



Clinical trial results:

Cabazitaxel in platinum pre-treated patients with locally advanced or metastatic transitional cell carcinoma who developed disease progression within 12 months of platinum based chemotherapy.

Summary

EudraCT number	2012-002552-16
Trial protocol	GB
Global end of trial date	31 December 2017

Results information

Result version number	v1 (current)
This version publication date	30 March 2019
First version publication date	30 March 2019

Trial information

Trial identification

Sponsor protocol code	RRK4368
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Additional study identifiers

ISRCTN number	ISRCTN76947550
ClinicalTrials.gov id (NCT number)	NCT01668459
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Birmingham NHS Foundation Trust
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom,
Public contact	Christopher Counsell, University Hospitals Birmingham NHS Foundation Trust, +44 01213714185, chris.counsell@uhb.nhs.uk
Scientific contact	Christopher Counsell, University Hospitals Birmingham NHS Foundation Trust, +44 01213714185, chris.counsell@uhb.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	31 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2017
Global end of trial reached?	Yes
Global end of trial date	31 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the overall response rate of patients administered cabazitaxel versus best supportive care (including single agent chemotherapy) in patients with transitional cell carcinoma who have previously progressed on a platinum-based regimen.

Protection of trial subjects:

Subjects were closely monitored during their participation in the study for all aspects of safety monitoring as per protocol. Patients were provided with office-hours study contacts and 24 hour contact in case of emergency and were also provided with access to the acute oncology service if required. Data protection: In correspondence between the site/sponsor and collaborators (Sanofi, Warwick University), patients were only referred to by their unique patient identification number for the study, initials and date of birth. The patient's consent was obtained for this. All patient data (paper and electronic) is securely stored and is only accessible to authorised personnel.

Background therapy:

As per standard cabazitaxel administration:

At least 30 minutes prior to each administration of cabazitaxel, patients were administered:

- Chlorphenamine 10mg IV bolus over one minute
- Dexamethasone 8mg IV bolus
- Ranitidine 59mg slow IV bolus over 2 minutes
- Ondansetron 8mg IV stat

To take home:

Ondansetron 8mg oral to take home and take if required

- Metoclopramide 10mg oral to take home and take if required
- Loperamide 4mg STAT then 2mg oral to take home and take if required
- Pegfilgrastim 6mg injection 24 hours after chemotherapy if required (recommended for patients with high-risk clinical features (age >65, poor performance status, previous episode of febrile neutropenia, extensive prior radiation ports, poor nutritional status or other serious comorbidities). ASCO and ESMO guidelines were followed.

Evidence for comparator:

Prior to protocol development for the study, a feasibility questionnaire from 16 sites all supported including some form of active second line treatment in the Best Supportive Care (BSC) arm. A trial in which only BSC (without active treatment) were available as the control arm was thought to potentially lead to either poor unfit patients (which then would not meet inclusion criteria) or lack of recruitment due to a disinterest in participating in a trial in which there is a risk of not receiving some form of potentially active treatment. Therefore BSC in this study required use of single agent chemotherapy. As the study was single-site, the BSC chemotherapy of choice was Paclitaxel.

Actual start date of recruitment	04 January 2013
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	4
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient consented 04-Jan-2013
Last patient consented 05-Sep-2016
Last patient last visit 25-Oct-2017
Study ended 31-Dec-2017

20 patients randomised
- 10 Cabazitaxel arm
- 10 Best Supportive Care (BSC) arm

1 patient on Cabazitaxel arm did not receive treatment due to ill-health prior to treatment commencing

Pre-assignment

Screening details:

47 patients assessed for eligibility from multi-disciplinary team meetings and referrals
- 20 randomised
- 27 excluded - 21 did not meet inclusion/exclusion criteria; 4 patients not well enough; 1 patient chose not to participate; 1 patient lived abroad

Period 1

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

Blinding implementation details:

n/a

Arms

Are arms mutually exclusive?	Yes
Arm title	Cabazitaxel

Arm description:

Cabazitaxel 25 mg/m² as a 1 hour intravenous infusion every 3 weeks for up to 6 cycles

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

Dosage and administration details:

Cabazitaxel was administered at a dose of 25 mg/m² (in either 0.9% sodium chloride solution or 5% dextrose solution) as a 1 hour intravenous infusion every three weeks for a maximum of 6 cycles

Arm title	Best Supportive Care
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Arm description:

Best Supportive Care at physicians decision (9 patients received Paclitaxel chemotherapy as per standard hospital treatment. 1 patient received radiotherapy)

Arm type	Best Supportive Care as per discretion of physicia
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No investigational medicinal product assigned in this arm

Number of subjects in period 1	Cabazitaxel	Best Supportive Care
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups

Reporting group title	Cabazitaxel
Reporting group description:	Cabazitaxel 25 mg/m ² as a 1 hour intravenous infusion every 3 weeks for up to 6 cycles
Reporting group title	Best Supportive Care
Reporting group description:	Best Supportive Care at physicians decision (9 patients received Paclitaxel chemotherapy as per standard hospital treatment. 1 patient received radiotherapy)

Reporting group values	Cabazitaxel	Best Supportive Care	Total
Number of subjects	10	10	20
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)	2	2	4
From 65-84 years	8	8	16
85 years and over	0	0	0
Age continuous			
Units: years			
median	70	69	
full range (min-max)	41 to 77	57 to 83	-
Gender categorical			
Units: Subjects			
Female	3	2	5
Male	7	8	15
Location of cancer - bladder or upper tract			
Not a stratification variable			
Units: Subjects			
Bladder	8	9	17
Upper urinary tract	2	1	3
Pathology			
Not a stratification variable			
Units: Subjects			
Transitional cell carcinoma (TCC)	8	10	18
Mixed pathology with predominately TCC	2	0	2
Disease stage			
Not a stratification variable			
Units: Subjects			
Locally advanced	1	0	1

Metastatic	9	10	19
Stratification variable - Time between last dose of chemotherapy and recurrence			
Units: Subjects			
<6 months	6	7	13
≥ 6 months	4	3	7

End points

End points reporting groups

Reporting group title	Cabazitaxel
Reporting group description:	Cabazitaxel 25 mg/m ² as a 1 hour intravenous infusion every 3 weeks for up to 6 cycles
Reporting group title	Best Supportive Care
Reporting group description:	Best Supportive Care at physicians decision (9 patients received Paclitaxel chemotherapy as per standard hospital treatment. 1 patient received radiotherapy)

Primary: Overall response rate

End point title	Overall response rate ^[1]
End point description:	The primary efficacy variable for the study was Overall Response Rate (ORR). Tumour response was assessed by investigators according to RECIST criteria for patients with measurable disease. CT scan of the abdomen and pelvis and other exams as clinically indicated to assess target and non-target lesions were performed to assess disease status at baseline. These were repeated (same method as used as baseline) following completion of 3 and 6 cycles of chemotherapy and whenever disease progression was suspected e.g., symptomatic deterioration. The investigator at the site was responsible for the assessment and collection of the radiographic information in compliance with the schedule of evaluations presented in this protocol. The overall response rate was defined as the proportion of patients with confirmed RECIST-defined complete response (CR) or partial response (PR) relative to the total number of patients in the analysis population considered.
End point type	Primary
End point timeframe:	From Randomisation to End of Treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: As the sample size is small, no formal statistical analysis has been done for the end-points. Results are descriptive only.

End point values	Cabazitaxel	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Number of patients				
Complete response	0	0		
Partial response	2	1		
Stable disease	2	4		
Progressive disease	2	1		
Not evaluated for response	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival
End point description: Progression free survival (PFS) was evaluated from the date of randomisation to the date of tumour progression (from radiological tumour assessments (CT/MRI of chest, abdomen and pelvis) or death (from any cause).	
End point type	Secondary
End point timeframe: From randomisation to end of study or death	

End point values	Cabazitaxel	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Months				
median (confidence interval 95%)	4.8 (0.7 to 8.3)	3.7 (1.0 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description: Overall survival (OS) is defined as the time interval from the date of randomization to the date of death due to any cause. In absence of confirmation of death, survival time was censored at the earlier of the last date the patient was known to be alive and the study cut-off date.	
End point type	Secondary
End point timeframe: From randomisation to end of study or death	

End point values	Cabazitaxel	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Months				
median (confidence interval 95%)	5.8 (0.7 to 14.6)	7.5 (1.0 to 10.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life
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End point description:

QOL was assessed by using a validated instrument; the EuroQOL (EQ-5D).

EQ-5D is a standardized health-related quality of life questionnaire developed by the EuroQOL Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQOL Group, 1990).

Values for the 243 theoretically possible health states defined by the EuroQOL classification will be calculated using a regression model and weighted according to the social preferences of the UK population.

Quality of life data from the EQ-5D was analysed by a standardised area-under-the-curve analysis for 'Health Today' and 'Utility Score'

End point type	Secondary
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End point timeframe:

Baseline to End of Treatment

End point values	Cabazitaxel	Best Supportive Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Score				
median (full range (min-max))				
Health Today	71 (44 to 89)	77 (32 to 91)		
Utility Score	0.72 (0.34 to 0.92)	0.76 (0.71 to 0.89)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to 30 days post last treatment

Adverse event reporting additional description:

Adverse events were reported at routine visits by patients, collated from clinic notes and laboratory abnormalities

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	Cabazitaxel
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Reporting group description:

Cabazitaxel 25 mg/m² as a 1 hour intravenous infusion every 3 weeks for up to 6 cycles

Reporting group title	Best Supportive Care
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Reporting group description:

Best Supportive Care at physicians decision (including single agent chemotherapy - paclitaxel)

Serious adverse events	Cabazitaxel	Best Supportive Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)	3 / 10 (30.00%)	
number of deaths (all causes)	9	8	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Neutropenic sepsis			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain	Additional description: Right side (non-cardiac) pain		
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea	Additional description: Diarrhoea & vomiting		

subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (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			
Kidney infection	Additional description: Pylonephritis		
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal function test abnormal	Additional description: Renal function deterioration		
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatinaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Caused by enterococcus infection		
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cabazitaxel	Best Supportive Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)	9 / 10 (90.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Flushing	Additional description: Face flushing		
subjects affected / exposed	0 / 10 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 10 (60.00%)	4 / 10 (40.00%)	
occurrences (all)	7	5	
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 10 (0.00%)	4 / 10 (40.00%)	
occurrences (all)	0	6	
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	3	

Irritability subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0 1 / 10 (10.00%) 1	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Hypercreatinaemia subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all) Hypokalaemia	1 / 10 (10.00%) 2 3 / 10 (30.00%) 6 1 / 10 (10.00%) 2 2 / 10 (20.00%) 11 5 / 10 (50.00%) 7	0 / 10 (0.00%) 0 3 / 10 (30.00%) 5 3 / 10 (30.00%) 3 1 / 10 (10.00%) 2 2 / 10 (20.00%) 3	

subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 10 (0.00%) 0	
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	1 / 10 (10.00%) 1	
Leukopenia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3	2 / 10 (20.00%) 3	
Injury, poisoning and procedural complications			
Haematoma	Additional description: Bruising on anterior abdominal wall following fall		
subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	4 / 10 (40.00%) 7	
Akathisia	Additional description: Restless legs		
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Dizziness subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Presyncope subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Hallucination subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	9 / 10 (90.00%) 58	8 / 10 (80.00%) 28	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
Constipation			
subjects affected / exposed	5 / 10 (50.00%)	4 / 10 (40.00%)	
occurrences (all)	5	5	
Diarrhoea			
subjects affected / exposed	7 / 10 (70.00%)	0 / 10 (0.00%)	
occurrences (all)	10	0	
Nausea			
subjects affected / exposed	4 / 10 (40.00%)	5 / 10 (50.00%)	
occurrences (all)	5	6	
Vomiting			
subjects affected / exposed	4 / 10 (40.00%)	1 / 10 (10.00%)	
occurrences (all)	6	2	
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Ascites	Additional description: Large volume ascites		
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal examination abnormal	Additional description: Bloating		
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 10 (20.00%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder	Additional description: Belching		

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 0	
Rectal haemorrhage subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Hiccups subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	5 / 10 (50.00%) 5	
Psoriasis	Additional description: Worsening of psoriasis		
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Skin discomfort	Additional description: Scalp pain		
subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 10 (10.00%) 1	
Renal and urinary disorders			
Cystitis noninfective subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 4	2 / 10 (20.00%) 2	
Haematuria subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	3 / 10 (30.00%) 3	
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 10 (20.00%) 2	
Arthralgia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 10 (10.00%) 1	
Myalgia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 10 (20.00%) 3	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	1 / 10 (10.00%) 1	
Dehydration subjects affected / exposed occurrences (all)	Additional description: Skin turgour decreased		
	1 / 10 (10.00%) 1	0 / 10 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2014	<ul style="list-style-type: none">- ISRCTN number added- Exclusion criteria added (Previous treatment with two or more lines of chemotherapy)- Recruitment timelines updated- Schedule of events updated- Requirement for lipid profile, coagulation and urine dipstick removed- EQ5D questionnaire to be completed at each treatment visit instead of every other visit- Dose reduction clarified- Section added to reflect the updated Investigator Brochure and Summary of Product Characteristics regarding the potential interaction of OATP1B1 substrates- Statistical sections updated following review- Minor grammatical and typographical errors corrected
14 December 2015	<ul style="list-style-type: none">- Change of contact telephone numbers- Inclusion criteria no 9 updated to include recurrence at any time point- Exclusion criteria no 2 removed – “previous treatment with two or more lines of chemotherapy”- Exclusion no 7 updated to exclude patients with creatinine clearance ≤ 15 mL/min/1.73m² (previously ≤ 30 mL/min/1.73m²)- Exclusion no 9 updated due to typographical error- Updates to toxicity sections due to updates to the Summary of Product Characteristics- Clarification that palliative radiotherapy is permitted

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 August 2014	Temporary suspension of recruitment by Sponsor due to site documentation and safety reporting concerns. Patient safety and data quality was not compromised. An action plan was put into place to remedy the issues and, following monitoring visits by the Sponsor and a number of changes to practice, recruitment resumed in December 2014 following MREC and MHRA approval of amendment 1.	02 December 2014

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations of the study were mainly the small numbers of patients able to be recruited at and the high numbers of patients from both arms not being evaluable for response due to toxicity of treatment, early progression and withdrawal from the study.

Notes:

