Clinical trial results:
A Phase I/II single-arm trial to evaluate the combination of cisplatin and gemcitabine with the mTOR inhibitor temsirolimus for treatment of advanced cancers, including first-line treatment of patients with advanced transitional cell carcinoma of the urothelium.

Summary

EudraCT number	2007-007615-82
Trial protocol	GB
Global end of trial date	15 March 2017

Results information

Result version number	v1 (current)
This version publication date	
First version publication date	
Summary attachment (see zip file)	CONSORT diagram (CONSORT diagram.jpg) Statistical final report (Statistical analysis final report v 1.0 for REC.docx)

Trial information

Trial identification

Sponsor protocol code	SPON417-07

Additional study identifiers

ISRCTN number	ISRCTN31546330
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cardiff University
Sponsor organisation address	30-36 Newport Road, Cardiff, United Kingdom,
Public contact	Ms Angela Casbard, Centre for Trials Research, 02920 687470, casbardac@cardiff.ac.uk
Scientific contact	Ms Angela Casbard, Centre for Trials Research, 02920 687470, casbardac@cardiff.ac.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	23 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2017
Global end of trial reached?	Yes
Global end of trial date	15 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The overall objective of this trial is to assess whether the addition of temsirolimus to standard cipslatin/gemcitabine cancer chemotherapy is a safe and effective treatment for patients with advanced malignancy and an effective treatment for patients with advanced urothelial cancer.

Phase I of the trial aims to establish the appropriate dose and schedule of temsirolimus when used in combination with gemcitabine and and cisplatin for patients with advanced non-haematological malignancy.

Phase II of the trial aims to establish activity, safety and feasibility of this combination in participants with advanced transitional cell carcinoma of the urothelium. Activity will be measured by determining the number of patients who are alive at six months and have responded completely or partially to treatment or who have stable disease, according to strict radiological criteria i.e. progression-free survival (PFS) six months after enrolment.

Protection of trial subjects:

The safety review committee (SRC) met to review each cohort of 3 patients and to decide whether or not to escalate to the next dose level, to recruit additional participants at the current dose level or to discontinue dose escalation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 December 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: 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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial open date: 31 December 2012 and Open for 38 months. Recruitment was stopped August 2015.

Pre-assignment

Screening details:

Main Inclusion Criteria: For all participants: 1) Locally advanced and/or metastatic disease. Not suitable for radical radiotherapy or curative surgery 2) Life expectancy ≥3 months 3) WHO Performance status 0-2 4) Fit to receive cisplatin-containing combination chemotherapy 5) Informed consent.

Pre-assignment period milestones

Number of subjects started	15
Number of subjects completed	14

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not eligible: 1

Period 1

Period 1 title	Cohort 1
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	Torisel
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 mg day 15

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

70 mg day 1 of every cycle

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

1000 mg day 1, 8

Number of subjects in period 1	Experimental		
Started	3		
Completed	2		
Not completed	1		
Physician decision	1		

Period 2	
Period 2 title	Cohort 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	Torisel
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 10 mg day 8 and 15	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 70 mg day 1 of every cycle	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 1000 mg day 1, 8	

Number of subjects in period 2	Experimental		
Started	4		
Completed	0		
Not completed	4		
Adverse event, non-fatal	1		
Ineligible	1		
Consent withdrawn by subject	1		
Disease progression	1		

Period 3	
Period 3 title	Cohort 3
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	Torisel
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 10 mg day 1, 8 and 15	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 70 mg day 1 of every cycle	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 1000 mg day 1, 8	

Number of subjects in period 3	Experimental		
Started	4		
Completed	2		
Not completed	2		
Physician decision	1		
Poor rationale for treatment in palliative setting	1		

Period 4	
Period 4 title	Cohort 3b
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	Torisel
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 10 mg day 2, 9 and 15	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 70 mg day 1 of every cycle	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 1000 mg day 1, 8	

Number of subjects in period 4	Experimental		
Started	4		
Completed	3		
Not completed	1		
Adverse event, non-fatal	1		

Period 5	
Period 5 title	Full trial
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	Torisel
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 10 mg at different days per cohort	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 70 mg day 1 of every cycle	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 1000 mg day 1, 8	

Number of subjects in period 5	Experimental		
Started	15		
Completed	7		
Not completed	8		
Physician decision	2		
Poor rationale for treatment in palliative setting	1		
Adverse event, non-fatal	2		
Ineligible	1		
Consent withdrawn by subject	1		
Disease progression	1		

Baseline characteristics

Reporting groups	
Reporting group title	Experimental

Reporting group description: -

Reporting group values	Experimental	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Age continuous Units: years			
median	63.5		
full range (min-max)	40 to 80	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	5	5	
Non-Urothelial Cancer Histology Units: Subjects			
Adenocarcinoma	2	2	
Adenosquamous Carcinoma	1	1	
Poorly differentiated/ insular carcinoma	1	1	
Large cell undifferentiated carcinoma	1	1	
Cholangiocarcinoma of biliary tract	1	1	
Non-small cell carcinoma	1	1	
Ovarian clear cell carcinoma	1	1	
Location of primary disease for Non-Urothelial Cancer patients Units: Subjects			
Lung	3	3	
Gallbladder	1	1	
Uterus	1	1	
Thyroid	1	1	
Biliary Tract	1	1	
Ovarian	1	1	
T - Stage for Non-Urothelial Cancer patients Units: Subjects			
TX	5	5	
T0	1	1	
T1	1	1	
T4A	1	1	
N - Stage for Non-Urothelial Cancer patients Units: Subjects			
N0	5	5	

N1	3	3	
M-Stage for Non-Urothelial Cancer patients Units: Subjects			
M1	8	8	
Urothelial Cancer histology Units: Subjects			
Pure TCC	4	4	
Mixed TCC	1	1	
Missing	1	1	
Location of primary disease for Urothelial Cancer patients Units: Subjects			
Bladder	3	3	
Renal Pelvis/Ureter	2	2	
Missing	1	1	
T - Stage for Urothelial Cancer patients Units: Subjects			
TX	3	3	
T2	1	1	
T3	2	2	
N - Stage for Urothelial Cancer patients Units: Subjects			
NX	1	1	
N0	1	1	
N1	3	3	
N3	1	1	
M-Stage for Urothelial Cancer patients Units: Subjects			
M0	1	1	
M1	5	5	
Current metastases Units: Subjects			
Liver	3	3	
Lung	6	6	
Bone	2	2	
Multiple	1	1	
Other	4	4	
Current nodes Units: Subjects			
Pelvic	3	3	
Supraclavicular	1	1	
Abdominal	2	2	
Axillary	2	2	
Multiple	3	3	
Other	5	5	
Previous (neo)adjuvant chemotherapy Units: Subjects			
Yes	9	9	
No	5	5	
Did any previous (neo)adjuvant chemotherapy include cisplatin			

Units: Subjects			
Yes	4	4	
No	5	5	
Previous Radiotherapy Units: Subjects			
Yes	2	2	
No	12	12	
Median number of cycles of previous (neo)adjuvant chemotherapy Units: Number of cycles			
median	6		
full range (min-max)	3 to 18	-	

Subject analysis sets

Subject analysis set title	Treated patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: One patient was deemed ineligible after they were recruited.	
Subject analysis set title	Cohort 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 1	
Subject analysis set title	Cohort 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 2	
Subject analysis set title	Cohort 3
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 3	
Subject analysis set title	Cohort 3b
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 3b	
Subject analysis set title	Urothelial Cancer Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Urothelial Cancer Patients only	
Subject analysis set title	Non-Urothelial Cancer Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Non-Urothelial Cancer Patients only	
Subject analysis set title	Pure TCC patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Pure TCC patients only	

Reporting group values	Treated patients	Cohort 1	Cohort 2
Number of subjects	14	3	3

Age categorical Units: Subjects			

Age continuous Units: years			
median	63.5	60	72
full range (min-max)	40 to 80	50 to 68	69 to 72
Gender categorical Units: Subjects			
Female	9	1	2
Male	5	2	1
Non-Urothelial Cancer Histology Units: Subjects			
Adenocarcinoma	2	0	2
Adenosquamous Carcinoma	1	0	0
Poorly differentiated/ insular carcinoma	1	0	0
Large cell undifferentiated carcinoma	1	0	0
Cholangiocarcinoma of biliary tract	1	0	0
Non-small cell carcinoma	1	0	0
Ovarian clear cell carcinoma	1	0	0
Location of primary disease for Non-Urothelial Cancer patients Units: Subjects			
Lung	3	0	1
Gallbladder	1	0	1
Uterus	1	0	0
Thyroid	1	0	0
Biliary Tract	1	0	0
Ovarian	1	0	0
T - Stage for Non-Urothelial Cancer patients Units: Subjects			
TX	5	0	1
T0	1	0	0
T1	1	0	1
T4A	1	0	0
N - Stage for Non-Urothelial Cancer patients Units: Subjects			
N0	5	0	1
N1	3	0	1
M-Stage for Non-Urothelial Cancer patients Units: Subjects			
M1	8	0	2
Urothelial Cancer histology Units: Subjects			
Pure TCC	4	2	1
Mixed TCC	1	1	0
Missing	1	0	0
Location of primary disease for			

Urothelial Cancer patients Units: Subjects			
Bladder	3	1	1
Renal Pelvis/Ureter	2	2	0
Missing	1	0	0
T - Stage for Urothelial Cancer patients Units: Subjects			
TX	3	0	1
T2	1	1	0
T3	2	2	0
N - Stage for Urothelial Cancer patients Units: Subjects			
NX	1	0	0
N0	1	1	0
N1	3	2	1
N3	1	0	0
M-Stage for Urothelial Cancer patients Units: Subjects			
M0	1	0	0
M1	5	3	1
Current metastases Units: Subjects			
Liver	3	1	0
Lung	6	1	1
Bone	2	0	1
Multiple	1	0	0
Other	4	1	1
Current nodes Units: Subjects			
Pelvic	3	1	1
Supraclavicular	1	0	0
Abdominal	2	2	0
Axillary	2	0	0
Multiple	3	1	0
Other	5	0	1
Previous (neo)adjuvant chemotherapy Units: Subjects			
Yes	9	1	0
No	5	2	3
Did any previous (neo)adjuvant chemotherapy include cisplatin Units: Subjects			
Yes	4	0	0
No	5	1	0
Previous Radiotherapy Units: Subjects			
Yes	2	0	1
No	12	3	2
Median number of cycles of previous (neo)adjuvant chemotherapy Units: Number of cycles			
median	6	4	0

full range (min-max)	3 to 18	4 to 4	0 to 0

Reporting group values	Cohort 3	Cohort 3b	Urothelial Cancer Patients
Number of subjects	4	4	6
Age categorical Units: Subjects			
Age continuous Units: years			
median	70.5	56.5	64
full range (min-max)	40 to 80	47 to 57	50 to 74
Gender categorical Units: Subjects			
Female	3	3	2
Male	1	1	4
Non-Urothelial Cancer Histology Units: Subjects			
Adenocarcinoma	0	0	
Adenosquamous Carcinoma	1	0	
Poorly differentiated/ insular carcinoma	1	0	
Large cell undifferentiated carcinoma	1	0	
Cholangiocarcinoma of biliary tract	0	1	
Non-small cell carcinoma	0	1	
Ovarian clear cell carcinoma	0	1	
Location of primary disease for Non-Urothelial Cancer patients Units: Subjects			
Lung	1	1	
Gallbladder	0	0	
Uterus	1	0	
Thyroid	1	0	
Biliary Tract	0	1	
Ovarian	0	1	
T - Stage for Non-Urothelial Cancer patients Units: Subjects			
TX	3	1	
T0	0	1	
T1	0	0	
T4A	0	1	
N - Stage for Non-Urothelial Cancer patients Units: Subjects			
N0	3	1	
N1	0	2	
M-Stage for Non-Urothelial Cancer patients Units: Subjects			

M1	3	3	
Urothelial Cancer histology Units: Subjects			
Pure TCC	0	1	
Mixed TCC	0	0	
Missing	1	0	
Location of primary disease for Urothelial Cancer patients Units: Subjects			
Bladder	0	1	
Renal Pelvis/Ureter	0	0	
Missing	1	0	
T - Stage for Urothelial Cancer patients Units: Subjects			
TX	1	1	
T2	0	0	
T3	0	0	
N - Stage for Urothelial Cancer patients Units: Subjects			
NX	1	0	
N0	0	0	
N1	0	0	
N3	0	1	
M-Stage for Urothelial Cancer patients Units: Subjects			
M0	0	1	
M1	1	0	
Current metastases Units: Subjects			
Liver	1	1	
Lung	2	2	
Bone	1	0	
Multiple	1	0	
Other	2	0	
Current nodes Units: Subjects			
Pelvic	0	1	
Supraclavicular	0	1	
Abdominal	0	0	
Axillary	0	2	
Multiple	0	2	
Other	2	2	
Previous (neo)adjuvant chemotherapy Units: Subjects			
Yes	4	4	
No	0	0	
Did any previous (neo)adjuvant chemotherapy include cisplatin Units: Subjects			
Yes	2	2	
No	2	2	
Previous Radiotherapy			

Units: Subjects			
Yes	1	0	
No	3	4	
Median number of cycles of previous (neo)adjuvant chemotherapy Units: Number of cycles			
median	10	4	
full range (min-max)	6 to 18	3 to 6	

Reporting group values	Non-Urothelial Cancer Patients	Pure TCC patients	
Number of subjects	8	4	
Age categorical Units: Subjects			
Age continuous Units: years			
median	62	64	
full range (min-max)	40 to 80	56 to 72	
Gender categorical Units: Subjects			
Female	7	0	
Male	1	4	
Non-Urothelial Cancer Histology Units: Subjects			
Adenocarcinoma			
Adenosquamous Carcinoma			
Poorly differentiated/ insular carcinoma			
Large cell undifferentiated carcinoma			
Cholangiocarcinoma of biliary tract			
Non-small cell carcinoma			
Ovarian clear cell carcinoma			
Location of primary disease for Non-Urothelial Cancer patients Units: Subjects			
Lung			
Gallbladder			
Uterus			
Thyroid			
Biliary Tract			
Ovarian			
T - Stage for Non-Urothelial Cancer patients Units: Subjects			
TX			
T0			
T1			
T4A			
N - Stage for Non-Urothelial Cancer patients Units: Subjects			
N0			

N1			
M-Stage for Non-Urothelial Cancer patients Units: Subjects			
M1			
Urothelial Cancer histology Units: Subjects			
Pure TCC Mixed TCC Missing			
Location of primary disease for Urothelial Cancer patients Units: Subjects			
Bladder Renal Pelvis/Ureter Missing			
T - Stage for Urothelial Cancer patients Units: Subjects			
TX T2 T3			
N - Stage for Urothelial Cancer patients Units: Subjects			
NX N0 N1 N3			
M-Stage for Urothelial Cancer patients Units: Subjects			
M0 M1			
Current metastases Units: Subjects			
Liver Lung Bone Multiple Other			
Current nodes Units: Subjects			
Pelvic Supraclavicular Abdominal Axillary Multiple Other			
Previous (neo)adjuvant chemotherapy Units: Subjects			
Yes No			
Did any previous (neo)adjuvant chemotherapy include cisplatin			

Units: Subjects			
Yes No			
Previous Radiotherapy Units: Subjects			
Yes No			
Median number of cycles of previous (neo)adjuvant chemotherapy Units: Number of cycles median full range (min-max)			

End points

End points reporting groups

Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Experimental
Reporting group description: -	
Subject analysis set title	Treated patients
Subject analysis set type	Intention-to-treat
Subject analysis set description: One patient was deemed ineligible after they were recruited.	
Subject analysis set title	Cohort 1
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 1	
Subject analysis set title	Cohort 2
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 2	
Subject analysis set title	Cohort 3
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 3	
Subject analysis set title	Cohort 3b
Subject analysis set type	Intention-to-treat
Subject analysis set description: Cohort 3b	
Subject analysis set title	Urothelial Cancer Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Urothelial Cancer Patients only	
Subject analysis set title	Non-Urothelial Cancer Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Non-Urothelial Cancer Patients only	
Subject analysis set title	Pure TCC patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: Pure TCC patients only	

Primary: Dose Limiting Toxicities

End point title	Dose Limiting Toxicities

End point description:

End point type	Primary

End point timeframe:

until cycle 2, day 1

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Subjects	0	0	2	2

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects	4			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[1]

Notes:

[1] - Univariates

Secondary: Deaths

End point title	Deaths

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Subjects				
Number	1	1	3	2

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects				
Number	7			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[2]

Notes:

[2] - Univariates

Secondary: Median doses cisplatin

End point title	Median doses cisplatin

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: doses				
median (full range (min-max))	70 (68 to 70)	70 (70 to 70)	70 (0 to 70)	65.8 (52 to 70)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			

Units: doses				
median (full range (min-max))	70 (0 to 70)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[3]

Notes:

[3] - Univariates

Secondary: Median doses gemcitabine

End point title	Median doses gemcitabine

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Doses				
median (full range (min-max))	1000 (0 to 1000)	750 (0 to 1000)	750 (0 to 1000)	750 (0 to 1000)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Doses				
median (full range (min-max))	750 (0 to 1000)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v

	Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[4]

Notes:
[4] - Univariates

Secondary: Median doses temsirolimus

End point title	Median doses temsirolimus

End point description:

End point type	Secondary

End point timeframe:
Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Doses				
median (full range (min-max))	0 (0 to 10)	5 (0 to 10)	10 (0 to 10)	10 (0 to 10)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Doses				
median (full range (min-max))	7.5 (0 to 10)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[5]

Notes:
[5] - Univariates

Secondary: Any dose reduction

End point title	Any dose reduction

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Subjects				
Number	2	3	4	4

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects				
Number	13			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[6]

Notes:

[6] - Univariates

Secondary: Median dose reduction cisplatin

End point title	Median dose reduction cisplatin

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Doses				
median (full range (min-max))	68 (68 to 68)	0 (0 to 0)	26 (0 to 52)	52 (52 to 53)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Doses				
median (full range (min-max))	52 (0 to 68)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[7]

Notes:

[7] - Univariates

Secondary: Median dose reductions gemcitabine

End point title	Median dose reductions gemcitabine

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Doses				
median (full range (min-max))	187.5 (0 to 750)	375 (0 to 750)	750 (0 to 750)	594 (0 to 750)

