Clinical trial results:
A PHASE II EVALUATION OF HIGH DOSE CHEMOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR INTESTINAL T CELL LYMPHOMAS

Summary

EudraCT number	2005-003906-27
Trial protocol	GB
Global end of trial date	14 November 2014

Results information

Result version number	v1 (current)
This version publication date	04 September 2016
First version publication date	04 September 2016

Trial information

Trial identification

Sponsor protocol code	UCL/05/93

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00669812
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, CR UK & UCL Cancer Trials Centre, ctc.sponsor@ucl.ac.uk
Scientific contact	Scientific Contact, CR 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	22 January 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In patients with T-cell lymphoma complete clinical remissions can be obtained with conventional treatment (usually CHOP based) but they are often short-lived. The disease has a tendency to relapse, and there may be an increased (over that of B-cell tumours) risk of CNS involvement at relapse. Consequently patients with T-cell lymphoma have poor long term outcomes with conventional CHOP based therapies.
The main objective of this study is to assess the efficacy and toxicity of intensive chemotherapy (alternating IVE and intermediate dose methotrexate) for treatment of aggressive T-cell lymphomas of defined histological subtypes.

Protection of trial subjects:

Intensive treatment of this kind has side effects, patients were monitored closely so that any side effects could be treated quickly.
Women who could become pregnant were informed that they must use an effective contraceptive during the course of the study as should male patients because the treatment can interfere with normal functioning of the female egg or male sperm.
Undergoing treatment of this intensity may affect future fertility and males were therefore advised to undergo sperm banking before the treatment begins if they wished to preserve fertility.

Background therapy:

Folinic acid and mesna are NIMPS in this study.

Five doses of calcium folinate 15mg/m2 are given at 3 hour intervals, between +36 hours and +48 hours post start of the Methotrexate infusion.

On day 1 of IVE, MESNA is given at 1800mg/m2 as IV bolus prior to administration of Ifosfamide, and on days 1-3 of IVE as two 11 hour IV infusions with Ifosfamide. On day 4 of IVE treatment, MESNA is given as a 12 hour infusion at 5400mg/m2.

Evidence for comparator:

N/A - no comparator used

Actual start date of recruitment	07 September 2009
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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	20
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient recruited: 07/09/2009, last patient recruited: 03/07/2013
sites open to recruitment: Beatson WOS, Bristol UH, Great Western Hospital, Royal Liverpool, Royal Victoria Infirmary, Southampton General, St James UH Leeds, Royal Devon & Exeter, UCLH, Royal Cornwall, Royal Bournemouth, Torbay, Derriford
4 of these sites entered no patients

Pre-assignment

Screening details:

See reporting group description

Period 1

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

Blinding implementation details:

N/A

Arms

Arm title	CHOP, IVE and intermediate dose methotrexate & BEAM autograft

Arm description:

1 course of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)
3 cycles of alternating IVE (ifosphamide, etoposide & epirubicin) and intermediate dose methotrexate (1.5g/m2)
BEAM (BCNU, etoposide, cytarabine, melphalan) autograft

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Given on day 1 of CHOP treatment as IV at 750mg/m2.

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

Dosage and administration details:

Given on day 1 of CHOP treatment as IV at 50mg/m2.

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

Dosage and administration details:

Given on day 1 of CHOP treatment as IV at 1.5mg/m2 (max 2mg).

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

Dosage and administration details:

Taken orally on days 1 to 5 of CHOP treatment at 40mgs/m2 daily.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Given on day 1 of IVE treatment at 50mg/m2 as IV (bolus). 3 cycles of IVE are given with intermediate doses Methotrexate.

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

Dosage and administration details:

Given on days 1 to 3 of IVE treatment at 200mg/m2/day as a 2 hour IV infusion. 3 cycles of IVE are given with intermediate doses Methotrexate.

Given on day –6 to day –3 of BEAM conditioning at 200 mg/m2 as IV infusion.

Investigational medicinal product name	Ifosfamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Given on days 1 to 3 of IVE treatment at 1500mg/m2 as a two 11 hour IV infusions. 3 cycles of IVE are given with intermediate doses Methotrexate.

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

Dosage and administration details:

Intermediate doses Methotrexate are given alternating with 3 cycles of IVE .
Methotrexate administration details:
- Pre-hydrate
4000ml 0.9% Sodium chloride+100mmol/l Sodium Bicarbonate at 125ml/m2/hour started 12 hours prior to methotrexate
- Check urine pH is >8
- Start methotrexate 1.5g/m2
10% of total dose over 1 hour in 100ml 0.9% Sodium chloride
90% of total dose over 23 hours in 1000ml 0.9% Sodium chloride
- Continue hydration alongside methotrexate
4000ml 0.9% Sodium chloride +100mmol/l Sodium Bicarbonate at 125ml/m2/hour

- Continue hydration at 125mls/m2/hour for 24 hours (reduced if patient is fluid overloaded). Run concurrently with calcium folinate rescue until Methotrexate level is <0.005 micromol/l.
Five doses of calcium folinate 15mg/m2 are given at 3 hour intervals, between +36 hours and +48 hours post start of the Methotrexate infusion.

4000ml 0.9% Sodium chloride

Investigational medicinal product name	Carmustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Given on day -7 of BEAM conditioning at 300mg/m2 as IV infusion.

Investigational medicinal product name	Lomustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

BEAM conditioning: In the unlikely event of Carmustinie (BCNU) supplies becoming limiting, oral Lomustine (CCNU) at a dose of 200 mg/m2 can be substituted.

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

Dosage and administration details:

Given on day –6 to day –3 of BEAM conditioning at 200 mg/m2 twice daily as IV infusion.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Given on day –2 of BEAM conditioning at 140 mg/m2 as IV infusion.

Number of subjects in period 1	CHOP, IVE and intermediate dose methotrexate & BEAM autograft
Started	22
Completed	20
Not completed	2
Lack of efficacy	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Inclusion criteria
- Newly confirmed diagnosis of intestinal T-cell / Enteropathy-type T-Cell lymphoma, Peripheral T-cell lymphoma NOS, Hepatosplenic T-cell lymphoma, ALK negative Anaplastic T-Cell Lymphoma and Extranodal NK/T-cell lymphoma according to the WHO classification
- Age greater than 18 years
- Physically able to tolerate the planned treatment programme (Patients with ETL not suitable for intensive treatment encouraged to participate in the registration study)
- Patients must give written informed consent

Exclusion criteria
- Pregnancy or breastfeeding
- Prior chemotherapy or radiotherapy for treatment of their lymphoma
- Serious concomitant medical or psychiatric condition (entered into registration study only)
- Active malignancy or treatment for malignancy in the last 5 years, excluding cervical intraepithelial neoplasia (CIN) or localised skin cancer
- Seropositivity for HBV HCV or HIV
- Severe impairment of liver / renal / cardiac / bone marrow function

Reporting group values	Overall trial	Total	
Number of subjects	22	22	
Age categorical			
This includes only subjects entered into the treatment arm of the study, not the registration study			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	20	20	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
Units: years			
median	56		
full range (min-max)	29 to 81	-	
Gender categorical			
Units: Subjects			
Female	7	7	
Male	15	15	

End points

End points reporting groups

Reporting group title	CHOP, IVE and intermediate dose methotrexate & BEAM autograft

Reporting group description:

1 course of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)
3 cycles of alternating IVE (ifosphamide, etoposide & epirubicin) and intermediate dose methotrexate (1.5g/m2)
BEAM (BCNU, etoposide, cytarabine, melphalan) autograft

Primary: Survival at 1 year

End point title	Survival at 1 year[1]

End point description:

The primary endpoint is to assess one year survival after high dose chemotherapy and autologous transplantation.

End point type	Primary

End point timeframe:

The primary endpoint of survival at 1 year is measured 12 months after registration of each patient

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: As advised on 23/Jun/16 by Chersoni Raffaella from the EMA service desk: we can post the result without entering the details of the statistical analysis because currently the system cannot accommodate one arm study.

End point values	CHOP, IVE and intermediate dose methotrexate & BEAM autograft			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: 14	14			

Attachments (see zip file)	Overall survival/Figure 1 - Overall survival.docx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred between informed consent & during trial treatment and all SAEs that occurred between informed consent and 30 days post transplant (or after this date if thought to be related to trial treatment) had to be reported

Adverse event reporting additional description:

During treatment patients were seen before each cycle of treatment commenced and were assessed for adverse events, including hematology and biochemistry. Adverse events were recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event were also be reported to UCL CTC using the trial specific SAE Report.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	4

Reporting groups

Reporting group title	CHOP, IVE and intermediate dose methotrexate & BEAM autograft

Reporting group description:

1 course of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone)
3 cycles of alternating IVE (ifosphamide, etoposide & epirubicin) and intermediate dose methotrexate (1.5g/m2)
BEAM (BCNU, etoposide, cytarabine, melphalan) autograft

Serious adverse events	CHOP, IVE and intermediate dose methotrexate & BEAM autograft		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 22 (86.36%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	1		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Vascular access complication			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Encephalopathy			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	10 / 22 (45.45%)		
occurrences causally related to treatment / all	9 / 10		
deaths causally related to treatment / all	0 / 0		
Anaemia			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Photophobia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colonic perforation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Perforation of ileal tumour			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Perforation of jejunal tumour			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal perforation			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal hemorrhage			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal function test abnormal			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			

subjects affected / exposed	3 / 22 (13.64%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infection with grade 3 or 4 neutrophils				
subjects affected / exposed	5 / 22 (22.73%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	1 / 1			
Infection with grade 4 neutrophils				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	CHOP, IVE and intermediate dose methotrexate & BEAM autograft		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Hypertension			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Phlebitis			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Thrombosis			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	11 / 22 (50.00%)		
occurrences (all)	11		
Fever			
subjects affected / exposed	15 / 22 (68.18%)		
occurrences (all)	15		
Oedema	Additional description: Oedema: limb (4), Oedema: head and neck (1)		
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Non-cardiac chest pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Sore throat			
subjects affected / exposed	6 / 22 (27.27%)		
occurrences (all)	6		
Cough			
subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Investigations White blood cell count decreased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Haemoglobin increased subjects affected / exposed occurrences (all) Weight loss subjects affected / exposed occurrences (all) Alanine aminotransferase increased subjects affected / exposed occurrences (all) Creatine urine increased subjects affected / exposed occurrences (all)	 4 / 22 (18.18%) 4 5 / 22 (22.73%) 5 22 / 22 (100.00%) 22 20 / 22 (90.91%) 20 2 / 22 (9.09%) 2 3 / 22 (13.64%) 3 3 / 22 (13.64%) 3 2 / 22 (9.09%) 2		
Cardiac disorders Paroxysmal atrial tachycardia subjects affected / exposed occurrences (all)	 3 / 22 (13.64%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Neurological	 6 / 22 (27.27%) 6		

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 22 (77.27%)		
occurrences (all)	17		
Febrile neutropenia			
subjects affected / exposed	9 / 22 (40.91%)		
occurrences (all)	9		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 22 (45.45%)		
occurrences (all)	10		
Diarrhoea			
subjects affected / exposed	15 / 22 (68.18%)		
occurrences (all)	15		
Flatulence			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Mucositis			
subjects affected / exposed	12 / 22 (54.55%)		
occurrences (all)	12		
Nausea			
subjects affected / exposed	18 / 22 (81.82%)		
occurrences (all)	18		
Perforation			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	15 / 22 (68.18%)		
occurrences (all)	15		
Abdominal pain			

subjects affected / exposed	8 / 22 (36.36%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Chest wall pain			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Infections and infestations			
Infection	Additional description: Infection - NOS (17), Infection - Other (Neutropenic sepsis) (1), Infection - Other (Cold) (1), Infection - Other (Staph aureus) (1)		
subjects affected / exposed	20 / 22 (90.91%)		
occurrences (all)	20		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Dehydration			

subjects affected / exposed	4 / 22 (18.18%)		
occurrences (all)	4		
Hypoalbuminaemia			
subjects affected / exposed	5 / 22 (22.73%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Hypomagnesemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2007	The original CTA listed all drugs used in this trial together with information on the companies who supply this drug. As hospitals use their own hospital stock for this trial we thought the CTA should tie in with the information in the approved protocol by allowing sites to use generic stock, hence why the CTA has been amended by omitting this information.
01 October 2008	Amendment to Protocol, PIS, Consent form: Page 9, 22 and 18 in protocol and page 36 and 37 in PIS- clarified that stem cells can be harvested after second or third cycle of IVE chemotherapy
11 June 2009	The amendment was for the addition of two new Principal Investigators and sites and some changes made to the CTA form. Details are as follows: 1. Dr. Claudius Rudin, Royal Devon & Exeter FT 2. Dr. Fergus Jack, Poole Hospital NHS FT The following changes were made to the CTA: - Change to sponsor & applicant identification - Changes made to section E.2.2 of the CTA - Change to exclusion criteria & primary endpoint (E.4 & 5) Change to central technical facilities
04 March 2010	Change in information on the NRES application form A change to the ionising radiation section of the form (Part B section 3, question B2) was made. The exposure (dose constraint) of the staging CT scan was increased from 12.5 mSv to 16mSv. This was reviewed to meet the NDRL for chest/abdo/pelvis

21 June 2010	After an audit carried out on the 17th of June 2010, it was discovered that the guidance given to patients in the PIS regarding contraception did not match the guidance contained within the SmPCs and investigator brochures, thus, it was decided that an urgent safety measure be taken to inform the Trial Subjects of the correct information. The PIS stated contraceptive should be used at least one month after treatment, while the SmPCs for ifosfamide, methotrexate and etoposide state that patients should use contraceptive measures for at least 6 months post last administration of these drugs. The following urgent safety measures were implemented: • Chief Investigator was notified of the circumstances surrounding the decision of the urgent safety measure and the actions to be taken • All relevant staff at the participating sites were notified of the urgent safety measure • The MHRA medical assessor (Dr Nagercoil) and the ethics committee coordinator were immediately informed by telephone of the urgent safety measure on 17th June 2010. • An addendum to the current Patient Information Sheet (PIS) informing patients of the correct information on contraception during and after treatment was sent out to sites for the re-consenting of patients already registered on the trial • A new version of the Patient Information Sheet with the correct information on how long contraception should be used after treatment has been sent out to sites, and should immediately supersede the information sheet currently being used • A process has also been put in place to monitor the re-consenting of the patients already on the trial
27 April 2011	The following main changes were made to the CT application form: Section A: • Change to the Full and short titles of the trial, to reflect the inclusion of other disease subtypes • Update to the sponsor's protocol code number • Inclusion of the US NCT number Section B: • Update of the sponsor's contact details • Addition of the contact point designated by the sponsor Section C: • Update to the request for Authorisation to Competent Authority Section D: • Update to IMPs information • Deletion of Mesna as an IMP • Inclusion of Lomustine as an IMP (as stated in the amended protocol v4. 0, pg 62) Section E: • Inclusion of subtypes of the medical condition to be investigated in the 'inclusion criteria' • Additional Information to the trial information – MedDRA • Change in the definition of 'End of Trial' • Addition of the recruitment start date Section G: • Addition of a central technical facility Section H: • Change of National Competent Authority details

09 May 2011	Cyclophosphamide, Doxorubicin, Vincristine, Ifosfamide, Etoposide, Epirubicin, Methotrexate, Cytarabine, Carmustine and Melphalan: We proposed not to apply IMP labelling to Cyclophosphamide, Doxorubicin, Vincristine, Ifosfamide, Etoposide, Epirubicin, Methotrexate, Cytarabine, Carmustine and Melphalan given IV as their use falls under the remit of Regulation 46(2) of the Medicines for Human Use (Clinical Trials) Regulations, for the following reasons: 1) The IMPs are marketed products, used broadly within their authorisations (i.e. cancer). 2) The IMPs to be dispensed to subjects in accordance with a prescription given by an authorised health care professional 3) The IMPs to be 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 Prednisolone Abridged labels to be used for Prednisolone tablets.
20 September 2011	This amendment concerns the change of the trial name, previously approved. The name was reverted back to the original trial name, ITCL.
18 January 2012	Retracted labels v1.0 07.04.11 for Prednisolone. Annex 13 labels v1.0 28.10.11 for Prednisolone for sites that are packing down. Exemption from labelling Lomustine which had been recently added as an IMP – approved on 04.05.11 – as it was being used within its licensed indication and will not dispensed for patients to take at home but dispensed as inpatient treatment only. Also minor amendments made to the PIS, GP Letter and Consent from

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' cannot be provided as only highest grade experienced by patients was collected on CRF; Subjects affected number is entered instead
-serious AEs & non-serious AEs are listed under non-serious adverse event

Notes: