0	0	0
II	0	3	1	2
III	0	7	3	4
IV	6	31	16	15
Bone Marrow involvement	5	31	16	15
Number of Prior Treatments				
Median (Range)	4 (1-4)	2 (1-7)	2 (1-7)	2 (1-7)
<2	1	11	6	5
2-3	2	21	12	9
>3	4	10	3	7
High-Dose Therapy	4	5	2	3

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Table III. Toxicity necessitating withdrawal from trial (Arm A vs. B)

Toxicity	Arm A	Arm B	Total
Neuropathy	5	3	8
GI	2	1	3
Haemorrhage	0	1	1
Chest infection	0	2	2
Cardiac	0	1	1
Fatigue & Lethargy	1	0	1
Total	8	8	16

Table IV. Response to treatment in Phase II component of trial

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Response	Arm A Velcade 1.3mg/m ² x 2/week	Arm B Velcade 1.6mg/m ² Weekly	Total
CR	3	4	7
PR	11	10	21
'Stable Disease'	2	4	6
Progression	5	5	10
Total	21	21	42
ORR	67%	67%	67%

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Table V. Response rate according to histological subtype in Phase II component of trial

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Response	Mantle Cell Lymphoma	Follicular Lymphoma	Waldenström Macroglobulinaemia
CR	3	4	0
PR	8	4	9
'Stable disease'	0	4	1
Progression	8	3	0
Total	19	15	10

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Fig.1. Treatment in Phase II component of trial

ARM A (total - 8 cycles)

Bortezomib: 1.3mg/m² i.v. on days 1, 4, 8 & 11 of a 21-day cycle.

Rituximab : 375mg/m² i.v. infusion on day 1 of each cycle

ARM B (total - 6 cycles)

Cycles 1 and 4

Bortezomib:1.6mg/m² i.v. on days 1, 8, 15 and 22 of a 35-day cycle

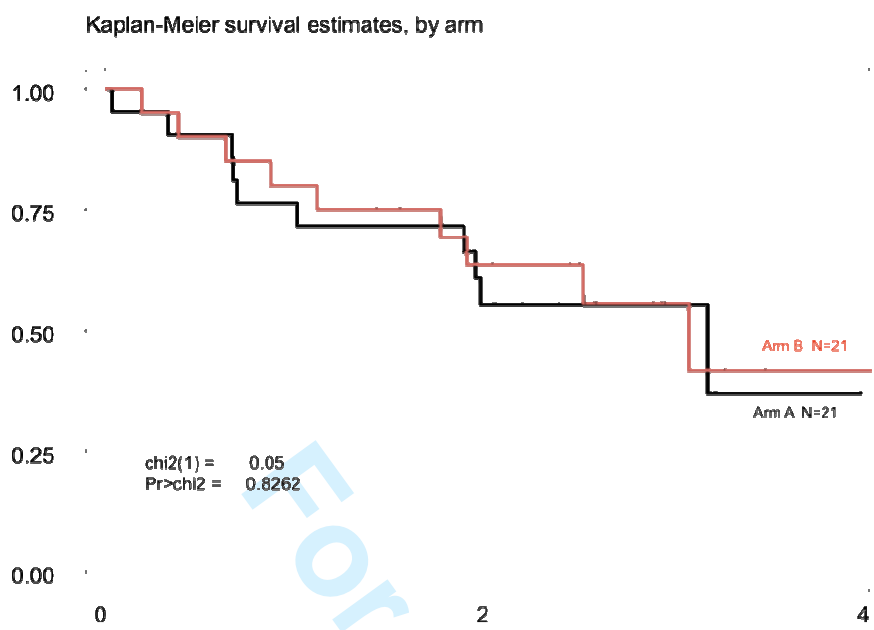
Rituximab : 375mg/m² i.v. infusion (same days as above)

Cycles 2,3,5 and 6

Bortezomib:1.6mg/m² i.v. on days 1, 8, 15 and 22, as above

Fig.2

Survival of patients treated with Velcade & Rituximab



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The proteasome inhibitor, Bortezomib, is active in follicular lymphoma (FL), mantle cell lymphoma (MCL) and Waldenström macroglobulinaemia (WM). Standard treatment for FL and MCL now includes rituximab. The combination was evaluated in a Phase I and subsequently a , randomised Phase II study. In the latter, 42 fForty-two patients with recurrent/refractory FL, MCL(19),FL(13), or WM [A1](r10) received either: Bortezomib 1.3mg/m² on days 1,4,8 and 11 of a 21-day cyclex2/week, for two consecutive weeks of a 21-day cycle[A2] (maximum 8 cycles), with Rituximab 375mg/m² on day 1 (21 patients) or: Bortezomib 1.6mg/m² and Rituximab on days 1, 8,15 and 22 weekly for 4 weeks of a 35-day5-week cycle (maximum 6, Rituximab being given only in cycles 1 and 4[A3]). Only 14Fourteen /42 patients completed therapy; 28 beingwere withdrawn (toxicity 16, progression 7, and 'patient choice' 5). The main clinical toxicities were neurologicalperipheral neuropathy and gastro-intestinal. tract symptoms. Grade I/II haematological toxicity occurred in >33%. >1/3[A4]. The overall response rate was 28/42 (67%,i.e. 7), [A5]i.e.7 complete and 21 partial 21 partial responses). ,Fourteen of 14/21 patients in each arm responded; overall response rates by histology were: FL 8/15, : MCL 11/19, FL 8/15, and WM 9/10. [A6]Twelve of 14 patients who completed therapy responded, as did 16/28 withdrawnin whom the planned treatment was not .completeddid not. Ten of the /28 responding patients who responded remain progression-free(atfor between 1 -one and 1-3.5 years),, 22/42 are alive, (atbetween 1.4 -and -4 years). The main toxicities were peripheral neuropathy and gastro-intestinal tract symptoms. There was no difference in Ttoxicity andor efficacy were equivalent between the two schedules. This combination has significant toxicity is toxic[A7] but is effective, and warrants further investigation, particularly in patients with WM.

Keywords: Bortezomib, Rituximab, B-cell malignancies

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