End point values	Experimental			
Subject group type	Reporting group			

Number of subjects analysed	14			
Units: Doses				
median (full range (min-max))	563 (0 to 750)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[8]

Notes:

[8] - Univariates

Secondary: Median dose reductions temsirolimus

End point title	Median dose reductions temsirolimus

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Doses				
median (full range (min-max))	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Doses				
median (full range (min-max))	0 (0 to 0)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28

Analysis specification	Pre-specified
Analysis type	other[9]

Notes:
[9] - Univariates

Secondary: Any dose delays

End point title	Any dose delays

End point description:

End point type	Secondary

End point timeframe:
Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Subjects				
Number	3	3	4	4

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Subjects				
Number	14			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[10]

Notes:
[10] - Univariates

Secondary: Median dose delays

End point title	Median dose delays

End point description:

End point type	Secondary

End point timeframe:

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Days				
median (full range (min-max))	1 (0 to 3)	4 (1 to 14)	1 (0 to 3)	0.5 (0 to 1)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Days				
median (full range (min-max))	0.5 (0 to 14)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[11]

Notes:

[11] - Univariates

Secondary: Mean percent dose intensity Cisplatin

End point title	Mean percent dose intensity Cisplatin

End point description:

End point type	Secondary

End point timeframe:

Cycles 1-3

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percent				
arithmetic mean (full range (min-max))	99 (99 to 99)	74.1 (74.1 to 74.1)	80.6 (80.6 to 80.6)	94 (94 to 94)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Percent				
arithmetic mean (full range (min-max))	87 (87 to 87)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[12]

Notes:

[12] - Univariates

Secondary: Mean percent dose intensity Gemcitabine

End point title	Mean percent dose intensity Gemcitabine

End point description:

End point type	Secondary

End point timeframe:

Cycles 1-3

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percent				
arithmetic mean (full range (min-max))	100 (100 to 100)	59.7 (59.7 to 59.7)	54.9 (54.9 to 54.9)	81 (81 to 81)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Percent				
arithmetic mean (full range (min-max))	73 (73 to 73)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[13]

Notes:

[13] - Univariates

Secondary: Mean percent dose intensity temsirolimus

End point title	Mean percent dose intensity temsirolimus

End point description:

End point type	Secondary

End point timeframe:

Cycles 1-3

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Percent				
arithmetic mean (full range (min-max))	100 (100 to 100)	68.5 (68.5 to 68.5)	48.1 (48.1 to 48.1)	75 (75 to 75)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Percent				
arithmetic mean (full range (min-max))	73 (73 to 73)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[14]

Notes:

[14] - Univariates

Secondary: Mean percent dose intensity Cisplatin all

End point title	Mean percent dose intensity Cisplatin all

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: percent				
arithmetic mean (full range (min-max))	88 (88 to 88)	50 (50 to 50)	62.5 (62.5 to 62.5)	84.3 (84.3 to 84.3)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percent				
arithmetic mean (full range (min-max))	72 (72 to 72)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[15]

Notes:

[15] - Univariates

Secondary: Mean percent dose intensity gemcitabine all

End point title	Mean percent dose intensity gemcitabine all

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: percent				
arithmetic mean (full range (min-max))	89 (89 to 89)	41 (41 to 41)	46.9 (46.9 to 46.9)	69.5 (69.5 to 69.5)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percent				
arithmetic mean (full range (min-max))	61 (61 to 61)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[16]

Notes:

[16] - Univariates

Secondary: Mean percent dose intensity temsirolimus all

End point title	Mean percent dose intensity temsirolimus all

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: percent				
arithmetic mean (full range (min-max))	89 (89 to 89)	36 (36 to 36)	37 (37 to 37)	69.4 (69.4 to 69.4)

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: percent				
arithmetic mean (full range (min-max))	58 (58 to 58)			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[17]

Notes:

[17] - Univariates

Secondary: Percent received at least 3 cycles of protocol treatment

End point title	Percent received at least 3 cycles of protocol treatment

End point description:

End point type	Secondary

End point timeframe:

First three cycles of treatment

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: percent				
number (not applicable)	66.7	0	25	25

End point values	Experimental			
Subject group type	Reporting group			

Number of subjects analysed	14			
Units: percent				
number (not applicable)	26.7			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[18]

Notes:

[18] - Univariates

Secondary: Withdrawal, drop outs or discontinuations

End point title	Withdrawal, drop outs or discontinuations

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	4	4	4
Units: Subjects				
Number	1	4	2	1

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects				
Number	8			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	30

Analysis specification	Pre-specified
Analysis type	other[19]

Notes:
[19] - Univariates

Secondary: AE greater than Grade 3

End point title	AE greater than Grade 3

End point description:

End point type	Secondary

End point timeframe:
Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Number of AEs	12	14	18	14

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number of AEs	58			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[20]

Notes:
[20] - Univariates

Secondary: Any AE

End point title	Any AE

End point description:

End point type	Secondary

End point timeframe:
Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Number of toxicities	207	140	169	213

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number of toxicities	729			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[21]

Notes:
[21] - Univariates

Secondary: Serious AEs

End point title	Serious AEs

End point description:

End point type	Secondary

End point timeframe:
Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Number of toxicities	4	1	4	1

End point values	Experimental			
Subject group type	Reporting group			

Number of subjects analysed	14			
Units: Number of toxicities	10			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[22]

Notes:

[22] - Univariates

Secondary: Serious Adverse Reactions

End point title	Serious Adverse Reactions

End point description:

End point type	Secondary

End point timeframe:

Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Number of toxicities	0	1	1	0

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number of toxicities	2			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[23]

Notes:
[23] - Univariates

Secondary: AE leading to discontinuation of temsirolimus

End point title	AE leading to discontinuation of temsirolimus

End point description:

End point type	Secondary

End point timeframe:
Entire trial

End point values	Experimental	Experimental	Experimental	Experimental
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	4	4
Units: Number of toxicities	1	2	0	0

End point values	Experimental			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Number of toxicities	3			

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Experimental v Experimental v Experimental v Experimental v Experimental
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[24]

Notes:
[24] - Univariates

Secondary: Disease response at the end of cycle 3

End point title	Disease response at the end of cycle 3

End point description:

End point type	Secondary

End point timeframe:
End of cycle 3

End point values	Treated patients	Urothelial Cancer Patients	Non-Urothelial Cancer Patients	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	6	8	
Units: Subjects				
CR	0	0	0	
PR	5	4	1	
SD	8	2	6	
PD	0	0	0	
NE	0	0	0	
Withdrawn but consented to follow up and missed vi	1	0	1	
Missing	0	0	0	
Died	0	0	0	

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Treated patients v Urothelial Cancer Patients v Non-Urothelial Cancer Patients
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[25]

Notes:

[25] - Univariates

Secondary: Disease response at the end of cycle 6

End point title	Disease response at the end of cycle 6

End point description:

End point type	Secondary

End point timeframe:

End of cycle 6

End point values	Treated patients	Urothelial Cancer Patients	Non-Urothelial Cancer Patients	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	6	8	
Units: Subjects				
CR	1	1	0	
PR	0	0	0	
SD	1	0	1	
PD	7	4	3	
NE	0	0	0	
Withdrawn but consented to follow up and missed vi	4	1	3	
Missing	0	0	0	

Died	1	0	1	

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Treated patients v Urothelial Cancer Patients v Non-Urothelial Cancer Patients
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[26]

Notes:

[26] - Univariates

Secondary: Disease response at 6 months

End point title	Disease response at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months follow up

End point values	Treated patients	Urothelial Cancer Patients	Non-Urothelial Cancer Patients	Pure TCC patients
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	6	8	4
Units: Subjects				
CR	1	1	0	1
PR	0	0	0	0
SD	1	0	1	0
PD	7	4	3	2
NE	0	0	0	0
Withdrawn but consented to follow up and missed vi	4	1	3	1
Missing	0	0	0	0
Died	1	0	1	0

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Treated patients v Urothelial Cancer Patients v Non-Urothelial Cancer Patients v Pure TCC patients
Number of subjects included in analysis	32
Analysis specification	Pre-specified

Analysis type	other[27]

Notes:
[27] - Univariates

Secondary: Disease response at 12 months

End point title	Disease response at 12 months

End point description:

End point type	Secondary

End point timeframe:
12 months follow up

End point values	Treated patients	Urothelial Cancer Patients	Non-Urothelial Cancer Patients	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	6	8	
Units: Subjects				
CR	1	1	0	
PR	0	0	0	
SD	0	0	0	
PD	1	1	0	
NE	0	0	0	
Withdrawn but consented to follow up and missed vi	4	1	3	
Missing	3	1	2	
Died	5	2	3	

Statistical analyses

Statistical analysis title	Univariates
Comparison groups	Treated patients v Urothelial Cancer Patients v Non-Urothelial Cancer Patients
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other[28]

Notes:
[28] - Univariates

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Cycles 1-6, 6 and 12 months follow up	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups	
Reporting group title	Experimental

Reporting group description: -

Serious adverse events	Experimental		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 14 (57.14%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Neutropenia fever			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic Sepsis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Vasovagal reaction			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Low Potassium			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Ano-rectal infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Experimental		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 14 (100.00%)		
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Phlebitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 14 (85.71%)		
occurrences (all)	47		
Fever			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Lethargy			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	14		
Flu like symptoms			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Weight loss			
subjects affected / exposed	4 / 14 (28.57%)		
occurrences (all)	6		
Oral thrush			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastro-oesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Inflammation in right wrist (possibly related to last infusion)			

subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Periorbital oedema				
subjects affected / exposed	3 / 14 (21.43%)			
occurrences (all)	4			
Occasional headaches				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	4			
Dehydration				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Sore throat				
subjects affected / exposed	4 / 14 (28.57%)			
occurrences (all)	7			
Flecks of blood when blowing nose				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Runny nose				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Dry mouth				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	3			
Mouth ulcers				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Mouth soreness				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Right eye bloodshot				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Urine stream stop/start				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Skin rash - left upper chest (insect				

bite)				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Left arm cellulitis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Bleeding (bruise) left arm - picc line insertion				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Swollen right hand				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	5			
Swollen left hand				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	5			
Allergic reaction				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Watering eyes				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Myalgias				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Left forearm swelling and pain				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Pins and needles in hands and feet				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Hot flushes				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Night sweats				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			

Psychiatric disorders Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 1 / 14 (7.14%) 1 2 / 14 (14.29%) 2		
Investigations ALT increased subjects affected / exposed occurrences (all) AST increased subjects affected / exposed occurrences (all) Cholesterol high subjects affected / exposed occurrences (all) Creatinine increased subjects affected / exposed occurrences (all) GGT increased subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Neutrophil count decreased subjects affected / exposed occurrences (all) Platelet count decreased subjects affected / exposed occurrences (all) White blood cell count increased subjects affected / exposed	 5 / 14 (35.71%) 12 3 / 14 (21.43%) 3 1 / 14 (7.14%) 3 1 / 14 (7.14%) 1 1 / 14 (7.14%) 5 5 / 14 (35.71%) 15 12 / 14 (85.71%) 36 11 / 14 (78.57%) 30 3 / 14 (21.43%)		

occurrences (all)	3		
Increased platelets			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	10		
Thrombocytopaenia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	19		
Epistaxis			
subjects affected / exposed	6 / 14 (42.86%)		
occurrences (all)	8		
Nose bleeds			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	17		
Haemoptysis/bronchopulmonary haemorphage			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 14 (57.14%)		
occurrences (all)	33		
Superficial left vein thrombosis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 9		
Dysgeusia (taste) subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 9		
Altered taste subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 4		
Neuropathy in left hand of uncertain origin subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 5		
Hypersensitivity to smells subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 5		
Headache subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Paresthesia subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Eye disorders Inflamed left eye lid subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Ear and labyrinth disorders Hearing impaired subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 3		
Tinnitus subjects affected / exposed occurrences (all)	5 / 14 (35.71%) 16		
External otitis			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	10 / 14 (71.43%)		
occurrences (all)	27		
Diarrhoea			
subjects affected / exposed	7 / 14 (50.00%)		
occurrences (all)	14		
Nausea			
subjects affected / exposed	14 / 14 (100.00%)		
occurrences (all)	46		
Vomiting			
subjects affected / exposed	9 / 14 (64.29%)		
occurrences (all)	20		
Stomatitis			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Mucositis			
subjects affected / exposed	8 / 14 (57.14%)		
occurrences (all)	16		
Abdominal cramping			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastric reflux			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Blisters on tongue			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		

Sub acute bowel obstruction subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 2		
Urinary frequency subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 5		
Nocturia subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 7		
Dysuria subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Left loin pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Urinary urgency subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Proteinuria subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 5		
Eczema (non infected) subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 6		
Alopecia subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 6		
Rash maculo-papular subjects affected / exposed	5 / 14 (35.71%)		

occurrences (all)	11			
Folliculitis				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Itchy skin				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	2			
Skin rash				
subjects affected / exposed	6 / 14 (42.86%)			
occurrences (all)	12			
Dry skin				
subjects affected / exposed	3 / 14 (21.43%)			
occurrences (all)	9			
Acne form rash anterior chest				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			
Musculoskeletal and connective tissue disorders				
Leg pain				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	2			
Coccygeal pain				
subjects affected / exposed	2 / 14 (14.29%)			
occurrences (all)	2			
Cramp (calf muscle)				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	2			
Left chest wall pain				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	5			
Bilateral ankle oedema				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	5			
Chest wall discomfort				
subjects affected / exposed	1 / 14 (7.14%)			
occurrences (all)	1			

Back pain subjects affected / exposed occurrences (all)	6 / 14 (42.86%) 8		
Back pain and left leg pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 5		
Whole body pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 2		
Pelvic pain subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Cramp (hands and toes) subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Endocrine disorders Salivary gland secretion increase subjects affected / exposed occurrences (all)	2 / 14 (14.29%) 3		
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 14 (7.14%) 1		
Metabolism and nutrition disorders Hypomagnesemia subjects affected / exposed occurrences (all)	6 / 14 (42.86%) 16		
Hyponatraemia subjects affected / exposed occurrences (all)	4 / 14 (28.57%) 15		
Hypophosphataemia subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 7		
Hyperglycaemia subjects affected / exposed occurrences (all)	3 / 14 (21.43%) 4		
Hypokalaemia subjects affected / exposed	7 / 14 (50.00%)		

occurrences (all)	9		
Appetite lost			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	3		
Reduced appetite			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	3		
Anorexia			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	4		
Infections and infestations			
Upper respiratory infection			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	4		
Lower respiratory tract infection (chest)			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Chest infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2011	Change of documents: Cover Letter 18/08/2011 Protocol v2.0 04/08/2011 Protocol Amendment Log v2.0 04/08/2011 PIS Phase II Amendment Log v1.0 to v2.0 04/08/2011 PIS Phase I Amendment Log v1.0 to v2.0 04/08/2011 PIS Phase II v2.0 (clean and tracked changes versions) 04/08/2011 PIS Phase I v2.0 (clean and tracked changes versions) 04/08/2011 Pregnancy PIS supporting information Pregnancy PIS and Consent v1.0 04/08/2011 Phase I/Phase II Consent Form Amendment Log v2.0 04/08/2011 Phase I/Phase II Consent Form v2.0 (clean and tracked changes versions) 04/08/2011 Participant Trial Card v1.0 04/08/2011 Trial Summary v2.0 (clean and tracked changes versions) 04/08/2011 Additional Sites: Calderdale Royal-Uschi Hoffmann York Teaching Hospitals NHS Foundation Trust –David Bottomley Weston Park Hospital, Cancer Clinical Trials Centre –Linda Evans Bristol Haematology and Oncology Centre-Amit Bahl Huddersfield Royal Infirmary-Uschi Hoffmann Royal Free Hospital-Maria Vilarino-Varela Castle Hill Hospital-Mohammad Buitt Leicester Royal Infirmary-Steve Nicholson Changes of PI: Royal Bournemouth General Hospital-Susannah Brock (replaced Tom Geldart) Leeds St James's –Satinder Jagdev (replaced John Chester) Removal of PI: Newcastle General Hospital –Trevor Roberts Velindre Cancer Centre-Jim Barber Queen Elizabeth Hospital (Bham)-Emilio Porfiri
20 March 2012	Addition of new sites and PI as follows: Addenbrookes Hospital –Simon Pacey
03 May 2013	Change of documents: Covering letter 08/07/2013 Protocol v3.0 dated 23/05/2013(clean copy) Protocol v3.0 dated 23/05/2013 (tracked changes) Protocol Amendment Log v2.0 to v3.0 04/07/2013 Phase I Participant Information Sheet v3.0 04/07/2013(clean copy) Phase I Participant Information Sheet v3.0 04/07/2013(tracked changes) Phase I Participant Information Sheet Amendment Log v2.0 to v3.0 08/07/2013 Phase II Participant Information Sheet v3.0 04/07/2013 (clean copy) Phase II Participant Information Sheet v3.0 04/07/2013 (tracked changes) Phase II Participant Information Sheet Amendment Log v2.0 to v3.0 08/07/2013 Phase I/Phase II Participant Consent Form v3.0 04/07/2013 (clean copy) Phase I/Phase II Participant Consent Form v3.0 04/07/2013 (tracked changes) Phase I/Phase II Participant Consent Form Amendment Log v2.0 to v3.0 08/07/2013

19 June 2014	Change of documents: TOTEM Clinical Trial Protocol (from v4.0 to version 5.0). Update the Reference Safety Information (RSI) for temsirolimus to the EMC update on 06/12/2013. Change the status of cisplatin and gemcitabine from nIMPs to IMPs. To seek a labelling exemption: for cisplatin and gemcitabine as IMPs. To change the person or organisation authorised by the sponsor responsible for the CTA: from Dr Gareth Griffiths to Dr Richard Adams. Provide simplified IMPD: for temsirolimus 11/07/14 Inform REC of non-substantial changes to protocol (v4.0 13.12.13)
08 December 2015	Change of documents: TOTEM Phase I PIS V7.0 12.11.15 TOTEM Consent Form Phase I/Phase II V7.0 12.11.15 TOTEM Clinical Trial Protocol (from v6.0 to v.7.0) To include Dr Simon Pacey as co-investigator To update Temsirolimus dose escalation schedule for Phase 1 with the inclusion of dose-level 3c To update Concomitant Medications Table

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported