



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 continuous 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 fulfils 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 were 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 were 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

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

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

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

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

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|--|------------------|-----------------|--|
| 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 | <p>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.</p> <p>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.</p> |

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>