Clinical trial results:
Phase II Study of Reduced Intensity Allogeneic Transplantation for Refractory Hodgkin Lymphoma

Summary

EudraCT number	2008-004956-60
Trial protocol	GB
Global end of trial date	02 July 2019

Results information

Result version number	v1 (current)
This version publication date	19 December 2020
First version publication date	19 December 2020

Trial information

Trial identification

Sponsor protocol code	UCL/08/0121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00908180
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London Cancer Trial Centre (UCL CTC)
Sponsor organisation address	90 Tottenham Court Road, London, United Kingdom, W1T 4TJ
Public contact	PAIReD Trial Coordinator, University College London & Cancer Trial Centre, +44 20 7679 9860, ctc.paired@ucl.ac.uk, +44 02076799283, ctc.paired@ucl.ac.uk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial objectives were to document the toxicity, feasibility and survival following reduced intensity transplantation from HLA-compatible sibling or unrelated donors in patients with primary refractory or relapsed refractory Hodgkin Lymphoma. More specifically, the trial included patients who were refractory to initial multi-agent induction or in first relapse and achieved <CR following salvage, but excluded those who havd progressive disease.
The primary end point was to assess progression free survival after reduced intensity allogeneic transplantation in a poor prognostic group of patients with Hodgkin lymphoma with persistent disease after treatment (either primary refractory or relapsed refractory disease).

Protection of trial subjects:

Patients underwent screening evaluations to confirm eligibility for the trial, these included: medical history, biochemistry tests (liver and renal function), bone marrow, infection screening, imaging, and cardiac function assessment. The donor also had serology testing and HLA typing.
Patients were given appropriate anti-bacterial, anti-fungal and anti-viral drugs to minimise the infection risks. This was according to local policy. Prophylaxis against GVHD was stipulated in the protocol - Campath infusion on D-1 and cyclosporine.
All patients were assessed for toxicity and monitored regularly for adverse events.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable- no comparator used

Actual start date of recruitment	19 March 2010
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: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	2
Adults (18-64 years)	32
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 32 patients were to be recruited over a period of 4 years. The 1st site was opened 19/03/2010 and the 1st patient recruited 14/05/2010. The trial recruited a total of 34 patients across 13 sites & closed to recruitment 13/02/2014. (2 ineligible and not transplanted,1 transplanted but with a mismatched donor, all 3 counted ineligible).

Pre-assignment

Screening details:

A total of 18 patients failed screening for the study. The reason for screen failure are outlined below:
Progressive disease=1
Patient death=2
Patient declined to enter trial=1
Complete remission=5
Absence of suitable donor=1
Patient referred to different hospital=2
Clinical decision=1
unable to arrange scan=1
private pt=2
previous HDT=2

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:

Not applicable

Arms

Arm title	Safety & Efficacy Population

Arm description:

34 patients were enrolled into the PAIReD trial and received conditioning with BEAm + Alemtuzumab (10mg/day for 5 days) with cyclosporine A as additional GVHD prophylaxis. DLI was used for the eradication of mixed chimerism and for the management of residual or relapsed disease.
3 patients were not included in the analysis as 2 patients were found to be ineligible and 1 patient was transplanted with a mismatch so not eligible.

Arm type	Safety & Efficacy
Investigational medicinal product name	Alemtuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 10mg should be given IV on days –5 to –1 inclusive. Patients should be premedicated with methylprednisolone 2mg/kg IV prior to the first dose; paracetamol (1g po), pethidine (25mg iv) and chlorpheniramine (10 mg iv) may also be required. During the first dose, the rate of infusion should be incrementally increased according to local policy or as follows: 1mg/h for 1st hour, 2mg/h for 2nd and 3rd hours, 3mg/h for 4th and subsequent hours.

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

Dosage and administration details:

300mg/m2 should be given by IV infusion over a 1-2 hour period, on day –6.

Investigational medicinal product name	Melphalan
Investigational medicinal product code	
Other name	Alkeran
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

140mg/m2 IV on day –1. It is recommended that melphalan Injection solution is injected slowly into a fast-running infusion solution via a swabbed injection port. If direct injection into a fast-running infusion is not appropriate, melphalan administered diluted in an infusion bag.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Cytarabine, Cytosine arabinoside, Cytosar-U, Tarabine
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 200 mg/m2 should be given IV twice daily (12 hourly over 15 mins) on days –5 to –2 inclusive. Water for injection, sodium chloride 0.9% or 5% dextrose are commonly used infusion fluids for Cytarabine.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	Etopophos, Vepesid, Etoposide phosphate, Eposin, Vepesid, VP-16
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A dose of 200 mg/m2 should be given IV on days –5 to –2 inclusive. Etoposide should not be used without diluting. It should be diluted with sodium chloride 0.9% or 5% dextrose. Solutions showing any signs of precipitation should not be used.

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

Dosage and administration details:

Lomustine should be given by mouth at a dose of 200mg/m2 on day –6, if carmustine is unavailable.

Number of subjects in period 1[1]	Safety & Efficacy Population
Started	31
Completed	31

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 3 patients were not included in the analysis as 2 patients were found to be ineligible and 1 patient was transplanted with a mismatch so not eligible

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description:

34 patients were enrolled into the PIAReD trial and received conditioning with BEAM + Alemtuzumab (10 mg/day for 5 days) with cyclosporine A as additional GvHD prophylaxis. DLI was used for the eradication of mixed chimerism and for the management of residual or relapsed disease. 3 patients were not included in the analysis as 2 patients were found to be ineligible and 1 patient was transplanted with a mismatch so not eligible.

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	31	31	
Age categorical			
Participants age was collected on the registration forms.			
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)	2	2	
Adults (18-64 years)	29	29	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Gender was collected during registration on the trial registration form.			
Units: Subjects			
Female	20	20	
Male	11	11	
Age at Transplant			
Age at transplant median 31 Age at transplant range lower 15 Age at transplant range upper 62			
Units: Subjects			
Age at transplant Median	27	27	
Age at transplant lower	2	2	
Age at transplant upper	2	2	
Stage at diagnosis			
Stage at diagnosis			
Units: Subjects			
Number of Stage II patients	15	15	
Number of Stage III patients	6	6	
Number of Stage IV patients	10	10	
WHO Performance status			
WHO Performance status			
Units: Subjects			
Performance Status 0	29	29	
Performance Status 1	2	2	

Histology subtype			
Histology subtype			
Units: Subjects			
Lymphocyte depleted	1	1	
Mixed cellularity	3	3	
Nodular lymphocyte predominant	1	1	
Nodular sclerosing	24	24	
Missing	2	2	
Extra nodal disease			
Extra nodal disease			
Units: Subjects			
Absent	15	15	
Present	16	16	
Previous treatment Relapsed or Refractory			
Previous treatment Relapsed or Refractory			
Units: Subjects			
Refractory	10	10	
Relapsed	21	21	
Original Chemotherapy			
Type of original chemotherapy			
Units: Subjects			
ABVD	20	20	
ABVD + BEACOPP	4	4	
CHLVPP/PABIED	1	1	
CHOP-R	1	1	
Ch/vpp/EBVD 'Hybrid'	1	1	
OEPA	1	1	
OEPA + COPDAC	2	2	
OEPA + Stanford V	1	1	
Consolidation RT after original Chemotherapy			
Whether the patient received Consolidation RT after original Chemotherapy			
Units: Subjects			
No	29	29	
Yes	2	2	
Number line of Salvage reported			
Total lines of salvage chemotherapy			
Units: Subjects			
One	7	7	
Two	19	19	
Three	5	5	
First salvage regimen			
First salvage regimen			
Units: Subjects			
DHAP	2	2	
ESHAP	22	22	
IVE	5	5	
miniBEAM	1	1	
ICE	1	1	
Second salvage regimen			
Second salvage regimen			

Units: Subjects			
DHAP	1	1	
IVE	3	3	
miniBEAM	9	9	
Brentuximab	10	10	
Mini LEAM	1	1	
No second salvage	7	7	
Was Rituximab given with second salvage			
Whether Rituximab was given with second salvage or not			
Units: Subjects			
No	24	24	
No second salvage	7	7	
Third salvage regimen			
Third salvage regimen			
Units: Subjects			
miniBEAM	1	1	
Gemcitibine	1	1	
Brentuximab	3	3	
No third salvage	26	26	
Was Rituximab given with third salvage			
Whether Rituximab was given with third salvage or not			
Units: Subjects			
No	5	5	
No third salvage	26	26	
Metabolically active disease at transplant			
Metabolically active disease at transplant			
Units: Subjects			
No	7	7	
Yes	24	24	
Donor related			
Whether donor is related or not			
Units: Subjects			
Matched unrelated donor	20	20	
Sibling	11	11	
Donor CMV Match			
Donor CMV match			
Units: Subjects			
Both negative	18	18	
Both positive	12	12	
Patient negative and donor positive	1	1	
HLA matching			
HLA matching			
Units: Subjects			
10/10	22	22	
9/10	9	9	
Donor sex			
Female/Male			
Units: Subjects			
Female	11	11	
Male	20	20	

Time from diagnosis to PAIRED transplant (months), median (range)			
Time from diagnosis to PAIRED transplant (months), median (range)			
Units: months median full range (min-max)	 15.9 7.5 to 131.1	 -	
Donor Age, median (range)			
Donor Age, median (range)			
Units: Years median full range (min-max)	 31 17 to 53	 -	

Subject analysis sets

Subject analysis set title	Safety and Efficacy Population
Subject analysis set type	Full analysis

Subject analysis set description:

This subject population represents the whole trial population excluding 3 patients: 2 patients were found to be ineligible and excluded. These 2 patients were not transplanted. 1 patient was transplanted with a mismatched donor so he/she was excluded from all analyses.

Reporting group values	Safety and Efficacy Population		
Number of subjects	31		
Age categorical			
Participants age was collected on the registration forms.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	2		
Adults (18-64 years)	29		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Gender was collected during registration on the trial registration form.			
Units: Subjects			
Female	20		
Male	11		
Age at Transplant			
Age at transplant median 31 Age at transplant range lower 15 Age at transplant range upper 62			
Units: Subjects			
Age at transplant Median	27		
Age at transplant lower	2		
Age at transplant upper	2		
Stage at diagnosis			
Stage at diagnosis			
Units: Subjects			

Number of Stage II patients	15		
Number of Stage III patients	6		
Number of Stage IV patients	10		
WHO Performance status			
WHO Performance status			
Units: Subjects			
Performance Status 0	29		
Performance Status 1	2		
Histology subtype			
Histology subtype			
Units: Subjects			
Lymphocyte depleted	1		
Mixed cellularity	3		
Nodular lymphocyte predominant	1		
Nodular sclerosing	24		
Missing	2		
Extra nodal disease			
Extra nodal disease			
Units: Subjects			
Absent	15		
Present	16		
Previous treatment Relapsed or Refractory			
Previous treatment Relapsed or Refractory			
Units: Subjects			
Refractory	10		
Relapsed	21		
Original Chemotherapy			
Type of original chemotherapy			
Units: Subjects			
ABVD	20		
ABVD + BEACOPP	4		
CHLVPP/PABIED	1		
CHOP-R	1		
Ch/vpp/EBVD 'Hybrid'	1		
OEPA	1		
OEPA + COPDAC	2		
OEPA + Stanford V	1		
Consolidation RT after original Chemotherapy			
Whether the patient received Consolidation RT after original Chemotherapy			
Units: Subjects			
No	29		
Yes	2		
Number line of Salvage reported			
Total lines of salvage chemotherapy			
Units: Subjects			
One	7		
Two	19		
Three	5		
First salvage regimen			
First salvage regimen			

Units: Subjects			
DHAP	2		
ESHAP	22		
IVE	5		
miniBEAM	1		
ICE	1		
Second salvage regimen			
Second salvage regimen			
Units: Subjects			
DHAP	1		
IVE	3		
miniBEAM	9		
Brentuximab	10		
Mini LEAM	1		
No second salvage	7		
Was Rituximab given with second salvage			
Whether Rituximab was given with second salvage or not			
Units: Subjects			
No	24		
No second salvage	7		
Third salvage regimen			
Third salvage regimen			
Units: Subjects			
miniBEAM	1		
Gemcitibine	1		
Brentuximab	3		
No third salvage	26		
Was Rituximab given with third salvage			
Whether Rituximab was given with third salvage or not			
Units: Subjects			
No	5		
No third salvage	26		
Metabolically active disease at transplant			
Metabolically active disease at transplant			
Units: Subjects			
No	7		
Yes	24		
Donor related			
Whether donor is related or not			
Units: Subjects			
Matched unrelated donor	20		
Sibling	11		
Donor CMV Match			
Donor CMV match			
Units: Subjects			
Both negative	18		
Both positive	12		
Patient negative and donor positive	1		
HLA matching			
HLA matching			

Units: Subjects			
10/10	22		
9/10	9		
Donor sex			
Female/Male			
Units: Subjects			
Female	11		
Male	20		
Time from diagnosis to PAIRED transplant (months), median (range)			
Time from diagnosis to PAIRED transplant (months), median (range)			
Units: months			
median	15.9		
full range (min-max)	7.5 to 131.1		
Donor Age, median (range)			
Donor Age, median (range)			
Units: Years			
median	31		
full range (min-max)	17 to 53		

End points

End points reporting groups

Reporting group title	Safety & Efficacy Population

Reporting group description:

34 patients were enrolled into the PAIReD trial and received conditioning with BEAm + Alemtuzumab (10mg/day for 5 days) with cyclosporine A as additional GVHD prophylaxis. DLI was used for the eradication of mixed chimerism and for the management of residual or relapsed disease.
3 patients were not included in the analysis as 2 patients were found to be ineligible and 1 patient was transplanted with a mismatch so not eligible.

Subject analysis set title	Safety and Efficacy Population
Subject analysis set type	Full analysis

Subject analysis set description:

This subject population represents the whole trial population excluding 3 patients: 2 patients were found to be ineligible and excluded. These 2 patients were not transplanted. 1 patient was transplanted with a mismatched donor so he/she was excluded from all analyses.

Primary: Progression Free Survival at 3 years

End point title	Progression Free Survival at 3 years[1]

End point description:

The sample size was calculated using a Fleming design requiring 26 patients, but was inflated to 32 to allow for dropouts. Success was defined as 10 patients alive and progression free at 3 years. However, as 31 patients were recruited with no dropouts the primary analysis presented in the paper focused on the 3 year Kaplan-Meier rate presented with a 95% CI. This has also been added to these results.
This was a single arm design based on a number of "successes" i.e. patients alive and progression free at 3 years. No statistical analyses which generate p-values were performed.

End point type	Primary

End point timeframe:

Progression Free Survival times were measured from the date of transplant until the date of the first event (progression or death from any cause). Patients not experiencing an event were censored at the date last seen. This is presented at 3 years.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single arm design based on a number of "successes" i.e. patients alive and progression free at 3 years. No statistical analyses which generate p-values were performed.

End point values	Safety & Efficacy Population	Safety and Efficacy Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31[2]	31[3]		
Units: Patients				
Alive and progression free at 3 years	21	21		
Progressed or died before 3 years	10	10		

Notes:

[2] - First 26 patients: 19/26 alive and progression free.
K-M rate (N=31): 67.7% (95% CI: 48.4 - 81.2)
[3] - First 26 patients: 19/26 alive and progression free.
K-M rate (N=31): 67.7% (95% CI: 48.4 - 81.2)

Attachments (see zip file)	PFS all transplanted patients/PFS_all_patients 60.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Donor engraftment rates at day 100

End point title	Donor engraftment rates at day 100

End point description:

This is the number of patients who engrafted by D100. Patients were excluded if they died or progressed (N=4) before this time point.

End point type	Secondary

End point timeframe:

Engraftment measured at day 100 post transplant

End point values	Safety and Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	27[4]			
Units: Patients				
Engrafted by day 100	22			
Late engraftment (>D100)	5			

Notes:

[4] - Patients who died before D100 have been excluded (N=4)

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of non-relapse mortality at 3 years

End point title	Cumulative incidence of non-relapse mortality at 3 years

End point description:

Cumulative incidence of Non Relapse Mortality is calculated using a competing risks model which treats relapse as a competing risk.

End point type	Secondary

End point timeframe:

Non Relapse Mortality is presented at 3 years

End point values	Safety and Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: percent				
number (confidence interval 95%)	16.1 (7.1 to 34.5)			

Attachments (see zip file)	CI curve NRM/cumulative incidence of NRM 60.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence, severity and timing of acute GvHD

End point title	Incidence, severity and timing of acute GvHD

End point description:

The incidence, severity and timing of acute GvHD in the analysis population was calculated and presented.

End point type	Secondary

End point timeframe:

Acute GvHD is measured within 100 days of transplant, patients who died before day 100 are excluded (N=4)

End point values	Safety and Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	27[5]			
Units: Patients				
Grade I	9			
Grade II	4			
Grade III	2			
No acute GvHD	12			

Notes:

[5] - Patients who died before day 100 have been excluded (N=4)

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of relapse

End point title	Cumulative incidence of relapse

End point description:

The cumulative incidence of relapse is caculated treating death in remission as a competing risk.

End point type	Secondary

End point timeframe:

The cumulative incidence of relapse is given at 3 years.

End point values	Safety and Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: percent				
number (confidence interval 95%)	16.1 (7.1 to 34.5)			

Attachments (see zip file)	CI relapse curve/cumulative incidence of relapse 60.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Response to donor lymphocyte infusions (DLI)

End point title	Response to donor lymphocyte infusions (DLI)

End point description:

Patients were given DLI for mixed chimerism (MC) or residual disease/disease progression (PD). 10 patients were given DLI, 8 for MC and 2 for residual disease/progression. Data reported here are for MC only.

Patients treated for PD: 1 progressed further and was retreated with chemotherapy, the second was also given RT along with DLI. Both remain in remission.
One patient was reported to have DLI for MC but had also progressed. This patient went back into remission with DLI alone but still has MC.

End point type	Secondary

End point timeframe:

Post transplant

End point values	Safety and Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	8[6]			
Units: Patients				
Converted to full donor	7			
Remained mixed	1			

Notes:

[6] - This is the 8 patients given DLI for MC

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival was defined as time from registration to death from any cause. Patients who were still

alive were censored at the time they were last known to be alive. An additional survival time calculated from time of admission for transplant to death from any cause was also calculated to account for patients who did not receive a transplant because of disease progression or an inability to collect stem cells.

End point type	Secondary

End point timeframe:

Overall survival times were measured from the date of transplant until the date of death (any cause). Patients who were alive were censored at the date last seen. The Kaplan Meier rate was presented at 3 years.

End point values	Safety and Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: percent				
number (confidence interval 95%)	80.7 (61.9 to 90.8)			

Attachments (see zip file)	OS K-M curve/OS_all_patients.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence, severity and timing of Chronic GvHD

End point title	Incidence, severity and timing of Chronic GvHD

End point description:

Incidence, severity and timing of Chronic GvHD

End point type	Secondary

End point timeframe:

Chronic GvHD is measured post day 100, patients who died before day 100 were excluded (N=4)

End point values	Safety and Efficacy Population			
Subject group type	Subject analysis set			
Number of subjects analysed	27[7]			
Units: patients				
Extensive	6			
Limited	7			
No chronic GvHD	14			

Notes:

[7] - Patients who died before day 100 have been excluded (N=4)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Between informed consent and 30 days post transplant (or after this date if the site investigator feels the event is related to the trial treatment).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Transplanted patients

Reporting group description:

All patients recruited into the PAIReD trial who have received a matched transplant

Serious adverse events	Transplanted patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 31 (25.81%)		
number of deaths (all causes)	6		
number of deaths resulting from adverse events	1		
Investigations			
Creatinine urine increased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
reversible posterior leukoencephalopathy			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumatosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Neutropenic sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 31 (3.23%)		
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	Transplanted patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 31 (100.00%)		
Vascular disorders			
Hot flush			

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Hypotension			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
edema face			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Edema limbs			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	23 / 31 (74.19%)		
occurrences (all)	23		
Fever			
subjects affected / exposed	22 / 31 (70.97%)		
occurrences (all)	22		
Rigors			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Chest pain			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Haemorrhage			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
mucositis NOS			

subjects affected / exposed	25 / 31 (80.65%)		
occurrences (all)	25		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	8 / 31 (25.81%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 31 (29.03%)		
occurrences (all)	9		
Dyspnea			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Pulmonary oedema			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Sore throat			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	27 / 31 (87.10%)		
occurrences (all)	27		

Platelet count decreased subjects affected / exposed occurrences (all)	6 / 31 (19.35%) 6		
Weight increased subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Weight loss subjects affected / exposed occurrences (all)	11 / 31 (35.48%) 11		
Cardiac disorders Other : tachycardia nos subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 5		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 4		
Headache subjects affected / exposed occurrences (all)	9 / 31 (29.03%) 9		
Paresthesia subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Reversible posterior leukoencephalopathy subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	16 / 31 (51.61%) 16		
Febrile neutropenia subjects affected / exposed occurrences (all)	4 / 31 (12.90%) 4		
Gastrointestinal disorders Abdominal pain			

subjects affected / exposed	7 / 31 (22.58%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	27 / 31 (87.10%)		
occurrences (all)	27		
Mucositis oral			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	27 / 31 (87.10%)		
occurrences (all)	27		
Vomiting			
subjects affected / exposed	17 / 31 (54.84%)		
occurrences (all)	17		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	11 / 31 (35.48%)		
occurrences (all)	11		
Dry skin			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	14 / 31 (45.16%)		
occurrences (all)	14		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Renal impairment			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		
Infections and infestations			
Other: fungal (nos)			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	5		
Other: neutropenic sepsis			
subjects affected / exposed	10 / 31 (32.26%)		
occurrences (all)	10		
Skin infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	16 / 31 (51.61%)		
occurrences (all)	16		
Hypokalemia			
subjects affected / exposed	5 / 31 (16.13%)		
occurrences (all)	5		
Hypomagnesaemia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Hypomagnesemia			
subjects affected / exposed	3 / 31 (9.68%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2010	Protocol amendment, Addition of pregnant partner consent form and information sheet, Change of contact person at UCL CTC.
02 February 2011	Submission of amended PIS (now v1.2-26jan11)
21 November 2011	Amended protoocl to v 3.0. Main changes: • Patient population (section 2.2.4): The list of salvage regimens that a patient can have had before entering the trial has been relaxed to allow for differences in local practice. • Patient population (section 2.2.4): clarification that 'CR' refers to 'metabolic CR'. • Patient population (section 2.2.4): removal of requirement for CT scans for re-evaluation of disease status. • Trial design (section 2.2.5): clarification that an alternative regimen can be used for the second cycle of salvage chemotherapy, if required. Further clarification that patients in CR after any additional therapy are considered eligible, providing they fulfilled study eligibility criteria following the first 2 cycles of salvage. • Site selection (section 3.1): Changed to reflect that mobile PET-CT scanners are now permitted for use in this trial. • Appendix 6 – Assessment of GVHD: Insertion of text to state that reactions to DLI occurring at any time-point during the trial are defined as acute GVHD.
29 May 2012	Protocol amendment to v4.0 and Consent form to v2.0, PIS 11-15 – v1.0, PIS 16+ - v2.0, PIS parents – v1.0. Main changes: - Changes to the inclusion criteria - Sample size reduced from 47 to 32 patients - Trial Objectives updated to incorporate patients in first relapse achieving <CR following salvage - Detailed explanation of which patients will now be eligible for the trial - Instructions regarding eligibility of primary refractory patients and patients in first relapse. Broadening of age range to allow patients >11 years of age to be recruited (previous lower age limit was >16 years of age). - adding Republic of Ireland as a target country (previously trial was conducted only in the UK)
11 February 2013	Amendment of Patient Information sheets & consent forms. Main changes: - Include the possibility of patient data being provided to a drug supplier after Genzyme Therapeutics surrendered the licence for Mabcampath (Alemtuzumab). This was not previously included in the patient information and consent as all drugs were previously sourced from hospital stock.
25 October 2013	Change of supply arrangements for Alemtuzumab: Genzyme provided commercial stock Alemtuzumab free of charge for use in the PAIReD trial. When Genzyme surrendered the manufacturing authorisation for MabCampath (Alemtuzumab), there was no further commercial stock available for patients on the PAIReD trial. To ensure continued supply of the IMP , Genzyme have agreed to provide sites with MabCampath manufactured on their behalf by Boehringer Ingelheim for the remainder of the trial. The IMP will be labelled and distributed by Penn. The CTA was amended to reflect the updated arrangements.

29 October 2013	Amendment to protocol v5 to bring it in line with the sponsor's current protocol at that time and to reflect changes to the trial monitoring plan following aan update to the risk assessment of the trial in Nov 2012. Reference Safety Information for the trial has changed: Appendix 4 which lists adverse events (AEs) expected for the treatment regimen, based on the clinical literature has been updated. The change was in response to discussions at the MHRA statutory GCP inspection of the UCL CTC in January 2013. Previously, the appendix 4 list of AEs expected for the treatment regimen was a generic list for transplants as a whole, and included AEs that were expected for combination conditioning chemotherapy regimens (including BEAM + Alemtuzumab, the regimen used in this trial), radiotherapy (TBI), and infused cells as a whole. This gave rise to concerns regarding a potential for under-reporting of SUSARs if AEs that were expected for the cells but not the drugs were classified as expected in line with the protocol appendix. The list in appendix 4 has been amended to remove any effects associated with total body irradiation, as it is not given as part of the transplant conditioning in this trial, and adverse events specifically associated with chemotherapy agents such as cyclophosphamide that are not used in the BEAM-Campath regimen. Expected AEs for transplanted cells were identified as exempt from SAE reporting. Details of complications of the stem cell infusion were collected as Urgent Events, to ensure the safety of the cell source continues to be assessed and recorded in the trial. Reported Serious Adverse Events not included in the list of AEs as expected for the chemotherapy conditioning continued to be assessed using the current SmPCs at that time for the individual IMPs.
15 September 2015	Change to the Reference Safety Information- New SPCs for Cytarabine, Etoposide and Carmustine

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.

AEs&SAES:Only events experienced by>=5% patients given
Relationships are to any IMP
Nonserious AEs:all events reported as AEs presented (include some serious events)
Total # of events:#patients experiencing an event as only worst grades reported

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31869413