



Clinical trial results:

A randomised phase II Trial of carboplatin and gemcitabine +/- vandetanib in first line treatment Of advanced Urothelial cell Cancer in patients who are not suitable to receive cisplatin

Summary

EudraCT number	2009-010140-33
Trial protocol	GB
Global end of trial date	05 September 2016

Results information

Result version number	v1 (current)
This version publication date	23 August 2017
First version publication date	23 August 2017

Trial information

Trial identification

Sponsor protocol code	SPON672-09
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Additional study identifiers

ISRCTN number	ISRCTN68146831
ClinicalTrials.gov id (NCT number)	NCT01191892
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom, CF24 0DE
Public contact	Tracie Madden, Wales Cancer Trials Unit, 0044 02920687953, MaddenTA1@cf.ac.uk
Scientific contact	Tracie Madden, Wales Cancer Trials Unit, 0044 02920687953, MaddenTA1@cf.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
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2015
Global end of trial reached?	Yes
Global end of trial date	05 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to assess whether the addition of vandetanib to standard carboplatin/gemcitabine cancer chemotherapy improves the clinical outcome for participants with advanced cancer of the urinary system (urothelial cancer).

Protection of trial subjects:

Toxicity data were reviewed by the IDMC after 20 and 40 patients had been randomised. This was to ensure patients receiving vandetanib were not experiencing excessive toxicity early on compared those on placebo.

Background therapy:

Patients received up to 6 cycles of carboplatin (AUC=4.5 using Calvert formula) IV over 30 minutes on day 1 and gemcitabine (1000mg/m²) IV over 30 minutes days 1 and 8 of a 21 day cycle.

Evidence for comparator:

N/A - A placebo tablet was used as the comparator.

Actual start date of recruitment	20 July 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: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	65
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

21 sites were opened between June 2010 and April 2013, and of these, 16 UK sites recruited at least one or more participants.

82 patients were recruited and randomised, during the recruitment period from July 2010 to December 2014.

Pre-assignment

Screening details:

The patient's written informed consent was obtained. The patient's medical history was reviewed against the participant eligibility criteria. Physical examination, including ECOG performance status, a 12 lead ECG with measurement of QTc, and blood pressure were performed. 212 patients were screened.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Patients were allocated treatment through a central interactive web response system.

The packaging and tablets appeared identical for both active and matching placebo treatments. The label attached to each package of blinded study material had a unique treatment kit number that was linked to the randomisation scheme. Upon randomisation, a label number was provided, and the package with a matching label number was dispensed to the patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Vandetanib
Investigational medicinal product code	
Other name	Zactima, Caprelsa
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One 100mg oral tablet once a day to be taken by mouth until 21 days after the last dose of carboplatin.

Arm title	Control
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

One oral tablet once a day to be taken by mouth until 21 days after the last dose of carboplatin.

Number of subjects in period 1	Experimental	Control
Started	40	42
Completed	8	17
Not completed	32	25
death	2	1
Adverse event, non-fatal	22	14
disease progression	3	7
Patient choice	3	1
Other unknown reason	2	2

Baseline characteristics

Reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Reporting group values	Experimental	Control	Total
Number of subjects	40	42	82
Age categorical 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)	9	6	15
From 65-84 years	31	34	65
85 years and over	0	2	2
Age continuous Units: years			
median	73.5	73.5	
inter-quartile range (Q1-Q3)	65.5 to 77	67 to 79	-
Gender categorical Units: Subjects			
Female	8	7	15
Male	32	35	67
Location of primary disease Units: Subjects			
Bladder	28	34	62
Other	12	8	20

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Primary: Progression-Free Survival

End point title	Progression-Free Survival
End point description:	
End point type	Primary
End point timeframe:	
The time in months from randomisation until disease progression or death.	

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: months				
median (confidence interval 95%)	6.8 (4.6 to 8.5)	8.8 (5.7 to 9)		

Attachments (see zip file)	Progression free survival/Fig 2A TOUCAN PFS.pdf
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Statistical analyses

Statistical analysis title	One-sided log rank test
Comparison groups	Experimental v Control
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.76
Variability estimate	Standard error of the mean
Dispersion value	0.27

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type	Secondary
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End point timeframe:

Months from randomisation until death

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: months				
median (confidence interval 95%)	10.8 (8 to 13)	13.8 (11.1 to 16.6)		

Attachments (see zip file)	Overall survival/Fig 2B TOUCAN OS.pdf
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Statistical analyses

Statistical analysis title	Overall survival
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Comparison groups	Experimental v Control
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Number of subjects included in analysis	82
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Analysis specification	Pre-specified
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Analysis type	superiority
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Parameter estimate	Cox proportional hazard
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Point estimate	1.41
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.79
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upper limit	2.52
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Variability estimate	Standard error of the mean
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Dispersion value	0.416
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Secondary: Objective response

End point title	Objective response
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End point description:

Best disease response, measured at each RECIST assessment of CT scans.

End point type	Secondary
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End point timeframe:

Best response seen during treatment and follow-up.

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: subjects				
Complete Response	2	2		
Partial response	18	21		
Stable disease	10	12		
Progressive disease	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title Objective response rate

End point description:

The number of patients reporting complete response or partial response as their best response.

End point type Secondary

End point timeframe:

During treatment and follow-up.

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	42		
Units: subjects	20	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Waterfall plot

End point title Waterfall plot

End point description:

Change of size of measurable lesions 9 weeks after start of chemotherapy (using Waterfall plots).

End point type Secondary

End point timeframe:

Between start of chemotherapy (baseline CT scan) and 9 weeks after the start of chemotherapy (9 week

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30 ^[1]	34 ^[2]		
Units: mm				
arithmetic mean (standard deviation)	-0.373 (\pm 0.32)	-0.277 (\pm 0.29)		

Notes:

[1] - 30 patients had RECIST data at 9 weeks.

[2] - 34 patients had RECIST data at 9 weeks.

Attachments (see zip file)	Waterfall plot/Fig 3 TOUCAN Waterfall.pdf
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Per protocol Progression-free survival

End point title	Per protocol Progression-free survival
End point description:	
End point type	Other pre-specified
End point timeframe:	
The time in months from randomisation until disease progression or death.	

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[3]	37 ^[4]		
Units: months				
median (confidence interval 95%)	6.8 (5.1 to 8.5)	8.3 (5.7 to 9)		

Notes:

[3] - Per protocol population. Patients confirmed to be eligible who started trial treatment.

[4] - Per protocol population. Patients confirmed to be eligible who started trial treatment.

Statistical analyses

Statistical analysis title	Progression-free survival
Comparison groups	Experimental v Control
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	0.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.69
Variability estimate	Standard error of the mean
Dispersion value	0.268

Other pre-specified: Per protocol overall survival

End point title	Per protocol overall survival
End point description:	
End point type	Other pre-specified
End point timeframe:	
Months from randomisation until death	

End point values	Experimental	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33 ^[5]	37 ^[6]		
Units: months				
median (confidence interval 95%)	10.5 (8 to 13)	15.8 (15.8 to 17.9)		

Notes:

[5] - Per protocol population. Patients confirmed to be eligible who started trial treatment.

[6] - Per protocol population. Patients confirmed to be eligible who started trial treatment.

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Control v Experimental
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Cox proportional hazard
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	2.54
Variability estimate	Standard error of the mean
Dispersion value	0.431

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation until data lock

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.0
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Reporting groups

Reporting group title	Experimental
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Reporting group description: -

Reporting group title	Control
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Reporting group description: -

Serious adverse events	Experimental	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 40 (70.00%)	22 / 42 (52.38%)	
number of deaths (all causes)	24	24	
number of deaths resulting from adverse events	1	1	
Vascular disorders			
Arterial ischemia			
subjects affected / exposed	1 / 40 (2.50%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 40 (5.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain - ischemic			

subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial swelling and redness			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 40 (5.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	3 / 40 (7.50%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Edema limbs	Additional description: swollen right leg		
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions - Other, symptom control			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Aspergillus pneumonia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chest infection			
subjects affected / exposed	2 / 40 (5.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory infection			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusion	Additional description: confusion due to hydronephrosis		
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Creatinine increased			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	7 / 40 (17.50%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	8 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 40 (2.50%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis	Additional description: hydronephrosis (urostomy tube inserted)		
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Collapse	Additional description: Syncope		
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 40 (2.50%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 40 (5.00%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 40 (5.00%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 40 (7.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleed			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 40 (2.50%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 40 (2.50%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cellulitis			
subjects affected / exposed	1 / 40 (2.50%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photosensitivity			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	2 / 40 (5.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 40 (10.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	0 / 40 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other, viral infection			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 40 (5.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 40 (2.50%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 40 (90.00%)	41 / 42 (97.62%)	
Investigations			
Alkaline phosphatase increased			
subjects affected / exposed	9 / 40 (22.50%)	9 / 42 (21.43%)	
occurrences (all)	17	15	
Alanine aminotransferase increased			
subjects affected / exposed	13 / 40 (32.50%)	12 / 42 (28.57%)	
occurrences (all)	33	34	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 40 (15.00%)	5 / 42 (11.90%)	
occurrences (all)	11	7	
Blood bilirubin increased			
subjects affected / exposed	3 / 40 (7.50%)	4 / 42 (9.52%)	
occurrences (all)	10	6	
Lymphocyte count decreased			
subjects affected / exposed	18 / 40 (45.00%)	12 / 42 (28.57%)	
occurrences (all)	49	31	

Platelet count decreased subjects affected / exposed occurrences (all)	23 / 40 (57.50%) 55	19 / 42 (45.24%) 49	
Weight loss subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 10	6 / 42 (14.29%) 9	
White blood cell count decreased subjects affected / exposed occurrences (all)	19 / 40 (47.50%) 49	21 / 42 (50.00%) 53	
Creatinine increased subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 27	7 / 42 (16.67%) 13	
Neutrophil count decreased subjects affected / exposed occurrences (all)	16 / 40 (40.00%) 27	15 / 42 (35.71%) 25	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 11	6 / 42 (14.29%) 13	
Nervous system disorders Insomnia subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 11	3 / 42 (7.14%) 8	
Dizziness subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 5	4 / 42 (9.52%) 5	
Dysgeusia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3	3 / 42 (7.14%) 3	
Paraesthesia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 6	3 / 42 (7.14%) 5	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	26 / 40 (65.00%) 76	25 / 42 (59.52%) 96	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	24 / 40 (60.00%)	30 / 42 (71.43%)	
occurrences (all)	73	59	
Oedema limbs			
subjects affected / exposed	3 / 40 (7.50%)	7 / 42 (16.67%)	
occurrences (all)	6	23	
Fever			
subjects affected / exposed	3 / 40 (7.50%)	5 / 42 (11.90%)	
occurrences (all)	3	6	
Pain			
subjects affected / exposed	14 / 40 (35.00%)	14 / 42 (33.33%)	
occurrences (all)	52	37	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 40 (12.50%)	9 / 42 (21.43%)	
occurrences (all)	14	14	
Constipation			
subjects affected / exposed	6 / 40 (15.00%)	11 / 42 (26.19%)	
occurrences (all)	17	17	
Diarrhoea			
subjects affected / exposed	15 / 40 (37.50%)	10 / 42 (23.81%)	
occurrences (all)	20	18	
Nausea			
subjects affected / exposed	14 / 40 (35.00%)	12 / 42 (28.57%)	
occurrences (all)	32	22	
Vomiting			
subjects affected / exposed	7 / 40 (17.50%)	13 / 42 (30.95%)	
occurrences (all)	10	21	
Dyspepsia			
subjects affected / exposed	4 / 40 (10.00%)	2 / 42 (4.76%)	
occurrences (all)	5	3	
Mucositis oral			
subjects affected / exposed	7 / 40 (17.50%)	7 / 42 (16.67%)	
occurrences (all)	10	9	
Respiratory, thoracic and mediastinal disorders			

Lung infection subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 8	3 / 42 (7.14%) 4	
Cough subjects affected / exposed occurrences (all)	10 / 40 (25.00%) 15	4 / 42 (9.52%) 8	
Dyspnoea subjects affected / exposed occurrences (all)	11 / 40 (27.50%) 28	7 / 42 (16.67%) 11	
Epistaxis subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 6	2 / 42 (4.76%) 2	
Skin and subcutaneous tissue disorders			
Photosensitivity reaction subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 11	0 / 42 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 6	4 / 42 (9.52%) 6	
Rash subjects affected / exposed occurrences (all)	19 / 40 (47.50%) 57	11 / 42 (26.19%) 16	
Alopecia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 3	5 / 42 (11.90%) 8	
Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 13	1 / 42 (2.38%) 1	
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 16	4 / 42 (9.52%) 7	
Haematuria subjects affected / exposed occurrences (all)	10 / 40 (25.00%) 17	8 / 42 (19.05%) 20	
Urinary tract infection			

subjects affected / exposed occurrences (all)	6 / 40 (15.00%) 14	4 / 42 (9.52%) 9	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	5 / 40 (12.50%) 13	2 / 42 (4.76%) 3	
Infections and infestations Skin infection subjects affected / exposed occurrences (all)	1 / 40 (2.50%) 1	4 / 42 (9.52%) 4	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	11 / 40 (27.50%) 20	8 / 42 (19.05%) 14	
Hypokalaemia subjects affected / exposed occurrences (all)	7 / 40 (17.50%) 11	2 / 42 (4.76%) 2	
Hypomagnesaemia subjects affected / exposed occurrences (all)	8 / 40 (20.00%) 19	8 / 42 (19.05%) 22	
Hypophosphataemia subjects affected / exposed occurrences (all)	9 / 40 (22.50%) 18	3 / 42 (7.14%) 5	
Dehydration subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 3	3 / 42 (7.14%) 4	
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 40 (5.00%) 2	4 / 42 (9.52%) 6	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 40 (7.50%) 4	2 / 42 (4.76%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 April 2010	<p>Change of PI at Southampton General Hospital: Dr Ben Mead replaced by Dr Simon Crabb</p> <p>Addition of new Principal Investigator/research sites: Kent and Canterbury Hospital, Canterbury – Dr Natasha Mithal William Harvey Hospital, Ashford – Dr Natasha Mithal Queen Elizabeth The Queen Mother Hospital, Margate – Dr Natasha Mithal Charing Cross Hospital, London – Dr Simon Stewart Hammersmith Hospital, London – Dr Simon Stewart; Royal Lancashire Infirmary, Lancaster – Dr Alison Birtle Churchill Hospital, Headington – Dr Andrew Protheroe Royal Bournemouth Hospital, Bournemouth – Dr Tom Geldart</p>
16 August 2010	<p>Change of PI: Royal Bournemouth Hospital, Bournemouth – Dr Tom Geldart replaced by Dr Sue Brock</p> <p>Addition of new site and PI: Castle Hill Hospital, Cottingham – Dr Mohammed Butt</p>
21 March 2013	<p>To add a new site: The Clatterbridge Cancer Centre NHS Foundation Trust –Syed Hussain</p> <p>To close an existing site: Edinburgh Cancer Centre Western General Hospital –Duncan McLaren</p> <p>Amendment of trial documentation as follows: 1. Protocol V1.2 dated 20.10.2012 superseded by V2.0 dated 08 March 2013 (update of trial assessments, concomitant medications, adverse events, safety reports, and withdrawal levels) 2. GP Letter V 1.0 dated 06.08.2009 superseded by v2.0 dated 14 March 2013 (update of concomitant medications) 3. PIS V1.2 dated 20.10.2009 superseded by V2.0 dated 14 March 2013 (sections re-written and simplified for a more user-friendly document) 4. Consent Form V1.2 dated 20.10.2009 superseded by V2.0 dated 14 March 2013 (inclusion of sub-sections for make clear difference between main and optional study) 5. Pregnancy PIS V1.0 dated 06 August 2009 superseded by V2.0 dated 14 March 2013 (inclusion of ISRCTN reference)</p>

28 July 2014	<p>Amendment of trial documentation as follows: Protocol v3.0 dated 13 December 2013 superseded by v4.0 dated 12 June 2013 (change of sample size from 122 to 82)</p> <p>To add new sites and PIs: Queen Elizabeth Hospital, Norfolk-Gail Horan Royal Derby Hospital-Pabir Chakaraboti Queens Hospital (Staffordshire)-Pugazhenthir Pattu Mount Vernon Hospital-Peter Hoskin Charing Cross Hospital-Steve Nicholson Weston Park Hospital-Linda Evans Ayr Hospital-Hilary Glen Royal Free Hospital-Maria Vilarino Varela West Suffolk NHS Trust-Cathryn Woodward Calderdale Royal Hospital-Uschi Hofmann Huddersfield Royal Infirmary-Uschi Hofmann Bristol Haematology and Oncology Centre-Mark Beresford Royal United Hospital-Olivia Firm</p> <p>To make minor details to the CTA: Update contact for Fisher Clinical Services Clarify duties performed by FCS Add sources of monetary or material support Add contact point for sponsor</p> <p>To inform the MHRA of the non-substantial changes that were made to protocol V 2.0 08/03/2013 to generate v3.0 13/12/13.</p>
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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.

Neither limitations nor caveats are applicable to this summary of the results.

Notes: