# 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 |
| **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 | Hanglüssgasse 4/1-3,, Vienna, Austria, A-1150 |
| Public contact | Dr Max Roessler, CESAR Central European Society for Anticancer Drug Research-EWIV , +43 1522309316, max.roessler@cesar.or.at |
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Notes:

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|---|---|
| **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

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|---|---|
| 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:

## Population of trial subjects

### Subjects enrolled per country

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

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 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 |

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/m² docetaxel [D] (d1), 15 mg temsirolimus [T] (d1, 8, 15)
DL 2: 60 mg/m² docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)
DL 3: 75 mg/m² 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/m² docetaxel [D] (d1)
DL 2: 60 mg/m² docetaxel (d1)
DL 3: 75 mg/m² 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/m² docetaxel [D] (d1), 15 mg temsirolimus [T] (d1, 8, 15)
DL 2: 60 mg/m² docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)
DL 3: 75 mg/m² 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/m² docetaxel (d1), 15 mg temsirolimus (d8, 15)
DL B 2: 60 mg/m² docetaxel (d1), 25 mg temsirolimus (d8, 15)
DL B 3: 75 mg/m² docetaxel (d1), 25 mg temsirolimus (d8, 15)
Steps for dose reduction were also pre-planned.

| **Number of subjects in period 1** | 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<br>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<br>Units: years | | | |
| arithmetic mean | 69.6 | | |
| standard deviation | ± 9.9 | - | |
| Gender categorical<br>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^2 docetaxel, 15mg temsirolimus

| Subject analysis set title | DL B1 |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:
DL B1: 60mg/m^2 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^2 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^2 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 |
|---|---|

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/m² docetaxel [D] (d1), 15 mg temsirolimus [T] (d1, 8, 15)
DL 2: 60 mg/m² docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)
DL 3: 75 mg/m² docetaxel (d1), 25 mg temsirolimus (d1, d8, 15)

| Subject analysis set title | DL 1 |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

DL 1: 60mg/m^2 docetaxel, 15mg temsirolimus

| Subject analysis set title | DL B1 |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

DL B1: 60mg/m^2 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^2 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^2 docetaxel (d1), 25mg temsirolimus (d8,15)

### Primary: Recommended Dose between 3 Dose Levels

| End point title | Recommended Dose between 3 Dose Levels[1] |
|---|---|

End point description:

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

| End point type | Primary |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Treatment period |

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 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 19 (36.84%) | | |
| occurrences causally related to treatment / all | 7 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 8 / 19 (42.11%) | | |
| occurrences causally related to treatment / all | 13 / 13 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 19 (15.79%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| 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<br>occurrences (all)<br><br>Blood uric acid increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Body temperature increased<br>subjects affected / exposed<br>occurrences (all)<br><br>C-reactive protein increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Reticulocyte count decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Weight decreased<br>subjects affected / exposed<br>occurrences (all)<br><br>Weight increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 19 (10.53%)<br>2<br><br>1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>4<br><br>1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>1<br><br>5 / 19 (26.32%)<br>5<br><br>1 / 19 (5.26%)<br>1 | | |
| Injury, poisoning and procedural complications<br>Femur fracture<br>subjects affected / exposed<br>occurrences (all)<br><br>Fall<br>subjects affected / exposed<br>occurrences (all) | 2 / 19 (10.53%)<br>2<br><br>1 / 19 (5.26%)<br>1 | | |
| Congenital, familial and genetic disorders | | | |

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

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

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

| | | | |
|---|---|---|---|
| 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<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 | | |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 | | |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 | | |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 9 / 19 (47.37%)<br>11 | | |
| Dehydration<br>subjects affected / exposed<br>occurrences (all) | 4 / 19 (21.05%)<br>4 | | |
| Electrolyte depletion<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 | | |
| Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 | | |
| Hyperuricaemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 19 (10.53%)<br>2 | | |
| Hypoalbuminaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 | | |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 | | |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>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:<br>The Inclusion criteria have been changed as follows:<br>(1) PSA level at study entry of ≥ 2 ng/ml within 1 week prior to treatment should no longer be required.<br>(2) The timeframe for discontinuation between antiandrogens such as bicalutamide and start of study treatment has been reduced from 4 to 2 weeks. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

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| None reported. |

Notes: