Clinical trial results:
A multi-centre phase II study using Carboplatin AUC-10 for metastatic seminoma with IGCCCG good prognosis disease - therapy directed by initial metabolic response on PET-CT [CAR-PET]

Summary

EudraCT number	2009-009882-33
Trial protocol	GB
Global end of trial date	13 October 2017

Results information

Result version number	v1 (current)
This version publication date	06 September 2018
First version publication date	06 September 2018

Trial information

Trial identification

Sponsor protocol code	TE-2009-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02272816
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	Joint Research Management Office (JRMO), 5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Dr Jonathan Shamash, Centre for Experimental Cancer Medicine, QMUL, bci-carpet@qmul.ac.uk
Scientific contact	Dr Jonathan Shamash, Barts Health NHS Trust, Jonathan.Shamash@bartshealth.nhs.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	13 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, efficacy and toxicity of carboplatin AUC-10 in metastatic seminoma in a multi centre setting.

Protection of trial subjects:

Participant safety was continuously monitored through reporting of adverse events and laboratory assessments. Requirements for platelets, white blood cells and neutrophil levels for treatment to proceed were specified in the protocol with guidance on management in the event that these parameters were below the required levels.

A Trial Steering Committee (TSC) convened periodically throughout the trial to review the conduct of the clinical trial to ensure continuing patient safety.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	13 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	47
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with metastatic chemotherapy and radiotherapy naïve seminoma who had International Germ Cell Cancer Collaborative Group (IGCCCG) good prognosis disease (i.e. no non-pulmonary visceral metastases) were recruited into the study at two centres in London, United Kingdom between Feb - 2012 and Apr - 2015.

Pre-assignment

Screening details:

48 patients were screened for the study and all were found to be eligible and were recruited into the study.

Pre-assignment period milestones

Number of subjects started	48
Number of subjects completed	48

Period 1

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

Arms

Arm title	Carboplatin AUC-10

Arm description:

Carboplatin AUC-10 according to the Calvert formula (10 x (GFR (ml/min) + 25) mg

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC 10 according to the Calvert formula (10 x (GFR (ml/min) + 25) mg was given in 5% glucose over 1 hour every 21 days. A PET-CT scan was carried out on day 17-21 of the first cycle. The PET - CT scans were centrally reviewed. If the PET - CT scan showed a complete response (Deauville ≤3) the patient would stop treatment after 3 cycles. If the PET – CT showed persistent activity (Deauville >3), then patients went on to have 4 cycles in total

Number of subjects in period 1	Carboplatin AUC-10
Started	48
Completed	48

Baseline characteristics

Reporting groups	
Reporting group title	On study

Reporting group description: -

Reporting group values	On study	Total	
Number of subjects	48	48	
Age categorical			
Age at time of enrolment.			
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)	47	47	
From 65-84 years	1	1	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	0	0	
Male	48	48	
Primary tumour Units: Subjects			
Testis	46	46	
Mediastinum	1	1	
Retroperitoneum	1	1	
Sites of metastases Units: Subjects			
Lung	2	2	
Lymph nodes	29	29	
Other	9	9	
Not recorded	8	8	
ECOG PS			
Eastern Cooperative Oncology Group Performance Status. 0 - Fully active, able to carry on all pre-disease performance without restriction. 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours. 3 - Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.			
Units: Subjects			
ECOG PS = 0	41	41	
ECOG PS = 1	2	2	
ECOG PS = 2	0	0	
ECOG PS = 3	0	0	
Not recorded	5	5	

Stage of disease Units: Subjects			
2A	13	13	
2B	23	23	
2C	11	11	
N/A (Mediastinal)	1	1	
Tumour marker: Alpha-fetoprotein Units: Subjects			
Normal	48	48	
Elevated	0	0	
Tumour marker: Beta-Human Chorionic Gonadotropin Units: Subjects			
Normal	36	36	
Elevated	12	12	
Tumour marker: Lactate dehydrogenase Units: Subjects			
Normal	34	34	
Elevated (< 3xULN)	11	11	
Elevated (≥ 3xULN)	2	2	
Not recorded	1	1	
Glomerular Filtration Rate			
EDTA clearance (43 subjects) or estimated creatinine clearance determined by Cockcroft-Gault equation (5 subjects).			
Units: Subjects			
25 - 120 ml/min	35	35	
> 120 ml/min	13	13	

End points

End points reporting groups

Reporting group title	Carboplatin AUC-10
Reporting group description:	
Carboplatin AUC-10 according to the Calvert formula (10 x (GFR (ml/min) + 25) mg	

Primary: Progression Free Survival

End point title	Progression Free Survival[1]
End point description:	
Number of subjects progression free at 2 years from registration.	
End point type	Primary
End point timeframe:	
2 years from 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: It is not possible to enter statistical analysis as at least 2 comparison groups are required for this.	

End point values	Carboplatin AUC-10			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Subjects				
Progression free	46			
Progressed	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolic Response Rate

End point title	Metabolic Response Rate
End point description:	
Number of subjects achieving i) complete metabolic response (CR) and ii) partial metabolic response (PR) after 1 cycle of treatment.	
End point type	Secondary
End point timeframe:	
21 days	

End point values	Carboplatin AUC-10			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Subjects				
CR	21			
PR	26			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Number of subjects alive at 2 years from registration.

End point type	Secondary

End point timeframe:

2 years from registration.

End point values	Carboplatin AUC-10			
Subject group type	Reporting group			
Number of subjects analysed	48			
Units: Subjects				
Alive	48			
Deceased	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Start of treatment until 30 days after last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Carboplatin AUC-10
Reporting group description: Carboplatin AUC-10 according to the Calvert formula (10 x (GFR (ml/min) + 25) mg	

Serious adverse events	Carboplatin AUC-10		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 48 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Carboplatin AUC-10		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 48 (97.92%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	44 / 48 (91.67%)		
occurrences (all)	111		
Pain			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Hiccups			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	4		
Mood swings			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	34 / 48 (70.83%)		
occurrences (all)	81		
Platelet count decreased			
subjects affected / exposed	28 / 48 (58.33%)		
occurrences (all)	53		
Weight decreased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		

Neuropathy peripheral subjects affected / exposed occurrences (all)	6 / 48 (12.50%) 7		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	27 / 48 (56.25%) 49		
Febrile neutropenia subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2		
Pancytopenia subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Ear and labyrinth disorders Hearing impaired subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Tinnitus subjects affected / exposed occurrences (all)	13 / 48 (27.08%) 15		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	17 / 48 (35.42%) 26		
Diarrhoea subjects affected / exposed occurrences (all)	7 / 48 (14.58%) 11		
Gastritis subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 2		
Nausea subjects affected / exposed occurrences (all)	37 / 48 (77.08%) 70		
Stomatitis subjects affected / exposed occurrences (all)	16 / 48 (33.33%) 24		
Vomiting			

subjects affected / exposed occurrences (all)	14 / 48 (29.17%) 19		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 8 / 48 (16.67%) 9 3 / 48 (6.25%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 1 / 48 (2.08%) 1		
Infections and infestations Infection subjects affected / exposed occurrences (all) Neutropenic sepsis subjects affected / exposed occurrences (all)	 4 / 48 (8.33%) 5 1 / 48 (2.08%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 22 / 48 (45.83%) 38		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2012	- Inclusion criterion 2 amended to specify minimum required glomerular filtration rate of 25ml/min (value was missing). - Inclusion criterion 5 amended to clarify that age range is inclusive of 18 and 75 years. - Full Blood Count added on Cycle 1 Day 13-17 to check blood counts prior to proceeding to cycle 4 (previous version specified only cycle 2-4). - CT scan within 28 days of completing treatment removed as not required.
29 May 2012	Change in Sponsor name from Barts and the London NHS Trust to Barts Health NHS Trust.
19 December 2012	- Removal of requirement for post - treatment PET - CT scan for patients who have complete remission after cycle 1. - Allowable window included for Day 1 procedures on Cycles 2 – 4. - Confirmation that dose banding is not permitted added.
24 October 2013	- Change in requirements for recording concomitant medications. The IMP for this study was a licensed product, therefore it was not deemed necessary to record concomitant medications administered as supportive care. - Clarification added for when to recalculate Carboplatin dose. The glomerular filtration rate determined by EDTA clearance was only assessed pretreatment. Therefore the dose only needed to be recalculated if serum Creatinine rose >20% above baseline.
12 February 2015	- Clarification of the process for sending images for central review. - Amendments to the reporting timelines for the central review. - Change in Sponsor's representative. - Addition of urgent safety measure procedures. - Update to the pregnancy reporting procedures.
21 September 2015	- Exemption of requirement for baseline CT scan if PET-CT scan was done instead if clinician already suspected diagnosis to avoid unnecessary scans for trial subjects.
10 October 2017	- Reduction of the follow-up period from three years to two years. This decision was made as normally less than 10% of the total recurrences occur beyond 2 years and hence it has now become convention to quote 2 year progression-free survival in germ cell tumour (GCT) studies. This change does not affect the scope or validity of trial results, and was made after review by the Chief Investigator and trial statistician. - The end of the study definition was changed from “the date the last patient has completed his final follow up visit” to “3 months after the date when the last patient has completed his final follow up visit”. This was to allow additional time for data collection, cleaning, and analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported