Clinical trial results:
A multicentre, phase II randomised controlled trial evaluating cabazitaxel versus docetaxel re-challenge for the treatment of metastatic Castrate Refractory Prostate Cancer, previously treated with docetaxel at inception of primary hormone therapy

Summary

EudraCT number	2012-003835-40
Trial protocol	GB
Global end of trial date	29 April 2016

Results information

Result version number	v1
This version publication date	14 May 2017
First version publication date	14 May 2017

Trial information

Trial identification

Sponsor protocol code	RG12-024

Additional study identifiers

ISRCTN number	ISRCTN16465571
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CRCTU reference number: PR2103, Sanofi study number: Cabaz_L_05879, Cancer Research UK number: A15721

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Room 119, Aston Webb Building, Birmingham, United Kingdom, B15 2TT
Public contact	Mr Nick Martin, Cancer Research UK Clinical Trials Unit, University of Birmingham, +44 01214145102, cantata@trials.bham.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	12 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 April 2016
Global end of trial reached?	Yes
Global end of trial date	29 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this phase II study are to determine the tolerability and activity of cabazitaxel compared with docetaxel re-challenge as second-line chemotherapy treatment in metastatic patients who received primary therapy with docetaxel.

Protection of trial subjects:

What are the key risks related to therapeutic interventions you plan to monitor in this trial? How will these risks be minimised?
For the following, clinical assessment 3 weekly will be carried out during treatment.
*CARDIAC DISORDERS. *EAR & LABYRINTH DISORDER *EYE DISORDERS *GASTROINTESTINAL DISORDERS*GENERAL DISORDERS & ADMINISTRATION SITE CONDITIONS *IMMUNE SYSTEM DISORDERS *BLOOD & LYMPHATIC SYSTEM DISORDERS *INFECTIONS & INFESTATIONS *METABOLISM & NUTRITION DISORDERS *RENAL & URINARY DISORDERS *MUSCULOSKELETAL & CONNECTIVE TISSUE DISORDERS *SKIN & SUBCUTANEOUS TISSUE DISORDERS *VASCULAR DISORDERS *RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS *NERVOUS SYSTEM DISORDERS *PSYCHIATRIC DISORDERS *REPRODUCTIVE SYSTEM & BREAST DISORDERS *INVESTIGATIONS (WEIGHT LOSS & RAISED LFTs)

Patients may be required to undergo 1 additional CT or MRI scan in order to verify progression at trial entry.

Data Protection:
In routine correspondence between the CRCTU and the site patients will be referred to by their unique Trial Number, initials and date of birth. The patient's consent will be obtained for this.
All patient data (both paper and electronic) is securely stored and will only be accessible by authorised personnel in accordance with the CRCTU Quality Management System (QMS).
In addition, patients who are participating in the STAMPEDE trial will be asked to consent to the sharing of some data between the CRCTU and the MRC CTU. This is to minimise the duplication of data taken from the same patient.

Background therapy:

Premedication Regimen: Administer intravenously 30 minutes before each dose of cabazitaxel:
* Antihistamine (chlorpheniramine 5 mg or equivalent antihistamine)
*Dexamethasone 8 mg or equivalent steroid
*H2 antagonist (ranitidine 50 mg or equivalent H2 antagonist)
*Antiemetic prophylaxis (oral or intravenous) is recommended as needed, and should follow local policy.
*Variations based on local practice can be considered after discussion with the Trial Office
G-CSF: Patients experiencing severe neutropenia or neutropenic sepsis should be considered for G-CSF prophylaxis with subsequent cycles.
The recommended anti-emetic regimen is:
30 minutes prior to docetaxel administration:
* Ondansetron 8mg IV stat or equivalent
* Dexamethasone 8mg IV stat or equivalent steroid
Followed by:

* Ondansetron 8mg BD/PRN for 3 days
* Domperidone 20mg PO QDS/PRN

Evidence for comparator:

Until recently there was a need for new treatments in advanced prostate cancer, but in 2010 de Bono and colleagues published the results of the TROPIC trial(10). TROPIC was a randomised phase III trial in men with mCRPC who had previously been treated with hormone therapy, but whose disease had progressed during or after treatment with docetaxel.
Based on the results of the TROPIC trial, cabazitaxel, in combination with prednisone or prednisolone, was approved by the US Food and Drug Administration (June 2010) and the European Medicines Agency (March 2011), for the treatment of patients with mCRPC who have previously been treated with docetaxel. There are also four clinical trials currently recruiting which are assessing cabazitaxel safety and efficacy in this group of patients (NCT00417079, NCT01308580, NCT01308567, NCT01324583).
In conclusion, treatment with cabazitaxel is a potential therapeutic option for patients with mCRPC whose disease has progressed during or after docetaxel-based therapy. Caution, however, must be employed due to its significant haematological toxicities.

Actual start date of recruitment	10 December 2012
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: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	3
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

15 patients randomised in total; 7 to Cabazitaxel and 8 to Docetaxel. 1 patient in the Docetaxel group was found to be ineligible post-randomisation but remain in analysis since protocol states that on an intention to treat basis, all ineligible patients will be included.
First patient randomised= 09-May-2013
Last patient randomised= 04-Jan-2016

Pre-assignment

Screening details:

Eligible: prostate CA, previously treated with 6 cycles of Docetaxel, confirmed progression, metastatic disease, ≥18, performance status 0-2, adequate blood results
Exclusion criteria: prior chemotherapy other than docetaxel, progessive disease on docetaxel, active infection, malignant disease in last 5 years, active peripheral neuropathy

Period 1

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

Blinding implementation details:

na

Arms

Are arms mutually exclusive?	Yes
Arm title	Cabazitaxel

Arm description:

Cabazitaxel 25mg/m2
3 weekly plus
prednisolone for up to
10 cycles

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258/RPR116258
Other name	Jevtana
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Cabazitaxel will be administered at a dose of 25 mg/m2 (in either 0.9% sodium chloride solution or 5% dextrose solution) as 1 hour intravenous infusion every three weeks, in combination with oral prednisolone 10 mg administered daily, throughout treatment.

Arm title	Docetaxel

Arm description:

Docetaxel 75mg/m2
3 weekly plus
prednisolone for up to
10 cycles

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Docetaxel will be administered at a dose of 75 mg/m2 (in either 0.9% sodium chloride solution or 5% dextrose solution) as 1 hour intravenous infusion every three weeks, in combination with oral prednisolone 10 mg administered daily, throughout treatment.

Number of subjects in period 1	Cabazitaxel	Docetaxel
Started	7	8
Completed	7	8

Period 2

Period 2 title	End of trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

na

Arms

Are arms mutually exclusive?	Yes
Arm title	Cabazitaxel

Arm description:

Cabazitaxel 25mg/m2
3 weekly plus
prednisolone for up to
10 cycles

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	XRP6258/RPR116258
Other name	Jevtana
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Cabazitaxel will be administered at a dose of 25 mg/m2 (in either 0.9% sodium chloride solution or 5% dextrose solution) as 1 hour intravenous infusion every three weeks, in combination with oral prednisolone 10 mg administered daily, throughout treatment.

Arm title	Docetaxel

Arm description:

Docetaxel 75mg/m2
3 weekly plus
prednisolone for up to
10 cycles

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Docetaxel will be administered at a dose of 75 mg/m2 (in either 0.9% sodium chloride solution or 5% dextrose solution) as 1 hour intravenous infusion every three weeks, in combination with oral prednisolone 10 mg administered daily, throughout treatment.

Number of subjects in period 2	Cabazitaxel	Docetaxel
Started	7	8
Completed	7	8

Baseline characteristics

Reporting groups	
Reporting group title	Cabazitaxel
Reporting group description:	
Cabazitaxel 25mg/m2 3 weekly plus prednisolone for up to 10 cycles	
Reporting group title	Docetaxel
Reporting group description:	
Docetaxel 75mg/m2 3 weekly plus prednisolone for up to 10 cycles	

Reporting group values	Cabazitaxel	Docetaxel	Total
Number of subjects	7	8	15
Age categorical			
Date of birth is collected at randomisation. All subjects are required to be over 18.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	1	5
From 65-84 years	3	7	10
85 years and over	0	0	0
Age continuous			
Units: years			
median	62.7	69.9	
inter-quartile range (Q1-Q3)	57.5 to 75.2	66.1 to 72.5	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	7	8	15
Experiencing disease related pain			
Stratification variable of whether a patient has disease related pain at randomisation			
Units: Subjects			
Disease related pain	4	5	9
No disease related pain	3	3	6
Prior exposure to a new generation hormone therapy			
Stratification variable of prior exposure to a new generation hormone therapy			
Units: Subjects			
Prior exposure to a new gen hormone therapy	1	2	3

No prior exposure to a new gen hormone therapy	6	6	12
Prior hormone used			
For those who used a prior new generation hormone			
Units: Subjects			
No prior hormone	6	6	12
Abiraterone	1	0	1
Enzalutamide	0	2	2
Other hormone	0	0	0

End points

End points reporting groups

Reporting group title	Cabazitaxel
Reporting group description:	
Cabazitaxel 25mg/m2 3 weekly plus prednisolone for up to 10 cycles	

Reporting group title	Docetaxel
Reporting group description:	
Docetaxel 75mg/m2 3 weekly plus prednisolone for up to 10 cycles	

Reporting group title	Cabazitaxel
Reporting group description:	
Cabazitaxel 25mg/m2 3 weekly plus prednisolone for up to 10 cycles	

Reporting group title	Docetaxel
Reporting group description:	
Docetaxel 75mg/m2 3 weekly plus prednisolone for up to 10 cycles	

Primary: Clinical Progression Free Survival (CPFS)

End point title	Clinical Progression Free Survival (CPFS)
End point description:	
Clinical progression is defined as the earliest time between date of randomisation and either date of occurrence of pain progression (date patient is seen in clinic and pain progression identified), date of occurrence of a cancer-related skeletal-related event or date of death from any cause. Patients who do not suffer one of the specified events are censored at the date they were last known to be event free.	
End point type	Primary
End point timeframe:	
The time between the date of randomisation and the date of clinical progression. 'Clinical progression' is an event defined as the clinician being of the opinion that disease has progressed.	

End point values	Cabazitaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Number of events (as defined below)				
Clinically Progressed	2	4		
Hasn't clinically progressed	5	4		

Statistical analyses

Statistical analysis title	Not enough patients for analysis

Statistical analysis description:

There are not enough patients to justify any form of formal statistical analysis since the trial stopped very short of numbers intended. One patient on the Docetaxel arm was ineligible but has been included due the protocol stating 'Intention to treat'. 2 out of 7 Cabazitaxel patients progressed (either had pain progression or died) and 4 out of 8 Docetaxel patients (either had pain progression or died) Therefore, it can only be a very descriptive statement

Comparison groups	Cabazitaxel v Docetaxel
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 1 [2]
Method	Not done
Parameter estimate	40

Notes:

[1] - Not enough patients to justify any form of formal statistical analysis since trial stopped very short of numbers intended.1 patient on the Docetaxel arm was ineligible but has been included due to the protocol stating 'Intention to treat'. For patients who received trial treatment (including ineligible patient) 2 out of 7 Cabazitaxel patients progressed and 4 out of 8 Docetaxel patients progressed. Therefore, it can only be descriptive.

[2] - There are not enough patients to justify any form of formal statistical analysis since the trial stopped very short of numbers intended. The p-value of 1 has been input by default to fill in the box. Also for parameter value.

Secondary: Skeletal-related-event-free-survival

End point title	Skeletal-related-event-free-survival

End point description:

No skeletal-related events have occured

End point type	Secondary

End point timeframe:

The time between the date of randomisation and the date of a skeletal-related event. Those who have no skeletal-related event are censored at last date of follow-up.

End point values	Cabazitaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Number of events (as defined below)				
Skeletal-related event	0	0		
No skeletal-related event	7	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Pain progression-free survival

End point title	Pain progression-free survival

End point description:

The number of patients who had pain progression following randomisation was extremely small (two on the Docetaxel arm and one on the Cabazitaxel arm). This is not enough patients to carry out any formal statistical testing.

End point type	Secondary

End point timeframe:

Time from date of randomisation to date of pain progression. Patients who are pain free are censored at the date of last follow-up visit.

End point values	Cabazitaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Number of events (as defined below)				
Pain progression	1	2		
No pain progression	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity (National Cancer Institute CTC V4)

End point title	Toxicity (National Cancer Institute CTC V4)

End point description:

Treatment safety is assessed by the number of patients developing adverse events (AE's) during treatment (acute toxicities) and after trial therapy has been completed (late toxicities). Late toxicity is defined as 30 days after the last injection of cabazitaxel or docetaxel. AE's will be classified by causality, grade, type, duration and system involved.

This information will be recorded in the Adverse events section.

End point type	Secondary

End point timeframe:

Adverse events are recorded both during treatment and after trial therapy has been completed

End point values	Cabazitaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: Number of patients developing AE's	7	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

There have been only 4 deaths in total; 1 on the Cabazitaxel arm and 3 on the Docetaxel arm. All 4 deaths were disease related. There are not enough events to carry out any formal statistical testing.

End point type	Secondary

End point timeframe:

Time between date of randomisation and the date of death from any cause. Patients who do not die will be censored at the date of last follow-up or date last known to be alive.

End point values	Cabazitaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Number of events (as defined below)				
Alive	6	6		
Died	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: PSA-progression free survival

End point title	PSA-progression free survival

End point description:

Nine patients had a least one raised PSA at a follow-up visit (5 Cabazitaxel and 4 Docetaxel). There are therefore not enough events to carry out any formal statistical testing.

End point type	Secondary

End point timeframe:

Time between date of randomisation and the date a biochemical failure (PSA progression). Patients who do not progress are censored at time of last follow up visit.

End point values	Cabazitaxel	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Number of events (as defined below)				
PSA progression	5	4		
No PSA progression	2	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events will be documented and reported from date of commemncement of treatment until 30 days after treatment finishes.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Cabazitaxel
Reporting group description: -	
Reporting group title	Docetaxel

Reporting group description:

One patient did not receive any treatment at all so will not be counted as being exposed.

Serious adverse events	Cabazitaxel	Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	2 / 7 (28.57%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cabazitaxel	Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	7 / 7 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Additional description: Cyst on groin		
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hot flashes			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 7 (57.14%)	4 / 7 (57.14%)	
occurrences (all)	25	21	
Fever			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Malaise			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pain			

subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
General disorders and administration site conditions- Other, specify	Additional description: Common cold		
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dyspnea			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	
occurrences (all)	8	2	
Epistaxis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	
occurrences (all)	5	0	
Sore throat			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders - Other, specify	Additional description: Watery nose		
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
depression			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Alkaline phosphatase increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	

Neutrophil count decreased			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Weight loss			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Investigations - Other, specify	Additional description: White blood cell count increased		
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	6	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
dysgeusia			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	
occurrences (all)	9	2	
Headache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Lethargy			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	
occurrences (all)	5	5	
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 7 (28.57%)	2 / 7 (28.57%)	
occurrences (all)	4	3	
Nervous system disorders - Other, specify	Additional description: Neurotoxicity fingers		
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 7 (71.43%)	2 / 7 (28.57%)	
occurrences (all)	21	6	
Febrile Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Eye disorders			
Blurred Vision			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Watering eyes			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	
occurrences (all)	1	5	
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)	3 / 7 (42.86%)	
occurrences (all)	8	16	
Dry mouth			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Mucositis oral			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	
occurrences (all)	3	5	
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	
occurrences (all)	3	2	

Gastrointestinal disorders- Other, specify			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	13	
Dry Skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nail ridging			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders - Other, specify	Additional description: Rash on Hand		
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Urinary frequency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	
occurrences (all)	2	7	
Bone pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	4 / 7 (57.14%)	
occurrences (all)	0	7	
Muscle weakness lower limb			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Muscle weakness upper limb			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Gum Infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	
occurrences (all)	3	3	
Hyperkalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	
occurrences (all)	10	0	
Hypokalaemia			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 3	0 / 7 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2012	Amendment number 1 Protocol v 2.0. Update to comply with MHRA request re original submission on 26-Oct-2012. Update inclusion/exclusion criteria: patients with bilirubin equal or larger than ULN must be excluded; ANC notation made consistent throughout protocol. New wording: The radiation dose received from an additional set of scans is equivalent to less than 10 years of background radiation. The risk to you from this extra radiation will be negligible. Comments/ explanation/ reasons for substantial amendment: Two sentences have been added to the original paragraph (PIS, page 7) in order to explain the risk of an additional set of scans to the patient. The addition of these sentences to the Patient Information Sheet was requested during the NHS R&D approval process so that the Patient Information Sheet would match the wording supplied by the Medical Physics Expert in the original ethics application (submitted 24 October 2012). (

27 June 2014	Amendment number 4 Substantial Amendment Inclusion of text regarding optional tissue collection sub-study; change to haemoglobin notation. Changes to protocol text include: 1. Change to version no and date on page 1 and page 2, and in header/footer 2. Addition of the ISRCTN on the cover pagethis had not been received when the protocol was first submitted. 3. Clarification of wording in screening section(Schedule of Assessments, page 10) patients should receive "up to" not "at least" 6 cycles of docetaxel in their prior treatment. 4. Addition of section 3.3 on page 21 regarding the optional future Tissue Collection Substudy. This substudy is mentioned in the Patient Information Sheet and included on the Informed Consent Form, but had been removed from the protocol at a draft stage and not reinstated. 5. Change to notation for haemoglobin: from 10g/dL to 100g/L. Most laboratories use the 100g/L notation now. 6. Before a new treatment cycle begins, the patient's platelet count must be greater than or equal to 100 x10^9 L. This has been corrected on pages 25 and 27. 7. On page 24, addition of information regarding the use of prednisolone as a NIMP. 8. On page 25, clarification that sites may be able to adhere to local practice if the site's premedication regimen is different to that currently listed in the protocol, but only after agreeing this regimen with the Trial Office. 9. Change to definition of end date for the purposes of the main REC approval on in section 11, page 39 (removing the reference to "latest data capture" as this phrase is unclear). 10. Change to section 12.4 to update the statistical information. The incorrect numbers were retained from an earlier draft of the protocol. 11. Corrections of several minor misspellings (on page 25).

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.

Early termination of trial occurred leadind to a small number of subjects analysed. MHRA and ethics informed on 29-Apr-2016.

Notes: