



Clinical trial results:

Phase III randomized sequential open-label study to evaluate the efficacy and safety of sorafenib followed by pazopanib versus pazopanib followed by sorafenib in the treatment of advanced / metastatic renal cell carcinoma (SWITCH 2)

Summary

EudraCT number	2011-004396-36
Trial protocol	DE AT NL
Global end of trial date	14 November 2016

Results information

Result version number	v1 (current)
This version publication date	04 January 2018
First version publication date	04 January 2018
Summary attachment (see zip file)	SWITCH-2 ICH-E3 Synopsis (SWITCH-2_CSR_FINAL_1.0_20OCT2017_StudyResults.pdf)

Trial information

Trial identification

Sponsor protocol code	16037
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00439636
WHO universal trial number (UTN)	-
Other trial identifiers	AUO study code number: AN 33/11

Notes:

Sponsors

Sponsor organisation name	Technical University Munich
Sponsor organisation address	Ismaninger Str. 22, Munich, Germany, 81675
Public contact	Clinical Research Organisation, iOMEDICO AG, 0049 0761152420, info@iomedico.com
Scientific contact	Clinical Research Organisation, iOMEDICO AG, 0049 0761152420, info@iomedico.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2016
Global end of trial reached?	Yes
Global end of trial date	14 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if progression -free survival from randomization to progression or death during second -line therapy (total PFS) of sorafenib followed by pazopanib ist non-inferior compared to pazopanib followed by sorafenib

Protection of trial subjects:

Informed consent of patient has been obtained in accordance with § 40 I 3 No. 3 Lit. b), II 1 AMG and § 40 I 3 No. 3 Lit. c). IIa 1&2 AMG by each investigator prior to inclusion of each patient to the study. In addition, informed consent of patients had been obtained in accordance with the respective legal obligations in Austria and the Netherlands.

The nature, objective and importance of the study, the possible benefits and disadvantages or risks, and the study procedures were explained to each patient orally and in writing. The patients were informed that their participation was voluntary, that they were free to withdraw from the study at any time, and that choosing not to participate would not impact on the patient's care or future treatment.

The patients were also informed that, by signing the Informed Consent Form, they explicitly permitted authorized representatives of the sponsor and the regulatory authorities access to study-related personal data to the extent permitted by the applicable law(s) and/or regulations without violating the confidentiality of the patient, to the extent permitted by the applicable law(s) and/or regulations. The patients were also informed that their consent to access their data might not be revoked.

Each patient was given sufficient time to read and discuss the ICF with the investigator prior to giving his/her written consent. Before entry to the study and prior to the conduct of any study-related procedure consent was recorded by means of the patient's dated signature.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 45
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Germany: 318
Worldwide total number of subjects	377
EEA total number of subjects	377

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)	149
From 65 to 84 years	227
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The investigators enrolled patients based on previously defined inclusion and exclusion criteria. All patients, who fulfilled all of the inclusion criteria and none of the exclusion criteria, were randomized centrally in a ratio of 1:1 to either Pazopanib or Sorafenib as first-line treatment.

Pre-assignment

Screening details:

Screening: starting on day -28 prior to randomization.

This study was a sequential, randomized, open-label (1:1), multicenter phase III study starting in first-line of metastatic / advanced RCC using in the experimental arm sorafenib until progression followed by pazopanib and in the control arm pazopanib until progression followed by sorafenib.

Pre-assignment period milestones

Number of subjects started	377
Intermediate milestone: Number of subjects	Screening and Randomization: 377
Number of subjects completed	377

Period 1

Period 1 title	Treatment Period - Switch Design (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable in this open label randomized study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A Sorafenib - Pazopanib (S-P)

Arm description:

Group A

First-line: Sorafenib 800 mg (daily total dose) 2*400 mg

Second-line: Pazopanib 800 mg (daily total dose) 1*800 mg

Arm type	Experimental
Investigational medicinal product name	Sorafenib followed by Pazopanib
Investigational medicinal product code	L01XE05 followed by L01XE11
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib 800 mg (daily dose) 2*400mg

Pazopanib 800 mg (daily dose) 1*800 mg

Arm title	Group B Pazopanib - Sorafenib (P-S)
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Arm description:

Group B

First-line: Pazopanib 800 mg (daily total dose) 1*800 mg

Second-line: Sorafenib 800 mg (daily total dose) 2*400 mg

Arm type	Active comparator
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Investigational medicinal product name	Pazopanib followed by Sorafenib
Investigational medicinal product code	L01XE11 followed by L01XE05
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sorafenib 800 mg (daily dose) 2*400mg

Pazopanib 800 mg (daily dose) 1*800 mg

Number of subjects in period 1	Group A Sorafenib - Pazopanib (S-P)	Group B Pazopanib - Sorafenib (P-S)
Started	189	188
Completed	153	146
Not completed	36	42
Consent withdrawn by subject	11	16
No Follow-up participation	7	8
Screening Failure	4	4
Lost to follow-up	10	9
other reason	4	5

Baseline characteristics

Reporting groups

Reporting group title	Group A Sorafenib - Pazopanib (S-P)
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Reporting group description:

Group A

First-line: Sorafenib 800 mg (daily total dose) 2*400 mg

Second-line: Pazopanib 800 mg (daily total dose) 1*800 mg

Reporting group title	Group B Pazopanib - Sorafenib (P-S)
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Reporting group description:

Group B

First-line: Pazopanib 800 mg (daily total dose) 1*800 mg

Second-line: Sorafenib 800 mg (daily total dose) 2*400 mg

Reporting group values	Group A Sorafenib - Pazopanib (S-P)	Group B Pazopanib - Sorafenib (P-S)	Total
Number of subjects	189	188	377
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	67.5	68.4	
full range (min-max)	31.3 to 83.7	25.6 to 85.6	-
Gender categorical			
Units: Subjects			
Female	53	51	104
Male	136	137	273
Karnofsky Performance Status at Screening			
Karnofsky Performance Status at Screening in categories (100, 90, 80, 70, missing)			
Units: Subjects			
KPS Screen 100	96	85	181
KPS Screen 90	32	46	78
KPS Screen 80	52	44	96
KPS Screen 70	9	12	21
KPS Screen missing	0	1	1
MSKCC			
MSKCC score at enrolment			
Units: Subjects			
High	4	5	9

Intermediate	90	89	179
Low	95	91	186
Unknown	0	2	2
Missing	0	1	1
Renal insufficiency			
Chronic renal insufficiency			
Units: Subjects			
Yes	26	29	55
No	156	149	305
Unknown	7	10	17
Weight			
Median weight at screening			
Units: kg			
median	80.3	81.7	
full range (min-max)	49 to 130	43.6 to 129	-
BMI			
Median Body Mass Index			
Units: kg/m ²			
median	27.2	26.5	
full range (min-max)	19.4 to 44.6	15.5 to 38.1	-
Time from diagnosis to randomization			
Median Time from Diagnosis to Randomization			
Units: months			
median	6.3	8.7	
full range (min-max)	0.22 to 221.4	0.2 to 245.6	-
Time from first relapse/metastatic disease to randomization			
Median time from first relapse/metastatic disease to randomization			
Units: months			
median	1.9	2.2	
full range (min-max)	0.1 to 123.1	0.1 to 155.7	-
Number of disease sites			
Median number of disease sites			
Units: number			
median	2	3	
full range (min-max)	1 to 6	1 to 5	-

End points

End points reporting groups

Reporting group title	Group A Sorafenib - Pazopanib (S-P)
Reporting group description:	
Group A	
First-line: Sorafenib 800 mg (daily total dose) 2*400 mg	
Second-line: Pazopanib 800 mg (daily total dose) 1*800 mg	
Reporting group title	Group B Pazopanib - Sorafenib (P-S)
Reporting group description:	
Group B	
First-line: Pazopanib 800 mg (daily total dose) 1*800 mg	
Second-line: Sorafenib 800 mg (daily total dose) 2*400 mg	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All subjects who were assigned a subject number at randomization are considered randomized subjects, even if they did not receive any trial treatment.	
All randomized subjects will be included in the Intention-to-treat (ITT) population. This population is the primary analysis population. In analyses of the ITT population, subjects will be assigned to the treatment to which they were randomized.	
The Safety analysis population consists of n=366 patients.	

Primary: Total Progression-free survival

End point title	Total Progression-free survival
End point description:	
The goal was to demonstrate that the PFS time in the experimental arm (Sorafenib first in sequence) was not inferior to the PFS time in the control arm (Pazopanib first in sequence).	
Primary analysis population: Intent to Treat (ITT).	
End point type	Primary
End point timeframe:	
Total PFS is defined as the time interval from randomization to progression or death (whichever comes first) during second-line therapy.	

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	8.6 (7.7 to 10.2)	12.9 (10.8 to 15.2)		

Attachments (see zip file)	Total PFS (ITT)/Fig_Total_PFS.docx
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Statistical analyses

Statistical analysis title	Analysis of primary endpoint
Statistical analysis description:	
To demonstrate total PFS time in the experimental arm (Sorafenib first) not inferior to total PFS time in the control arm. Definition non-inferiority: in the experimental arm, upper limit of the one-sided 95% CI of the hazard ratio is not above 1.225 (corresponding to a decrease to 13.1 months compared to an assumed median total PFS in the control group of 16 months). 383 events needed to be observed to have 80% power to reject the null hypotheses of inferiority ($HR \geq 1.225$), when true $HR=0.95$.	
Comparison groups	Group A Sorafenib - Pazopanib (S-P) v Group B Pazopanib - Sorafenib (P-S)
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Cox proportional hazard
Point estimate	1.36
Confidence interval	
level	95 %
sides	1-sided
upper limit	1.68

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
End point description:	
Patients without tumor progression at the time of analysis will be censored at their last date of tumor evaluation.	
End point type	Secondary
End point timeframe:	
Total TTP is defined as the time interval from randomization to the date of progression during second-line therapy.	

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	8.5 (7.4 to 10.2)	12.9 (10.7 to 15.3)		

Attachments (see zip file)	Total Time to Progression (TTP - ITT)/Fig_TTP_Total.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Time to first-line treatment failure (TTF)

End point title	Time to first-line treatment failure (TTF)
End point description: Reasons for end of treatment that count for an event (treatment failure) are adverse event, death, patient non-compliance, investigator's decision, progression of disease and use of illicit drugs. Patients with all other reasons will be censored at the end date of first-line treatment.	
End point type	Secondary
End point timeframe: TTF is defined by the time interval between the date of randomization and the date of stopping first-line treatment due to treatment failure.	

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	5.5 (3.9 to 5.8)	7.8 (5.8 to 9.6)		

Attachments (see zip file)	Time to first-line treatment failure (ITT)/Fig_TTF.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: PFS first-line

End point title	PFS first-line
End point description: PFS in first line therapy is defined as the time from randomization to first progression or death from any cause, whatever occurs first. The primary analysis of PFS in first-line will be performed with the ITT population.	
End point type	Secondary
End point timeframe: Time from randomization to first progression or death from any cause, whatever occurs first.	

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	5.6 (4.7 to 6.3)	9.3 (7.4 to 10.6)		

Attachments (see zip file)	First-line PFS/Fig_PFS_1line.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: PFS-Second-line

End point title	PFS-Second-line
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End point description:

PFS in second-line therapy is defined as the time from start of second-line therapy to progression or death from any cause, whatever occurs first, during second line therapy. The primary analysis of PFS in second line will be performed with the ITT population.

End point type	Secondary
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End point timeframe:

Time from start of second-line therapy to progression or death from any cause, whatever occurs first.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	2.9 (2 to 3.7)	2.1 (1.8 to 3.5)		

Attachments (see zip file)	Second-line PFS/Fig_PFS_2line.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival is defined as the time from randomization to death of any cause. The primary analysis of OS will be performed with the ITT population. Time to last observation will be used if a patient has no documented date of death and OS for the patient will be considered censored.

End point type	Secondary
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End point timeframe:

Time from randomization to death of any cause.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: months				
median (confidence interval 95%)	22.7 (17.4 to 28.6)	28.0 (22.6 to 34.1)		

Attachments (see zip file)	Overall Survival (ITT)/Fig_OS.docx
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Statistical analyses

No statistical analyses for this end point

Secondary: PRO FKSI change from BL to last available value - first-line

End point title	PRO FKSI change from BL to last available value - first-line
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End point description:

Patient-reported outcome (PRO) FKSI Score, change from baseline to last available value in first-line. If no worsening happens, patients will be censored with the date of last available questionnaire per treatment line.

End point type	Secondary
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End point timeframe:

The time to health state deterioration is defined as the time from baseline questionnaire to the date of first worsening of 4 points compared to baseline in the total score per treatment line.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	132		
Units: points				
median (inter-quartile range (Q1-Q3))	-2.0 (-6.1 to 0.0)	-3.0 (-8 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: PRO FACIT-F change from BL to last available value - first-line

End point title	PRO FACIT-F change from BL to last available value - first-line
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End point description:

Patient-reported outcomes (PROs) of FACIT-F subscores, total score and single items are summarized per visit and treatment arm.

Following Cella et al (Cella, Eton, Lai, Peterman, & Merkel, 2002), the minimal important difference (MID) indicating clinically important QoL changes in cancer clinical trials is assumed to be 3 points for the Fatigue Scale and 4 points for the FACT-G respectively. If no worsening happens, patients will be censored with the date of last available questionnaire per treatment line.

End point type	Secondary
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End point timeframe:

The time to health state deterioration is defined as the time from baseline questionnaire to the date of first worsening of MID compared to baseline in the total score per treatment line.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	131		
Units: points				
median (inter-quartile range (Q1-Q3))	-1 (-19.4 to 1.2)	-7.4 (-24.8 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: PRO FKSI change from BL to last available value - second-line

End point title	PRO FKSI change from BL to last available value - second-line
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End point description:

Patient-reported outcome (PRO) FKSI Score, change from baseline to last available value in second-line. If no worsening happens, patients will be censored with the date of last available questionnaire per treatment line.

End point type	Secondary
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End point timeframe:

The time to health state deterioration is defined as the time from baseline questionnaire to the date of first worsening of 4 points compared to baseline in the total score per treatment line.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	67		
Units: points				
median (inter-quartile range (Q1-Q3))	0 (-3 to 1)	0 (-5 to 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: PRO FACIT-F change from BL to last available value - second-line

End point title	PRO FACIT-F change from BL to last available value - second-line
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End point description:

Patient-reported outcome (PRO) FACIT-F Score, change from Baseline to last available value in second-line. If no worsening happens, patients will be censored with the date of last available questionnaire per treatment line.

End point type	Secondary
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End point timeframe:

The time to health state deterioration is defined as the time from baseline questionnaire to the date of first worsening of MID compared to baseline in the total score per treatment line.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	62		
Units: points				
median (inter-quartile range (Q1-Q3))	0 (-7.2 to 3.3)	-1.2 (-14.9 to 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate - First-line (ORR-1)

End point title	Overall Response Rate - First-line (ORR-1)
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End point description:

The sum of rates of complete response and partial response as best response.

End point type	Secondary
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End point timeframe:

Relevant response evaluations for first-line treatment are all evaluations before start of second-line therapy.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: Number	54	87		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate - Second-line (ORR-2)

End point title	Overall Response Rate - Second-line (ORR-2)
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End point description:

The overall response rate (ORR) is defined as the sum of rates of complete response and partial response as best response.

End point type	Secondary
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End point timeframe:

Relevant response evaluations for second-line treatment are all evaluations after start of second-line therapy.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	87		
Units: Number	21	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate - First-line (DCR-1)

End point title	Disease Control Rate - First-line (DCR-1)
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End point description:

The disease control rate (DCR) is defined as the sum of rates of complete response, partial response and stable disease based on the best response.

End point type	Secondary
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End point timeframe:

Relevant response evaluations for first-line treatment are all evaluations before start of second-line therapy.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	188		
Units: Number	128	146		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate - Second-line (DCR-2)

End point title	Disease Control Rate - Second-line (DCR-2)
End point description:	The disease control rate (DCR) is defined as the sum of rates of complete response, partial response and stable disease based on the best response.
End point type	Secondary
End point timeframe:	Relevant response evaluations for second-line treatment are all evaluations after start of second-line therapy.

End point values	Group A Sorafenib - Pazopanib (S- P)	Group B Pazopanib - Sorafenib (P-S)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	87		
Units: Number	60	38		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication.

Adverse event reporting additional description:

Adverse Events (AEs) will be graded according to the CTCAE, version 4.03.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Arm A: S-P First-line
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Reporting group description:

Arm A: Sorafenib - Pazopanib First-line

(Note: Only fatal TEAE were analysed per reporting group, in total 94 patients died in Arm A upon study completion (LPLV)).

Reporting group title	Arm B: P-S First-line
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Reporting group description:

Pazopanib - Sorafenib First-line

(Note: Only fatal TEAE were analysed per reporting group, in total 82 patients died in Arm B upon study completion (LPLV)).

Reporting group title	Arm A: S-P Second-line
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Reporting group description:

Sorafenib - Pazopanib Second-line

(Note: Only fatal TEAE were analysed per reporting group, in total 94 patients died in Arm A upon study completion (LPLV)).

Reporting group title	Arm B: P-S Second-line
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Reporting group description:

Arm B: Pazopanib - Sorafenib Second-line

(Note: Only fatal TEAE were analysed per reporting group, in total 82 patients died in Arm B upon study completion (LPLV)).

Serious adverse events	Arm A: S-P First-line	Arm B: P-S First-line	Arm A: S-P Second-line
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 183 (52.46%)	97 / 183 (53.01%)	51 / 106 (48.11%)
number of deaths (all causes)	19	23	19
number of deaths resulting from adverse events	19	23	19
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Cancer pain			

subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	11 / 183 (6.01%)	10 / 183 (5.46%)	7 / 106 (6.60%)
occurrences causally related to treatment / all	0 / 11	0 / 10	1 / 7
deaths causally related to treatment / all	0 / 11	0 / 8	1 / 7
Malignant pleural effusion			
subjects affected / exposed	1 / 183 (0.55%)	3 / 183 (1.64%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Metastases to bone			
subjects affected / exposed	1 / 183 (0.55%)	2 / 183 (1.09%)	0 / 106 (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
Metastases to central nervous system			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to perineum			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Metastases to skin			

subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Neoplasm			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Neoplasm progression			
subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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 cancer metastatic			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			

subjects affected / exposed	1 / 183 (0.55%)	2 / 183 (1.09%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 183 (0.55%)	4 / 183 (2.19%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Vena cava thrombosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	0 / 106 (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
Meniscus removal			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Nephrectomy			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Skin lesion removal			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Death			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	3 / 183 (1.64%)	0 / 183 (0.00%)	0 / 106 (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
General physical health deterioration			
subjects affected / exposed	3 / 183 (1.64%)	2 / 183 (1.09%)	5 / 106 (4.72%)
occurrences causally related to treatment / all	1 / 3	1 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Impaired healing			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Malaise			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Oedema peripheral			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Pain			
subjects affected / exposed	1 / 183 (0.55%)	3 / 183 (1.64%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 183 (1.09%)	2 / 183 (1.09%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unevaluable event			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Hypersensitivity			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 183 (0.55%)	3 / 183 (1.64%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1

Haemoptysis			
subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	0 / 106 (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
Hyperventilation			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (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
Pleural effusion			
subjects affected / exposed	7 / 183 (3.83%)	5 / 183 (2.73%)	6 / 106 (5.66%)
occurrences causally related to treatment / all	1 / 8	0 / 5	0 / 10
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Pneumonitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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 spontaneous			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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 embolism			
subjects affected / exposed	1 / 183 (0.55%)	5 / 183 (2.73%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Pulmonary mass			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Respiratory failure			

subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Personality change			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 183 (0.00%)	6 / 183 (3.28%)	3 / 106 (2.83%)
occurrences causally related to treatment / all	0 / 0	6 / 6	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Eastern Cooperative Oncology Group performance status worsened			

subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Fibrin D dimer increased			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
General physical condition abnormal			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	4 / 106 (3.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic enzyme increased			
subjects affected / exposed	0 / 183 (0.00%)	4 / 183 (2.19%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (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
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Myocardial strain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Transaminases increased			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			

subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	0 / 106 (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
Concussion			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Lower limb fracture			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Overdose			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Patella fracture			

subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Pelvic fracture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Radiation proctitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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 compression fracture			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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 fracture			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Thoracic vertebral fracture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Tibia fracture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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 disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Angina pectoris			
subjects affected / exposed	3 / 183 (1.64%)	0 / 183 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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	2 / 183 (1.09%)	4 / 183 (2.19%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure acute			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Myocardial infarction			
subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Myocarditis			

subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Pericardial effusion			
subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Pericarditis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Right ventricular failure			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Supraventricular tachycardia			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Tachycardia			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Cerebral infarction			
subjects affected / exposed	1 / 183 (0.55%)	2 / 183 (1.09%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Dizziness			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Drug withdrawal headache			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 183 (0.55%)	2 / 183 (1.09%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Intracranial pressure increased			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
IVth nerve paralysis			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Nerve compression			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paralysis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Paraplegia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Paresis			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
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 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Leukopenia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Thrombocytopenia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Retinal haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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 disorders			
Abdominal pain			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (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
Abdominal pain upper			
subjects affected / exposed	1 / 183 (0.55%)	2 / 183 (1.09%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute abdomen			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Anal fissure			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Colitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Constipation			
subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Diarrhoea			
subjects affected / exposed	5 / 183 (2.73%)	5 / 183 (2.73%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	5 / 5	3 / 5	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	0 / 106 (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
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Dysphagia			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Faecaloma			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Gastric ulcer			

subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	0 / 106 (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
Gastritis erosive			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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 haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Ileus			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Inguinal hernia			
subjects affected / exposed	3 / 183 (1.64%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Large intestine perforation			

subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 183 (1.09%)	1 / 183 (0.55%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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 acute			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Stomatitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Vomiting			
subjects affected / exposed	4 / 183 (2.19%)	3 / 183 (1.64%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	1 / 5	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Cholecystitis acute			

subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Drug-induced liver injury			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Hepatic failure			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hepatic function abnormal			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (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
Hepatotoxicity			
subjects affected / exposed	0 / 183 (0.00%)	8 / 183 (4.37%)	3 / 106 (2.83%)
occurrences causally related to treatment / all	0 / 0	8 / 8	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Jaundice			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Erythema			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Pain of skin			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 183 (1.64%)	0 / 183 (0.00%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 183 (0.55%)	2 / 183 (1.09%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haematuria			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Proteinuria			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Renal pain			

subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Urethral haemorrhage			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary retention			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	2 / 106 (1.89%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Flank pain			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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

Intervertebral disc protrusion			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Muscular weakness			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Osteolysis			
subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Pain in extremity			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Pathological fracture			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Spinal instability			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (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
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Abscess intestinal			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Abscess jaw			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Bacterial infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Candida infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Device related infection			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Empyema			

subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Epididymitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Erysipelas			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Gastroenteritis			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (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
Herpes zoster			
subjects affected / exposed	2 / 183 (1.09%)	0 / 183 (0.00%)	0 / 106 (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
Influenza			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Liver abscess			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site infection			
subjects affected / exposed	0 / 183 (0.00%)	2 / 183 (1.09%)	0 / 106 (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
Meningitis			

subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Nasopharyngitis			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Necrotising fasciitis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Peritonitis			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	0 / 106 (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
Pneumonia			
subjects affected / exposed	7 / 183 (3.83%)	5 / 183 (2.73%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	1 / 7	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Sepsis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Septic shock			
subjects affected / exposed	0 / 183 (0.00%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Staphylococcal sepsis			

subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 183 (0.00%)	1 / 183 (0.55%)	0 / 106 (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
Urinary tract infection			
subjects affected / exposed	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Urosepsis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 183 (1.09%)	2 / 183 (1.09%)	0 / 106 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Hypocalcaemia			
subjects affected / exposed	3 / 183 (1.64%)	0 / 183 (0.00%)	0 / 106 (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
Hypoglycaemia			
subjects affected / exposed	1 / 183 (0.55%)	2 / 183 (1.09%)	0 / 106 (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
Hypokalaemia			

subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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	1 / 183 (0.55%)	1 / 183 (0.55%)	0 / 106 (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
Malnutrition			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	0 / 106 (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
Metabolic acidosis			
subjects affected / exposed	1 / 183 (0.55%)	0 / 183 (0.00%)	1 / 106 (0.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Serious adverse events	Arm B: P-S Second-line		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 87 (36.78%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	9		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lymphangiosis carcinomatosa subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression subjects affected / exposed	6 / 87 (6.90%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 5			
Malignant pleural effusion subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to bone subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to perineum subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to skin subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neoplasm subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neoplasm progression				

subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Non-small cell lung cancer			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal adenocarcinoma			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal cancer metastatic			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Embolism			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meniscus removal			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrectomy			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin lesion removal			
subjects affected / exposed	0 / 87 (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	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Fatigue				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 87 (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 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Performance status decreased				

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Unevaluable event			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperventilation			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pleural effusion			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pneumonitis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax spontaneous			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Personality change			

subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eastern Cooperative Oncology Group performance status worsened			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fibrin D dimer increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical condition abnormal			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hepatic enzyme increased subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver function test increased subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial necrosis marker increased subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial strain subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transaminases increased subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Weight decreased subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cervical vertebral fracture subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Concussion				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Overdose				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Patella fracture				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Radiation proctitis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal fracture			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			

subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericarditis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug withdrawal headache			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			

subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hemiplegia				
subjects affected / exposed	0 / 87 (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 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
IVth nerve paralysis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nerve compression				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paralysis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraplegia				

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paresis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Retinal detachment			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute abdomen			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal fissure			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	2 / 87 (2.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis erosive				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis haemorrhagic				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal perforation				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mallory-Weiss syndrome				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				

subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 87 (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 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatotoxicity			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erythema			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain of skin			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Acute kidney injury				
subjects affected / exposed	2 / 87 (2.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Haematuria				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Proteinuria				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal pain				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tubulointerstitial nephritis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urethral haemorrhage				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteolysis			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Osteonecrosis of jaw			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal instability			
subjects affected / exposed	0 / 87 (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 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess intestinal			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abscess jaw			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			

subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Candida infection				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Empyema				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epididymitis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Liver abscess				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Medical device site infection				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Necrotising fasciitis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				

subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal sepsis				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 87 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 87 (1.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			

subjects affected / exposed	0 / 87 (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	Arm A: S-P First-line	Arm B: P-S First-line	Arm A: S-P Second-line
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 183 (93.99%)	178 / 183 (97.27%)	91 / 106 (85.85%)
Vascular disorders			
Hypertension			
subjects affected / exposed	48 / 183 (26.23%)	81 / 183 (44.26%)	15 / 106 (14.15%)
occurrences (all)	59	97	18
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	66 / 183 (36.07%)	82 / 183 (44.81%)	16 / 106 (15.09%)
occurrences (all)	71	96	19
Oedema peripheral			
subjects affected / exposed	6 / 183 (3.28%)	18 / 183 (9.84%)	7 / 106 (6.60%)
occurrences (all)	8	19	7
Pain			
subjects affected / exposed	18 / 183 (9.84%)	21 / 183 (11.48%)	4 / 106 (3.77%)
occurrences (all)	20	23	4
Immune system disorders			
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 183 (2.19%)	19 / 183 (10.38%)	1 / 106 (0.94%)
occurrences (all)	7	31	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 183 (9.84%)	17 / 183 (9.29%)	2 / 106 (1.89%)
occurrences (all)	20	20	2
Dyspnoea			
subjects affected / exposed	16 / 183 (8.74%)	14 / 183 (7.65%)	6 / 106 (5.66%)
occurrences (all)	18	16	6
Epistaxis			

subjects affected / exposed occurrences (all)	12 / 183 (6.56%) 14	17 / 183 (9.29%) 21	6 / 106 (5.66%) 9
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	3 / 183 (1.64%) 7	21 / 183 (11.48%) 30	3 / 106 (2.83%) 2
Weight decreased subjects affected / exposed occurrences (all)	30 / 183 (16.39%) 33	14 / 183 (7.65%) 17	4 / 106 (3.77%) 4
Nervous system disorders			
Ageusia subjects affected / exposed occurrences (all)	6 / 183 (3.28%) 6	16 / 183 (8.74%) 18	3 / 106 (2.83%) 3
Dizziness subjects affected / exposed occurrences (all)	8 / 183 (4.37%) 9	18 / 183 (9.84%) 26	4 / 106 (3.77%) 4
Dysgeusia subjects affected / exposed occurrences (all)	9 / 183 (4.92%) 10	28 / 183 (15.30%) 31	4 / 106 (3.77%) 5
Headache subjects affected / exposed occurrences (all)	22 / 183 (12.02%) 23	29 / 183 (15.85%) 34	10 / 106 (9.43%) 11
Dysphonia subjects affected / exposed occurrences (all)	19 / 183 (10.38%) 20	10 / 183 (5.46%) 12	1 / 106 (0.94%) 1
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	7 / 183 (3.83%) 7	10 / 183 (5.46%) 12	1 / 106 (0.94%) 3
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	7 / 183 (3.83%) 8	12 / 183 (6.56%) 13	7 / 106 (6.60%) 8
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	9 / 183 (4.92%) 10	21 / 183 (11.48%) 24	3 / 106 (2.83%) 3

Abdominal pain upper subjects affected / exposed occurrences (all)	12 / 183 (6.56%) 13	19 / 183 (10.38%) 22	4 / 106 (3.77%) 4
Constipation subjects affected / exposed occurrences (all)	20 / 183 (10.93%) 23	21 / 183 (11.48%) 22	4 / 106 (3.77%) 4
Diarrhoea subjects affected / exposed occurrences (all)	100 / 183 (54.64%) 160	107 / 183 (58.47%) 158	29 / 106 (27.36%) 40
Dry mouth subjects affected / exposed occurrences (all)	11 / 183 (6.01%) 12	6 / 183 (3.28%) 6	2 / 106 (1.89%) 2
Dyspepsia subjects affected / exposed occurrences (all)	8 / 183 (4.37%) 10	10 / 183 (5.46%) 12	2 / 106 (1.89%) 2
Flatulence subjects affected / exposed occurrences (all)	6 / 183 (3.28%) 6	11 / 183 (6.01%) 13	1 / 106 (0.94%) 1
Nausea subjects affected / exposed occurrences (all)	44 / 183 (24.04%) 47	65 / 183 (35.52%) 87	27 / 106 (25.47%) 28
Stomatitis subjects affected / exposed occurrences (all)	32 / 183 (17.49%) 35	19 / 183 (10.38%) 27	2 / 106 (1.89%) 2
Vomiting subjects affected / exposed occurrences (all)	25 / 183 (13.66%) 30	33 / 183 (18.03%) 45	15 / 106 (14.15%) 15
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	46 / 183 (25.14%) 47	11 / 183 (6.01%) 13	5 / 106 (4.72%) 5
Dry skin subjects affected / exposed occurrences (all)	17 / 183 (9.29%) 17	4 / 183 (2.19%) 4	0 / 106 (0.00%) 0
Erythema			

subjects affected / exposed	25 / 183 (13.66%)	5 / 183 (2.73%)	2 / 106 (1.89%)
occurrences (all)	28	6	2
Hair colour changes			
subjects affected / exposed	0 / 183 (0.00%)	26 / 183 (14.21%)	1 / 106 (0.94%)
occurrences (all)	0	26	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	61 / 183 (33.33%)	30 / 183 (16.39%)	4 / 106 (3.77%)
occurrences (all)	89	38	7
Pruritus			
subjects affected / exposed	30 / 183 (16.39%)	9 / 183 (4.92%)	0 / 106 (0.00%)
occurrences (all)	39	12	0
Rash			
subjects affected / exposed	29 / 183 (15.85%)	14 / 183 (7.65%)	6 / 106 (5.66%)
occurrences (all)	32	16	6
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	7 / 183 (3.83%)	25 / 183 (13.66%)	1 / 106 (0.94%)
occurrences (all)	7	26	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 183 (8.20%)	17 / 183 (9.29%)	2 / 106 (1.89%)
occurrences (all)	21	22	2
Back pain			
subjects affected / exposed	20 / 183 (10.93%)	14 / 183 (7.65%)	5 / 106 (4.72%)
occurrences (all)	21	16	5
Muscle spasms			
subjects affected / exposed	9 / 183 (4.92%)	12 / 183 (6.56%)	1 / 106 (0.94%)
occurrences (all)	11	13	1
Pain in extremity			
subjects affected / exposed	18 / 183 (9.84%)	13 / 183 (7.10%)	3 / 106 (2.83%)
occurrences (all)	23	16	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 183 (4.92%)	13 / 183 (7.10%)	3 / 106 (2.83%)
occurrences (all)	10	19	3
Urinary tract infection			

subjects affected / exposed occurrences (all)	14 / 183 (7.65%) 15	9 / 183 (4.92%) 11	6 / 106 (5.66%) 6
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	36 / 183 (19.67%) 41	44 / 183 (24.04%) 48	7 / 106 (6.60%) 8

Non-serious adverse events	Arm B: P-S Second-line		
Total subjects affected by non-serious adverse events subjects affected / exposed	77 / 87 (88.51%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 9		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 10 5 / 87 (5.75%) 5 1 / 87 (1.15%) 1		
Immune system disorders Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Epistaxis	3 / 87 (3.45%) 3 1 / 87 (1.15%) 1		

subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4		
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1		
Weight decreased subjects affected / exposed occurrences (all)	5 / 87 (5.75%) 7		
Nervous system disorders			
Ageusia subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2		
Dizziness subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1		
Headache subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2		
Dysphonia subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 6		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 7		
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	7 / 87 (8.05%) 7		

Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2		
Constipation subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 10		
Diarrhoea subjects affected / exposed occurrences (all)	25 / 87 (28.74%) 35		
Dry mouth subjects affected / exposed occurrences (all)	8 / 87 (9.20%) 8		
Dyspepsia subjects affected / exposed occurrences (all)	1 / 87 (1.15%) 1		
Flatulence subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2		
Nausea subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3		
Stomatitis subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 7		
Vomiting subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 7		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	9 / 87 (10.34%) 10		
Dry skin subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3		
Erythema			

subjects affected / exposed	7 / 87 (8.05%)		
occurrences (all)	7		
Hair colour changes			
subjects affected / exposed	0 / 87 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	20 / 87 (22.99%)		
occurrences (all)	28		
Pruritus			
subjects affected / exposed	11 / 87 (12.64%)		
occurrences (all)	12		
Rash			
subjects affected / exposed	17 / 87 (19.54%)		
occurrences (all)	24		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	4 / 87 (4.60%)		
occurrences (all)	4		
Muscle spasms			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	3		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Urinary tract infection			

subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	6 / 87 (6.90%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2012	Amendment I, Germany
27 June 2012	Amendment II, Germany [Austria N/A; The Netherlands N/A]
14 February 2014	Amendment III, Germany [Austria (07-Apr-2014); The Netherlands (24-Mar-2014)]
25 July 2016	Amendment IV, Germany [Austria (07-Jul-2016); The Netherlands (08-Jul-2016)]

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/20100962>

<http://www.ncbi.nlm.nih.gov/pubmed/19451442>