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 met 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/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.

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/m^2 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/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.

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/m^2 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 >=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*10^9/L; Grade 4, <0.5*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*10^9/L; Grade 4, <25.0*10^9/L. Leukocytes, Grade 3, <2.0-1.0*10^9/L; Grade 4, <1.0*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. Hypernatremia(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		
Phosporus (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 msecs (n=600, 548)	550	497		
450-500 msecs (n=600, 548)	43	48		
>500 msecs (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:

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.

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 msecs increase (n=591, 540)	203	199		
>30 to 60 msecs increase (n=591, 540)	52	47		
>60 msecs 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/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.	

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			

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			

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			

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			

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			

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			

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			

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			

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

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

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

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