Clinical trial results:
A Parallel Randomised Phase II Trial of CHOP Chemotherapy With or Without Bortezomib in Relapsed Mantle Cell Lymphoma

Summary

EudraCT number	2006-006090-24
Trial protocol	GB
Global end of trial date	11 August 2014

Results information

Result version number	v1 (current)
This version publication date	08 September 2019
First version publication date	08 September 2019

Trial information

Trial identification

Sponsor protocol code	Ply-26s

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00513955
WHO universal trial number (UTN)	-
Other trial identifiers	MREC: 07/Q2103/7

Notes:

Sponsors

Sponsor organisation name	University Hospitals Plymouth NHS Trust (previously known as Plymouth Hospitals NHS Trust)
Sponsor organisation address	Research Office, L2 MSCP, Bircham Park Offices, 1 Roscoff Rise, Derriford, Plymouth, United Kingdom, PL6 5FP
Public contact	Dr Chris Rollinson, Research Governance Manager, University Hospitals Plymouth NHS Trust, Research Development and Innovation, 01752 432842, c.rollinson@nhs.net
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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	31 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 August 2014
Global end of trial reached?	Yes
Global end of trial date	11 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the rates of overall response in terms of Complete Response (CR), Complete Response unconfirmed (CRu), and Partial Response (PR).

Protection of trial subjects:

The study is approved by the MHRA and the South West - Cornwall & Plymouth (Formerly Cornwall and Plymouth) Research Ethics Committee (NRES). Study monitoring and 10% source data verification is conducted by UHPNT and an Independent Data Monitoring Comittee (IDMC) is set up for the study oversight and to review patient safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2007
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: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	17
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study population comprised of eligible patients with primary refractory mantle cell lymphoma and patients who had relapsed after completion of their first line therapy.

Pre-assignment

Screening details:

At screening, patients were required to have an absolute neutrophil count (ANC) ≥10 9 109 cells/l, platelet count ≥30 9 109 cells/l and good renal and liver function.

Pre-assignment period milestones

Number of subjects started	46
Number of subjects completed	46

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bortezomib plus CHOP (BCHOP)

Arm description:

Patients receive Bortezomib SC on days 1 and 8; Doxorubicin hydrochloride IV, Cyclophosphamide IV, and Vincristine IV on day 1; and oral Prednisolone on days 1-5.

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

Dosage and administration details:

Patients receive Bortezomib IV 1.6mg on days 1 and 8. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Investigational medicinal product name	Doxorubicin hydrochloride
Investigational medicinal product code	
Other name	Adriamycin, Caelyx, Myocet
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive Doxorubicin hydrochloride 50mg IV on day 1. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Cytophosphane, Cytoxan, Endoxan, Cytoxan, Neosar, Procytox, Revimmune, Cycloblastin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive Cyclophosphamide 750mg IV on day 1. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Investigational medicinal product name	Vincristine sulfate
Investigational medicinal product code	
Other name	Leurocristine, Oncovin, Vincasar
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive Vincristine 1.4mg IV on day 1. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients receive oral Prednisolone 100mg on days 1-5. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Arm title	CHOP alone

Arm description:

Patients receive Doxorubicin hydrochloride IV, Cyclophosphamide IV, and Vincristine IV on day 1 and oral Prednisolone on days 1-5.

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin hydrochloride
Investigational medicinal product code	
Other name	Adriamycin, Caelyx, Myocet
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive Doxorubicin hydrochloride 50mg IV on day 1. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	Cytophosphane, Cytoxan, Endoxan, Cytoxan, Neosar, Procytox, Revimmune, Cycloblastin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive Cyclophosphamide 750mg IV on day 1. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Investigational medicinal product name	Vincristine sulfate
Investigational medicinal product code	
Other name	Leurocristine, Oncovin, Vincasar
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients receive Vincristine 1.4mg IV on day 1. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients receive oral Prednisolone 100mg on days 1-5. Treatment repeats every 21 days for up to 8 courses in the absence of disease progression or unacceptable toxicity.

Number of subjects in period 1	Bortezomib plus CHOP (BCHOP)	CHOP alone
Started	23	23
Completed	14	9
Not completed	9	14
Adverse event, serious fatal	2	1
Physician decision	5	6
Consent withdrawn by subject	1	6
Lost to follow-up	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Bortezomib plus CHOP (BCHOP)
Reporting group description:	
Patients receive Bortezomib SC on days 1 and 8; Doxorubicin hydrochloride IV, Cyclophosphamide IV, and Vincristine IV on day 1; and oral Prednisolone on days 1-5.	
Reporting group title	CHOP alone
Reporting group description:	
Patients receive Doxorubicin hydrochloride IV, Cyclophosphamide IV, and Vincristine IV on day 1 and oral Prednisolone on days 1-5.	

Reporting group values	Bortezomib plus CHOP (BCHOP)	CHOP alone	Total
Number of subjects	23	23	46
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	69	71	
inter-quartile range (Q1-Q3)	48 to 73	50 to 83	-
Gender categorical			
Units: Subjects			
Female	8	2	10
Male	15	21	36
Disease Stage			
Units: Subjects			
Stage I	0	2	2
Stage II	4	1	5
Stage III	7	5	12
Stage IV	12	15	27
Previous Rituximab Therapy (Y/N)			
Units: Subjects			
Yes	10	4	14
No	13	19	32
Time Since Diagnosis			
Units: Months			
median	24.7	19.7	
full range (min-max)	4.8 to 60.2	2.4 to 91.1	-
ECOG (Performance Status)			

Units: Grade			
median	0	1	
full range (min-max)	0 to 2	0 to 2	-

End points

End points reporting groups

Reporting group title	Bortezomib plus CHOP (BCHOP)
Reporting group description:	
Patients receive Bortezomib SC on days 1 and 8; Doxorubicin hydrochloride IV, Cyclophosphamide IV, and Vincristine IV on day 1; and oral Prednisolone on days 1-5.	
Reporting group title	CHOP alone
Reporting group description:	
Patients receive Doxorubicin hydrochloride IV, Cyclophosphamide IV, and Vincristine IV on day 1 and oral Prednisolone on days 1-5.	

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
End point description:	
End point type	Primary
End point timeframe:	
Response Assessment taken mid treatment, 30 day and 1st 3mly.	

End point values	Bortezomib plus CHOP (BCHOP)	CHOP alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Percentage of participants	19	11		

Statistical analyses

Statistical analysis title	Summary Statistics
Comparison groups	Bortezomib plus CHOP (BCHOP) v CHOP alone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	Chi-squared

Primary: Complete Response (CR) rate

End point title	Complete Response (CR) rate
End point description:	
End point type	Primary

End point timeframe:

Response Assessment taken mid treatment, 30 day and 1st 3mly.

End point values	Bortezomib plus CHOP (BCHOP)	CHOP alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Percentage of participants	8	5		

Statistical analyses

Statistical analysis title	Summary Statistics
Comparison groups	Bortezomib plus CHOP (BCHOP) v CHOP alone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.33
Method	Chi-squared

Primary: Partial Response (PR) rate

End point title	Partial Response (PR) rate

End point description:

End point type	Primary

End point timeframe:

Response Assessment taken mid treatment, 30 day and 1st 3mly.

End point values	Bortezomib plus CHOP (BCHOP)	CHOP alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Percentage of participants	11	6		

Statistical analyses

Statistical analysis title	Summary Statistics
Comparison groups	Bortezomib plus CHOP (BCHOP) v CHOP alone

Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.13
Method	Chi-squared

Secondary: Progression-Free survival (PFS)

End point title	Progression-Free survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

Disease Progression Assessment: 30 day, 1st 3mly, Subsequent 1/4ly reviews. Survival Status: Post-progression.

End point values	Bortezomib plus CHOP (BCHOP)	CHOP alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Months	16	8		

Statistical analyses

Statistical analysis title	Summary Statistics
Comparison groups	Bortezomib plus CHOP (BCHOP) v CHOP alone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.12
Method	Chi-squared

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

End point type	Secondary

End point timeframe:

Disease Progression Assessment: 30 day, 1st 3mly, subsequent 1/4ly reviews. Survival Status: Post-progression.

End point values	Bortezomib plus CHOP (BCHOP)	CHOP alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Months	36	12		

Statistical analyses

Statistical analysis title	Summary Statistics
Comparison groups	Bortezomib plus CHOP (BCHOP) v CHOP alone
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	Chi-squared

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Any SAEs are to be reported to the to the trial coordinator within 24 hours. All SUSARs are reported to the regulatory authorities, Johnson and Johnson and the trial sponsor within 24 hours.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	CHOP

Reporting group description:

Trial Arm/Treatment: CHOP

Reporting group title	BCHOP

Reporting group description:

Trial Arm/Treatment: CHOP + Bortezomib

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The non-serious adverse events data was not available to the EudraCT Data Inputter.

Serious adverse events	CHOP	BCHOP	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 23 (78.26%)	23 / 23 (100.00%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	0	
Vascular disorders			
Swelling	Additional description: 2 swollen toes		
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Hypotension			
subjects affected / exposed	1 / 23 (4.35%)	3 / 23 (13.04%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			

subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
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			
Neutropenia			
subjects affected / exposed	12 / 23 (52.17%)	11 / 23 (47.83%)	
occurrences causally related to treatment / all	14 / 14	19 / 19	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thrombocytopenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 23 (8.70%)	7 / 23 (30.43%)	
occurrences causally related to treatment / all	4 / 4	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectal haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 23 (0.00%)	3 / 23 (13.04%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)	3 / 23 (13.04%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 23 (8.70%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 23 (4.35%)	5 / 23 (21.74%)	
occurrences causally related to treatment / all	2 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia	Additional description: E-coil infection		
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria	Additional description: Protein & blood in urine		
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
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	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pseudomonal sepsis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Varicella	Additional description: Chicken pox		
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	5 / 23 (21.74%)	5 / 23 (21.74%)	
occurrences causally related to treatment / all	3 / 5	5 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Herpes zoster	Additional description: Shingles		
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CHOP	BCHOP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2007	Protocol V2, 19/02/2007: An updated Velcade Investigator Brochure (Edition 10) necessitated a change to the patient information sheet with regard to the severity of some adverse reactions to Velcade. More detailed information relating to reactions was incorporated into a revised protocol. The requirement for patients to have a bone marrow biopsy and trephine was added to the pre-study assessments. This was considered part of routine care for patients with clinical signs of disease progression, and for this reason was not included in the first version of the protocol. However, following consultation with some of the Principal Investigators, it was suggested that this should be added to the obligatory assessments. Any patient with bone marrow involvement at baseline was required to undergo further bone marrow aspiration following cycle 4, and at the end of their treatment.
21 April 2008	Protocol V3, 19/02/2008; A revised Investigator Brochure (Edition 11) necessitated changes to the protocol to incorporate new data related to adverse reactions, overdose and drug stability. All incidences of IMP overdose to be reported as SAEs.
15 April 2010	Protocol V4, 22/02/2010; Recruitment period extended to 30th April 2011 as accrual slower than anticipated. Also incorporated in this protocol are: Section 7.1.2 All patients randomised to this group must be prescribed acyclovir 400 mgs twice daily for the duration of the trial medication. This is to reduce the incidences of herpes zoster / simplex. Section 16 all investigator sites will receive one carton containing 10 vials of Bortezomib following the initiation meeting. Further supplies will be forwarded to the centre when a new patient is randomised into combination group at the centre. Pharmacy information: Johnson and Johnson have asked that their own protocol number for this study be added to the drug supply records and the drug container labels, therefore in addition to the EudraCT number the labels will also have Lym - 2015 added to them.
13 January 2011	Protocol V5, 03/11/2010; Trial website (eCRFs) to close and be replaced by paper CRFs following DMC review. Protocol revised to change the methods of data capture and randomisation of new patients, and also the reporting of Serious Adverse Events and SUSARs.
21 September 2012	Protocol V6, 26/07/2012; The Data Monitoring Committee considered the "interim" analysis (data of the first 46 participants), and a review of other trial results which were suggestive that the standard arm was significantly inferior to the research arm of the study. Consequently, the Data Monitoring Committee advised that it would be unethical to continue with the standard arm and that it should be closed to recruitment. The DMC also recommended the continuation of patient recruitment to the research arm in order to increase safety and efficacy data of CHOP + Bortezomib. A substantial amendment was therefore submitted in which the "standard" (CHOP alone) arm of the trial was to be closed, and any further patients entered would receive the research treatment (CHOP + Bortezomib). Johnson & Johnson had further developed Bortezomib with evidence to suggest that administration subcutaneously (SC) rather than intravenously (IV) offered identical efficacy, but conferred less neurotoxicity. Furthermore, there had been a widespread switch from IV to SC Bortezomib across NHS practice, where the drug had been licensed as a consequence. It was therefore planned that recruitment would continue with all patients receiving subcutaneous Bortezomib.

21 December 2012	Protocol V7, 29/10/2012; New safety information received from J&J required the safety section of the protocol and the patient information leaflet to be updated. There had been 7 reported incidences of Progressive Multifocal Leukoencephalopathy (PML). Six of these had involved patients with Multiple Myeloma and one with Acute Myeloid Leukaemia; there had been no incidences reported in patients with MCL.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25146720