



Clinical trial results:

A Randomized Double-Blind Phase 3 Trial Comparing Docetaxel Combined with Dasatinib to Docetaxel Combined with Placebo in Castration-Resistant Prostate Cancer

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2008-000701-11 |
| Trial protocol | DE IE HU FR IT GB CZ FI SE GR |
| Global end of trial date | 30 July 2015 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 11 August 2016 |
| First version publication date | 11 August 2016 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA180-227 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00744497 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Bristol-Myers Squibb International Corporation, Chaussée 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 | 30 July 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 July 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 overall survival for dasatinib plus docetaxel and prednisone versus placebo plus docetaxel and prednisone in subjects with metastatic castration-resistant prostate cancer.

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:

Docetaxel and prednisolone were used as background therapy in this study.

Evidence for comparator:

Docetaxel is used as a standard of care for the treatment of mCRPC and confers a survival advantage. If a subject discontinued docetaxel with no evidence of objective disease progression, then the subject was permitted to continue treatment with dasatinib/placebo until progression (with or without prednisone) at the investigator's discretion.

| | |
|---|-----------------|
| Actual start date of recruitment | 30 October 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 120 |
| Country: Number of subjects enrolled | Australia: 104 |
| Country: Number of subjects enrolled | Brazil: 107 |
| Country: Number of subjects enrolled | Canada: 109 |
| Country: Number of subjects enrolled | Czech Republic: 39 |
| Country: Number of subjects enrolled | Finland: 12 |
| Country: Number of subjects enrolled | France: 95 |
| Country: Number of subjects enrolled | Germany: 78 |
| Country: Number of subjects enrolled | Greece: 36 |
| Country: Number of subjects enrolled | Hungary: 17 |
| Country: Number of subjects enrolled | India: 74 |
| Country: Number of subjects enrolled | Ireland: 54 |
| Country: Number of subjects enrolled | Italy: 63 |
| Country: Number of subjects enrolled | Korea, Republic of: 54 |
| Country: Number of subjects enrolled | Mexico: 108 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Norway: 16 |
| Country: Number of subjects enrolled | Peru: 48 |
| Country: Number of subjects enrolled | Poland: 25 |
| Country: Number of subjects enrolled | Romania: 31 |
| Country: Number of subjects enrolled | Russian Federation: 80 |
| Country: Number of subjects enrolled | South Africa: 23 |
| Country: Number of subjects enrolled | Spain: 113 |
| Country: Number of subjects enrolled | Sweden: 45 |
| Country: Number of subjects enrolled | United Kingdom: 74 |
| Country: Number of subjects enrolled | United States: 405 |
| Worldwide total number of subjects | 1930 |
| EEA total number of subjects | 698 |

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) | 618 |
| From 65 to 84 years | 1293 |
| 85 years and over | 19 |

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at 187 sites worldwide.

Pre-assignment

Screening details:

1930 subjects were enrolled, and 1522 were randomised; 1518 received at least 1 dose of dasatinib (761) or placebo (757). Reason for 408 not randomised were: adverse event-7, subject withdrew consent-42, death-6, lost to follow-up-2, poor/non-compliance-3, subject did not meet study criteria-332, administrative reason by sponsor-1, other reasons-15.

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, Monitor, Data analyst, Carer |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Subjects received placebo, tablets, orally, once daily, plus docetaxel, 75 mg/m², intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity.

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with placebo tablets, orally once daily.

| | |
|--|------------|
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with Prednisone 5 mg tablet, orally twice daily to make the total daily dose of 10 mg up to disease progression or toxicity.

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

Dosage and administration details:

Subjects were administered with Docetaxel 75 mg/m² via intravenous infusion over 1 hour every 3 weeks up to disease progression or toxicity.

| | |
|------------------|-----------|
| Arm title | Dasatinib |
|------------------|-----------|

Arm description:

Subjects received dasatinib, 100 mg, tablet, orally, once daily plus docetaxel, 75 mg/m², given

intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dasatinib |
| Investigational medicinal product code | BMS-354825 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with dasatinib 20 mg/50 mg tablets orally once daily to make the total daily dose of 100 mg up to disease progression or toxicity.

| | |
|--|------------|
| Investigational medicinal product name | Prednisone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered with prednisone 5 mg tablet, orally twice daily to make the total daily dose of 10 mg up to disease progression or toxicity.

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

Dosage and administration details:

Subjects were administered with docetaxel 75 mg/m² via intravenous infusion over 1 hour every 3 weeks up to disease progression or toxicity.

| Number of subjects in period 1^[1] | Placebo | Dasatinib |
|---|---------|-----------|
| Started | 760 | 762 |
| Received Treatment | 757 | 761 |
| Completed | 0 | 0 |
| Not completed | 760 | 762 |
| Consent withdrawn by subject | 21 | 18 |
| Disease progression | 312 | 219 |
| Study drug toxicity | 68 | 141 |
| Death | 11 | 9 |
| Maximum clinical benefit | 141 | 142 |
| Adverse event unrelated to study drug | 78 | 122 |
| Other reasons | 19 | 13 |
| Lost to follow-up | 4 | 2 |
| Poor/non-compliance | 9 | 5 |
| Subject no longer meets study criteria | 7 | 3 |
| Subject requested to discontinue study treatment | 65 | 80 |

| | | |
|----------------------------------|----|---|
| Administrative reason by sponsor | 25 | 8 |
|----------------------------------|----|---|

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: Out of 1930 subjects who were enrolled, 1522 subjects were randomised and 1518 subjects received at least 1 dose of dasatinib or placebo (761 in dasatinib group and 757 in placebo group).

Baseline characteristics

Reporting groups

| | |
|---|-----------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo, tablets, orally, once daily, plus docetaxel, 75 mg/m ² , intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity. | |
| Reporting group title | Dasatinib |
| Reporting group description: | |
| Subjects received dasatinib, 100 mg, tablet, orally, once daily plus docetaxel, 75 mg/m ² , given intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity. | |

| Reporting group values | Placebo | Dasatinib | Total |
|---|---------|-----------|-------|
| Number of subjects | 760 | 762 | 1522 |
| Age categorical | | | |
| Units: Subjects | | | |
| <65 years | 263 | 251 | 514 |
| 65 - <75 years | 323 | 333 | 656 |
| >=75 years | 174 | 178 | 352 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 67.9 | 68.2 | |
| standard deviation | ± 8.31 | ± 8.15 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 0 | 0 |
| Male | 760 | 762 | 1522 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian | 56 | 55 | 111 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 2 |
| Black or African American | 34 | 23 | 57 |
| White | 645 | 656 | 1301 |
| Other | 24 | 27 | 51 |
| Type of metastatic disease | | | |
| Units: Subjects | | | |
| Bone disease only | 286 | 307 | 593 |
| Visceral/nodal disease only | 73 | 80 | 153 |
| Both bone and visceral/nodal disease | 399 | 373 | 772 |
| No evidence of metastatic disease | 2 | 2 | 4 |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo, tablets, orally, once daily, plus docetaxel, 75 mg/m ² , intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity. | |
| Reporting group title | Dasatinib |
| Reporting group description: Subjects received dasatinib, 100 mg, tablet, orally, once daily plus docetaxel, 75 mg/m ² , given intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity. | |

Primary: Overall Survival: Time From Randomisation to Date of Death

| | |
|---|--|
| End point title | Overall Survival: Time From Randomisation to Date of Death |
| End point description: Overall survival was defined as time in months from the randomization date to the date of death due to any cause (in the randomised population). If the subject did not die, survival was censored on the last date he or she was known to be alive. The analysis was performed in all the subjects who were randomised to receive any treatment. | |
| End point type | Primary |
| End point timeframe: From randomisation to death or date of last contact (maximum reached: 45 months) | |

| End point values | Placebo | Dasatinib | | |
|----------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 760 | 762 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 21.2 (20 to 23.4) | 21.5 (20.3 to 22.8) | | |

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Overall Survival: Dasatinib vs Placebo |
| Statistical analysis description: Analysis compared survival in arms by 2-sided, alpha=0.05 level, log-rank test, stratified by bisphosphonate intake (yes/no) and urinary N-telopeptide category (<60 vs ≥60 nmol/mmol creatinine) as defined at randomisation. Null hypothesis=survival was equal in both arms. Power calculations indicated that ≥858 deaths would lead to ≥90% power at 5% level for rejecting null hypothesis, given a true hazard ratio of 0.8. | |
| Comparison groups | Placebo v Dasatinib |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 1522 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9009 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.13 |

Notes:

[1] - An interim analysis on survival was performed. Final analyses included a multiplicity correction.

Secondary: Percentage of Subjects With an Objective Tumor Response by Modified Response Evaluation Criteria in Solid Tumors (RECIST)

| | |
|-----------------|---|
| End point title | Percentage of Subjects With an Objective Tumor Response by Modified Response Evaluation Criteria in Solid Tumors (RECIST) |
|-----------------|---|

End point description:

Objective tumor response rate=percentage of randomised subjects with a best tumor response of partial (PR) or complete response (CR), within 42 days of end of dosing, divided by total number of subjects who were evaluable. By RECIST: CR=disappearance of clinical and radiologic evidence of target and nontarget lesions confirmed by another evaluation at least 6 weeks later. PR=a >30% or greater decrease in the sum of longest diameter (LD) of target lesions in reference to the baseline sum LD confirmed by another evaluation at least 6 weeks later. Stable disease=neither sufficient increase to qualify for PD nor shrinkage to qualify for PR, and at least 8 weeks since start of study therapy. Progressive disease=a 20% or greater increase in sum of LD of all target lesions, taking as reference the smallest sum of LD at or following baseline, or unequivocal progression on existing nontarget lesions, or new lesions are present. Subjects with at least 1 target lesion at baseline were analysed.

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

End point timeframe:

Baseline, every 12 weeks thereafter to end of treatment, at end of treatment, and at follow-up (within 42 days of end of dosing)

| End point values | Placebo | Dasatinib | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 383 | 381 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 31.85 (27.21 to 36.78) | 30.45 (25.86 to 35.34) | | |

Statistical analyses

| | |
|----------------------------|---------------------------|
| Statistical analysis title | Objective Tumor Response: |
| Comparison groups | Placebo v Dasatinib |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 764 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.935 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.688 |
| upper limit | 1.271 |

Notes:

[2] - Since superiority of the dasatinib treatment group was not demonstrated for Overall Survival, secondary endpoints were not tested. The odds ratio is presented for experimental to control group.

Secondary: Time to First Skeletal-related Event (SRE)

| | |
|-----------------|--|
| End point title | Time to First Skeletal-related Event (SRE) |
|-----------------|--|

End point description:

Time to first SRE is defined as the time in months from the date of randomisation to the date of first SRE (unless SRE occurred while the subject was undergoing subsequent cancer therapy). Subjects with a first SRE while on subsequent cancer therapy, those who died without a reported SRE, and those who did not have an SRE were censored on the date of their last SRE assessment prior to start of subsequent cancer therapy, if any. Subjects who had no SRE assessments were censored on the day they were randomised. The analysis was performed in all the subjects who were randomised to receive any treatment. Here '99999' represents not estimable data.

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

End point timeframe:

From day of randomisation to date of first SRE or to last SRE assessment, if subsequent cancer therapy begun or no SRE (maximum reached: 42 months)

| End point values | Placebo | Dasatinib | | |
|----------------------------------|----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 760 | 762 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 31.1 (28.8 to 99999) | 99999 (99999 to 99999) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Time to First SRE: Dasatinib vs Placebo |
| Comparison groups | Placebo v Dasatinib |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 1522 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.81 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.02 |

Notes:

[3] - Since superiority of the dasatinib treatment group was not demonstrated for Overall Survival, secondary endpoints were not tested. The hazard ratio is presented for experimental to control group.

Secondary: Percentage of Subjects With A Reduction in Urinary N-telopeptide (uNTx) Level From Baseline

| | |
|-----------------|---|
| End point title | Percentage of Subjects With A Reduction in Urinary N-telopeptide (uNTx) Level From Baseline |
|-----------------|---|

End point description:

The percentage of Subjects who had an on-study uNTx value confirmed (at least 3 weeks later) within normal limits (or ≥ 3 and < 60 nmol/mmol creatinine, if normal limits were missing) or an on-study uNTx level reduction from baseline of $\geq 35\%$, even when on-study uNTx value remained abnormal. Subjects who entered the study with baseline urinary N-telopeptide values higher than the upper limit of normal (ULN), or ≥ 60 nmol/mmol creatinine, if ULN was missing were analysed.

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

End point timeframe:

Baseline, prior to each docetaxel infusion (every 3 weeks) to end of treatment, at end of treatment, and at follow-up (within 14 days of end of dosing)

| End point values | Placebo | Dasatinib | | |
|----------------------------------|-----------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 335 | 321 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 60.6 (55.14 to 65.86) | 66.04 (60.58 to 71.21) | | |

Statistical analyses

| | |
|---|---------------------------------------|
| Statistical analysis title | Reduction in uNTx Level from baseline |
| Comparison groups | Placebo v Dasatinib |
| Number of subjects included in analysis | 656 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.28 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.93 |
| upper limit | 1.763 |

Notes:

[4] - Since superiority of the dasatinib treatment group was not demonstrated for Overall Survival, secondary endpoints were not tested. The odds ratio is presented for experimental to control group.

Secondary: Progression-free Survival (PFS)

| | |
|-----------------|---------------------------------|
| End point title | Progression-free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS is defined as the time from the randomisation date until the date of earliest evidence of disease progression or death, for subjects who progressed or died before subsequent cancer therapy. Those who progressed or died while on subsequent cancer therapy and those who did not die or progress were censored at their last radiologic bone scan/imaging, skeletal related-event, or tumor assessment or at measurement of prostate specific antigen levels, whichever occurred last prior to start of subsequent cancer therapy, if any. Subjects with no assessments were censored on the day of randomisation. The analysis was performed in all the subjects who were randomised to receive any treatment.

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

End point timeframe:

From day of randomisation to disease progression or death (or to last clinical assessment, if subsequent cancer therapy started or no progression or death) (maximum reached: approximately 43 months)

| End point values | Placebo | Dasatinib | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 760 | 762 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.1 (10.8 to 11.7) | 11.8 (11.1 to 13.4) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | PFS: Dasatinib vs Placebo |
| Comparison groups | Placebo v Dasatinib |
| Number of subjects included in analysis | 1522 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.05 |

Notes:

[5] - Since superiority of the dasatinib treatment group was not demonstrated for Overall Survival, secondary endpoints were not tested. The hazard ratio is presented for experimental to control group.

Secondary: Time to Prostate Specific Antigen (PSA) Progression

| | |
|-----------------|---|
| End point title | Time to Prostate Specific Antigen (PSA) Progression |
|-----------------|---|

End point description:

PSA progression is defined as the time from randomisation to the date of the first PSA level measurement that led to confirmed PSA progression, for subjects who had not started subsequent cancer therapy. For subjects who did not progress or who progressed on cancer therapy, PSA progression is defined as the time from randomisation to the date of the last PSA level measurement before the start of cancer therapy, if any. Subjects who had no on-study PSA level measurements were censored on the day they were randomised. The analysis was performed in all subjects who were randomised to receive any treatment.

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

End point timeframe:

From randomisation to date of first PSA measurement leading to confirmed PSA progression (or to last bone scan assessment, if no progression or if cancer therapy started) (maximum reached: 30 months)

| End point values | Placebo | Dasatinib | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 760 | 762 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.9 (6.5 to 7.4) | 7.2 (6.6 to 7.9) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Time to PSA Progression |
| Comparison groups | Placebo v Dasatinib |
| Number of subjects included in analysis | 1522 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.79 |
| upper limit | 1.01 |

Notes:

[6] - Since superiority of the dasatinib treatment group was not demonstrated for Overall Survival, secondary endpoints were not tested. The hazard ratio is presented for of experimental to control group.

Secondary: Percentage of Subjects With a Reduction in Pain Intensity From Baseline

| | |
|-----------------|---|
| End point title | Percentage of Subjects With a Reduction in Pain Intensity From Baseline |
|-----------------|---|

End point description:

The percentage of subjects with reduction in pain intensity from baseline was defined as the number of subjects who achieved a 30% or more decrease in pain intensity from baseline for at least 2 consecutive pain assessments (at least 14 days apart) within 14 days of end of dosing divided by the number of randomised subjects who had a baseline pain intensity of at least 2. Pain intensity was assessed based on question 3 of the brief pain inventory questionnaire. The analysis was performed in all the evaluable subjects with a baseline pain intensity of 2 or greater.

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

End point timeframe:

Baseline, prior to each docetaxel infusion (every 3 weeks), at end of treatment, and at follow-up (within 14 days of end of dosing)

| End point values | Placebo | Dasatinib | | |
|----------------------------------|------------------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 467 | 419 | | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 71.52 (67.19 to 75.57) | 66.59 (61.85 to 71.09) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Reduction from Baseline in Pain Intensity |
| Comparison groups | Placebo v Dasatinib |
| Number of subjects included in analysis | 886 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[7] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.791 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.594 |
| upper limit | 1.052 |

Notes:

[7] - Since superiority of the dasatinib treatment group was not demonstrated for Overall Survival, secondary endpoints were not tested. The odds ratio is presented for experimental to control group.

Other pre-specified: Number of Subjects With Death as Outcome, Serious Adverse Events (SAEs), Drug-related SAEs, Adverse Events (AEs) Leading to Discontinuation, and Drug-related AEs Leading to Discontinuation

| | |
|-----------------|--|
| End point title | Number of Subjects With Death as Outcome, Serious Adverse Events (SAEs), Drug-related SAEs, Adverse Events (AEs) Leading to Discontinuation, and Drug-related AEs Leading to Discontinuation |
|-----------------|--|

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a 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. Drug-related=having certain, probable, possible, or missing relationship to study drug. The analysis was performed in all the subjects who received the treatment.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to >=30 days after last dose of study drug until resolution of drug-related toxicity, or when toxicity was deemed irreversible, whichever shorter.

| End point values | Placebo | Dasatinib | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 757 | 761 | | |
| Units: Subjects | | | | |
| All Deaths | 505 | 506 | | |
| Deaths on or within 30 days of treatment | 50 | 79 | | |
| All SAEs | 317 | 381 | | |
| Drug-related SAEs | 90 | 150 | | |
| AEs leading to discontinuation | 186 | 293 | | |
| Drug-related AEs leading to discontinuation | 76 | 144 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Adverse Events (AEs) of Special Interest

| | |
|-----------------|--|
| End point title | Number of Subjects With Adverse Events (AEs) of Special Interest |
|-----------------|--|

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. AEs of Special Interest=recognized events in other agents within this drug class or events for which safety data from nonclinical and clinical studies with dasatinib indicate that careful evaluation is warranted. AEs of Special Interest were identified by the medical and safety representatives of the sponsor based on MedDRA preferred terms or laboratory data.

ANC=absolute neutrophil count. The analysis was performed in all the subjects who received the treatment.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline up to ≥ 30 days after last dose of study drug until resolution of drug-related toxicity, or when toxicity was deemed irreversible, whichever was shorter

| End point values | Placebo | Dasatinib | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 757 | 761 | | |
| Units: Subjects | | | | |
| Myelosuppression: Hemoglobin (n=746, 739) | 712 | 720 | | |
| Myelosuppression: White blood cells (n=746, 738) | 128 | 149 | | |
| Myelosuppression: ANC (n=745, 737) | 84 | 161 | | |
| Myelosuppression: Platelets (n=746, 738) | 108 | 100 | | |
| Hypocalcemia (n=739, 719) | 308 | 377 | | |

| | | | | |
|---|-----|-----|--|--|
| Hypophosphotemia (n=733, 720) | 189 | 257 | | |
| Hypomagnesemia (n=734, 721) | 108 | 98 | | |
| Diarrhea (n=757, 761) | 167 | 229 | | |
| Nausea/vomiting (n=757, 761) | 127 | 170 | | |
| Fatigue (n=757, 761) | 216 | 236 | | |
| Myalgias/arthralgias (n=757, 761) | 29 | 29 | | |
| Rash (n=757, 761) | 46 | 72 | | |
| Gastrointestinal tract bleeding (n=757, 761) | 6 | 14 | | |
| Central nervous system bleeding (n=757, 761) | 1 | 2 | | |
| Other hemorrhage (n=757, 761) | 14 | 24 | | |
| Pulmonary arterial hypertension (n=757, 761) | 0 | 0 | | |
| Fluid retention: Superficial edema (n=757, 761) | 77 | 76 | | |
| Fluid retention: Pleural effusion (n=757, 761) | 13 | 87 | | |
| Fluid retention: Other (n=757, 761) | 37 | 52 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Abnormalities in Results of Clinical Laboratory Tests in Hematology

| | |
|-----------------|---|
| End point title | Number of Subjects With Abnormalities in Results of Clinical Laboratory Tests in Hematology |
|-----------------|---|

End point description:

Abnormalities were graded according to the Common Toxicity Criteria (CTC), version 3.0, of the National Cancer Institute. CTC are graded from 1 (least severe) to 4 (life threatening). Grade 3 and 4 criteria are defined as follows: Absolute neutrophil count, Grade 3, neutrophils $<1.0-0.5 \times 10^9/L$; Grade 4, $<0.5 \times 10^9/L$. Hemoglobin, Grade 3, $<4.9-4.0$ mmol/L; Grade 4, <4.0 mmol/L. Platelets, Grade 3, $<50.0-25.0 \times 10^9/L$; Grade 4, $<25.0 \times 10^9/L$. Leukocytes, Grade 3, $<2.0-1.0 \times 10^9/L$; Grade 4, $<1.0 \times 10^9/L$. The analysis was performed in all the subjects who received treatment.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At baseline, within 3 days prior to each infusion of docetaxel (each cycle) and at end of treatment. If docetaxel is discontinued, every other cycle.

| End point values | Placebo | Dasatinib | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 757 | 761 | | |
| Units: Subjects | | | | |
| Absolute neutrophil count (All grades) | 84 | 161 | | |
| Absolute neutrophil count (Grades 3 and 4) | 41 | 46 | | |
| Hemoglobin (All grades) | 712 | 720 | | |
| Hemoglobin (Grades 3 and 4) | 44 | 59 | | |
| Platelets (All grades) | 108 | 100 | | |

| | | | | |
|-----------------------------|-----|-----|--|--|
| Platelets (Grades 3 and 4) | 6 | 3 | | |
| Leukocytes (All grades) | 128 | 149 | | |
| Leukocytes (Grades 3 and 4) | 32 | 30 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Abnormalities in Results of Clinical Laboratory Tests Assessing Liver Function, Renal Function, and Electrolytes

| | |
|-----------------|--|
| End point title | Number of Subjects With Abnormalities in Results of Clinical Laboratory Tests Assessing Liver Function, Renal Function, and Electrolytes |
|-----------------|--|

End point description:

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal. Abnormalities were graded according to the Common Toxicity Criteria (CTC), version 3.0, of the National Cancer Institute. CTC are graded from 1 (least severe) to 4 (life threatening). ALP, ALT, and AST, Grade 3, >5.0-20.0*ULN; Grade 4, >20.0*ULN. Total bilirubin, Grade 3, >3.0-10.0*ULN; Grade 4, >10.0*ULN. Creatinine, Grade 3, >3.0-6.0*ULN; Grade 4, >6.0*ULN. Hypercalcemia(serum calcium(SC), mmol/L), Grade 3, >3.1-3.4; Grade 4, >3.4. Hypocalcemia(SC, mmol/L), Grade 3, <1.75-1.5; Grade 4, <1.5. Hyperkalemia(SC, mmol/L), Grade 3, >6.0-7.0; Grade 4, >7.0. Hypokalemia(SC, mmol/L), Grade 3, <3.0-2.5; Grade 4, <2.5. Hyponatremia(SC, mmol/L), Grade 3, >155-160; Grade 4, >160. Hyponatremia(serum sodium(SS), mmol/L), Grade 3, <130-120; Grade 4, <120. Phosphorus (SS, mmol/L), Grade 3, <0.6-0.3; Grade 4, <0.3. The analysis was performed in all the subjects who received treatment.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At baseline, within 3 days prior to each infusion of docetaxel (each cycle), to end of treatment. If docetaxel is discontinued, every other cycle

| End point values | Placebo | Dasatinib | | |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 757 | 761 | | |
| Units: Subjects | | | | |
| ALP (All grades) | 447 | 375 | | |
| ALP (Grades 3 and 4) | 91 | 68 | | |
| ALT (All grades) | 186 | 256 | | |
| ALT (Grades 3 and 4) | 5 | 6 | | |
| AST (All grades) | 212 | 266 | | |
| AST (Grades 3 and 4) | 4 | 5 | | |
| Total bilirubin (All grades) | 49 | 41 | | |
| Total bilirubin (Grades 3 and 4) | 1 | 3 | | |
| Creatinine (All grades) | 153 | 184 | | |
| Creatinine (Grades 3 and 4) | 3 | 5 | | |
| Hypercalcemia (All grades) | 56 | 34 | | |
| Hypercalcemia (Grades 3 and 4) | 1 | 1 | | |
| Hypocalcemia (All grades) | 308 | 377 | | |
| Hypocalcemia (Grades 3 and 4) | 23 | 25 | | |
| Hyperkalemia (All grades) | 164 | 152 | | |
| Hyperkalemia (Grades 3 and 4) | 11 | 14 | | |

| | | | | |
|--------------------------------|-----|-----|--|--|
| Hypokalemia (All grades) | 107 | 152 | | |
| Hypokalemia (Grades 3 and 4) | 6 | 16 | | |
| Hypernatremia (All grades) | 93 | 101 | | |
| Hypernatremia (Grades 3 and 4) | 0 | 0 | | |
| Hyponatremia (All grades) | 230 | 241 | | |
| Hyponatremia (Grades 3 and 4) | 36 | 43 | | |
| Phosphorus (All grades) | 189 | 257 | | |
| Phosphorus (Grades 3 and 4) | 43 | 93 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Abnormal Results in Urinalysis

| | |
|-----------------|--|
| End point title | Number of Subjects With Abnormal Results in Urinalysis |
|-----------------|--|

End point description:

Abnormal=positive, defined as the presence of ≥ 30 mg/dL of protein; a small, moderate, or large amount of blood; or >0 g/dL glucose in urine. BL=baseline; neg=negative. The analysis was performed in all the subjects who received the treatment.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At baseline, within 3 days prior to each infusion of docetaxel (each cycle), to end of treatment. If docetaxel is discontinued, every other cycle

| End point values | Placebo | Dasatinib | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 757 | 761 | | |
| Units: Subjects | | | | |
| Protein, urine: positive | 246 | 336 | | |
| Blood, urine: positive | 289 | 307 | | |
| Glucose, urine: positive | 179 | 154 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects by Maximal On-study Fridericia-corrected QTc Interval by Electrocardiogram

| | |
|-----------------|---|
| End point title | Number of Subjects by Maximal On-study Fridericia-corrected QTc Interval by Electrocardiogram |
|-----------------|---|

End point description:

The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval was corrected for heart rate using Fridericia's (QTcF) formula. QTc interval were measured in milliseconds (msec). The analysis was performed in all the subjects who received the treatment. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.

| | |
|--|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| At baseline, approximately 12 weeks after starting treatment, and then whenever clinically indicated up to within 30 days of end of dosing | |

| End point values | Placebo | Dasatinib | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 757 | 761 | | |
| Units: Subjects | | | | |
| <450 msec (n=600, 548) | 550 | 497 | | |
| 450-500 msec (n=600, 548) | 43 | 48 | | |
| >500 msec (n=600, 548) | 7 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Changes From Baseline in Fridericia-corrected QTc Interval by Electrocardiogram

| | |
|---|---|
| End point title | Number of Subjects With Changes From Baseline in Fridericia-corrected QTc Interval by Electrocardiogram |
| End point description: | |
| <p>The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval was corrected for heart rate using Fridericia's (QTcF) formula. QTc interval were measured in milliseconds (msec). A change from baseline QT and QTc (corrected for heart rate by Fridericia formula) were presented. The analysis was performed in all the subjects who received the treatment. Here, 'n' signifies evaluable subjects for specified categories in respective treatment arms.</p> | |
| End point type | Other pre-specified |
| End point timeframe: | |
| At baseline, approximately 12 weeks after starting treatment, and then whenever clinically indicated up to within 30 days of end of dosing | |

| End point values | Placebo | Dasatinib | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 757 | 761 | | |
| Units: Subjects | | | | |
| 0 to 30 msec increase (n=591, 540) | 203 | 199 | | |
| >30 to 60 msec increase (n=591, 540) | 52 | 47 | | |
| >60 msec increase (n=591, 540) | 32 | 26 | | |
| Decrease (n=591, 540) | 304 | 268 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With and Without Pericardial Effusion at Baseline and On-study and With Left Ventricular Ejection Fraction (LVEF) <40% and ≥40% On-study by Echocardiogram

| | |
|-----------------|---|
| End point title | Number of Subjects With and Without Pericardial Effusion at Baseline and On-study and With Left Ventricular Ejection Fraction (LVEF) <40% and ≥40% On-study by Echocardiogram |
|-----------------|---|

End point description:

BL=baseline; OS=on-study. Echocardiogram were performed at baseline and once during treatment. the analysis was done in all the subjects who were randomised to receive any treatment.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

At baseline, approximately 12 weeks after start of treatment, and thereafter whenever clinically indicated

| End point values | Placebo | Dasatinib | | |
|---|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 760 | 762 | | |
| Units: Subjects | | | | |
| Pericardial effusion at BL/absent OS | 3 | 1 | | |
| Pericardial effusion at BL/present OS | 0 | 1 | | |
| Pericardial effusion at BL/not reported OS | 1 | 0 | | |
| Pericardial effusion absent at BL/ absent OS | 584 | 545 | | |
| Pericardial effusion absent at BL/present OS | 24 | 26 | | |
| Pericardial effusion absent at BL/not reported OS | 132 | 184 | | |
| Pericardial not reported at BL | 16 | 5 | | |
| LVEF OS <40% | 2 | 2 | | |
| LVEF OS ≥40% | 607 | 566 | | |
| LVEF not reported OS | 151 | 194 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On Study (i.e. events from 1st dose date through last dose date + 30 days).

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

Dictionary used

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

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

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo, tablets, orally, once daily, plus docetaxel, 75 mg/m², intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity.

| | |
|-----------------------|-----------|
| Reporting group title | Dasatinib |
|-----------------------|-----------|

Reporting group description:

Subjects received dasatinib, 100 mg, tablet, orally, once daily plus docetaxel, 75 mg/m², given intravenously every 3 weeks as a 1-hour infusion, plus prednisone, 5 mg, given orally twice daily up to disease progression or toxicity.

| Serious adverse events | Placebo | Dasatinib | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 317 / 757 (41.88%) | 381 / 761 (50.07%) | |
| number of deaths (all causes) | 50 | 79 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenosquamous cell lung cancer | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Astrocytoma malignant | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cancer pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colorectal cancer recurrent | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningioma | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastasis | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastatic neoplasm | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic squamous cell carcinoma | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm progression | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 2 | |
| Prostate cancer metastatic | | | |
| subjects affected / exposed | 10 / 757 (1.32%) | 9 / 761 (1.18%) | |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 8 | 0 / 7 | |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal cancer | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of the oral cavity | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic dissection | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 10 / 757 (1.32%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 5 / 12 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 8 / 757 (1.06%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 5 / 8 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infarction | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vasculitis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (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 | 7 / 757 (0.92%) | 13 / 761 (1.71%) | |
| occurrences causally related to treatment / all | 6 / 8 | 8 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Chest pain | | | |
| subjects affected / exposed | 8 / 757 (1.06%) | 9 / 761 (1.18%) | |
| occurrences causally related to treatment / all | 1 / 8 | 3 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Condition aggravated | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 3 | |
| Device occlusion | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Face oedema | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 9 / 757 (1.19%) | 15 / 761 (1.97%) | |
| occurrences causally related to treatment / all | 3 / 9 | 8 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthermia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-Organ failure | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Oedema | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 6 / 761 (0.79%) | |
| occurrences causally related to treatment / all | 2 / 3 | 5 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 9 / 757 (1.19%) | 7 / 761 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 14 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 757 (1.85%) | 29 / 761 (3.81%) | |
| occurrences causally related to treatment / all | 5 / 15 | 12 / 37 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Sudden death | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema genital | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Penile pain | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatic obstruction | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Testicular mass | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|------------------|------------------|--|
| Alveolitis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 10 / 757 (1.32%) | 21 / 761 (2.76%) | |
| occurrences causally related to treatment / all | 3 / 11 | 8 / 23 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| 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 | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 19 / 761 (2.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 21 / 25 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Pneumonitis | | | |
| subjects affected / exposed | 7 / 757 (0.92%) | 7 / 761 (0.92%) | |
| occurrences causally related to treatment / all | 2 / 8 | 5 / 7 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Productive cough | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 17 / 757 (2.25%) | 5 / 761 (0.66%) | |
| occurrences causally related to treatment / all | 3 / 17 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary venous thrombosis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 7 / 761 (0.92%) | |
| occurrences causally related to treatment / all | 0 / 2 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 2 | 1 / 2 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 6 / 761 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Depression suicidal | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow myelogram abnormal | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium test positive | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eastern cooperative oncology group performance status worsened | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemoglobin | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 9 / 761 (1.18%) | |
| occurrences causally related to treatment / all | 1 / 4 | 2 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anastomotic leak | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (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 | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis radiation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal anastomotic leak | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint injury | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple fractures | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 6 / 757 (0.79%) | 11 / 761 (1.45%) | |
| occurrences causally related to treatment / all | 0 / 6 | 5 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural complication | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation proctitis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheal obstruction | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ulna fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous injury | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 8 / 757 (1.06%) | 8 / 761 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 8 | 3 / 8 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Cardiac disorder | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Cardio-Respiratory arrest | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiopulmonary failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 757 (0.26%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| 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 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebral ischaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 4 / 757 (0.53%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Coma | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| 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 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| 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 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iiird nerve disorder | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monoplegia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Motor dysfunction | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nerve root compression | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 757 (0.53%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| 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 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 6 / 757 (0.79%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 5 / 757 (0.66%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 1 / 7 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Agranulocytosis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 15 / 757 (1.98%) | 21 / 761 (2.76%) | |
| occurrences causally related to treatment / all | 4 / 16 | 6 / 24 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| 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 | 27 / 757 (3.57%) | 32 / 761 (4.20%) | |
| occurrences causally related to treatment / all | 13 / 30 | 15 / 33 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 3 | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypochromic anaemia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 757 (0.92%) | 9 / 761 (1.18%) | |
| occurrences causally related to treatment / all | 3 / 12 | 4 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 18 / 757 (2.38%) | 19 / 761 (2.50%) | |
| occurrences causally related to treatment / all | 9 / 29 | 6 / 28 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Normochromic normocytic anaemia | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Eye disorders | | | |
| Amaurosis fugax | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Maculopathy | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 6 / 761 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fistula | | | |

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|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 10 / 757 (1.32%) | 5 / 761 (0.66%) | |
| occurrences causally related to treatment / all | 1 / 10 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 757 (1.32%) | 44 / 761 (5.78%) | |
| occurrences causally related to treatment / all | 8 / 11 | 33 / 51 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer perforation | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (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 | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterovesical fistula | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer perforation | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis erosive | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 7 / 757 (0.92%) | 8 / 761 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 8 | 4 / 8 | |
| deaths causally related to treatment / all | 1 / 3 | 0 / 1 | |
| Gastrointestinal ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intra-Abdominal haemorrhage | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Megacolon | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 7 / 757 (0.92%) | 13 / 761 (1.71%) | |
| occurrences causally related to treatment / all | 2 / 8 | 9 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctitis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 5 / 757 (0.66%) | 8 / 761 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 6 | 2 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reflux gastritis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toothache | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Volvulus | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 10 / 757 (1.32%) | 14 / 761 (1.84%) | |
| occurrences causally related to treatment / all | 4 / 11 | 6 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic pain | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peau d'orange | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyoderma gangrenosum | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 4 / 757 (0.53%) | 8 / 761 (1.05%) | |
| occurrences causally related to treatment / all | 1 / 4 | 3 / 8 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Bladder neck obstruction | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder obstruction | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder outlet obstruction | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 18 / 757 (2.38%) | 10 / 761 (1.31%) | |
| occurrences causally related to treatment / all | 0 / 19 | 2 / 22 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobinuria | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage urinary tract | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 6 / 761 (0.79%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstructive uropathy | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal disorder | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 5 / 757 (0.66%) | 5 / 761 (0.66%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 2 | |
| Renal impairment | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric obstruction | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ureteric stenosis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral stenosis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder polyp | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 9 / 757 (1.19%) | 9 / 761 (1.18%) | |
| occurrences causally related to treatment / all | 0 / 9 | 1 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urogenital haemorrhage | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 12 / 757 (1.59%) | 7 / 761 (0.92%) | |
| occurrences causally related to treatment / all | 1 / 13 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 7 / 757 (0.92%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| 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 | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercreatinaemia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| 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 | 4 / 757 (0.53%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (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 | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (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 / 757 (0.40%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic lupus erythematosus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess intestinal | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal abscess | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Balanoposthitis infective | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Candida infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 9 / 761 (1.18%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cellulitis of male external genital organ | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |

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|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 757 (0.40%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Empyema | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis bacterial | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fungal oesophagitis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 757 (0.40%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 2 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 4 / 757 (0.53%) | 8 / 761 (1.05%) | |
| occurrences causally related to treatment / all | 2 / 4 | 5 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal sepsis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| 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 | 0 / 757 (0.00%) | 5 / 761 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal infection | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Perirectal abscess | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 22 / 757 (2.91%) | 33 / 761 (4.34%) | |
| occurrences causally related to treatment / all | 3 / 23 | 11 / 36 | |
| deaths causally related to treatment / all | 1 / 5 | 0 / 2 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (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 | 1 / 757 (0.13%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Scrotal abscess | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 6 / 757 (0.79%) | 7 / 761 (0.92%) | |
| occurrences causally related to treatment / all | 2 / 6 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Septic shock | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 10 / 761 (1.31%) | |
| occurrences causally related to treatment / all | 1 / 3 | 3 / 10 | |
| deaths causally related to treatment / all | 1 / 2 | 1 / 5 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tooth infection | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 757 (0.92%) | 10 / 761 (1.31%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 4 / 757 (0.53%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 757 (0.53%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 11 / 757 (1.45%) | 21 / 761 (2.76%) | |
| occurrences causally related to treatment / all | 4 / 14 | 10 / 22 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Fluid overload | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 757 (0.40%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 6 / 757 (0.79%) | 4 / 761 (0.53%) | |
| occurrences causally related to treatment / all | 4 / 6 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 4 / 757 (0.53%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 757 (0.26%) | 3 / 761 (0.39%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 757 (0.40%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 757 (0.13%) | 0 / 761 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 0 / 757 (0.00%) | 2 / 761 (0.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 757 (0.13%) | 1 / 761 (0.13%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo | Dasatinib | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 701 / 757 (92.60%) | 716 / 761 (94.09%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 42 / 757 (5.55%) | 22 / 761 (2.89%) | |
| occurrences (all) | 51 | 26 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 143 / 757 (18.89%) | 163 / 761 (21.42%) | |
| occurrences (all) | 236 | 258 | |
| Chest pain | | | |
| subjects affected / exposed | 34 / 757 (4.49%) | 49 / 761 (6.44%) | |
| occurrences (all) | 40 | 60 | |
| Fatigue | | | |

| | | | |
|---|--------------------|--------------------|--|
| subjects affected / exposed | 329 / 757 (43.46%) | 334 / 761 (43.89%) | |
| occurrences (all) | 566 | 572 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 52 / 757 (6.87%) | 70 / 761 (9.20%) | |
| occurrences (all) | 80 | 106 | |
| Oedema | | | |
| subjects affected / exposed | 47 / 757 (6.21%) | 36 / 761 (4.73%) | |
| occurrences (all) | 50 | 42 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 207 / 757 (27.34%) | 162 / 761 (21.29%) | |
| occurrences (all) | 254 | 213 | |
| Pain | | | |
| subjects affected / exposed | 62 / 757 (8.19%) | 47 / 761 (6.18%) | |
| occurrences (all) | 73 | 55 | |
| Pyrexia | | | |
| subjects affected / exposed | 71 / 757 (9.38%) | 132 / 761 (17.35%) | |
| occurrences (all) | 88 | 174 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 112 / 757 (14.80%) | 137 / 761 (18.00%) | |
| occurrences (all) | 148 | 181 | |
| Dyspnoea | | | |
| subjects affected / exposed | 127 / 757 (16.78%) | 154 / 761 (20.24%) | |
| occurrences (all) | 163 | 205 | |
| Epistaxis | | | |
| subjects affected / exposed | 41 / 757 (5.42%) | 33 / 761 (4.34%) | |
| occurrences (all) | 57 | 35 | |
| Pleural effusion | | | |
| subjects affected / exposed | 28 / 757 (3.70%) | 117 / 761 (15.37%) | |
| occurrences (all) | 29 | 145 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 95 / 757 (12.55%) | 76 / 761 (9.99%) | |
| occurrences (all) | 114 | 84 | |
| Investigations | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 27 / 757 (3.57%) 31 | 49 / 761 (6.44%) 56 | |
| Weight decreased subjects affected / exposed occurrences (all) | 77 / 757 (10.17%) 88 | 121 / 761 (15.90%) 130 | |
| Weight increased subjects affected / exposed occurrences (all) | 64 / 757 (8.45%) 71 | 36 / 761 (4.73%) 42 | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 61 / 757 (8.06%) 69 | 64 / 761 (8.41%) 77 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 147 / 757 (19.42%) 236 | 165 / 761 (21.68%) 254 | |
| Headache subjects affected / exposed occurrences (all) | 65 / 757 (8.59%) 98 | 82 / 761 (10.78%) 111 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 109 / 757 (14.40%) 132 | 83 / 761 (10.91%) 99 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 59 / 757 (7.79%) 70 | 44 / 761 (5.78%) 60 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 106 / 757 (14.00%) 132 | 98 / 761 (12.88%) 141 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 142 / 757 (18.76%) 205 | 217 / 761 (28.52%) 285 | |
| Neutropenia subjects affected / exposed occurrences (all) | 67 / 757 (8.85%) 89 | 79 / 761 (10.38%) 113 | |
| Eye disorders | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| Lacrimation increased subjects affected / exposed occurrences (all) | 86 / 757 (11.36%) 92 | 48 / 761 (6.31%) 53 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 67 / 757 (8.85%) 79 | 66 / 761 (8.67%) 81 | |
| Constipation subjects affected / exposed occurrences (all) | 189 / 757 (24.97%) 266 | 157 / 761 (20.63%) 230 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 312 / 757 (41.22%) 636 | 414 / 761 (54.40%) 975 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 59 / 757 (7.79%) 76 | 50 / 761 (6.57%) 60 | |
| Nausea subjects affected / exposed occurrences (all) | 231 / 757 (30.52%) 389 | 288 / 761 (37.84%) 531 | |
| Stomatitis subjects affected / exposed occurrences (all) | 47 / 757 (6.21%) 69 | 47 / 761 (6.18%) 83 | |
| Vomiting subjects affected / exposed occurrences (all) | 117 / 757 (15.46%) 152 | 166 / 761 (21.81%) 245 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 326 / 757 (43.06%) 336 | 311 / 761 (40.87%) 323 | |
| Dry skin subjects affected / exposed occurrences (all) | 46 / 757 (6.08%) 49 | 54 / 761 (7.10%) 56 | |
| Nail disorder subjects affected / exposed occurrences (all) | 119 / 757 (15.72%) 130 | 80 / 761 (10.51%) 84 | |
| Rash | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 75 / 757 (9.91%) 101 | 106 / 761 (13.93%) 133 | |
| Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all) | 44 / 757 (5.81%) 59 | 46 / 761 (6.04%) 72 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 124 / 757 (16.38%) 165 | 104 / 761 (13.67%) 129 | |
| Back pain subjects affected / exposed occurrences (all) | 194 / 757 (25.63%) 248 | 148 / 761 (19.45%) 186 | |
| Bone pain subjects affected / exposed occurrences (all) | 70 / 757 (9.25%) 93 | 61 / 761 (8.02%) 83 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 42 / 757 (5.55%) 53 | 15 / 761 (1.97%) 20 | |
| Muscular weakness subjects affected / exposed occurrences (all) | 51 / 757 (6.74%) 56 | 38 / 761 (4.99%) 40 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 40 / 757 (5.28%) 46 | 35 / 761 (4.60%) 49 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 55 / 757 (7.27%) 67 | 62 / 761 (8.15%) 77 | |
| Myalgia subjects affected / exposed occurrences (all) | 54 / 757 (7.13%) 61 | 50 / 761 (6.57%) 68 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 128 / 757 (16.91%) 176 | 115 / 761 (15.11%) 135 | |
| Infections and infestations | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| Urinary tract infection subjects affected / exposed occurrences (all) | 67 / 757 (8.85%) 102 | 73 / 761 (9.59%) 111 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 151 / 757 (19.95%) 207 | 207 / 761 (27.20%) 283 | |
| Dehydration subjects affected / exposed occurrences (all) | 23 / 757 (3.04%) 24 | 44 / 761 (5.78%) 52 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 55 / 757 (7.27%) 68 | 41 / 761 (5.39%) 57 | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 24 / 757 (3.17%) 42 | 40 / 761 (5.26%) 45 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 20 June 2008 | The purpose of this amendment was to permit the collection and storage of blood samples for use in future exploratory pharmacogenetic research studies. |
| 17 April 2009 | The Purpose of this amendment was to: <ul style="list-style-type: none">• Expand number of allowable cycles of docetaxel, route and schedule of dexamethasone and exclude agents with known effect on bone turnover,• Set minimum period of time for definition of stable disease for Response Evaluation Criteria in Solid Tumor (RECIST) evaluable subjects and provide specification around timing and need for valuations such as computed tomography (CT) and magnetic resonance imaging (MRI) scans,• Clarification of Subjective Significance Questionnaire, dose modifications, requirements for follow-up of toxicity and progression,• Change in requirement of collection of bone-specific alkaline phosphatase. |
| 22 September 2009 | The Purpose of this amendment was to: <ul style="list-style-type: none">• Allow use of alternate imaging modalities (skeletal survey supported by CT/MRI) to evaluate bone if/when bone scan is unable to be conducted due to lack of Technetium 99,• Reclassify 2 objectives from Secondary to Exploratory (To estimate the objective tumor response rate, by modified RECIST criteria for subjects with measurable disease at baseline in each treatment arm; and to estimate the rate of stable disease by bone scan or other approved imaging modality at 24 weeks in each treatment arm),• Clarify Inclusion criteria timelines and dose modifications for toxicities, and modification of serious adverse event submission process. |
| 12 July 2011 | The Purpose of this amendment was to: <ul style="list-style-type: none">• Address Regulatory feedback by reducing number of interim analyses for overall survival from two to one,• Remove radiological progression on bone scan/imaging from the Skeletal Related Event definition, to now be a "stand alone" progression event,• Add Progression Free Survival as a secondary objective/endpoint,• Move Objective Tumor Response Rate to Secondary objectives/endpoints,• Adjust hierarchy of Secondary objectives/endpoints,• Clarify terminology and correct typographical errors. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported