Clinical trial results:
An open-label, multi-center, expanded access study for postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have progressed following prior endocrine therapy, investigating the treatment of everolimus (RAD001) in combination with exemestane

Summary

EudraCT number	2012-000073-23
Trial protocol	AT NL SE NO ES DK FI BE CZ IT HU IE SK BG
Global end of trial date	01 September 2014

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	CRAD001YIC04

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety of everolimus in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer after recurrence or progression following Non-steroidal aromatase inhibitors (NSAIs) treatment.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 71
Country: Number of subjects enrolled	Norway: 20
Country: Number of subjects enrolled	Poland: 47
Country: Number of subjects enrolled	Slovakia: 20
Country: Number of subjects enrolled	Spain: 429
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 237
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	Hungary: 67
Country: Number of subjects enrolled	Italy: 1153
Country: Number of subjects enrolled	Romania: 26
Worldwide total number of subjects	2133
EEA total number of subjects	2133

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)	1171
From 65 to 84 years	950
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

This was a multi-center, open-label, single arm, Phase III b, expanded access study. In this study up to 2500 patients from up to 500 centers were to be recruited.

Pre-assignment

Screening details:

A total of 2133 postmenopausal female subjects with advanced or metastatic breast cancer were enrolled in the study, out of which, 2131 were included in the safety population.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Everolimus + Exemestane

Arm description:

Subjects received everolimus 10 mg (2x5mg) in combination with exemestane 25 mg, orally, once daily.

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

Dosage and administration details:

Two everolimus tablets 5 mg or one everolimus tablet 10 mg, orally, once daily.

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Exemestane 25 mg tablet, orally, once daily.

Number of subjects in period 1	Everolimus + Exemestane
Started	2133
Completed	82
Not completed	2051
Abnormal laboratory value(s)	11
Disease progression	786
Unsatisfactory therapeutic effect	6
Administrative problems	2
Adverse event(s)	338

Abnormal test procedure result(s)	1
Subject withdrew consent	72
Everolimus locally reimbursed	713
Protocol violation	35
Death	32
Other	28
Subject's condition no longer requires study drug	14
Lost to follow-up	13

Baseline characteristics

Reporting groups	
Reporting group title	Everolimus + Exemestane
Reporting group description:	
Subjects received everolimus 10 mg (2x5mg) in combination with exemestane 25 mg, orally, once daily.	

Reporting group values	Everolimus + Exemestane	Total	
Number of subjects	2133	2133	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1171	1171	
From 65-84 years	950	950	
85 years and over	12	12	
Age continuous			
Units: years			
arithmetic mean	62.7		
standard deviation	± 9.86	-	
Gender categorical			
Units: Subjects			
Female	2133	2133	
Male	0	0	

End points

End points reporting groups

Reporting group title	Everolimus + Exemestane

Reporting group description:

Subjects received everolimus 10 mg (2x5mg) in combination with exemestane 25 mg, orally, once daily.

Primary: Number of Subjects with Adverse Events (AEs)

End point title	Number of Subjects with Adverse Events (AEs)[1]

End point description:

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs or symptoms occurring in any phase of the clinical study whether or not considered related to the study medication. Safety population included all subjects who received at least one dose of everolimus or exemestane and had at least one post-baseline safety assessment.

End point type	Primary

End point timeframe:

From first dose of study treatment through 28 days after last dose of study treatment (Up to approximately 24 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical hypothesis was planned for this endpoint.

End point values	Everolimus + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	2131			
Units: Subjects				
number (not applicable)	2018			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Grade 3/4 AEs

End point title	Number of Subjects with Grade 3/4 AEs

End point description:

Subjects with grade 3 and 4 severity AE were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, unless otherwise specified. If CTCAE grading did not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to grade 1 to grade 4, was used. Safety population included all subjects who received at least one dose of everolimus or exemestane and had at least one post-baseline safety assessment.

End point type	Secondary

End point timeframe:

From first dose of study treatment through 28 days after last dose of study treatment (Up to approximately 24 months)

End point values	Everolimus + Exemestane			
Subject group type	Reporting group			
Number of subjects analysed	2131			
Units: Subjects				
number (not applicable)	214			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Without Chemo in Metastatic Setting

Reporting group description:

Without Chemo in Metastatic Setting

Reporting group title	With Chemo in Metastatic Setting

Reporting group description:

With Chemo in Metastatic Setting

Serious adverse events	Without Chemo in Metastatic Setting	With Chemo in Metastatic Setting	
Total subjects affected by serious adverse events			
subjects affected / exposed	163 / 847 (19.24%)	288 / 1284 (22.43%)	
number of deaths (all causes)	24	97	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant ascites			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic pain			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour of ampulla of Vater			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 847 (0.12%)	5 / 1284 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	2 / 847 (0.24%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			

subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 847 (0.12%)	9 / 1284 (0.70%)	
occurrences causally related to treatment / all	0 / 1	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 847 (0.12%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 3	
Disease progression			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Face oedema			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 847 (0.47%)	7 / 1284 (0.55%)	
occurrences causally related to treatment / all	4 / 4	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 847 (0.47%)	12 / 1284 (0.93%)	
occurrences causally related to treatment / all	0 / 4	2 / 12	
deaths causally related to treatment / all	0 / 0	1 / 2	
Hyperpyrexia			

subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia malignant			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 847 (0.00%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	3 / 847 (0.35%)	6 / 1284 (0.47%)	
occurrences causally related to treatment / all	1 / 3	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 847 (0.12%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 847 (0.94%)	26 / 1284 (2.02%)	
occurrences causally related to treatment / all	3 / 8	9 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sense of oppression			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Breast ulceration			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal inflammation			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 847 (0.12%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 847 (0.12%)	6 / 1284 (0.47%)	
occurrences causally related to treatment / all	0 / 1	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	17 / 847 (2.01%)	35 / 1284 (2.73%)	
occurrences causally related to treatment / all	7 / 18	13 / 35	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	5 / 847 (0.59%)	5 / 1284 (0.39%)	
occurrences causally related to treatment / all	5 / 5	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	12 / 847 (1.42%)	14 / 1284 (1.09%)	
occurrences causally related to treatment / all	3 / 12	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	14 / 847 (1.65%)	33 / 1284 (2.57%)	
occurrences causally related to treatment / all	14 / 14	29 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 847 (0.12%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 847 (0.47%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 847 (0.24%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 847 (0.24%)	6 / 1284 (0.47%)	
occurrences causally related to treatment / all	0 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 847 (0.12%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social avoidant behaviour			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 847 (0.00%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 847 (0.00%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	3 / 847 (0.35%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood electrolytes decreased			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern cooperative oncology group performance status worsened			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 847 (0.00%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sputum abnormal			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 847 (0.00%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis chemical			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic pain			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 847 (0.35%)	5 / 1284 (0.39%)	
occurrences causally related to treatment / all	0 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 847 (0.24%)	8 / 1284 (0.62%)	
occurrences causally related to treatment / all	1 / 2	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	2 / 847 (0.24%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia paroxysmal			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 847 (0.00%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma hepatic			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysgeusia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Headache			
subjects affected / exposed	0 / 847 (0.00%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Loss of consciousness			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 847 (0.94%)	19 / 1284 (1.48%)	
occurrences causally related to treatment / all	6 / 8	11 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 847 (0.12%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 847 (0.00%)	5 / 1284 (0.39%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytosis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diplopia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid ptosis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital oedema			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 847 (0.35%)	11 / 1284 (0.86%)	
occurrences causally related to treatment / all	0 / 3	3 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal inflammation			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			

subjects affected / exposed	3 / 847 (0.35%)	10 / 1284 (0.78%)	
occurrences causally related to treatment / all	0 / 3	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	14 / 847 (1.65%)	6 / 1284 (0.47%)	
occurrences causally related to treatment / all	10 / 14	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric disorder			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			

subjects affected / exposed	0 / 847 (0.00%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	4 / 847 (0.47%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	5 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema mouth			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	6 / 847 (0.71%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	6 / 6	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	0 / 847 (0.00%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	6 / 847 (0.71%)	7 / 1284 (0.55%)	
occurrences causally related to treatment / all	3 / 6	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 847 (0.24%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			

subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Acute febrile neutrophilic dermatosis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash pruritic			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Crush syndrome			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			

subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyuria			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 847 (0.47%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	4 / 847 (0.47%)	7 / 1284 (0.55%)	
occurrences causally related to treatment / all	4 / 4	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	2 / 847 (0.24%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 847 (0.12%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 847 (0.24%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone pain			
subjects affected / exposed	0 / 847 (0.00%)	5 / 1284 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 847 (0.00%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 847 (0.24%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus mononucleosis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 847 (0.24%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 847 (0.00%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster disseminated			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			

subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 847 (0.47%)	7 / 1284 (0.55%)	
occurrences causally related to treatment / all	2 / 4	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyopneumothorax			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 847 (0.12%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 847 (0.12%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal sepsis			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 847 (0.12%)	4 / 1284 (0.31%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval abscess			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	2 / 847 (0.24%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Decreased appetite			

subjects affected / exposed	3 / 847 (0.35%)	7 / 1284 (0.55%)	
occurrences causally related to treatment / all	2 / 3	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 847 (0.24%)	3 / 1284 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 847 (0.00%)	2 / 1284 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 847 (0.12%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolaemia			
subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	8 / 847 (0.94%)	7 / 1284 (0.55%)	
occurrences causally related to treatment / all	8 / 8	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipidaemia			

subjects affected / exposed	0 / 847 (0.00%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	2 / 847 (0.24%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	4 / 847 (0.47%)	5 / 1284 (0.39%)	
occurrences causally related to treatment / all	2 / 4	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	5 / 847 (0.59%)	1 / 1284 (0.08%)	
occurrences causally related to treatment / all	2 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polydipsia			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 847 (0.12%)	0 / 1284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Without Chemo in Metastatic Setting	With Chemo in Metastatic Setting	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	770 / 847 (90.91%)	1153 / 1284 (89.80%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	38 / 847 (4.49%)	28 / 1284 (2.18%)	
occurrences (all)	43	29	
Lymphoedema			
subjects affected / exposed	23 / 847 (2.72%)	22 / 1284 (1.71%)	
occurrences (all)	24	22	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	193 / 847 (22.79%)	284 / 1284 (22.12%)	
occurrences (all)	215	323	
Fatigue			
subjects affected / exposed	126 / 847 (14.88%)	163 / 1284 (12.69%)	
occurrences (all)	140	169	
Oedema peripheral			
subjects affected / exposed	115 / 847 (13.58%)	138 / 1284 (10.75%)	
occurrences (all)	129	169	
Pyrexia			
subjects affected / exposed	96 / 847 (11.33%)	176 / 1284 (13.71%)	
occurrences (all)	117	213	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	108 / 847 (12.75%)	142 / 1284 (11.06%)	
occurrences (all)	117	158	
Dyspnoea			
subjects affected / exposed	71 / 847 (8.38%)	111 / 1284 (8.64%)	
occurrences (all)	75	118	
Epistaxis			
subjects affected / exposed	58 / 847 (6.85%)	88 / 1284 (6.85%)	
occurrences (all)	59	97	
Pneumonitis			

subjects affected / exposed	63 / 847 (7.44%)	104 / 1284 (8.10%)	
occurrences (all)	69	108	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	25 / 847 (2.95%)	40 / 1284 (3.12%)	
occurrences (all)	25	41	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	47 / 847 (5.55%)	66 / 1284 (5.14%)	
occurrences (all)	49	75	
Aspartate aminotransferase increased			
subjects affected / exposed	41 / 847 (4.84%)	69 / 1284 (5.37%)	
occurrences (all)	43	76	
Blood cholesterol increased			
subjects affected / exposed	16 / 847 (1.89%)	43 / 1284 (3.35%)	
occurrences (all)	18	43	
Blood creatinine increased			
subjects affected / exposed	28 / 847 (3.31%)	26 / 1284 (2.02%)	
occurrences (all)	28	32	
Blood lactate dehydrogenase increased			
subjects affected / exposed	17 / 847 (2.01%)	31 / 1284 (2.41%)	
occurrences (all)	17	31	
Gamma-glutamyltransferase increased			
subjects affected / exposed	41 / 847 (4.84%)	84 / 1284 (6.54%)	
occurrences (all)	42	87	
Weight decreased			
subjects affected / exposed	80 / 847 (9.45%)	135 / 1284 (10.51%)	
occurrences (all)	83	140	
Nervous system disorders			
Dizziness			
subjects affected / exposed	23 / 847 (2.72%)	19 / 1284 (1.48%)	
occurrences (all)	24	19	
Dysgeusia			
subjects affected / exposed	84 / 847 (9.92%)	92 / 1284 (7.17%)	
occurrences (all)	89	93	

Headache			
subjects affected / exposed	54 / 847 (6.38%)	84 / 1284 (6.54%)	
occurrences (all)	55	97	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	107 / 847 (12.63%)	179 / 1284 (13.94%)	
occurrences (all)	130	204	
Leukopenia			
subjects affected / exposed	19 / 847 (2.24%)	22 / 1284 (1.71%)	
occurrences (all)	23	25	
Neutropenia			
subjects affected / exposed	24 / 847 (2.83%)	51 / 1284 (3.97%)	
occurrences (all)	27	68	
Thrombocytopenia			
subjects affected / exposed	35 / 847 (4.13%)	88 / 1284 (6.85%)	
occurrences (all)	42	123	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 847 (3.19%)	30 / 1284 (2.34%)	
occurrences (all)	29	31	
Abdominal pain upper			
subjects affected / exposed	28 / 847 (3.31%)	37 / 1284 (2.88%)	
occurrences (all)	29	39	
Aphthous stomatitis			
subjects affected / exposed	17 / 847 (2.01%)	25 / 1284 (1.95%)	
occurrences (all)	17	27	
Constipation			
subjects affected / exposed	37 / 847 (4.37%)	70 / 1284 (5.45%)	
occurrences (all)	39	76	
Diarrhoea			
subjects affected / exposed	158 / 847 (18.65%)	187 / 1284 (14.56%)	
occurrences (all)	183	225	
Dry mouth			
subjects affected / exposed	25 / 847 (2.95%)	34 / 1284 (2.65%)	
occurrences (all)	25	35	
Nausea			

subjects affected / exposed	94 / 847 (11.10%)	156 / 1284 (12.15%)	
occurrences (all)	103	167	
Stomatitis			
subjects affected / exposed	474 / 847 (55.96%)	649 / 1284 (50.55%)	
occurrences (all)	608	850	
Vomiting			
subjects affected / exposed	73 / 847 (8.62%)	94 / 1284 (7.32%)	
occurrences (all)	79	106	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	6 / 847 (0.71%)	28 / 1284 (2.18%)	
occurrences (all)	6	31	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	27 / 847 (3.19%)	19 / 1284 (1.48%)	
occurrences (all)	27	19	
Dry skin			
subjects affected / exposed	36 / 847 (4.25%)	39 / 1284 (3.04%)	
occurrences (all)	38	41	
Erythema			
subjects affected / exposed	30 / 847 (3.54%)	33 / 1284 (2.57%)	
occurrences (all)	35	36	
Pruritus			
subjects affected / exposed	76 / 847 (8.97%)	90 / 1284 (7.01%)	
occurrences (all)	82	96	
Rash			
subjects affected / exposed	161 / 847 (19.01%)	190 / 1284 (14.80%)	
occurrences (all)	177	213	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	63 / 847 (7.44%)	96 / 1284 (7.48%)	
occurrences (all)	71	101	
Back pain			
subjects affected / exposed	47 / 847 (5.55%)	50 / 1284 (3.89%)	
occurrences (all)	48	52	

Bone pain			
subjects affected / exposed	52 / 847 (6.14%)	71 / 1284 (5.53%)	
occurrences (all)	53	81	
Myalgia			
subjects affected / exposed	27 / 847 (3.19%)	36 / 1284 (2.80%)	
occurrences (all)	30	37	
Pain in extremity			
subjects affected / exposed	37 / 847 (4.37%)	52 / 1284 (4.05%)	
occurrences (all)	39	54	
Infections and infestations			
Bronchitis			
subjects affected / exposed	17 / 847 (2.01%)	12 / 1284 (0.93%)	
occurrences (all)	17	13	
Cystitis			
subjects affected / exposed	23 / 847 (2.72%)	33 / 1284 (2.57%)	
occurrences (all)	24	36	
Nasopharyngitis			
subjects affected / exposed	18 / 847 (2.13%)	21 / 1284 (1.64%)	
occurrences (all)	18	24	
Urinary tract infection			
subjects affected / exposed	37 / 847 (4.37%)	23 / 1284 (1.79%)	
occurrences (all)	39	29	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	134 / 847 (15.82%)	200 / 1284 (15.58%)	
occurrences (all)	136	220	
Hypercholesterolaemia			
subjects affected / exposed	71 / 847 (8.38%)	144 / 1284 (11.21%)	
occurrences (all)	76	151	
Hyperglycaemia			
subjects affected / exposed	118 / 847 (13.93%)	142 / 1284 (11.06%)	
occurrences (all)	128	167	
Hypertriglyceridaemia			
subjects affected / exposed	49 / 847 (5.79%)	74 / 1284 (5.76%)	
occurrences (all)	53	79	
Hypocalcaemia			

subjects affected / exposed	22 / 847 (2.60%)	21 / 1284 (1.64%)	
occurrences (all)	25	22	
Hypokalaemia			
subjects affected / exposed	27 / 847 (3.19%)	33 / 1284 (2.57%)	
occurrences (all)	32	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2012	The protocol was amended to reflect the indication granted by European Commission in Jul 2012, i.e. "Afinitor is indicated for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2/neu) negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor" • Inclusion criteria 1 updated to "Adult women (≥ 18 years of age) with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy, whose disease recurred or progressed following a Non-steroidal aromatase inhibitor (NSAI) treatment • The wording "refractory to NSAIs" has been changed to "after recurrence or progression following NSAIs treatment" • Addition of only PgR-positive breast cancer and the deletion of disease refractory to NSAIs • Exclusion criteria was updated to for Delete criteria regarding previous treatment with exemestane or mammalian target of rapamycin (mTOR) inhibitors, bilateral diffuse lymphangitic carcinomatosis, and subjects who test positive for hepatitis B or C • Added criteria regarding pre-menopausal, pregnant or lactating women, the known hypersensitivity to exemestane or any excipients, the rare hereditary problems of galactose intolerance and subject with positive baseline hepatitis B or C results the Screening period was extended to 28 days to allow time for prophylactic treatment • Management guidelines for specific toxicities were updated.
20 December 2012	The protocol was updated to better clarify the subject population. "Radiological or clinical evidence of recurrence or progression on last therapy prior to enrollment" has been added to inclusion criteria in order to make sure that subjects have relapsed on the last therapy prior to enrollment • A local sub-study was planned in two countries (Italy and Belgium) in 110 subjects newly enrolled in the core study with the aim of evaluating if Caphosol® is more effective than "standard care" (good mouth hygiene and mouth washes with normal saline) in reduction of incidence and severity of oral mucositis (OM) due to everolimus combination with exemestane.
10 September 2013	The protocol was updated to extend the study duration from 31 Jan 2014 till 30 June 2014 and to increase the number of subjects from 2200 to 2500 • The local sub-study that was planned to be performed in two countries (Italy and Belgium) in 110 subjects newly enrolled in the core study was dropped with this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported