

**Clinical trial results:**

**Phase I/II study with Temsirolimus versus no add-on in patients with castration resistant prostate cancer (CRPC) receiving first-line Docetaxel chemotherapy**

**CESAR Study in Prostrate Cancer with Temsirolimus added to standard Docetaxel therapy (CEPTAS)**

**Summary**

EudraCT number	2010-018370-21
Trial protocol	DE
Global end of trial date	25 September 2014

**Results information**

Result version number	v1 (current)
This version publication date	27 March 2020
First version publication date	27 March 2020

**Trial information****Trial identification**

Sponsor protocol code	C-II-007
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**Additional study identifiers**

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

Notes:

**Sponsors**

Sponsor organisation name	CESAR Central European Society for Anticancer Drug Research-EWIV
Sponsor organisation address	Hanglössgasse 4/1-3,, Vienna, Austria, A-1150
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Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
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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	18 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2014
Global end of trial reached?	Yes
Global end of trial date	25 September 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective in the Phase I Part is to evaluate feasibility of dose level DL1 to DL3 and defining a recommended dose (RD) for the Phase II part using the dose levels DL1-DL3 of the phase I part.

The primary objective in the study's Phase II Part is to evaluate the activity of the addition of temsirolimus to standard treatment on the disease progression-free survival in patients with castration resistant prostate cancer receiving first-line docetaxel chemotherapy.

Protection of trial subjects:

Patient are treated in accordance with clinical routine.

Background therapy:

All enrolled patients with castration resistant prostate cancer receive first-line docetaxel chemotherapy as background therapy.

Evidence for comparator:

Temsirolimus (Torisel R) is a selective inhibitor of the mammalian target of rapamycin (mTOR), a serine threonine kinase that regulates a signalling cascade controlling growth factor-induced cell proliferation. Temsirolimus inhibits mTOR-dependent protein translation induced by growth factor stimulation. In addition to cell-cycle proteins, the translation of other classes of protein is selectively regulated by mTOR. Thus, inhibition of mTOR by temsirolimus can impair tumor growth indirectly through inhibition of micro-environmental factors (e.g. VEGF) that support tumor growth. Temsirolimus is indicated for the first-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors and was approved in 2007.

Inactivating mutations and deletions of the lipid phosphatase PTEN gene commonly occur in many epithelial cancers including prostate cancer thus activating the PI3P/akt signaling cascade. Inhibition of mTOR can inhibit this pathway and therefore seems to be an interesting target in cancer therapy and specifically also in patients with prostate cancer. The inhibition of mTOR with temsirolimus has proven clinical efficacy in pretreated renal cell cancer and mantle cell lymphoma with acceptable toxicity.

Temsirolimus (TORISEL R) was registered in 2007 both in the US and Europe (including Switzerland) in the indication of renal cell carcinoma. Two preclinical studies demonstrated efficacy of temsirolimus on PTEN negative prostate cancer in mouse xenografts: in combination with chemotherapy it was shown, that resistance to doxorubicin could be overcome by the addition of temsirolimus. Since the mechanism of action of temsirolimus provides a basis for testing temsirolimus in the setting of CRPC, and in prostate cancer PTEN is frequently mutated, especially in advanced cases, it seems worthwhile to explore temsirolimus treatment in these patients with highly unmet medical need.

Actual start date of recruitment	30 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

Notes:

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#### Subjects enrolled per age group

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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)	5
From 65 to 84 years	14
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment of patients was performed at 4 study sites in Germany.

### Pre-assignment

Screening details:

The screening criteria were defined by the inclusion and exclusion criteria as defined in the study protocol.

### Period 1

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

### Arms

Arm title	treatment arm
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Arm description:

Primary objective:

To evaluate feasibility of dose level DLB1 to DLB3 and define a recommended dose for further studies.

DL 1: 60 mg/m<sup>2</sup> docetaxel [D] (d1), 15 mg temsirolimus [T] (d1, 8, 15)

DL 2: 60 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)

DL 3: 75 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)

Arm type	dose finding
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	L01CD02
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DL 1: 60 mg/m<sup>2</sup> docetaxel [D] (d1)

DL 2: 60 mg/m<sup>2</sup> docetaxel (d1)

DL 3: 75 mg/m<sup>2</sup> docetaxel (d1)

Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	L01XE09
Other name	Torisel
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

DL 1: 60 mg/m<sup>2</sup> docetaxel [D] (d1), 15 mg temsirolimus [T] (d1, 8, 15)

DL 2: 60 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)

DL 3: 75 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)

Due to safety problems with this scheme in DL1, the study was amended (Protocol 2.0) to include:

DL B 1: 60 mg/m<sup>2</sup> docetaxel (d1), 15 mg temsirolimus (d8, 15)

DL B 2: 60 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d8, 15)

DL B 3: 75 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d8, 15)

Steps for dose reduction were also pre-planned.

<b>Number of subjects in period 1</b>	treatment arm
Started	19
Completed	19

## Baseline characteristics

### Reporting groups

Reporting group title	Treatment period
Reporting group description: -	

Reporting group values	Treatment period	Total	
Number of subjects	19	19	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	69.6		
standard deviation	± 9.9	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	19	19	

### Subject analysis sets

Subject analysis set title	DL 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
DL 1: 60mg/m <sup>2</sup> docetaxel, 15mg temsirolimus	
Subject analysis set title	DL B1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
DL B1: 60mg/m <sup>2</sup> docetaxel (d1), 15mg temsirolimus (d8,15)	
Subject analysis set title	DL B2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
DL B2: 60mg/m <sup>2</sup> docetaxel (d1), 25mg temsirolimus (d8,15)	
Subject analysis set title	DL B3
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
DL B3: 75mg/m <sup>2</sup> docetaxel (d1), 25mg temsirolimus (d8,15)	

Reporting group values	DL 1	DL B1	DL B2
Number of subjects	3	4	8
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	74.8	75.5	67.3
standard deviation	± 1.0	± 3.4	± 8.9
Gender categorical Units: Subjects			
Female	0	0	0
Male	3	4	8

Reporting group values	DL B3		
Number of subjects	4		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	64.5		
standard deviation	± 16.3		
Gender categorical Units: Subjects			
Female	0		
Male	4		

## End points

### End points reporting groups

Reporting group title	treatment arm
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Reporting group description:

Primary objective:

To evaluate feasibility of dose level DLB1 to DLB3 and define a recommended dose for further studies.

DL 1: 60 mg/m<sup>2</sup> docetaxel [D] (d1), 15 mg temsirolimus [T] (d1, 8, 15)

DL 2: 60 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)

DL 3: 75 mg/m<sup>2</sup> docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)

Subject analysis set title	DL 1
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

DL 1: 60mg/m<sup>2</sup> docetaxel, 15mg temsirolimus

Subject analysis set title	DL B1
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

DL B1: 60mg/m<sup>2</sup> docetaxel (d1), 15mg temsirolimus (d8,15)

Subject analysis set title	DL B2
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

DL B2: 60mg/m<sup>2</sup> docetaxel (d1), 25mg temsirolimus (d8,15)

Subject analysis set title	DL B3
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

DL B3: 75mg/m<sup>2</sup> docetaxel (d1), 25mg temsirolimus (d8,15)

### Primary: Recommended Dose between 3 Dose Levels

End point title	Recommended Dose between 3 Dose Levels <sup>[1]</sup>
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End point description:

Recommended Dose (RD) chosen between the three DLs based on the dose escalation scheme.

End point type	Primary
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End point timeframe:

Dose-finding study for combination of docetaxel + temsirolimus using dose escalation scheme or 3+3 rule, with three sequential combination DLs. One cycle is a 3 week period (docetaxel on day 1, and temsirolimus on days 8 and 15).

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: Nineteen patients were enrolled in the Phase I part in order to define the recommended dose of docetaxel in combination with temsirolimus and to evaluate safety of the combination therapy. Three different dose levels were investigated. For this dose-finding study the traditional dose escalation scheme or 3+3 rule, see e.g. Edler & Burkholder (2006), was applied. Regular Safety Meetings were held to decide on dose escalation, and to evaluate safety. No statistical analysis performed.

End point values	treatment arm	DL 1	DL B1	DL B2
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	3	4	8
Units: 19	19	3	4	8



End point values	DL B3			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: 19	4			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Adverse events

End point title	Adverse events
End point description: Adverse events which were assessed using the National Cancer Institute (CTCAE v4.0).	
End point type	Secondary
End point timeframe: First patient in until last patient out (Aug 2010 - Sep 2014).	

End point values	treatment arm	DL 1	DL B1	DL B2
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	3	4	8
Units: 19	19	3	4	8

End point values	DL B3			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: 19	4			

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First patient in until last patient out (Aug 2010 - Sep 2014).

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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### Reporting groups

Reporting group title	Treatment period
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Reporting group description: -

Serious adverse events	Treatment period		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 19 (84.21%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Investigations			
Blood creatine increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Blood and lymphatic system disorders</b>			
<b>Anaemia</b>			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Leukopenia</b>			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
<b>Neutropenia</b>			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences causally related to treatment / all	13 / 13		
deaths causally related to treatment / all	0 / 0		
<b>Thrombocytopenia</b>			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Febrile neutropenia</b>			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
<b>General disorders and administration site conditions</b>			
<b>Catheter site haemorrhage</b>			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Fatigue</b>			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General physical health deterioration			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Stomatitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	2 / 19 (10.53%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Lipoma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Arteriosclerosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Circulatory collapse			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Haematoma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypotension			

subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Vascular pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Central venous catheterisation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Catheter site haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Catheter site pain			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Drug intolerance			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	13 / 19 (68.42%)		
occurrences (all)	23		
Gait disturbance			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
General physical health deterioration			

subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Mucosal inflammation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	6		
Pyrexia			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	5		
Xerosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Penile oedema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchitis chronic			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	3 / 19 (15.79%)		
occurrences (all)	3		
Dysphonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	3		
Epistaxis			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nasal dryness			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fear			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Blood creatine increased			



subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Blood uric acid increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Body temperature increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	4		
C-reactive protein increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Reticulocyte count decreased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	5		
Weight increased			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			

Congenital cystic kidney disease subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Cardiac disorders			
Atrioventricular block first degree subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Bradycardia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Cardiovascular disorder subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Nervous system disorders			
Ataxia subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 3		
Dizziness subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 4		
Dysgeusia subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 4		
Facial pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Polyneuropathy subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	13		
Leukopenia			
subjects affected / exposed	13 / 19 (68.42%)		
occurrences (all)	39		
Lymphopenia			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	12		
Neutropenia			
subjects affected / exposed	17 / 19 (89.47%)		
occurrences (all)	46		
Thrombocytopenia			
subjects affected / exposed	5 / 19 (26.32%)		
occurrences (all)	12		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Eye disorders			
Eyelid oedema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Anal ulcer			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Aphthous ulcer			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	7 / 19 (36.84%)		
occurrences (all)	10		
Dry mouth			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Faecalith			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	2		
Faecaloma			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastrointestinal inflammation			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Glossodynia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	8 / 19 (42.11%)		
occurrences (all)	9		
Rectal haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	6 / 19 (31.58%)		
occurrences (all)	10		
Tongue ulceration			

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Decubitus ulcer			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Erythema			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nail discolouration			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Nail dystrophy			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Onychoclasia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		

<p>Skin fissures</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 19 (5.26%)</p> <p>1</p>		
<p>Skin ulcer</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 19 (5.26%)</p> <p>1</p>		
<p>Renal and urinary disorders</p> <p>Dysuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Haematuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Obstructive nephropathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Renal failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Renal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 19 (5.26%)</p> <p>1</p> <p>2 / 19 (10.53%)</p> <p>2</p> <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Bone pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Groin pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Iliolumbar syndrome</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Chest pain</p>	<p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p> <p>1 / 19 (5.26%)</p> <p>1</p>		

subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Osteoarthritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Osteonecrosis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Pain in jaw			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Fungal infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Gingival discomfort			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Osteomyelitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		

Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 19 (47.37%)		
occurrences (all)	11		
Dehydration			
subjects affected / exposed	4 / 19 (21.05%)		
occurrences (all)	4		
Electrolyte depletion			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	2 / 19 (10.53%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 19 (5.26%)		
occurrences (all)	1		



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2011	Amendment 1: In order to avoid severe Neutropenia, simultaneous administration of docetaxel and temsirolimus on day1, as defined in protocol v1.0, was changed to administration of docetaxel on day 1 and temsirolimus on day 8 and 15 of a 21-day cycle.
24 October 2011	Amendment 2: The Inclusion criteria have been changed as follows: (1) PSA level at study entry of $\geq 2$ ng/ml within 1 week prior to treatment should no longer be required. (2) The timeframe for discontinuation between antiandrogens such as bicalutamide and start of study treatment has been reduced from 4 to 2 weeks.

Notes:

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### 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.

None reported.

Notes: