Clinical trial results:
Orteronel maintenance therapy in patients with metastatic castration resistant prostate cancer and non-progressive disease after first-line docetaxel therapy: A multicenter randomized double-blind placebo-controlled phase III trial.

Summary

EudraCT number	2011-002965-39
Trial protocol	GB
Global end of trial date	20 July 2016

Results information

Result version number	v1 (current)
This version publication date	21 December 2018
First version publication date	21 December 2018

Trial information

Trial identification

Sponsor protocol code	SAKK 08/11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01707966
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Kelly Cozens, University of Southampton Clinical Trials Unit, +44 02380795154, kc8@soton.ac.uk
Scientific contact	Kelly Cozens, University of Southampton Clinical Trials Unit, +44 2380795154, kc8@soton.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	15 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2014
Global end of trial reached?	Yes
Global end of trial date	20 July 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to establish whether or not giving patients the trial drug orteronel (an androgen synthesis blocker) after their disease has been stabilised by chemotherapy (docetaxel), will lengthen the time that they are 'event free' (alive and without evidence of clinical progression of their cancer) in comparison to patients who receive a placebo.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continouus assessment of laboratory values (blood chemistry) and vital signs.

Background therapy:

Background therapy was best supportive care (BSC). BSC was to be administered according to local standards and included but was not limited to appropriate pain management, management of disease related complications (e.g., urinary obstruction, hydronephrosis,
skeletal related events), continued androgen deprivation in non-surgically castrated patients (mandatory).

Evidence for comparator:

All patients received best supportive care and either orteronel or placebo. A placebo-controlled study design was chosen to test the effect of orteronel on patient status after disease stabilization succeeding docetaxel treatment.

Actual start date of recruitment	09 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 41
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	47
EEA total number of subjects	6

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)	9
From 65 to 84 years	37
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

192 patients were planned to be enrolled. 47 patients had been enrolled in Great Britain (2 centres; 6 patients) and Switzerland (15 centres; 41 patients) from 09-Nov-2012 to 17-Jul-2014. The trial was prematurely closed for accrual after the inclusion of 47 patients.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fullfils all inclusion criteria and not any of the exclusion criteria, he/she was randomized.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	A - Orteronel

Arm description:

Treatment arm A - Patients receiving BSC and orteronel

Arm type	Experimental
Investigational medicinal product name	Orteronel
Investigational medicinal product code	TAK-700
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg orteronel twice daily (b.i.d.)

Arm title	B - Placebo

Arm description:

Treatment arm B - Patients receiving BSC and placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo twice daily (b.i.d.)

Number of subjects in period 1	A - Orteronel	B - Placebo
Started	23	24
Completed	23	24

Period 2

Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Blinding implementation details:

Treatment allocation was unblinded for:
1) eight patients in Treatment arm A - Orteronel: Reasons for unblinding were a) for further treatment decision after progression (2 patients), b) patients wish after premature closure (3 patients), c) serious adverse event (2 patients), d) other (1 Patient)
2) seven patients in Treatment arm B - Placebo: Reasons for unblinding were a) for further treatment decision after progression (4 patients), b) patients wish after premature closure (3 patients)

Arms

Are arms mutually exclusive?	Yes
Arm title	A - Orteronel

Arm description:

Treatment arm A - Patients receiving BSC and orteronel

Arm type	Experimental
Investigational medicinal product name	Orteronel
Investigational medicinal product code	TAK-700
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg orteronel twice daily (b.i.d.)

Arm title	B - Placebo

Arm description:

Treatment arm B - Patients receiving BSC and placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo twice daily (b.i.d.)

Number of subjects in period 2	A - Orteronel	B - Placebo
Started	23	24
Completed	0	0
Not completed	23	24
Physician decision	1	-
Consent withdrawn by subject	4	4
Progression	15	20
Unacceptable toxicity	3	-

Baseline characteristics

Reporting groups	
Reporting group title	A - Orteronel
Reporting group description:	
Treatment arm A - Patients receiving BSC and orteronel	
Reporting group title	B - Placebo
Reporting group description:	
Treatment arm B - Patients receiving BSC and placebo	

Reporting group values	A - Orteronel	B - Placebo	Total
Number of subjects	23	24	47
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			
median	70.0	70.5	
full range (min-max)	51.0 to 80.0	63.0 to 85.0	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	23	24	47

End points

End points reporting groups

Reporting group title	A - Orteronel
Reporting group description:	
Treatment arm A - Patients receiving BSC and orteronel	
Reporting group title	B - Placebo
Reporting group description:	
Treatment arm B - Patients receiving BSC and placebo	
Reporting group title	A - Orteronel
Reporting group description:	
Treatment arm A - Patients receiving BSC and orteronel	
Reporting group title	B - Placebo
Reporting group description:	
Treatment arm B - Patients receiving BSC and placebo	
Subject analysis set title	ITT Population - Arm A
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients were included in the ITT Population.	
Subject analysis set title	ITT Population - Arm B
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients were included in the ITT Population.	
Subject analysis set title	Safety Population - Arm A
Subject analysis set type	Safety analysis
Subject analysis set description:	
As all patients received at least one dose of orteronel/placebo, all patients were included in the safety population.	
Subject analysis set title	Safety Population - Arm B
Subject analysis set type	Safety analysis
Subject analysis set description:	
As all patients received at least one dose of orteronel/placebo, all patients were included in the safety population.	
Subject analysis set title	Eligible Population - Arm A
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Two patients failed to satisfy major entry criteria and were thus excluded from Arm A of the eligible population (EP). The decision to exclude patients from the EP was made by the coordinating investigators together with the trial team prior to the unblinding of the study and without looking at outcome data.	
Subject analysis set title	Eligible Population - Arm B
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
One patient failed to satisfy major entry criteria and was thus excluded from Arm B of the eligible population (EP). The decision to exclude patients from the EP was made by the coordinating investigators together with the trial team prior to the unblinding of the study and without looking at outcome data.	
Subject analysis set title	RECIST-evaluable Population - Arm A
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The RECIST-evaluable population was defined as the subset of patients who had measurable disease by modified RECIST 1.1 at the baseline assessment. 26 patients did not have measurable disease at baseline and where thus excluded from the RECIST-evaluable population.	

Subject analysis set title	RECIST-evaluable Population - Arm B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The RECIST-evaluable population was defined as the subset of patients who had measurable disease by modified RECIST 1.1 at the baseline assessment. 26 patients did not have measurable disease at baseline and where thus excluded from the RECIST-evaluable population.

Primary: Event-free survival (EFS)

End point title	Event-free survival (EFS)[1]

End point description:

The primary endpoint of this trial was event-free survival (EFS). EFS was calculated from registration until the event of interest. Patients not experiencing an event were censored at the date of the last available assessment or at initiation of a different treatment. Patients who were unblinded before they experienced an Event were censored at the date of the unblinding.

End point type	Primary

End point timeframe:

From registration until event of interest.

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: Statistical analyses of this endpoint are implemented in Primary Endpoint "Median EFS".

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Number of EFS events				
EFS event - Yes	14	20		
EFS event - No	9	4		

Statistical analyses

No statistical analyses for this end point

Primary: Median EFS

End point title	Median EFS

End point description:

End point type	Primary

End point timeframe:

From registration until event of interest.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	20		
Units: Median EFS				
median (confidence interval 95%)	8.5 (3.2 to 16.0)	2.9 (2.7 to 3.9)		

Statistical analyses

Statistical analysis title	Log-Rank Test
Statistical analysis description: Log-Rank Test	
Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Logrank

Statistical analysis title	Cox Regression
Statistical analysis description: Cox Regression | Hazard Ratio	
Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.65

Primary: Event-free survival (EFS) - Supportive Analysis 1	
End point title	Event-free survival (EFS) - Supportive Analysis 1[2]
End point description: A supportive analysis not censoring patients that were unblinded before they experienced an event was performed for the primary endpoint.	
End point type	Primary
End point timeframe: From registration until event of interest.	

Notes:

[2] - 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: Statistical analyses of this endpoint are implemented in Primary Endpoint "Median EFS - Supportive Analysis 1".

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Number of EFS events				
EFS event - Yes	16	21		
EFS event - No	7	3		

Statistical analyses

No statistical analyses for this end point

Primary: Median EFS - Supportive Analysis 1

End point title	Median EFS - Supportive Analysis 1

End point description:

End point type	Primary

End point timeframe:

From registration until event of interest.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Median EFS				
median (confidence interval 95%)	8.2 (3.2 to 14.2)	2.9 (2.7 to 3.9)		

Statistical analyses

Statistical analysis title	Log-Rank Test

Statistical analysis description:

Log-Rank Test

Comparison groups	ITT Population - Arm B v ITT Population - Arm A

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Logrank

Statistical analysis title	Cox Regression
Statistical analysis description:	
Cox Regression | Hazard Ratio	
Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.65

Primary: Event-free survival (EFS) - Supportive Analysis 2

End point title	Event-free survival (EFS) - Supportive Analysis 2[3]

End point description:

A supportive analysis counting unconfirmed PSA progressions and unconfirmed progressions on bone scans within the first 12 weeks as progressions was performed for the primary endpoint

End point type	Primary

End point timeframe:

From registration until event of interest.

Notes:

[3] - 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: Statistical analyses of this endpoint are implemented in Primary Endpoint "Median EFS - Supportive Analysis 2".

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Number of EFS events				
EFS event - Yes	17	21		
EFS event - No	6	3		

Statistical analyses

No statistical analyses for this end point

Primary: Median EFS - Supportive Analysis 2

End point title	Median EFS - Supportive Analysis 2

End point description:

End point type	Primary

End point timeframe:

From registration until event of interest.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Median EFS				
median (confidence interval 95%)	7.0 (3.2 to 14.2)	2.9 (2.7 to 3.9)		

Statistical analyses

Statistical analysis title	Log-Rank Test - Supportive Analysis 2

Statistical analysis description:

Log-Rank Test

Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.001
Method	Logrank

Statistical analysis title	Cox Regression - Supportive Analysis

Statistical analysis description:

Cox Regression | Hazard Ratio

Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.002
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.67

Primary: Event-free survival (EFS) - Efficacy Subset

End point title	Event-free survival (EFS) - Efficacy Subset[4]

End point description:

A supportive analysis based on the evaluable patients (EP) population was performed for the primary endpoint.

End point type	Primary

End point timeframe:

From registration until event of interest.

Notes:

[4] - 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: Statistical analyses of this endpoint are implemented in Primary Endpoint "Median EFS - Efficacy Subset".

End point values	Eligible Population - Arm A	Eligible Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	23		
Units: Number of EFS events				
EFS event - Yes	13	19		
EFS event - No	8	4		

Statistical analyses

No statistical analyses for this end point

Primary: Median EFS - Efficacy Subset

End point title	Median EFS - Efficacy Subset

End point description:

End point type	Primary

End point timeframe:

From registration until event of interest.

End point values	Eligible Population - Arm A	Eligible Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	23		
Units: Median EFS				
median (confidence interval 95%)	8.2 (3.1 to 16.0)	2.8 (2.6 to 3.9)		

Statistical analyses

Statistical analysis title	Log-Rank Test
Statistical analysis description:	
Log-Rank Test	
Comparison groups	Eligible Population - Arm A v Eligible Population - Arm B
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.003
Method	Logrank
Notes:	
[5] - Log-Rank Test	

Statistical analysis title	Cox Regression
Statistical analysis description:	
Cox Regression | Hazard Ratio	
Comparison groups	Eligible Population - Arm A v Eligible Population - Arm B
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.005
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.72

Secondary: PSA response (30%, 50%, 90%)

End point title	PSA response (30%, 50%, 90%)
End point description:	
Only PSA values under treatment were be used for this endpoint. The number and proportion of 30%, 50% and 60% PSA responses are displayed together with 95% 2-sided exact Clopper-Pearson CIs.	
End point type	Secondary

End point timeframe:

From registration until any point under treatment.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: PSA response				
number (confidence interval 95%)				
30% PSA response (% patients)	73.9 (51.6 to 89.8)	8.3 (1.0 to 27.0)		
50% PSA response (% patients)	56.5 (34.5 to 76.8)	4.2 (0.1 to 21.1)		
90% PSA response (% patients)	8.7 (1.1 to 28.0)	0.0 (0.0 to 0.0)		

Statistical analyses

Statistical analysis title	PSA response (30%, 50% and 90%) - Fisher’s exact

Statistical analysis description:

Fisher’s exact test

Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [6]
Method	Fisher exact

Notes:

[6] - 0.001 for 30% PSA Response
0.001 for 50% PSA Response

Secondary: PSA response (best PSA response)

End point title	PSA response (best PSA response)

End point description:

Best response is summarized by treatment. The Wilcoxon-rank sum test was used to compare the treatment arms.

End point type	Secondary

End point timeframe:

From registration until any point under treatment.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Best PSA response				
median (full range (min-max))	-57.5 (-91.7 to 68.8)	10.8 (-82.5 to 135.4)		

Statistical analyses

Statistical analysis title	PSA response (best PSA response) - Wilcoxon
Statistical analysis description: Wilcoxon rank-sum test	
Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of PSA response (50%)

End point title	Duration of PSA response (50%)
End point description: Of the 13 patients in the Orteronel arm who had a 50% PSA response, 8 patients had a confirmed PSA progression and 3 patients an unconfirmed PSA Progression. The patient in the Placebo arm who has a 50% PSA response did not have a PSA Progression.	
End point type	Secondary
End point timeframe: Duration of PSA response is defined as the time from appearance of 50% PSA response to the time point of PSA Progression.	

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	0[7]		
Units: Duration of PSA response (50%) | months				
median (full range (min-max))	6.5 (2.0 to 15.0)	(to)		

Notes:

[7] - The patient in the Placebo arm who had a 50% PSA response did not had a PSA Progression.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of PSA response (50%) incl. unconfirmed progression

End point title	Duration of PSA response (50%) incl. unconfirmed progression

End point description:

Of the 13 patients in the Orteronel arm who had a 50% PSA response, 8 patients had a confirmed PSA progression and 3 patients an unconfirmed PSA Progression. The patient in the Placebo arm who has a 50% PSA response did not have a PSA Progression.

End point type	Secondary

End point timeframe:

Duration of PSA response is defined as the time from appearance of 50% PSA response to the time point of PSA Progression.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	0[8]		
Units: Duration of PSA response (50%)				
median (full range (min-max))	6.0 (2.0 to 15.0)	(to)		

Notes:

[8] - The patient in the Placebo arm who had a 50% PSA response did not had a PSA Progression.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA progression

End point title	Time to PSA progression

End point description:

Patients not experiencing a PSA progression were censored at the date of the last available assessment or at initiation of a different treatment. Patients who were unblinded before they experienced an event will be censored at the date of the unblinding. Unconfirmed PSA progressions were not counted as progressions. PSA rise within the first 12 weeks was not considered as PSA Progression.

End point type	Secondary

End point timeframe:

Time to PSA progression was defined as the time from registration to the time point of PSA progression.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Number of patients with PSA progression	9	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA progression - Median time

End point title	Time to PSA progression - Median time

End point description:

Patients not experiencing a PSA progression were censored at the date of the last available assessment or at initiation of a different treatment. Patients who were unblinded before they experienced an event will be censored at the date of the unblinding. Unconfirmed PSA progressions were not counted as progressions. PSA rise within the first 12 weeks was not considered as PSA progression.

End point type	Secondary

End point timeframe:

Time to PSA progression was defined as the time from registration to the time point of PSA progression.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Median time to PSA progression				
median (confidence interval 95%)	8.5 (4.5 to 16.0)	3.9 (2.8 to 12.6)		

Statistical analyses

Statistical analysis title	Time to PSA progression - Log-Rank Test

Statistical analysis description:

Log-Rank Test

Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Logrank

Statistical analysis title	Time to PSA progression - Cox Regression

Statistical analysis description:

Cox Regression | Hazard Ratio

Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.33

Secondary: Time to PSA progression (incl. first 12 weeks)

End point title	Time to PSA progression (incl. first 12 weeks)

End point description:

Patients not experiencing a PSA progression were censored at the date of the last available assessment or at initiation of a different treatment. Patients who were unblinded before they experienced an event will be censored at the date of the unblinding. Unconfirmed PSA progressions were not counted as progressions. PSA rise within the first 12 weeks was not considered as PSA Progression.

As quite many PSA progressions occurred within the first 12 weeks, especially in the placebo arm, another analysis was performed counting also (confirmed) PSA progressions within the first 12 weeks.

End point type	Secondary

End point timeframe:

Time to PSA progression was defined as the time from registration to the time point of PSA progression.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Number of patients with PSA	15	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to PSA progression (incl. first 12 weeks) - Median time

End point title	Time to PSA progression (incl. first 12 weeks) - Median time

End point description:

Patients not experiencing a PSA progression were censored at the date of the last available assessment or at initiation of a different treatment. Patients who were unblinded before they experienced an event will be censored at the date of the unblinding. Unconfirmed PSA progressions were not counted as progressions. PSA rise within the first 12 weeks was not considered as PSA Progression.

As quite many PSA progressions occurred within the first 12 weeks, especially in the placebo arm, another analysis was performed counting also (confirmed) PSA progressions within the first 12 weeks.

End point type	Secondary

End point timeframe:

Time to PSA progression was defined as the time from registration to the time point of PSA progression.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Median time to PSA progression				
median (confidence interval 95%)	6.5 (2.7 to 10.3)	1.8 (1.1 to 2.9)		

Statistical analyses

Statistical analysis title	Time to PSA progression (II) - Log-Rank Test
Statistical analysis description: Log-Rank Test	
Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.004
Method	Logrank

Statistical analysis title	Time to PSA progression (II) - Cox Regression
Statistical analysis description: Cox Regression | Hazard Ratio	
Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.006
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.75

Secondary: Radiographic progression-free survival (rPFS)

End point title	Radiographic progression-free survival (rPFS)

End point description:

Patients not experiencing an event were censored at the date of the last available assessment or at initiation of a different treatment. Patients who were unblinded before they experienced an event were censored at the date of the unblinding. Unconfirmed progressions on bone scans within the first 12 weeks were counted as progressions.

End point type	Secondary

End point timeframe:

Radiographic progression-free survival was defined as the time from baseline to radiographic disease progression or death due to disease or treatment, whichever occurs earlier.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Number of events	13	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic progression-free survival (rPFS) - Median rPFS

End point title	Radiographic progression-free survival (rPFS) - Median rPFS

End point description:

Patients not experiencing an event were censored at the date of the last available assessment or at initiation of a different treatment. Patients who were unblinded before they experienced an event will be censored at the date of the unblinding. Unconfirmed progressions on bone scans within the first 12 weeks were counted as progressions.

End point type	Secondary

End point timeframe:

Radiographic progression-free survival was defined as the time from baseline to radiographic disease progression or death due to disease or treatment, whichever occurs earlier.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Median rPFS				
median (confidence interval 95%)	8.5 (3.5 to 14.2)	2.8 (2.7 to 5.6)		

Statistical analyses

Statistical analysis title	Radiographic progression-free survival - Log-Rank

Statistical analysis description:

Log-Rank Test

Comparison groups	ITT Population - Arm A v ITT Population - Arm B

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Logrank

Statistical analysis title	Radiographic progression-free survival - Cox Regr.
Statistical analysis description: Cox Regression | Hazard Ratio	
Comparison groups	ITT Population - Arm A v ITT Population - Arm B
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.91

Secondary: Overall survival

End point title	Overall survival
End point description: Patients not experiencing an event were censored at the last known date they were known to be alive.	
End point type	Secondary
End point timeframe: OS was calculated from randomization until death from any cause.	

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24		
Units: Number of deaths	16	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival - Median OS

End point title	Overall survival - Median OS

End point description:

Patients not experiencing an event were censored at the last known date they were known to be alive.

End point type	Secondary

End point timeframe:

OS was calculated from randomization until death from any cause.

End point values	ITT Population - Arm A	ITT Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	23	24[9]		
Units: Median OS				
median (confidence interval 95%)	17.2 (10.6 to 35.4)	22.3 (7.6 to 9999.9)		

Notes:

[9] - upper confidence interval not available due to statistical reasons; dummy value (9999.9) entered

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Event-free survival (EFS) - Subgroup analysis I

End point title	Event-free survival (EFS) - Subgroup analysis I

End point description:

A subgroup analysis based on the RECIST-evaluable patients population was performed for the primary endpoint.

End point type	Other pre-specified

End point timeframe:

From registration until event of interest.

End point values	RECIST-evaluable Population - Arm A	RECIST-evaluable Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	11		
Units: Number of events	6	10		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Median EFS - Subgroup analysis I

End point title	Median EFS - Subgroup analysis I

End point description:

A subgroup analysis based on the RECIST-evaluable patients population was performed for the primary endpoint.

End point type	Other pre-specified

End point timeframe:

From registration until event of interest.

End point values	RECIST-evaluable Population - Arm A	RECIST-evaluable Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[10]	11		
Units: Median EFS				
median (confidence interval 95%)	6.3 (2.7 to 9999.9)	2.9 (2.1 to 3.9)		

Notes:

[10] - upper confidence interval not available due to statistical reasons; dummy value (9999.9) entered

Statistical analyses

Statistical analysis title	Median EFS - Subgroup analysis I - Log-Rank Test
Comparison groups	RECIST-evaluable Population - Arm A v RECIST-evaluable Population - Arm B
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.09
Method	Logrank

Statistical analysis title	Median EFS - Subgroup analysis I - Cox Regression

Statistical analysis description:

Cox-Regression | Hazard Ratio

Comparison groups	RECIST-evaluable Population - Arm A v RECIST-evaluable Population - Arm B
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.19

Other pre-specified: Radiographic progression-free survival - Subgroup analysis II

End point title	Radiographic progression-free survival - Subgroup analysis II

End point description:

A subgroup analysis based on the RECIST-evaluable patients population was performed for the endpoint rPFS.

End point type	Other pre-specified

End point timeframe:

From registration until event of interest.

End point values	RECIST-evaluable Population - Arm A	RECIST-evaluable Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	11		
Units: Number of events	5	9		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Median rPFS - Subgroup analysis II

End point title	Median rPFS - Subgroup analysis II

End point description:

A subgroup analysis based on the RECIST-evaluable patients population was performed for the endpoint rPFS.

End point type	Other pre-specified

End point timeframe:

From registration until event of interest.

End point values	RECIST-evaluable Population - Arm A	RECIST-evaluable Population - Arm B		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10[11]	11		
Units: Median rPFS				
median (confidence interval 95%)	8.2 (2.6 to 9999.9)	2.8 (2.1 to 5.6)		

Notes:

[11] - upper confidence interval not available due to statistical reasons; dummy value (9999.9) entered

Statistical analyses

Statistical analysis title	rPFS - Subgroup analysis - Log-Rank Test
Statistical analysis description:	
Log-Rank Test	
Comparison groups	RECIST-evaluable Population - Arm A v RECIST-evaluable Population - Arm B
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.08
Method	Logrank

Statistical analysis title	rPFS - Subgroup analysis - Cox Regression
Statistical analysis description:	
Cox Regression | Hazard Ratio	
Comparison groups	RECIST-evaluable Population - Arm A v RECIST-evaluable Population - Arm B
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	1.2

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse Events were reported from registration until 30 days after treatment stop.	
Adverse event reporting additional description:	
All AEs from baseline until 30 days after treatment stop were reported	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	A - Orteronel
Reporting group description:	
Treatment arm A - Patients receiving BSC and orteronel	
Reporting group title	B - Placebo
Reporting group description:	
Treatment arm B - Patients receiving BSC and placebo	

Serious adverse events	A - Orteronel	B - Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 23 (39.13%)	6 / 24 (25.00%)	
number of deaths (all causes)	16	14	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour progression	Additional description: (suspected brain metastases)		
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ventricular tachycardia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Symptomatic spinal canal stenosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresthesia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema	Additional description: (upper belly, thigh, penis, scrotum)		
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like Symptoms			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
EBV-associated mucocutaneous colonic ulcer			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythroderma			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lung infection			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	A - Orteronel	B - Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	23 / 24 (95.83%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Disease progression			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Tumor pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Vascular disorders			
Hot flashes			
subjects affected / exposed	5 / 23 (21.74%)	2 / 24 (8.33%)	
occurrences (all)	6	2	
Hypertension			

subjects affected / exposed	7 / 23 (30.43%)	7 / 24 (29.17%)	
occurrences (all)	21	11	
Hypertension, due to pain both legs			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Lympoedema			
subjects affected / exposed	2 / 23 (8.70%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Peripheral ischemia, pain in lower leg			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatique			
subjects affected / exposed	15 / 23 (65.22%)	10 / 24 (41.67%)	
occurrences (all)	29	15	
Pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Left hip and groin pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Oedema limbs			
subjects affected / exposed	3 / 23 (13.04%)	6 / 24 (25.00%)	
occurrences (all)	3	6	
Oedema limbs, peripheral oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Fever			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Flu like symptoms			

subjects affected / exposed	1 / 23 (4.35%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Mild cold			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Penis oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	3	
Scrotum oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	3	
Sweating			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Thigh oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	3	
Underbelly oedema			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Locilized oedema			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Localized oedema, oedema in lower legs			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pain, bilateral shoulder pain			
subjects affected / exposed	2 / 23 (8.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pain, elbow pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pain, groin pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

Pain, left knee pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pain, sciatica			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Pain, shoulder pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	3 / 23 (13.04%)	4 / 24 (16.67%)	
occurrences (all)	5	4	
Pain in extremity, pain hip left			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Gynecomastia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 23 (13.04%)	2 / 24 (8.33%)	
occurrences (all)	6	3	
Dyspnoea			
subjects affected / exposed	4 / 23 (17.39%)	5 / 24 (20.83%)	
occurrences (all)	10	6	
Pleural effusion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			
subjects affected / exposed	2 / 23 (8.70%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			

Depressive affection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Agitation			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Confusion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 23 (4.35%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Psychosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Suicidal ideation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Creatinine increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
GGT increased			

subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Lipase increased			
subjects affected / exposed	4 / 23 (17.39%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Serum amylase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Weight loss			
subjects affected / exposed	2 / 23 (8.70%)	1 / 24 (4.17%)	
occurrences (all)	6	1	
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
2/6 systolic bruit			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Frequency correction due to Bigeminus			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Sensory neuropathy to feet			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	3 / 23 (13.04%)	1 / 24 (4.17%)	
occurrences (all)	9	1	
Dysesthesia			

subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	3 / 23 (13.04%)	1 / 24 (4.17%)	
occurrences (all)	3	2	
Memory impairment			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Symptomatic spinal canal stenosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Paresthesia			
subjects affected / exposed	4 / 23 (17.39%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Paresthesia, feet			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Paresthesia, lower lip and chin			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 23 (13.04%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Somnolence			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			

subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pressure			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gastrointestinal disorders, loss of appetite			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	2 / 23 (8.70%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Bloating			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
colonic stenosis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Colonic ulcer			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	3 / 23 (13.04%)	4 / 24 (16.67%)	
occurrences (all)	5	5	
Diarrhoea			
subjects affected / exposed	8 / 23 (34.78%)	2 / 24 (8.33%)	
occurrences (all)	13	2	
Dyspepsia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 24 (0.00%)	
occurrences (all)	11	0	
Dysphagia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastritis			

subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Gastroparesis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hemorrhoidal hemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	12 / 23 (52.17%)	6 / 24 (25.00%)	
occurrences (all)	19	7	
Rash acneiform			
subjects affected / exposed	2 / 23 (8.70%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	5 / 23 (21.74%)	3 / 24 (12.50%)	
occurrences (all)	7	4	
Hepatobiliary disorders			
Splenomegaly			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 23 (17.39%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Erythroderma			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nail discolouration			

subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nail loss			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Hyperkeratosis tibial right			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin ulceration			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Hesitancy, poor urine flow			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nycturia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Pain left side			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Prostatitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Urinary frequency, Nycturia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Urinary tract obstruction			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Urinary tract pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 23 (8.70%)	3 / 24 (12.50%)	
occurrences (all)	2	4	
Arthralgia, left hip			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	3 / 23 (13.04%)	6 / 24 (25.00%)	
occurrences (all)	5	7	
Back pain, Lower back pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	
Back pain, lumbal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Bone pain			
subjects affected / exposed	3 / 23 (13.04%)	3 / 24 (12.50%)	
occurrences (all)	7	7	
Bone pain, left spina			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Bone pain, orbita			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Bone pain, thoracal rip pain due to fall			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Buttock pain			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	2	
Flank pain			

subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Generalized muscle weakness			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Muscle weakness upper limb, weakness leg			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Back, shoulder, leg aches			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Iliosacral			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Leg aches			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pain shoulder both sides			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	3 / 23 (13.04%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Neck pain			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Chills after change of the nephrostoma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Bladder infection			

subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Conjunctivitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Herpes labialis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Infection upper respiratory system			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Viral gastroenteritis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Viral infection respiratory airways with cough			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Lip infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Lung infection			
subjects affected / exposed	1 / 23 (4.35%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Paronychia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Prostate infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	2 / 23 (8.70%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Anorexia			
subjects affected / exposed	3 / 23 (13.04%)	4 / 24 (16.67%)	
occurrences (all)	4	6	
Hyperglycaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Hypocalcemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Hypokalemia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Hyponatraemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	Amended protocol version 2.0 of 13.08.2013 contains updated information on handling of orteronel/placebo and minor administrative changes regarding the Patient insurance for patients enrolled in the UK and Germany. Amended UK-specific appendix An amended UK-specific appendix (Version 2.0 of 19.08.2013) has been issued in order to reflect the amended protocol version 2.0 of 13.08.2013. Section 1 concerning abbreviations has been deleted. Otherwise, no changes to the content have been made.

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.

As patients in the trial were selected in the sense that they all had derived clinical benefit from docetaxel (PR or SD) and due to the small number of patients included the trial results have to be interpreted with caution.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27457964