Clinical trial results:
An open-label, multicenter phase II study to compare the efficacy and safety of RAD001 as first-line followed by second-line sunitinib versus sunitinib as first-line followed by second-line RAD001 in the treatment of patients with metastatic renal cell carcinoma

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies and data using 999 as data points are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results

Summary

EudraCT number	2009-011056-21
Trial protocol	DK ES GB DE IT FR NL
Global end of trial date	20 May 2015
Results information	
Result version number	v1 (current)
This version publication date	18 July 2018
First version publication date	18 July 2018

Trial information

Trial identification	
Sponsor protocol code	CRAD001L2202
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00903175
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	20 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the probability that progression-free survival (PFS) during or after first-line treatment (PFS-1L) in patients who received everolimus was non-inferior to PFS during or after first-line treatment in patients who received sunitinib as treatment for metastatic renal cell carcinoma (mRCC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 October 2009
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: 12
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Brazil: 39
Country: Number of subjects enrolled	Canada: 53
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Hong Kong: 14
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Korea, Republic of: 35
Country: Number of subjects enrolled	Mexico: 13
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Peru: 15
Country: Number of subjects enrolled	Spain: 10

Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Thailand: 13
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 160
Worldwide total number of subjects	471
EEA total number of subjects	87

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)	279
From 65 to 84 years	189
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

238 patients were randomized to everolimus as 1st line followed by 2nd line sunitinib. All patients in this group were treated. 233 patients were randomized to the sunitinib as 1st line followed by 2nd line everolimus. However 2 of the 233 patients were not treated in this group.

Pre-assignment

Screening details:

The trial had a crossover design: first-line therapy until disease progression followed by second-line therapy until disease progression.Patients were randomized 1:1 to either everolimus-sunitinib or sunitinib-everolimus treatment sequence and were
stratified by MSKCC risk criteria

Period 1

Period 1 title	Period 1 - First Line
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	everolimus 1L/sunitinib 2L

Arm description:

everolimus First Line: 10 mg orally, once daily, (two 5 mg tablets), continuous treatment. sunitinib Second Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2)

Arm type	Experimental
Investigational medicinal product name	everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was administered orally at 10 mg/day. Everolimus was formulated as tablets of 5 mg strength.

Arm title	sunitinib 1L/everolimus 2L

Arm description:

sunitinib First Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2) everolimus Second Line: 10 mg orally, once daily (two 5 mg tablets), continuous treatment

Arm type	Experimental
Investigational medicinal product name	sunitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Sunitinib was supplied as hard gelatin capsules of 12.5 mg, 25 mg, or 50 mg strength according to local practice.

Number of subjects in period 1	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L
Started	238	233
Completed	161	142
Not completed	77	91
Adverse event, serious fatal	17	10
Abnormal lab value(s)	-	1
Consent withdrawn by subject	8	12
Adverse event, non-fatal	36	50
Administrative problems	12	13
Untreated	-	2
Abnormal test procedure result(s)	1	-
Protocol deviation	3	3

Period 2

Period 2 title	Period 2 - Second Line
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	everolimus 1L/sunitinib 2L

Arm description:

everolimus First Line: 10 mg orally, once daily, (two 5 mg tablets), continuous treatment. sunitinib Second Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2)

Arm type	Experimental
Investigational medicinal product name	everolimus
Investigational medicinal product code	RAD001
Other name	
Pharmaceutical forms	Capsule, hard, Tablet
Routes of administration	Oral use

Dosage and administration details:

Everolimus was administered orally at 10 mg/day. Everolimus was formulated as tablets of 5 mg strength.

Arm title	sunitinib 1L/everolimus 2L

Arm description:

sunitinib First Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2) everolimus Second Line: 10 mg orally, once daily (two 5 mg tablets), continuous treatment

Arm type	Experimental
Investigational medicinal product name	sunitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Sunitinib was supplied as hard gelatin capsules of 12.5 mg, 25 mg, or 50 mg strength according to local practice.

Number of subjects in period 2	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L
Started	128	116
Completed	79	80
Not completed	49	36
Adverse event, serious fatal	5	2
Consent withdrawn by subject	7	5
Adverse event, non-fatal	16	20
Administrative problems	19	9
Lost to follow-up	1	-
Missing	1	-

Baseline characteristics

Reporting groups	
Reporting group title	everolimus 1L/sunitinib 2L
Reporting group description:	
everolimus First Line: 10 mg orally, once daily, (two 5 mg tablets), continuous treatment. sunitinib Second Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2)	
Reporting group title	sunitinib 1L/everolimus 2L
Reporting group description:	
sunitinib First Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2) everolimus Second Line: 10 mg orally, once daily (two 5 mg tablets), continuous treatment	

Reporting group values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L	Total
Number of subjects	238	233	471
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	135	144	279
From 65-84 years	100	89	189
85 years and over	3	0	3
Age Continuous Units: years			
arithmetic mean	61.36	60.84	
standard deviation	± 12.102	± 11.627	-
Gender categorical Units: Subjects			
Female	166	176	342
Male	72	57	129

End points

End points reporting groups

Reporting group title	everolimus 1L/sunitinib 2L
Reporting group description:	
everolimus First Line: 10 mg orally, once daily, (two 5 mg tablets), continuous treatment. sunitinib Second Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2)	
Reporting group title	sunitinib 1L/everolimus 2L
Reporting group description:	
sunitinib First Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2) everolimus Second Line: 10 mg orally, once daily (two 5 mg tablets), continuous treatment	
Reporting group title	everolimus 1L/sunitinib 2L
Reporting group description:	
everolimus First Line: 10 mg orally, once daily, (two 5 mg tablets), continuous treatment. sunitinib Second Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2)	
Reporting group title	sunitinib 1L/everolimus 2L
Reporting group description:	
sunitinib First Line: 50 mg orally, once daily, 4 weeks on treatment followed by 2 weeks off (4/2) everolimus Second Line: 10 mg orally, once daily (two 5 mg tablets), continuous treatment	

Primary: Progression Free Survival First-Line (PFS 1-L)

End point title	Progression Free Survival First-Line (PFS 1-L)
End point description:	
PFS_1L based on investigator assessment of radiology data by RECIST 1.0, was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause during or after first-line treatment with everolimus or sunitinib. Radiological assessments : every 12 weeks until disease progression, the start of another antineoplastic therapy or for any other reason.	
End point type	Primary
End point timeframe:	
Time from randomization to date of first disease progression or death during or after 1-L treatment, or last tumor assessment, reported between date of 1st participant randomized until 03-sep-2012, cutoff date (i.e. when 340 PFS-1L events were observed)	

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	7.85 (5.55 to 8.25)	10.71 (8.18 to 11.53)		

Statistical analyses

Statistical analysis title	Cox reggresssion model for PFS-1L
Comparison groups	everolimus 1L/sunitinib 2L v sunitinib 1L/everolimus 2L

Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.77

Notes:

[1] - Primary objective was to assess the non-inferiority of everolimus as compared to Sunitinib in terms of PFS-1L & was based on Bayesian methodology. If the estimated HR for PFS-1L had a value ≤ 1.1, non-inferiority of everolimus to Sunitinib would be declared. Non-inferiority of everolimus compared with Sunitinib as a first-line therapy was not achieved. The estimated HR for PFS-1L was 1.43 which did not satisfy the protocol-defined non-inferiority margin of a HR ≤ 1.1.

Statistical analysis title	Cox regression model for PFS-1L
Comparison groups	everolimus 1L/sunitinib 2L v sunitinib 1L/everolimus 2L
Number of subjects included in analysis	471
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Regression, Cox
Parameter estimate	Log hazard ratio
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.15
upper limit	1.77

Secondary: Progression-free survival combined (PFS-C)

End point title	Progression-free survival combined (PFS-C)

End point description:

PFS-C (1L and 2L study drugs combined) was a composite endpoint which combined both lines of study treatment. It was defined as the time from the date of randomization to the first of the following: date of death due to any cause, or date of the first radiologically documented progression disease during or after the second-line treatment period for patients with a radiologically documented progression disease in the first-line treatment period and who had crossed-over to second-line treatment no more than 6 weeks after progression. Radiological assessments : every 12 weeks until disease progression, the start of another antineoplastic therapy or for any other reason.

End point type	Secondary

End point timeframe:

Time from randomization to date of 1st disease progression during or after 2-L treatment or date of death, or last tumor assessment, reported between date of 1st participant randomized until 3 years after last patient randomized (date cutoff : 16Jun2014)

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	21.68 (15.05 to 26.71)	22.18 (16.03 to 29.83)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival was defined as the time from date of randomization to date of death due to any cause. The analysis of OS included all deaths in the FAS regardless of when they were observed.

End point type	Secondary

End point timeframe:

Time from randomization to the date of death from any cause, reported between the date of first participant randomized and up to 3 years after the last participant randomized (date cutoff: 16Jun2014)

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	22.41 (18.6 to 33.28)	29.47 (22.83 to 33.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) - First -Line (1-L)

End point title	Overall response rate (ORR) - First -Line (1-L)

End point description:

ORR was defined as the number of participants with best overall response (BOR) of complete response (CR) or partial response (PR) and was based on investigator assessment of radiology data per RECIST. Participants with best overall response of 'Unknown' were treated as non-responders in the calculation of the ORR. Confirmed CR = at least two determinations of CR at least 4 weeks apart before progression. Confirmed PR = at least two determinations of PR or better at least 4 weeks apart before progression. CR required a disappearance of all target and non-target lesions. PR required at least a 30% decrease in the sum of the longest diameters of all target lesions, taking as a reference the baseline sum of the longest diameters. Radiological assessments : every 12 weeks until disease progression, the start of another antineoplastic therapy or for any other reason.

End point type	Secondary

End point timeframe:

time from first participant randomized until 03-sep-2012, cutoff date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: percentage of participants				
Complete Response (CR)	1	3		
Partial Response (PR)	18	59		
Overall Response Rate (CR + PR)	19	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DoR) - First-Line (1-L)

End point title	Duration of response (DoR) - First-Line (1-L)

End point description:

Duration of overall response (CR or PR) applies only to patients whose Best Overall Response (BOR) was Complete Response (CR) or Partial Response (PR) during the first-line treatment period. The start date was the date of first documented response (CR or PR) during the first-line treatment and the end date was the date of the event defined as the first documented progression or death due to underlying cancer during or after the same treatment line.

End point type	Secondary

End point timeframe:

Time from first documented response date to date of disease progression, death from any cause during or after the 1-L period or last tumor assessment, reported between the date of first participant randomized until 03-sep-2012, cut-off date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	62		
Units: Months				
median (confidence interval 95%)	13.37 (8.3 to 999)	17.25 (11.4 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the FKSI-DRS risk score by at least 3 score units by first-line drug

End point title	Time to definitive deterioration of the FKSI-DRS risk score by at least 3 score units by first-line drug

End point description:

The Functional Assessment of Cancer Therapy – Kidney Symptom Index, Disease Related Symptoms (FKSI-DRS) is a set of items to assess symptoms experienced by patients with advanced kidney cancer. These symptoms include fatigue, pain, weight loss, dyspnea, cough, fever and hematuria. Each item is scored on a 5-point scale (0 = not at all; 4 = very much). The FKSI-DRS total score ranges from 0 (most severe symptoms) to 36 (no symptoms). Definitive deterioration was defined as a decrease by at least 3 units compared to baseline, with no later increase above this threshold observed during the 1-L of treatment. A single measure reporting a decrease of at least 3 units was considered definitive only if it was the last one available for the patient. PRO questionnaires were to be completed on day 1, day 28 of every cycle, at the end of treatment visit, at the 28-day FUP visit, and monthly thereafter for up to 3 months or until the initiation of another anticancer therapy.

End point type	Secondary

End point timeframe:

Time from randomization to date of definitive deterioration (defined as no later increase above threshold observed during the 1-L period), or date of last assessment, reported between date of first patient randomized until 03-sep-2012, cutoff date)

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	12.65 (7.9 to 19.4)	16.66 (13.7 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the FKSI-DRS risk score by at least 3 score units by first and second-line drugs combined

End point title	Time to definitive deterioration of the FKSI-DRS risk score by at least 3 score units by first and second-line drugs combined

End point description:

The Functional Assessment of Cancer Therapy – Kidney Symptom Index, Disease Related Symptoms (FKSI-DRS) is a set of items to assess symptoms experienced by patients with advanced kidney cancer. These symptoms include fatigue, pain, weight loss, dyspnea, cough, fever and hematuria. Each item is scored on a 5-point scale (0 = not at all; 4 = very much). The FKSI-DRS total score ranges from 0 (most severe symptoms) to 36 (no symptoms). Definitive deterioration was defined as a decrease by at least 3 units compared to baseline, with no later increase above this threshold observed during the 1-L or 2-L treatment. A single measure reporting a decrease of at least 3 units was considered definitive only if it was the last one available for the patient. PRO questionnaires were to be completed on day 1, day 28 of every cycle, at the end of treatment visit, at the 28-day FUP visit, and monthly thereafter for up to 3 months or until the initiation of another anticancer therapy.

End point type	Secondary

End point timeframe:

Time from randomization to date of definitive deterioration (defined as no later increase above threshold observed during the 1-L or 2-L period), or date of last assessment, reported between date of first patient randomized until 03-sep-2012, cutoff date)

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	14.23 (12 to 19.4)	15.97 (13.7 to 20.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the physical functioning (PF) scale of the EORTC QLQ-C30 - by First-Line (1L) drug

End point title	Time to definitive deterioration of the physical functioning (PF) scale of the EORTC QLQ-C30 - by First-Line (1L) drug

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items. These include a global health status/QoL scale, five functional scales, three symptom scales, and six single items. The standardized score for the PF, fatigue subscales and global health status ranges from 0 to 100, with a higher score representing a high level of functioning/high level of symptom/high quality of life. Definitive deterioration by at least 10% was defined as a decrease in score by at least 10% compared to baseline, with no later increase above this threshold observed during the first line of treatment. A single measure reporting a decrease of at least 10% was considered definitive only if it was the last one available for the participant.

End point type	Secondary

End point timeframe:

Time from randomization to the date of definitive deterioration (defined as no later increase above the threshold observed during the 1-L period), or date of last assessment, reported between date of first patient randomized until 03-sep-2012, cutoff date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	13.47 (7.9 to 20.6)	14.03 (12.1 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the physical functioning scale of the EORTC QLQ-C30 - by First and Second-Line drugs combined

End point title	Time to definitive deterioration of the physical functioning scale of the EORTC QLQ-C30 - by First and Second-Line drugs combined

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items. These include a global health status/QoL scale, five functional scales, three symptom scales, and six single items.The standardized score for the PF, fatigue subscales and global health status ranges from 0 to 100, with a higher score representing a high level of functioning/high level of symptom/high quality of life. Definitive deterioration by at least 10% was defined as a decrease in score by at least 10% compared to baseline, with no later increase above this threshold observed during the first line or second line treatment. A single measure reporting a decrease of at least 10% was considered definitive only if it was the last one available for the participant.

End point type	Secondary

End point timeframe:

Time from randomization to date of definitive deterioration (defined as no later increase above threshold observed during the 1-L or 2-L period), or date of last assessment, reported between date of 1st patient randomized until 03-sep-2012, cutoff date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	12.25 (9.5 to 16.3)	14.03 (12 to 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the global health status/QoL scores of the EORTC QLQ-C30 by First-Line drug

End point title	Time to definitive deterioration of the global health status/QoL scores of the EORTC QLQ-C30 by First-Line drug

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items. These include a global health status/QoL scale, five functional scales, three symptom scales, and six single items.The standardized score for the PF, fatigue subscales and global health status ranges from 0 to 100, with a higher score representing a high level of functioning/high level of symptom/high quality of life. Definitive deterioration by at least 10% was defined as a decrease in score by at least 10% compared to baseline, with no later increase above this threshold observed during the first line of treatment. A single measure reporting a decrease of at least 10% was considered definitive only if it was the last one available for the participant.

End point type	Secondary

End point timeframe:

Time from randomization to the date of definitive deterioration (defined as no later increase above the threshold observed during the 1-L period), or date of last assessment, reported between date of first patient randomized until 03-sep-2012, cutoff date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	7.92 (5.6 to 12.1)	12.25 (7.9 to 14.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the global health status/QoL scores of the EORTC QLQ-C30 by First and Second-Line drugs combined

End point title	Time to definitive deterioration of the global health status/QoL scores of the EORTC QLQ-C30 by First and Second-Line drugs combined

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items. These include a global health status/QoL scale, five functional scales, three symptom scales, and six single items. The standardized score for the PF, fatigue subscales and global health status ranges from 0 to 100, with a higher score representing a high level of functioning/high level of symptom/high quality of life. Definitive deterioration by at least 10% was defined as a decrease in score by at least 10% compared to baseline, with no later increase above this threshold observed during the first line or second line treatment. A single measure reporting a decrease of at least 10% was considered definitive only if it was the last one available for the participant.

End point type	Secondary

End point timeframe:

Time from randomization to date of definitive deterioration (defined as no later increase above threshold observed during the 1-L or 2-L period), or date of last assessment, reported between dates of 1st patient randomized until 03-sep-2012, cutoff date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	10.84 (7.5 to 13.8)	12.71 (10.5 to 14.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the fatigue scale of the EORTC QLQ-C30 by First-Line drug

End point title	Time to definitive deterioration of the fatigue scale of the EORTC QLQ-C30 by First-Line drug

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items. These include a global health status/QoL scale, five functional scales, three symptom scales, and six single items.The standardized score for the PF, fatigue subscales and global health status ranges from 0 to 100, with a higher score representing a high level of functioning/high level of symptom/high quality of life. Definitive deterioration by at least 10% was defined as a decrease in score by at least 10% compared to baseline, with no later increase above this threshold observed during the first line of treatment. A single measure reporting a decrease of at least 10% was considered definitive only if it was the last one available for the participant.

End point type	Secondary

End point timeframe:

Time from randomization to the date of definitive deterioration (defined as no later increase above the threshold observed during the 1-L period), or date of last assessment, reported between date of first patient randomized until 03-sep-2012, cutoff date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
median (confidence interval 95%)	9.2 (6.2 to 12.6)	11.37 (9.3 to 13.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of the fatigue scale of the EORTC QLQ-C30 by First and Second-Line drugs combined

End point title	Time to definitive deterioration of the fatigue scale of the EORTC QLQ-C30 by First and Second-Line drugs combined

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) contains 30 items. These include a global health status/QoL scale, five functional scales, three symptom scales, and six single items. The standardized score for the PF, fatigue subscales and global health status ranges from 0 to 100, with a higher score representing a high level of functioning/high level of symptom/high quality of life. Definitive deterioration by at least 10% was defined as a decrease in score by at least 10% compared to baseline, with no later increase above this threshold observed during the first line or second line treatment. A single measure reporting a decrease of at least 10% was considered definitive only if it was the last one available for the participant.

End point type	Secondary

End point timeframe:

Time from randomization to date of definitive deterioration (defined as no later increase above threshold observed during the 1-L or 2-L period), or date of last assessment, reported between date of 1st patient randomized until 03-sep-2012, cutoff date

End point values	everolimus 1L/sunitinib 2L	sunitinib 1L/everolimus 2L		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	233		
Units: Months				
arithmetic mean (confidence interval 95%)	11.56 (7.9 to 14.1)	13.34 (10.8 to 15.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until L:ast Patient Last Visit (LPLV). All Adverse Events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Everolimus 1L

Reporting group description:

Everolimus 1L

Reporting group title	Sunitinib 1L

Reporting group description:

Sunitinib 1L

Reporting group title	Everolimus 2L

Reporting group description:

Everolimus 2L

Reporting group title	Sunitinib 2L

Reporting group description:

Sunitinib 2L

Serious adverse events	Everolimus 1L	Sunitinib 1L	Everolimus 2L
Total subjects affected by serious adverse events			
subjects affected / exposed	107 / 238 (44.96%)	113 / 231 (48.92%)	43 / 116 (37.07%)
number of deaths (all causes)	34	15	11
number of deaths resulting from adverse events	2	3	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant ascites			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour associated fever			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Waldenstrom's macroglobulinaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 238 (0.00%)	4 / 231 (1.73%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 238 (0.00%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	3 / 238 (1.26%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 238 (0.84%)	4 / 231 (1.73%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	1 / 2	2 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	5 / 238 (2.10%)	3 / 231 (1.30%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	2 / 5	3 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 238 (1.26%)	3 / 231 (1.30%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 3	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			

subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucous membrane disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 238 (0.42%)	3 / 231 (1.30%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic mass			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			

subjects affected / exposed	1 / 238 (0.42%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	6 / 238 (2.52%)	7 / 231 (3.03%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vaginal haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	2 / 238 (0.84%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	11 / 238 (4.62%)	8 / 231 (3.46%)	5 / 116 (4.31%)
occurrences causally related to treatment / all	3 / 11	1 / 10	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epistaxis			
subjects affected / exposed	1 / 238 (0.42%)	2 / 231 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	3 / 238 (1.26%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive airways disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	8 / 238 (3.36%)	7 / 231 (3.03%)	5 / 116 (4.31%)
occurrences causally related to treatment / all	0 / 10	0 / 8	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	4 / 238 (1.68%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 238 (0.00%)	2 / 231 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary granuloma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 238 (0.42%)	2 / 231 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	6 / 238 (2.52%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Confusional state			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disorientation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 238 (1.26%)	3 / 231 (1.30%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	3 / 4	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Body temperature increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine renal clearance decreased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eastern cooperative oncology group performance status worsened			

subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram T wave abnormal			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin I increased			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Femoral neck fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat stroke			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax traumatic			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic pain			

subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scar			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 238 (0.00%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia supraventricular			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	5 / 238 (2.10%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 238 (0.00%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiomyopathy			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 238 (1.26%)	1 / 231 (0.43%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Myocardial ischaemia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			

subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular dysfunction			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain oedema			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysgeusia			

subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningorrhagia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 238 (0.00%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	4 / 238 (1.68%)	2 / 231 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 238 (0.00%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual field defect			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	16 / 238 (6.72%)	3 / 231 (1.30%)	6 / 116 (5.17%)
occurrences causally related to treatment / all	7 / 22	3 / 4	4 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	0 / 238 (0.00%)	9 / 231 (3.90%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	9 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Corneal disorder			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 238 (0.84%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	3 / 238 (1.26%)	6 / 231 (2.60%)	3 / 116 (2.59%)
occurrences causally related to treatment / all	1 / 3	4 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain lower			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	2 / 238 (0.84%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 238 (0.42%)	3 / 231 (1.30%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 238 (0.42%)	3 / 231 (1.30%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	5 / 238 (2.10%)	5 / 231 (2.16%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	5 / 5	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			

subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal obstruction			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal erosion			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 238 (0.42%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haematochezia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	3 / 238 (1.26%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised intraabdominal fluid collection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 238 (0.84%)	3 / 231 (1.30%)	3 / 116 (2.59%)
occurrences causally related to treatment / all	1 / 2	3 / 4	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal ulcer			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral pain			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal adhesions			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	4 / 238 (1.68%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 238 (0.84%)	6 / 231 (2.60%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	2 / 2	6 / 7	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 238 (0.42%)	3 / 231 (1.30%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 2	1 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemobilia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis			

subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised erythema			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 238 (3.36%)	7 / 231 (3.03%)	3 / 116 (2.59%)
occurrences causally related to treatment / all	3 / 8	2 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anuria			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Azotaemia			
subjects affected / exposed	2 / 238 (0.84%)	2 / 231 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			

subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	5 / 238 (2.10%)	2 / 231 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	2 / 5	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal vein thrombosis			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			

subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 238 (0.00%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	3 / 238 (1.26%)	1 / 231 (0.43%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	0 / 3	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 238 (0.84%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscular weakness			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 238 (0.42%)	3 / 231 (1.30%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral lesion			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess oral			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillus infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial prostatitis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 238 (0.84%)	2 / 231 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 2	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 238 (0.42%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal viral infection			

subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis A			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected bites			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	2 / 238 (0.84%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	14 / 238 (5.88%)	8 / 231 (3.46%)	7 / 116 (6.03%)
occurrences causally related to treatment / all	4 / 16	0 / 8	3 / 8
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 238 (0.84%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonella sepsis			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 238 (0.84%)	3 / 231 (1.30%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	4 / 238 (1.68%)	2 / 231 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 238 (1.26%)	3 / 231 (1.30%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	1 / 3	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	7 / 238 (2.94%)	6 / 231 (2.60%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	3 / 8	4 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 238 (0.00%)	0 / 231 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Feeding disorder			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food intolerance			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 238 (0.42%)	5 / 231 (2.16%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			

subjects affected / exposed	4 / 238 (1.68%)	1 / 231 (0.43%)	4 / 116 (3.45%)
occurrences causally related to treatment / all	3 / 4	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	2 / 238 (0.84%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 238 (0.42%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 238 (0.42%)	0 / 231 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			

subjects affected / exposed	0 / 238 (0.00%)	1 / 231 (0.43%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Sunitinib 2L		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 128 (38.28%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant ascites			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Malignant neoplasm progression				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to bone				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal cell carcinoma				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour associated fever				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Waldenstrom's macroglobulinaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				

Aortic aneurysm				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic dissection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	4 / 128 (3.13%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Generalised oedema				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised oedema				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Mucous membrane disorder				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				

subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic mass			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Performance status decreased			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral swelling			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pelvic pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine haemorrhage				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine polyp				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vaginal haemorrhage				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchial disorder				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cough			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Obstructive airways disorder			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			

subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary granuloma				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Completed suicide			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Disorientation			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental status changes			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Panic attack			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Body temperature increased			

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Creatinine renal clearance decreased				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eastern cooperative oncology group performance status worsened				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram T wave abnormal				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Troponin				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Troponin I increased				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Troponin increased				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femoral neck fracture				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Heat stroke				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				

subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax traumatic				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haematoma				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post-traumatic pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Scar				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subdural haemorrhage				

subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Arrhythmia supraventricular				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Atrial flutter				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block second degree				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				

subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stress cardiomyopathy				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular dysfunction				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Balance disorder				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Brain oedema				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Coma				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysgeusia				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoaesthesia				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracranial pressure increased				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningorrhagia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuralgia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Status epilepticus				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual field defect				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Coagulopathy				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymph node pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphopenia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Corneal disorder				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diplopia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Optic ischaemic neuropathy				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Visual impairment				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal distension				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Abdominal pain lower				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Anal fissure				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal obstruction				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal erosion				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal inflammation				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gingival bleeding				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised intraabdominal fluid collection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophageal ulcer				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oral pain				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Peritoneal adhesions				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemobilia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic function abnormal				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic haemorrhage				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperbilirubinaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Jaundice cholestatic				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Angioedema				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised erythema				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Anuria				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Azotaemia				

subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calculus ureteric			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysuria			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrotic syndrome			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proteinuria			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			

subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal vein thrombosis			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract obstruction			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		

Bone pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flank pain				
subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Fracture pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis of jaw				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				

subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Spinal column stenosis				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertebral lesion				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal abscess				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abscess oral				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal abscess				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspergillus infection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial prostatitis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial sepsis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cellulitis				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile infection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Empyema				

subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal viral infection			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis A			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infected bites			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Kidney infection			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Localised infection			

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 128 (2.34%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Salmonella sepsis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	6 / 128 (4.69%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrolyte imbalance				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Feeding disorder				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Food intolerance				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gout				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperglycaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoalbuminaemia				
subjects affected / exposed	1 / 128 (0.78%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				

subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypovolaemia				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Everolimus 1L	Sunitinib 1L	Everolimus 2L
Total subjects affected by non-serious adverse events			
subjects affected / exposed	230 / 238 (96.64%)	228 / 231 (98.70%)	107 / 116 (92.24%)
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 238 (10.08%)	81 / 231 (35.06%)	6 / 116 (5.17%)
occurrences (all)	29	121	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 238 (12.61%)	53 / 231 (22.94%)	15 / 116 (12.93%)
occurrences (all)	39	109	17
Chills			
subjects affected / exposed	22 / 238 (9.24%)	17 / 231 (7.36%)	5 / 116 (4.31%)
occurrences (all)	28	17	5
Face oedema			

subjects affected / exposed	6 / 238 (2.52%)	18 / 231 (7.79%)	1 / 116 (0.86%)
occurrences (all)	6	32	1
Fatigue			
subjects affected / exposed	108 / 238 (45.38%)	122 / 231 (52.81%)	40 / 116 (34.48%)
occurrences (all)	137	204	47
Non-cardiac chest pain			
subjects affected / exposed	23 / 238 (9.66%)	22 / 231 (9.52%)	11 / 116 (9.48%)
occurrences (all)	26	24	13
Oedema peripheral			
subjects affected / exposed	60 / 238 (25.21%)	42 / 231 (18.18%)	23 / 116 (19.83%)
occurrences (all)	93	60	35
Peripheral swelling			
subjects affected / exposed	12 / 238 (5.04%)	6 / 231 (2.60%)	5 / 116 (4.31%)
occurrences (all)	13	7	5
Pyrexia			
subjects affected / exposed	53 / 238 (22.27%)	33 / 231 (14.29%)	17 / 116 (14.66%)
occurrences (all)	73	40	22
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	91 / 238 (38.24%)	55 / 231 (23.81%)	28 / 116 (24.14%)
occurrences (all)	126	71	32
Dyspnoea			
subjects affected / exposed	57 / 238 (23.95%)	39 / 231 (16.88%)	24 / 116 (20.69%)
occurrences (all)	70	46	25
Dyspnoea exertional			
subjects affected / exposed	13 / 238 (5.46%)	10 / 231 (4.33%)	7 / 116 (6.03%)
occurrences (all)	13	12	8
Epistaxis			
subjects affected / exposed	43 / 238 (18.07%)	46 / 231 (19.91%)	12 / 116 (10.34%)
occurrences (all)	60	75	16
Oropharyngeal pain			
subjects affected / exposed	23 / 238 (9.66%)	12 / 231 (5.19%)	10 / 116 (8.62%)
occurrences (all)	27	14	10
Pneumonitis			

subjects affected / exposed	16 / 238 (6.72%)	0 / 231 (0.00%)	7 / 116 (6.03%)
occurrences (all)	20	0	7
Productive cough			
subjects affected / exposed	18 / 238 (7.56%)	10 / 231 (4.33%)	11 / 116 (9.48%)
occurrences (all)	22	11	15
Rhinorrhoea			
subjects affected / exposed	20 / 238 (8.40%)	11 / 231 (4.76%)	7 / 116 (6.03%)
occurrences (all)	25	12	10
Psychiatric disorders			
Anxiety			
subjects affected / exposed	18 / 238 (7.56%)	16 / 231 (6.93%)	4 / 116 (3.45%)
occurrences (all)	20	18	4
Depression			
subjects affected / exposed	16 / 238 (6.72%)	10 / 231 (4.33%)	3 / 116 (2.59%)
occurrences (all)	16	10	3
Insomnia			
subjects affected / exposed	36 / 238 (15.13%)	28 / 231 (12.12%)	13 / 116 (11.21%)
occurrences (all)	44	35	13
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 238 (5.46%)	15 / 231 (6.49%)	4 / 116 (3.45%)
occurrences (all)	15	19	4
Blood creatinine increased			
subjects affected / exposed	30 / 238 (12.61%)	28 / 231 (12.12%)	15 / 116 (12.93%)
occurrences (all)	34	51	17
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 238 (4.20%)	13 / 231 (5.63%)	4 / 116 (3.45%)
occurrences (all)	10	16	5
Haemoglobin decreased			
subjects affected / exposed	18 / 238 (7.56%)	19 / 231 (8.23%)	9 / 116 (7.76%)
occurrences (all)	26	25	17
Neutrophil count decreased			
subjects affected / exposed	0 / 238 (0.00%)	15 / 231 (6.49%)	1 / 116 (0.86%)
occurrences (all)	0	21	1
Platelet count decreased			

subjects affected / exposed	0 / 238 (0.00%)	17 / 231 (7.36%)	0 / 116 (0.00%)
occurrences (all)	0	31	0
Weight decreased			
subjects affected / exposed	53 / 238 (22.27%)	36 / 231 (15.58%)	14 / 116 (12.07%)
occurrences (all)	56	42	14
Nervous system disorders			
Dizziness			
subjects affected / exposed	31 / 238 (13.03%)	25 / 231 (10.82%)	9 / 116 (7.76%)
occurrences (all)	38	35	9
Dysgeusia			
subjects affected / exposed	53 / 238 (22.27%)	71 / 231 (30.74%)	8 / 116 (6.90%)
occurrences (all)	60	110	9
Headache			
subjects affected / exposed	47 / 238 (19.75%)	43 / 231 (18.61%)	9 / 116 (7.76%)
occurrences (all)	68	63	9
Neuropathy peripheral			
subjects affected / exposed	6 / 238 (2.52%)	12 / 231 (5.19%)	2 / 116 (1.72%)
occurrences (all)	6	13	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	62 / 238 (26.05%)	50 / 231 (21.65%)	33 / 116 (28.45%)
occurrences (all)	88	71	43
Leukopenia			
subjects affected / exposed	7 / 238 (2.94%)	14 / 231 (6.06%)	1 / 116 (0.86%)
occurrences (all)	7	17	4
Neutropenia			
subjects affected / exposed	8 / 238 (3.36%)	44 / 231 (19.05%)	4 / 116 (3.45%)
occurrences (all)	10	73	4
Thrombocytopenia			
subjects affected / exposed	10 / 238 (4.20%)	57 / 231 (24.68%)	4 / 116 (3.45%)
occurrences (all)	18	95	6
Eye disorders			
Periorbital oedema			
subjects affected / exposed	2 / 238 (0.84%)	11 / 231 (4.76%)	1 / 116 (0.86%)
occurrences (all)	2	13	1
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	7 / 238 (2.94%)	4 / 231 (1.73%)	4 / 116 (3.45%)
occurrences (all)	8	4	4
Abdominal distension			
subjects affected / exposed	9 / 238 (3.78%)	15 / 231 (6.49%)	1 / 116 (0.86%)
occurrences (all)	9	18	2
Abdominal pain			
subjects affected / exposed	40 / 238 (16.81%)	33 / 231 (14.29%)	13 / 116 (11.21%)
occurrences (all)	50	40	16
Abdominal pain upper			
subjects affected / exposed	21 / 238 (8.82%)	32 / 231 (13.85%)	4 / 116 (3.45%)
occurrences (all)	23	42	4
Aphthous stomatitis			
subjects affected / exposed	14 / 238 (5.88%)	1 / 231 (0.43%)	1 / 116 (0.86%)
occurrences (all)	19	1	2
Constipation			
subjects affected / exposed	48 / 238 (20.17%)	57 / 231 (24.68%)	14 / 116 (12.07%)
occurrences (all)	55	71	16
Diarrhoea			
subjects affected / exposed	92 / 238 (38.66%)	134 / 231 (58.01%)	17 / 116 (14.66%)
occurrences (all)	151	361	22
Dry mouth			
subjects affected / exposed	13 / 238 (5.46%)	18 / 231 (7.79%)	4 / 116 (3.45%)
occurrences (all)	16	21	4
Dyspepsia			
subjects affected / exposed	12 / 238 (5.04%)	56 / 231 (24.24%)	7 / 116 (6.03%)
occurrences (all)	16	82	9
Dysphagia			
subjects affected / exposed	14 / 238 (5.88%)	8 / 231 (3.46%)	4 / 116 (3.45%)
occurrences (all)	14	8	4
Gastritis			
subjects affected / exposed	6 / 238 (2.52%)	12 / 231 (5.19%)	0 / 116 (0.00%)
occurrences (all)	6	19	0
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 238 (2.52%)	24 / 231 (10.39%)	4 / 116 (3.45%)
occurrences (all)	9	29	4

Mouth ulceration			
subjects affected / exposed	16 / 238 (6.72%)	7 / 231 (3.03%)	8 / 116 (6.90%)
occurrences (all)	20	9	15
Nausea			
subjects affected / exposed	83 / 238 (34.87%)	115 / 231 (49.78%)	21 / 116 (18.10%)
occurrences (all)	104	193	25
Oral pain			
subjects affected / exposed	7 / 238 (2.94%)	12 / 231 (5.19%)	1 / 116 (0.86%)
occurrences (all)	7	17	1
Stomatitis			
subjects affected / exposed	125 / 238 (52.52%)	135 / 231 (58.44%)	37 / 116 (31.90%)
occurrences (all)	197	267	49
Vomiting			
subjects affected / exposed	48 / 238 (20.17%)	67 / 231 (29.00%)	9 / 116 (7.76%)
occurrences (all)	77	119	13
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	7 / 238 (2.94%)	15 / 231 (6.49%)	0 / 116 (0.00%)
occurrences (all)	7	15	0
Dermatitis acneiform			
subjects affected / exposed	18 / 238 (7.56%)	6 / 231 (2.60%)	4 / 116 (3.45%)
occurrences (all)	26	6	4
Dry skin			
subjects affected / exposed	26 / 238 (10.92%)	31 / 231 (13.42%)	8 / 116 (6.90%)
occurrences (all)	31	37	12
Erythema			
subjects affected / exposed	8 / 238 (3.36%)	15 / 231 (6.49%)	4 / 116 (3.45%)
occurrences (all)	9	17	7
Hair colour changes			
subjects affected / exposed	1 / 238 (0.42%)	16 / 231 (6.93%)	1 / 116 (0.86%)
occurrences (all)	1	17	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	13 / 238 (5.46%)	92 / 231 (39.83%)	2 / 116 (1.72%)
occurrences (all)	13	271	2
Pruritus			

subjects affected / exposed	41 / 238 (17.23%)	29 / 231 (12.55%)	11 / 116 (9.48%)
occurrences (all)	50	31	12
Rash			
subjects affected / exposed	89 / 238 (37.39%)	56 / 231 (24.24%)	22 / 116 (18.97%)
occurrences (all)	150	93	30
Skin discolouration			
subjects affected / exposed	1 / 238 (0.42%)	11 / 231 (4.76%)	0 / 116 (0.00%)
occurrences (all)	1	13	0
Yellow skin			
subjects affected / exposed	1 / 238 (0.42%)	28 / 231 (12.12%)	0 / 116 (0.00%)
occurrences (all)	1	31	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	16 / 238 (6.72%)	11 / 231 (4.76%)	5 / 116 (4.31%)
occurrences (all)	19	12	5
Haematuria			
subjects affected / exposed	5 / 238 (2.10%)	16 / 231 (6.93%)	2 / 116 (1.72%)
occurrences (all)	6	18	4
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 238 (0.84%)	14 / 231 (6.06%)	0 / 116 (0.00%)
occurrences (all)	2	15	0
Hypothyroidism			
subjects affected / exposed	5 / 238 (2.10%)	56 / 231 (24.24%)	1 / 116 (0.86%)
occurrences (all)	5	57	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	39 / 238 (16.39%)	30 / 231 (12.99%)	15 / 116 (12.93%)
occurrences (all)	49	44	17
Back pain			
subjects affected / exposed	46 / 238 (19.33%)	54 / 231 (23.38%)	19 / 116 (16.38%)
occurrences (all)	60	70	20
Flank pain			
subjects affected / exposed	17 / 238 (7.14%)	12 / 231 (5.19%)	7 / 116 (6.03%)
occurrences (all)	19	16	9
Muscle spasms			

subjects affected / exposed	10 / 238 (4.20%)	10 / 231 (4.33%)	1 / 116 (0.86%)
occurrences (all)	11	16	3
Muscular weakness			
subjects affected / exposed	6 / 238 (2.52%)	12 / 231 (5.19%)	3 / 116 (2.59%)
occurrences (all)	7	13	3
Musculoskeletal chest pain			
subjects affected / exposed	10 / 238 (4.20%)	7 / 231 (3.03%)	4 / 116 (3.45%)
occurrences (all)	12	11	4
Musculoskeletal pain			
subjects affected / exposed	19 / 238 (7.98%)	17 / 231 (7.36%)	4 / 116 (3.45%)
occurrences (all)	20	19	4
Myalgia			
subjects affected / exposed	14 / 238 (5.88%)	18 / 231 (7.79%)	6 / 116 (5.17%)
occurrences (all)	15	25	6
Neck pain			
subjects affected / exposed	9 / 238 (3.78%)	12 / 231 (5.19%)	2 / 116 (1.72%)
occurrences (all)	11	13	3
Pain in extremity			
subjects affected / exposed	32 / 238 (13.45%)	36 / 231 (15.58%)	11 / 116 (9.48%)
occurrences (all)	43	55	13
Infections and infestations			
Influenza			
subjects affected / exposed	12 / 238 (5.04%)	6 / 231 (2.60%)	2 / 116 (1.72%)
occurrences (all)	14	6	2
Nasopharyngitis			
subjects affected / exposed	24 / 238 (10.08%)	16 / 231 (6.93%)	2 / 116 (1.72%)
occurrences (all)	30	17	2
Pneumonia			
subjects affected / exposed	12 / 238 (5.04%)	2 / 231 (0.87%)	8 / 116 (6.90%)
occurrences (all)	13	2	9
Upper respiratory tract infection			
subjects affected / exposed	22 / 238 (9.24%)	29 / 231 (12.55%)	9 / 116 (7.76%)
occurrences (all)	31	38	11
Urinary tract infection			
subjects affected / exposed	19 / 238 (7.98%)	20 / 231 (8.66%)	5 / 116 (4.31%)
occurrences (all)	30	37	9

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	75 / 238 (31.51%)	82 / 231 (35.50%)	32 / 116 (27.59%)
occurrences (all)	93	130	34
Dehydration			
subjects affected / exposed	12 / 238 (5.04%)	21 / 231 (9.09%)	4 / 116 (3.45%)
occurrences (all)	13	27	5
Hypercholesterolaemia			
subjects affected / exposed	19 / 238 (7.98%)	8 / 231 (3.46%)	5 / 116 (4.31%)
occurrences (all)	22	8	5
Hyperglycaemia			
subjects affected / exposed	37 / 238 (15.55%)	13 / 231 (5.63%)	17 / 116 (14.66%)
occurrences (all)	51	22	20
Hyperkalaemia			
subjects affected / exposed	10 / 238 (4.20%)	10 / 231 (4.33%)	6 / 116 (5.17%)
occurrences (all)	10	14	6
Hypertriglyceridaemia			
subjects affected / exposed	17 / 238 (7.14%)	12 / 231 (5.19%)	4 / 116 (3.45%)
occurrences (all)	20	22	5

Non-serious adverse events	Sunitinib 2L		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 128 (96.88%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	42 / 128 (32.81%)		
occurrences (all)	52		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	20 / 128 (15.63%)		
occurrences (all)	32		
Chills			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	10		
Face oedema			
subjects affected / exposed	9 / 128 (7.03%)		
occurrences (all)	12		

Fatigue			
subjects affected / exposed	49 / 128 (38.28%)		
occurrences (all)	69		
Non-cardiac chest pain			
subjects affected / exposed	11 / 128 (8.59%)		
occurrences (all)	13		
Oedema peripheral			
subjects affected / exposed	26 / 128 (20.31%)		
occurrences (all)	39		
Peripheral swelling			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	18 / 128 (14.06%)		
occurrences (all)	26		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 128 (14.84%)		
occurrences (all)	27		
Dyspnoea			
subjects affected / exposed	19 / 128 (14.84%)		
occurrences (all)	24		
Dyspnoea exertional			
subjects affected / exposed	6 / 128 (4.69%)		
occurrences (all)	6		
Epistaxis			
subjects affected / exposed	13 / 128 (10.16%)		
occurrences (all)	28		
Oropharyngeal pain			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	8		
Pneumonitis			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences (all)	0		
Productive cough			

subjects affected / exposed	9 / 128 (7.03%)		
occurrences (all)	9		
Rhinorrhoea			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences (all)	7		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences (all)	4		
Insomnia			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	10		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences (all)	3		
Blood creatinine increased			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 128 (3.91%)		
occurrences (all)	5		
Haemoglobin decreased			
subjects affected / exposed	5 / 128 (3.91%)		
occurrences (all)	6		
Neutrophil count decreased			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences (all)	8		
Platelet count decreased			
subjects affected / exposed	6 / 128 (4.69%)		
occurrences (all)	8		
Weight decreased			

subjects affected / exposed	16 / 128 (12.50%)		
occurrences (all)	18		
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 128 (10.16%)		
occurrences (all)	15		
Dysgeusia			
subjects affected / exposed	30 / 128 (23.44%)		
occurrences (all)	38		
Headache			
subjects affected / exposed	17 / 128 (13.28%)		
occurrences (all)	18		
Neuropathy peripheral			
subjects affected / exposed	5 / 128 (3.91%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 128 (14.06%)		
occurrences (all)	23		
Leukopenia			
subjects affected / exposed	6 / 128 (4.69%)		
occurrences (all)	7		
Neutropenia			
subjects affected / exposed	16 / 128 (12.50%)		
occurrences (all)	23		
Thrombocytopenia			
subjects affected / exposed	30 / 128 (23.44%)		
occurrences (all)	39		
Eye disorders			
Periorbital oedema			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences (all)	13		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences (all)	7		
Abdominal distension			

subjects affected / exposed	10 / 128 (7.81%)			
occurrences (all)	15			
Abdominal pain				
subjects affected / exposed	15 / 128 (11.72%)			
occurrences (all)	22			
Abdominal pain upper				
subjects affected / exposed	12 / 128 (9.38%)			
occurrences (all)	14			
Aphthous stomatitis				
subjects affected / exposed	0 / 128 (0.00%)			
occurrences (all)	0			
Constipation				
subjects affected / exposed	23 / 128 (17.97%)			
occurrences (all)	31			
Diarrhoea				
subjects affected / exposed	69 / 128 (53.91%)			
occurrences (all)	125			
Dry mouth				
subjects affected / exposed	3 / 128 (2.34%)			
occurrences (all)	4			
Dyspepsia				
subjects affected / exposed	25 / 128 (19.53%)			
occurrences (all)	28			
Dysphagia				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences (all)	2			
Gastritis				
subjects affected / exposed	2 / 128 (1.56%)			
occurrences (all)	3			
Gastrooesophageal reflux disease				
subjects affected / exposed	9 / 128 (7.03%)			
occurrences (all)	9			
Mouth ulceration				
subjects affected / exposed	5 / 128 (3.91%)			
occurrences (all)	9			
Nausea				

subjects affected / exposed	48 / 128 (37.50%)		
occurrences (all)	82		
Oral pain			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences (all)	11		
Stomatitis			
subjects affected / exposed	36 / 128 (28.13%)		
occurrences (all)	48		
Vomiting			
subjects affected / exposed	34 / 128 (26.56%)		
occurrences (all)	77		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 128 (7.03%)		
occurrences (all)	9		
Dermatitis acneiform			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	14		
Erythema			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences (all)	6		
Hair colour changes			
subjects affected / exposed	5 / 128 (3.91%)		
occurrences (all)	7		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	37 / 128 (28.91%)		
occurrences (all)	80		
Pruritus			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences (all)	5		
Rash			

subjects affected / exposed	18 / 128 (14.06%)		
occurrences (all)	23		
Skin discolouration			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	13		
Yellow skin			
subjects affected / exposed	11 / 128 (8.59%)		
occurrences (all)	13		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences (all)	3		
Haematuria			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences (all)	19		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 128 (1.56%)		
occurrences (all)	2		
Hypothyroidism			
subjects affected / exposed	25 / 128 (19.53%)		
occurrences (all)	27		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 128 (14.84%)		
occurrences (all)	25		
Back pain			
subjects affected / exposed	19 / 128 (14.84%)		
occurrences (all)	24		
Flank pain			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	8		
Muscle spasms			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	9		
Muscular weakness			

subjects affected / exposed	9 / 128 (7.03%)		
occurrences (all)	9		
Musculoskeletal chest pain			
subjects affected / exposed	8 / 128 (6.25%)		
occurrences (all)	8		
Musculoskeletal pain			
subjects affected / exposed	11 / 128 (8.59%)		
occurrences (all)	13		
Myalgia			
subjects affected / exposed	6 / 128 (4.69%)		
occurrences (all)	8		
Neck pain			
subjects affected / exposed	1 / 128 (0.78%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	20 / 128 (15.63%)		
occurrences (all)	30		
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences (all)	6		
Pneumonia			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	5 / 128 (3.91%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	3 / 128 (2.34%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	40 / 128 (31.25%)		
occurrences (all)	53		
Dehydration			
subjects affected / exposed	7 / 128 (5.47%)		
occurrences (all)	12		
Hypercholesterolaemia			
subjects affected / exposed	0 / 128 (0.00%)		
occurrences (all)	0		
Hyperglycaemia			
subjects affected / exposed	6 / 128 (4.69%)		
occurrences (all)	7		
Hyperkalaemia			
subjects affected / exposed	4 / 128 (3.13%)		
occurrences (all)	8		
Hypertriglyceridaemia			
subjects affected / exposed	6 / 128 (4.69%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2010	The main purpose of this amendment was the introduction of safety language standard for the everolimus clinical development program:Guidance was provided regarding the identification of patients at risk for HBV infection/reactivation, providing them with prophylactic treatment prior to and throughout everolimus therapy, and monitoring them for reactivation of HBV. Guidance on the management f patients at risk of HVC viral reactivation was also provided. A Adequate contraception was to be used while on study and for 8 weeks after the last dose of study drug. Elevations of serum creatinine had been observed in the everolimus clinical development program. Measurement of blood urea nitrogen or serum creatinine, was recommended prior to the start of therapy with everolimus and periodically thereafter. Hyperglycemia has been reported in everolimus clinical trials. Monitoring of fasting serum glucose was recommended prior to the start of everolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting therapy. The use of live vaccines during treatment with everolimus was not recommended; immunosuppressants, including everolimus, may diminish the effectiveness of vaccination. The fatigue scale of the EORTC QLQ-C30 was added to the list of planned PRO/QoL endpoints. The recruitment period was changed from 12 months to 18 months. The maximum allowed time of the interline period was changed from 6 weeks to 35 days, to have the same time interval as the baseline assessment for second line. This change did not impact any patient on study, because no patient had finished the first-line of treatment. Administration of everolimus was to occur only after meals.
02 February 2011	The amendment revised the initial assumption of a 5% PFS-1L censoring rate. A 20% rate was assumed in the amended protocol, leading to an increase of the sample size (from 390 to 460 patients) & extension of the enrollment period, thereby ensuring that the pre-defined target number PFS-1L events would be observed by the end of the trial. For OS, a descriptive Bayesian analysis of the survival data was added in alignment with the primary efficacy analysis approach which would calculate the whole posterior distribution of HR for OS. In particular, the posterior probability for HR being inferior or equal to some threshold of interest could be reported. 1 of these thresholds of interest is the non-inferiority margin which was pre-defined as 1.06. The assumption regarding the expected cross-over rate to 2-L treatment was also revised, based on the ongoing blinded data monitoring of the trial and published results of the cross-over rates to 2-L after a 1-L treatment; >55% of patients receiving a 1-L therapy had crossed-over into 2-L therapy as reported in Motzer 2009 and Escudier 2010. The expected number of PFS events during or after 2-L was revised accordingly. In addition to the 2-sided 95% CIs, 2-sided 80% CIs would be reported for the estimated HR of the time-to-event variables for the key secondary efficacy endpoints analyses to facilitate the interpretation of results.The definition and safety recommendations concerning HBV reactivation and HCV flare were modified. The definition of HBV reactivation was amended to require only an increase of greater than 1 log10 IU/mL in HBV-DNA relative to baseline levels, and there was no longer a requirement for the increase in ALT levels. HCV flare (HCV reactivation) was removed from the study protocol. Further to recommendations made by expert hepatologists, the definition of HCV flare was amended to incorporate 2 separate clinical criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

PRO Tools - completed on Days 1 & 28 of a cycle. Assessments on D1 coincided with end of a 14-day break for patients on sunitinib but not everolimus. So D1 assessments of patients in sunitinib arm may be less impacted by potential toxicity effects.

Notes: