Clinical trial results:
Subcutaneous Bortezomib, Cyclophosphamide and Rituximab (BCR) versus Fludarabine, Cyclophosphamide and Rituximab (FCR) for initial therapy of Waldenstrm macroglobulinaemia: a randomised phase II study.

Summary

EudraCT number	2011-005156-34
Trial protocol	GB
Global end of trial date	02 August 2020

Results information

Result version number	v1 (current)
This version publication date	20 August 2021
First version publication date	20 August 2021

Trial information

Trial identification

Sponsor protocol code	UCL/11/0353

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01592981
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Haematology Trials Group, Cancer Research UK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Haematology Trials Group, Cancer Research UK and UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk

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	10 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 August 2020
Global end of trial reached?	Yes
Global end of trial date	02 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase II trial of bortezomib / cyclophosphamide / rituximab (BCR) in initial therapy of Waldenstrom's Macroglobulinaemia (WM). The overall aim was to make a preliminary examination of the safety and efficacy of the proposed BCR combination in patients with symptomatic, previously untreated WM and determine whether BCR warrants further investigation in a randomised phase III setting.
During the first non-randomised stage of the trial, the number and severity of adverse events experienced by patients treated with BCR were analysed.
Only when the BCR combination was considered tolerable (as defined in the study protocol), the trial continued to a randomised second stage where efficacy of BCR was assessed in terms of response to treatment and a second arm of fludarabine, cyclophosphamide and rituximab (FCR) was added to the design. The two arms were randomised in a 2:1 ratio.

Protection of trial subjects:

The risks to the safety of the trial subjects were those generally associated with chemotherapy. With limited published data on the BCR combination of drugs in WM, a safety run-in phase was designed to assess the safety and tolerability of the regimen. This included 6 patients with regular monitoring of the laboratory and safety data. A formal review followed after the 6th patient reached day 1 of the second treatment cycle. The IDMC confirmed the study could continue with the laboratory and safety data continuing to be monitored regularly by trials unit staff and the TMG, with an annual review by the IDMC. The protocol contained specific instructions regarding clinical assessments for potential side effects, including neuropathy, and resultant dose modifications, or cessation of treatment. The protocol also had instructions on medications that should be used with caution and those that could be prescribed for specific conditions at the discretion of the treating physician.
Patients were counselled about the potential side effects prior to starting treatment. Pregnant or lactating women were excluded from the study. Women of childbearing potential and male patients were informed they must use an effective form of contraception during the course of the study.

Background therapy:

Supportive care for this study was as per local guidelines with the following recommendations:
- Aciclovir prophylaxis should be given whilst patients are receiving treatment because of the increased incidence of herpes zoster infection reported in patients treated on a similar regimen
- Anti-emetic prophylaxis is recommended for at least 5 days with a 5 HT3 antagonist
- Allopurinol is advised for the first cycle of therapy

Evidence for comparator:

There is no agreed standard on first-line therapy of WM but a consensus panel of international experts has provided treatment recommendations based on the most recently published clinical trial results. Combination therapy of rituximab with purine analogues with or without alkylators or with cyclophosphamide based therapies have been recommended in the front-line setting with comparable response rates for both Fludarabine, Cyclophosphamide, Rituximab (FCR) and Dexamethasone, Rituximab, Cyclophosphamide (DRC). Within the UK, experience is greatest with FCR which is favoured by the participating centres as the non-comparative control arm following the results of a national survey.

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 60
Worldwide total number of subjects	60
EEA total number of subjects	0

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)	23
From 65 to 84 years	36
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The 60 trial subjects were recruited between 20/02/2013 and 04/09/2015 from 24 trial hospitals.

Pre-assignment

Screening details:

Treatment-naïve patients with symptomatic WM were enrolled. Patients aged ≥18 years with a confirmed diagnosis of WM according to World Health Organisation (WHO) criteria and ECOG Performance Status 0-2 were included.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BCR (experimental) arm

Arm description:

BCR (experimental) arm:
Bortezomib: 1.6 mg/m2 s.c. days 1, 8, 15
Cyclophosphamide: 250 mg/m2 oral days 1, 8, 15
Rituximab: 375 mg/m2 i.v. days 1, 8, 15, 22 cycles 2 & 5 only
Cycle repeated every 28 days

After 3 cycles of treatment, patients were reassessed and those with evidence of progression stopped trial treatment.
All other patients continued with a further 3 cycles (to a total of 6) unless a clear clinical contraindication to further treatment existed.

Arm type	Experimental
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	Velcade
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

1.6 mg/m2.
- Based on body surface area (BSA) calculated using actual body weight according to local policy
- Calculated prior to each cycle and remained the same throughout each cycle and if a patient experienced a notable change in weight (e.g. loss or gain of 8lbs or 3.6kg or 5% change in weight) within a cycle

Administration:
Suggested anatomical areas were the thighs or abdomen and injection sites were rotated within a treatment cycle.
Intravenous bortezomib administration was allowed if a patient did not tolerate subcutaneous administration (e.g. >grade 2 local reaction). The change of administration route would have been approved by the Chief Investigator. Patients who switched to the IV route maintained this route for the remaining treatment.
Where bortezomib needed to be administered intravenously, the most recent SPC was checked for details on diluent, volume, duration of infusion, stability and storage of bortezomib.
Schedule:
Days 1, 8 and 15 of each cycle

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Powder for solution for injection

Routes of administration	Oral use, Intravenous use

Dosage and administration details:

250mg/m2 - based on BSA calculated using actual body weight according to local policy
Administration:
Oral
If the oral preparation of cyclophosphamide is not tolerated this can be given intravenously at the same dose (250 mg/m2).
Schedule:
BCR (experimental) arm: days 1, 8 and 15 of each cycle

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

Dosage and administration details:

375mg/m2

Administration:
i.v infusion
If the IgM paraprotein is ≥ 50g/L at the time of the first treatment, prophylactic use of plasmapheresis is recommended before the administration of rituximab because of the potential for rituximab-mediated IgM flare and aggravation of hyperviscosity.
If the IgM paraprotein is ≥ 50g/L but plasmapheresis is not available, Rituximab administration should be delayed to cycle 3 and 6.
Administration of rituximab including pre-medications (paracetamol, anti-histamines, steroids) and infusion rates during the first and subsequent infusions are according to the site local guidelines and policies.
Rituximab must not be administered as an intravenous bolus injection.
Schedule:
days 1, 8, 15 and 22 of cycles 2 and 5 only

Arm title	FCR (control) arm

Arm description:

Fludarabine: 40 mg/m2 oral days 1-3
Cyclophosphamide: 250 mg/m2 oral days 1-3
Rituximab 375 mg/m2 i.v. days 1, 8, 15, 22 cycles 2 & 5 only
Cycle repeated every 28 days
After 3 cycles of treatment, patients were reassessed and those with evidence of progression stopped trial treatment.
All other patients continued with a further 3 cycles (to a total of 6) unless a clear clinical contraindication to further treatment existed.

Arm type	Active comparator
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/m2
Based on BSA calculated using actual body weight according to local policy.
Administration:
Oral
If the oral preparation of fludarabine is not tolerated this can be given intravenously at 25 mg/m2.
Schedule:
days 1, 2 and 3 of each cycle

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

250mg/m2 - based on BSA calculated using actual body weight according to local policy
Administration:
Oral
If the oral preparation of cyclophosphamide is not tolerated this can be given intravenously at the same dose (250 mg/m2).
Schedule:
BCR (experimental) arm: days 1, 8 and 15 of each cycle

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

Dosage and administration details:

375mg/m2

Administration:
i.v infusion
If the IgM paraprotein is ≥ 50g/L at the time of the first treatment, prophylactic use of plasmapheresis is recommended before the administration of rituximab because of the potential for rituximab-mediated IgM flare and aggravation of hyperviscosity.
If the IgM paraprotein is ≥ 50g/L but plasmapheresis is not available, Rituximab administration should be delayed to cycle 3 and 6.
Administration of rituximab including pre-medications (paracetamol, anti-histamines, steroids) and infusion rates during the first and subsequent infusions are according to the site local guidelines and policies.
Rituximab must not be administered as an intravenous bolus injection.
Schedule:
days 1, 8, 15 and 22 of cycles 2 and 5 only

Number of subjects in period 1	BCR (experimental) arm	FCR (control) arm
Started	43	17
Completed	39	13
Not completed	4	4
Physician decision	-	1
Adverse event, non-fatal	2	3
Ineligible for study, withdrawn mid cycle 1	1	-
Patient withdrew prior to treatment	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)
Reporting group description:	

Patient Inclusion Criteria
-Age ≥ 18 years
-Confirmed diagnosis of WM (according to consensus panel / WHO criteria) with measurable IgM paraprotein
-Previously untreated disease at any stage requiring therapy
-Performance status grade 0 - 2
-Life expectancy of greater than 6 months
-Informed consent
-Agreed compliance with recommended contraceptive precautions where appropriate
Exclusion Criteria
-Lymphoplasmacytic lymphoma with no detectable serum IgM paraprotein
-Severe pre-existing neuropathy (> grade 2)
-Autoimmune cytopenias
-Evidence of active Hepatitis B or C infection
-Serological positivity for HIV
-Pregnant or lactating women
-Life expectancy severely limited by other illness
-Diagnosed or treated for a malignancy other than WM within 5 years
-Renal failure
-Severe impairment of liver function
-Concurrent treatment with another investigational agent
-Severe or life-threatening cardiac, pulmonary, neurological, psychiatric or metabolic disease

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	60	60	
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)	23	23	
From 65-84 years	36	36	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	16	16	
Male	44	44	
IPSSWM			
International Prognostic Scoring System for WM			
Units: Subjects			
Low risk	16	16	
Intermediate risk	17	17	
High risk	27	27	
Hyperviscosity Units: Subjects			

Present	38	38	
Not present	22	22	
Lymphadenopathy Units: Subjects			
Present	18	18	
Not present	42	42	
B symptoms Units: Subjects			
Present	18	18	
Not present	42	42	
Splenomegaly Units: Subjects			
Present	9	9	
Not present	51	51	
Peripheral neuropathy Units: Subjects			
Present	8	8	
Not present	52	52	
MYD88 L265P mutation Units: Subjects			
Demonstrable	53	53	
Non demonstrable	4	4	
Not evaluable	3	3	
CXCR4 mutation Units: Subjects			
Demonstrable	6	6	
Not demonstrable	21	21	
Not evaluable	33	33	
Haemoglobin Units: g/dl			
median	9.8		
full range (min-max)	6.5 to 14	-	
Serum IgM paraprotein Units: g/L			
median	34.0		
full range (min-max)	3.2 to 80.2	-	

End points

End points reporting groups

Reporting group title	BCR (experimental) arm

Reporting group description:

BCR (experimental) arm:
Bortezomib: 1.6 mg/m2 s.c. days 1, 8, 15
Cyclophosphamide: 250 mg/m2 oral days 1, 8, 15
Rituximab: 375 mg/m2 i.v. days 1, 8, 15, 22 cycles 2 & 5 only
Cycle repeated every 28 days

After 3 cycles of treatment, patients were reassessed and those with evidence of progression stopped trial treatment.
All other patients continued with a further 3 cycles (to a total of 6) unless a clear clinical contraindication to further treatment existed.

Reporting group title	FCR (control) arm

Reporting group description:

Fludarabine: 40 mg/m2 oral days 1-3
Cyclophosphamide: 250 mg/m2 oral days 1-3
Rituximab 375 mg/m2 i.v. days 1, 8, 15, 22 cycles 2 & 5 only
Cycle repeated every 28 days
After 3 cycles of treatment, patients were reassessed and those with evidence of progression stopped trial treatment.
All other patients continued with a further 3 cycles (to a total of 6) unless a clear clinical contraindication to further treatment existed.

Primary: Overall response rate

End point title	Overall response rate[1]

End point description:

End point type	Primary

End point timeframe:

Baseline to end of treatment

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: This endpoint is the number/proportion of patients in each of the response categories. No specific statistical analyses are required to establish the percentage of patients. This can be calculated using the number of patients who were in the trial and the number of patients in each response category.

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Patients				
Complete response	1	0		
Very good partial response	8	3		
Partial response	24	10		
Stable disease	1	2		
Minor response	7	1		
Not evaluated	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Speed of response

End point title	Speed of response

End point description:

End point type	Secondary

End point timeframe:

Start of treatment to 25% reduction (minor response) in serum IgM

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Months				
median (confidence interval 95%)	2.1 (1.6 to 2.5)	1.5 (0.7 to 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

Baseline to two and three year follow up

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Patients				
Patients progression free at 2 years	38	14		
Patients progression free at 3 years	33	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to next treatment

End point title	Time to next treatment

End point description:

Number of patients receiving further treatment within 61.2 months

End point type	Secondary

End point timeframe:

Baseline to a median follow up of 61.2 months

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Patients	8	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity

End point title	Toxicity

End point description:

End point type	Secondary

End point timeframe:

Baseline to End of Trial

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Patients				
No. stopping treatment early due to toxicity	2	4		
No. developing treatment related myelodysplasia	0	3		
No. requiring dose reductions	16	9		
No. requiring treatment delays	27	11		
No. with grade 3 or higher adverse events	27	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall surivival

End point title	Overall surivival
End point description:	
Number of patients who died	
End point type	Secondary
End point timeframe:	
Baseline to End of Trial	

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Patients	2	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life

End point title	Quality of life
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to End of Trial	

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Patients				
Baseline Mobility - No problems	24	13		
End of Trial Mobiility - No Problems	24	12		
Baseline Mobility - Some problems	12	3		
End of Trial Mobility - Some Problems	11	1		
Baseline Mobility - Extreme problems	0	0		
End of Trial Mobility - Extreme problems	0	0		
Baseline Mobility - Missing	5	1		
End of Trial Mobility - Missing	6	4		
Baseline Self-care - No problems	34	15		
End of Trial Self-care - No problems	31	13		
Baseline Self-care - Some problems	2	1		
End of Trial Self-care - Some problems	4	0		
Baseline Self-care - Extreme problems	0	0		
End of Trial Self-care - Extreme problems	0	0		
Baseline Self-care - Missing	5	1		
End of Trial Self-care - Missing	6	4		
Baseline Usual Activities - No problems	17	14		
End of Trial Usual Activities - No problems	22	10		
Baseline Usual Activities - Some problems	17	2		
End of Trial Usual Activities - Some problems	12	3		
Baseline Usual Activities - Extreme problems	2	0		
End of Trial Usual Activities - Extreme problems	1	0		
Baseline Usual Activities - Missing	5	1		
End of Trial Usual Activities - Missing	6	4		
Baseline Pain/discomfort - No problems	17	12		
End of Trial Pain/discomfort - No problems	20	9		
Baseline Pain/discomfort - Some problems	19	4		
End of Trial Pain/discomfort - Some problems	12	4		
Baseline Pain/discomfort - Extreme problems	0	0		
End of Trial Pain/discomfort - Extreme problems	3	0		
Baseline Pain/discomfort - Missing	5	1		
End of Trial Pain/discomfort - Missing	6	4		
Baseline Anxiety/depression - No problems	22	12		
End of Trial Anxiety/depression - No problems	27	11		

Baseline Anxiety/depression - Some problems	14	4		
End of Trial Anxiety/depression - Some problems	8	2		
Baseline Anxiety/depression - Extreme problems	0	0		
End of Trial Anxiety/depression - Extreme Problems	0	0		
Baseline Anxiety/depression -Missing	5	4		
End of Trial Anxiety/depression - Missing	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

End point type	Secondary

End point timeframe:

Response to two or three year follow up

End point values	BCR (experimental) arm	FCR (control) arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	17		
Units: Patients				
Number of patients with a two-year response	36	15		
Number of patients with a three year response	32	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events, and all serious adverse events (SAEs), that occurred between informed consent and 30 days post last trial treatment administration (or after this date if thought to be related to trial treatment) had to be reported.

Adverse event reporting additional description:

Adverse events were recorded in the patient notes and trial Case Report Forms. Those meeting the definition of a Serious Adverse Event were also reported to UCL CTC using the trial specific SAE Report Form.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	BCR (experimental) arm

Reporting group description:

BCR (experimental) arm:
Bortezomib: 1.6 mg/m2 s.c. days 1, 8, 15
Cyclophosphamide: 250 mg/m2 oral days 1, 8, 15
Rituximab: 375 mg/m2 i.v. days 1, 8, 15, 22 cycles 2 & 5 only
Cycle repeated every 28 days

After 3 cycles of treatment, patients were reassessed and those with evidence of progression stopped trial treatment.
All other patients continued with further 3 cycles (to a total of 6) unless a clear clinical contraindication to further treatment existed.

Reporting group title	FCR (control) arm

Reporting group description:

Fludarabine: 40 mg/m2 oral days 1-3
Cyclophosphamide: 250 mg/m2 oral days 1-3
Rituximab 375 mg/m2 i.v. days 1, 8, 15, 22 cycles 2 & 5 only
Cycle repeated every 28 days
After 3 cycles of treatment, patients were reassessed and those with evidence of progression stopped trial treatment.
All other patients continued with further 3 cycles (to a total of 6) unless a clear clinical contraindication to further treatment existed.

Serious adverse events	BCR (experimental) arm	FCR (control) arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 42 (19.05%)	9 / 17 (52.94%)	
number of deaths (all causes)	2	7	
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 42 (0.00%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Other: Malignant polyp			
subjects affected / exposed	1 / 42 (2.38%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 42 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus Bradycardia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 42 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 42 (4.76%)	2 / 17 (11.76%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms			
subjects affected / exposed	2 / 42 (4.76%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 42 (2.38%)	5 / 17 (29.41%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	1 / 42 (2.38%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 42 (2.38%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 42 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 42 (2.38%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 42 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory infection			
subjects affected / exposed	1 / 42 (2.38%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BCR (experimental) arm	FCR (control) arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)	17 / 17 (100.00%)	
Investigations			
Febrile neutropenia			
subjects affected / exposed	2 / 42 (4.76%)	5 / 17 (29.41%)	
occurrences (all)	2	5	
Neutrophil count decreased			
subjects affected / exposed	24 / 42 (57.14%)	15 / 17 (88.24%)	
occurrences (all)	24	15	
Platelet count decreased			
subjects affected / exposed	23 / 42 (54.76%)	11 / 17 (64.71%)	
occurrences (all)	23	11	
Vascular disorders			
Hypotension			
subjects affected / exposed	8 / 42 (19.05%)	1 / 17 (5.88%)	
occurrences (all)	8	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 42 (28.57%)	2 / 17 (11.76%)	
occurrences (all)	12	2	
Dysgeusia			
subjects affected / exposed	2 / 42 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Headache			

subjects affected / exposed	8 / 42 (19.05%)	1 / 17 (5.88%)	
occurrences (all)	8	1	
Peripheral motor neuropathy			
subjects affected / exposed	9 / 42 (21.43%)	0 / 17 (0.00%)	
occurrences (all)	9	0	
Peripheral sensory neuropathy			
subjects affected / exposed	20 / 42 (47.62%)	1 / 17 (5.88%)	
occurrences (all)	20	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	31 / 42 (73.81%)	11 / 17 (64.71%)	
occurrences (all)	31	11	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	8 / 42 (19.05%)	1 / 17 (5.88%)	
occurrences (all)	8	1	
Fatigue			
subjects affected / exposed	26 / 42 (61.90%)	10 / 17 (58.82%)	
occurrences (all)	26	10	
Fever			
subjects affected / exposed	4 / 42 (9.52%)	2 / 17 (11.76%)	
occurrences (all)	4	2	
Flu like symptoms			
subjects affected / exposed	4 / 42 (9.52%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Injection site reaction			
subjects affected / exposed	8 / 42 (19.05%)	0 / 17 (0.00%)	
occurrences (all)	8	0	
Pain			
subjects affected / exposed	8 / 42 (19.05%)	1 / 17 (5.88%)	
occurrences (all)	8	1	
Rituximab infusion related reaction			
subjects affected / exposed	15 / 42 (35.71%)	4 / 17 (23.53%)	
occurrences (all)	15	4	
Eye disorders			

Blurred vision			
subjects affected / exposed	5 / 42 (11.90%)	0 / 17 (0.00%)	
occurrences (all)	5	0	
Conjunctivitis			
subjects affected / exposed	2 / 42 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 42 (21.43%)	4 / 17 (23.53%)	
occurrences (all)	9	4	
Constipation			
subjects affected / exposed	21 / 42 (50.00%)	7 / 17 (41.18%)	
occurrences (all)	21	7	
Diarrhoea			
subjects affected / exposed	21 / 42 (50.00%)	4 / 17 (23.53%)	
occurrences (all)	21	4	
Dyspepsia			
subjects affected / exposed	4 / 42 (9.52%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Mucositis oral			
subjects affected / exposed	2 / 42 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	28 / 42 (66.67%)	14 / 17 (82.35%)	
occurrences (all)	28	14	
Vomiting			
subjects affected / exposed	6 / 42 (14.29%)	2 / 17 (11.76%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Anorexia			
subjects affected / exposed	5 / 42 (11.90%)	2 / 17 (11.76%)	
occurrences (all)	5	2	
Cough			
subjects affected / exposed	3 / 42 (7.14%)	3 / 17 (17.65%)	
occurrences (all)	3	3	
Dyspnea			

subjects affected / exposed	4 / 42 (9.52%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Epistaxis			
subjects affected / exposed	1 / 42 (2.38%)	2 / 17 (11.76%)	
occurrences (all)	1	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 42 (7.14%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Rash maculo-papular			
subjects affected / exposed	0 / 42 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 42 (9.52%)	0 / 17 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 42 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	2 / 42 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Myalgia			
subjects affected / exposed	4 / 42 (9.52%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Pain in extremity			
subjects affected / exposed	8 / 42 (19.05%)	0 / 17 (0.00%)	
occurrences (all)	8	0	
Other: Joint pain			
subjects affected / exposed	2 / 42 (4.76%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Other: Muscle cramp			
subjects affected / exposed	4 / 42 (9.52%)	1 / 17 (5.88%)	
occurrences (all)	4	1	
Infections and infestations			

Upper respiratory infection subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	2 / 17 (11.76%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2013	Documents updated: Protocol v2.0 30/11/2012 PIS-stage1 v2.0 30/11/2012 PIS-stage2 v2.0 30/11/2012 Pregnancy Monitoring IS (patient) v1 30/11/2012 Pregnancy Monitoring IS (partner) v1 30/11/2012 Pregnancy Monitoring IC (patient) v1 30/11/2012 Pregnancy Monitoring IC (partner) v1 30/11/2012 Main Changes: Protocol - Details for patients who may need to switch to IV bortezomib added, removal of NHS number from sample label, clarification to analysis of 'speed and duration of response', list of expected AEs for sc bortezomib removed and replaced with reference to the current SPC as it covers both sc and iv administration, reference to bortezomib IB removed and replaced with current SPC PIS: - Section on bortezomib side effects expanded as requested by company supplying bortezomib - Removal of statement regarding 'commercial use' of biological samples as this may be misleading
13 September 2013	Documents updated: Protocol v3.0 08/08/2013 PIS-stage1 v3.0 08/08/2013 PIS-stage2 v3.0 08/08/2013 CTA Main Changes: Protocol - Paragraph clarifying whether interpreter may be required to be provided by the site to obtain informed consent - Clarification that patients must be consented before any trial specific screening investigations are carried out - Clarification that FBC can be performed 1 day before D1 and 8 of each cycle, and that patients in the FCR arm need checked only on D1 (or -1) - Neutropenia changed from unusual to common side effect to reflect changes in the SPC - Addition of optional plasma viscosity test for cycle 1-3 - Removing requirement for Sites to have written procedures for informing Sponsor of Serious Breaches - Clarification to 'failure to start cycle 2 on time' when due to grade 3 or 4 heamatological toxicities - Reducing number of blood samples to be sent to Leeds during treatment and follow up - Serum samples for SFLC/ HeveyLite analysis to be sent to HMDS Leeds instead of Binding Site, Birmingham - NHS number to be listed on biological sample label (if applicable) - Clarification that either M protein or serum IgM can be used to assess changes in serum IgM level PIS: - Statement that Quality of Life questionnaire will be completed at 3 visits added - Addition of PML as a rare side effect of bortezomib - Details added to the paragraph on confidentiality that NHS numbers will be used - Reference to the Binding Site in Birmingham removed

11 April 2014	Documents changed: Protocol v4.0 18/02/2014 PIS-stage2 v4.0 18/02/2014 Main Changes: Protocol - 1. Clarification that the Hep B serology tests include HBsAg, HBsAb and HBcAB; HBV DNA test required if HBcAb result is positive (Prerandomisation evaluation section 5.1 of protocol). 2. Details regarding rituximab administration (premedication, infusion rates during 1st and subsequent infusion) removed and sites referred to their local policy (Treatment details section 7.3 Rituximab). 3. Addition that dose banding and dose capping for IMPs is allowed according to the site's standard practice' (Treatment details section 7.3 of protocol). 4. Addition of details regarding 'dose attenuation' at treatment start for patients with cytopenia or PS=2 randomised to FCR (Dose modifications section 7.4 of protocol). 5. Clarification on FBC timing during treatment (within 3 days of D1 and D8 of each cycle, repeated on the day if abnormal) (sections 7.4.1 Haematological toxicity and 8.2 Assessments during treatment). 6. Clarification that nonhaematological treatmentrelated grade 3 or higher adverse events are used to assess the toxicity rate (Interim analyses section 15.6 of protocol). 7. Correction of error in the 'number of patients' corresponding to toxicity rate of 20% in the second randomised stage of the study (Interim analyses section 15.6 of protocol). 8. Addition of 'febrile neutropenia' and 'fever' to the list of expected AEs for the FCR regimen, and of 'rituximab related infusion reactions' to the BCR arm (Expected Adverse Events Appendix 5 of protocol). PIS: 1. Addition of 'hyperaemia' as uncommon side effect and of thrombocytosis, amyloidosis, erythrosis, cough syndrome, coma and multiorgan failure as rare side effects of bortezomib. 2. Addition of hypogammaglobulinaemia and increased risk of infection as a side effect of rituximab
24 October 2014	Documents updated: PIS RSI update Main changes: PIS - Further information on rituximab side effects added RSI - Cyclophosphamide SPC tablets changed from Pharmacia to the SPC from Baxter as the section on 'undesirable effects' in the latter contained a more comprehensive and detailed list of the known side effects using the System Organ Class and frequency - Bortezomib and rituximab SPCs changed to the most recent (at the time) of bortezomib (10/01/2014) and rituximab (23/05/2014).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Serious and non-serious adverse events are listed under non-serious adverse events
Non-serious AEs:'Occurrences all number' cannot be provided-only the highest grade experienced by patients was collected. Subjects affected number is entered instead.

Notes: