Clinical trial results:
Phase III, multicentre, randomised study of fludarabine/cyclophosphamide combination with or without Rituximab in patients with untreated mantle cell lymphoma

Summary

EudraCT number	2006-001965-41
Trial protocol	GB
Global end of trial date	22 April 2015

Results information

Result version number	v1 (current)
This version publication date	23 August 2019
First version publication date	23 August 2019

Trial information

Trial identification

Sponsor protocol code	BRD/06/052

Additional study identifiers

ISRCTN number	ISRCTN81133184
ClinicalTrials.gov id (NCT number)	NCT00641095
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	MCL Trial Coordinator Haematology & Brain Trials Group , University College London CR UK & UCL Cancer Trials Centre , 44 2076799860, ctc.sponsor@ucl.ac.uk
Scientific contact	MCL Trial Coordinator Haematology & Brain Trials Group , University College London CR UK & UCL Cancer Trials Centre , 44 2076799860, 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	25 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall survival of patients treated with cyclophoshamide and fludarabine in comparison to rituximab, cyclophosphamide and fludarabine.

Protection of trial subjects:

The protocol suggested intravenous fludarabine for patients who could not tolerate the oral administration of the drug. Rituximab was administered in an environment where full resuscitation facilities were available and under close supervision of experienced clinicians. All patients were given paracetamol and anti-histamine 30-60 minutes prior to Rituximab infusion.

The speed of the Rituximab infusion was increased gradually to alleviate infusion reactions. The initial dose rate was given at 50mg/hr for the first hour with increment steps of 50mg/hr every 30 minutes to a maximum of 400mg/hr. Vital signs were monitored every 15 minutes for the first hour and then hourly. Halving the speed of infusion was recommended in the case of specific adverse events. Septrin/Pentamidine was essential as an infection prophylaxis during treatment and for 6 months post therapy. Acyclovir was given during the course of therapy as a prophylaxis.

For patients in need of it following fludarabine, all blood products were irradiated to reduce the risk of transfusion related GvHD. For specified haematological and renal toxicity, fludarabine and cyclophosphamide doses were to be reduced.

Background therapy:

Septrin / Pentamidine
Acyclovir

Supportive care was as per institutional practice but Pneumocystis jirovecci (PJP) prophylaxis was mandated as was the use of irradiated blood products.

Evidence for comparator:

Mantle Cell Lymphoma (MCL) is an uncommon and usually aggressive form of non-Hodgkin lymphoma with an annual incidence of approximately 1/100,000 population. In younger patients, the treatment of choice included a high-dose cytarabine-containing regimen usually followed by autologous stem cell transplantation. However, with a median age at presentation in the mid sixth decade, such therapy was not applicable to the majority of patients. There was no generally accepted standard of care for older patients and a variety of treatments had been widely used.

As a single agent, Rituximab, a chimeric anti-CD20 monoclonal antibody produced response rates of approximately 35% in MCL and when added to the standard chemotherapeutic regimen CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) within a phase II single arm study the combination demonstrated a very high overall response rate. A subsequent meta-analysis of 3 subsequent phase II randomised trials which included MCL patients, suggested an OS benefit for the addition of Rituximab. However, no individual phase-III study has yet demonstrated such a benefit, and thus the true impact of Rituximab remains uncertain.

The purine nucleoside analogue class of drugs have demonstrable activity in the treatment of MCL, Fludarabine is the most widely used nucleoside analogue and when combined with cyclophosphamide in patients with MCL high response rates are achieved. As such a UK based randomised trial was initiated

exploring the addition of Rituximab to oral FC.

Actual start date of recruitment	02 September 2002
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: 348
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Poland: 17
Worldwide total number of subjects	370
EEA total number of subjects	365

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)	153
From 65 to 84 years	214
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

370 trial subjects were recruited over a period of 8 years and 3 months, 02/09/2002 – 02/12/2010, which included both the phase 2 and phase 3 subjects.

Pre-assignment

Screening details:

Eligible patients aged ≥18 years with previously untreated MCL were eligible. Central pathl confirmation of MCL diagnosis was performed retrospectively. Patients required adequate organ function and a life expectancy of ≥3 months. No malignancy in last 5 years, negative HBC, HCV or HIV and no condition which may affect compliance

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FCR Arm

Arm description:

Fludarabine, Cyclophosphamide & Rituximab

Arm type	Experimental
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	L01BB05
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	L01BB05
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

25mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment
For patients who could not tolerate oral administration of fludarabine, intravenous administration was allowed

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

250mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

250mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment
For patients who could not tolerate oral administration of cyclophosphamide, intravenous administration was allowed

Investigational medicinal product name	Rituximab
Investigational medicinal product code	L01XC02
Other name	Mabthera
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

375mg/m^2 to be given on day 1 of each 28-day cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on response to treatment

Rituximab was not be given as an intravenous bolus injection

Arm title	FC Arm

Arm description:

Fludarabine and Cyclophosphamide

Arm type	Active comparator
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	L01BB05
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

40mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment

Investigational medicinal product name	Fludarabine
Investigational medicinal product code	L01BB05
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

25mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment
For patients who could not tolerate oral administration of fludarabine, intravenous administration was allowed

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

250mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	L01AA01
Other name	

Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

250mg/m^2 on days 1-3 in a 28-day repeated cycle for a minimum of 4 cycles to a maximum of 8 cycles depending on the response to treatment
For patients who could not tolerate oral administration of cyclophosphamide, intravenous administration was allowed

Number of subjects in period 1	FCR Arm	FC Arm
Started	186	184
Completed	186	184

Baseline characteristics

Reporting groups	
Reporting group title	FCR Arm
Reporting group description: Fludarabine, Cyclophosphamide & Rituximab	
Reporting group title	FC Arm
Reporting group description: Fludarabine and Cyclophosphamide	

Reporting group values	FCR Arm	FC Arm	Total
Number of subjects	186	184	370
Age categorical			
Age at Trial entry			
Units: Subjects			
Adults (18-64 years)	78	75	153
From 65-84 years	106	108	214
85 years and over	2	1	3
Age continuous			
Units: years			
median	66	66	
full range (min-max)	36 to 88	37 to 85	-
Gender categorical			
Units: Subjects			
Female	49	38	87
Male	137	146	283
ECOG performance status			
Score 0 - Asymptomatic and fully active Score 1 - Symptomatic; fully ambulatory, restricted in physically strenuous activity Score 2 - Symptomatic; ambulatory, capable of self-care; more than 50% of waking hours are spent out of bed Score 3 - Symptomatic - limited self-care; spends more than 50% of time in bed, but not bedridden Score 4 - Disabled - Completely disabled; no self-care; bedridden			
Units: Subjects			
Score 0	93	87	180
Score 1	62	64	126
Score 2	17	15	32
Score 3	0	5	5
Score 4	0	1	1
Missing	14	12	26
B symptoms			
Systemic symptoms of fever, night sweats, and weight loss			
Units: Subjects			
Absent	97	106	203
Present	81	74	155
Missing	8	4	12
Disease Stage			
Units: Subjects			
Stage 1	4	2	6
Stage II	15	11	26

Stage III	25	32	57
Stage IV	134	134	268
Missing	8	5	13
Serum LDH Level Units: Subjects			
Normal	96	99	195
Elevated	77	80	157
Missing	13	5	18
MIPI Risk Group Units: Subjects			
Low	37	45	82
Intermediate	75	63	138
High	55	60	115
Missing	19	16	35

End points

End points reporting groups	
Reporting group title	FCR Arm
Reporting group description: Fludarabine, Cyclophosphamide & Rituximab	
Reporting group title	FC Arm
Reporting group description: Fludarabine and Cyclophosphamide	
Subject analysis set title	Patients who started trial treatment
Subject analysis set type	Intention-to-treat
Subject analysis set description: This population is used for response and toxicity endpoints	

Primary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description:	
End point type	Primary
End point timeframe: Analysis of OS was done after 240 events had occurred and all patients completed treatment	

End point values	FCR Arm	FC Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	184		
Units: Months				
number (not applicable)	44.5	37.0		

Attachments (see zip file)	OS K-M Curve/MCPIII_KM_plot_OS12 Jun 2015.tif

Statistical analyses

Statistical analysis title	Overall survival HR
Comparison groups	FCR Arm v FC Arm
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.9

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

End point type	Secondary

End point timeframe:

Analysis of PFS was done after 291 events had occurred and all patients completed treatment

End point values	FCR Arm	FC Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	184		
Units: Months				
number (not applicable)	29.8	14.9		

Attachments (see zip file)	PFS K-M curve/MCPIII_KM_plot_PFS_HR.tif

Statistical analyses

Statistical analysis title	HR for PFS
Comparison groups	FCR Arm v FC Arm
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.67

Secondary: Tumour response

End point title	Tumour response

End point description:

Objective response rate at last response assessment.

End point type	Secondary

End point timeframe:

End of treatment

End point values	FCR Arm	FC Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[1]	170[2]		
Units: Number of patients	137	125		

Notes:

[1] - All patients assessed for response

[2] - All patients assessed for response

Statistical analyses

Statistical analysis title	Response
Comparison groups	FCR Arm v FC Arm
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (including serious) that occurred between informed consent and 30 days post last trial treatment administration

Adverse event reporting additional description:

Trial subjects were assessed for adverse events prior the start of each treatment cycle. All adverse events (AEs) were recorded in the patient notes and the trial CRFs. Those meeting the definition of SAEs were also reported using the trial specific SAE Reporting template.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI - CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	FCR Arm

Reporting group description:

Fludarabine, Cyclophosphamide & Rituximab

Reporting group title	FC Arm

Reporting group description:

Fludarabine and Cyclophosphamide

Serious adverse events	FCR Arm	FC Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 186 (33.87%)	45 / 183 (24.59%)	
number of deaths (all causes)	108	132	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplasia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			

subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 186 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 186 (1.08%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction to excipient			
subjects affected / exposed	4 / 186 (2.15%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytokine release syndrome			
subjects affected / exposed	2 / 186 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Non-cardiac chest pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	2 / 186 (1.08%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary NOS			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 186 (0.54%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			

subjects affected / exposed	1 / 186 (0.54%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain - cardiac			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS Ischaemia			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemoglobin			
subjects affected / exposed	5 / 186 (2.69%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolysis			

subjects affected / exposed	1 / 186 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count			
subjects affected / exposed	8 / 186 (4.30%)	7 / 183 (3.83%)	
occurrences causally related to treatment / all	0 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	7 / 186 (3.76%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count			
subjects affected / exposed	1 / 186 (0.54%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	9 / 186 (4.84%)	10 / 183 (5.46%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema limb			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured spleen			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anorexia nervosa			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 186 (0.54%)	3 / 183 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 186 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 186 (0.00%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			

subjects affected / exposed	2 / 186 (1.08%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 186 (0.54%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (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			
Cellulitis			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other: Chest			
subjects affected / exposed	2 / 186 (1.08%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	6 / 186 (3.23%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 186 (1.08%)	4 / 183 (2.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary/upper respiratory - lower respiratory tract			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	5 / 186 (2.69%)	2 / 183 (1.09%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General - Blood			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection (documented clinically) with grade 3 or 4 ANC			
subjects affected / exposed	2 / 186 (1.08%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC			
subjects affected / exposed	2 / 186 (1.08%)	1 / 183 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC - pulmonary/upper respiratory - lung (pneumonia)			
subjects affected / exposed	3 / 186 (1.61%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			

subjects affected / exposed	1 / 186 (0.54%)	0 / 183 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	FCR Arm	FC Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 186 (75.81%)	127 / 183 (69.40%)	
Blood and lymphatic system disorders			
Haemoglobin			
subjects affected / exposed	24 / 186 (12.90%)	25 / 183 (13.66%)	
occurrences (all)	24	25	
Leukocytes			
subjects affected / exposed	99 / 186 (53.23%)	79 / 183 (43.17%)	
occurrences (all)	99	79	
Neutrophil count			
subjects affected / exposed	102 / 186 (54.84%)	87 / 183 (47.54%)	
occurrences (all)	102	87	
Platelet count			
subjects affected / exposed	53 / 186 (28.49%)	31 / 183 (16.94%)	
occurrences (all)	53	31	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 186 (6.45%)	16 / 183 (8.74%)	
occurrences (all)	12	16	
Immune system disorders			
Allergy NOS			
subjects affected / exposed	10 / 186 (5.38%)	1 / 183 (0.55%)	
occurrences (all)	10	1	
Blood and platelet reaction			
subjects affected / exposed	0 / 186 (0.00%)	1 / 183 (0.55%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Pulmonary NOS subjects affected / exposed occurrences (all)	7 / 186 (3.76%) 7	10 / 183 (5.46%) 10	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	7 / 186 (3.76%) 7	10 / 183 (5.46%) 10	
Infections and infestations Infection subjects affected / exposed occurrences (all)	23 / 186 (12.37%) 23	21 / 183 (11.48%) 21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2008	Protocol was updated to change the contact details for drug supply order
02 December 2008	The protocol, Patient Information Sheet and Informed Consent form were updated to reflect the change in the samples to be collected from trial subjects. The Trial outline in the protocol was re-designed to make it easier to understand. The pharmacovigilance section of the protocol was also updated.
28 April 2009	On reviewing the timings of investigations at study entry, the time period for CT scan and bone marrow biopsy were extended to 6 weeks before randomisation. The protocol was updated to reflect this and the Mabthera order form was removed as an appendix.
21 June 2010	An audit of the patient information sheet showed that contraception guidelines given to patients in the PIS was not accurate, the patient information sheet did not specify for how long after completing treatment patients should continue using contraception, thus leading to an Urgent Safety Measure being taken. The PIS was amended to advice patients to use adequate contraception for 12 months after stopping trial treatment (as suggested in the IB v 14 May 2009 for Rituximab, which is one of the trial drugs for the study). A paragraph justifying the need of using contraception and listing examples of reliable forms of contraception was also added to the PIS. An Addendum to the previous PIS emphasising the need to use contraception for 12 months post trial treatment and Consent form confirming patient is aware of this new information was also sent to sites with clear instructions that all patients of child bearing potential or with female partners of child bearing potential, patients on treatment or who have completed treatment within 12 months needed to be re-consented.
13 September 2010	In the protocol; a requirement for contraceptive precautions up to 12 months post last trial treatment was included as an exclusion criteria, the statistical consideration was reviewed and the sample size was reduced with new calculations given, participating sites were no longer required to perform evaluation of SAE expectedness as this was transferred to UCL CTC, SAE expectedness assessment against the current IB/SmPCs was included as a requirement thus removing the existing AEs list for each separate IMP from the appendix. The PIS was updated to include new safety information regarding Rituximab and an addendum was created to be used to re-consent trial patients randomised to the Rituximab arm to the new safety information from Roche.
22 March 2011	Reg 46 Labelling exemption was granted for intravenous fludarabine and cyclophosphamide based on the facts that they were marketed products used broadly within their authorisations, they were to be dispensed to subjects in accordance with a prescription given by an authorised health care professional and they were labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 that apply in relation to dispensed relevant medicinal products. Abridged labels were to be used for the oral administrations of these drugs. Rituximab, given intravenously, was supplied from Roche as commercial stock. They were to be labelled on receipt at pharmacy and designated as use for the trial. Rituximab labels were amended to comply with Annex 13 requirements.

19 June 2014	The protocol was amended to update the change in the End of Trial definition, so as to include the time points for the primary endpoint, Overall Survival.

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.

Non-serious AEs: occurrences all number can't be provided as only highest grade experienced by patients are collected on CRFs; subjects affected is entered instead (only grade 3-4 reported)
Treatment related death/relatedness to SAEs not available

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26611473