Clinical trial results:
A Phase II Single Arm Study of the use of CODOX-M/IVAC with Rituximab (R-CODOX-M/IVAC) in the treatment of patients with Diffuse Large B-Cell Lymphoma (DLBCL) or Burkitt's Lymphoma (BL) of International Prognostic Index (IPI) High or High-Intermediate Risk

Summary

EudraCT number	2005-003479-19
Trial protocol	GB
Global end of trial date	26 May 2016

Results information

Result version number	v1 (current)
This version publication date	03 January 2020
First version publication date	03 January 2020

Trial information

Trial identification

Sponsor protocol code	UCL/05/134

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00974792
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	Public Contact, Cancer Research UK & UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific Contact, Cancer Research UK & 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	03 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does the combination of Rituximab and CODOX-M/IVAC improve the progression free survival in patients with newly diagnosed diffuse large B cell lymphoma or Burkitt's lymphoma of international prognostic index high or high-intermediate risk?

Caveats
AEs: Only events experienced by 5% or more patients are given.
Relationships are to R-CODOX-M/R-IVAC treatment (i.e. any IMP)

Non-serious AEs:
- Non-serious adverse events includes both serious and non-serious events. Only grade 3+ events given.
- Some terms were not recorded as per CTCAE so e.g. "Neurological - NOS" so could not be categorised any further.
- The total number of events is the number of patients experiencing an event as only worst grades were reported

Protection of trial subjects:

CODOX-M/IVAC had previously been given to patients with Burkitt lymphoma and it was suggested that DLBCL patients would do better with the more intense regimen. Rituximab was added as it was unlikely to alter the toxicity but could improve responses.

Etoposide was used outside its licensed indication (testicular tumour, small cell lung cancer and monoblastic leukaemia). Drug accountability logs were kept by sites, and sent to UCL CTC on request. Though DLBCL is not listed as an indication for etoposide in the SmPC, more than a dozen published clinical trials have used this drug in the treatment of DLBCL patients. Only investigators/nurses experienced in using these IMPs according to the protocol were delegated treatment responsibilities. IDMC committee met at least annually to review safety data.

Patients were closely monitored for toxicity and the protocol detailed non-haematological toxicity dose modifications.

Background therapy:

Leucovorin (15mg/m^2, IV) was administered as part of the R-CODOX-M regimen. It was administered at hour 36 and then every three hours until hour 48. From then it was administered every 6 hours until methotrexate level was below 5x10^-8M.

Patients also received Mesna as part of the R-IVAC regimen on days 1-5. Intravenous Mesna 300mg/m^2 was administered mixed with ifosfamide (1.5g/m^2) over a one hour period.

Co-trimoxazole 480mg (PO) was administered twice daily on Mondays, Wednesdays and Fridays during treatment and for six months post therapy.

Mouth care, antacids and anti-emetics were given according to local protocols. The suggested regimen

was: Corsdyl 5ml qd mouthwash; Acyclovir 200mg qd or 400mg bd; lansoprazole 30mg od (po); metoclompramide 10mg tds for 3 days.

Radiotherapy was permitted in specific situations and the protocol detailed guidance on CNS prophlyaxis and treatment, and post-treatment neutropenia.

Evidence for comparator:

This trial was a single arm study and therefore no comparator was used.

Actual start date of recruitment	05 December 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 150
Worldwide total number of subjects	150
EEA total number of subjects	150

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)	146
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first site opened on the 5th December 2007 and the first patient was recruited on the 21st May 2008. Recruitment completed on the 2nd April 2013 with a total of 150 patients recruited to the trial. A total of 52 sites participated in the trial, 36 sites recruited patients and 16 sites did not recruit any patients.

Pre-assignment

Screening details:

No screening information to provide for this trial. Patients were screened for eligibility for inclusion into the trial as per trial protocol.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Arm title	CODOX-M/IVAC with Rituximab

Arm description:

A phase II single arm study of the use of CODOX-M/IVAC with rituximab (R-CODOX-M/IVAC) in the treatment of patients with diffuse large B-cell lymphoma DLBCL) or Burkitt's lymphoma (BL) of international Prognostic Index (PI) high or high intermediate risk.

Efficacy, compliance and Baseline tables are given for eligible patients only (N=27 BL and N=111). Toxicity is given for all patients who started treatment (N=145)

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

Dosage and administration details:

Four 375mg/m2 IV doses of rituximab given with 2 cycles of CODOX-M on Day 1 and Day 11, and two IV 375mg/m2 doses of rituxmimab given with 2 cycles of IVAC on Day 1. Two further IV doses of rituximab given on Day 21 and Day 42 after day one of the final course of IVAC.

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

Dosage and administration details:

Cyclophosphamide given IV on Day 1 800mg/m2 and Day 2-5 200mg/m2 daily of CODOX-M treatment.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	L01C A02
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Given IV on Day 1 1.5mg/m2 (max 2mg) and Day 8 1.5mg/m2 (max 2mg) of CODOX-M.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	L01DB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

40mg/m2 given IV on Day 1 of CODOX-M.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	L01BC01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intrathecal use, Intravenous use

Dosage and administration details:

Given on Day 2 70mg intrathecal, Day 4 70mg intrathecal, Day 6 (for patients with proven or suspected CNS disease) 70mg intrathecal of CODOX-M.
For IVAC - given on Day 1 & 2 2g/m2 IV over 3 hours, 12 hourly total of 4 doses; Day 7 (for patients with proved or suspected CNS disease) 70mg intrathecal; Day 9 (for patients with proven or suspected CNS disease) 70mg intrathecal.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	L01BA01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For R-CODOX-M: Given on Day 10 300mg/m2 IV for 1 hour and 2700mg/m2 IV given over 23 hours. It was given on Day 15 12mg intrathecal and Day 17 (for patients with proven or suspected CNS disease) 12mg intrathecal.
For IVAC: Given on day 5 12mg intrathecal.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	L01CB01
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For IVAC: Days 1-5 etoposide 60mg/m2 IV (in 500ml of N. saline or 5% dextrose) daily over 1 hour.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	L01AA06
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

For IVAC: Day 1-5 Ifosfamide IV 1.5g/m2 daily over an hour.

Investigational medicinal product name	Pegylated G-CSF
Investigational medicinal product code	L03AA13
Other name	Neulasta
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

For R-CODOX-M: Day 13 Neulasta 6mg subcutaneous
For IVAC: Day 7 Neulasta 6mg subcutaneous

Number of subjects in period 1	CODOX-M/IVAC with Rituximab
Started	150
Completed	107
Not completed	43
Adverse event, serious fatal	4
Patient refusal	2
death (NHL)	2
Consent withdrawn by subject	1
Not eligible	12
Adverse event, non-fatal	16
Lack of understanding	1
Other medical conditions	1
Rapid progression (did not start)	1
Progressive disease	1
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	CODOX-M/IVAC with Rituximab

Reporting group description:

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Efficacy, compliance and Baseline tables are given for eligible patients only (N=27 BL and N=111). Toxicity is given for all patients who started treatment (N=145)

Reporting group values	CODOX-M/IVAC with Rituximab	Total	
Number of subjects	150	150	
Age categorical Units: Subjects			
BL Under 40 yrs	15	15	
BL 40-60 yrs	10	10	
BL 60 yrs and over	2	2	
DLBCL 60 yrs and under	98	98	
DLBCL Over 60 yrs	13	13	
Ineligible	12	12	
Age continuous			
BL Age Median = 35 years BL Range = 20-64 years DLBCL Age Median = 50 years DLBCL Range = 18-65 years			
Units: years			
median	48		
full range (min-max)	18 to 65	-	
Gender categorical Units: Subjects			
BL Female	3	3	
BL Male	24	24	
DLBCL Female	45	45	
DLBCL Male	66	66	
Ineligible	12	12	
Diagnosis Units: Subjects			
DLBCL	111	111	
BL	27	27	
Ineligible	12	12	
WHO performance status Units: Subjects			
BL Nil (0)	6	6	
BL One (1)	8	8	
BL Two (2)	8	8	
BL Three (3)	5	5	
DLBCL Nil (0)	23	23	
DLBCL One (1)	28	28	
DLBCL Two (2)	38	38	

DLBCL Three (3)	22	22	
Ineligible	12	12	
>1 extra nodal sites Units: Subjects			
BL >1 extra nodal site - Yes	24	24	
BL >1 extra nodal site - No	3	3	
DLBCL >1 extra nodal site - Yes	88	88	
DLBCL >1 extra nodal site - No	23	23	
Ineligible	12	12	
CNS involvement Units: Subjects			
BL - Yes	4	4	
BL - No	23	23	
DLBCL - Yes	10	10	
DLBCL - No	101	101	
Ineligible	12	12	
B Symptoms Units: Subjects			
BL Absent	12	12	
BL Present	15	15	
DLBCL Absent	34	34	
DLBCL Present	77	77	
Ineligible	12	12	
Tumour Stage Units: Subjects			
BL Stage III	3	3	
BL Stage IV	24	24	
DLBCL Stage III	7	7	
DLBCL Stage IV	104	104	
Ineligible	12	12	
Lactate Dehydrogenase Units: Subjects			
BL Elevated LDH	27	27	
DLBCL LDH above upper limit of normal - No	5	5	
DLBCL LDH above upper limit of normal - Yes	106	106	
Ineligible	12	12	
IPI Score Units: Subjects			
BL Three (3)	14	14	
BL Four (4)	13	13	
DLBCL Three (3)	67	67	
DLBCL Four (4)	43	43	
DLBCL Five (5)	1	1	
Ineligible	12	12	
Bone marrow involvement Units: Subjects			
BL No	10	10	
BL Yes	14	14	
BL Unknown	3	3	

DLBCL bone marrow at baseline not involved	111	111	
Ineligible	12	12	
HIV Status Units: Subjects			
BL Negative	22	22	
BL Positive	5	5	
DLBCL Negative	108	108	
DLBCL Positive	1	1	
DLBCL Unknown	2	2	
Ineligible	12	12	

End points

End points reporting groups

Reporting group title	CODOX-M/IVAC with Rituximab

Reporting group description:

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Efficacy, compliance and Baseline tables are given for eligible patients only (N=27 BL and N=111). Toxicity is given for all patients who started treatment (N=145)

Primary: Progression-free survival (BL)

End point title	Progression-free survival (BL)[1]

End point description:

End point type	Primary

End point timeframe:

2 years from time of registration

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: No statistical test for this endpoint, the historical rate was compared to the 2 year PFS found and its confidence interval.

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27[2]			
Units: % patients alive without PD				
number (confidence interval 90%)	77.2 (60.1 to 87.6)			

Notes:

[2] - BL cohort only

Attachments (see zip file)	PFS KM curve BL all/PFS_BL_all.tif

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (DLBCL)

End point title	Progression Free Survival (DLBCL)[3]

End point description:

End point type	Primary

End point timeframe:

2 years from ranomisation

Notes:

[3] - 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: No statistical test for this endpoint, the historical rate was compared to the 2 year PFS found and its confidence interval.

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	111[4]			
Units: % of patients alive without PD				
number (confidence interval 90%)	67.9 (59.9 to 74.6)			

Notes:

[4] - DLBCL cohort only

Attachments (see zip file)	PFS KM curve DLBCL all/PFS_DLBCL_all.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (BL)

End point title	Overall Survival (BL)

End point description:

End point type	Secondary

End point timeframe:

2 years

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27[5]			
Units: % alive at 2 years				
number (confidence interval 90%)	80.7 (63.8 to 90.3)			

Notes:

[5] - BL cohort only

Attachments (see zip file)	OS KM curve BL all/OS_BL_all.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (DLBCL)

End point title	Overall Survival (DLBCL)

End point description:

End point type	Secondary

End point timeframe:

2 years

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	111[6]			
Units: % alive at 2 years				
number (confidence interval 90%)	76.0 (68.5 to 82.0)			

Notes:

[6] - DLBCL cohort only

Statistical analyses

No statistical analyses for this end point

Secondary: Response (BL)

End point title	Response (BL)

End point description:

End point type	Secondary

End point timeframe:

End of treatment

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27[7]			
Units: patients				
CR	17			
CRu	4			
PR	2			
SD	0			
PD	0			
Not evaluable	4			

Notes:

[7] - BL cohort only

Statistical analyses

No statistical analyses for this end point

Secondary: Response (DLBCL)

End point title	Response (DLBCL)

End point description:

End point type	Secondary

End point timeframe:
end of treatment

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	110[8]			
Units: patients				
CR	41			
CRu	11			
PR	30			
SD	3			
PD	4			
Not evaluable	21			

Notes:
[8] - DLBCL who started treatment only

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment compliance (BL)

End point title	Treatment compliance (BL)

End point description:
Numbers of patients who were given cycles 1-4

End point type	Secondary

End point timeframe:
End of treatment

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	27[9]			
Units: Patients				
Cycle 1	1			
Cycle 2	2			
Cycle 3	2			

Cycle 4	22			

Notes:

[9] - BL cohort only

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Compliance (DLBCL)

End point title	Treatment Compliance (DLBCL)

End point description:

Number of patients who were given each cycle

End point type	Secondary

End point timeframe:

End of treatment

End point values	CODOX-M/IVAC with Rituximab			
Subject group type	Reporting group			
Number of subjects analysed	110[10]			
Units: Patients				
Cycle 1	16			
Cycle 2	3			
Cycle 3	6			
Cycle 4	85			

Notes:

[10] - DLBCL patients who started treatment only

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) that occur between informed consent and 30 days post treatment.

Adverse event reporting additional description:

Patients were assessed for adverse events prior to each treatment cycle. Pre-existing conditions did not qualify as adverse events unless they worsened. Relationships are to R-CODOX-M R-IVAC treatment (i.e. counted as related if possibly, probably or definitely related to any IMP in the regimen). 145 out of 145 patients experienced at least one AE.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Overall trial

Reporting group description:

AEs are reported including both cohorts (DLBCL and BL). Both groups were given the trial treatment as per protocol; alternating CODOX-M/IVAC x 2 cycles + G-CSF, + rituximab x 8 doses, + cytarabine (4/7 doses), + methotrexate (4/5 doses).

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 145 (48.28%)		
number of deaths (all causes)	39		
number of deaths resulting from adverse events	6		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Hypotension			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac infarction			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage			
subjects affected / exposed	7 / 145 (4.83%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	1 / 1		
Mood altered			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cranial neuropathy			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Personality change				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disturbance				
subjects affected / exposed	2 / 145 (1.38%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
CNS Ischemia				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Motor neuropathy				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 145 (1.38%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 145 (1.38%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Bone marrow suppression				

subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	20 / 145 (13.79%)		
occurrences causally related to treatment / all	20 / 20		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	4 / 145 (2.76%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain GI abdomen			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hearing			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Enteritis			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Ileus			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anorexia nervosa			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Perforated small bowel			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small bowel obstruction			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 145 (1.38%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Mucositis			
subjects affected / exposed	7 / 145 (4.83%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			

subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	4 / 145 (2.76%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	1 / 1			
Reproductive system and breast disorders				
Haemorrhage				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Testicular pain				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary haemorrhage				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	2 / 145 (1.38%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Plural effusion				
subjects affected / exposed	1 / 145 (0.69%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Adult Respiratory Distress Syndrome (ARDS)			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Radionecrosis spinal cord			
subjects affected / exposed	1 / 145 (0.69%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection NOS			
subjects affected / exposed	17 / 145 (11.72%)		
occurrences causally related to treatment / all	17 / 17		
deaths causally related to treatment / all	4 / 4		
Febrile neutropenia			
subjects affected / exposed	14 / 145 (9.66%)		
occurrences causally related to treatment / all	14 / 14		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 145 (100.00%)		
Investigations			
Hypokalaemia			
subjects affected / exposed	8 / 145 (5.52%)		
occurrences (all)	8		
Cardiac disorders			

Cardiac NOS subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 11		
Nervous system disorders Neurological not specified subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	11 / 145 (7.59%) 11 8 / 145 (5.52%) 8		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	15 / 145 (10.34%) 15 140 / 145 (96.55%) 140 38 / 145 (26.21%) 38 136 / 145 (93.79%) 136		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Fever subjects affected / exposed occurrences (all)	9 / 145 (6.21%) 9 29 / 145 (20.00%) 29		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea	16 / 145 (11.03%) 16		

subjects affected / exposed	14 / 145 (9.66%)		
occurrences (all)	14		
Anorexia			
subjects affected / exposed	13 / 145 (8.97%)		
occurrences (all)	13		
Vomiting			
subjects affected / exposed	9 / 145 (6.21%)		
occurrences (all)	9		
Mucositis			
subjects affected / exposed	47 / 145 (32.41%)		
occurrences (all)	47		
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	27 / 145 (18.62%)		
occurrences (all)	27		
Infection NOS			
subjects affected / exposed	95 / 145 (65.52%)		
occurrences (all)	95		
Sepsis			
subjects affected / exposed	3 / 145 (2.07%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2006	An amendment to the protocol containing the following changes: • For each of the IVAC courses the Depocyte is given on day 5 not on day 1 • Consequently Dexamethasone is moved to day 5-10 instead of day 1-5 • The Depocyte will be given on day 5 as a part of treatment of patients with CNS disease
19 October 2006	The protocol was amended as follows: • International Prognostic Index has replaced the Age Adjusted IPI in Appendix 1 and reference made to this changed throughout the protocol • The Declaration of Helsinki was added, appendix 11 • Reference to Rasburicase removed • Information on who will be supplying what drugs was added • Rituximab amended to be given on day 11 as opposed to day 10 • Section on safety reporting has had additions made to it, providing more comprehensive information to sites as well as a flow diagram on assessing and notifying the Lymphoma Trials Office of events • A reference has been removed • Appendix 3 addition of information prophylaxis has been added • Patient Information Sheet, reference to 'age adjusted' has been removed as well as reference to Rasburicase • Consent form part I and II, reference to 'age adjusted' has been removed • GP letter, reference to 'age adjusted' has been removed. • Contact details have changed for Cathy Burton.
28 August 2007	The protocol, PIS, consent form and GP letter were amended as below: • International Prognostic Index replaced the Age Adjusted IPI in Appendix 1 and reference made to this was changed throughout the protocol • The Declaration of Helsinki was added, appendix 11 • Reference to Rasburicase was removed • Information on who will be supplying what drugs was added • Rituximab was amended to be given on day 11 as opposed to day 10 • Section on safety reporting had additions made to it, providing more comprehensive information to sites as well as a flow diagram on assessing and notifying the Lymphoma Trials Office of events • Pg 42, a reference was removed • Appendix 3 addition of information on prophylaxis was added • Patient Information Sheet reference to 'age adjusted' was removed as well as reference to Rasburicase • Consent form part I and II reference to 'age adjusted' was removed • GP letter reference to 'age adjusted' was removed • Contact details changed for Cathy Burton
20 August 2008	An Urgent Safety Measure (USM) led to an amendment to the protocol, PIS and consent form. This was following a decision to remove Depocyte (liposomal cytarabine) from the protocol treatment schedule due to safety concerns over it's use with high dose chemotherapy, Depocyte was replaced in the protocol amendment with a proven safe and effective option. The PIS was also amended to include an update to the the number of times patients would receive intrathecal treatment.

19 May 2009	The title of the study and the protocol was amended to include Burkitt's Lymphoma (BL). The decision to include BL patients into the trial was based upon published data which suggested promising results had been reported using CODOX-M/IVAC in this group of patients at the time. The protocol amendment included: • Change of primary outcome measure and endpoint to progression free survival • More information given on non-haematological toxicity & dose modification (section 8.2) • Statistical Consideration section was changed to reflect the change in endpoint and inclusion of Burkitt's lymphoma patients (section 13) • Additional information added to Appendix 5, recommending that Septrin be stopped once week prior to the administration of high dose methotrexate to avoid any potential drug reactions • Appendix 6 included an extensive list of toxicities expected with chemotherapy drugs • PIS , consent form and GP letter removed as appendices and provided as stand alone documents • The inclusion of BL patients was added to the PIS and GP letter, the title of the consent form was changed on the consent form, GP letter and the PIS. The PIS was also updated to include the advice by Roche over the concern of patients developing Progressive Leukoencephalopathy (PML) having been treated with rituximab.
09 August 2010	The protocol was amended to include the following changes: • Change of protocol cover page and authorisation signature page • Additional information to the site selection section (section 3.0) • Addition of a section on Informed consent (section 4.0) • Change in the patient selection section; baseline investigations and eligibility criteria. Maximum age of inclusion was increased from 60 years as stated in the original application to 65 years of age. Echocardiogram or nuclear medicine scan (MUGA) was made mandatory for patients aged from 61 to 65 years. (sections 5.1 and 5.3.1) • Addition of sections on pregnancy /birth control and long term infertility (sections 5.3.3 and 5.3.4) • Additional sections on trial monitoring and oversight, withdrawal of patients and trial closure (sections 14.0, 15.0 & 16.0,) • Additional information to the ethical and regulatory approvals section (section 18.0) • Additional sections on sponsorship & indemnity, funding and publication policy (section 19.0, 20.0 and 21.0) • Removal of the expected toxicities for each chemotherapy drug from the appendix, and the addition of expected adverse events for the treatment regimen. The expected adverse events for each drug will be based on the individual SmPCs (appendix 9) The PIS and consent form were also updated to reflect the changes to the protocol.
28 January 2011	The protocol was amended following an urgent safety measure (USM) which lead to amending the treatment schedule so vincristine was no longer scheduled on the same day as the intrathecal drugs.
06 June 2011	The protocol was amended to include: • Update of the Trial Synopsis to include patients with positive serology for HIV • Inclusion of a section on the training requirements for site staff • Additional information for patients pre-treated with steroids • Addition of patients with positive serology for HIV with criteria to be satisfied in the 'inclusion criteria' • Addition of Neulasta to the list of IMPs as stated in the CT application • Update of rituximab administration to fall in line with the information given in its SPC • Update of the dose modification for renal impairment toxicity • Update to the data management, pharmacovigilance, trial monitoring and oversight sections of the protocol • Addition of a reference to the existing list • Update to the appendix on Methotrexate administration and uroprotection • Update to the appendix on protocol version history

14 October 2015	The protocol was amended to clarify timelines for adverse event reporting. The wording was amended to state' adverse events that occur between informed consent and 30 days days post trial treatment must be recorded in the patient notes and the trial CRFs'.

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.

See 'general information about the trial' section.

Notes: