



Clinical trial results:

A Randomized, Double-Blind, Phase 3 Trial Comparing Ipilimumab vs. Placebo

Following Radiotherapy in Subjects with Castration Resistant Prostate Cancer That Have Received Prior Treatment with Docetaxel.

Summary

| | |
|--------------------------|--|
| EudraCT number | 2008-003314-97 |
| Trial protocol | DE AT NL IT CZ DK ES IE BE GB HU FR GR |
| Global end of trial date | 03 June 2015 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 20 August 2016 |
| First version publication date | 20 August 2016 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA184-043 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00861614 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com |

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 | 03 June 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare OS of subjects with castration resistant prostate cancer (CRPC), that had progressed during or following docetaxel treatment, when randomized to treatment with bone-directed radiotherapy followed by ipilimumab versus bone-directed radiotherapy followed by placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 26 May 2009 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Romania: 24 |
| Country: Number of subjects enrolled | Netherlands: 42 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Spain: 42 |
| Country: Number of subjects enrolled | United Kingdom: 31 |
| Country: Number of subjects enrolled | Austria: 20 |
| Country: Number of subjects enrolled | Belgium: 19 |
| Country: Number of subjects enrolled | Czech Republic: 16 |
| Country: Number of subjects enrolled | Denmark: 46 |
| Country: Number of subjects enrolled | France: 77 |
| Country: Number of subjects enrolled | Germany: 30 |
| Country: Number of subjects enrolled | Greece: 4 |
| Country: Number of subjects enrolled | Hungary: 21 |
| Country: Number of subjects enrolled | Ireland: 8 |
| Country: Number of subjects enrolled | Italy: 52 |
| Country: Number of subjects enrolled | Argentina: 73 |
| Country: Number of subjects enrolled | Australia: 33 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Brazil: 79 |
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | Chile: 32 |
| Country: Number of subjects enrolled | Colombia: 7 |
| Country: Number of subjects enrolled | Israel: 10 |
| Country: Number of subjects enrolled | Mexico: 46 |
| Country: Number of subjects enrolled | Peru: 19 |
| Country: Number of subjects enrolled | Puerto Rico: 4 |
| Country: Number of subjects enrolled | Russian Federation: 29 |
| Country: Number of subjects enrolled | United States: 215 |
| Worldwide total number of subjects | 988 |
| EEA total number of subjects | 434 |

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) | 327 |
| From 65 to 84 years | 655 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 153 sites in 27 countries.

Pre-assignment

Screening details:

988 enrolled, 799 randomized (399 ipilimumab, 400 placebo); 149 no longer met study criteria, 17 withdrew, 6 adverse events, 4 died, 1 lost to follow-up, 12 unspecified. 789 treated with radiotherapy (393 ipilimumab, 396 placebo); 2 no longer met study criteria, 3 withdrew consent, 1 died, 2 had adverse events, 2 had disease progression.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ipilimumab + Radiotherapy |

Arm description:

Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | BMS-734016 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|------------------|------------------------|
| Arm title | Placebo + Radiotherapy |
|------------------|------------------------|

Arm description:

Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|-----------------------|
| Investigational medicinal product name | Sodium Chloride |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

Placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|--|-----------------------|
| Investigational medicinal product name | Dextrose |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous drip use |

Dosage and administration details:

Placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| Number of subjects in period 1^[1] | Ipilimumab + Radiotherapy | Placebo + Radiotherapy |
|---|----------------------------------|-------------------------------|
| Started | 399 | 400 |
| Completed | 22 | 28 |
| Not completed | 377 | 372 |
| Adverse event, serious fatal | 32 | 19 |
| Consent withdrawn by subject | 35 | 37 |
| Adverse event, non-fatal | 27 | 23 |
| Unspecified | 21 | 23 |
| Study Drug Toxicity | 79 | 6 |
| Disease Progression | 183 | 264 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 988 enrolled, 799 randomized (399 ipilimumab, 400 placebo); 149 no longer met study criteria, 17 withdrew, 6 adverse events, 4 died, 1 lost to follow-up, 12 unspecified. 789 treated with radiotherapy (393 ipilimumab, 396 placebo); 2 no longer met study criteria, 3 withdrew consent, 1 died, 2 had adverse events, 2 had disease progression.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Ipilimumab + Radiotherapy |
|-----------------------|---------------------------|

Reporting group description:

Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Radiotherapy |
|-----------------------|------------------------|

Reporting group description:

Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| Reporting group values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | Total |
|--|---------------------------|------------------------|-------|
| Number of subjects | 399 | 400 | 799 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| <70 years | 215 | 234 | 449 |
| >=70 years | 184 | 166 | 350 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 68.2 | 67.1 | |
| standard deviation | ± 7.53 | ± 7.56 | - |
| Gender, Male/Female | | | |
| Units: subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 399 | 400 | 799 |

End points

End points reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Ipilimumab + Radiotherapy |
|-----------------------|---------------------------|

Reporting group description:

Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Radiotherapy |
|-----------------------|------------------------|

Reporting group description:

Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|----------------------------|---|
| Subject analysis set title | All Randomized Subjects Ipilimumab + Radiotherapy Arm |
|----------------------------|---|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of ipilimumab.

| | |
|----------------------------|---|
| Subject analysis set title | All Randomized Subjects in Placebo + Radiotherapy Arm |
|----------------------------|---|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of placebo.

| | |
|----------------------------|--|
| Subject analysis set title | Pain-Evaluable Subjects in Ipilimumab + Radiotherapy Arm |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of ipilimumab with a baseline average daily worst pain score of 4 or higher for a 5 day period.

| | |
|----------------------------|---|
| Subject analysis set title | Pain-Evaluable Subjects in Placebo + Radiotherapy Arm |
|----------------------------|---|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of placebo with a baseline average daily worst pain score of 4 or higher for a 5 day period.

| | |
|----------------------------|--|
| Subject analysis set title | Subjects with Pain Response in Ipilimumab + Radiotherapy Arm |
|----------------------------|--|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of ipilimumab with a baseline average daily worst pain score of 4 or higher for a 5 day period.

| | |
|----------------------------|---|
| Subject analysis set title | Subjects with pain response in Placebo + Radiotherapy Arm |
|----------------------------|---|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of placebo with a baseline average daily worst pain score of 4 or higher for a 5 day period.

Primary: Overall survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time in months from randomization date to date of death due to any cause in all randomized subjects. For subjects alive at the time of the database cutoff date, OS was censored at the last date the subject was known to be alive. The analysis population included all randomized subjects defined as all enrolled subjects that were randomized.

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| Date of randomization to date of death, approximately 5 years | |

| End point values | All Randomized Subjects Ipilimumab + Radiotherapy Arm | All Randomized Subjects in Placebo + Radiotherapy Arm | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 399 | 400 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.04 (9.46 to 12.48) | 10.02 (8.38 to 11.17) | | |

Statistical analyses

| Statistical analysis title | Overall Survival Comparison |
|---|---|
| Comparison groups | All Randomized Subjects Ipilimumab + Radiotherapy Arm v All Randomized Subjects in Placebo + Radiotherapy Arm |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0127 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 0.96 |

Primary: Overall Survival Rate

| | |
|---|--------------------------------------|
| End point title | Overall Survival Rate ^[1] |
| End point description: | |
| The overall survival (OS) rate was a percentage, representing the fraction of all randomized subjects who were alive following one year of treatment. OS was defined as the time between the date of randomization and the date of death as a result of any cause. Survival rates were determined via Kaplan-Meier estimates. The analysis population included all randomized subjects. | |
| End point type | Primary |
| End point timeframe: | |
| Date of randomization to date of death, approximately 5 years | |

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: Only descriptive summary statistics were planned for this outcome measure.

| End point values | All Randomized Subjects Ipilimumab + Radiotherapy Arm | All Randomized Subjects in Placebo + Radiotherapy Arm | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 399 | 400 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| OS Rate at Year 1 | 46.5 (41.6 to 51.4) | 40.8 (35.9 to 45.6) | | |
| OS Rate at Year 2 | 25.2 (20.9 to 29.6) | 16.6 (12.9 to 20.3) | | |
| OS Rate at Year 3 | 15.3 (15.3 to 18.9) | 7.9 (5.2 to 10.6) | | |
| OS Rate at Year 4 | 10.1 (6.9 to 13.3) | 3.3 (1.3 to 5.3) | | |
| OS Rate at Year 5 | 7.9 (4.4 to 11.4) | 2.7 (0.8 to 4.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

| | |
|--|---------------------------------|
| End point title | Progression Free Survival (PFS) |
| End point description: | |
| All PFS events were based on investigator's assessment. Subjects who were alive and did not experience a PFS event were censored at the earlier of the latest prostate-specific antigen (PSA) or radiological tumor assessment date. Subjects who did not die, showed no clinical deterioration, and who had no recorded post-baseline PSA or radiological tumor assessment were censored at randomization date. The analysis population included all randomized subjects. | |
| End point type | Secondary |
| End point timeframe: | |
| Date of randomization to earliest date of confirmed PSA or radiological progression, clinical deterioration or death, up to November 2012, approximately 3.5 years | |

| End point values | All Randomized Subjects Ipilimumab + Radiotherapy Arm | All Randomized Subjects in Placebo + Radiotherapy Arm | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 399 | 400 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.01 (3.65 to 4.34) | 3.06 (2.86 to 3.42) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Progression Free Survival Comparison |
| Comparison groups | All Randomized Subjects Ipilimumab + Radiotherapy Arm v All Randomized Subjects in Placebo + Radiotherapy Arm |
| Number of subjects included in analysis | 799 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 0.82 |

Secondary: Pain Response

| | |
|--|---------------|
| End point title | Pain Response |
| End point description: The percentage of subjects with a pain response assessed using the Brief Pain Inventory Short Form (BPI-SF) completed by subjects throughout the study in a daily diary log. Pain-evaluable subjects were defined as those with a decrease in the average daily worst pain intensity by at least 30% from baseline, maintained over 2 consecutive evaluations without the use of any rescue analgesic medication or increase in analgesic use in the same time period. The analysis population included all pain-evaluable subjects. | |
| End point type | Secondary |
| End point timeframe: Assessed at screening, weeks 12, 18, 24, and at the end of treatment visit | |

| End point values | Pain-Evaluable Subjects in Ipilimumab + Radiotherapy Arm | Pain-Evaluable Subjects in Placebo + Radiotherapy Arm | | |
|----------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 197 | 186 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 3.55 (1.44 to 7.18) | 0.54 (0.01 to 2.96) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Pain Response

| | |
|---|---------------------------|
| End point title | Duration of Pain Response |
| End point description: The time between the initial date of pain response and completion date of pain response. The initial date when the pain response criterion was achieved was considered the pain response date. The earlier of | |

date of death, date of tumor resection surgery, or date when pain response criterion was no longer met was considered the completion date of the pain response. If none of these scenarios occurred, the completion of the pain response was set to the last known alive date. The analysis population included all pain-evaluable subjects with a pain response. Here -99999 to 99999 signifies that no confidence interval is applicable due to only one subject being analyzed.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day of initial pain response to day of completion of pain response or date of death | |

| End point values | Subjects with Pain Response in Ipilimumab + Radiotherapy Arm | Subjects with pain response in Placebo + Radiotherapy Arm | | |
|----------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 7 | 1 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.5 (1.5 to 3) | 1.5 (-99999 to 99999) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Duration of Pain Response Comparison |
| Comparison groups | Subjects with pain response in Placebo + Radiotherapy Arm v Subjects with Pain Response in Ipilimumab + Radiotherapy Arm |
| Number of subjects included in analysis | 8 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.02 |
| upper limit | 4 |

Secondary: Number of Subjects With Severe Adverse Events (AEs), Serious Adverse Events (SAEs), Treatment-Related AEs, Deaths, Discontinuation of Study Drug Due to AEs, Immune-Related Adverse Events (irAE) and Immune-Mediated Adverse Reaction (imAR)

| | |
|-----------------|---|
| End point title | Number of Subjects With Severe Adverse Events (AEs), Serious Adverse Events (SAEs), Treatment-Related AEs, Deaths, Discontinuation of Study Drug Due to AEs, Immune-Related Adverse Events (irAE) and Immune-Mediated Adverse Reaction (imAR) |
|-----------------|---|

End point description:

AE=new unfavorable symptom, sign, disease or worsening preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or

significant disability/incapacity or drug dependency/abuse; is life-threatening, an important medical event or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, possible or missing relationship to study drug. Death=during study and up to 70 days after last dose. IrAEs=AEs potentially associated with inflammation, considered to be causally related to study drug and grouped into gastrointestinal (GI), hepatic, skin, endocrine and neurological. ImARs were collected prospectively and grouped into enterocolitis, hepatitis, dermatitis, neuropathies and endocrinopathies. Grading used Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Ver.3.0. The analysis population included all treated subjects

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Randomization to date of death, up to approximately 5 years | |

| End point values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | | |
|---|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 396 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| SAE | 257 | 164 | | |
| Treatment-Related AE | 296 | 180 | | |
| Any Death | 346 | 371 | | |
| Deaths Due to Study Drug Toxicity | 7 | 1 | | |
| Discontinuation of Study Drug due to AEs | 137 | 62 | | |
| Immune-Related AE (any grade) | 250 | 86 | | |
| Immune-Mediated Adverse Reaction (Grade ≥2) | 203 | 40 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Grade 3 or 4 Immune-Related Adverse Event (irAE)

| | |
|-----------------|---|
| End point title | Time to Onset of Grade 3 or 4 Immune-Related Adverse Event (irAE) |
|-----------------|---|

End point description:

The time between first dose of study drug and date of earliest Grade 3 or 4 irAE. These irAEs are AEs of unknown etiology, consistent with an immune phenomenon and considered as causally related to drug exposure. The five subcategories of irAE examined include gastrointestinal (GI), liver, skin, endocrine, and neurological and are graded using the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. The analysis population included all treated subjects assessed for onset of adverse events. Here 99999 signifies that there were no subjects in this treatment arm who displayed irAEs of this type and -99999 to 99999 signifies that no confidence interval was applicable due to only one subject being analyzed.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to 70 days after last dose of study drug | |

| End point values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | | |
|----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 396 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | | | | |
| Gastrointestinal (n= 71,3) | 5.71 (5 to 7) | 5.71 (0.57 to 31.86) | | |
| Liver (n= 18,5) | 9.14 (8.29 to 10.43) | 6 (3.14 to 8.57) | | |
| Skin (n=4,0) | 3.71 (2.57 to 6.43) | 99999 (-99999 to 99999) | | |
| Endocrine (n=8,2) | 7.93 (4.14 to 11.14) | 5 (4.29 to 5.71) | | |
| Neurological (n= 1,0) | 11.4 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Grade 3 or 4 Immune-Related Adverse Event (irAE)

| | |
|-----------------|--|
| End point title | Time to Resolution of Grade 3 or 4 Immune-Related Adverse Event (irAE) |
|-----------------|--|

End point description:

Time between the date of onset of a Grade 3 or 4 irAE and the date of improvement to Grade 1 or less or the worst grade at baseline. The analysis population included all treated subjects assessed for onset of adverse events. Here 99999 signifies that there were no subjects in this treatment arm who displayed irAEs of this type and -99999 to 99999 signifies that no confidence interval was applicable due to only one subject being analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 to 70 days after last dose of study drug

| End point values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | | |
|----------------------------------|---------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 396 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | | | | |
| Gastrointestinal (n=71,3) | 2.9 (1.6 to 4.7) | 0.9 (0.4 to 1.1) | | |
| Liver (n=18,5) | 4.1 (3.6 to 8.1) | 6 (1.9 to 99999) | | |
| Skin (n=4,0) | 3.6 (2.6 to 5.9) | 99999 (-99999 to 99999) | | |
| Endocrine (n=8,2) | 11.1 (2.4 to 99999) | 5.9 (0.9 to 10.9) | | |
| Neurological (n=1,0) | 99999 (-99999 to 99999) | 99999 (-99999 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Grade 3 to 5 Immune-Mediated Adverse Reaction (imAR)

| | |
|-----------------|--|
| End point title | Time to Onset of Grade 3 to 5 Immune-Mediated Adverse Reaction (imAR) ^[2] |
|-----------------|--|

End point description:

The time between first dose of study drug and date of earliest Grade 3 or 4 imAR. ImARs were collected prospectively and grouped into enterocolitis, hepatitis, dermatitis, neuropathies and endocrinopathies and graded using Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Ver. 3.0.

Only the Ipilimumab + Radiotherapy group of subjects was included in the analysis because ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity likely to be related to its mechanism of action. The analysis population included all treated subjects in the Ipilimumab + radiology arm.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 to time of onset of the imAR of interest

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only the arm receiving study drug was analyzed for this endpoint. Ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity.

| End point values | Ipilimumab + Radiotherapy | | | |
|-------------------------------|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 393 | | | |
| Units: weeks | | | | |
| median (full range (min-max)) | | | | |
| Enterocolitis (n=65) | 3.4 (0.3 to 16.6) | | | |
| Hepatitis (n=17) | 9 (1.7 to 16.9) | | | |
| Dermatitis (n=3) | 2.4 (0.1 to 3.1) | | | |
| Endocrinopathies (n=6) | 7.9 (1.7 to 10.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Grade 3 to 5 to Grade 0 Immune-Mediated Adverse Reactions (imARs) to Grade 0

| | |
|-----------------|---|
| End point title | Time to Resolution of Grade 3 to 5 to Grade 0 Immune-Mediated Adverse Reactions (imARs) to Grade 0 ^[3] |
|-----------------|---|

End point description:

Time between the date of onset of an imAR to the date of resolution date of the event or the last known date subject was alive if an event did not resolve.

Only the Ipilimumab + Radiotherapy group of subjects was included in the analysis because ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity likely to be related to its mechanism of action. The analysis population included all treated subjects in the Ipilimumab + radiotherapy arm. Here 99999 signifies that there were no subjects in this treatment arm who displayed irAEs of this type and -99999 to 99999 signifies that no confidence interval was applicable due to only one subject being analyzed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 to 70 days after last dose of study drug

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only the arm receiving study drug was analyzed for this endpoint. Ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity.

| End point values | Ipilimumab + Radiotherapy | | | |
|-------------------------------|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 393 | | | |
| Units: weeks | | | | |
| median (full range (min-max)) | | | | |
| Enterocolitis (n=52) | 6 (0.1 to 40.1) | | | |
| Hepatitis (n=15) | 8.6 (1.1 to 19) | | | |
| Dermatitis (n=3) | 6.9 (4 to 12.1) | | | |
| Endocrinopathies (n=0) | 99999 (-99999 to 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Hematology Common Toxicity Criteria (CTC) Grade and Shift from Baseline

| | |
|-----------------|--|
| End point title | Number of Subjects with Worst On-Study Hematology Common Toxicity Criteria (CTC) Grade and Shift from Baseline |
|-----------------|--|

End point description:

Comparison of baseline versus worst grade hematology laboratory tests as measured by white blood count (WBC), absolute neutrophil count (ANC), platelet count, hemoglobin and lymphocyte results. National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr). Gr 0: within normal range. Abnormal values for WBC were based on Gr 1: 3.0 - < Lower Limit of Normal (LLN); Gr 2: 2.0 - < 3.0; Gr 3: 1.0 - < 2.0; Gr4: < 1.0. Abnormal values for Hemoglobin were based on Gr 1: 10.0 - < LLN; Gr 2: 8.0 - < 10.0; Gr 3: 6.5 - < 8.0; Gr 4: < 6.5. Abnormal values for Lymphocytes were based on Gr 1: 0.8 - < 1.5; Gr 2: 0.5 - < 0.8; Gr 3): 0.2 - < 0.5; Gr 4: < 0.2. Abnormal values for ANC were based on Gr 1: 1.5 - < 2.0; Gr 2: 1.0 - < 1.5; Gr 3: 0.5 - < 1.0; Gr 4: < 0.5. Abnormal values for Platelets were based on Gr 1: 75.0 - < LLN; Gr 2: 50.0 - < 75.0; Gr 3: 25.0 - < 50.0; Gr 4: < 25.0. Analysis population included all treated subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 2 to 70 days after last dose of study drug

| End point values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | | |
|--|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 396 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| WBC Gr 0 at Baseline to Gr 3-4 | 3 | 2 | | |
| WBC Gr 1 at Baseline to Gr 3-4 | 0 | 1 | | |
| WBC Gr 2 at Baseline to Gr 3-4 | 0 | 1 | | |
| WBC Gr 3 at Baseline to Gr 3-4 | 0 | 0 | | |
| WBC Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| WBC Not Reported at Baseline to Gr 3-4 | 0 | 0 | | |
| ANC Gr 0 at Baseline to Gr 3-4 | 4 | 6 | | |
| ANC Gr 1 at Baseline to Gr 3-4 | 0 | 0 | | |
| ANC Gr 2 at Baseline to Gr 3-4 | 0 | 0 | | |
| ANC Gr 3 at Baseline to Gr 3-4 | 0 | 0 | | |
| ANC Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| ANC Not Reported at Baseline to Gr 3-4 | 1 | 0 | | |
| Platelet Count Gr 0 at Baseline to Gr 3-4 | 1 | 6 | | |
| Platelet Count Gr 1 at Baseline to Gr 3-4 | 1 | 1 | | |
| Platelet Count Gr 2 at Baseline to Gr 3-4 | 0 | 0 | | |
| Platelet Count Gr 3 at Baseline to Gr 3-4 | 0 | 0 | | |
| Platelet Count Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| Platelet Count Not Reported at Baseline to Gr 3-4 | 1 | 1 | | |
| Hemoglobin Gr 0 at Baseline to Gr 3-4 | 0 | 3 | | |
| Hemoglobin Gr 1 at Baseline to Gr 3-4 | 16 | 25 | | |
| Hemoglobin Gr 2 at Baseline to Gr 3-4 | 13 | 11 | | |
| Hemoglobin Gr 3 at Baseline to Gr 3-4 | 0 | 1 | | |
| Hemoglobin Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| Hemoglobin Not Reported at Baseline to Gr 3-4 | 0 | 1 | | |
| Lymphocytes Gr 0 at Baseline to Gr 3-4 | 4 | 1 | | |
| Lymphocytes Gr 1 at Baseline to Gr 3-4 | 6 | 11 | | |
| Lymphocytes Gr 2 at Baseline to Gr 3-4 | 11 | 17 | | |
| Lymphocytes Gr 3 at Baseline to Gr 3-4 | 8 | 7 | | |
| Lymphocytes Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| Lymphocytes Not Reported at Baseline to Gr 3-4 | 3 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Liver Common Toxicity Criteria (CTC) Grade and Shift from Baseline

| | |
|-----------------|---|
| End point title | Number of Subjects with Worst On-Study Liver Common Toxicity Criteria (CTC) Grade and Shift from Baseline |
|-----------------|---|

End point description:

Comparison of baseline versus worst grade liver function as measured by alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and alkaline phosphatase (ALP). National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr). Gr 0:

within normal range. Abnormal values for ALP, ALT and AST were based on grades; Gr 1: > 1.0 - 2.5 * upper limits of normal (ULN); Gr 2: > 2.5 - 5.0 * ULN; Gr 3: > 5.0 - 20.0 * ULN; Gr 4: > 20.0 * ULN. Abnormal values for Total Bilirubin were based on Gr 1: > 1.0 - 1.5 * upper limits of normal (ULN); Gr 2: > 1.5 - 3.0 * ULN; Gr 3: > 3.0 - 10.0 * ULN; Gr 4: > 10.0 * ULN. Analysis population included all treated subjects.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 2 to 70 days after last dose of study drug | |

| End point values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | | |
|--|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 396 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| ALT Gr 0 at Baseline to Gr 3-4 | 16 | 1 | | |
| ALT Gr 1 at Baseline to Gr 3-4 | 1 | 1 | | |
| ALT Gr 2 at Baseline to Gr 3-4 | 0 | 0 | | |
| ALT Gr 3 at Baseline to Gr 3-4 | 0 | 0 | | |
| ALT Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| ALT Not reported at Baseline to Gr 3-4 | 1 | 0 | | |
| AST Gr 0 at Baseline to Gr 3-4 | 15 | 6 | | |
| AST Gr 1 at Baseline to Gr 3-4 | 5 | 1 | | |
| AST Gr 2 at Baseline to Gr 3-4 | 1 | 1 | | |
| AST Gr 3 at Baseline to Gr 3-4 | 1 | 0 | | |
| AST Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| AST Not Reported at Baseline to Gr 3-4 | 1 | 0 | | |
| Total Bilirubin Gr 0 at Baseline to Gr 3-4 | 6 | 2 | | |
| Total Bilirubin Gr 1 at Baseline to Gr 3-4 | 1 | 0 | | |
| Total Bilirubin Gr 2 at Baseline to Gr 3-4 | 1 | 0 | | |
| Total Bilirubin Gr 3 at Baseline to Gr 3-4 | 0 | 0 | | |
| Total Bilirubin Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| Total Bilirubin Not Reported at Baseline to Gr 3-4 | 0 | 0 | | |
| ALP Gr 0 at Baseline to Gr 3-4 | 1 | 1 | | |
| ALP Gr 1 at Baseline to Gr 3-4 | 10 | 17 | | |
| ALP Gr 2 at Baseline to Gr 3-4 | 21 | 29 | | |
| ALP Gr 3 at Baseline to Gr 3-4 | 27 | 42 | | |
| ALP Gr 4 at Baseline to Gr 3-4 | 1 | 0 | | |
| ALP Not Reported at Baseline to Gr 3-4 | 0 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Serum Chemistry Common Toxicity Criteria (CTC) Grade and Shift from Baseline

| | |
|-----------------|---|
| End point title | Number of Subjects with Worst On-Study Serum Chemistry Common Toxicity Criteria (CTC) Grade and Shift from Baseline |
|-----------------|---|

End point description:

Comparison of baseline versus worst grade serum chemistry as measured by lipase and amylase analysis. National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr). Gr 0: within normal range. Abnormal values for lipase: Gr1: > 1.0 - 1.5 * ULN; Gr2: > 1.5 - 2.0 * ULN; Gr 3: > 2.0 - 5.0 * ULN; Gr4: > 5.0*ULN. Abnormal values for amylase: Gr1: > 1.0 - 1.5 * ULN; Gr 2: > 1.5 - 2.0 * ULN; Gr 3: > 2.0 - 5.0 * ULN; Gr4: > 5.0 * ULN. Analysis population included all treated subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 2 to 70 days after last dose of study drug

| End point values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | | |
|--|---------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 396 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| Lipase Gr 0 at Baseline to Gr 3-4 | 21 | 10 | | |
| Lipase Gr 1 at Baseline to Gr 3-4 | 1 | 1 | | |
| Lipase Gr 2 at Baseline to Gr 3-4 | 1 | 0 | | |
| Lipase Gr 3 at Baseline to Gr 3-4 | 0 | 1 | | |
| Lipase Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| Lipase Not reported at Baseline to Gr 3-4 | 0 | 0 | | |
| Amylase Gr 0 at Baseline to Gr 3-4 | 4 | 4 | | |
| Amylase Gr 1 at Baseline to Gr 3-4 | 1 | 1 | | |
| Amylase Gr 2 at Baseline to Gr 3-4 | 3 | 1 | | |
| Amylase Gr 3 at Baseline to Gr 3-4 | 1 | 0 | | |
| Amylase Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| Amylase Not Reported at Baseline to Gr 3-4 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Renal Function Common Toxicity Criteria (CTC) Grade and Shift from Baseline

| | |
|-----------------|--|
| End point title | Number of Subjects with Worst On-Study Renal Function Common Toxicity Criteria (CTC) Grade and Shift from Baseline |
|-----------------|--|

End point description:

Comparison of baseline versus worst grade renal function as measured by creatinine analysis. National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr).Gr 0: within normal range. Abnormal values for Creatinine were based on Gr 1: > 1.0 - 1.5*ULN; Gr 2: > 1.5 - 3.0*ULN; Gr 3: > 3.0 - 6.0*ULN; Gr 4: > 6.0*ULN. Analysis population included all treated subjects.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 2 to 70 days after last dose of study drug

| End point values | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | | |
|--|--------------------------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 393 | 396 | | |
| Units: subjects | | | | |
| number (not applicable) | | | | |
| Creatinine Gr 0 at Baseline to Gr 3-4 | 3 | 3 | | |
| Creatinine Gr 1 at Baseline to Gr 3-4 | 0 | 0 | | |
| Creatinine Gr 2 at Baseline to Gr 3-4 | 0 | 0 | | |
| Creatinine Gr 3 at Baseline to Gr 3-4 | 0 | 0 | | |
| Creatinine Gr 4 at Baseline to Gr 3-4 | 0 | 0 | | |
| Creatinine Not Reported at Baseline to Gr 3-4 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to 70 days following the last dose of study drug

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Ipilimumab + Radiotherapy |
|-----------------------|---------------------------|

Reporting group description:

Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1 and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| | |
|-----------------------|------------------------|
| Reporting group title | Placebo + Radiotherapy |
|-----------------------|------------------------|

Reporting group description:

Subjects receive radiotherapy at 8 Gy to at least 1 and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

| Serious adverse events | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | |
|---|---------------------------|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 257 / 393 (65.39%) | 164 / 396 (41.41%) | |
| number of deaths (all causes) | 81 | 62 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellopontine angle tumour | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphangiosis carcinomatosa | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malignant neoplasm of spinal cord | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 36 / 393 (9.16%) | 31 / 396 (7.83%) | |
| occurrences causally related to treatment / all | 0 / 36 | 0 / 31 | |
| deaths causally related to treatment / all | 0 / 34 | 0 / 29 | |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell myeloma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemic shock | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasculitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 393 (2.29%) | 4 / 396 (1.01%) | |
| occurrences causally related to treatment / all | 6 / 11 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 3 / 396 (0.76%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 13 / 393 (3.31%) | 10 / 396 (2.53%) | |
| occurrences causally related to treatment / all | 5 / 16 | 2 / 10 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 16 / 393 (4.07%) | 8 / 396 (2.02%) | |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 5 | |
| Malaise | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 7 / 393 (1.78%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 9 / 10 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-Organ failure | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 4 / 396 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 4 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 6 / 393 (1.53%) | 10 / 396 (2.53%) | |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 4 | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 393 (4.33%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 8 / 19 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Immune system disorders | | | |
| Autoimmune disorder | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 8 / 393 (2.04%) | 6 / 396 (1.52%) | |
| occurrences causally related to treatment / all | 1 / 14 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypoxia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 393 (1.02%) | 6 / 396 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 4 / 396 (1.01%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 2 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 3 / 396 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hallucination | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Self injurious behaviour | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 393 (1.53%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase | | | |

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|--|------------------|-----------------|--|
| increased | | | |
| subjects affected / exposed | 7 / 393 (1.78%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 7 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatine phosphokinase decreased | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-Reactive protein increased | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eastern cooperative oncology group performance status worsened | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 13 / 393 (3.31%) | 7 / 396 (1.77%) | |
| occurrences causally related to treatment / all | 1 / 17 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |

| | | | |
|--|-----------------|-----------------|--|
| General physical condition abnormal subjects affected / exposed | 0 / 393 (0.00%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal subjects affected / exposed | 3 / 393 (0.76%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased subjects affected / exposed | 0 / 393 (0.00%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Red blood cell count decreased subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone fissure subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|-----------------|-----------------|--|
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subdural haematoma | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Arrhythmia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 393 (0.76%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac valve disease | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-Respiratory arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 393 (0.51%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brachial plexopathy | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system haemorrhage | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Cerebral haematoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cerebrovascular disorder | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 3 / 396 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lethargy | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological symptom | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Paraplegia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paresis | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 4 / 393 (1.02%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 4 / 393 (1.02%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tongue paralysis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal nerve disorder | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 15 / 393 (3.82%) | 18 / 396 (4.55%) | |
| occurrences causally related to treatment / all | 0 / 17 | 1 / 22 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | |
| Anaemia of malignant disease | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 6 / 396 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Macular degeneration | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Papilloedema | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pupils unequal | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal vein thrombosis | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 393 (1.02%) | 5 / 396 (1.26%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |

| | | | |
|---|-------------------|-----------------|--|
| subjects affected / exposed | 21 / 393 (5.34%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 21 / 22 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis ulcerative | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 7 / 393 (1.78%) | 3 / 396 (0.76%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 59 / 393 (15.01%) | 6 / 396 (1.52%) | |
| occurrences causally related to treatment / all | 65 / 69 | 4 / 6 | |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Duodenitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral hernia incarcerated | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal pain | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haemorrhage | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 11 / 393 (2.80%) | 8 / 396 (2.02%) | |
| occurrences causally related to treatment / all | 7 / 13 | 4 / 10 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 11 / 393 (2.80%) | 10 / 396 (2.53%) | |
| occurrences causally related to treatment / all | 9 / 14 | 4 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oesophageal perforation | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Enterocolitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Chronic gastritis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatitis | | | |
| subjects affected / exposed | 4 / 393 (1.02%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 393 (0.76%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute prerenal failure | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anuria | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder dilatation | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder obstruction | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 3 / 396 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 6 / 393 (1.53%) | 6 / 396 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 393 (1.02%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal injury | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral obstruction | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 7 / 393 (1.78%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 393 (0.51%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 4 / 393 (1.02%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophysitis | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypopituitarism | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Adrenocorticotrophic hormone deficiency | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (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 | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 7 / 393 (1.78%) | 8 / 396 (2.02%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 393 (1.02%) | 4 / 396 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 5 / 393 (1.27%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 5 / 396 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Anal abscess | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal infection | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 3 / 396 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | |
| Cavernous sinus thrombosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Central nervous system infection | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epstein-Barr virus infection | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Labyrinthitis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 18 / 393 (4.58%) | 5 / 396 (1.26%) | |
| occurrences causally related to treatment / all | 0 / 19 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 11 | 0 / 3 | |
| Periorbital cellulitis | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 6 / 393 (1.53%) | 3 / 396 (0.76%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 3 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 393 (3.05%) | 4 / 396 (1.01%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Urosepsis | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord infection | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 2 / 396 (0.51%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dehydration | | | |
| subjects affected / exposed | 18 / 393 (4.58%) | 10 / 396 (2.53%) | |
| occurrences causally related to treatment / all | 12 / 23 | 0 / 11 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 4 | |
| Failure to thrive | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Hypoglycaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 393 (0.00%) | 1 / 396 (0.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 393 (0.51%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 393 (0.25%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 393 (0.76%) | 0 / 396 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Ipilimumab + Radiotherapy | Placebo + Radiotherapy | |
|---|--------------------------------------|-----------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 350 / 393 (89.06%) | 333 / 396 (84.09%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 26 / 393 (6.62%) | 9 / 396 (2.27%) | |
| occurrences (all) | 31 | 11 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 31 / 393 (7.89%) | 21 / 396 (5.30%) | |
| occurrences (all) | 35 | 24 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 26 / 393 (6.62%) | 20 / 396 (5.05%) | |
| occurrences (all) | 34 | 27 | |
| Weight decreased | | | |
| subjects affected / exposed | 91 / 393 (23.16%) | 56 / 396 (14.14%) | |
| occurrences (all) | 94 | 56 | |

| | | | |
|--|--------------------|--------------------|--|
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 20 / 393 (5.09%) | 13 / 396 (3.28%) | |
| occurrences (all) | 22 | 18 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 22 / 393 (5.60%) | 18 / 396 (4.55%) | |
| occurrences (all) | 22 | 23 | |
| Headache | | | |
| subjects affected / exposed | 38 / 393 (9.67%) | 31 / 396 (7.83%) | |
| occurrences (all) | 48 | 35 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 79 / 393 (20.10%) | 81 / 396 (20.45%) | |
| occurrences (all) | 105 | 99 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 80 / 393 (20.36%) | 64 / 396 (16.16%) | |
| occurrences (all) | 95 | 71 | |
| Fatigue | | | |
| subjects affected / exposed | 144 / 393 (36.64%) | 120 / 396 (30.30%) | |
| occurrences (all) | 156 | 121 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 46 / 393 (11.70%) | 33 / 396 (8.33%) | |
| occurrences (all) | 46 | 34 | |
| Pain | | | |
| subjects affected / exposed | 33 / 393 (8.40%) | 44 / 396 (11.11%) | |
| occurrences (all) | 39 | 43 | |
| Pyrexia | | | |
| subjects affected / exposed | 81 / 393 (20.61%) | 50 / 396 (12.63%) | |
| occurrences (all) | 97 | 77 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 33 / 393 (8.40%) | 25 / 396 (6.31%) | |
| occurrences (all) | 34 | 27 | |
| Constipation | | | |

| | | | |
|--|---|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>66 / 393 (16.79%)</p> <p>70</p> <p>186 / 393 (47.33%)</p> <p>281</p> <p>126 / 393 (32.06%)</p> <p>155</p> <p>107 / 393 (27.23%)</p> <p>134</p> | <p>82 / 396 (20.71%)</p> <p>97</p> <p>94 / 396 (23.74%)</p> <p>120</p> <p>104 / 396 (26.26%)</p> <p>122</p> <p>80 / 396 (20.20%)</p> <p>102</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>36 / 393 (9.16%)</p> <p>36</p> <p>47 / 393 (11.96%)</p> <p>49</p> | <p>27 / 396 (6.82%)</p> <p>27</p> <p>32 / 396 (8.08%)</p> <p>33</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Pruritus</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>99 / 393 (25.19%)</p> <p>119</p> <p>81 / 393 (20.61%)</p> <p>112</p> | <p>22 / 396 (5.56%)</p> <p>23</p> <p>27 / 396 (6.82%)</p> <p>31</p> | |
| <p>Psychiatric disorders</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Depression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>31 / 393 (7.89%)</p> <p>31</p> <p>10 / 393 (2.54%)</p> <p>10</p> | <p>34 / 396 (8.59%)</p> <p>33</p> <p>20 / 396 (5.05%)</p> <p>22</p> | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>44 / 393 (11.20%)</p> <p>45</p> | <p>57 / 396 (14.39%)</p> <p>59</p> | |

| | | | |
|------------------------------------|--------------------|-------------------|--|
| Back pain | | | |
| subjects affected / exposed | 56 / 393 (14.25%) | 74 / 396 (18.69%) | |
| occurrences (all) | 60 | 77 | |
| Bone pain | | | |
| subjects affected / exposed | 31 / 393 (7.89%) | 53 / 396 (13.38%) | |
| occurrences (all) | 32 | 53 | |
| Pain in extremity | | | |
| subjects affected / exposed | 31 / 393 (7.89%) | 41 / 396 (10.35%) | |
| occurrences (all) | 35 | 46 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 32 / 393 (8.14%) | 44 / 396 (11.11%) | |
| occurrences (all) | 30 | 51 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 24 / 393 (6.11%) | 24 / 396 (6.06%) | |
| occurrences (all) | 30 | 25 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 119 / 393 (30.28%) | 97 / 396 (24.49%) | |
| occurrences (all) | 124 | 99 | |
| Dehydration | | | |
| subjects affected / exposed | 26 / 393 (6.62%) | 15 / 396 (3.79%) | |
| occurrences (all) | 30 | 18 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 20 / 393 (5.09%) | 10 / 396 (2.53%) | |
| occurrences (all) | 22 | 12 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 28 October 2009 | Clarified the following: pretreatment radiotherapy and use of standard-of-care radiotherapy while on study; discontinuation of anti-androgen therapy prior to randomization; weight measurement for dose calculation; exclusion of subjects with brain metastases; retreatment with docetaxel following progression after a prior docetaxel-containing regimen as a separate anti-cancer regimen |
| 27 January 2010 | Clarified inclusion/exclusion criteria pertaining to the allowable number of prior regimens and performance status in order to more accurately reflect evolving current clinical practice; Modified requirement for saline flush at end of study drug infusion; Updated Appendix 3 to contain complete patient pain diary and added Appendix 5 (SSQ). |
| 02 September 2010 | Removed requirement for disease progression during or within 6 months of receiving docetaxel treatment for metastatic CRPC prior to enrollment; Updated that for eligibility purposes, all docetaxel-containing regimens are counted as a single regimen; AEs were to be reported for 90 days after the last dose of study medication; |
| 17 December 2010 | Reinstated requirement that subjects were to have received a prior regimen of docetaxel that contained at least 2 cycles of docetaxel; Reinstated requirement that subjects were to have progressed while receiving, or within 6 months of receiving, a docetaxel-containing regimen, and clarified that subjects that have received additional anti-cancer therapy after docetaxel must also have demonstrated progression on that therapy. |
| 03 July 2012 | Removed interim analysis that was planned to occur at 435 events (deaths); Added Extension Phase to study design to allow for continued collection of survival and safety data after the database lock for the primary analysis. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported